

~~What is claimed:~~ **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) 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;
 - (b) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 105, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 106, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 107, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 108, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 109, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 110;
 - (c) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 115, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 116, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 117, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 118, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 119, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 120;

- (d) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 135, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 136, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 137, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 138, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 139, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 140;
- (e) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 145, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 146, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 147, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 148, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 149, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 150;
- (f) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 5, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 6, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 7, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 8, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 9, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 10;
- (g) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 15, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 16, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 18, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 19, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 20;

- (h) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30;
- (i) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 35, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 36, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 37, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 38, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 39, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 40;
- (j) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 58, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 59, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 60;
- (k) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 65, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 66, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 67, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 68, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 69, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 70;

- (l) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 75, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 76, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 77, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 78, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 79, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 80;
- (m) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 85, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 86, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 87, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 90;
- (n) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 95, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 96, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 97, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 98, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 99, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 100;
- (o) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 125, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 126, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 127, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 128, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 129, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 130;

- (p) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 155, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 156, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 157, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 158, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 159, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 160; or
- (q) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 165, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 166, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 167, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 168, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 169, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 170.

1. —.

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 K_D of 10 nM or less as measured by BIACORE™; ~~or~~

(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, wherein the N-terminal extracellular domain of human CCR8 comprises the amino acid sequence set forth in SEQ ID NO: 172.~~

~~4. The antibody or antigen binding portion thereof of any one of claims 1 to 3, which binds to at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten amino acids set forth in SEQ ID NO: 172.~~

~~5. The antibody or antigen binding portion thereof of any one of claims 1 to 4, which binds to at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten contiguous amino acids set forth in SEQ ID NO: 172.~~

~~6. The antibody or antigen binding portion thereof of any one of claims 1 to 6, which binds to an amino acid sequence selected from SEQ ID NOs: 180-200.~~

~~7. The antibody or antigen binding portion thereof of any one of claims 1 to 7, which further binds cyno CCR8.~~

8. — The antibody or antigen-binding portion thereof of any one of claims 1 to 7, which binds human CCR8 with a K_D of 10 nM or less as measured by BIACORE™.
9. — The antibody or antigen-binding portion thereof of any one of claims 1 to 8, which binds human CCR8 with a K_D of 1 nM or less as measured by BIACORE™.
10. — The antibody or antigen-binding portion thereof of any one of claims 1 to 9, which induces antibody dependent cellular cytotoxicity (ADCC) in a subject following administration of the anti-CCR8 antibody.
11. — The antibody or antigen-binding portion thereof of claim 10, wherein the ADCC comprises an EC50 of 1 µg/mL or less following the administration of the antibody or antigen-binding portion thereof.
12. — The antibody or antigen-binding portion thereof of claim 10 or 11, wherein the ADCC comprises an EC50 of 0.1 µg/mL or less following the administration of the antibody or antigen-binding portion thereof.
13. — The antibody or antigen-binding portion thereof of any one of claims 1 to 12, which is capable of inducing activation of NK cells.
14. — The antibody or antigen-binding portion thereof of any one of claims 1 to 13, which is capable of inducing upregulation of 4-1BB, ICAM-1, or both 4-1BB and ICAM-1 on the surface of NK cells.
15. — The antibody or antigen-binding portion thereof of any one of claims 1 to 14, which is capable of inducing down-regulation of CD16 on the surface of NK cells in the subject.
16. — The antibody or antigen-binding portion thereof of any one of claims 1 to 15, which is capable of inducing NK cell mediated killing of tumor infiltrating T_{reg} cells in the subject.
17. — The antibody or antigen-binding portion thereof of any one of claims 1 to 16, which induces depletion in the number of tumor infiltrating T_{reg} cells in a subject

~~following administration of the antibody or antigen binding portion thereof, relative to the number of tumor infiltrating T_{reg} cells prior to the administration.~~

- ~~18. The antibody or antigen binding portion thereof of claim 17, wherein the number of tumor infiltrating T_{reg} cells is depleted by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% relative to the number of tumor infiltrating T_{reg} cells prior to the administration.~~
- ~~19. The antibody or antigen binding portion thereof of any one of claims 1 to 18, which induces internalization of CCR8 by tumor infiltrating T_{reg} cells.~~
- ~~20. The antibody or antigen binding portion thereof of any one of claims 1 to 19, comprising a variable heavy (VH) chain, comprising a VH complementarity determining region (CDR) 1, a VH CDR2, and a VH CDR3; wherein the VH CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 7, 17, 27, 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 137, 147, 157, and 167.~~
- ~~21. The antibody or antigen binding portion thereof of claim 21, wherein the VH CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 6, 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, and 166.~~
- ~~22. The antibody or antigen binding portion thereof of any one of claims 21 to 25, wherein the VH CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 5, 15, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, 155, and 165.~~
- ~~23. The antibody or antigen binding portion thereof of any one of claims 21 to 28, wherein the VL CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, and 170.~~

24. ~~The antibody or antigen binding portion thereof of any one of claims 21 to 31, wherein the VL CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 9, 19, 29, 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 139, 149, 159, and 169.~~
25. ~~The antibody or antigen binding portion thereof of any one of claims 21 to 34, wherein the VL CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 8, 18, 28, 38, 48, 58, 68, 78, 88, 98, 108, 118, 128, 138, 148, 158, and 168.~~
26. ~~The antibody or antigen binding portion thereof of any one of claims 1 to 6 and 8 to 25, which does not bind cyno CCR8.~~
27. ~~The antibody or antigen binding portion thereof of claim 26, comprising a variable heavy (VH) chain, comprising a VH complementarity determining region (CDR) 1, a VH CDR2, and a VH CDR3; wherein the VH CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 47, 107, 117, 137, and 147.~~
28. ~~The antibody or antigen binding portion thereof of claim 27, wherein the VH CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 46, 106, 116, 136, and 146.~~
29. ~~The antibody or antigen binding portion thereof of claim 27 or 28, wherein the VH CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 45, 105, 115, 135, and 145.~~
30. ~~The antibody or antigen binding portion thereof of any one of claims 27 to 29, wherein the VL CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 50, 110, 120, 140, and 150.~~
31. ~~The antibody or antigen binding portion thereof of any one of claims 27 to 30, wherein the VL CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 49, 109, 119, 139, and 149.~~

- ~~32. The antibody or antigen binding portion thereof of any one of claims 27 to 31, wherein the VL CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 48, 108, 118, 138, and 148.~~
- ~~33. The antibody or antigen binding portion thereof of any one of claims 27 to 32, which comprises:~~
- ~~(a) a VH CDR1 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 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;~~
 - ~~(b) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 105, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 106, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 107, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 108, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 109, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 110;~~
 - ~~(c) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 115, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 116, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 117, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 118, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 119, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 120;~~
 - ~~(d) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 135, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID~~

~~NO: 136, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 137, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 138, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 139, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 140; or~~

- (e) ~~a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 145, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 146, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 147, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 148, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 149, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 150.~~

~~34.3.~~ The antibody or antigen-binding portion thereof of any one of claims 27 to 33 claim 1 or 2, wherein the VH chain comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 41, 101, 111, 131, and 141, 1, 11, 21, 31, 51, 61, 71, 81, 91, 121, 151, and 161.

~~35.4.~~ The antibody or antigen-binding portion thereof of any one of claims 27 to 34 1 to 3, wherein the VL chain comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 4243, 102103, 112113, 132133, and 142143, 3, 13, 23, 33, 53, 63, 73, 83, 93, 123, 153, and 163.

~~36.5.~~ The antibody or antigen-binding portion thereof of any one of claims 27 to 35 1 to 3, which comprises:

- (a) 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: ~~4243~~;
- (b) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 101 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: ~~102103~~;

- (c) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 111 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: ~~112~~113;
- (d) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 131 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: ~~132~~133; ~~or~~
- (e) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 141 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: ~~142~~143;
- (f) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 1 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 3;
- (g) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 11 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 13;
- (h) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 21 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 23;
- (i) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 31 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 33;
- (j) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 51 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 53;
- (k) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 61 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 63;

- (l) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 71 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 73;
- (m) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 81 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 83;
- (n) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 91 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 93;
- (o) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 121 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 123;
- (p) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 151 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 153; or
- (q) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 161 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 163.

~~37. The antibody or antigen-binding portion thereof of any one of claims 1 to 6 and 8 to 25, which binds human CCR8 and cyno CCR8.~~

~~38. The antibody or antigen-binding portion thereof of claim 37, comprising a variable heavy (VH) chain, comprising a VH complementarity determining region (CDR) 1, a VH CDR2, and a VH CDR3; wherein the VH CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 7, 17, 27, 37, 57, 67, 77, 87, 97, 127, 157, and 167.~~

- ~~39. The antibody or antigen binding portion thereof of claim 38, wherein the VH CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 6, 16, 26, 36, 56, 66, 76, 86, 96, 126, 156, and 166.~~
- ~~40. The antibody or antigen binding portion thereof of claim 38 or 39, wherein the VH CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 5, 15, 25, 35, 55, 65, 75, 85, 95, 125, 155, and 165.~~
- ~~41. The antibody or antigen binding portion thereof of any one of claims 38 to 40, wherein the VL CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 10, 20, 30, 40, 60, 70, 80, 90, 100, 130, 160, and 170.~~
- ~~42. The antibody or antigen binding portion thereof of any one of claims 38 to 41, wherein the VL CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 9, 19, 29, 39, 59, 69, 79, 89, 99, 129, 159, and 169.~~
- ~~43. The antibody or antigen binding portion thereof of any one of claims 38 to 42, wherein the VL CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 8, 18, 28, 38, 58, 68, 78, 88, 98, 128, 158, and 168.~~
- ~~44. The antibody or antigen binding portion thereof of any one of claims 38 to 43, which comprises:~~
- ~~(a) a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 5, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 6, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 7, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 8, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 9, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 10;~~

- (b) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 15, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 16, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 18, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 19, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 20;
- (c) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30;
- (d) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 35, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 36, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 37, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 38, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 39, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 40;
- (e) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 58, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 59, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 60;

- (f) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 65, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 66, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 67, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 68, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 69, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 70;
- (g) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 75, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 76, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 77, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 78, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 79, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 80;
- (h) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 85, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 86, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 87, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 90;
- (i) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 95, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 96, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 97, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 98, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 99, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 100;

- ~~(j) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 125, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 126, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 127, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 128, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 129, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 130;~~
 - ~~(k) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 155, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 156, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 157, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 158, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 159, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 160; or~~
 - ~~(l) — a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 165, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 166, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 167, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 168, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 169, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 170.~~
- ~~45. — The antibody or antigen binding portion thereof of any one of claims 38 to 44, wherein the VH chain comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 1, 11, 21, 31, 51, 61, 71, 81, 91, 121, 151, and 161.~~
- ~~46. — The antibody or antigen binding portion thereof of any one of claims 37 to 45, wherein the VL chain comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 2, 12, 22, 32, 52, 62, 72, 82, 92, 122, 152, and 162.~~

~~47. The antibody or antigen binding portion thereof of any one of claims 37 to 46, which comprises:~~

- ~~(a) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 1 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 2;~~
- ~~(b) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 11 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 12;~~
- ~~(c) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 21 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 22;~~
- ~~(d) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 31 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 32;~~
- ~~(e) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 51 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 52;~~
- ~~(f) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 61 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 62;~~
- ~~(g) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 71 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 72;~~
- ~~(h) a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 81 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 82;~~

- (i) ~~— a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 91 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 92;~~
- (j) ~~— a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 121 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 122;~~
- ~~(k) — a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 151 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 152; or~~
- (l) ~~— a VH chain comprising the amino acid sequence set forth in SEQ ID NO: 161 and a VL chain comprising the amino acid sequence set forth in SEQ ID NO: 162.~~

6. The antibody or antigen-binding portion thereof of any one of claims 1 to 475, which is a human antibody, a humanized antibody, or a chimeric antibody.

48.7. The antibody or antigen-binding portion thereof of any one of claims 1 to 6, which is an afucosylated antibody.

49.8. The antibody or antigen-binding portion thereof of any one of claims 1 to 487, which comprises a single-chain variable fragment (scFv) of an antibody.

50.9. The antibody or antigen-binding portion thereof of any one of claims 1 to 498, 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.

51.10. A bispecific antibody or a multispecific antibody comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 498.

52.11. A BiTe comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 498.

~~53. A multispecific antibody comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 49.~~

~~54.12. A biparatopic antibody comprising the antibody or antigen-binding portion thereof of any one of claims 1 to 498.~~

13. ~~The bispecific or multispecific antibody of claim 5410, BiTe of claim 5211, multispecific of claim 53, or biparatopic antibody of claim 5412, which 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~~

(a) 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;

(b) the first VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 105, the first VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 106, the first VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 107, the first VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 108, the first VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 109, and the first VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 110;

(c) the first VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 115, the first VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 116, the first VH CDR3 comprises the amino acid sequence

set forth in SEQ ID NO: 117, the first VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 118, the first VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 119, and the first VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 120;

(d) the first VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 135, the first VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 136, the first VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 137, the first VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 138, the first VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 139, and the first VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 140; or

55.(e) the first VH CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 145, the first VH CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 146, the first VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 147, the first VL CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 148, the first VL CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 149, and the first VL CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 150.

~~(a) the first VH CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 45, 105, 115, 135, and 145;~~

~~(b) the first VH CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 46, 106, 116, 136, and 146;
and~~

~~(c) the first VH CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 47, 107, 117, 137, and 147.~~

~~56. The bispecific antibody of claim 51, BiTe of claim 52, multispecific of claim 53, or biparatopic antibody of claim 55, wherein:~~

- (a) ~~the first VL CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 48, 108, 118, 138, and 148;~~
- (b) ~~the first VL CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 49, 109, 119, 139, and 149;~~
~~and~~
- (c) ~~the first VL CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 50, 110, 120, 140, and 150.~~

14. ~~The biparatopic antibody of claim 55-13 or 56,~~ 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: 15, the second VH CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 15, 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

57.(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.

- ~~(a) the second VH CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 5, 15, 25, 35, 55, 65, 75, 85, 95, 125, 155, and 165;~~
- ~~(b) the second VH CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 6, 16, 26, 36, 56, 66, 76, 86, 96, 126, 156, and 166; and~~
- ~~(c) the second VH CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 7, 17, 27, 37, 57, 67, 77, 87, 97, 127, 157, and 167.~~

~~58.~~ The biparatopic antibody of any one of claims ~~55 to 57~~, wherein:

- ~~(a) the second VL CDR1 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 8, 18, 28, 38, 58, 68, 78, 88, 98, 128, 158, and 168;~~
- ~~(b) the second VL CDR2 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 9, 19, 29, 39, 59, 69, 79, 89, 99, 129, 159, and 169; and~~
- ~~(c) the second VL CDR3 comprises an amino acid sequence selected from the amino acid sequence set forth in SEQ ID NOs: 10, 20, 30, 40, 60, 70, 80, 90, 100, 130, 160, and 170.~~

~~59.15.~~ An immunoconjugate comprising the antibody or antigen-binding portion thereof of any one of claims 1 to ~~498~~.

~~60.16.~~ The immunoconjugate of claim ~~59.15~~, which is an antibody-drug conjugate.

~~61.17.~~ A chimeric antigen receptor (CAR) comprising the antibody or antigen-binding portion thereof of any of any one of claims 1 to ~~498~~.

~~62.18.~~ A T cell receptor (TCR) comprising the antibody or antigen-binding portion thereof of any of any one of claims 1 to ~~498~~.

~~63.19.~~ 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 ~~509~~, the bispecific or multispecific antibody of claim ~~51.10~~, the BiTE of claim ~~52.11~~, ~~the multispecific antibody of claim 53~~, the biparatopic antibody of any one of claims ~~54.12 to 58.14~~, the immunoconjugate of claim ~~59.15~~ or ~~60.16~~, the CAR of claim ~~61.17~~, or the TCR of claim ~~62.18~~.

~~64.20.~~ A vector or a set of vectors comprising the nucleic acid molecule or the set of nucleic acid molecules of claim ~~63.19~~.

~~65.21.~~ A cell comprising the CAR of claim ~~64~~17, the TCR of claim ~~62~~18, the nucleic acid molecule or the set of nucleic acid molecules of claim ~~63~~19, or the vector or the set of vectors of claim ~~64~~20.

~~66.22.~~ The cell of claim ~~65~~21, which is a host cell.

~~67.~~ The cell of claim ~~65~~ or ~~66~~, which is an immune cell.

~~68.~~ The cell of any one of claims ~~65~~ to ~~67~~, which is a T cell.

~~69.23.~~ A pharmaceutical composition comprising the antibody or antigen-binding portion thereof of any one of claims 1 to ~~50~~9, the bispecific or multispecific antibody of claim ~~54~~10, the BiTE of claim ~~52~~11, ~~the multispecific antibody of claim 53~~, the biparatopic antibody of any one of claims ~~54~~12 to ~~14~~58, the immunoconjugate of claim ~~59~~15 or ~~60~~16, the CAR of claim ~~64~~17, the TCR of claim ~~62~~18, the nucleic acid molecule or the set of nucleic acid molecules of claim ~~63~~19, the vector or the set of vectors of claim ~~64~~20, or the cell of ~~any one of claims 65 to 68~~claim 21 or 22, and a pharmaceutically acceptable carrier.

~~24.~~ ~~A method~~Use of treating a tumor in a subject in need thereof, comprising administering to the subject the antibody or an antigen-binding portion thereof of any one of claims 1 to ~~50~~9, the bispecific or multispecific antibody of claim ~~54~~10, the BiTE of claim ~~52~~11, ~~the multispecific antibody of claim 53~~, the biparatopic antibody of any one of claims ~~54~~12 to ~~58~~14, the immunoconjugate of claim ~~15~~59 or ~~60~~16, the CAR of claim ~~64~~17, the TCR of claim ~~62~~18, the nucleic acid molecule or the set of nucleic acid molecules of claim ~~63~~19, the vector or the set of vectors of claim ~~64~~20, the cell of ~~any one of claims~~claim 21 or 22 ~~65 to 68~~, or the pharmaceutical composition of claim ~~69~~23 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 ("T_{reg}") cells;
and/or

70.(c) activating NK cells or inducing NK cell mediated killing of tumor infiltrating regulatory T ("T_{reg}") cells.

~~71. A method of reducing, depleting, or killing tumor infiltrating regulatory T ("T_{reg}") cells, comprising contacting Treg cells with the antibody or an antigen-binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, the TCR of claim 62, the nucleic acid molecule or the set of nucleic acid molecules of claim 63, the vector or the set of vectors of claim 64, the cell of any one of claims 65 to 68, or the pharmaceutical composition of claim 69.~~

~~72. A method of activating NK cells or inducing NK cell mediated killing of tumor infiltrating regulatory T ("T_{reg}") cells, comprising contacting T_{reg} cells with the antibody or an antigen-binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, the TCR of claim 62, the nucleic acid molecule or the set of nucleic acid molecules of claim 63, the vector or the set of vectors of claim 64, the cell of any one of claims 65 to 68, or the pharmaceutical composition of claim 69.~~

~~73. The method of claim 71 or 72, wherein the contacting is in vitro or ex vivo.~~

~~74. The method of claim 71 or 72, wherein the contacting is in vivo.~~

25. The method use of any one of claims 70 to 74claim 24, 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 T_{reg} cells;
- (e) induces NK cell mediated killing of tumor infiltrating T_{reg} cells;
- (f) depletes the number of tumor infiltrating T_{reg} cells relative to the number of tumor infiltrating T_{reg} cells in the absence of the antibody or antigen binding portion thereof;
- (g) depletes the number of tumor infiltrating T_{reg} cells by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% relative to the number of tumor infiltrating T_{reg} cells in the absence of the antibody or antigen binding portion thereof; and/or
- 75.(h) induces internalization of CCR8 by tumor infiltrating T_{reg} cells.

- ~~76.—The method of any one of claims 70 to 75, wherein the antibody or antigen-binding portion thereof induces upregulation of 4-1BB, ICAM-1, or both 4-1BB and ICAM-1 on the surface of NK cells.~~
- ~~77.—The method of any one of claims 70 to 76, wherein the antibody or antigen-binding portion thereof induces down-regulation of CD16 on the surface of NK cells.~~
- ~~78.—The method of any one of claims 70 to 77, wherein the antibody or antigen-binding portion thereof induces NK cell mediated killing of tumor infiltrating T_{reg} cells.~~
- ~~79.—The method of any one of claims 70 to 78, wherein the antibody or antigen-binding portion thereof depletes the number of tumor infiltrating T_{reg} cells relative to the number of tumor infiltrating T_{reg} cells in the absence of the antibody or antigen binding portion thereof.~~

80. ~~The method of any one of claims 70 to 79, wherein the antibody or antigen binding portion thereof depletes the number of tumor infiltrating T_{reg} cells by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% relative to the number of tumor infiltrating T_{reg} cells in the absence of the antibody or antigen binding portion thereof.~~
81. ~~The method of any one of claims 70 to 80, wherein the antibody or antigen binding portion thereof induces internalization of CCR8 by tumor infiltrating T_{reg} cells.~~
- 82.26. The use method of claim 24 or 25 ~~of any one of claims 70 to 81~~, 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, meningioma, 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.

~~83. The method of any one of claims 70 to 82, wherein the tumor is refractory or relapsed.~~

~~84. The method of any one of claims 70 to 83, wherein the tumor is advanced, locally advanced, or metastatic.~~

~~85.27. The use method of any one of claims 70-24 to 8426, further comprising administering wherein an additional anticancer agent is to be administered.~~

~~86.28. The use method of claim 8527, wherein the additional anticancer agent is selected from a small molecule, a polypeptide, a radiation therapy, a surgery, and a combination thereof.~~

~~29. The use method of claim 85-27 or 8628, 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

87.(l) the additional anticancer agent comprises an agent that induces NK cell activation.

~~88. The method of claim 87, wherein the chemotherapy comprises a platinum-based chemotherapy.~~

~~89. The method of any one of claims 85 to 88, wherein the additional anticancer agent comprises a PD-1 antagonist, a PD-L1 inhibitor, a TIM-3 inhibitor, a LAG-3 inhibitor, a TIGIT inhibitor, a CD112R inhibitor, a TAM inhibitor, a STING agonist, a 4-1BB agonist, a CCL22 inhibitor, an agent that induces NK cell activation or a combination thereof.~~

~~90. The method of any one of claims 85 to 89, wherein the additional anticancer agent comprises a PD-1 antagonist.~~

~~91. The method of claim 90, 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.~~

~~92. The method of any one of claims 85 to 91, wherein the additional anticancer agent comprises a PD-L1 inhibitor.~~

93. ~~The method of claim 92, wherein the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559.~~
94. ~~The method of any one of claims 85 to 93, wherein 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-rwle (LIBTAYO[®]), tislelizumab, spartalizumab, and any combination thereof.~~
95. ~~The method of any one of claims 85 to 94, wherein the additional anticancer agent comprises a TIM-3 inhibitor.~~
96. ~~The method of claim 95, wherein the TIM-3 inhibitor is MGB453 or TSR-022.~~
97. ~~The method of any one of claims 85 to 96, wherein the additional anticancer agent comprises a LAG-3 inhibitor.~~
98. ~~The method of claim 97, wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, and TSR-033.~~
99. ~~The method of any one of claims 85 to 98, wherein the additional anticancer agent comprises a TIGIT inhibitor.~~

~~100. The method of any one of claims 85 to 99, wherein the additional anticancer agent comprises a CD112R inhibitor.~~

~~101. The method of any one of claims 85 to 100, wherein the additional anticancer agent comprises a TAM (Axl, Mer, Tyro) inhibitor.~~

~~102. The method of any one of claims 85 to 101, wherein the additional anticancer agent comprises a 4-1BB agonist.~~

~~103. The method of any one of claims 85 to 102, wherein the additional anticancer agent comprises a Tyrosine Kinase Inhibitor (TKI).~~

~~104. The method of any one of claims 85 to 103, wherein the additional anticancer agent comprises a CCL2 inhibitor.~~

~~105. The method of any one of claims 85 to 104, wherein the additional anticancer agent comprises an agent that induces NK cell activation.~~

30. The use method of any one of claims 85-27 to 10529, wherein:

(a) the antibody or antigen-binding portion thereof is to be administered prior to the additional anticancer agent;

(b) the antibody or antigen-binding portion thereof is to be administered after the additional anticancer agent; or

~~106.~~(c) the antibody or antigen-binding portion thereof and the additional anticancer agent are to be co-administered.

~~107. The method of any one of claims 85 to 105, wherein the antibody or antigen-binding portion thereof is administered after the additional anticancer agent.~~

~~108. The method of any one of claims 85 to 105, wherein the antibody or antigen-binding portion thereof and the additional anticancer agent are co-administered.~~

~~109.31.~~ A method of making an antibody or an antigen-binding portion thereof, comprising culturing the cell of ~~any one of claims 65 to 68~~ claim 21 or 22 under suitable conditions.

~~110.~~ The method of claims 109, further comprising isolating the antibody or antigen-binding portion thereof.

~~111.~~ Use of the antibody or antigen-binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, the TCR of claim 62, the nucleic acid molecule or the set of nucleic acid molecules of claim 63, the vector or the set of vectors of claim 64, the cell of any one of claims 65 to 68, or the pharmaceutical composition of claim 69 for the manufacture of a medicament in treating a tumor in a subject in need thereof.

~~112.~~ Use of the antibody or antigen-binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, the TCR of claim 62, the nucleic acid molecule or the set of nucleic acid molecules of claim 63, the vector or the set of vectors of claim 64, the cell of any one of claims 65 to 68, or the pharmaceutical composition of claim 69 for the manufacture of a medicament in reducing, depleting, or killing tumor infiltrating T_{reg} cells in a subject in need thereof.

~~113.~~ Use of the antibody or antigen-binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, the TCR of claim 62, the nucleic acid molecule or

~~the set of nucleic acid molecules of claim 63, the vector or the set of vectors of claim 64, the cell of any one of claims 65 to 68, or the pharmaceutical composition of claim 69 for the manufacture of a medicament in activating NK cells or inducing NK cell mediated killing of tumor infiltrating T_{reg} cells in a subject in need thereof.~~

~~114. The antibody or antigen binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, the TCR of claim 62, the nucleic acid molecule or the set of nucleic acid molecules of claim 63, the vector or the set of vectors of claim 64, the cell of any one of claims 65 to 68, or the pharmaceutical composition of claim 69 for use in a method of treating a tumor in a subject in need thereof.~~

~~115. The antibody or antigen binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, the TCR of claim 62, the nucleic acid molecule or the set of nucleic acid molecules of claim 63, the vector or the set of vectors of claim 64, the cell of any one of claims 65 to 68, or the pharmaceutical composition of claim 69 for use in a method of reducing, depleting, or killing tumor infiltrating T_{reg} cells in a subject in need thereof.~~

~~116. The antibody or antigen binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, the TCR of claim 62, the nucleic acid molecule or the set of nucleic acid molecules of claim 63, the vector or the set of vectors of claim 64, the cell of any one of claims 65 to 68, or the pharmaceutical composition~~

of claim 69 for use in a method of activating NK cells or inducing NK cell mediated killing of tumor infiltrating T_{reg} cells in a subject in need thereof.

- ~~117. The antibody or antigen binding portion thereof of any one of claims 1 to 50, the bispecific antibody of claim 51, the BiTE of claim 52, the multispecific antibody of claim 53, the biparatopic antibody of any one of claims 54 to 58, the immunoconjugate of claim 59 or 60, the CAR of claim 61, or the TCR of claim 62, wherein the antibody or the antigen binding portion thereof is afucosylated.~~
- ~~118. The method of any one of claims 70 to 110, wherein the antibody or the antigen binding portion thereof is afucosylated.~~