

CLAIMS

What is claimed is:

1. An anti-CTLA4 antibody, wherein the antibody binds human CTLA4 and is cross-reactive with cynomolgus monkey, mouse, rat, and dog CTLA4.
2. The antibody of claim 1, wherein the antibody binds to human CTLA4, cynomolgus monkey CTLA4, mouse CTLA4, rat CTLA4, and dog CTLA4 with a dissociation constant (K_D) of about 350 nM or less.
3. The antibody of claim 2, wherein the K_D is measured by surface plasmon resonance (SPR).
4. The antibody of any one of claims 1-3, wherein binding of the anti-CTLA4 antibody induces antibody-dependent cell cytotoxicity (ADCC) against a CTLA4-expressing human cell or a human Treg cell, wherein the ADCC activity of the anti-CTL4 antibody is higher than the ADCC activity of ipilimumab.
5. The antibody of any one of claims 1-4, wherein (a) the antibody specifically binds to an epitope comprising amino acid residues Y105 and L106 of human CTLA4 but does not comprise residue I108, wherein the numbering of the amino acid residues is according to SEQ ID NO: 207; and/or (b) the anti-CTLA4 antibody has an IC50 higher than the IC50 of ipilimumab for blocking binding of CD80 and/or CD86 to human CTLA4 in an assay wherein either when CD80 and/or CD86 are plate bound or when human CTLA4 is present on cell surface.
6. The antibody of any one of claims 1-5, wherein the antibody comprises a heavy chain variable region and a light chain variable region,
 - a) wherein the heavy chain variable region comprises an HVR-H1, an HVR-H2, and an HVR-H3,
wherein the HVR-H1 comprises an amino acid sequence according to a formula selected from the group consisting of:

Formula (I): X1TFSX2YX3IHWV (SEQ ID NO: 1), wherein X1 is F or Y, X2 is D or G, and X3 is A, G, or W;

Formula (II): YSIX1SGX2X3WX4WI (SEQ ID NO: 2), wherein X1 is S or T, X2 is H or Y, X3 is H or Y, and X4 is A, D, or S; and

Formula (III): FSLSTGGVAVX1WI (SEQ ID NO: 3), wherein X1 is G or S;

wherein the HVR-H2 comprises an amino acid sequence according to a formula selected from the group consisting of:

Formula (IV): IGX1IX2HSGSTYYX3SLKSRV (SEQ ID NO: 4), wherein X1 is D or E, X2 is S or Y, and X3 is P or Q;

Formula (V): IGX1ISPSX2GX3TX4YAQKFQGRV (SEQ ID NO: 5), wherein X1 is I or W, X2 is G or S, X3 is G or S, and X4 is K or N; and

Formula (VI): VSX1ISGX2GX3X4TYYADSVKGRF (SEQ ID NO: 6), wherein X1 is A, G, or S, X2 is S or Y, X3 is G or S, and X4 is S or T; and

wherein the HVR-H3 comprises an amino acid sequence according to a formula selected from the group consisting of:

Formula (VII): ARX1X2X3X4FDX5 (SEQ ID NO: 7), wherein X1 is G, R, or S, X2 is A, I, or Y, X3 is D, V, or Y, X4 is A, E, or Y, and X5 is I or Y;

Formula (VIII): ARX1GX2GYFDX3 (SEQ ID NO: 8), wherein X1 is D or L, X2 is F or Y, and X3 is V or Y;

Formula (IX): ARX1X2X3X4AX5X6FDY (SEQ ID NO: 9), wherein X1 is L or R, X2 is I or P, X3 is A or Y, X4 is S or T, X5 is T or Y, and X6 is A or Y;

Formula (X): ARDX1X2X3GSSGYX4GFDX5 (SEQ ID NO: 10), wherein X1 is I or V, X2 is A or H, X3 is P or S, X4 is D or Y, and X5 is F or V; and

b) wherein the light chain variable region comprises an HVR-L1, an HVR-L2, and an HVR-L3, wherein the HVR-L1 comprises an amino acid sequence according to a formula selected from the group consisting of:

Formula (XI): RASQX1X2X3SX4LX5 (SEQ ID NO: 11), wherein X1 is G or S, X2 is I or V, X3 is G or S, X4 is S or Y, and X5 is A or N;

Formula (XII): RASQX1VX2X3RX4LA (SEQ ID NO: 12), wherein X1 is S or T, X2 is F, R, or S, X3 is G or S, and X4 is F or Y; and

Formula (XIII): RASX1SVDFX2GX3SFLX4 (SEQ ID NO: 13), wherein X1 is E or Q, X2 is D, F, H, or Y, X3 is F, I, or K, and X4 is A, D, or H;

wherein the HVR-L2 comprises an amino acid sequence according to Formula (XIV): X1ASX2X3X4X5GX6 (SEQ ID NO: 14), wherein X1 is A or D, X2 is N, S, or T, X3 is L or R, X4 is A, E, or Q, X5 is S or T, and X6 is I or V; and

wherein the HVR-L3 comprises an amino acid sequence according to a formula selected from the group consisting of:

Formula (XV): YCX1X2X3X4X5X6PX7T (SEQ ID NO: 15), wherein X1 is E, Q, or V, X2 is H or Q, X3 is A, G, H, R, or S, X4 is D, L, S, or Y, X5 is E, G, P, Q, or S, X6 is L, T, V, or W, and X7 is F, L, P, W, or Y;

Formula (XVI): YCQX1X2X3WPPWT (SEQ ID NO: 16), wherein X1 is S or Y, X2 is D or Y, and X3 is Q or Y; and

Formula (XVII): YCQX1YX2SSPPX3YT (SEQ ID NO: 17), wherein X1 is H or Q, X2 is T or V, and X3 is E or V.

7. The antibody of any one of claims 1-3, wherein the HVR-H1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 18-29, the HVR-H2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 30-39, the HVR-H3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 40-52, the HVR-L1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 53-65, the HVR-L2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 66-69, and the HVR-L3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 70-81.

8. The antibody of any one of claims 1-3, wherein the antibody comprises:

a) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 18, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 30, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 40, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 53, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 70;

b) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 19, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 31, an HVR-H3 comprising the amino acid

sequence of SEQ ID NO: 41, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 54, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 67, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 71;

c) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 20, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 32, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 42, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 55, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 72;

d) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 21 an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 43, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 56, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 68, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 73;

e) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 22, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 34, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 57, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74;

f) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 35, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 45, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 58, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 75;

g) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 24, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 32, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 46, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 59, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 76;

h) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 25, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 47, an HVR-L1 comprising the amino acid sequence of SEQ ID NO:

60, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 69, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 77;

i) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 26, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 37, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 48, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 61, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 78;

j) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 27, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 32, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 49, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 62, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 67, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 79;

k) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 28, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 37, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 50, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 63, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 67, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 80;

l) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 18, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 38, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 51, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 64, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 67, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 81; or

m) an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 29, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 39, an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 52, an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 65, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 68, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 77.

9. The antibody of claim 7 or claim 8, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 82-94 or an amino acid sequence having at least 90% sequence identity to a sequence selected from the group consisting

of SEQ ID NOS: 82-94, and/or the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 95-107 or an amino acid sequence having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NOS: 95-107.

10. The antibody of any one of claim 7-9, wherein the antibody comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 82, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 95;
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96;
- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 84, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97;
- d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 85, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98;
- e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 86, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 99;
- f) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 87, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100;
- g) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 88, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 101;
- h) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 89, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 102;
- i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 90, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103;
- j) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 104;
- k) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 92, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 105;
- l) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 93, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 106; or

m) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 94, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 107.

11. The antibody of any one of claims 1-5, wherein the antibody comprises: (a) a heavy chain variable region comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 35, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 45, and/or a light chain variable region comprising an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 58, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 75; or (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 87 or an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 87, and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 100 or an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 100.

12. The antibody of any one of claims 1-11, wherein the antibody is a human antibody.

13. The antibody of any one of claims 1-12, wherein the antibody is an antibody fragment selected from the group consisting of a Fab, Fab', Fab'-SH, F(ab')₂, Fv and scFv fragment.

14. The antibody of any one of claims 1-13, wherein the antibody comprises a human IgG1, IgG2, IgG3, or IgG4 Fc region.

15. An antibody that cross-competes for binding to human CTLA4 with an antibody of any one of claims 9-11.

16. An activatable antibody comprising:

a polypeptide comprising, from N-terminus to C-terminus, a masking moiety (MM), a cleavable moiety (CM), and a target binding moiety (TBM),

wherein the MM comprises an amino acid sequence according to Formula (XVIII):

$X_mCX_nCZ_o$ (SEQ ID NO: 134), wherein m is from 2-10, n is from 3-10, and o is from 1-10, wherein each X is independently an amino acid selected from the group consisting of

A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, and Y, and wherein each Z is independently an amino acid selected from the group consisting of D, A, Y, S, T, N, I, L, F, V, H, and P; wherein the MM inhibits the binding of the activatable antibody to human CTLA4 when the CM is not cleaved;

wherein the CM comprises at least a first cleavage site;

wherein:

- a) the TBM comprises an antibody light chain variable region (VL), and the activatable antibody further comprises a second polypeptide comprising an antibody heavy chain variable region (VH);
- b) the TBM comprises an antibody heavy chain variable region (VH), and the activatable antibody further comprises a second polypeptide comprising an antibody light chain variable region (VL);
- c) the TBM comprises from the N-terminus to the C-terminus, an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH); or
- d) the TBM comprises from the N-terminus to the C-terminus, an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL); and

wherein the activatable antibody binds to human CTLA4 via the VH and VL when the CM is cleaved.

- 17. The activatable antibody of claim 16, wherein the TBM comprises an antibody light chain variable region (VL), and the activatable antibody further comprises a second polypeptide comprising an antibody heavy chain variable region (VH).
- 18. The activatable antibody of claim 16 or 17, wherein m is 2 or 3-10.
- 19. The activatable antibody of any one of claims 16-18, wherein n is from 6-8.
- 20. The activatable antibody of any one of claims 16-18, wherein n is 6.

21. The activatable antibody of any one of claims 16-20, wherein o is from 1-2.
22. The activatable antibody of any one of claims 16-20, wherein o is 2.
23. The activatable antibody of any one of claims 16-22, wherein each X is not M, W, or C.
24. The activatable antibody of any one of claims 16-23, wherein each X in X_m of Formula (XVIII) is independently an amino acid selected from the group consisting of D, A, Y, S, T, N, I, L, F, V, H, and P.
25. The activatable antibody of any one of claims 16-24, wherein each X in X_n of Formula (XVIII) is independently an amino acid selected from the group consisting of D, A, Y, S, T, N, I, L, F, V, H, and P.
26. The activatable antibody of any one of claims 16-25, wherein the MM comprises an amino acid sequence selected from the group consisting of X_m CPDHPYPCXX (SEQ ID NO:181), X_m CDAFYPCXX (SEQ ID NO:182), X_m CDSHYPCXX (SEQ ID NO:183), and X_m CVPYYYACXX (SEQ ID NO:184), and where m is from 2-10, and where each X is independently an amino acid selected from the group consisting of A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, and Y.
27. The activatable antibody of any one of claims 16-26, wherein the MM further comprises, at its N-terminus, an additional amino acid sequence.
28. The activatable antibody of claim 27, wherein the additional amino acid sequence comprises the amino acid sequence of SEQ ID NO: 148.
29. The activatable antibody of any one of claims 16-28, wherein the first cleavage site is a protease cleavage site for a protease selected from the group consisting of urokinase-type plasminogen activator (uPA), matrix metalloproteinase-1 (MMP-1), MMP-2, MMP-3, MMP-8, MMP-9, MMP-14, Tobacco Etch Virus (TEV) protease, plasmin, Thrombin, Factor X, PSA, PSMA, Cathepsin D, Cathepsin K, Cathepsin S, ADAM10, ADAM12, ADAMTS, Caspase-1, Caspase-2, Caspase-3, Caspase-4, Caspase-5, Caspase-6, Caspase-7, Caspase-8, Caspase-9, Caspase-10, Caspase-11, Caspase-12, Caspase-13, Caspase-14, and TACE.

30. The activatable antibody of any one of claims 16-29, wherein the CM further comprises a first linker (L₁) C-terminal to the first cleavage site.
31. The activatable antibody of claim 30, wherein the L₁ comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 156-163.
32. The activatable antibody of any one of claims 16-31, wherein the CM further comprises a second cleavage site.
33. The activatable antibody of claim 32, wherein the second cleavage site is C-terminal to the L₁.
34. The activatable antibody of claim 32 or 33, wherein the second cleavage site is a protease cleavage site for a protease selected from the group consisting of urokinase-type plasminogen activator (uPA), matrix metalloproteinase-1 (MMP-1), MMP-2, MMP-3, MMP-8, MMP-9, MMP-14, Tobacco Etch Virus (TEV) protease, plasmin, Thrombin, Factor X, PSA, PSMA, Cathepsin D, Cathepsin K, Cathepsin S, ADAM10, ADAM12, ADAMTS, Caspase-1, Caspase-2, Caspase-3, Caspase-4, Caspase-5, Caspase-6, Caspase-7, Caspase-8, Caspase-9, Caspase-10, Caspase-11, Caspase-12, Caspase-13, Caspase-14, and TACE.
35. The activatable antibody of any one of claims 32-34, wherein the first and second cleavage sites are different.
36. The activatable antibody of any one of claims 32-35, wherein the CM further comprises a second linker (L₂) C-terminal to the second cleavage site.
37. The activatable antibody of claim 36, wherein the L₂ comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 156-163.
38. The activatable antibody of any one of claims 16-37, wherein the CM further comprises a third linker (L₃) N-terminal to the first cleavage site.
39. The activatable antibody of any one of claims 16-38, wherein the CM comprises at least a first protease cleavage site and is cleaved with one or more proteases selected from the group consisting of urokinase-type plasminogen activator (uPA), matrix metalloproteinase-1 (MMP-1),

MMP-2, MMP-3, MMP-8, MMP-9, MMP-14, Tobacco Etch Virus (TEV) protease, plasmin, Thrombin, Factor X, PSA, PSMA, Cathepsin D, Cathepsin K, Cathepsin S, ADAM10, ADAM12, ADAMTS, Caspase-1, Caspase-2, Caspase-3, Caspase-4, Caspase-5, Caspase-6, Caspase-7, Caspase-8, Caspase-9, Caspase-10, Caspase-11, Caspase-12, Caspase-13, Caspase-14, and TACE.

40. The activatable antibody of any one of claims 16-39, wherein the activatable antibody comprises an amino acid sequence according to Formula (XXIX):

EVGSYX1X2X3X4X5X6CX7X8X9X10X11X12CX13X14SGRSAGGGGTENLYFQSGSGS (SEQ ID NO: 164), wherein X1 is A, D, I, N, P, or Y, X2 is A, F, N, S, or V, X3 is A, H, L, P, S, V, or Y, X4 is A, H, S, or Y, X5 is A, D, P, S, V, or Y, X6 is A, D, L, S, or Y, X7 is D, P, or V, X8 is A, D, H, P, S, or T, X9 is A, D, F, H, P, or Y, X10 is L, P, or Y, X11 is F, P, or Y, X12 is A, P, S, or Y, X13 is A, D, N, S, T, or Y, and X14 is A, S, or Y.

41. The activatable antibody of any one of claims 16-40, wherein the activatable antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 165-179.

42. The activatable antibody of any one of claims 16-41, wherein the VL comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 58, an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 75.

43. The activatable antibody of any one of claims 16-42, wherein the VL comprises the amino acid sequence of SEQ ID NO: 100, or an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 100.

44. The activatable antibody of any one of claims 16-43, wherein the VH comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 23, an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 35, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 45.

45. The activatable antibody of any one of claims 16-44, wherein the VH comprises the amino acid sequence of SEQ ID NO: 87, or an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 87.
46. A polynucleotide encoding the antibody of any one of claims 1-15 or the activatable antibody of any one of claims 16-45.
47. A polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 108-133.
48. A vector comprising the polynucleotide of claim 46 or claim 47.
49. The vector of claim 48, wherein the vector is an expression vector and/or a display vector.
50. A host cell comprising the polynucleotide or vector of any one of claims 46-49.
51. The host cell of claim 50, wherein the host cell is a eukaryotic cell.
52. The host cell of claim 50 or claim 51, wherein the host cell is a Chinese Hamster Ovary (CHO) cell.
53. A method of making an antibody or activatable antibody comprising culturing the host cell of any one of claims 50-52 under conditions suitable for producing the antibody or activatable antibody.
54. The method of claim 53, further comprising recovering the antibody or activatable antibody produced by the cell.
55. A pharmaceutical composition comprising the antibody of any one of claims 1-15 or the activatable antibody of any one of claims 16-45 and a pharmaceutically acceptable carrier.
56. A method of treating or delaying progression of cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-15, the activatable antibody of any one of claims 16-45, or the pharmaceutical composition of claim 55.

57. A method of reducing size of a solid tumor in a subject in need thereof, wherein the solid tumor has a size of about 400-1000 mm³, the method comprises administering to the subject an effective amount of the antibody of any one of claims 1-15, the activatable antibody of any one of claims 16-45, or the pharmaceutical composition of claim 55.

58. The method of claim 57, further comprising administering to the subject an effective amount of at least one additional therapeutic agent.

59. The method of claim 58, wherein the at least one additional therapeutic agent is selected from the group consisting of viral gene therapy, immune checkpoint inhibitors, target therapies, radiation therapies, vaccination therapies, and chemotherapies.

60. The method of claim 58 or claim 59, wherein the at least one additional therapeutic agent is selected from the group consisting of pomalyst, revlimid, lenalidomide, pomalidomide, thalidomide, a DNA-alkylating platinum-containing derivative, cisplatin, 5-fluorouracil, cyclophosphamide, an anti-CD137 antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-CD20 antibody, an anti-CD40 antibody, an anti-DR5 antibody, an anti-CD1d antibody, an anti-TIM3 antibody, an anti-SLAMF7 antibody, an anti-KIR receptor antibody, an anti-OX40 antibody, an anti-HER2 antibody, an anti-ErbB-2 antibody, an anti-EGFR antibody, cetuximab, rituximab, trastuzumab, pembrolizumab, radiotherapy, single dose radiation, fractionated radiation, focal radiation, whole organ radiation, IL-12, IFN α , GM-CSF, a chimeric antigen receptor, adoptively transferred T cells, an anti-cancer vaccine, and an oncolytic virus.

61. The method of any one of claims 56-60, wherein the method comprises administering to the subject an effective amount of the antibody, the activatable antibody, or the pharmaceutical composition prior to a surgery or after a surgery to remove a solid tumor in the subject.