

CLAIMS

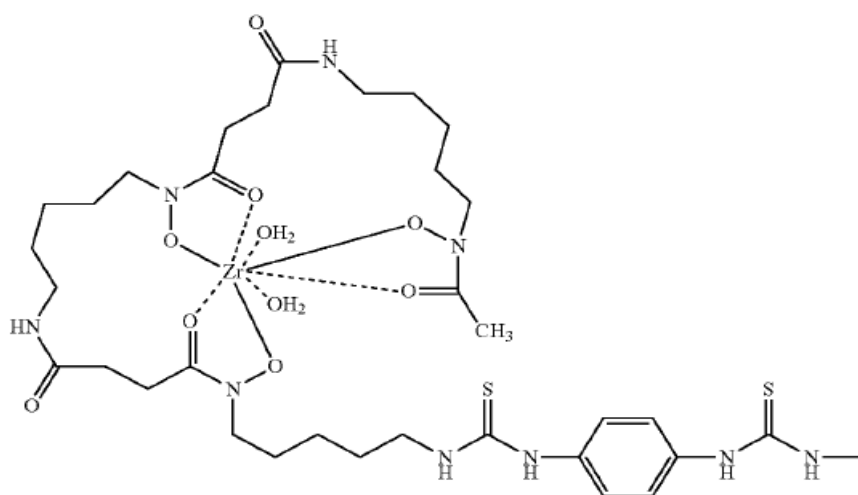
What is claimed is:

1. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to CD8, wherein the antibody or fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.
2. The isolated antibody of claim 1, comprising an HCVR amino acid sequence of SEQ ID NO: 2.
3. The isolated antibody of claim 1, comprising an LCVR amino acid sequence of SEQ ID NO: 10.
4. The isolated antibody of claim 1, comprising an HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 2/10.
5. A pharmaceutical composition comprising a therapeutically effective amount of one or more isolated human monoclonal antibodies, or antigen-binding fragments thereof, wherein the antibody or fragment thereof comprises the three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and the three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10 together, with one or more pharmaceutically acceptable excipients.
6. A nucleic acid molecule encoding a human monoclonal antibody or antigen-binding fragment thereof that binds to CD8, wherein the antibody or fragment thereof comprises the three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and the three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.
7. An expression vector comprising the nucleic acid molecule encoding a human monoclonal antibody or fragment thereof that binds to CD8 according to claim 6.

8. A host cell containing the expression vector of claim 7.
9. A radiolabeled antibody conjugate comprising an antibody according to claim 1 or antigen-binding fragment thereof that binds CD8 and a positron emitter.
10. A radiolabeled antibody conjugate comprising an antibody according to claim 1 or antigen-binding fragment thereof that binds CD8, a chelating moiety, and a positron emitter.
11. The conjugate of claim 10, wherein the antibody or antigen-binding fragment thereof is covalently bonded to the chelating moiety, L, of formula (A):

$$-L-M_z$$

wherein M is the positron emitter; and z, independently at each occurrence, is 0 or 1; and wherein at least one of z is 1.
12. The conjugate of claim 10, wherein the chelating moiety comprises desferrioxamine.
13. The conjugate of claim 9, wherein the positron emitter is ^{89}Zr .
14. The conjugate of claim 11, wherein Zr is Zr^{89} and wherein -L-M is



15. The conjugate of claim 11, wherein antibody or antigen-binding fragment thereof is covalently bonded to one, two, or three moieties of Formula (A).

16. The conjugate of claim 9, wherein the antibody has one or more properties selected from the group consisting of:
- (a) binds human CD8 with a binding dissociation equilibrium constant (K_D) of less than about 3.5×10^{-8} M as measured by surface plasmon resonance;
 - (b) binds to human CD8 α ;
 - (c) inhibits IFN γ production in activated CD8 T cells;
 - (d) inhibits transcription factor activator-protein (AP-1) in activated T cells; and
 - (e) cross-reacts with human and monkey CD8.
17. The conjugate of claim 9, wherein the antibody comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 2/10.
18. A method of imaging a tissue that expresses CD8 comprising administering a radiolabeled antibody conjugate to the tissue; and visualizing CD8 expression by positron emission tomography (PET) imaging; wherein the antibody or fragment thereof comprises the three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within the HCVR amino acid sequence of SEQ ID NO: 2; and the three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within the LCVR amino acid sequence of SEQ ID NO: 10.
19. Use of a radiolabeled antibody conjugate in the manufacture of a medicament for the treatment of a subject having a solid tumor wherein the treatment comprises subjecting the solid tumor to an anti-tumor therapy; wherein the anti-tumor therapy comprises (a) determining whether the solid tumor comprises CD8 positive T-cells comprising administering the radiolabeled antibody conjugate to the tissue; and visualizing CD8 expression by positron emission tomography (PET) imaging; wherein the radiolabeled antibody conjugate comprises an antibody or fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10; and (b) if the tumor comprises CD8 positive T-cells, one or more doses of the anti-tumor therapy is to be administered to the subject, wherein the presence of CD8 positive T-cells in the tumor indicates the responsiveness of the tumor to the treatment with the anti-tumor therapy.
20. The use of claim 19, wherein the subject is to be administered with 0.1-10 mg/kg of the radiolabeled antibody conjugate.
21. The use of claim 19, wherein T-cell function is unimpaired by administration of the

radiolabeled antibody conjugate.

22. The use of claim 19, wherein the radiolabeled antibody conjugate is to be administered subcutaneously or intravenously to the subject.

23. The use of claim 19, wherein PET imaging is performed 2-7 days after administering the radiolabeled antibody conjugate.

24. The use of claim 19, wherein step (a) is carried out before step (b).

25. The use of claim 19 wherein the anti-tumor therapy further comprising: (c) repeating step (a) after treating the subject with at least one dose of an anti-tumor therapy; and wherein an increase from the baseline in the area of localization of the radiolabeled antibody conjugate in the tumor indicates efficacy of the anti-tumor therapy.

26. The use of claim 19, wherein the subject is to be administered with the radiolabeled antibody conjugate 1 to 20 weeks after administration of the anti-tumor therapy.

27. The use of claim 19, further comprising the step of determining that the solid tumor is PD-1 positive by administering the radiolabeled anti-PD-1 conjugate to the subject in need thereof, and imaging localization of the radiolabeled anti-PD-1 conjugate in the tumor by PET imaging, wherein presence of the radiolabeled anti-PD-1 conjugate in the tumor indicates that the tumor is PD-1-positive.

28. The use of claim 19, wherein the anti-tumor therapy is selected from the group consisting of an inhibitor of the PD-1/PD-L1 signaling axis, a CTLA-4 inhibitor, a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or ligand, an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist, an Ang2 inhibitor, a transforming growth factor beta (TGF.beta.) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a CD20 inhibitor, an antibody to a tumor-specific antigen, a cancer vaccine, a bispecific antibody, a cytotoxin, a chemotherapeutic agent, cyclophosphamide, radiotherapy, an IL-6R inhibitor, an IL-4R inhibitor, an IL-10 inhibitor, IL-2, IL-7, IL-21, IL-15, and an antibody-drug conjugate (ADC).

29. The use of claim 19, wherein the anti-tumor therapy is selected from the group consisting of REGN2810, BGB-A317, nivolumab, pidilizumab, pembrolizumab, atezolizumab, avelumab,

durvalumab, MDX-1105, REGN3504, ipilimumab, an anti-CD-28 antibody, an anti-2B4 antibody, an anti-LY108 antibody, an anti-LAIR1 antibody, an anti-ICOS antibody, an anti-CD160 antibody, an anti-VISTA antibody, aflibercept, bevacizumab, ranibizumab, sunitinib, sorafenib, pazopanib, nesvacumab, erlotinib, cetuximab, rituximab, an anti-CA9 antibody, an anti-CA125 antibody, an anti-melanoma-associated antigen 3 (MAGE3) antibody, an anti-carcinoembryonic antigen (CEA) antibody, an anti-vimentin antibody, an anti-tumor-M2-PK antibody, an anti-prostate-specific antigen (PSA) antibody, an anti-mucin-1 antibody, an anti-MART-1 antibody, an anti-CA19-9 antibody, Bacillus Calmette-Guerin, a CD3xCD20 bispecific antibody, a PSMAxCD3 bispecific antibody, dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, vincristine, cyclophosphamide, radiotherapy, sarilumab, dupilumab, anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC.

30. The use of claim 19, wherein the anti-tumor therapy is selected from the group consisting of an anti-PD-1 antibody and an anti-PD-L1 antibody.

31. The use of claim 28, wherein the inhibitor of the PD-1/PD-L1 signaling axis is an anti-PD-1 antibody or antigen-binding fragment thereof.

32. The use of claim 31, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is REGN2810, nivolumab, or pembrolizumab.

33. The use of claim 31, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is REGN2810.

34. The use of claim 28, wherein the inhibitor of the PD-1/PD-L1 signaling axis is an anti-PD-L1 antibody or antigen-binding fragment thereof.

35. The use of claim 34, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is atezolizumab, avelumab, or durvalumab.

36. The use of claim 19, wherein the tumor is selected from the group consisting of blood cancer, brain cancer, renal cell cancer, ovarian cancer, bladder cancer, prostate cancer, breast cancer, hepatic cell carcinoma, bone cancer, colon cancer, non-small-cell lung cancer, squamous cell carcinoma of head and neck, colorectal cancer, mesothelioma, B cell lymphoma, and melanoma.

37. Use of a radiolabeled anti-CD8 antibody conjugate in the manufacture of a diagnostic agent for predicting a positive response to an anti-tumor therapy in a subject having a solid tumor, wherein the diagnostic agent comprises the radiolabeled anti-CD8 antibody conjugate to be administered to the subject to determine the presence of CD8 positive cells in the solid tumor; wherein the presence of CD8 positive cells predicts a positive response to the anti-tumor therapy, wherein the radiolabeled anti-CD8 antibody conjugate comprises an antibody or fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.

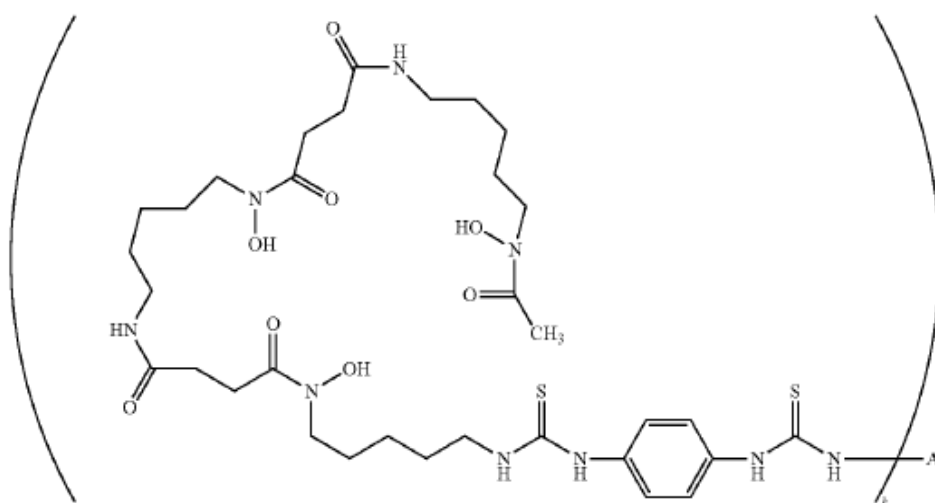
38. Use of a radiolabeled anti-CD8 antibody conjugate in the manufacture of a diagnostic agent for monitoring a response to an anti-tumor therapy of a tumor in a subject, wherein the diagnostic agent comprises (a) one or more doses of an anti-tumor therapy which are to be administered to the subject; and (b) at least one dose of the radiolabeled anti-CD8 antibody conjugate which are to be administered to the subject 1 to 20 weeks after administration of the anti-tumor therapy to determine the presence of CD8 positive cells in the solid tumor; wherein the presence of CD8 positive cells indicates a positive response to the anti-tumor therapy, wherein the radiolabeled anti-CD8 antibody conjugate comprises an antibody or fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.

39. Use of a radiolabeled anti-CD8 antibody conjugate in the manufacture of a diagnostic agent for predicting or monitoring efficacy of an anti-tumor therapy in a subject with a tumor, wherein said anti-tumor therapy comprises: (a) determining the level of CD8 positive T-cells in the tumor comprising administering the radiolabeled anti-CD8 antibody conjugate to the tumor; and visualizing CD8 expression by positron emission tomography (PET) imaging; and (b) correlating the level of CD8 positive T-cells with successful anti-tumor therapy; wherein an elevated level above a certain threshold is predictive or indicative of successful anti-tumor therapy, wherein the radiolabeled anti-CD8 antibody conjugate comprises an antibody or fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.

40. Use of a radiolabeled anti-CD8 antibody conjugate in the manufacture of a diagnostic agent for monitoring T-cell presence in a tumor over time, wherein the diagnostic agent comprises: (a) the

radiolabeled anti-CD8 antibody conjugate which is to be administered at a first timepoint to a subject having the tumor and determining the presence of CD8 positive T-cells in the tumor; (b) one or more doses of an anti-tumor therapy which are to be administered to the subject; and (c) the radiolabeled anti-CD8 antibody conjugate which is to be administered at a second timepoint to the subject 1 to 20 weeks after administration of the anti-tumor therapy and determining the presence of CD8 positive T-cells in the tumor; wherein the presence of T-cells in the tumor indicates a positive response to the anti-tumor therapy, wherein the radiolabeled anti-CD8 antibody conjugate comprises an antibody or fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.

41. The use of claim 40, wherein step (c) is repeated over the course of treatment with the anti-tumor therapy.
42. The use of claim 40, wherein the first timepoint occurs prior to (b).
43. The use of claim 40, wherein the CD8 positive T-cells according to (a) are compared relative to the CD8 positive T-cells according to (c) and an increase in CD8 positive T-cells over time indicates a positive response to the anti-tumor therapy.
44. A compound of Formula (III):

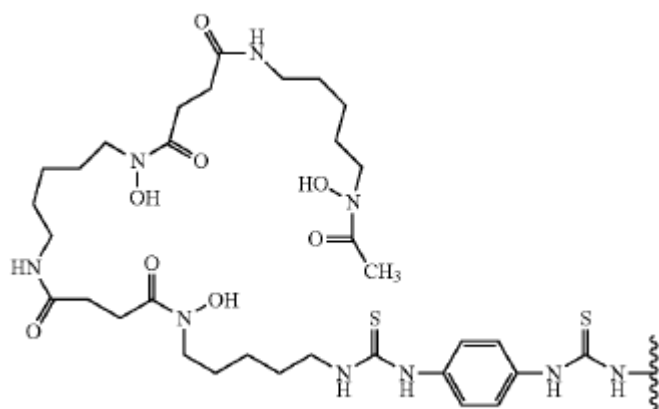


wherein A is an antibody or antigen-binding fragment thereof that binds CD8 and k is an integer from 1-30, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.

45. The compound of claim 44, wherein k is 1 or 2.

46. An antibody conjugate comprising (i) an antibody or antigen-binding fragment thereof that binds CD8 and (ii) one or more chelating moieties, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.

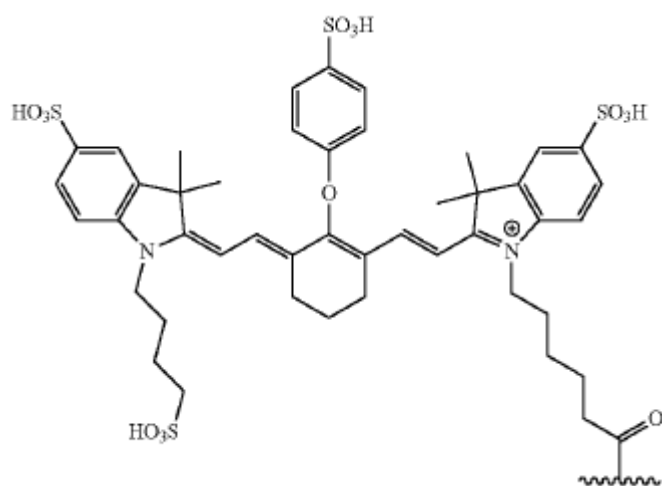
47. The antibody conjugate of claim 46, wherein the chelating moiety is



wherein  is a covalent bond to the antibody or antigen-binding fragment thereof.

48. The antibody conjugate of claim 46, wherein said conjugate has a chelating moiety to antibody ratio (DAR) of from 1.0 to 2.0.

49. The antibody conjugate of claim 46, wherein the chelating moiety-to-antibody ratio is about 1.7.
50. An antibody conjugate comprising (i) an antibody or antigen-binding fragment thereof that binds CD8 and (ii) fluorescent dye, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.
51. The antibody conjugate of claim 50, wherein the fluorescent dye is a near-infrared dye.
52. The antibody conjugate of claim 51, wherein the dye is IRDye800CW or VivoTag680XL.
53. The antibody conjugate of claim 50, wherein the antibody conjugate has the following structure: Ab-[D]_n, wherein Ab is the anti-CD8 antibody or antigen-binding fragment thereof, D is a fluorescent dye, and n is an integer from 1-4.
54. The antibody conjugate of claim 53, wherein D is:



or a pharmaceutically acceptable salt thereof.

55. A method of imaging a tissue that expresses CD8, the method comprising:

(a) contacting an antibody conjugate comprising: (i) an antibody or antigen-binding fragment thereof that binds CD8; and (ii) fluorescent dye to the tissue; and

(b) visualizing CD8 expression by imaging the tissue using fluorescence imaging, wherein the antibody or antigen-binding fragment thereof that binds CD8 comprises three heavy chain CDRs (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 2; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10.

56. An isolated monoclonal antibody of claim 1 or antigen-binding fragment thereof that binds to CD8, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (a) is a fully human monoclonal antibody; (b) binds to CD8 with a K_D equal to or less than 3.5×10^{-8} M as measured by surface plasmon resonance; (c) binds to human CD8 α ; (d) inhibits IFN γ production in activated CD8 T cells; (e) inhibits transcription factor activator-protein (AP-1) in activated T cells; and (f) cross-reacts with human and monkey CD8.