

THE CLAIMS

1. A humanized antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain variable region comprises an amino acid sequence at least about 90% identical to a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6; and wherein the light chain variable region comprises an amino acid sequence at least about 90% identical to a sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 8 and SEQ ID NO: 9, wherein the antibody or antigen binding fragment thereof binds to human poliovirus receptor (CD155).
2. The humanized antibody or antigen binding fragment thereof according to claim 1, wherein the heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 47.
3. The humanized antibody or antigen binding fragment thereof according to claim 1, wherein the light chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 48.
4. The humanized antibody or antigen binding fragment thereof according to any one of claims 1 to 3, wherein the heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 47; and the light chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 48.
5. The humanized antibody or antigen binding fragment thereof of any one of claims 1 to 4, wherein the heavy chain variable region comprising:
 - i. a set of three CDR sequences comprising the sequences set forth in SEQ ID Nos. 10-12; and
 - ii. a set of four heavy chain framework (FR) sequences: (A) FR-H1 selected from the group consisting of SEQ ID NOs: 18, 22, and 26; (B) FR-H2 selected from the group consisting of SEQ ID NOs: 19, 23, and 28; (C) FR-H3 selected from the group consisting of SEQ ID NOs: 20, 24, 27, and 29; and (D) FR-H4 selected from the group consisting of SEQ ID NOs: 21 and 25.
6. The humanized antibody or antigen binding fragment thereof of any one of claims 1 to 5, wherein the light chain variable region comprising:

- i. a set of three CDR sequences comprising the sequences set forth in SEQ ID Nos. 13-15; and
 - ii. a set of four light chain framework sequences: (A) FR-L1 selected from the group consisting of SEQ ID NOs: 30 and 34; (B) FR-L2 selected from the group consisting of SEQ ID NOs: 31 and 37; (C) FR-L3 selected from the group consisting of SEQ ID NOs: 32, 35, and 36; and (D) FR-L4 is SEQ ID NOs: 33.
7. The humanized antibody or antigen binding fragment thereof of claim 1, wherein the heavy chain variable region comprises an amino acid sequence at least about 95% identical to a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6; and wherein the light chain variable region comprises an amino acid sequence at least about 95% identical to a sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 8 and SEQ ID NO: 9.
8. The humanized antibody or antigen binding fragment thereof of claim 1, wherein the heavy chain variable region comprises an amino acid sequence at least about 97% identical to a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, and wherein the light chain variable region comprises an amino acid sequence at least about 97% identical to a sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 8 and SEQ ID NO: 9.
9. The humanized antibody or antigen binding fragment thereof of claim 1, wherein the heavy chain variable region comprises an amino acid sequence identical to a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, and wherein the light chain variable region comprises an amino acid sequence identical to a sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 8 and SEQ ID NO: 9.
10. The humanized antibody or antigen binding fragment thereof of any one of claims 1 and 9, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 1, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 2.
11. The humanized antibody or antigen binding fragment thereof of any one of claims 1 to 10, wherein the humanized antibody or antigen binding fragment thereof is an IgG antibody.

12. The humanized antibody or antigen binding fragment thereof of claim 11, wherein the humanized antibody or antigen binding fragment thereof comprises an IgG4 or IgG1 heavy chain constant region.
13. The humanized antibody or antigen binding fragment thereof according to claim 12,
5 wherein the humanized antibody or antigen binding fragment thereof comprises an IgG4 heavy chain constant region having an alteration of a serine residue substituted for proline at position 228 of said IgG4 heavy chain constant region.
14. The humanized antibody or antigen binding fragment thereof of any one of claims 1 to 10,
10 wherein the humanized antibody or antigen binding fragment thereof is a Fab, F(ab)₂, a single-domain antibody, or a single chain variable fragment (scFv).
15. A single chain variable fragment (scFv) of a humanized antibody according to any one of claims 1 to 14, comprising an amino acid sequence selected from SEQ ID NO: 56, SEQ ID NO: 57, and an analog thereof having at least 90% sequence similarity to any of said sequences.
- 15 16. The humanized antibody or antigen binding fragment thereof of any one of claims 1 to 15, wherein the humanized antibody inhibits binding of PVR to at least one of TIGIT, CD96, and CD226.
17. A nucleic acid encoding at least one chain or region of the humanized antibody or antigen binding fragment thereof of any one of claims 1 to 166.
- 20 18. A cell line comprising the nucleic acid of claim 17.
19. The cell line of claim 18, wherein the cell line is a Chinese Hamster Ovary cell line.
20. A chimeric antigen receptor (CAR) comprising a combination of heavy and light chain variable region sequences of the humanized antibody according to any one of claims 1 to 16.
- 25 21. The CAR of claim 20, wherein the heavy chain variable region comprises an amino acid sequence with at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6; and the light chain variable region comprises an amino acid sequence with at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO:
30 2, SEQ ID NO: 7, SEQ ID NO: 8 and SEQ ID NO: 9.
22. The CAR of claim 21, comprising a scFv comprising an amino acid sequence selected from SEQ ID NO: 56, SEQ ID NO: 57, and an analog thereof having at least 90% sequence similarity to any of said sequences.

23. The CAR of any one of claims 20 to 22, comprising at least one domain selected from the group consisting of: CD8 Stalk domain, a CD28 TM domain, a 41BB domain, and a CD3Z domain.
24. A pharmaceutical composition comprising the humanized antibody or antigen binding
5 fragment thereof of any one of claims 1 to 16 or the CAR according to any one of claims 20 and 23, and a pharmaceutically acceptable excipient, carrier, or diluent.
25. The pharmaceutical composition of claim 24, formulated for intravenous administration.
26. The pharmaceutical composition of claim 24, formulated for intratumoral administration.
27. The humanized antibody or antigen binding fragment thereof of any one of claims 1 to 16,
10 the CAR of claims 20 or 23, or the pharmaceutical composition of any one of claims 24 to 26 for use in increasing surface expression and/or signaling of CD226 on CD8+ T cells.
28. The humanized antibody or antigen binding fragment thereof of any one of claims 1 to 16, the CAR of claims 20 or 23, or the pharmaceutical composition of any one of claims 24 to 26 for use in treating cancer in an individual.
- 15 29. The humanized antibody or antigen binding fragment thereof or the CAR or the pharmaceutical composition for use of claim 28, wherein the cancer comprises a solid tumor.
30. The humanized antibody or antigen binding fragment thereof, or the CAR, or the pharmaceutical composition for use of claim 28, wherein the cancer is selected from the
20 group consisting of lung cancer, colon cancer, adrenal cancer, uterine cancer, head and neck cancer, pancreatic cancer, and breast cancer.
31. A method of increasing surface expression and/or signaling of CD226 in the CD8+ T cells of an individual comprising administering to the individual a therapeutically effective amount of the humanized antibody or antigen binding fragment thereof of any one of
25 claims 1 to 16, the CAR of claims 20 or 23, or the pharmaceutical composition of any one of claims 24 to 26.
32. The method of claim 31, wherein the CD8+ T cells are tumor infiltrating CD8+ T cells.
33. A method of treating a cancer in an individual afflicted with a cancer comprising administering to the individual a therapeutically effective amount of the humanized
30 antibody or antigen binding fragment thereof of any one of claims 1 to 16, the CAR of claims 20 or 23 or the pharmaceutical composition of any one of 24 to 26.
34. A method of treating a cancer in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of the humanized antibody or antigen

binding fragment thereof of any one of claims 1 to 16, the CAR of claims 20 or 23, or the pharmaceutical composition of any one of 24 to 26, and an inhibitor of PD-1, PD-L1, CTLA-4 or CD112R signaling.

35. The method of any one of claims 33 and 34, wherein the cancer comprises a solid tumor.
- 5 36. The method of claim 33, wherein the cancer is selected from the group consisting of glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, colon cancer, cervical cancer, prostate cancer, and lung cancer.
37. The method of any one of claims 33 and 34, wherein the cancer is a hematological cancer.
- 10 38. The method of any one of claims 34 to 37 wherein the inhibitor of PD-1 signaling is an antibody or fragment thereof that binds to PD-1.
39. The method of claim 38, wherein the antibody or fragment thereof that binds to PD-1 is selected from Pembrolizumab, Nivolumab, AMP-514, Tislelizumab, Spartalizumab, and a PD-1 binding fragment thereof.
- 15 40. The method of any one of claims 34 to 37, wherein the inhibitor of PD-1 signaling is an antibody that specifically binds PD-L1 or PD-L2.
41. The method of claim 40, wherein the antibody that specifically binds PD-L1 or PD-L2 is selected from Durvalumab, Atezolizumab, Avelumab, BMS-936559, or FAZ053, or a PD-L1 and PD-L2 binding fragment thereof.
- 20 42. The method of any one of claims 34 to 37, wherein the inhibitor of PD-1 signaling comprises a small molecule inhibitor of PD-1, PD-L1, or PD-L2.
43. A method of preparing a composition for treating a cancer in an individual in need thereof, comprising admixing the humanized antibody or antigen binding fragment thereof of any one of claims 1 to 16 and a pharmaceutically acceptable excipient, carrier, or diluent.
- 25 44. The method of claim 43, wherein the cancer comprises a solid tumor.
45. The method of claim 44, wherein the cancer is selected from the group consisting of glioblastoma, pancreatic cancer, breast cancer, bladder cancer, kidney cancer, head and neck cancer, ovarian cancer, colon cancer, cervical cancer, prostate cancer, and lung cancer.
- 30 46. The method of claim 43, wherein the cancer is a hematological cancer.
47. A method of producing the humanized antibody or antigen binding fragment thereof of any one of claims 1 to 16 comprising incubating a cell line that contains a nucleic acid encoding the humanized antibody or antigen binding fragment thereof, in a cell culture medium

under conditions sufficient to allow expression and secretion of the humanized antibody or antigen binding fragment thereof.

48. A method of diagnosing or prognosing cancer in a subject, the method comprises determining the expression level of PVR in a biological sample of said subject using at least one humanized antibody or fragment thereof according to any one of claims 1 to 16.
49. The method of claim 48 comprising a step of diagnosing or prognosing cancer in a subject if the expression of PVR is higher than a control or a reference value.
50. A kit comprising at least one antibody or antibody fragment according to any one of claims 1 to 16 and means for measuring PVR expression.

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