

WHAT IS CLAIMED IS:

1. An isolated antibody comprising:
 - i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 1; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 2; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 3; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 4; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 5; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 6; or
 - ii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 101; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 102; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 103; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 104; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 105; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 106; or
 - iii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 201; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 202; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 203; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 204; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 205; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 206; or
 - iv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 301; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 302; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 303; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 304; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 305; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 306; or
 - v) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 401; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 402; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 403; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 404; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 405; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 406; or
 - vi) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 501; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 502; (c) HCDR3

- comprising the amino acid sequence of SEQ ID NO: 503; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 504; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 505; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 506; or
- vii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 601; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 602; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 603; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 604; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 605; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 606; or
- viii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 701; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 702; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 703; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 704; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 705; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 706; or
- ix) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 801; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 802; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 803; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 804; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 805; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 806; or
- x) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 901; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 902; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 903; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 904; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 905; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 906; or
- xi) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 1001; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 1002; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 1003; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 1004; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 1005; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 1006; or

- xii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 2001; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 2002; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 2003; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 2004; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 2005; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 2006; or
- xiii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 3001; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 3002; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 3003; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 3004; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 3005; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 3006; or
- xiv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 4001; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 4002; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 4003; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 4004; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 4005; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 4006.

2. The isolated antibody of claim 1, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:

- i) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 12 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 18; or
- ii) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 112 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 118; or
- iii) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 212 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 218; or
- iv) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 312 and the VL is at

- least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 318; or
- v) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 412 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 418; or
- vi) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 512 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 518; or
- vii) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 612 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 618; or
- viii) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 712 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 718; or
- ix) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 812 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 818; or
- x) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 912 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 918; or
- xi) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 1012 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 1018; or
- xii) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 2012 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 2018; or

- xiii) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 3012 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 3018; or
 - xiv) the VH is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 4012 and the VL is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 4018.
3. The isolated antibody of claim 1 or claim 2, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:
- i) the VH comprises the amino acid sequence of SEQ ID NO: 12 and the VL comprises the amino acid sequence of SEQ ID NO: 18; or
 - ii) the VH comprises the amino acid sequence of SEQ ID NO: 112 and the VL comprises the amino acid sequence of SEQ ID NO: 118; or
 - iii) the VH comprises the amino acid sequence of SEQ ID NO: 212 and the VL comprises the amino acid sequence of SEQ ID NO: 218; or
 - iv) the VH comprises the amino acid sequence of SEQ ID NO: 312 and the VL comprises the amino acid sequence of SEQ ID NO: 318; or
 - v) the VH comprises the amino acid sequence of SEQ ID NO: 412 and the VL comprises the amino acid sequence of SEQ ID NO: 418; or
 - vi) the VH comprises the amino acid sequence of SEQ ID NO: 512 and the VL comprises the amino acid sequence of SEQ ID NO: 518; or
 - vii) the VH comprises the amino acid sequence of SEQ ID NO: 612 and the VL comprises the amino acid sequence of SEQ ID NO: 618; or
 - viii) the VH comprises the amino acid sequence of SEQ ID NO: 712 and the VL comprises the amino acid sequence of SEQ ID NO: 718; or
 - ix) the VH comprises the amino acid sequence of SEQ ID NO: 812 and the VL comprises the amino acid sequence of SEQ ID NO: 818; or
 - x) the VH comprises the amino acid sequence of SEQ ID NO: 912 and the VL comprises the amino acid sequence of SEQ ID NO: 918; or
 - xi) the VH comprises the amino acid sequence of SEQ ID NO: 1012 and the VL comprises the amino acid sequence of SEQ ID NO: 1018; or
 - xii) the VH comprises the amino acid sequence of SEQ ID NO: 2012 and the VL comprises the amino acid sequence of SEQ ID NO: 2018; or

- xiii) the VH comprises the amino acid sequence of SEQ ID NO: 3012 and the VL comprises the amino acid sequence of SEQ ID NO: 3018; or
 - xiv) the VH comprises the amino acid sequence of SEQ ID NO: 4012 and the VL comprises the amino acid sequence of SEQ ID NO: 4018.
4. The isolated antibody of any one of the preceding claims, wherein the antibody is a monoclonal antibody.
 5. The isolated antibody of any one of the preceding claims, wherein the antibody is an antibody fragment.
 6. The isolated antibody of claim 6, wherein the fragment is a Fab, Fab', Fv, scFv or (Fab')₂.
 7. The isolated antibody of any one of claims 1-5, wherein the antibody is a full-length antibody.
 8. The isolated antibody of any one of claims 1-8, wherein the Fc region of the antibody comprises IgG1, IgG2, IgG3, or IgG4.
 9. The isolated antibody of any one of claims 1-8, wherein the antibody comprises a human IgG1 heavy chain constant region.
 10. The isolated antibody of any one of claims 1-8, wherein the antibody comprises a human IgG4 heavy chain constant region.
 11. The isolated antibody of claim 11, wherein the antibody comprises a mutant human IgG4 heavy chain constant region.
 12. The isolated antibody of claim 11, wherein the mutant IgG4 heavy chain constant region comprises a mutation selected from a substitution at Ser228, a substitution at Leu235, a substitution at Asn297, or a combination thereof, numbering according to EU numbering.
 13. The isolated antibody of claim 11, wherein the mutant IgG4 heavy chain constant region comprises an S228P substitution and an L235E substitution, numbering according to EU numbering.
 14. The isolated antibody of any one of claims 1-9, wherein the antibody comprises a human IgG1 heavy chain constant region, and wherein the antibody
 - i) increases NK cell degranulation; and/or
 - ii) increases activation of NK cells; and/or
 - iii) increases activation of intra-tumoral NK cells when presented in combination with an anti-TIGIT antibody; and/or
 - iv) inhibits tumor growth in vivo; and/or

v) prevents tumor engraftment upon re-challenge with tumor.

15. A humanized or fully human version of the antibody of any one of the preceding claims.

16. A composition comprising the antibody of any one of claims 1-15 and a pharmaceutically acceptable carrier.

17. The composition of claim 16 further comprising an antagonist of PD-1, PD-L1, CTLA-4, Lag-3 or TIM-3.

18. A method of enhancing, increasing and/or sustaining an anti-tumor immune response in a subject comprising administering the antibody of any one of claims 1-15 or the composition of claim 16 or 17 to a subject having a tumor.

19. A method of enhancing CD8 T cell activation in a subject comprising administering the antibody of any one of claims 1-15 or the composition of claim 16 or 17 to a subject in need of CD8 T cell activation.

20. A method of enhancing CD8 T cell interferon gamma production in a subject comprising administering the antibody of any one of claims 1-15 or the composition of claim 16 or 17 to a subject in need of CD8 T cell interferon gamma production.

21. A method of enhancing NK cell activation in a subject comprising administering the antibody of any one of claims 1-15 or the composition of claim 16 or 17 to a subject in need of NK cell activation.

22. A method of enhancing NK cell mediated cytotoxicity in a subject comprising administering the antibody of any one of claims 1-15 or the composition of claim 16 or 17 to a subject in need of increasing NK cell mediated cytotoxicity.

23. A method of treating cancer in a subject comprising administering the antibody of any one of claims 1-15 or the composition of claim 16 or 17 to a subject having cancer.

24. The method of claim 23, wherein the cancer is carcinoma, lymphoma, blastoma, sarcoma, or leukemia.

25. The method of claim 23, wherein the cancer is squamous cell cancer, small-cell lung cancer, pituitary cancer, esophageal cancer, astrocytoma, soft tissue sarcoma, non-small cell lung cancer (including squamous cell non-small cell lung cancer), adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, renal cell carcinoma, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer,

endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer, melanoma, or various types of head and neck cancer (including squamous cell carcinoma of the head and neck).

26. A method of enhancing CD226 interactions with CD112 in a subject comprising administering the antibody of any one of claims 1-15 or the composition of claim 16 or 17 to a subject.

27. The method of any one of claims 18-26, wherein the method further comprises administering a second therapy.

28. The method of claim 27, wherein the second therapy is radiotherapy or surgery.

29. The method of claim 27, wherein the second therapy is administration of a chemotherapy, an opsonizing agent, or a regulatory T cell depleting agent.

30. The method of claim 27, wherein the second therapy is administration of an antagonist of PD-1, PD-L1, CTLA-4, Lag-3 or TIM-3.

31. The method of claim 27, wherein the second therapy is administration of an antagonist of TIGIT or CD96.

32. The method of claim 27, wherein the second therapy is administration of an antagonist of PVRL1, PVRL2, PVRL3, PVRL4, and CD155.

33. The method of claim 27, wherein the second therapy is administration of an antagonist of CD47.

34. The method of claim 27, wherein the second therapy is administration of an antagonist of CD39.

35. The method of claim 27, wherein the second therapy is administration of an antagonist of IL-27.

36. The method of claim 27, wherein the second therapy is administration of a STING agonist.

37. The method of any one of claims 30-35, wherein the antagonist is an antibody.

38. A nucleic acid encoding the antibody of any one of claims 1-15.

39. A host cell comprising the nucleic acid of claim 38.

40. A method of producing the antibody of any one of claims 1-15 comprising culturing the host cell of claim 39 under conditions wherein the antibody is expressed.

41. The method of claim 40, further comprising purifying the antibody.