

CLAIMS

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 isolated 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 isolated 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 claim 1, comprising (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.
 5. The isolated antibody of claim 3 or 4, wherein 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.
 6. The isolated antibody of any one of the preceding claims, wherein the isolated antibody is a monoclonal antibody.
 7. The isolated antibody of any one of the preceding claims, wherein the isolated antibody is an antibody fragment.
 8. The isolated antibody of claim 7, wherein the fragment is a Fab, Fab', Fv, scFv or (Fab')₂.
 9. The isolated antibody of any one of claims 1-6, wherein the isolated antibody is a full-length antibody.
 10. The isolated antibody of claim 9, wherein the Fc region of the isolated antibody comprises IgG1, IgG2, IgG3, or IgG4.
 11. The isolated antibody of any one of claims 1-10, wherein the isolated antibody comprises a human IgG1 heavy chain constant region.
 12. The isolated antibody of any one of claims 1-10, wherein the isolated antibody comprises a human IgG4 heavy chain constant region.
 13. The isolated antibody of claim 12, wherein the isolated antibody comprises a mutant human IgG4 heavy chain constant region.

14. The isolated antibody of claim 13, 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.
15. The isolated antibody of claim 13, wherein the mutant IgG4 heavy chain constant region comprises an S228P substitution and an L235E substitution, numbering according to EU numbering.
16. The isolated antibody of any one of claims 1-11, wherein the isolated antibody comprises a human IgG1 heavy chain constant region, and wherein the isolated 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.
17. The isolated antibody of any one of the previous claims, wherein the antibody binds to human CD112R.
18. A humanized or fully human version of the isolated antibody of any one of the preceding claims.
19. A composition comprising the isolated antibody of any one of claims 1-18 and a pharmaceutically acceptable carrier.
20. The composition of claim 19, further comprising an antagonist of PD-1, PD-L1, CTLA-4, Lag-3, TIGIT, CD96 or TIM-3.
21. The isolated antibody of any one of claims 1-17 or the composition of claim 19 or 20 for use in enhancing, increasing and/or sustaining an anti-tumor immune response in a subject having a tumor.
22. The isolated antibody of any one of claims 1-17 or the composition of claim 19 or 20 for use in enhancing CD8 T cell activation in a subject.
23. The isolated antibody of any one of claims 1-17 or the composition of claim 19 or 20 for use in enhancing CD8 T cell interferon gamma production in a subject.
24. The isolated antibody of any one of claims 1-17 or the composition of claim 19 or 20 for use in enhancing NK cell activation in a subject.

25. The isolated antibody of any one of claims 1-17 or the composition of claim 19 or 20 for use in enhancing NK cell mediated cytotoxicity in a subject.
26. The isolated antibody of any one of claims 1-17 or the composition of claim 19 or 20 for use in treating cancer in a subject having the cancer.
27. The isolated antibody or the composition of claim 26, wherein the cancer is carcinoma, lymphoma, blastoma, sarcoma, or leukemia.
28. The isolated antibody or the composition of claim 26, 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).
29. The isolated antibody of any one of claims 1-17 or the composition of claim 19 or 20 for use in enhancing CD226 interactions with CD112 in a subject.
30. The isolated antibody or the composition of any one of claims 21-29, for use with at least a second therapy.
31. The isolated antibody or the composition of claim 30, wherein the second therapy is radiotherapy or surgery.
32. The isolated antibody or the composition of claim 30, wherein the second therapy is a chemotherapy, an opsonizing agent, or a regulatory T cell depleting agent.
33. The isolated antibody or the composition of claim 30, wherein the second therapy is an antagonist of PD-1, PD-L1, CTLA-4, Lag-3 or TIM-3.
34. The isolated antibody or the composition of claim 30, wherein the second therapy is an antagonist of TIGIT or CD96.
35. The isolated antibody or the composition of claim 30, wherein the second therapy is of an antagonist of PVRL1, PVRL2, PVRL3, PVRL4, or CD155.

36. The isolated antibody or the composition of claim 30, wherein the second therapy is an antagonist of CD47.
37. The isolated antibody or the composition of claim 30, wherein the second therapy is an antagonist of CD39.
38. The isolated antibody or the composition of claim 30, wherein the second therapy is an antagonist of IL-27.
39. The isolated antibody or the composition of claim 30, wherein the second therapy is a STING agonist.
40. The isolated antibody or the composition of any one of claims 33-38, wherein the antagonist is an antibody.
41. A nucleic acid encoding the isolated antibody of any one of claims 1-17.
42. A host cell comprising the nucleic acid of claim 41.
43. A method of producing the isolated antibody of any one of claims 1-17, the method comprising culturing the host cell of claim 42 under conditions wherein the isolated antibody is expressed.
44. The method of claim 43, further comprising purifying the isolated antibody.