

supporting the high co-expression levels of the ligands of TIGIT and CD112R (CD155 and CD112) on tumor cells. The data provided herein support that, while blocking the single interaction of TIGIT or CD112R with its ligand enhances primary human T cell activity, the simultaneous blockade of both receptors (TIGIT and CD112R) from binding to their respective ligands greatly enhances primary human T cell activity. The data furthermore support that blockade of yet a third interaction involving PD-1 and its ligand, in addition to the blockade of TIGIT and CD112R interactions, significantly increases the overall primary human T cell activity. The increase in activity achieved with the blockade of all three molecules (PD-1, TIGIT, CD112R) is beyond that achieved with single blockade (TIGIT only or CD112R only) and double blockade (blockade of both TIGIT and CD112R, both TIGIT and PD-1, or both CD112R and PD-1).

[0007] Accordingly, the present disclosure provides TIGIT antigen binding proteins (e.g., antibodies and antigen binding fragments thereof), CD112R antigen binding proteins (e.g., antibodies and antigen binding fragments thereof), and combinations thereof. Compositions comprising TIGIT antigen binding proteins, CD112R antigen binding proteins and PD-1 antigen binding proteins are furthermore provided by the present disclosure. In certain embodiment examples, the compositions comprise a TIGIT antibody or TIGIT-binding fragment thereof and/or a CD112R antibody or CD112R-binding fragment thereof, and/or a PD-1 antibody or PD-1 binding fragment thereof. In preferred embodiment examples, the composition comprises a TIGIT antibody and a CD112R antibody. Related conjugates, fusion proteins, nucleic acids, vectors, host cells and kits are provided herein.

[0007a] Accordingly, in one aspect, the present disclosure provides a CD112R antigen-binding protein comprising (a) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (e) an LC CDR2 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; and (f) an LC CDR3 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity, optionally, wherein the CD112R antigen-binding protein comprises

the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 amino acid sequences for 24F1 as set forth in Table A1.

[0007b] In another aspect, the present disclosure provides a nucleic acid encoding the CD112R antigen binding protein of the disclosure.

[0007c] In another aspect, the present disclosure provides a nucleic acid encoding the light chain, the heavy chain, or both the light chain and the heavy chain of the disclosure.

[0007d] In another aspect, the present disclosure provides a vector comprising one or more nucleic acids of the disclosure.

[0007e] In another aspect, the present disclosure provides a host cell comprising one or more nucleic acids of the disclosure or one or more vectors of the disclosure.

[0007f] In another aspect, the present disclosure provides a TIGIT antigen-binding protein comprising (a) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (e) an LC CDR2 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; and (f) an LC CDR3 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity, optionally, wherein the CD112R antigen-binding protein comprises the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 amino acid sequences for 43B7.002.015 as set forth in Table A2.

[0007g] In another aspect, the present disclosure provides a nucleic acid encoding the TIGIT antigen binding protein of the disclosure.

[0007h] In another aspect, the present disclosure provides a nucleic acid encoding the light chain, the heavy chain or both the light chain and the heavy chain of the antibody of the disclosure.

[0007i] In another aspect, the present disclosure provides a vector comprising one or more nucleic acids of the disclosure.

[0007j] In another aspect, the present disclosure provides a host cell comprising one or more nucleic acids of the disclosure or one or more vectors of the disclosure.

[0007k] In another aspect, the present disclosure provides a composition comprising a CD112R antigen binding protein of the disclosure and a TIGIT antigen binding protein of the disclosure, optionally, wherein the composition comprises a CD112R antigen-binding protein comprising a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 of SEQ ID NOs: 33-38, respectively, and a TIGIT antigen-binding protein comprising a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 of SEQ ID NOs: 203-208, respectively.

[0007l] In another aspect, the present disclosure provides a kit comprising an antigen-binding protein of the disclosure, the nucleic acid of the disclosure, the vector of the disclosure, the host cell of the disclosure, a composition of the disclosure, or a combination thereof, and a container.

[0007m] In another aspect, the present disclosure provides a pharmaceutical composition comprising an antigen-binding protein of the disclosure, the nucleic acid of the disclosure, the vector of the disclosure, the host cell of the disclosure, a composition of the disclosure, or a combination thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0007n] In another aspect, the present disclosure provides a method of making CD112R antigen-binding protein comprising culturing the host cell of the disclosure so as to express the CD112R antigen-binding protein and harvesting the expressed CD112R antigen-binding protein.

[0007o] In another aspect, the present disclosure provides a method of making TIGIT antigen-binding protein comprising culturing the host cell of the disclosure so as to express the TIGIT antigen-binding protein and harvesting the expressed TIGIT antigen-binding protein.

[0007p] In another aspect, the present disclosure provides a pharmaceutical composition of the disclosure for use in therapy.

[0007q] In another aspect, the present disclosure provides a use of a pharmaceutical composition of the disclosure in the manufacture of a medicament for treating a solid tumor.

[0007r] In another aspect, the present disclosure provides a first pharmaceutical composition comprising a CD112R antigen-binding protein and a TIGIT antigen-binding protein and a second pharmaceutical composition comprising a PD-1 inhibitor for use in therapy.

[0007s] In another aspect, the present disclosure provides a use of a first pharmaceutical composition comprising a CD112R antigen-binding protein and a TIGIT antigen-binding protein in the manufacture of a first medicament and use of a second pharmaceutical composition comprising a PD-1 inhibitor in the

manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating a solid tumor in a subject.

[0008] The present disclosure also provides pharmaceutical compositions comprising a TIGIT antigen binding protein, CD112R antigen binding protein, or combinations thereof, optionally, further comprising a PD-1 antigen binding protein, or a conjugate, fusion protein, nucleic acid, vector, or host cell, and a pharmaceutically acceptable carrier, diluent, or excipient. In preferred ~~embodiment~~examples, the pharmaceutical composition comprises a 1:1 ratio of a TIGIT antibody and a CD112R antibody.

[0009] Methods of making the antigen binding proteins are provided. Also, methods of treating subjects in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, are provided.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure 1A is a series of plots depicting co-expression profiles of cells of the indicated tumor indication. In the top row, co-expression of TIGIT family members with each other and with PD-1 is shown. In the bottom row, co-expression of ligands of the TIGIT family members with each other and with PD-1 is shown.

WHAT IS CLAIMED:

1. A CD112R antigen-binding protein comprising (a) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (e) an LC CDR2 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; and (f) an LC CDR3 amino acid sequence set forth in Table A1 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity, optionally, wherein the CD112R antigen-binding protein comprises the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 amino acid sequences for 24F1 as set forth in Table A1.
2. The CD112R antigen-binding protein of claim 1 or 2, comprising six CDR amino acid sequences listed in a single row of Table A1 or comprising six CDR amino acid sequences selected from the group consisting of: (a) SEQ ID NOs: 13-18; (b) SEQ ID NOs: 23-28; (c) SEQ ID NOs: 33-38; (d) SEQ ID NOs: 43-48; (e) SEQ ID NOs: 53-58; (f) SEQ ID NOs: 63-68; (g) SEQ ID NOs: 73-78; (h) SEQ ID NOs: 83-88, (i) SEQ ID NOs: 93-98, (j) SEQ ID NOs: 103-108, (k) SEQ ID NOs: 233-238, (l) SEQ ID NOs: 1973-1978, (m) SEQ ID NOs: 1983-1988, (n) SEQ ID NOs: 1993-1998, and (o) SEQ ID NOs: 2003-2008, optionally, wherein the CD112R antigen-binding protein comprises the six CDR amino acid sequences of SEQ ID NOs: 33-38.
3. The CD112R antigen binding protein of any one of the preceding claims, comprising (a) a HC variable region amino acid sequence set forth in Table B1 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of Table B1; (b) a LC variable region amino acid sequence set forth in Table B1 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable region amino acid sequence of Table B1, or (c) a combination of

- (a) and (b) , optionally, wherein the CD112R antigen-binding protein comprises the HC variable region amino acid sequence and the LC variable region amino acid sequence for 24F1 as set forth in Table B1.
4. The CD112R antigen-binding protein of claim 4, comprising a pair of HC variable region and LC variable region amino acid sequences listed in a single row of Table B1 or comprising a pair of amino acid sequences selected from the group consisting of: (a) SEQ ID NOs: 11-12; (b) SEQ ID NOs: 21-22; (c) SEQ ID NOs: 31-32; (d) SEQ ID NOs: 41-42; (e) SEQ ID NOs: 51-52; (f) SEQ ID NOs: 61-62; (g) SEQ ID NOs: 71-72; (h) SEQ ID NOs: 81-82, (i) SEQ ID NOs: 91-92, (j) SEQ ID NOs: 101-102, (k) SEQ ID NOs: 231-232, (l) SEQ ID NOs: 1971-1972, (m) SEQ ID NOs: 1981-1982, (n) SEQ ID NOs: 1991-1992, and (o) SEQ ID NOs: 2001-2002, , optionally, wherein the CD112R antigen-binding protein comprises a HC variable region amino acid sequence of SEQ ID NO: 31 and a LC variable region amino acid sequence of SEQ ID NO: 32.
5. The CD112R antigen binding protein of any one of the preceding claims, comprising (a) a full-length (FL) HC amino acid sequence set forth in Table B1 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL HC amino acid sequence of Table B1; (b) a FL LC amino acid sequence set forth in Table B1 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL LC amino acid sequence of Table B1, or (c) a combination of (a) and (b) , optionally, wherein the CD112R antigen-binding protein comprises the FL HC amino acid sequence and the FL LC amino acid sequence for 24F1 as set forth in Table B1.
6. The CD112R antigen-binding protein of claim 5, comprising a pair of full-length (FL) HC and FL LC amino acid sequences listed in a single row of Table B or comprising a pair of amino acid sequences selected from the group consisting of: (a) SEQ ID NOs: 9-10; (b) SEQ ID NOs: 19-20; (c) SEQ ID NOs: 29-30; (d) SEQ ID NOs: 39-40; (e) SEQ ID NOs: 49-50; (f) SEQ ID NOs: 59-60; (g) SEQ ID NOs: 69-70; (h) SEQ ID NOs: 79-80, (i) SEQ ID NOs: 89-90, (j) SEQ ID NOs: 99-100, (k) SEQ ID NOs: 229-230, (l) SEQ ID NOs: 1969-1970, (m) SEQ ID NOs: 1979-1980, (n) SEQ ID NOs: 1989-1990, and (o) SEQ ID NOs: 1999-2000, , optionally, wherein the CD112R antigen-binding protein comprises a FL HC amino acid sequence of SEQ ID NO: 29 and a FL LC amino acid sequence of SEQ ID NO: 30.

7. The CD112R antigen-binding protein of any one of the preceding claims, which is an antibody.
8. The CD112R antigen-binding protein of claim 7, comprising:
 - a. a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence of SEQ ID NO: 33 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence of SEQ ID NO: 34 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence of SEQ ID NO: 35 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence of SEQ ID NO: 36 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (e) an LC CDR2 amino acid sequence of SEQ ID NO: 37 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (f) an LC CDR3 amino acid sequence of SEQ ID NO: 38 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; or
 - (b) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence of SEQ ID NO: 63 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence of SEQ ID NO: 64 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence of SEQ ID NO: 65 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence of SEQ ID NO: 66 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (e) an LC CDR2 amino acid sequence of SEQ ID NO: 67 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (f) an LC CDR3 amino acid sequence of SEQ ID NO: 68 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; or

- (c) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence of SEQ ID NO: 83 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence of SEQ ID NO: 84 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence of SEQ ID NO: 85 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence of SEQ ID NO: 86 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (e) an LC CDR2 amino acid sequence of SEQ ID NO: 87 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (f) an LC CDR3 amino acid sequence of SEQ ID NO: 88 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; or
- (d) comprising (a) a HC variable region amino acid sequence of SEQ ID NO :31 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of SEQ ID NO: 31; (b) a LC variable region amino acid sequence of SEQ ID NO: 32 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable region amino acid sequence of SEQ ID NO: 32, or (c) a combination of (a) and (b); or
- (e) comprising (a) a HC variable region amino acid sequence of SEQ ID NO: 61 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of SEQ ID NO: 61; (b) a LC variable region amino acid sequence of SEQ ID NO: 62 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable region amino acid sequence of SEQ ID NO: 62, or (c) a combination of (a) and (b); or
- (f) comprising (a) a HC variable region amino acid sequence of SEQ ID NO: 81 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of SEQ ID NO: 81; (b) a LC variable region amino acid sequence of SEQ

ID NO: 82 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable region amino acid sequence of SEQ ID NO: 82, or (c) a combination of (a) and (b); or

- (g) (a) a full-length (FL) HC amino acid sequence of SEQ ID NO: 29 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL HC amino acid sequence of SEQ ID NO: 29; (b) a FL LC amino acid sequence set forth of SEQ ID NO: 30 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL LC amino acid sequence of SEQ ID NO: 30, or (c) a combination of (a) and (b); or
- (h) (a) a full-length (FL) HC amino acid sequence of SEQ ID NO: 59 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL HC amino acid sequence of SEQ ID NO: 59; (b) a FL LC amino acid sequence set forth of SEQ ID NO: 60 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL LC amino acid sequence of SEQ ID NO: 60, or (c) a combination of (a) and (b); or
- (i) (a) a full-length (FL) HC amino acid sequence of SEQ ID NO: 79 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL HC amino acid sequence of SEQ ID NO: 79; (b) a FL LC amino acid sequence set forth of SEQ ID NO: 80 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL LC amino acid sequence of SEQ ID NO: 80, or (c) a combination of (a) and (b).

- 9. The CD112R antigen-binding protein of any one of claims 1-6, which is an antigen-binding fragment of an antibody.
- 10. The CD112R antigen-binding protein of any one of claims 1-6, which is an antibody protein product, optionally, an scFv.
- 11. A nucleic acid encoding the CD112R antigen binding protein of any one of the preceding claims.

12. A nucleic acid encoding the light chain, the heavy chain, or both the light chain and the heavy chain of the antibody of claim 7 or 8.
13. The nucleic acid of claim 11 or 12 wherein the nucleotide sequence encodes (a) a HC variable region amino acid sequence set forth in Table B1 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of Table B1; (b) a LC variable region amino acid sequence set forth in Table B1 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable region amino acid sequence of Table B1, or (c) both (a) and (b).
14. A vector comprising one or more nucleic acids of any one of claims 11 to 13.
15. A host cell comprising one or more nucleic acids of any one of claims 11 to 13 or one or more vectors of claim 14.
16. The host cell of claim 15, wherein the host cell produces a CD112R antigen binding protein of any of claims 1-10.
17. A TIGIT antigen-binding protein comprising (a) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (e) an LC CDR2 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; and (f) an LC CDR3 amino acid sequence set forth in Table A2 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity. optionally, wherein the CD112R antigen-binding protein comprises the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 amino acid sequences for 43B7.002.015 as set forth in Table A2.
18. The TIGIT antigen binding protein of embodiment 17, comprising:

- (a) a LC CDR1 amino acid sequence comprising **Gln27**, or a conservative amino acid substitution thereof, **Ser28**, or a conservative amino acid substitution thereof, or any combination thereof; a LC CDR2 amino acid sequence comprising **Glu1**, or a conservative amino acid substitution thereof; and a LC CDR3 amino acid sequence comprising **Ser91**, or a conservative amino acid substitution thereof, **Ser92**, or a conservative amino acid substitution thereof, **Ser93**, or a conservative amino acid substitution thereof, **Leu94**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR1 amino acid sequence comprising **Val32**, or a conservative amino acid substitution thereof, **Tyr33**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR2 amino acid sequence comprising **Tyr52**, or a conservative amino acid substitution thereof, **Tyr54**, or a conservative amino acid substitution thereof, **Tyr55**, or a conservative amino acid substitution thereof, **Ser56**, or a conservative amino acid substitution thereof, **Gly57**, or a conservative amino acid substitution thereof, **Gly58**, or a conservative amino acid substitution thereof, **Thr59**, or a conservative amino acid substitution thereof, **Tyr60**, or a conservative amino acid substitution thereof, **Pro63**, or a conservative amino acid substitution thereof, **Arg66**, or a conservative amino acid substitution thereof, or any combination thereof; and a HC CDR3 amino acid sequence comprising **Ile102**, or a conservative amino acid substitution thereof, **Ala104**, or a conservative amino acid substitution thereof, **Gly107**, or a conservative amino acid substitution thereof, **Tyr108**, or a conservative amino acid substitution thereof, **Phe109**, or a conservative amino acid substitution thereof, **Tyr110**, or a conservative amino acid substitution thereof, **Tyr111**, or a conservative amino acid substitution thereof, or any combination thereof; wherein the position number is relative the LC variable region amino acid sequence of the TIGIT antigen binding protein
- (b) a LC CDR1 amino acid sequence comprising **Gln27**, or a conservative amino acid substitution thereof, **Ser28**, or a conservative amino acid substitution thereof, **Val29**, or a conservative amino acid substitution thereof, **Ser30**, or a conservative amino acid substitution thereof, **Ser31**, or a conservative amino acid substitution thereof, **Thr32**, or a conservative amino acid substitution thereof, **Tyr33**, or a conservative amino acid substitution thereof, or any combination thereof; a LC CDR2 amino acid sequence comprising **Glu1**, or a conservative amino acid substitution thereof, **Ile2**, or a conservative amino acid substitution thereof, **Ser68**, or a conservative amino acid substitution thereof, **Gly69**, or a conservative amino acid substitution thereof, or any

combination thereof; a LC CDR3 amino acid sequence comprising **Tyr92**, or a conservative amino acid substitution thereof, **Asp93**, or a conservative amino acid substitution thereof, **Val94**, or a conservative amino acid substitution thereof, **Ser95**, or a conservative amino acid substitution thereof, **Pro96**, or a conservative amino acid substitution thereof, **Trp97**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR1 amino acid sequence comprising **Gly32**, or a conservative amino acid substitution thereof, **Tyr35**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR2 amino acid sequence comprising **Tyr52**, or a conservative amino acid substitution thereof, **Tyr54**, or a conservative amino acid substitution thereof, **Tyr55**, or a conservative amino acid substitution thereof, **Ser56**, or a conservative amino acid substitution thereof, **Ser58**, or a conservative amino acid substitution thereof, **Thr59**, or a conservative amino acid substitution thereof, **Phe60**, or a conservative amino acid substitution thereof, **Pro63**, or a conservative amino acid substitution thereof, **Lys66**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR3 amino acid sequence comprising **Arg102**, or a conservative amino acid substitution thereof, **Asn104**, or a conservative amino acid substitution thereof, **Trp105**, or a conservative amino acid substitution thereof, **Asn106**, or a conservative amino acid substitution thereof, **Tyr107**, or a conservative amino acid substitution thereof, or any combination thereof; wherein the position number is relative the LC variable region amino acid sequence of the TIGIT antigen binding protein

- (c) a LC CDR1 amino acid sequence comprising **Arg30**, or a conservative amino acid substitution thereof, **Arg31**, or a conservative amino acid substitution thereof, **Tyr32**, or a conservative amino acid substitution thereof, or any combination thereof; a LC CDR3 amino acid sequence comprising **Ser91**, or a conservative amino acid substitution thereof, **Tyr92**, or a conservative amino acid substitution thereof, **Ser93**, or a conservative amino acid substitution thereof, **Thr94**, or a conservative amino acid substitution thereof, or any combination thereof., wherein the position number is relative the LC variable region amino acid sequence of the TIGIT antigen binding protein; a HC CDR1 amino acid sequence comprising **Thr30**, or a conservative amino acid substitution thereof, **Gly31** or a conservative amino acid substitution thereof, **Tyr32**, or a conservative amino acid substitution thereof, **Tyr33**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR2 amino acid sequence comprising **Trp47**, or a conservative amino acid

substitution thereof, a **Trp50**, or a conservative amino acid substitution thereof, **Ser52**, or a conservative amino acid substitution thereof, **Thr54**, or a conservative amino acid substitution thereof, **Ser55**, or a conservative amino acid substitution thereof, **Ala57**, or a conservative amino acid substitution thereof, **Thr58**, or a conservative amino acid substitution thereof, **Gly59**, or a conservative amino acid substitution thereof, **Tyr60**, or a conservative amino acid substitution thereof, **Gln65**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR3 amino acid sequence comprising **Asn101**, or a conservative amino acid substitution thereof, **Ser102**, or a conservative amino acid substitution thereof, **Val103**, or a conservative amino acid substitution thereof, **Leu104**, or a conservative amino acid substitution thereof, **Tyr105**, or a conservative amino acid substitution thereof, **Tyr106**, or a conservative amino acid substitution thereof, **Tyr107**, or a conservative amino acid substitution thereof, or any combination thereof; wherein the position number is relative the HC variable region amino acid sequence of the TIGIT antigen binding protein;

- (d) a LC CDR1 amino acid sequence comprising **Gln27**, or a conservative amino acid substitution thereof, **Leu30**, or a conservative amino acid substitution thereof, **Ser32**, or a conservative amino acid substitution thereof, or any combination thereof; a LC CDR3 amino acid sequence comprising **Ser96**, or a conservative amino acid substitution thereof, **Ile97**, or a conservative amino acid substitution thereof, **Gln98**, or a conservative amino acid substitution thereof, **Leu99**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR1 amino acid sequence comprising **Asp33**, or a conservative amino acid substitution thereof; a HC CDR2 amino acid sequence comprising **Tyr52**, or a conservative amino acid substitution thereof, a **Tyr54**, or a conservative amino acid substitution thereof, **Tyr55**, or a conservative amino acid substitution thereof, **Ser56**, or a conservative amino acid substitution thereof, **Gly57**, or a conservative amino acid substitution thereof, **Gly58**, or a conservative amino acid substitution thereof, **Thr59**, or a conservative amino acid substitution thereof, **Tyr60**, or a conservative amino acid substitution thereof, **Pro63**, or a conservative amino acid substitution thereof, **Lys66**, or a conservative amino acid substitution thereof, or any combination thereof; a HC CDR3 amino acid sequence comprising **Ile102**, or a conservative amino acid substitution thereof, **Ala104**, or a conservative amino acid substitution thereof, **Gly107**, or a conservative amino acid substitution thereof, **Tyr108**, or a conservative

amino acid substitution thereof, **Phe109**, or a conservative amino acid substitution thereof, **Tyr110**, or a conservative amino acid substitution thereof, **Phe111**, or a conservative amino acid substitution thereof, or any combination thereof; wherein the position number is relative the HC variable region amino acid sequence of the TIGIT antigen binding protein.

19. The TIGIT antigen-binding protein of claim 17 or 18, comprising six CDR amino acid sequences listed in a single row of Table A2 or comprising six CDR amino acid sequences selected from the group consisting of: (a) SEQ ID NOs: 113-118; (b) SEQ ID NOs: 123-128; (c) SEQ ID NOs: 133-138; (d) SEQ ID NOs: 143-148; (e) SEQ ID NOs: 153-158; (f) SEQ ID NOs: 163-168; (g) SEQ ID NOs: 173-178; (h) SEQ ID NOs: 183-188, (i) SEQ ID NOs: 193-198, (j) SEQ ID NOs: 203-208, (k) SEQ ID NOs: 213-218, (l) SEQ ID NOs: 223-228, and (m) SEQ ID NOs: 2013-2018, optionally, wherein the TIGIT antigen-binding protein comprises the six CDR amino acid sequences of SEQ ID NOs: 203-208.
20. The TIGIT antigen binding protein of any one of claims 17-19, comprising (a) a HC variable region amino acid sequence set forth in Table B2 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of Table B2; (b) a LC variable region amino acid sequence set forth in Table B2 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable region amino acid sequence of Table B2, or (c) a combination of (a) and (b), optionally, wherein the TIGIT antigen-binding protein comprises the HC variable region amino acid sequence and the LC variable region amino acid sequence for 43B7.002.015 as set forth in Table B2.
21. The TIGIT antigen-binding protein of claim 20, comprising a pair of HC variable region and LC variable region amino acid sequences listed in a single row of Table B2 or comprising a pair of amino acid sequences selected from the group consisting of: (a) SEQ ID NOs: 111-112, (b) SEQ ID NOs: 121-122, (c) SEQ ID NOs: 131-132, (d) SEQ ID NOs: 141-142, (e) SEQ ID NOs: 151-152, (f) SEQ ID NOs: 161-162, (g) SEQ ID NOs: 171-172, (h) SEQ ID NOs: 181-182, (i) SEQ ID NOs: 191-192, (j) SEQ ID NOs: 201-202, (k) SEQ ID NOs: 211-212, (l) SEQ ID NOs: 221-222, and (m) SEQ ID NOs: 2011-2012, optionally, wherein the

TIGIT antigen-binding protein comprises a HC variable region amino acid sequence of SEQ ID NO: 201 and LC variable region amino acid sequence of SEQ ID NO: 202.

22. The TIGIT antigen binding protein of any one of claims 17-21, comprising (a) a full-length (FL) HC amino acid sequence set forth in Table B2 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL HC amino acid sequence of Table B2; (b) a FL LC amino acid sequence set forth in Table B2 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL LC amino acid sequence of Table B2, or (c) a combination of (a) and (b), optionally, wherein the TIGIT antigen-binding protein comprises the FL HC amino acid sequence and the FL LC amino acid sequence for 43B7.002.015 as set forth in Table B2.
23. The TIGIT antigen-binding protein of claim 22, comprising a pair of full-length (FL) HC and FL LC amino acid sequences listed in a single row of Table B2 or comprising a pair of amino acid sequences selected from the group consisting of: (a) SEQ ID NOs: 109-110, (b) SEQ ID NOs: 119-120, (c) SEQ ID NOs: 129-130, (d) SEQ ID NOs: 139-140, (e) SEQ ID NOs: 149-150, (f) SEQ ID NOs: 159-160, (g) SEQ ID NOs: 169-170, (h) SEQ ID NOs: 179-180, (i) SEQ ID NOs: 189-190, (j) SEQ ID NOs: 199-200, (k) SEQ ID NOs: 209-210, (l) SEQ ID NOs: 219-220, and (m) SEQ ID NOs: 2009-2010, optionally, wherein the TIGIT antigen-binding protein comprises a FL HC amino acid sequence of SEQ ID NO: 199 and FL LC amino acid sequence of SEQ ID NO: 200.
24. The TIGIT antigen-binding protein of any one of claims 17-23, which is an antibody.
25. The TIGIT antigen-binding protein of claim 24, comprising:
- (a) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence of SEQ ID NO: 203 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence of SEQ ID NO: 204 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence of SEQ ID NO: 205 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence of SEQ ID NO: 206 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least

- or about 90% sequence identity; (e) an LC CDR2 amino acid sequence of SEQ ID NO: 207 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (f) an LC CDR3 amino acid sequence of SEQ ID NO: 208 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; or
- (b) a heavy chain (HC) complementarity-determining region (CDR) 1 amino acid sequence of SEQ ID NO: 223 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (b) an HC CDR2 amino acid sequence of SEQ ID NO: 224 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (c) an HC CDR3 amino acid sequence of SEQ ID NO: 225 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (d) a light chain (LC) CDR1 amino acid sequence of SEQ ID NO: 226 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (e) an LC CDR2 amino acid sequence of SEQ ID NO: 227 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; (f) an LC CDR3 amino acid sequence of SEQ ID NO: 228 or a variant sequence thereof which differs by only 1-4 amino acids or which has at least or about 90% sequence identity; or
- (c) comprising (a) a HC variable region amino acid sequence of SEQ ID NO: 201 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of SEQ ID NO: 201; (b) a LC variable region amino acid sequence of SEQ ID NO: 202 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable region amino acid sequence of SEQ ID NO: 202, or (c) a combination of (a) and (b); or
- (d) comprising (a) a HC variable region amino acid sequence of SEQ ID NO: 221 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of SEQ ID NO: 221; (b) a LC variable region amino acid sequence of SEQ ID NO: 222 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable

region amino acid sequence of SEQ ID NO: 222, or (c) a combination of (a) and (b);
or

- (e) (a) a full-length (FL) HC amino acid sequence of SEQ ID NO: 199 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL HC amino acid sequence of SEQ ID NO: 199; (b) a FL LC amino acid sequence set forth of SEQ ID NO: 200 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL LC amino acid sequence of SEQ ID NO: 200, or (c) a combination of (a) and (b); or
- (f) (a) a full-length (FL) HC amino acid sequence of SEQ ID NO: 219 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL HC amino acid sequence of SEQ ID NO: 219; (b) a FL LC amino acid sequence set forth of SEQ ID NO: 220 or a variant sequence thereof which differs by only 1-50 amino acids or which has at least or about 90% or about 95% sequence identity to the FL LC amino acid sequence of SEQ ID NO: 220, or (c) a combination of (a) and (b).

26. The TIGIT antigen-binding protein of any one of claims 17-23, which is an antigen-binding fragment of an antibody.

27. The TIGIT antigen-binding protein of any one of claims 17-23, which is an antibody protein product, optionally, an scFv.

28. A nucleic acid encoding the TIGIT antigen binding protein of any one of the preceding claims.

29. A nucleic acid encoding the light chain, the heavy chain or both the light chain and the heavy chain of the antibody of claim 24 or 25.

30. The nucleic acid of claim 28 or 29, wherein the nucleotide sequence encodes (a) a HC variable region amino acid sequence set forth in Table B2 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the HC variable region amino acid sequence of Table B2; (b) a LC variable region amino acid sequence set forth in Table B2 or a variant sequence thereof which differs by only 1-15 amino acids or which has at least or about 90% or about 95% sequence identity to the LC variable region amino acid sequence of Table B2, or (c) both (a) and (b).

31. A vector comprising one or more nucleic acids of any one of claims 28 to 30.
32. A host cell comprising one or more nucleic acids of any one of claims 28 to 30 or one or more vectors of claim 31.
33. The host cell of claim 31, wherein the host cell produces a TIGIT antigen binding protein of any of claims 17-27.
34. A composition comprising a CD112R antigen binding protein of any one of claims 1-10 and a TIGIT antigen binding protein of any one of claims 17-27, optionally, wherein the composition comprises a CD112R antigen-binding protein comprising a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 of SEQ ID NOs: 33-38, respectively, and a TIGIT antigen-binding protein comprising a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 of SEQ ID NOs: 203-208, respectively.
35. The composition of claim 34, wherein (A) the CD112R antigen binding protein is 1E1, 1E1.016, 24F1, 29E10, 24F1.001, 29E10_CONS.020, 29E10_CONS.021, 29E10_CONS.022, 29E10_CONS.025, 11E4, 31B3, 27G12, 28F9, 28H7, or 36C8 as described in Table A1 or Table B1, optionally, 24F1, 29E10_CONS.020 or 29E10_CONS.022, (B) the TIGIT antigen binding protein is any one of 55G7.041.008, 58A7.003.008.075, 4G10, 11A3, 28B8, 39D2, 43B7, 55G7, 66H9, 43B7.002.015, 58A7.003.08, 66H9.009, or 58A7 as described in Table A2 or Table B2, optionally, the 43B7.002.015 or 66H9.009, or a combination of (A) and (B).
36. The composition of claim 34 or 35, wherein the composition comprises (A) 24F1 and 43B7.002.015, (B) 24F1 and 66H9.009, (C) 29E10_CONS.020 and 43B7.002.015, (D) 29E10_CONS.020 and 66H9.009, (E) 29E10_CONS.022 and 43B7.002.015, (F) 29E10_CONS.022 and 66H9.009, (G) 43B7.002.015 and 1E1.016, (H) 43B7.002.015 and 24F1, (I) 43B7.002.015 and 29E10, (J) 66H9.009 and 1E1.016, (K) 66H9.009 and 29E10, (L) 43B7 and 29E10, (M) 43B7 and 24F1, or (N) 43B7 and 11E4.
37. The composition of any one of claims 34-36, wherein the CD112R antigen binding protein and the TIGIT antigen binding protein is present in the composition at a ratio of about 1:1.
38. The composition of any one of claims 34-37 further comprising a PD-1 antigen binding protein.

39. A kit comprising an antigen-binding protein of any one of claims 1-10 and 17-27, the nucleic acid of any one of claims 11-13 and 28-30, the vector of claim 14 or 31, the host cell of any one of claims 15, 16, 32, and 33, a composition of any one of claims 34-38, or a combination thereof, and a container.
40. The kit of claim 39 further comprising a PD-1 antigen binding protein.
41. A pharmaceutical composition comprising an antigen-binding protein of any one of claims 1-10 and 17-27, the nucleic acid of any one of claims 11-13 and 28-30, the vector of claim 14 or 31, the host cell of any one of claims 15, 16, 32, and 33, a composition of any one of claims 33-36, or a combination thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.
42. The pharmaceutical composition of claim 41 further comprising a PD-1 antigen binding protein.
43. A method of making CD112R antigen-binding protein comprising culturing the host cell of any one of claims 15 or 16 so as to express the CD112R antigen-binding protein and harvesting the expressed CD112R antigen-binding protein.
44. A method of making TIGIT antigen-binding protein comprising culturing the host cell of any one of claims 32 or 33 so as to express the TIGIT antigen-binding protein and harvesting the expressed TIGIT antigen-binding protein.
45. A ~~method of treating a subject in need thereof, comprising administering to the subject in need thereof a~~ pharmaceutical composition of claim 41 or 42 ~~in an amount effective to treat the subject~~ for use in therapy.
46. Use of a pharmaceutical composition of claim 41 or 42 in the manufacture of a medicament for treating ~~The method of claim 45, wherein the subject has a solid tumor and the pharmaceutical composition is administered to the subject in an amount effective to treat the solid tumor in the subject.~~
47. A ~~method of treating a subject in need thereof, comprising administering to the subject in need thereof a~~ first pharmaceutical composition comprising a CD112R antigen-binding protein and a TIGIT antigen-binding protein and a second pharmaceutical composition comprising a PD-1 inhibitor for use in therapy.

48. ~~The method of claim 47, wherein the subject has a solid tumor and the~~ Use of a first pharmaceutical composition comprising a CD112R antigen-binding protein and a TIGIT antigen-binding protein in the manufacture of a first medicament and ~~the use of a~~ second pharmaceutical composition comprising a PD-1 inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating ~~are administered to the subject in amounts effective to treat the~~ solid tumor in ~~the~~ a subject.