CD155) directly suppresses NK cell cytotoxicity through its cytoplasmic ITIM domain. Knockout of the TIGIT gene or antibody blockade of the TIGIT/PVR interaction has shown to enhance NK cell killing in vitro, as well as to exacerbate autoimmune diseases in vivo. In addition to its direct effects on T- and NK cells, TIGIT can induce PVR-mediated signaling in dendritic or tumor cells, leading to the increase in production of anti-inflammatory cytokines such as IL10. In T-cells TIGIT can also inhibit lymphocyte responses by disrupting homodimerization of the costimulatory receptor CD226, and by competing with it for binding to PVR.

[0012] TIGIT is highly expressed on lymphocytes, including Tumor Infiltrating Lymphocytes (TILs) and Tregs, that infiltrate different types of tumors. PVR is also broadly expressed in tumors, suggesting that the TIGIT-PVR signaling axis may be a dominant immune escape mechanism for cancer. Notably, TIGIT expression is tightly correlated with the expression of another important coinhibitory receptor, PD1. TIGIT and PD1 are co-expressed on the TILs of numerous human and murine tumors. Unlike TIGIT and CTLA4, PD1 inhibition of T cell responses does not involve competition for ligand binding with a costimulatory receptor.

[0013] Accordingly, TIGIT is an attractive target for monoclonal antibody therapy, and in addition in combination with additional antibodies including anti-PVRIG antibodies.

III. SUMMARY

[0014] Accordingly, in one example, the disclosure provides compositions comprising an antigen binding domain that binds to human TIGIT (SEQ ID NO:97) comprising a variable heavy domain comprising SEQ ID NO:160 and a variable light domain comprising SEQ ID NO:165. Additionally, the antigen binding domain comprises a variable heavy domain comprising SEQ ID NO:150 and a variable light domain comprising SEQ ID NO:155. Additionally, the antigen binding domain comprises a variable heavy domain comprising SEQ ID NO:560 and a variable light domain comprising SEQ ID NO:565.

[0014a] In one aspect, the present disclosure provides an anti-TIGIT antibody comprising: (1) vhCDR1 of SEQ ID NO:161, vhCDR2 of SEQ ID NO:162, vhCDR3 of SEQ ID NO:163, vlCDR1 of SEQ ID NO:166, vlCDR2 of SEQ ID NO:167, and vlCDR3 of SEQ ID NO:168; or (2) vhCDR1 of SEQ ID NO:151, vhCDR2 of SEQ ID NO:152, vhCDR3 of SEQ ID NO:153, vlCDR1 of SEQ ID NO:156, vlCDR2 of SEQ ID NO:157, and vlCDR3 of SEQ ID NO:158. In another aspect, the present disclosure provides a composition comprising the anti-TIGIT antibody as described herein, for use in therapy. In yet another aspect, the present disclosure provides a use of the anti-TIGIT antibody as described herein in the manufacture of a medicament for treating cancer.

[0014b] In a further aspect, the present disclosure provides a composition comprising an antibody that binds to human TIGIT, wherein said antibody comprises: the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:160; and the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:165; or a vhCDR1 from SEQ ID NO:161 comprising 0-2 amino acid substitutions; ii) a vhCDR2 from SEQ ID NO:162 comprising 0-2 amino acid substitutions; iii) a vhCDR3 from SEQ ID NO:163; iv) a vlCDR1 from SEQ ID NO:166 comprising 0-2 amino acid substitutions; v) a vlCDR2 from SEQ ID NO:167 comprising 0-2 amino acid substitutions; and vi) a vlCDR3 from SEQ ID NO:168; or a variable heavy domain comprising an amino acid sequence exhibiting at least 90% or at least 95% identity to SEQ ID NO:160, and ii) a variable light domain comprising an amino acid sequence exhibiting at least 90% or at least 95% identity to SEQ ID NO:165; or the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:150; and the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:155; or a variable heavy domain having SEQ ID NO:150 and a variable light domain having SEQ ID NO:155; or a vhCDR1 from SEQ ID NO:151 comprising 0-2 amino acid substitutions; ii) a vhCDR2 from SEQ ID NO:152 comprising 0-2 amino acid substitutions; iii) a vhCDR3 from SEQ ID NO:153; iv) a vlCDR1 from SEQ ID NO:156 comprising 0-2 amino acid substitutions; v) a vlCDR2 from SEQ ID NO:157 comprising 0-2 amino acid substitutions; and vi) a vlCDR3 from SEQ ID NO:158; or a variable heavy domain comprising an amino acid sequence exhibiting at least 90% or at least 95% identity to SEQ ID NO:150, and ii) a variable light domain comprising an amino acid sequence exhibiting at least 90% or at least 95% identity to SEQ ID NO:155.

[0014c] In a further aspect, the present disclosure provides a composition for activating T-cells and/or NK cells of a patient with cancer comprising an antigen binding domain that binds to human TIGIT, wherein said antigen binding domain comprises: a) a variable heavy domain comprising SEQ ID NO:160; and b) a variable light domain comprising SEQ ID NO:165, or a) a variable heavy domain comprising SEQ ID NO:150; and b) a variable light domain comprising SEQ ID NO:155.

[0014d] In a further aspect, the present disclosure provides a composition for activating T-cells and/or NK cells of a patient with cancer comprising the antibody as disclosed herein.

[0015] In a further example, the disclosure provides composition comprising antibodies comprising a heavy chain comprising VH-CH1-hinge-CH2-CH3, wherein said VH comprises SEQ ID NO:160 and a light chain comprising VL-VC, wherein said VL comprising SEQ ID NO:165 and VC is either kappa or lambda. Additionally, the antibody can comprise a heavy chain comprising VH-CH1-hinge-CH2-CH3, wherein the VH comprises SEQ ID NO:150; and a light chain comprising VL-VC, wherein said VL comprising SEQ ID NO:159 and VC is either kappa or lambda. Additionally, the antibody can comprise a heavy chain comprising VH-CH1-hinge-CH2-CH3, wherein the VH comprises SEQ ID NO:560; and a light chain comprising VL-VC, wherein said VL comprising SEQ ID NO:565 and VC is either kappa or lambda.

[0016] In some examples, the sequence of the CH1-hinge-CH2-CH3 is selected from human IgG1, IgG2 and IgG4, and variants thereof. In some examples, the heavy chain has SEQ ID NO:164 and the light chain has SEQ ID NO:169.

[0017] In an additional example, the compositions can further comprise a second antibody that binds to a human checkpoint receptor protein, which can be human PD-1 or human PVRIG. The second antibody can comprises an antigen binding domain comprising a variable heavy domain comprising SEQ ID NO:5 and a variable light domain comprising SEQ ID NO:10, or a heavy chain having SEQ ID NO:9 and a light chain having SEQ ID NO:14.

[0018] In a further example, the disclosure provides nucleic acid compositions comprising a first nucleic acid encoding a variable heavy domain comprising SEQ ID NO:160 and a second nucleic acid encoding a variable light domain comprising SEQ ID NO:165. Alternatively, the nucleic acid compositions comprise a first nucleic acid encoding a variable heavy domain comprising SEQ ID NO:150 and a second nucleic acid encoding a variable light domain comprising SEQ ID NO:155. Alternatively, the nucleic acid compositions comprise a first nucleic acid encoding a variable heavy domain comprising SEQ ID NO:560 and a second nucleic acid encoding a variable light domain comprising SEQ ID NO:565.

[0019] In a further example, the disclosure provides expression vector compositions comprising these nucleic acid compositions are provided as well, such as a first expression vector comprising a first nucleic acid and a second expression vector comprising a second nucleic acid, or alternatively an expression vector that comprises both first and second nucleci acids.

[0020] In an additional example, the disclosure provides host cells comprising the expression vector compositions, and methods of making the antibodies comprising culturing the host cells under conditions wherein the antibodies are produced and recovering the antibody.

[0021] In a further example the disclosure provides anti-PVRIG antibodies comprising a heavy chain having SEQ ID NO:9 and a light chain having SEQ ID NO:14. The disclosure further provides antibodies having a heavy chain having SEQ ID NO:19; and a light chain having SEQ ID NO:24.

[0022] In an additional example, an anti-PVRIG antibody (either CHA.7.518.1.H4(S241P) or CHA.7.538.1.2.H4(S241P) are co-administered with a second antibody that binds to a human checkpoint receptor protein, such as an antibody that binds PD-1.

[0023] In a further example, an anti-PVRIG antibody (either CHA.7.518.1.H4(S241P) or CHA.7.538.1.2.H4(S241P)) are co-administered with a second antibody that binds to a human checkpoint receptor protein, such as an antibody that binds human TIGIT, such as CPA.9.086 or CPA.9.083 or CHA.9.547.13.

[0024] In a further example, the disclosure provides nucleic acid compositions comprising a first nucleic acid encoding the heavy chain of either CHA.7.518.1.H4(S241P) or CHA.7.538.1.2.H4(S241P)) and a second nucleic acid encoding the light chain of either CHA.7.518.1.H4(S241P) or CHA.7.538.1.2.H4(S241P), respectively.

[0025] In a further example, the disclosure provides expression vector compositions comprising these nucleic acid compositions are provided as well, such as a first expression vector comprising a first nucleic acid and a second expression vector comprising a second nucleic acid, or alternatively an expression vector that comprises both first and second nucleci acids.

[0026] In an additional example, the disclosure provides host cells comprising the expression vector compositions, and methods of making the antibodies comprising culturing the host cells under conditions wherein the antibodies are produced and recovering the antibody.

[0027] In a further example, the disclosure provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVR protein; iii) PD-1 protein; iv) PD-L1 protein; and v) an isotype control; c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVR, PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq$ 1% for all 4 receptors, e) administering antibodies to TIGIT and PD-1 to said patient.

[0028] In an additional example, the disclosure provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PVRL2 protein; iii) PD-1 protein; iv) PD-L1 protein; and v) an isotype control; c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq$ 1% for all 4 receptors, e) administering antibodies to PVRIG and PD-1 to said patient.

[0029] In a further example, the disclosure provides methods comprising a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PVRL2 protein; iii) TIGIT protein; iv) PVR protein; and v) an isotype control; c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, TIGIT and PVR, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq$ 1% for all 4 receptors, e) administering antibodies to PVRIG and TIGIT to said patient.

CLAIMS

1. An anti-TIGIT antibody comprising:

(1)

vhCDR1 of SEQ ID NO:161,

vhCDR2 of SEQ ID NO:162,

vhCDR3 of SEQ ID NO:163,

vlCDR1 of SEQ ID NO:166,

vlCDR2 of SEQ ID NO:167, and

vlCDR3 of SEQ ID NO:168;

or

(2)

vhCDR1 of SEQ ID NO:151,

vhCDR2 of SEQ ID NO:152,

vhCDR3 of SEQ ID NO:153,

vlCDR1 of SEQ ID NO:156,

vlCDR2 of SEQ ID NO:157, and

vlCDR3 of SEQ ID NO:158.

2. A composition comprising the anti-TIGIT antibody of claim 1, for use in therapy.

3. Use of the anti-TIGIT antibody of claim 1 in the manufacture of a medicament for treating cancer.

4. A composition comprising an antibody that binds to human TIGIT, wherein said antibody comprises:

the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:160; and the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:165; or

a vhCDR1 from SEQ ID NO:161 comprising 0-2 amino acid substitutions; ii) a vhCDR2 from SEQ ID NO:162 comprising 0-2 amino acid substitutions; iii) a vhCDR3 from SEQ ID NO:163; iv) a vlCDR1 from SEQ ID NO:166 comprising 0-2 amino acid substitutions; v) a vlCDR2 from SEQ ID NO:167 comprising 0-2 amino acid substitutions; and vi) a vlCDR3 from SEQ ID NO:168; or

a variable heavy domain comprising an amino acid sequence exhibiting at least 90% or at least 95% identity to SEQ ID NO:160, and ii) a variable light domain comprising an amino acid sequence exhibiting at least 90% or at least 95% identity to SEQ ID NO:165; or

the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:150; and the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:155; or

a variable heavy domain having SEQ ID NO:150 and a variable light domain having SEQ ID NO:155; or

a vhCDR1 from SEQ ID NO:151 comprising 0-2 amino acid substitutions; ii) a vhCDR2 from SEQ ID NO:152 comprising 0-2 amino acid substitutions; iii) a vhCDR3 from SEQ ID NO:153; iv) a vlCDR1 from SEQ ID NO:156 comprising 0-2 amino acid substitutions; v) a vlCDR2 from SEQ ID NO:157 comprising 0-2 amino acid substitutions; and vi) a vlCDR3 from SEQ ID NO:158; or

a variable heavy domain comprising an amino acid sequence exhibiting at least 90% or at least 95% identity to SEQ ID NO:150, and ii) a variable light domain comprising an amino acid sequence exhibiting at least 90% or at least 95% identity to SEQ ID NO:155.

5. The composition according to claim 4, wherein the antibody comprises

a heavy chain having SEQ ID NO:154 and a light chain having SEQ ID NO:159.

6. The composition according to claim 4, wherein said antibody comprises:

i) the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:160; and

ii) the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:165, and

wherein said antibody comprises a CH1-hinge-CH2-CH3 region from human IgG1, IgG2, or IgG4, or variants thereof.

7. The composition according to claim 4 wherein said antibody comprises:

i) the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:160; and

ii) the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:165, and

wherein said antibody comprises a VC region, wherein said VC is either kappa or lambda.

8. A composition for activating T-cells and/or NK cells of a patient with cancer comprising

an antigen binding domain that binds to human TIGIT,

wherein said antigen binding domain comprises:

a) a variable heavy domain comprising SEQ ID NO:160; and

b) a variable light domain comprising SEQ ID NO:165,

or

a) a variable heavy domain comprising SEQ ID NO:150; and

b) a variable light domain comprising SEQ ID NO:155.

9. The composition according to claim 8, wherein said T-cells are cytotoxic T-cells (CTLs).

10. The composition according to claim 8, wherein said T-cells are selected from the group consisting of CD4+ T-cells and CD8+ T-cells.

11. The composition according to claim 8, wherein said activation is measured as an increase in interferon-γ production and/or an increase in cytokine secretion.

12. The composition according to claim 8, wherein said antigen binding domain is an antibody, and wherein said antibody comprises:

a) a heavy chain comprising VH-CH1-hinge-CH2-CH3, wherein said VH comprises SEQ ID NO:150; and

b) a light chain comprising VL-VC, wherein said VL comprising SEQ ID NO:155 and VC is either kappa or lambda.

13. The composition according to claim 12, wherein said heavy chain has SEQ ID NO:154 and said light chain has SEQ ID NO:159.

14. A composition for activating T-cells and/or NK cells of a patient with cancer comprising the antibody according to claims 1 or 4.