

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 aspect, the present disclosure refers to a composition comprising an antigen binding domain that binds to human TIGIT (SEQ ID NO:97) comprising: (a) a variable heavy domain comprising SEQ ID NO:160; and (b) 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.

[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 aspect, the present disclosure refers to a nucleic acid composition comprising: a) a first nucleic acid encoding a variable heavy domain comprising SEQ ID NO:160; and b) 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 nucleic acids.

[0019a] In another aspect, the present disclosure refers to an expression vector composition comprising a first expression vector comprising said first nucleic acid as disclosed herein and a second expression vector comprising said second nucleic acid as disclosed herein, respectively.

[0019b] In another aspect, the present disclosure refers to an expression vector composition comprising a expression vector comprising said first nucleic acid as disclosed herein and said second nucleic acid as disclosed herein, respectively.

[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.

[0020a] In another aspect, the present disclosure refers to a host cell comprising said expression vector composition as disclosed herein.

[0020b] In another aspect, the present disclosure refers to a method of making an anti-TIGIT antibody comprising: a) culturing said host cell as disclosed herein under conditions wherein said antibody is expressed; and b) recovering said 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 nucleic 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.

[0029a] In another aspect, the present disclosure refers to use of a composition as disclosed herein in the manufacture of a medicament for treating cancer by activating T cells and/or NK cells.

CLAIMS

1. A composition comprising an antigen binding domain that binds to human TIGIT (SEQ ID NO:97) comprising:
 - a) a variable heavy domain comprising SEQ ID NO:160; and
 - b) a variable light domain comprising SEQ ID NO:165.
2. A composition according to claim 1 wherein said composition is an antibody comprising:
 - a) a heavy chain comprising VH-CH1-hinge-CH2-CH3, wherein said VH comprises SEQ ID NO:160; and
 - b) a light chain comprising VL-VC, wherein said VL comprising SEQ ID NO:165 and VC is either kappa or lambda.
3. A composition according to claim 2 wherein the sequence said CH1-hinge-CH2-CH3 is selected from human IgG1, IgG2 and IgG4, and variants thereof.
4. A composition according to claim 2 or 3 wherein said heavy chain has SEQ ID NO:164 and said light chain has SEQ ID NO:169.
5. A composition according to any of claims 2 to 4 further comprising a second antibody that binds to a human checkpoint receptor protein.
6. A composition according to claim 5 wherein said second antibody binds human PD-1 or PD-L1.
7. A composition according to claim 5 wherein said second antibody binds human PVRIG (SEQ ID NO:2).
8. A composition according to claim 7 wherein said second antibody 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.
9. A composition according to claim 7 wherein the heavy chain of said second antibody has SEQ ID NO:9 and the light chain of said second antibody has SEQ ID NO:14.
10. A nucleic acid composition comprising:
 - a) a first nucleic acid encoding a variable heavy domain comprising SEQ ID NO:160; and
 - b) a second nucleic acid encoding a variable light domain comprising SEQ ID NO:165.
11. A nucleic acid composition according to claim 10 wherein said first nucleic acid encodes a heavy chain comprising VH-CH1-hinge-CH2-CH3, wherein said VH comprises SEQ ID NO:160; and said second nucleic acid encodes a light chain comprising VL-VC, wherein said VL comprising SEQ ID NO:165 and VC is the lambda domain.
12. An expression vector composition comprising a first expression vector comprising said first nucleic acid according to claim 10 or 11 and a second expression vector comprising said second nucleic acid according to claim 10 or 11, respectively.

13. An expression vector composition comprising a expression vector comprising said first nucleic acid according to claim 10 or 11 and said second nucleic acid according to claim 10 or 11, respectively.
14. A host cell comprising said expression vector composition according to claim 12 or 13.
15. A method of making an anti-TIGIT antibody comprising:
 - a) culturing said host cell of claim 14 under conditions wherein said antibody is expressed; and
 - b) recovering said antibody.
16. Use of a composition according to any of claims 1 to 9 in the manufacture of a medicament for treating cancer by activating T cells and/or NK cells.
17. A composition according to claim 7 wherein said second antibody comprises an antigen binding domain comprising a variable heavy domain comprising SEQ ID NO:15 and a variable light domain comprising SEQ ID NO:20.
18. A composition according to claim 7 wherein the heavy chain of said second antibody has SEQ ID NO:19 and the light chain of said second antibody has SEQ ID NO:24.
19. A composition according to claim 7 wherein said second antibody comprises:
 - i) the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:5 and
 - ii) the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:10.
20. A composition according to claim 7 wherein said second antibody comprises:
 - i) the vhCDR1, vhCDR2, and vhCDR3 from SEQ ID NO:15 and
 - ii) the vlCDR1, vlCDR2, and vlCDR3 from SEQ ID NO:20.
21. The use according to claim 16 wherein said T-cells are cytotoxic T-cells (CTLs).
22. The use according to claim 16 wherein said T-cells are selected from the group consisting of CD4⁺ T-cells and CD8⁺ T-cells.
23. The use according to claim 16 wherein said activation is measured as an increase in interferon- γ production and/or an increase in cytokine secretion.
24. The use according to claim 16, wherein a combination of the anti-TIGIT antibody and another checkpoint receptor antibody is to be administered.

25. The use according to claim 24, wherein the other checkpoint receptor antibody is selected from the group consisting of anti-PVRIG antibodies, anti-PD-1 antibodies, anti-CTLA-4 antibodies, anti-PD-L1 antibodies, anti-LAG-3 antibodies, anti-TIM-3 antibodies and anti-BTLA antibodies.
26. The use according to claim 24 or 25, wherein the other checkpoint receptor antibody is an anti-PVRIG antibody.
27. The use according to claim 25 or 26, wherein the anti-PVRIG antibody comprises
- a VH domain having SEQ ID NO:5 and a VL domain having SEQ ID NO:10, or
 - a VH domain having SEQ ID NO:15 and a VL domain having SEQ ID NO:20.
28. The use according to at least one of claims 25 to 27, wherein the anti-PVRIG antibody comprises
- a heavy chain having SEQ ID NO:9 and a light chain having SEQ ID NO:14, or
 - a heavy chain having SEQ ID NO:19 and a light chain having SEQ ID NO:24.
29. The use according to claim 25, wherein the anti-PD- 1 antibody is pembrolizumab or nivolumab.
30. The use according to claim 25, wherein the anti-CTLA-4 antibody is ipilimumab or tremelimumab.
31. The use according to claim 25, wherein the anti-PD-L1 antibody is atezolizumab, avelumab or durvalumab.
32. The use according to claim 25, wherein the anti-LAG-3 antibody is BMS-986016, GSK2831781, Merck clone 22D2, Merck clone 11C9 or Merck clone 4A10.
33. The use according to claim 25, wherein the anti-TIM-3 antibody is TSR-022.
34. The use according to at least one of claims 24 to 33, wherein the anti-TIGIT antibody and the other checkpoint receptor antibody act additively.
35. The use according to at least one of claims 24 to 33 wherein the anti-TIGIT antibody and the other checkpoint receptor antibody act synergistically.