polypeptide amino acid sequence of one or more of an alanine at amino acid position corresponding to amino acid position 67 of human TIGIT, a glycine at an amino acid position corresponding to amino acid position 74 of human TIGIT, a proline at an amino acid position corresponding to amino acid position 114 of human TIGIT, and a glycine at an amino acid position corresponding to amino acid position 116 of human TIGIT. In another embodiment, the disclosure provides a method for identifying one or more members of the TLP protein family by identifying proteins in one or more sequence databases whose amino acid sequences comprise at least one amino acid selected from an alanine at amino acid position corresponding to amino acid position 67 of human TIGIT, a glycine at an amino acid position corresponding to amino acid position 74 of human TIGIT, a proline at an amino acid position corresponding to amino acid position 114 of human TIGIT, and a glycine at an amino acid position corresponding to amino acid position 116 of human TIGIT.

In another embodiment, the disclosure provides an isolated agent that specifically interacts with one or more conserved or substantially conserved regions of TLP family members. In one aspect, there is provided an isolated TIGIT-like protein (TLP)-interacting agent that specifically interacts with one or more of the following structural submotifs:

(a) V/I^{54}- S/T^{55}-Q^{56};

(b) A^{67}- X^{68}- X^{69}-X^{71}-X^{72}-X^{73}-G^{74}, herein X is any amino acid; and/or

(c) T^{112}-F/Y^{113}-P^{114}-X^{115}-G^{116}, wherein X is any amino acid,

wherein the TLP-interacting agent is an antagonizing antibody, or antigen-binding fragment thereof, that antagonizes the activity of TIGIT and/or PVR and is capable of binding to mouse TIGIT and human TIGIT. In one embodiment, the agent is an antagonist of the expression and/or activity of a TLP family member. In another embodiment, the antagonist is selected from a small molecule inhibitor, an inhibitory antibody or antigen-binding fragment thereof, an aptamer, an inhibitory nucleic acid, and an inhibitory polypeptide. In another embodiment, the agent is an agonist of the expression and/or activity of a TLP family member. In another embodiment, the agonist is selected from an agonizing antibody or antigen-binding fragment thereof, an agonizing peptide, and a small molecule or protein that activates TIGIT binding to PVR and/or TIGIT intracellular signaling mediated by PVR. In another embodiment, the disclosure provides a method of identifying or detecting one or more TLP family members by contacting a putative TLP family member polypeptide with at least one of the above agents and determining the binding of the at least one agent to the putative TLP family member.

In another embodiment, the disclosure provides a method of determining whether a test immune cell is an activated or normal T_{reg}, memory T cell, NK cell, or T_{Fh} cell, comprising assessing the level of expression of TIGIT in the test immune cell and comparing it to the level of expression of TIGIT in a known activated or normal Treg, memory T cell, NK cell, or TFh cell, or by comparing the level of expression of TIGIT in the test immune cell to known standard TIGIT expression value(s). In another embodiment, the disclosure provides a method for modulating immune system function and/or activity comprising modulating the binding of TIGIT to one or more of PVR, PVRL3, and PVRL2.

or in vivo with TIGIT, an agonist of TIGIT expression and/or activity, an agonist of PVR expression and/or activity, or by stimulating intracellular signaling mediated by TIGIT binding to PVR. In another embodiment, the modulating is increasing or stimulating proliferation of one or more immune cells or proinflammatory cytokine release by one or more immune cells by treating the cells in vitro or in vivo with an antagonist of TIGIT expression and/or activity, an antagonist of PVR expression and/or activity, or by inhibiting intracellular signaling mediated by TIGIT binding to PVR.

In one aspect, there is provided use of the TLP-interacting agent described herein in the manufacture of a medicament for increasing or stimulating proliferation of one or more immune cells or proinflammatory cytokine release by one or more immune cells in a subject in need thereof. In one embodiment, the disclosure provides a method of inhibiting an immune response by administering in vitro or in vivo TIGIT, an agonist of TIGIT expression and/or activity, an agonist of PVR expression and/or activity, or by stimulating intracellular signaling mediated by TIGIT binding to PVR. In another embodiment, the disclosure provides a method of increasing or stimulating an immune response by administering in vitro or in vivo an antagonist of TIGIT expression and/or activity, an antagonist of PVR expression and/or activity, or by inhibiting intracellular signaling mediated by TIGIT binding to PVR. Disclosed is a method of increasing or stimulating an immune response by administering in vitro the TLP-interacting agent described herein. In another aspect, there is provided use of the TLP-interacting agent described herein in the manufacture of a medicament for stimulating an immune response in a subject having cancer. In another embodiment, the disclosure provides a method of modulating the type and/or amount of cytokine production from an immune cell by modulating TIGIT or PVR expression and/or activity in vitro or in vivo. In one aspect, there is provided a method of modulating the type and/or amount of cytokine production from an immune cell by administering *in vitro* the TLP-interacting agent described herein. Provided is use of the TLP-interacting agent described herein in the manufacture of a medicament for modulating the type and/or amount of cytokine production from an immune cell in a subject in need thereof. In one embodiment, proinflammatory cytokine production is stimulated and/or increased by administration of an antagonist of TIGIT expression and/or activity, an antagonist of PVR expression and/or activity, or by inhibiting intracellular signaling mediated by TIGIT binding to PVR. In another embodiment, proinflammatory cytokine production is inhibited by administration of an agonist of TIGIT expression and/or activity, an agonist of PVR expression and/or activity, or by stimulating intracellular signaling mediated by TIGIT binding to PVR.

In another embodiment, the disclosure provides a method of stimulating ERK phosphorylation and/or intracellular signaling through the ERK pathway in one or more immune cells comprising treating the one or more immune cells with TIGIT, an agonist of TIGIT expression and/or activity, or an agonist of PVR expression and/or activity.

In another aspect, there is provided a method of diagnosing an immune-related disease relating to aberrant immune cell response in a subject comprising determining the expression and/or activity of TIGIT in an isolated sample from the subject and comparing the expression and/or activity of TIGIT to a reference amount of TIGIT expression and/or activity or the amount of TIGIT expression and/or activity in an isolated sample from a normal subject, wherein the determining comprises use of the TLP-interacting agent described herein. In one embodiment, the immune-related disease is selected from psoriasis, arthritis, inflammatory bowel disease or cancer. In another embodiment, the cancer is breast cancer. In one aspect, there is provided a method of diagnosing a cancer in a subject comprising determining the expression and/or activity of TIGIT in an isolated sample from the subject and comparing the expression and/or activity of TIGIT to a reference amount of TIGIT expression and/or activity or the amount of TIGIT expression and/or activity in an isolated sample from a normal subject, wherein the determining comprises use of the TLP-interacting agent described herein. In another

aspect, there is provided a method of assessing the severity of an immune-related disease relating to aberrant immune cell response in a subject comprising determining the expression and/or activity of TIGIT in an isolated sample from the subject and comparing the expression and/or activity of TIGIT to a reference amount of TIGIT expression and/or activity or the amount of TIGIT expression and/or activity in an isolated sample from a normal subject, wherein the determining comprises use of the TLP-interacting agent described herein. In one embodiment, the immune-related disease is selected from psoriasis, arthritis, inflammatory bowel disease or cancer. In one aspect, there is provided a method of assessing the severity of a cancer in a subject comprising determining the expression and/or activity of TIGIT in an isolated sample from the subject and comparing the expression and/or activity of TIGIT to a reference amount of TIGIT expression and/or activity or the amount of TIGIT expression and/or activity in an isolated sample from a normal subject, wherein the determining comprises use of the TLP-interacting agent described herein. In one embodiment, the cancer is breast cancer. In another embodiment, the disclosure provides a method of preventing an immune-related disease relating to aberrant immune cell response in a subject comprising modulating the expression and/or activity of TIGIT in the subject. In one aspect, there is provided use of the TLP-interacting agent described herein in the manufacture of a medicament for preventing an immune-related disease relating to aberrant immune cell response in a subject in need thereof, wherein the immune-related disease is selected from the group consisting of psoriasis, arthritis, inflammatory bowel disease, and cancer. In one embodiment, the immune-related disease is selected from psoriasis, arthritis, inflammatory bowel disease or cancer. In another embodiment, the cancer is breast cancer. In another embodiment, the disclosure provides a method of treating or lessening the severity of an immune-related disease relating to aberrant immune cell response in a subject comprising modulating the expression and/or activity of TIGIT in the subject. In one aspect, there is provided use of the TLP-interacting agent described herein in the manufacture of a medicament for treating or lessening the severity of an immune-related disease relating to aberrant immune cell response in a subject in need thereof, wherein the immune-related disease is selected from the group consisting of psoriasis, arthritis, inflammatory bowel disease, and cancer. In one embodiment, the immune-related disease is selected from psoriasis, arthritis, inflammatory bowel disease or cancer. In another embodiment, the cancer is breast cancer. In one aspect, there is provided use of the TLP-interacting agent described herein in the manufacture of a medicament for treating or lessening the severity of a cancer a subject in need thereof.

In another aspect, there is provided a method of detecting the presence or expression level of TIGIT in a sample from a subject comprising contacting the sample with the TLP-interacting agent described herein and detecting the presence of the bound TLP-interacting agent.

In yet another aspect, there is provided an article of manufacture suitable for use in the diagnosis or treatment of an immune-related disease in a subject, wherein the article of manufacture comprises the TLP-interacting agent described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts an alignment of human, mouse, rhesus and dog TIGIT protein sequences. Shading indicates positions containing identical amino acids in three or four species. The signal sequence is indicated by a dashed line, the immunoglobulin V-set domain is indicated by a double line, N-glycosylation sites are indicated by a thin line above the requisite position, the transmembrane domain is indicated by a thick line, and the putative extended ITIM motif is indicated by a double dashed line. Human TIGIT shares 88%, 67%, and 58% identity with rhesus, dog and mouse sequences, respectively.

Figures 2A and 2B depict an alignment of protein sequences of IgV domains of the indicated PVR family proteins. Side chains that share similarity across sequences are marked according to property. V-frame fingerprint residues (black circle) and PVR-related fingerprint residues (thick line boxed residues) are indicated. For comparative purposes, six IgV domain sequences (set forth under the horizontal line) from non-PVR family members are also aligned.

What is claimed:

1. An isolated TIGIT-like protein (TLP)-interacting agent that specifically interacts with one or more of the following structural submotifs:

(a) V/I^{54}- S/T^{55}-Q^{56};

(b) A^{67}- X^{68}- X^{69}-X^{71}-X^{72}-X^{73}-G^{74}, herein X is any amino acid; and/or

(c) T^{112}-F/Y^{113}-P^{114}-X^{115}-G^{116}, wherein X is any amino acid,

wherein the TLP-interacting agent is an antagonizing antibody, or antigen-binding fragment thereof, that antagonizes the activity of TIGIT and/or PVR and is capable of binding to mouse TIGIT and human TIGIT.

2. The TLP-interacting agent of claim 1, wherein the antagonizing antibody or antigen-binding fragment thereof is selected from the group consisting of a humanized antibody, a chimeric antibody, a bispecific antibody, a heteroconjugate antibody, and an immunotoxin.

3. The TLP-interacting agent of claim 1 or 2, wherein the antagonist specifically binds TIGIT and blocks TIGIT interaction with PVR.

4. The TLP-interacting agent of claim 3, wherein the antagonist inhibits intracellular signaling mediated by TIGIT binding to PVR.

5. Use of the TLP-interacting agent of any one of claims 1-4 in the manufacture of a medicament for increasing or stimulating proliferation of one or more immune cells or proinflammatory cytokine release by one or more immune cells in a subject in need thereof.

6. Use of the TLP-interacting agent of any one of claims 1-4 in the manufacture of a medicament for stimulating an immune response in a subject having cancer.

7. A method of modulating the type and/or amount of cytokine production from an immune cell by administering in vitro the TLP-interacting agent of any one of claims 1-4.

8. The method of claim 7, wherein proinflammatory cytokine production is stimulated and/or increased by the TLP-interacting agent.

9. A method of detecting the presence or expression level of TIGIT in a sample from a subject comprising contacting the sample with the TLP-interacting agent of any one of claims 1-4 and detecting the presence of the bound TLP-interacting agent.

10. Use of the TLP-interacting agent of any one of claims 1-4 in the manufacture of a medicament for preventing an immune-related disease relating to aberrant immune cell response in a subject in need thereof, wherein the immune-related disease is selected from the group consisting of psoriasis, arthritis, inflammatory bowel disease, and cancer.

11. Use of the TLP-interacting agent of any one of claims 1-4 in the manufacture of a medicament for treating or lessening the severity of an immune-related disease relating to aberrant immune cell response in a subject in need thereof, wherein the immune-related disease is selected from the group consisting of psoriasis, arthritis, inflammatory bowel disease, and cancer.

12. A method of diagnosing an immune-related disease relating to aberrant immune cell response in a subject comprising determining the expression and/or activity of TIGIT in an isolated sample from the subject and comparing the expression and/or activity of TIGIT to a reference amount of TIGIT expression and/or activity or the amount of TIGIT expression and/or activity in an isolated sample from a normal subject, wherein the determining comprises use of the TLP-interacting agent of any one of claims 1-4.

13. A method of assessing the severity of an immune-related disease relating to aberrant immune cell response in a subject comprising determining the expression and/or activity of TIGIT in an isolated sample from the subject and comparing the expression and/or activity of TIGIT to a reference amount of TIGIT expression and/or activity or the amount of TIGIT expression and/or activity in an isolated sample from a normal subject, wherein the determining comprises use of the TLP-interacting agent of any one of claims 1-4.

14. An article of manufacture suitable for use in the diagnosis or treatment of an immune-related disease in a subject, wherein the article of manufacture comprises the TLP-interacting agent of any one of claims 1-4.

15. The article of manufacture of claim 14, wherein the article of manufacture further comprises an instruction or a label for using the TLP-interacting agent to detect TIGIT in a sample from a subject.

16. The method of claim 12 or 13, or the article of manufacture of claim 14 or 15, wherein the immune-related disease is selected from the group consisting of psoriasis, arthritis, inflammatory bowel disease, and cancer.

17. Use of the TLP-interacting agent of any one of claims 1-4 in the manufacture of a medicament for treating or lessening the severity of a cancer a subject in need thereof.

18. A method of diagnosing a cancer in a subject comprising determining the expression and/or activity of TIGIT in an isolated sample from the subject and comparing the expression and/or activity of TIGIT to a reference amount of TIGIT expression and/or activity or the amount of TIGIT expression and/or activity in an isolated sample from a normal subject, wherein the determining comprises use of the TLP-interacting agent of any one of claims 1-4.

19. A method of assessing the severity of a cancer in a subject comprising determining the expression and/or activity of TIGIT in an isolated sample from the subject and comparing the expression and/or activity of TIGIT to a reference amount of TIGIT expression and/or activity or the amount of TIGIT expression and/or activity in an isolated sample from a normal subject, wherein the determining comprises use of the TLP-interacting agent of any one of claims 1-4.