

homodimerization. (Blake et al., S, *Clin Cancer Res*; 2016; 22(21): 5182-5188; Johnston et al., *Cancer Cell* 2014; 26: 923–937; Mahnke et al, *Journal of Investigative Dermatology* 2016; 136: 9-11).

Anti-TIGIT antibodies are known in the art, including those which are disclosed
5 in US 2016/0355589, US 2017/143825 , US 2017/088613, US 2016/376365, US
2018/169238, US 2016/176963 , and US 2019/100591. However, no anti-human TIGIT
antibody has received regulatory approval for therapeutic use in humans, alone or in
combination with an anti-human PD-L1 or an anti-human PD-1 antibody. Furthermore,
no bispecific antibody targeting TIGIT and PD-1 or TIGIT and PD-L1 has received
10 regulatory approval for therapeutic use in humans. Thus, there exists a need for additional
treatments that target immune checkpoint pathways.

Summary

In a first aspect, the present disclosure refers to a polypeptide molecule that binds
to human TIGIT (SEQ ID NO:31), comprising the amino acid sequences of SEQ ID
15 NOS:1-6.

In another aspect, the present disclosure refers to a mammalian cell capable of
expressing the polypeptide molecule disclosed herein.

In yet another aspect, the present disclosure refers to a DNA molecule comprising
a polynucleotide encoding one or more of the amino acid sequences of SEQ ID NO:21,
20 SEQ ID NO: 22, SEQ ID NO: 23 and SEQ ID NO: 24.

In a further aspect, the present disclosure refers to a mammalian cell comprising
the DNA molecule of disclosed herein.

In another aspect, the present disclosure refers to a process for producing an
antibody, comprising cultivating the mammalian cell disclosed herein, and recovering the
25 polypeptide molecule.

In yet another aspect, the present disclosure refers to the polypeptide molecule
produced by the method disclosed herein.

In a further aspect, the present disclosure refers to a pharmaceutical composition
comprising the polypeptide molecule disclosed herein, and an acceptable carrier, diluent,
30 or excipient.

In another aspect, the present disclosure refers to the polypeptide molecule disclosed herein, for use in therapy.

In a further aspect, the present disclosure refers to a use of the polypeptide molecule disclosed herein, in the manufacture of a medicament for treating a solid tumor
5 cancer.

Description

Accordingly, the present invention is directed to novel anti-human TIGIT antibodies and novel anti-human TIGIT/anti-human PD-1 bispecific antibodies. Furthermore, unlike other anti-human TIGIT antibodies, the antibodies of the present
10 invention are effector function null, i.e., are engineered to minimize Fc receptor binding. Thus, unlike other anti-human TIGIT antibodies, the antibodies of the present invention do not contain a native human IgG1 framework that can contribute to T regulatory cell depletion and immune response adverse events. In addition, the anti-human TIGIT/anti-
15 human PD-1 bispecific antibodies of the present invention contain different types of light chains, wherein the anti-human TIGIT arm light chain is a kappa light chain, and the anti-human PD-1 light chain is a lambda light chain, which facilitates heteromab bispecific antibody formation by decreasing the potential for light chain-light chain dimerization.

The preparation of bispecific molecules is generally known to be an unpredictable endeavor. For example, coexpressing two heavy chains and two light chains to generate
20 an IgG bispecific antibody can result in some missassembly and unwanted byproducts, ameheterodimeric interactions within antibody Fabs (Lewis SM *et al.*, *Nature Biotechnology* 2014; 32: 191-202; Leaver-Fay A, *et al.*, *Structure* 2016; 24: 641-651). Thus, the present invention provides an anti-human TIGIT/anti-human PD-1 bispecific molecule that minimized Fc receptor binding, minimizes oxidation, facilitates heteromab
25 assembly, and is cross-reactive with human TIGIT/PD-1 and cynomolgous TIGIT/PD-1, and exhibits *in vivo* efficacy in an established tumor model.

WE CLAIM:

1. A polypeptide molecule that binds to human TIGIT (SEQ ID NO:31), comprising the amino acid sequences of SEQ ID NOS:1-6.
- 5 2. The polypeptide molecule of Claim 1, further comprising the amino acid sequences of SEQ ID NOS: 7-12, wherein the polypeptide molecule also binds to human PD-1 (SEQ ID NO: 29).
3. The polypeptide molecule of Claim 1 or Claim 2, wherein the polypeptide molecule is an scFv molecule.
- 10 4. The polypeptide molecule of Claim 3, wherein the scFv molecule is a polyspecific scFv molecule.
5. The polypeptide molecule of Claim 4, wherein the polyspecific scFv molecule is a bispecific scFv molecule.
6. The polypeptide molecule of Claim 1, wherein the polypeptide molecule is an antibody, or a TIGIT-binding fragment thereof.
- 15 7. The polypeptide molecule of Claim 6, wherein the polypeptide molecule is an antibody.
8. The polypeptide molecule of Claim 7, wherein the antibody is a mono-specific antibody.
- 20 9. The polypeptide molecule of Claim 7, wherein the polypeptide molecule is a polyspecific antibody.
10. The polypeptide molecule of Claim 9, wherein the polypeptide molecule is a bispecific antibody.
11. The polypeptide molecule of any one of Claims 6-10, wherein the polypeptide molecule is an antibody or a TIGIT-binding fragment thereof comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO: 13 and a light chain variable region having the amino acid sequence of SEQ ID NO: 14.
- 25 12. The polypeptide molecule of any one of Claims 6-11, wherein the polypeptide molecule is an antibody comprising a heavy chain having the amino acid sequence of SEQ ID NO: 21 and a light chain having the amino acid sequence of SEQ ID NO: 22.
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13. The polypeptide molecule of any one of Claims 6-12, wherein the antibody or TIGIT-binding fragment thereof also binds to human PD-1 (SEQ ID NO: 29) and further comprises the amino acid sequences of SEQ ID NOS: 7-12.
14. The polypeptide molecule of claim 13, wherein the polypeptide molecule is an antibody, or a human TIGIT and human PD-1 binding fragment thereof, comprising:
- a) a first heavy chain variable region having the amino acid sequence of SEQ ID NO: 13;
 - b) a first light chain variable region having the amino acid sequence of SEQ ID NO: 14;
 - c) a second heavy chain variable region having the amino acid sequence of SEQ ID NO: 17; and
 - d) a second light chain variable region having the amino acid sequence of SEQ ID NO: 18.
15. The polypeptide molecule of claim 14, wherein the polypeptide molecule is an antibody comprising:
- a) a first heavy chain having the amino acid sequence of SEQ ID NO:21;
 - b) a first light chain having the amino acid sequence of SEQ ID NO:22;
 - c) a second heavy chain having the amino acid sequence of SEQ ID NO:23; and
 - d) a second light chain having the amino acid sequence of SEQ ID NO:24.
16. A mammalian cell capable of expressing the polypeptide molecule of any one of claims 1-15.
17. A DNA molecule comprising a polynucleotide encoding one or more of the amino acid sequences of SEQ ID NO:21, SEQ ID NO: 22, SEQ ID NO: 23 and SEQ ID NO: 24.
18. The DNA molecule of claim 17, wherein the polynucleotide comprises one or more of the DNA sequences of SEQ ID NO:25, SEQ ID NO: 26, SEQ ID NO: 27 and SEQ ID NO: 28.
19. A mammalian cell comprising the DNA molecule of Claim 17 or claim 18.
20. A process for producing an antibody, comprising cultivating the mammalian cell of Claim 16 or Claim 18, and recovering the polypeptide molecule.

21. The polypeptide molecule produced by the method of Claim 20.
22. A pharmaceutical composition comprising the polypeptide molecule of any one of Claims 1-15 or 21, and an acceptable carrier, diluent, or excipient.
23. The polypeptide molecule of any one of Claims 1-15 or 21, for use in therapy.
- 5 24. The polypeptide molecule for use of Claim 23, for use in treating a solid tumor cancer.
25. The polypeptide molecule for use of Claim 24, wherein the solid tumor cancer is lung cancer, breast cancer, head and neck cancer, melanoma, liver cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, prostate cancer, ovarian cancer, endometrial cancer, or hepatocellular carcinoma.
- 10 26. The polypeptide molecule for use of Claim 25, wherein the lung cancer is non-small cell lung cancer.
27. The polypeptide molecule for use of Claim 25, wherein the lung cancer is small cell lung cancer.
- 15 28. The polypeptide molecule for use of Claim 25, wherein the breast cancer is triple-negative breast cancer.
29. The polypeptide molecule for use of any one of Claims 23-28, wherein the polypeptide molecule is administered in simultaneous, separate, or sequential combination with ionizing radiation.
- 20 30. The polypeptide molecule for use of any one of Claims 23-29, wherein the polypeptide molecule is administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.
31. Use of the polypeptide molecule of any one of Claims 1-15 or 21, in the manufacture of a medicament for treating a solid tumor cancer.
- 25 32. The use of Claim 31, wherein the cancer is lung cancer, breast cancer, head and neck cancer, melanoma, liver cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, prostate cancer, ovarian cancer, endometrial cancer, or hepatocellular carcinoma.
33. The use of Claim 32, wherein the lung cancer is non-small cell lung cancer.
- 30 34. The use of Claim 32, wherein the lung cancer is small cell lung cancer.
35. The use of Claim 32, wherein the breast cancer is triple negative breast cancer.

36. The use of any one of Claims 31-35, wherein the polypeptide molecule is administered in simultaneous, separate, or sequential combination with ionizing radiation.
- 5 37. The use of any one of Claims 31-36, wherein the polypeptide molecule is administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.