

Exhausted T cells often co-express negative regulatory receptors such as PD1 and LAG3.

Despite encouraging clinical results of PD1 antagonistic monoclonal antibodies nivolumab and pembrolizumab, up to 70% of treated patients do not respond to treatment. Preclinical data with patient-derived T cells as well as from syngeneic tumor mouse models have demonstrated that tumor-derived T cells frequently express other inhibitory receptors in addition to PD1. Combined neutralization of PD1 and LAG3 using antagonistic monoclonal antibody molecules increased reactivation of T cells and improved tumor rejection compared to PD1 neutralization alone, in *in vitro* and *in vivo* models. Based on these results, it is expected that neutralization of LAG3 will enhance the efficacy of antagonistic PD1 mAbs.

However, existing anti-PD1 antibody molecules suffer from problems associated with the failure of a large proportion of patients to respond to treatment. There is therefore a need to identify more efficacious PD1 antagonistic monoclonal antibodies with manageable side effect profiles when compared to the prior art existing antibody medicaments when used alone or in combination with other therapeutic molecules, particularly additional antagonistic molecules to further T-cell checkpoint inhibitors.

From this background, the inventors sought to generate further anti-PD1 and anti-LAG3 antibodies having improved therapeutic profile over the known molecules.

BRIEF SUMMARY

There are provided anti-PD1 antibody molecules. As described further herein, the anti-PD1 antibody molecules of the present disclosure have surprising and advantageous properties over other anti-PD1 antibodies. In particular, they demonstrate improved activation of T cells and longer terminal half-life than reference anti-PD1 antibody molecules. As will be

appreciated, such properties are desirable for anti-PD1 antibody molecules for use in treating cancers.

5 Nucleic acid molecules encoding the anti-PD1 antibody molecules, expression vectors, host cells and methods of making the anti-PD1 antibody molecules of the disclosure are also provided. Pharmaceutical compositions comprising the anti-PD1 antibody molecules of the disclosure are also provided. The anti-PD-1 antibody molecules disclosed herein can be used to treat cancerous disorders, including solid and soft-tissue tumors.

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More specifically, an anti-PD1 antibody molecule of the disclosure comprises: (a) heavy chain CDRs comprising the amino acid sequence of SEQ ID NO:1 (hcCDR1), SEQ ID NO:2 (hcCDR2) and SEQ ID NO:3 (hcCDR3) and has light chain CDRs comprising the amino acid sequence of SEQ ID NO:4 (lcCDR1),
15 SEQ ID NO:5 (lcCDR2) and SEQ ID NO:6 (lcCDR3); or, b) heavy chain CDRs comprising the amino acid sequence of SEQ ID NO:7 (hcCDR1), SEQ ID NO:8 (hcCDR2) and SEQ ID NO:9 (hcCDR3) and has light chain CDRs comprising the amino acid sequence of SEQ ID NO:10 (lcCDR1), SEQ ID NO:11 (lcCDR2) and SEQ ID NO:12 (lcCDR3); or (c) heavy chain CDRs comprising the amino acid
20 sequence of SEQ ID NO:13 (hcCDR1), SEQ ID NO:14 (hcCDR2) and SEQ ID NO:15 (hcCDR3) and has light chain CDRs comprising the amino acid sequence of SEQ ID NO:16 (lcCDR1), SEQ ID NO:17 (lcCDR2) and SEQ ID NO:18 (lcCDR3).

In one aspect, there is provided an anti-PD1 antibody molecule comprising:

(a) a heavy chain variable region having three CDRs comprising the amino acid sequence of SEQ ID NO:1 (hcCDR1), SEQ ID NO:2 (hcCDR2) and SEQ ID NO:3 (hcCDR3) and a light chain variable region having three light chain CDRs

5 comprising the amino acid sequence of SEQ ID NO:4 (lcCDR1), SEQ ID NO:5 (lcCDR2) and SEQ ID NO:6 (lcCDR3); or,

(b) a heavy chain variable region having three CDRs comprising the amino acid sequence of SEQ ID NO:7 (hcCDR1), SEQ ID NO:8 (hcCDR2) and SEQ ID NO:9 (hcCDR3) and a light chain variable region having three light chain CDRs

10 comprising the amino acid sequence of SEQ ID NO:10 (lcCDR1), SEQ ID NO:11 (lcCDR2) and SEQ ID NO:12 (lcCDR3); or,

(c) a heavy chain variable region having three CDRs comprising the amino acid sequence of SEQ ID NO:13 (hcCDR1), SEQ ID NO:14 (hcCDR2) and SEQ ID NO:15 (hcCDR3) and a light chain variable region having three light chain CDRs

15 comprising the amino acid sequence of SEQ ID NO:16 (lcCDR1), SEQ ID NO:17 (lcCDR2) and SEQ ID NO:18 (lcCDR3).

In another aspect, there is provided an isolated nucleic acid molecule encoding a heavy chain of an antibody molecule as defined herein, and a light chain of an antibody molecule as defined herein.

20 In another aspect, there is provided an expression vector containing a nucleic acid molecule encoding a heavy chain of an antibody molecule as defined herein, and a light chain of an antibody molecule as defined herein.

25 In another aspect, there is provided a host cell having an expression vector encoding a heavy chain of an antibody molecule as defined herein, and an expression vector encoding a light chain of an antibody molecule as defined herein.

30 In another aspect, there is provided the anti-PD1 antibody molecule as defined herein for use in medicine.

In another aspect, there is provided the anti-PD1 antibody molecule as defined herein for use in treating cancer.

5 In another aspect, there is provided the anti-PD1 antibody molecule as defined herein for use in treating cancer, wherein the use further comprises an anti-LAG3 antibody molecule to be administered.

10 In another aspect, there is provided a pharmaceutical composition comprising an anti-PD1 antibody as defined herein and a pharmaceutically acceptable carrier.

In another aspect, there is provided a kit of parts comprising an anti-PD1 antibody as defined herein and an anti-LAG3 antibody molecule.

15 In another aspect, there is provided use of the anti-PD1 antibody molecule as defined herein in preparing a pharmaceutical composition for treating cancer.

There is also provided anti-LAG3 antibody molecules. As described further herein, the anti-LAG3 antibody molecules of the present disclosure have surprising and advantageous properties over other anti-LAG3 antibody molecules.

20 In particular, they demonstrate improved activation of T cells when used in combination with the anti-PD1 antibody molecules of the present disclosure than reference anti-PD1 antibody molecules and anti-LAG3 antibody molecules. As will be appreciated, such

properties are desirable for anti-LAG3 antibody molecules for use in treating cancers.

5 Nucleic acid molecules encoding the antibody molecules, expression vectors, host cells and methods of making the anti-LAG3 antibody molecules are also provided. Pharmaceutical compositions comprising the anti-LAG3 antibody molecules of the disclosure are also provided. The anti-LAG3 antibody molecules disclosed herein can be used to treat cancerous disorders, including solid and soft-tissue tumors.

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According to a preferred example, an anti-LAG3 antibody molecule of the disclosure bind an epitope of human LAG3 comprising the amino acid sequence LLRRAGVT (SEQ ID NO: 111) and/or YRAAVHLRDRA (SEQ ID NO: 112). Methods of determining the epitope to which an antibody binds are provided
15 herein.

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According to a preferred example, the anti-LAG3 antibody molecule of the disclosure comprises (a) heavy chain CDRs comprising the amino acid sequence of SEQ ID NO:39 (hcCDR1), SEQ ID NO:40 (hcCDR2) and SEQ ID NO:41
20 (hcCDR3) and has light chain CDRs comprising the amino acid sequence of SEQ ID NO:42 (lcCDR1), SEQ ID NO:43 (lcCDR2) and SEQ ID NO:44 (lcCDR3); or (b) heavy chain CDRs comprising the amino acid sequence of SEQ ID NO:45 (hcCDR1), SEQ ID NO:46 (hcCDR2) and SEQ ID NO:47 (hcCDR3) and has light chain CDRs comprising the amino acid sequence of SEQ ID NO:48 (lcCDR1),
25 SEQ ID NO:49 (lcCDR2) and SEQ ID NO:50 (lcCDR3).

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There is also provided methods for the treatment of cancers in which anti-PD1 antibody molecules of the disclosure may be used in combination with the anti-LAG3 antibody molecules of the disclosure. Examples of the disclosure include
30 where the anti-LAG3 antibody is to be administered simultaneously, concurrently, sequentially, successively, alternatively or separately, with the anti-PD1 antibody molecules.

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Further examples of the disclosure include where the anti-PD1 antibody molecules is to be administered simultaneously, concurrently, sequentially, successively, alternatively or separately, with the anti-LAG3 antibody molecules. Further examples of the disclosure include where said uses of the antibody molecules of the disclosure can be combined with other therapeutic agents.

Further aspects, embodiments, examples, uses and methods involving the antibody molecules of the disclosure will become clear from the following detailed description of the disclosure and from the appended claims.

The disclosure provides for novel antibody molecules that allow a more efficient treatment of several cancer types, such as lung cancer, particularly NSCLC.

Figure Legends

Figure 1: Amino acid sequences of the variable domain of anti-PD1 antibody molecules. 77E11 is the name of the murine progenitor antibody. PD1-1, PD1-2, PD1-3, PD1-4 and PD1-5 are anti-PD1 antibodies as defined herein. The CDR sequences are underlined. VK 77E11 (SEQ ID NO: 113); VK PD1-1 (SEQ ID NO: 20); VK PD1-2; (SEQ ID NO: 22); VK PD1-3 (SEQ ID NO: 24); VK PD1-4, (SEQ ID NO: 26); VK PD1-5 (SEQ ID NO: 28); VH 77E11 (SEQ ID NO: 114); VH PD1-1 (SEQ ID NO: 19); VH PD1-2; (SEQ ID NO: 21); VH PD1-3 (SEQ ID NO: 23); VH PD1-4, (SEQ ID NO: 25); VH PD1-5 (SEQ ID NO: 27).

Figure 2: Inhibition of human PD1-L1/L2 binding to PD1 by anti-PD1 antibody molecules. (A) Shows anti-PD1 antibodies of the invention induced blockade of PD-L1 binding to human PD-1 expressed on the surface of CHO cells. (B) Shows anti-PD1 antibodies of the invention induced blockade of PD-L2 binding to human PD-1 expressed on the surface of CHO cells.

CLAIMS

1. An anti-PD1 antibody molecule comprising:

- 5 (a) a heavy chain variable region having three CDRs comprising the amino acid sequence of SEQ ID NO:1 (hcCDR1), SEQ ID NO:2 (hcCDR2) and SEQ ID NO:3 (hcCDR3) and a light chain variable region having three light chain CDRs comprising the amino acid sequence of SEQ ID NO:4 (lcCDR1), SEQ ID NO:5 (lcCDR2) and SEQ ID NO:6 (lcCDR3); or,
- 10 (b) a heavy chain variable region having three CDRs comprising the amino acid sequence of SEQ ID NO:7 (hcCDR1), SEQ ID NO:8 (hcCDR2) and SEQ ID NO:9 (hcCDR3) and a light chain variable region having three light chain CDRs comprising the amino acid sequence of SEQ ID NO:10 (lcCDR1), SEQ ID NO:11 (lcCDR2) and SEQ ID NO:12 (lcCDR3); or,
- 15 (c) a heavy chain variable region having three CDRs comprising the amino acid sequence of SEQ ID NO:13 (hcCDR1), SEQ ID NO:14 (hcCDR2) and SEQ ID NO:15 (hcCDR3) and a light chain variable region having three light chain CDRs comprising the amino acid sequence of SEQ ID NO:16 (lcCDR1), SEQ ID NO:17 (lcCDR2) and SEQ ID NO:18 (lcCDR3).

20 2. The anti-PD1 antibody molecule of claim 1 wherein said antibody molecule has

- a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 20, or
- 25 a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 21 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 22, or
- a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 23 and a light chain variable domain comprising the amino acid sequence of
- 30 SEQ ID NO: 24, or

a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 25 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 26, or

5 a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 28.

3. The anti-PD1 antibody molecule of any of the previous claims wherein said antibody molecule has

10 a heavy chain comprising the amino acid sequence of SEQ ID NO: 29 and a light chain comprising the amino acid sequence of SEQ ID NO: 30 or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 31 and a light chain comprising the amino acid sequence of SEQ ID NO: 32, or

15 a heavy chain comprising the amino acid sequence of SEQ ID NO: 33 and a light chain comprising the amino acid sequence of SEQ ID NO: 34, or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 35 and a light chain comprising the amino acid sequence of SEQ ID NO: 36, or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 37 and a light chain comprising the amino acid sequence of SEQ ID NO: 38.

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4. An isolated nucleic acid molecule encoding a heavy chain of an antibody molecule of any one of claims 1 to 3, and a light chain of an antibody molecule of any of claims 1 to 3.

25 5. An expression vector containing a nucleic acid molecule encoding a heavy chain of an antibody molecule of any one of claims 1 to 3, and a light chain of an antibody molecule of any one of claims 1 to 3.

6. A host cell having an expression vector encoding a heavy chain of an antibody molecule of any one of claims 1 to 3, and an expression vector encoding
30 a light chain of an antibody molecule of any one of claims 1 to 3.

7. The anti-PD1 antibody molecule of any of claims 1 to 3 for use in medicine.

8. The anti-PD1 antibody molecule of any of claims 1 to 3 for use in treating cancer.

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9. The anti-PD1 antibody molecule of any of claims 1 to 3 for use in treating cancer, wherein the use further comprises an anti-LAG3 antibody molecule to be administered.

10 10. A pharmaceutical composition comprising an anti-PD1 antibody of any of claims 1 to 3 and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10 further comprising an anti-LAG3 antibody molecule.

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12. A kit of parts comprising an anti-PD1 antibody of any of claims 1 to 3 and an anti-LAG3 antibody molecule.

13. The anti-PD1 antibody molecule for use of claim 9, the composition of
20 claim 11 or the kit of claim 12 wherein said anti-LAG3 antibody molecule binds an epitope of human LAG3 comprising the amino acid sequence LLRRAGVT (SEQ ID NO: 111) and/or YRAAVHLRDRA (SEQ ID NO: 112).

14. The anti-PD1 antibody molecule for use according to claim 12, or the
25 composition or kit according to claim 12, wherein said anti-LAG3 antibody molecule comprises:

(a) heavy chain CDRs comprising the amino acid sequence of SEQ ID NO:39 (hcCDR1), SEQ ID NO:40 (hcCDR2) and SEQ ID NO:41 (hcCDR3) and has light chain CDRs comprising the amino acid sequence of SEQ ID NO:42
30 (lcCDR1), SEQ ID NO:43 (lcCDR2) and SEQ ID NO:44 (lcCDR3);or,

(b) heavy chain CDRs comprising the amino acid sequence of SEQ ID NO:45 (hcCDR1), SEQ ID NO:46 (hcCDR2) and SEQ ID NO:47 (hcCDR3) and

has light chain CDRs comprising the amino acid sequence of SEQ ID NO:48 (lcCDR1), SEQ ID NO:49 (lcCDR2) and SEQ ID NO:50 (lcCDR3).

15. Use of the anti-PD1 antibody molecule of any of claims 1 to 3 in preparing
5 a pharmaceutical composition for treating cancer.

16. The use of claim 15 further comprising an anti-LAG3 antibody molecule.

17. The anti-PD1 antibody molecule for use of any one of claims 9, 13 or 14 or
10 use of claim 16 wherein the anti-PD1 antibody molecule is to be administered simultaneously, concurrently, sequentially, successively, alternatively or separately, with the anti-LAG3 antibody molecule.

18. The pharmaceutical composition of any one of claims 11, 13 or 14 wherein
15 the anti-PD1 antibody molecule is selected from the group consisting of anti-PD1 antibody molecules PD1-1, PD1-2, PD1-3, PD1-4, and PD1-5, and the anti-LAG3 antibody molecule selected from the group consisting of anti-LAG3 antibody molecules LAG3-1, LAG3-2, LAG3-3, LAG3-4, and LAG3-5.

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