

SUMMARY

The disclosure provides anti-PD1 antibodies and methods of using the same.

The disclosure provides an anti-PD1 antibody, wherein the antibody:

- 5 i) competes for binding to PD-1 with an anti-PD1 antibody comprising the VH and VL of PD1-0103, and/or
- ii) binds to a human and cynomolgus PD-1; and/or
- iii) enhances the interferon-gamma (IFN-gamma) secretion by allogenic stimulated T cells by 85% or more at an antibody concentration of 10µg/ml ; and/ or
- 10 iv) enhances the tumor necrosis factor alpha (TNF alpha) secretion by allogenic stimulated T cells by 200% or more at an antibody concentration of 10µg/ml.

15 The disclosure also provides for an antibody that binds to human PD1, wherein the antibody enhances the interferon-gamma (IFN-gamma) secretion by allogenic stimulated T cells by 85% or more at an antibody concentration of 10µg/ml in a Mixed Lymphocyte Reaction (MLR) assay.

The disclosure also provides for an antibody that binds to human PD1, wherein the antibody enhances the tumor necrosis factor alpha (TNF alpha) secretion by allogenic stimulated T cells by 200% or more at an antibody concentration of 10µg/ml in a Mixed Lymphocyte Reaction (MLR) assay.

- 5 In one aspect, the disclosure provides for an isolated antibody that binds to human PD1, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:71; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:72; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:73; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:74; (e)
10 HVR-L2 comprising the amino acid sequence of SEQ ID NO:75; (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:76, and (g) FR-H3 comprising the amino acid sequence of SEQ ID NO: 77 (of RDN) at positions of 71, 72 and 73 according to Kabat numbering.

15 The disclosure provides an isolated antibody that binds to human PD1, wherein the antibody comprises

- A) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:3; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4; (e) HVR-L2
20 comprising the amino acid sequence of SEQ ID NO:5; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6; or
- B) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:9; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:10; (c) HVR-

In another aspect, the disclosure provides an isolated antibody that binds to human PD1, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:3; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:5; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6.

The disclosure further provides an isolated antibody that binds to human PD1, wherein the antibody comprises

- 10 A) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:3; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:5 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6; or
- 15 B) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:10, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:11; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:12; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:13 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:14; or
- 20 C) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:18, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:19; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:20; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:21 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22; or.
- 25 D) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:25, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:26, and (iii) HVR-H3 comprising an amino acid
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sequence selected from SEQ ID NO:27; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:28; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:29 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30; or

- 5 E) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:33, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:34, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:35; and (b) a VL domain comprising

(i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:36; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:37 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:38; or

- 5 F) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:41, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:42, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:43; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:44; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:45 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:46; or
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- G) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:49, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:50, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:51; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:52; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:53 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:54.
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20 In another aspect, the disclosure provides an isolated antibody that binds to human PD1, wherein the antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:3; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4; (ii) HVR-L2

comprising the amino acid sequence of SEQ ID NO:5 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6.

The disclosure further provides an isolated antibody that binds to human PD1, wherein the antibody

5 A)

- i) comprises a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8;
- ii) or humanized variant of the VH and VL of the antibody under i);

or B)

- 10 i) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58.
- ii) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59.
- 15 iii) comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60.

ii) or humanized variant of the VH and VL of the antibody under i).

In another aspect, the disclosure provides an isolated antibody that binds to human PD1, wherein the antibody comprises

A)

- 5 i) a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8; or
ii) humanized variant of the VH and VL of the antibody under i);

or B)

- i) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58;
ii) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59;
10 iii) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60; or
iv) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:61.

In another aspect, the disclosure provides an isolated antibody that binds to human PD1, wherein the antibody comprises i) a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8; or ii) humanized variant of the VH and VL of the
15 antibody under i).

In another aspect, the disclosure provides an isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58.

In another aspect, the disclosure provides an isolated antibody that binds to human
20 PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59.

In another aspect, the disclosure provides an isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60.

25 In another aspect, the disclosure provides an isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:61.

In one embodiment the anti-PD1 antibody according to the disclosure is a monoclonal antibody.

30 In one embodiment the anti-PD1 antibody according to the disclosure is a human, humanized, or chimeric antibody.

In one embodiment the anti-PD1 antibody according to the disclosure which is an antibody fragment that binds to PD1.

In one embodiment the anti-PD1 antibody according to the disclosure which is Fab fragment.

5 In another aspect, the disclosure provides an isolated nucleic acid encoding the antibody as described herein.

In another aspect, the disclosure provides a host cell comprising such nucleic acid.

10 In another aspect, the disclosure provides a method of producing an antibody comprising culturing the host cell as described herein so that the antibody is produced.

The disclosure provides such method of producing an antibody, further comprising recovering the antibody from the host cell.

In another aspect, the disclosure provides a pharmaceutical formulation comprising the antibody described herein and a pharmaceutically acceptable carrier.

15 In another aspect, the disclosure provides the antibody described herein for use as a medicament.

In another aspect, the disclosure provides the antibody described herein for use in treating cancer.

20 The disclosure provides the use of the antibody described herein in the manufacture of a medicament. In one embodiment the medicament is for treatment of cancer. In another aspect, the disclosure provides use of the antibody as described herein in the manufacture of a medicament for the treatment of cancer.

25 The disclosure provides a method of treating an individual having cancer comprising administering to the individual an effective amount of the antibody described herein.

Patent Claims

1. An isolated antibody that binds to human PD1, wherein the antibody comprises
 - (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:71; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:72; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:73; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:74; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:75; (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:76, and (g) FR-H3 comprising the amino acid sequence of SEQ ID NO: 77 (of RDN) at positions of 71, 72 and 73 according to Kabat numbering.

2. The isolated antibody that binds to human PD1 according to claim 1, wherein the antibody comprises
 - A)
 - i) a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8; or
 - ii) humanized variant of the VH and VL of the antibody under i);
 - or B)
 - i) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58;
 - ii) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59;
 - iii) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60; or
 - iv) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:61.

3. An isolated antibody that binds to human PD1, wherein the antibody comprises
 - (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:3; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:5; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6.

4. An isolated antibody that binds to human PD1, wherein the antibody comprises

- (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:3; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:4; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:5 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:6.
5. An isolated antibody that binds to human PD1, wherein the antibody comprises
- A)
- i) a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8; or
 - ii) humanized variant of the VH and VL of the antibody under i);
- or B)
- i) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58;
 - ii) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59;
 - iii) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60; or
 - iv) a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:61.
6. An isolated antibody that binds to human PD1, wherein the antibody comprises
- i) a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8; or
 - ii) humanized variant of the VH and VL of the antibody under i).
7. An isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:58.
8. An isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:59.
9. An isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:60.

10. An isolated antibody that binds to human PD1, wherein the antibody comprises a VH sequence of SEQ ID NO:57 and a VL sequence of SEQ ID NO:61.
11. The antibody according to any one of the preceding claims, which is a full length IgG1 antibody with mutations L234A, L235A and P329G (numbering according to the EU index of Kabat).
12. Isolated nucleic acid encoding the antibody according to any one of the preceding claims.
13. A host cell comprising the nucleic acid of claim 12.
14. A method of producing an antibody comprising culturing the host cell of claim 13 so that the antibody is produced.
15. The method of claim 14, further comprising recovering the antibody from the host cell.
16. A pharmaceutical formulation comprising the antibody according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.
17. The antibody according to any one of claims 1 to 10 for use as a medicament.
18. The antibody according to any one of claims 1 to 10 for use in treating cancer.
19. Use of the antibody according to any one of claims 1 to 10 in the manufacture of a medicament for the treatment of cancer.