

inflammation. US2012/189617 relates to anti-TIM-3 antibodies which exhibit higher effector activity such as an antibody-dependent cellular cytotoxicity (ADCC activity) for diseases relating to a human TIM-3 expressing cell.

SUMMARY

5 The disclosure provides anti-TIM3 antibodies and methods of using the same.

One aspect of the disclosure is an isolated antibody that binds to TIM3, wherein the antibody:

- 10 • induces internalization of TIM3 (in a FACS assay on TIM3 expressing RPMI8226 cells (ATCC ® CCL-155™)) of at least 45% after 120 Minutes at 37 °C.

In one embodiment, the anti-TIM3 antibody according to the disclosure:

- 15 • competes for binding to TIM3 with an anti-Tim3 antibody comprising the VH of SEQ ID NO:7 and VL of SEQ ID NO: 8
- binds to a human and cynomolgus TIM3
- shows as immunoconjugate a cytotoxic activity on TIM3 expressing cells
- induces interferon-gamma release.

20 In one embodiment the anti-TIM3 antibody according to the disclosure is a monoclonal antibody.

In one embodiment the anti-TIM3 antibody according to the disclosure is a human, humanized, or chimeric antibody.

25 In one embodiment the anti-TIM3 antibody according to the disclosure is an antibody fragment that binds to TIM3.

In one embodiment the anti-TIM3 antibody according to the disclosure which is Fab fragment.

In one embodiment the anti-TIM3 antibody according to the disclosure comprises

- 5 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
- 10 B) (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:11; (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 C) (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:12; (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
- 20 D) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:13, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:14, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:15; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:16; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:17 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:18; or
- 25 E) (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:21, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:22, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:23; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:24; (ii) HVR-L2
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comprising the amino acid sequence of SEQ ID NO:64; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:65 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:66;

5 The disclosure, in another aspect, provides an isolated antibody that binds to human TIM3, 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
10 ID NO:12; (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 TIM3, wherein the antibody comprises wherein the antibody comprises

- 15 i) a VH sequence of SEQ ID NO:79 and a VL sequence of SEQ ID NO:80, or
ii) a VH sequence of SEQ ID NO:81 and a VL sequence of SEQ ID NO:82.

The disclosure, in another aspect, provides an isolated antibody that binds to human TIM3, wherein the antibody comprises (a) a VH domain comprising (i)
20 HVR-H1 comprising the amino acid sequence of SEQ ID NO:37, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:38, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:39; and (b) a VL domain comprising (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:40; (ii) HVR-L2 comprising the amino acid sequence of SEQ ID
25 NO:41 and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42.

The disclosure further provides an isolated antibody that binds to human TIM3, wherein the antibody comprises

- 30 i) a VH sequence of SEQ ID NO:83 and a VL sequence of SEQ ID NO:84, or
ii) a VH sequence of SEQ ID NO:85 and a VL sequence of SEQ ID NO:86.

In one embodiment the anti-TIM3 antibody according to the disclosure is a full length IgG1 antibody.

5 In one embodiment the anti-TIM3 antibody according to the disclosure is a full length IgG1 antibody with mutations L234A, L235A and P329G (numbering according to the EU index of Kabat).

Another aspect of the disclosure is an isolated nucleic acid encoding the antibody according to the disclosure.

Another aspect of the disclosure is a host cell comprising the nucleic acid according to the disclosure.

10 Another aspect of the disclosure is a method of producing an antibody comprising culturing the host cell according to the disclosure so that the antibody is produced.

Another aspect of the disclosure is an immunoconjugate comprising the antibody according to the disclosure and a cytotoxic agent.

15 In one preferred embodiment of the disclosure is such an immunoconjugate wherein the cytotoxic agent is Pseudomonas Exotoxin A or an Amatoxin.

Another aspect of the disclosure is a pharmaceutical formulation comprising the antibody according to the disclosure or the immunoconjugate according to the disclosure and a pharmaceutically acceptable carrier.

20 Another aspect of the disclosure is an antibody according to the disclosure or an immunoconjugate according to the disclosure for use as a medicament.

Another aspect of the disclosure is an antibody according to the disclosure or the immunoconjugate according to the disclosure for use in treating cancer.

25 Another aspect of the disclosure is the use of an antibody according to the disclosure or the immunoconjugate according to the disclosure for use in the manufacture of a medicament.

The disclosure also relates to the use of an antibody according to the disclosure or the immunoconjugate according to the disclosure for use in the manufacture of a medicament for treatment of cancer.

5 The disclosure also relates to a method of treating an individual having cancer comprising administering to the individual an effective amount of an antibody according to the disclosure or the immunoconjugate according to the disclosure.

The anti-TIM3 antibodies of the present disclosure show highly valuable properties like a rapid and strong internalization on TIM3-expressing cancer cells, a strong

16. The antibody of 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)
- 5 17. Isolated nucleic acid encoding the antibody according to any one of the preceding claims.
18. A host cell comprising the nucleic acid of claim 17.
19. A method of producing an antibody comprising culturing the host cell of claim 18 so that the antibody is produced.
- 10 20. The method of claim 31, further comprising recovering the antibody from the host cell.
21. An immunoconjugate comprising the antibody according any one of claims 1 to 16 and a cytotoxic agent.
22. A pharmaceutical formulation comprising the antibody according any one of claims 1 to 16 or the immunoconjugate of claim 21 and a pharmaceutically acceptable carrier.
- 15 23. The antibody according any one of claims 1 to 16 or the immunoconjugate of claim 21 for use as a medicament.
24. The antibody according any one of claims 1 to 16 or the immunoconjugate of claim 21 for use in treating cancer.
- 20 25. Use of the antibody according any one of claims 1 to 16 or the immunoconjugate of claim 21 for use in the manufacture of a medicament.
26. The use of claim 25, wherein the medicament is for treatment of cancer.