(i.e. reduced deamidation sites) compared to antibody 25F7. Furthermore, LAG3 antibodies are disclosed in WO 2015/138920 (for example BAP050), WO 2014/140180, WO 2015/116539, WO 2016/028672, WO 2016/126858, WO 2016/200782 and WO 2017/015560.

SUMMARY

The disclosure provides anti-LAG3 antibodies and methods of using the same.

The disclosure provides, in one aspect, an isolated antibody that binds to human LAG3, 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 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-H3 comprising the amino acid sequence of SEQ ID NO:11; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:12; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:13; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:14; or

C) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:17; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:18; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:19; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:20; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:21; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:22; or

D) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:25; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:26; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:27; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:28; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:29;

and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:30; or

E) (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:33; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:34; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:35; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:36; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:37; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:38.

The disclosure further provides, in another aspect, an isolated antibody that binds to human LAG3, wherein the antibody comprises

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

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

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:11; 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

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 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

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.

The disclosure further provides, in another aspect, an isolated antibody that binds to human LAG3, wherein the antibody

i) comprises a VH sequence of SEQ ID NO:7 and a VL sequence of SEQ ID NO:8;

ii) comprises a VH sequence of SEQ ID NO:15 and a VL sequence of SEQ ID NO:16;

iii) comprises a VH sequence of SEQ ID NO:23 and a VL sequence of SEQ ID NO:24;

iv) comprises a VH sequence of SEQ ID NO:31 and a VL sequence of SEQ ID NO:32; or

v) comprises a VH sequence of SEQ ID NO:39 and a VL sequence of SEQ ID NO:40.

The disclosure further provides, in another aspect, isolated antibody that binds to human LAG3, wherein the antibody:

i) competes for binding to LAG3 with an anti-LAG3 antibody comprising the VH with the amino acid sequence of SEQ ID NO:7 and VL with the amino acid sequence of SEQ ID NO:8, and/ or

ii) binds to a human and cynomolguoes LAG3; and/ or

iii) inhibits binding of MHC-II expressed on human A375 tumor cells; and/ or

iv) enhances granzyme B or IL-2 release in a mixed lymphocyte reaction (mMLR) assay.

In one example the anti-LAG3 antibody according to the disclosure is a monoclonal antibody.

In one example the anti-LAG3 antibody according to the disclosure is a human, humanized, or chimeric antibody.

In one example the anti-LAG3 antibody according to the disclosure which is an antibody fragment that binds to LAG3.

In one example the anti-LAG3 antibody according to the disclosure which is Fab fragment.

The disclosure provides, in another aspect, an isolated nucleic acid encoding the antibody described herein.

The disclosure provides, in another aspect, a host cell comprising the nucleic acid described herein.

The disclosure provides, in another aspect, a method of producing an antibody comprising culturing the host cell 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.

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

The disclosure provides, in another aspect, the antibody described herein for use as a medicament.

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

The disclosure provides, in another aspect, the use of the antibody described herein in the manufacture of a medicament. In one embodiment the medicament is for treatment of cancer, for treating or delaying progression of an immune related disease such as tumor immunity, or for stimulating an immune response or function, such as T cell activity.

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

The antibodies of the present disclosure show valuable properties the induction of Granzyme B release, IFN-γ release and IL-2 secretion by human CD4 T cells and can therefore stimulate immune response via T cells (enhanced tumor-antigen specific T cell effector functions) either alone or in combination PD1 inhibitors.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Effect of anti-LAG-3 antibodies on on cytotoxic Granzyme B release and IL-2 secretion by human CD4 T cells cocultured with allogeneic mature dendritic cells
Fig 1A: Granzyme B secretion
Fig 1B: IL-2 secretion

Figure 2: Effect of anti-LAG-3 antibodies on cytotoxic Granzyme B release by human CD4 T cells cocultured with a B cell-lymphoblatoid cell line (ARH77).

Figure 3: Effect of anti-LAG-3 antibodies on Treg suppression of Granzyme B and IFN-γ release by human CD4 T cells cocultured with irradiated allogeneic PBMCs.
Fig 3A: Granzyme B release
Fig 3B: IFN-γ release

DETAILED DESCRIPTION OF THE INVENTION

An “acceptor human framework” for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a