

CLAIMS

1. An isolated antibody or antigen-binding fragment thereof that binds specifically to human lymphocyte activation gene 3 (LAG3) protein, wherein (a) the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) with at least 90% identity to SEQ ID NO: 418 and a light chain variable region with at least 90% identity to SEQ ID NO: 426 and/or (b) the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) of SEQ ID NO: 418 with 10 or fewer conservative amino acid substitutions and a light chain variable region (LCVR) of SEQ ID NO: 426 with 10 or fewer conservative amino acid substitutions; wherein the HCVR comprises a heavy chain complementarity determining region (HCDR)1 sequence set forth in SEQ ID NO: 420, an HCDR2 sequence set forth in SEQ ID NO: 422, and an HCDR3 sequence set forth in SEQ ID NO: 424, and wherein the LCVR comprises a light chain complementarity determining region (LCDR)1 sequence set forth in SEQ ID NO: 428, an LCDR2 sequence set forth in SEQ ID NO: 430 and an LCDR3 sequence set forth in SEQ ID NO: 432.
2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein:
 - (a) the HCVR has at least 95% identity to SEQ ID NO: 418 and/or the LCVR has at least 95% identity to SEQ ID NO: 426; or
 - (b) the HCVR has at least 98% identity to SEQ ID NO: 418 and/or the LCVR has at least 98% identity to SEQ ID NO: 426.
3. The isolated antibody or antigen-binding fragment thereof of claim 1, which comprises an HCVR of SEQ ID NO: 418 with eight or fewer, six or fewer, four or fewer or two conservative amino acid substitutions and/or an LCVR of SEQ ID NO: 426 with eight or fewer, six or fewer, four or fewer or two conservative amino acid substitutions.

4. The isolated antibody or antigen-binding fragment thereof of claim 1, which comprises an HCVR of SEQ ID NO: 418 with one addition, deletion or substitution and/or an LCVR of SEQ ID NO: 426 with one addition, deletion or substitution, optionally wherein the substitution(s) are conservative amino acid substitutions.

5. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 – 4, which exhibits biological activity which is essentially equivalent to an antibody comprising an HCVR/LCVR sequence pair of SEQ ID NOs: 418/426.

6. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 – 5, wherein the antibody or antigen-binding fragment thereof has one or more properties selected from the group consisting of:

(a) binds monomeric human LAG3 with a K_D less than 2nM as measured in a surface plasmon resonance assay at 37°C;

(b) binds dimeric human LAG3 with a K_D less than 20pM as measured in a surface plasmon resonance assay at 25°C;

(c) binds dimeric human LAG3 with a K_D less than 90pM as measured in a surface plasmon resonance assay at 37°C;

(d) binds to a hLAG3-expressing cell with an EC_{50} less than 2nM as measured in a flow cytometry assay;

(e) binds to a mLAG3-expressing cell with a EC_{50} less than 2.3nM as measured in a flow cytometry assay;

(f) blocks binding of hLAG3 to human MHC class II with IC_{50} less than 20nM as determined by a cell adherence assay;

- (g) blocks binding of hLAG3 to mouse MHC class II with IC_{50} less than 15nM as determined by a cell adherence assay;
- (h) blocks binding of hLAG3 to MHC class II by more than 90% as determined by a cell adherence assay;
- (i) rescues LAG3-mediated inhibition of T cell activity with EC_{50} less than 2.5nM as determined in a luciferase reporter assay; and
- (j) binds to activated CD4+ and CD8+ T cells with EC_{50} less than 1.2nM, as determined in a fluorescence assay.

7. The isolated antibody antigen-binding fragment thereof of any one of claims 1 – 6, wherein the antibody or antigen-binding fragment thereof comprises an IgG1 or IgG4 isotype.

8. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 – 7, wherein the antibody or antigen-binding fragment thereof is a multi-specific antigen-binding molecule.

9. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1 – 8 and a pharmaceutically acceptable carrier or diluent.

10. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an HCVR and/or an LCVR of the antibody as set forth in any one of claims 1 – 8.

11. A combination of nucleic acid molecules comprising:

(a) a first nucleic acid molecule encoding an HCVR having the amino acid sequence of SEQ ID NO: 418 and a second nucleic acid molecule encoding an LCVR having the amino acid sequence of SEQ ID NO: 426, and/or

(b) a first nucleic acid molecule encoding an antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 577 and a second nucleic acid molecule encoding an antibody light chain comprising the amino acid sequence of SEQ ID NO: 578.

12. A vector comprising the polynucleotide sequence of claim 10, or the combination of nucleic acid molecules of claim 11.

13. A cell expressing the vector of claim 12.

14. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 – 8 in the manufacture of a medicament for inhibiting growth of a tumor or a tumor cell in a subject comprising a therapeutically effective amount of the antibody or antigen-binding fragment thereof to be administered to the subject in need thereof.

15. The use of claim 14, wherein the tumor is a primary or a recurrent tumor.

16. The use of claim 14, wherein the tumor is an established tumor.

17. The use of claim 14, wherein the tumor is present in a subject with a disease or disorder selected from the group consisting of blood cancer, brain cancer, renal cell cancer, ovarian cancer, bladder cancer, prostate cancer, breast cancer, hepatic cell carcinoma, bone cancer,

colon cancer, non-small-cell lung cancer, squamous cell carcinoma of head and neck, colorectal cancer, mesothelioma, B cell lymphoma, and melanoma.

18. The use of claim 14, wherein the antibody or antigen-binding fragment thereof is to be administered as an initial dose followed by one or more secondary doses, wherein each secondary dose is to be administered 1 to 4 weeks after the immediately preceding dose.

19. The use of claim 18, wherein the antibody or antigen-binding fragment thereof is to be administered at a dose of about 1, 3 or 10 mg/kg of body weight of the subject.

20. The use of claim 14, wherein the antibody or antigen-binding fragment thereof is to be administered to the subject in combination with a second therapeutic agent.

21. The use of claim 20, wherein the second therapeutic agent is selected from the group consisting of a CTLA inhibitor, an antibody to a tumor specific antigen, an antibody to a virally-infected-cell antigen, a PD-L1 inhibitor, a CD20 inhibitor, a bispecific antibody against CD20 and CD3, a dietary supplement such as an antioxidant, a VEGF antagonist, a chemotherapeutic agent, a cytotoxic agent, radiation, a NSAID, a corticosteroid, and any other therapy useful for ameliorating at least one symptom associated with the disease or disorder.

22. The use of claim 20, wherein the second therapeutic agent is a PD-1 inhibitor.

23. The use of claim 22, wherein the PD-1 inhibitor is REGN2810, nivolumab or pembrolizumab.

24. The use of claim 23, wherein the PD-1 inhibitor is to be administered at a dose of 1, 3 or 10 mg/kg of the subject's body weight.

25. The use of claim 14, wherein the antibody or antigen-binding fragment thereof is to be administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially.

26. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 – 8 in the manufacture of a medicament for treating a disease or disorder that is treatable by antagonizing LAG3 comprising a therapeutically effective amount of the antibody or antigen-binding fragment thereof to be administered to a subject in need thereof.

27. The use of claim 26, wherein the disease or disorder is a chronic viral infection caused by a virus selected from the group consisting of human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), human papilloma virus (HPV), lymphocytic choriomeningitis virus (LCMV) and simian immunodeficiency virus (SIV).

28. The use of claim 26, wherein the disease or disorder is selected from the group consisting of blood cancer, brain cancer, renal cell cancer, ovarian cancer, bladder cancer, prostate cancer, breast cancer, hepatic cell carcinoma, bone cancer, colon cancer, non-small-cell lung cancer, squamous cell carcinoma of head and neck, colorectal cancer, mesothelioma, B cell lymphoma, and melanoma.

29. A method of producing an anti-LAG-3 antibody or antigen-binding fragment thereof, said method comprising growing the cell set forth in claim 13 under conditions permitting

production of the antibody or fragment thereof, and recovering the antibody or fragment thereof so produced.