

CLAIMS

What is claimed is:

1. An isolated antibody, or antigen-binding fragment thereof, that specifically binds $\alpha v\beta 8$ integrin, wherein the antibody or antigen-binding fragment thereof is at least one antibody or antigen-binding fragment thereof selected from the group consisting of:

(a) an antibody or antigen-binding fragment thereof, comprising a light chain complementarity determining region 1 (CDR-L1) comprising the amino acid sequence of SEQ ID NO:11; a CDR-L2 comprising the amino acid sequence of SEQ ID NO:12; a CDR-L3 comprising the amino acid sequence of SEQ ID NO:13; a heavy chain CDR1 (CDR-H1) comprising the amino acid sequence of SEQ ID NO:8; a CDR-H2 comprising the amino acid sequence of SEQ ID NO:9; and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:10;

(b) an antibody or antigen-binding fragment thereof, comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:17; a CDR-L2 comprising the amino acid sequence of SEQ ID NO:18; a CDR-L3 comprising the amino acid sequence of SEQ ID NO:19; a CDR-H1 comprising the amino acid sequence of SEQ ID NO:14; a CDR-H2 comprising the amino acid sequence of SEQ ID NO:15; and a CDR-H3 comprising the amino acid sequence of SEQ ID NO:16;

(c) an antibody or antigen-binding fragment thereof, comprising a variable light (VL) region comprising an amino acid sequence encoded by the insert of the plasmid deposited with the ATCC and having Accession Number PTA-124918, and a variable heavy (VH) region comprising an amino acid sequence encoded by the insert of the plasmid deposited with the ATCC having Accession Number PTA-124917;

(d) an antibody or antigen-binding fragment thereof, comprising a VL region comprising the amino acid sequence of SEQ ID NO:7, and a VH region comprising the amino acid sequence of SEQ ID NO:6;

(e) an antibody or antigen-binding fragment thereof, comprising a VL region comprising the amino acid sequence selected from the group consisting of SEQ ID NO:62-66, and a VH region comprising the amino acid sequence selected from the group consisting of SEQ ID NO:34-38;

(f) an antibody or antigen-binding fragment thereof, comprising a VL region comprising the amino acid sequence selected from the group consisting of SEQ ID NO:47 and 92, and a VH region comprising the amino acid sequence selected from the group consisting of SEQ ID NO:39 and 88-91;

(g) an antibody or antigen-binding fragment thereof, comprising a VL region comprising the amino acid sequence selected from the group consisting of SEQ ID NO:7 and 67-69, and a VH region comprising the amino acid sequence selected from the group consisting of SEQ ID NO:6 and 93;

(h) an antibody or antigen-binding fragment thereof, comprising a VL region comprising the amino acid sequence selected from the group consisting of SEQ ID NO:7, 47-69 and 92, and a VH region comprising the amino acid sequence selected from the group consisting of SEQ ID NO:6, 34-46, 88-91 and 93;

(i) an antibody or antigen-binding fragment thereof, comprising a light chain (LC) region comprising the amino acid sequence of SEQ ID NO:5, and a heavy chain (HC) region comprising the amino acid sequence of SEQ ID NO:2;

(j) an antibody or antigen-binding fragment thereof, comprising a LC region comprising the amino acid sequence of SEQ ID NO:5, and a HC region comprising the amino acid sequence of SEQ ID NO:3;

(k) an antibody or antigen-binding fragment thereof, comprising a LC region comprising the amino acid sequence of SEQ ID NO:123, and a HC region comprising the amino acid sequence of SEQ ID NO:124 or 182;

(l) an antibody or antigen-binding fragment thereof, comprising a VL region encoded by the nucleic acid sequence of SEQ ID NO:186, and a VH region encoded by the nucleic acid sequence of SEQ ID NO:190; and

(m) an antibody or antigen-binding fragment thereof, comprising a LC region encoded by the nucleic acid sequence of SEQ ID NO:185, and a HC region encoded by the nucleic acid sequence of SEQ ID NO:189 or 191.

2. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a VL region comprising an amino acid sequence at least 95% identical to SEQ ID NO:7, and a VH region comprising an amino acid sequence at least 95% identical to SEQ ID NO:6.
3. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising a LC region comprising an amino acid sequence at least 95% identical to SEQ ID NO:5, and a HC region comprising an amino acid sequence at least 95% identical to SEQ ID NO:2 or 3.
4. An isolated antibody that specifically binds $\alpha v \beta 8$ integrin, comprising a LC consisting of the amino acid sequence of SEQ ID NO:5, and HC consisting of the amino acid sequence of SEQ ID NO:2 or 3.
5. An isolated antibody that specifically binds $\alpha v \beta 8$ integrin, comprising:
 - an antibody VL region comprising the CDR-L1, CDR-L2 and CDR-L3 from the VL region comprising the amino acid sequence of SEQ ID NO:7; and
 - an antibody VH region comprising the CDR-H1, CDR-H2, and CDR-H3 from the VH region comprising the amino acid sequence of SEQ ID NO:6.
6. The isolated antibody of claim 5, comprising an antibody heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 181 or 184 and an antibody light chain constant region comprising the amino acid sequence of SEQ ID NO: 83.
7. An isolated antibody, or antigen-binding fragment thereof, that specifically binds $\alpha v \beta 8$ integrin, comprising an antibody VH comprising the amino acid sequence encoded by the insert deposited with the ATCC and having the Accession Number PTA-124917, and an antibody VL comprising the amino acid sequence encoded by the insert deposited with the ATCC and having the Accession Number PTA-124918.
8. The isolated antibody or antigen-binding fragment thereof, of claim 1, comprising a human IgG1 Fc region comprising one or more substitutions selected from positions L234, L235, and G237, as numbered according to the Eu numbering of Kabat.
9. The isolated antibody or antigen-binding fragment thereof, of claim 1, wherein the antibody is a humanized antibody, a human antibody, a murine antibody, or a chimeric antibody.

10. The isolated antibody or antigen-binding fragment thereof, of claim 1, which comprises a heavy chain isotype selected from IgG1, IgG2, IgG3, IgG4, or any variant thereof; and/or a light chain constant region chosen from kappa or lambda.
11. The isolated antibody or antigen-binding fragment thereof, of claim 1 wherein the antibody heavy chain isotype is IgG1 and/or wherein the light chain constant region is a kappa light chain.
12. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, of claim 1, and a pharmaceutically acceptable carrier or excipient.
13. The pharmaceutical composition of claim 12, comprising i) an antibody or antigen-binding fragment thereof comprising an antibody heavy chain encoded by the amino acid sequence of SEQ ID NO:2 and an antibody light chain encoded by the amino acid sequence of SEQ ID NO:5, ii) an antibody or antigen-binding fragment thereof comprising an antibody heavy chain encoded by the amino acid sequence of SEQ ID NO:3 and an antibody light chain encoded by the amino acid sequence of SEQ ID NO:5, or iii) both i) and ii).
14. A kit comprising the antibody or fragment of claim 1 and optionally comprising a modulator of an immune checkpoint molecule selected from the group consisting of an anti-PD1 antibody, an anti-PD-L1 antibody, an anti-PD-L2 antibody, an anti-CTLA-4 antibody, a soluble CTLA-4 fusion protein and a combination thereof, and wherein the anti-PD-L1 antibody is not avelumab.
15. An isolated nucleic acid molecule that encodes the antibody or antigen-binding fragment thereof of claim 1.
16. The isolated nucleic acid of claim 15, wherein the isolated nucleic acid encodes the VH region, VL region, or both, of the antibody, or antigen-binding fragment thereof, and wherein said nucleic acid comprises: the nucleic acid sequence of SEQ ID NO:190, the nucleic acid sequence of SEQ ID NO:186, or both.
17. The isolated nucleic acid of claim 15, wherein the isolated nucleic acid encodes the heavy chain constant region, the light chain constant region, or both, of the antibody, or antigen-binding fragment thereof, and wherein the nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 192 or 193; the nucleic acid sequence of SEQ ID NO: 194; or both.

18. The isolated nucleic acid of claim 15, wherein the isolated nucleic acid encodes the HC, LC, or both, of the antibody or antigen-binding fragment thereof, and wherein said nucleic acid comprises: the nucleic acid sequence of SEQ ID NO:189 or 190; the nucleic acid sequence of SEQ ID NO185; or both.
19. The isolated nucleic acid of claim 15, wherein the isolated nucleic acid comprises the nucleic acid sequence of the insert of the plasmid deposited with the ATCC and having the Accession Number PTA-124917, the nucleic acid sequence of the insert of the plasmid deposited with the ATCC and having the Accession Number PTA-124918, or both.
20. The isolated nucleic acid of claim 15, wherein the isolated nucleic acid comprises a nucleic acid sequence having at least 80% sequence identity to SEQ ID NO: 185, SEQ ID NO: 189, or SEQ ID NO: 191.
21. A vector comprising the nucleic acid of any of claim 15.
22. A host cell comprising the nucleic acid of any of claim 15.
23. The host cell of claim 22, wherein the host cell is a mammalian cell selected from the group consisting of a CHO cell, a COS cell, a HEK-293 cell, an NS0 cell, a PER.C6® cell, and an Sp2.0 cell.
24. A method of making an isolated antibody, or antigen-binding fragment thereof, comprising culturing the host cell of claim 22, under conditions wherein the antibody or fragment is expressed by the host cell and isolating the antibody or fragment.
25. Use of an isolated antibody, or antigen-binding fragment thereof according to claim 1 in the manufacture of a medicament for treating cancer in a subject.
26. The use according to claim 25, wherein the medicament is to be administered with a cytotoxic agent, a cytostatic agent, a chemotherapeutic agent, a hormone treatment, a vaccine, an immunotherapy, surgery, radiation, cryosurgery, thermotherapy, or a combination thereof.
27. The use according to claim 26, wherein the medicament is to be administered simultaneously, sequential or separate from the administration of the cytotoxic agent, the

cytostatic agent, the chemotherapeutic agent, the hormone treatment, the vaccine, the immunotherapy, the surgery, the radiation, the cryosurgery, the thermotherapy, or the combination thereof.

28. The use according to claim 26, wherein the immunotherapy comprises a modulator of an immune checkpoint molecule selected from the group consisting of an anti-PD1 antibody, an anti-PD-L1 antibody, an anti-PD-L2 antibody, an anti-CTLA-4 antibody, a soluble CTLA-4 fusion protein and a combination thereof, wherein the anti-PD-L1 antibody is not avelumab.

29. The use according to claim 25, wherein the cancer is selected from the group consisting of squamous cell carcinoma of the head and neck, renal cell carcinoma with clear cell or papillary cell type, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, gastric cancer, gastroesophageal junction cancer, oesophageal cancer, lung squamous cell cancer, pancreatic ductal adenocarcinoma, cholangiocarcinoma, uterine cancer, melanoma, urothelial carcinoma and combinations thereof.

30. Use of a therapeutically effective amount of an antibody or antigen-binding fragment thereof according to claim 1 in the manufacture of a medicament for treating cancer in a subject, wherein the medicament is to be administered to the subject in combination with a modulator of PD1, PD-L1 or PD-L2.

31. The use of claim 30, wherein the cancer is squamous cell carcinoma.

32. The use of claim 30, wherein the cancer is breast or colon cancer.

33. The use of claim 30, wherein the modulator is selected from the group consisting of an anti-PD1 antibody, an anti-PD-L1 antibody, and an anti-PD-L2 antibody.