

## CLAIMS

What is claimed is:

1. ~~An isolated antibody, or antigen-binding fragment thereof, that specifically binds  $\alpha\text{v}\beta 8$  integrin, wherein the antibody or fragment is at least one antibody or fragment 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 the amino acid sequence of SEQ ID NO:7, and a VH region comprising the amino acid sequence of SEQ ID NO:6.~~

~~3. The isolated antibody or antigen-binding fragment thereof of claim 1 or 2, 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.~~

~~4. The isolated antibody or antigen-binding fragment thereof of claim 1, 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:2 or 3.~~

~~5. The isolated antibody or antigen-binding fragment thereof of claim 1 or 4, 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.~~

~~6. An isolated antibody, or antigen-binding fragment thereof, that specifically binds  $\alpha v \beta 8$  integrin, wherein the antibody or fragment comprises a VH region comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:6, 34-46, 88-91, and 93, and/or a VL region comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 47-69, and 92.~~

~~7. An isolated antibody, or antigen-binding fragment thereof, that specifically binds  $\alpha v \beta 8$  integrin, wherein the antibody or fragment comprises:~~

~~(i) an antibody HC comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 2 or 3; and/or~~

~~(ii) an antibody LC comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 5.~~

~~8. 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.~~

~~9. 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.~~

~~10. The isolated antibody of claim 9, 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.~~

~~11. An isolated antibody that specifically binds  $\alpha v \beta 8$  integrin, comprising:~~

~~—— a) an antibody VL region comprising the first, second and third CDRs from the VL region comprising the amino acid sequence of SEQ ID NO:7;~~

~~—— an antibody VH region comprising the first, second and third CDRs from the VH region comprising the amino acid sequence of SEQ ID NO:6;~~

~~—— an antibody light chain constant (CL) region comprising the amino acid sequence of SEQ ID NO:83; and~~

~~—— an antibody heavy chain (CH) constant region comprising the amino acid sequence of SEQ ID NO:181 or 184;~~

~~—— b) an antibody VL region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 7; and an antibody VH region comprising an amino acid sequence at least 95% identical to SEQ ID NO:6; or~~

~~—— c) an antibody LC region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 5, and an antibody HC comprising an amino acid sequence at least 95% identical to SEQ ID NO: 2 or 3.~~

~~12. An isolated antibody, or antigen-binding fragment thereof, that specifically binds  $\alpha v \beta 8$  integrin, comprising an antibody VH comprising an amino acid sequence encoded by the insert deposited with the ATCC and having the Accession Number PTA-124917, and an antibody VL comprising an amino acid sequence encoded by the insert deposited with the ATCC and having the Accession Number PTA-124918.~~

~~13. An isolated antibody, or antigen-binding fragment thereof, that specifically binds  $\alpha v \beta 8$  integrin, wherein the antibody or fragment has at least one of the following properties:~~

~~a. a binding affinity, expressed as  $K_D$ , for human  $\alpha v \beta 8$  integrin that is less than the  $K_D$  for the murine antibody ADWA11, e.g., less than about 536 pM;~~

~~b. a  $K_D$  for human  $\alpha v \beta 8$  integrin that is less than or equal to about 100 pM;~~

~~c. a  $K_D$  for mouse  $\alpha v \beta 8$  integrin that is less than the  $K_D$  for the murine antibody ADWA11, e.g., less than about 489 pM;~~

~~d. a  $K_D$  for mouse  $\alpha v \beta 8$  integrin that is less than about 100 pM;~~

~~e. a  $K_D$  for cynomolgus monkey  $\alpha v \beta 8$  integrin that is less than the  $K_D$  for the murine antibody ADWA11, e.g., less than about 507 pM;~~

- ~~f. a KD for cynomolgus monkey  $\alpha\beta 8$  integrin that is less than or equal to about 100 pM;~~
- ~~g. a KD for rat  $\alpha\beta 8$  integrin that is about 160 pM;~~
- ~~h. approximately equivalent affinity for at least two, three, or all of human, cynomolgus, mouse, and rat  $\alpha\beta 8$  integrin, e.g., with a KD that is less than about 100 pM as determined using a Biacore affinity assay;~~
- ~~i. an IC<sub>50</sub> for inhibiting TGF $\beta$  transactivation that is about 100 pM to about 300 pM;~~
- ~~j. an EC<sub>30</sub> for U251 cells of about 100 pM to about 400 pM;~~
- ~~k. an EC<sub>50</sub> for C8-S cells of about 110 pM to about 180 pM; and~~
- ~~l. at least one predicted human pharmacokinetic (PK) parameter selected from:
 
  - ~~i. a clearance from central compartment (CL) of about 0.12 mL/h/kg;~~
  - ~~ii. an inter-compartmental distribution clearance (CLF) of about 0.51 mL/h/kg;~~
  - ~~iii. a volume of distribution for the central compartment (V1) of about 36 mL/kg;~~
  - ~~iv. a volume of distribution for the peripheral compartment (V2) of about 33 mL/kg;~~
  - ~~v. a terminal half-life ( $t_{1/2}$ ) of about 15 to 17 days; and~~
  - ~~vi. no detectable binding to human Fc $\gamma$  receptors or C1q.~~~~

~~14. The isolated antibody or antigen-binding fragment thereof, of any of the preceding claims, comprising a human IgG1 Fc region comprising one or more substitutions selected from positions L234, L235, and G237 (e.g., one or more of L234A, L235A, and G237A), as numbered according to the Eu numbering of Kabat.~~

~~15. The isolated antibody or antigen-binding fragment thereof, of any of the preceding claims, wherein the antibody is a humanized antibody, a human antibody, a murine antibody, chimeric antibody, or a camelid antibody.~~

~~16. The isolated antibody or antigen-binding fragment thereof, of any of the preceding claims, wherein the antibody heavy chain isotype is selected from IgG1, IgG2, IgG3, IgG4, or any variant thereof; and/or wherein the light chain constant region is chosen from kappa or lambda.~~

~~17. The isolated antibody or antigen-binding fragment thereof, of any of the preceding claims, wherein the antibody heavy chain isotype is IgG1 and/or wherein the light chain constant region is a kappa light chain.~~

~~18. An antibody, or antigen-binding fragment thereof, that competes for binding to  $\alpha v \beta 8$  integrin with an antibody, or antigen-binding fragment thereof, of claim 4.~~

~~19. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, of any of the preceding claims, and a pharmaceutically acceptable carrier or excipient.~~

~~20. The pharmaceutical composition of claim 19, 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.~~

~~21. An isolated nucleic acid molecule that encodes the antibody or antigen-binding fragment thereof of any of claims 1-18.~~

~~22. The isolated nucleic acid of claim 21, 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.~~

~~23. The isolated nucleic acid of claim 21, 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.~~

~~24. The isolated nucleic acid of claim 21, 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 NO:185; or both.~~

~~25. The isolated nucleic acid of claim 21, 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.~~

~~26. The isolated nucleic acid of claim 21, wherein the isolated nucleic acid comprises a nucleic acid sequence having at least 80%, 85%, 87%, 90%, 92%, 93%, 95%, 97%, 98%, or 100% sequence identity to SEQ ID NO: 189 or SEQ ID NO: 191; a nucleic acid sequence having at least 80%, 85%, 87%, 90%, 92%, 93%, 95%, 97%, 98%, or 100% sequence identity to SEQ ID NO: 185; or both.~~

~~27. A vector comprising the nucleic acid of any of claims 21-26.~~

~~28. A host cell comprising the nucleic acid of any of claims 21-26 or the vector of claim 27.~~

~~29. The host cell of claim 27, 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.~~

~~30. A method of making an isolated antibody, or antigen-binding fragment thereof, comprising culturing the host cell of claim 28, under conditions wherein the antibody or fragment is expressed by the host cell and isolating the antibody or fragment.~~

~~31. A method of reducing  $\alpha\text{v}\beta 3$  integrin activity in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the antibody, or antigen-binding fragment thereof, of any of claims 1-18, or the pharmaceutical composition of claims 19 or 20.~~

~~32. A method of treating cancer, comprising administering to a subject in need thereof, a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any of claims 1-18, or the pharmaceutical composition of claims 19 or 20.~~

~~33. The method of claim 32, further administration of a cytotoxic agent, a cytostatic agent, a chemotherapeutic agent, a hormone treatment, a vaccine, an immunotherapy, surgery, radiation, cryosurgery, thermotherapy, or a combination thereof.~~

~~34. The method of claim 33, wherein the further administration is simultaneous, sequential or separate from the administration of the therapeutically effective amount of the antibody, or antigen-binding fragment thereof, or the pharmaceutical combination.~~

~~35. The method of claim 33, 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, and wherein the anti-PD-L1 antibody is not avelumab.~~

~~36. The method of any one of claims 32-35, 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, esophageal cancer, lung squamous cell cancer, pancreatic ductal adenocarcinoma, cholangiocarcinoma, uterine cancer, melanoma, urothelial carcinoma and combinations thereof.~~

~~37. A method of detecting  $\alpha v \beta 8$  integrin in a sample, tissue or cell using the antibody, or antigen-binding fragment thereof, of claims 1-18, comprising contacting the sample, tissue or cell with the antibody, or antigen-binding fragment thereof, and detecting the antibody, or antigen-binding fragment thereof.~~

~~38. A kit comprising the antibody or fragment of any of claims 1-18, or the pharmaceutical composition of claims 19 or 20 and optionally comprising the modulator of claim 35.~~

~~39. The antibody or antigen-binding fragment thereof according to any of claims 1-18, or the pharmaceutical composition of claims 19 or 20 for use in reducing  $\alpha v \beta 8$  integrin activity in a subject in need thereof, for treatment of cancer.~~

~~40. The antibody, or antigen-binding fragment thereof, of any of claims 1-18, or the pharmaceutical composition of claims 19 or 20 for use in treating cancer, optionally wherein the antibody, or antigen-binding fragment thereof, or the pharmaceutical composition is for administration simultaneously, sequentially or separately in combination with immunotherapy wherein the combination optionally provides a synergistic therapeutic effect.~~

~~41. The antibody or antigen-binding fragment thereof, or the pharmaceutical composition for use according to claim 40, 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, esophageal cancer, lung squamous cell cancer, pancreatic ductal adenocarcinoma, cholangiocarcinoma, uterine cancer, melanoma, urothelial carcinoma and combinations thereof, optionally wherein the antibody, or antigen-binding fragment thereof, or the pharmaceutical composition or combination are for use together with administration of immunotherapy or radiation therapy.~~

~~42. Use of an antibody, or antigen-binding fragment thereof, of any one of claims 1-18, or the pharmaceutical composition of claims 19 or 20 for treating cancer.~~

~~43. Use of an antibody, or antigen-binding fragment thereof, of any one of claims 1-18 in the manufacture of a medicament for treating cancer.~~

~~44. — A method of treating cancer, comprising administering to a subject in need thereof, a therapeutically effective amount of (i) an antibody or antigen-binding fragment thereof that specifically binds  $\alpha v \beta 8$  integrin and (ii) a modulator of an anti-PD1, anti-PD-L1 or anti-PD-L2 immune checkpoint molecule.~~

~~45. — The method of claim 44, wherein the cancer is a squamous cell carcinoma.~~

~~46. — The method of claim 44, wherein the cancer is breast or colon cancer.~~

~~47. — The method of claim 44, 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.~~

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  $\alpha\text{v}\beta 8$  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 NO:185; 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 of 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, cholangiocarcacinoma, 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.