NOVEL ANTI- α5β1 ANTIBODIES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[00001] This application claims the benefit of U.S. Provisional Patent Application No. 61/ 163241, filed March 25, 2009, the disclosure of which is incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[00002] The present invention relates to novel $\alpha_5\beta_1$ antibodies, compositions and kits comprising the antibodies and methods for using the antibodies.

BACKGROUND OF THE INVENTION

[00003] α5β1 integrin is a cell membrane glycoprotein that mediates cell-ECM interactions through its major ligand, fibronectin. α5β1 integrin plays a role in cell migration, differentiation and survivial. Levels of α5β1 integrin are elevated in tumor vascular endothelium (*e.g.*, gastric, colorectal hepatocellular, uterocervial, and breast carcinomas) and other angiogenic vessels. α5β1 integrin modulates mural cell association with endothelial cells and the assembly of the endothelial extracellular matrix during angiogenesis. As such, α5β1 integrin is a useful target for inhibition of angiogenesis and sensitization of cells to the effects of a VEGF antagonist.

[00004] Thus, there is a need in the art for compositions and methods for targeting α5β1 integrin. The present invention meets this and other needs.

SUMMARY

[00005] The present disclosure provides novel anti-$\alpha_5\beta_1$ antibodies derived from the monoclonal antibody 18C12, kits and compositions comprising the novel anti- $\alpha_5\beta_1$ antibodies, and methods of making and/or using them.

One example of the disclosure provides an anti-$\alpha_5\beta_1$ antibody comprising a VL domain comprising a CDR-L1 comprising TL-S/T-S/P/T-Q/N-H-F/S-T/I-Y-K/T-I-G/D/S (SEQ ID NO:15); a CDR-L2 comprising L/I-N/T-S-D/H/S-G/S-S/L/T-H/Y-N/K/Q/I-K/T-G/A-D/S/V (SEQ ID NO:16); a CDR-L3 comprising G/A-S/A/Y-S/Y-Y-S/A/Y-S/Y/T-GY-V/I (SEQ ID NO:17); and a VH domain comprising a CDH-H1 comprising GFTFS-N/A-RW-I/V-Y (SEQ ID NO:18); a CDR-H2 comprising GIKTKP-N/A/T-I/R-YAT-E/Q-YADSVKG (SEQ ID NO:19); and a CDR-H1 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20). In some examples, the anti-$\alpha_5\beta_1$ antibody comprises a VL domain comprising a CDR-L1, CDR-L2, and CDR-L3 each comprising a sequence set forth in Figure 3 and a VH domain comprising a CDR-H1, CDR-H2, and CDR-H3 each comprising a sequence set forth in Figure 3, *i.e.*, a VL domain comprising a CDR-L1 comprising a sequence set forth in SEQ ID NO: 21, 22, 23, or 24, a CDR-L2 comprising a sequence set forth in SEQ ID NO: 25, 26, 27, or 28, and a CDR-L3 comprising a sequence set forth in SEQ ID NO: 29, 30, 31, or 32; and a VH domain comprising a CDR-H1 comprising a sequence set forth in SEQ ID NO: 34 or 35, a CDR-H2 comprising a sequence set forth in SEQ ID NO: 36 or 37, and a CDR-H3 comprising a sequence set forth in SEQ ID NO: 38, 39, or 40. In some examples, the anti-$\alpha_5\beta_1$ antibody comprises a VL domain comprising any one of SEQ ID NOS:3-8 and a VH domain comprising any one of SEQ ID NOS:11-14. In some examples, the anti-$\alpha_5\beta_1$ antibody comprises a VL domain comprising SEQ ID NO:4 and a VH domain comprising SEQ ID NO:11. In some examples, the anti-$\alpha_5\beta_1$ antibody comprises a VL domain comprising SEQ ID NO:5 and a VH domain comprising SEQ ID NO:12. In some examples, the anti-$\alpha_5\beta_1$ antibody comprises a VL domain comprising SEQ ID NO:6 and a VH domain comprising SEQ ID NO:13. In some examples, the anti-$\alpha_5\beta_1$ antibody comprises a VL domain comprising SEQ ID NO:7 and a VH domain comprising SEQ ID NO:13. In some examples, the anti-$\alpha_5\beta_1$ antibody comprises a VL domain comprising SEQ ID NO:8 and a VH domain comprising SEQ ID NO:14. In some examples, the anti-$\alpha_5\beta_1$ antibody is human, humanized or chimeric. In one example, the anti-$\alpha_5\beta_1$ antibody is a monoclonal antibody. In some examples, the anti-$\alpha_5\beta_1$ antibody competes with the 18C12 antibody for binding to $\alpha_5\beta_1$ integrin. In some examples, the monoclonal antibody is a chimeric antibody. In some examples, the anti-$\alpha_5\beta_1$ antibody is an antibody fragment that binds $\alpha_5\beta_1$. In some examples, the anti-$\alpha_5\beta_1$ antibody is selected from: a Fab, Fab', a F(ab)'$_2$, single-chain Fv (scFv), an Fv fragment; a diabody and a linear antibody. In some examples, the anti-$\alpha_5\beta_1$ antibody is a full length IgG1 or a full length IgG4. In some examples, the anti-$\alpha_5\beta_1$ antibody is a

bispecific antibody or a multispecific antibody. In some examples, the bispecific antibody binds VEGF and $\alpha_5\beta_1$ and is a VEGF antagonist. In some examples, the anti-$\alpha_5\beta_1$ antibody has an altered effector function. In some examples, the anti-$\alpha_5\beta_1$ antibody is altered to decrease or prevent antibody dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) activity (*e.g.*, by altering the nucleic acid sequence encoding the Fc portion of the antibody). In some examples, the Fc portion of the antibody comprises a N297A substitution. In some examples, the anti-$\alpha_5\beta_1$ antibody has been modified to increase or decrease its half-life in humans (*e.g.*, by altering the nucleic acid sequence encoding the Fc portion of the antibody). In some example, the $\alpha_5\beta_1$ antibody is part of an an immunoonjugate conjugated to another entity (*e.g.*, a therapeutic agent or a detectable label). In some examples, the therapeutic entity is a cytotoxic agent (*e.g.*, radioactive isotope, a toxin, a growth-inhibitory agent, or a chemotherapeutic agent). In some examples, the detectable label is a fluorescent dye, a radioisotope, or an enzyme.

[00005a] In one aspect, the present disclosure refers to an anti-α5β1 antibody comprising a VL domain comprising a CDR-L1 comprising TL-S/T-S/P/T-Q/N-H-F/S-T/I-Y-K/T-I-G/D/S (SEQ ID NO:15); a CDR-L2 comprising L/I-N/T-S-D/H/S-G/S-S/L/T-H/Y-N/K/Q/I-K/T-G/A-D/S/V (SEQ ID NO:16); a CDR-L3 comprising G/A-S/A/Y-S/Y-Y-S/A/Y-S/Y/T-GY-V/I (SEQ ID NO:17); and

a VH domain comprising a CDH-H1 comprising GFTFS-N/A-RW-I/V-Y (SEQ ID NO:18); a CDR-H2 comprising GIKTKP-N/A/T-I/R-YAT-E/Q-YADSVKG (SEQ ID NO:19); and a CDR-H3 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20).

[00005b] In another aspect, the present disclosure refers to an anti-α5β1 antibody comprising: a VL domain comprising a CDR-L1 comprising TL-S/T-S/P/T-Q/N-H-F/S-T/I-Y-K/T-I-G/D/S (SEQ ID NO: 15); a CDR-L2 comprising L/I-N/T-S-D/H/S-G/S-S/L/T-H/Y-N/K/Q/I-K/T-G/A-D/S/V (SEQ ID NO: 16); a CDR-L3 comprising G/A-S/A/Y-S/Y-Y-S/A/Y-S/Y/T-GY-V/I (SEQ ID NO: 17); and

a VH domain comprising a CDH-H1 comprising GFTFS-N/A-RW-I/V-Y (SEQ ID NO: 18); a CDR-H2 comprising GIKTKP-N/A/T-I/R-YAT-E/Q-YADSVKG (SEQ ID NO:
19); and a CDR-H3 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20) or is a variant comprising one or more alterations in one or more of the CDR domains.

[00005c] In another aspect, the present disclosure refers to an anti-α5β1 antibody comprising: a VL domain comprising a CDR-L3 comprising G/A-S/A/Y-S/Y-Y-S/A/Y-S/Y/T-GY-V/I (SEQ

ID NO: 17); and a VH domain comprising a CDR-H3 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20).

[00005d] In another aspect, the present disclosure refers to an anti-α5β1 antibody comprising a VL domain and a VH domain, wherein the VH domain comprises a CDH-HI comprising GFTFS-N/A-RW-I/V-Y (SEQ ID NO: 18); a CDR-H2 comprising GIKTKP-N/A/T-I/R-YAT-E/Q-YADSVKG (SEQ ID NO: 19); and a CDR-H3 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20).

[00005e] In another aspect, the present disclosure refers to an anti-α5β1 antibody comprising a VL domain and a VH domain, wherein the VH domain comprises SEQ ID NO: 14.

[00005f] In another aspect, the present disclosure refers to an anti-α5β1 antibody comprising a VL domain comprising a CDR-L1 comprising SEQ ID NO: 21, a CDR-L2 comprising residues 49-61 of SEQ ID NO: 8, and a CDR-L3 comprising SEQ ID NO: 30; and
a VH domain comprising a CDR-HI comprising residues 26-35 of SEQ ID NO:14, a CDR-H2 comprising residues 50-65 of SEQ ID NO:14, and a CDR-H3 comprising residues 95-102 of SEQ ID NO:14.

[00006] Further examples of the disclosure provide nucleic acid molecules encoding any of the anti-$\alpha_5\beta_1$ antibodies described herein, expression vectors comprising the nucleic acids, and host cells comprising the nucleic acids. Yet further examples of the disclosure provide methods of producing any of the anti-$\alpha_5\beta_1$ antibodies described herein, the methods comprising culturing the host cells so that the antibody is produced. In some examples, the methods further comprise recovering the antibody from the host cell.

[00006a] In another aspect, the present disclosure refers to an isolated nucleic acid molecule encoding the antibody as disclosed herein.

[00006b] In another aspect, the present disclosure refers to a host cell comprising the nucleic acid molecule as disclosed herein.

[00006c] In another aspect, the present disclosure refers to a method of producing an anti-α5β1 antibody comprising culturing the host cell as disclosed herein so that the antibody is produced.

[00007]Additional examples of the disclosure provide pharmaceutical compositions comprising a $\alpha_5\beta_1$ antibody of this disclosure and a pharmaceutically acceptable carrier. In some examples, the pharmaceutical compositions further comprise at least one, two, three, four, or more additional agent(s)

including, e.g., a VEGF antagonist. In some examples, the additional agent(s) are selected from a cytotoxic agent, a chemotherapeutic agent, a growth-inhibitory agent, or an anti-angiogenic agent. In some examples, the VEGF antagonist is an anti-VEGF antibody. In some examples, the anti-VEGF antibody is bevacizumab. The disclosure also provides articles of manufacture and kits comprising instructions for detecting $\alpha_5\beta_1$ (e.g., in a subject who has been treated with a VEGF antagonist).

[00007a] In another aspect, the present disclosure refers to an immunoconjugate comprising the antibody as disclosed herein and a cytotoxic agent.

[00007b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier.

[00008] Another example of the disclosure provides methods of treating subjects suffering from a disease or disorder involving abnormal angiogenesis, vascular permeability, or vascular leakage. The methods comprising administering a therapeutically effective amount of the anti-$\alpha_5\beta_1$ antibodies described herein to the subject, thereby treating the disease or disorder (*e.g.*, by partially or completely inhibiting abnormal angiogenesis, vascular

permeability, or vascular leakage). In some examples, a VEGF antagonist is also administered to the subject. In some examples, the VEGF antagonist and the anti-$\alpha_5\beta_1$ antibody are administered concurrently. In some examples, the VEGF antagonist and the anti-$\alpha_5\beta_1$ antibody are administered sequentially. In some examples, the disease or disorder is responsive to VEGF antagonist therapies. In some examples, the disease or disorder is selected from: a cancer, an immune disease or an ocular disease. According to one example, the disease or disorder is selected from: a solid tumor, a metastatic tumor, a soft tissue tumor, a disease having ocular neovascularisation, an inflammatory disease having abnormal angiogenesis, a disease arising after transplantation into the subject and a disease having abnormal proliferation of fibrovascular tissue. According to another example, the cancer is selected from: breast cancer (including metastatic breast cancer), cervical cancer, colorectal cancer (including metastatic colorectal cancer), lung cancer (including non-small cell lung cancer), non-Hodgkins lymphoma (NHL), chronic lymphocytic leukemia, renal cell cancer, prostate cancer including homone refractory prostate cancer, liver cancer, head and neck cancer, melanoma, ovarian cancer, mesothelioma, soft tissue cancer, gastrointestinal stromal tumor, glioblastoma multiforme and multiple myeloma. According to another example, the disease is selected from: retinopathy, age-related macular degeneration (*e.g.*, wet AMD), diabetic macular edema, retinal vein occlusion (RVO), and dry AMD/geographic atrophy (for prevention of progression to wet AMD) rubeosis; psoriasis, an inflammatory renal disease, haemolytic uremic syndrome, diabetic nephropathy (*e.g.*, proliferative diabetic retinopathy), arthritis (*e.g.*, psoriatic arthritis, osteoarthritis, rheumatoid arthritis), inflammatory bowel disease, chronic inflammation, chronic retinal detachment, chronic uveitis, chronic vitritis, corneal graft rejection, corneal neovascularization, corneal graft neovascularization, Crohn's disease, myopia, ocular neovascular disease, Pagets disease, pemphigoid, polyarteritis, post-laser radial keratotomy, retinal neovascularization, Sogrens syndrome, ulcerative colitis, graft rejection, lung inflammation, nephrotic syndrome, edema, ascites associated with malignancies, stroke, angiofibroma and neovascular glaucoma. In one example, the methods further comprise administering an additional therapeutic agent (*e.g.*, an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent, or a cytotoxic agent) to the subject.
[00008a] In another aspect, the present disclosure refers to use of the antibody as disclosed herein in the manufacture of a medicament for treating an individual having a disease or disorder involving abnormal angiogenesis and/or vascular permeability or leakage.
[00008b] In another aspect, the present disclosure refers to use of the antibody as disclosed herein in the manufacture of a medicament for inhibiting angiogenesis.

[00009] Yet another example of the disclosure provides methods of treating cancer in a subject, the methods comprising: administering therapeutically effective amount of a VEGF antagonist and an anti-$\alpha_5\beta_1$ antibody to the subject. In some examples, the VEGF antagonist and the anti-$\alpha_5\beta_1$ antibody are administered concurrently. In some

examples, the VEGF antagonist and the anti-$\alpha_5\beta_1$ antibody are administered sequentially. In some examples, the cancer is responsive to VEGF antagonist therapies.

[00010] A further example of the disclosure provides methods of treating age related macular degeneration (AMD) (including, *e.g.*, wet age-related macular degeneration) in a subject suffering from AMD, the methods comprising: administering a therapeutically effective amount of a VEGF antagonist and an anti-$\alpha_5\beta_1$ antibody to the subject. In some examples, the VEGF antagonist and the anti-$\alpha_5\beta_1$ antibody are administered concurrently. In some examples, the VEGF antagonist and the anti-$\alpha_5\beta_1$ antibody are administered sequentially. In yet another example, a method of treating an autoimmune disease in a subject comprising the step of administering a therapeutically effective amount of a VEGF antagonist and an $\alpha_5\beta_1$ antagonist concurrently or sequentially is provided.

[00011] In some examples, the VEGF antagonist is initially administered to the subject to be treated and the anti-$\alpha_5\beta_1$ antibody is subsequently administered to the subject. In some examples, the VEGF antagonist and the $\alpha_5\beta_1$ antagonist are administered to the subject simultaneously. In some examples, the anti-$\alpha_5\beta_1$ antibody VEGF antagonist is initially administered to the subject to be treated and the VEGF antagonist is subsequently administered to the subject. In some examples, the subject is treated with the VEGF antagonist until the subject is unresponsive to VEGF antagonist treatment and then the subject is treated with the anti-$\alpha_5\beta_1$ antibody. In one particular example, the subject is treated with the VEGF antagonist when the cancer is non-invasive or early stage and treated with the anti-$\alpha_5\beta_1$ antibody when the cancer is invasive. In another example, subject being treated with the the anti-$\alpha_5\beta_1$ antibody has elevated $\alpha_5\beta_1$ levels in a diseased tissue compared to tissue from a subject not suffering from the disease or compared to non-diseased tissue. In this instance, the method can further include the step of detecting $\alpha_5\beta_1$ in the subject, *e.g.*, in a diseased tissue after treatment with a VEGF antagonist. According to one example, the invasive cancer is a metastasized cancer. According to another example, the early stage cancer is a cancer treated by adjuvant therapy (*e.g.*, chemotherapy or surgical removal).

[00012] According to one example of this disclosure, the subject to be treated with an anti-$\alpha_5\beta_1$ antibody is suffering from a relapse after VEGF antagonist treatment or has become refractory to VEGF antagonist treatment. According to another example, the subject to be treated with an anti-$\alpha_5\beta_1$ antibody and a VEGF antagonist is suffering from a metastatic cancer or has previously been treated with adjuvant therapy. In one example, the candidate patient is relapsed, refractory or resistant to a chemotherapeutic agent such as

irinotecan. Examples of such diseases, include but are not limited to, metastatic colorectal cancer, relapsed metastatic colorectal cancer, metastatic breast cancer, relapsed metastatic breast cancer, metastatic HER2$^+$ breast cancer, adjuvant breast cancer, adjuvant HER2$^+$ breast cancer, metastatic pancreatic cancer, adjuvant colon cancer, adjuvant non-small cell lung cancer, adjuvant rectal cancer, adjuvant non small cell lung cancer, metastatic non small cell lung cancer, metastatic ovarian cancer, metastatic renal cell cancer and adjuvant renal cell cancer.

[00013] According to one example, the subject suffering from a disease described herein is administered a maintenance therapy after treatment for the disease with a VEGF antagonist, wherein the maintenance therapy is an $\alpha_5\beta_1$ antagonist alone or sequentially or concurrently with a VEGF antagonist.

[00014] In some examples, the VEGF antagonist is selected from: an antibody, an immunoadhesin, a peptibody, a small molecule and a nucleic acid that hybridizes to a nucleic acid molecule encoding VEGF under stringent conditions (*e.g.*, ribozyme, siRNA and aptamer). In some examples, the VEGF antagonist is an antibody (*e.g.*, a monoclonal antibody). According to one example, the anti-VEGF antibody is capable of being competitively inhibited from binding to human VEGF by the Avastin® antibody. According to another example, the anti-VEGF antibody is human, humanized or chimeric. According one specific example, the anti-VEGF antibody is the Avastin® antibody. According to another example, the anti-VEGF antibody is selected from the group consisting of a Fab, Fab', a F(ab)'$_2$, single-chain Fv (scFv), an Fv fragment; a diabody and a linear antibody. According to another example, the VEGF antagonist is a bispecific antibody that binds both VEGF and $\alpha_5\beta_1$ and is also a $\alpha_5\beta_1$ antagonist.

[00015] A further example of the disclosure provides methods of detecting $\alpha_5\beta_1$ protein in a sample suspected of containing the $\alpha_5\beta_1$ protein. The methods comprising (1) contacting the antibodies described herein with the sample; and detecting formation of a complex between the the anti- $\alpha_5\beta_1$ antibody and the $\alpha_5\beta_1$ protein. In some examples, the sample is from a patient diagnosed with a disease characterized by abnormal angiogenesis , abnormal vascular permeability, and/or vascular leakage.

[00015a] In another aspect, the present disclosure refers to a method of detecting α5β1 protein in a sample suspected of containing the α5β1 protein, the method comprising
(a) contacting the antibody of as disclosed herein with the sample; and
(b) detecting formation of a complex between the the anti-α5β1 antibody and the α5β1 protein.

[00015b] In another aspect, the present disclosure refers to a kit for detecting α5β1 in a subject treated with a VEGF antagonist, said kit comprising the antibody as disclosed herein.

[00016] These and other examples of the disclosure are further described in the detailed description that follows.

WE CLAIM:

1. An anti-α5β1 antibody comprising

a VL domain comprising a CDR-L1 comprising TL-S/T-S/P/T-Q/N-H-F/S-T/I-Y-K/T-I-G/D/S (SEQ ID NO:15); a CDR-L2 comprising L/I-N/T-S-D/H/S-G/S-S/L/T-H/Y-N/K/Q/I-K/T-G/A-D/S/V (SEQ ID NO:16); a CDR-L3 comprising G/A-S/A/Y-S/Y-Y-S/A/Y-S/Y/T-GY-V/I (SEQ ID NO:17); and

a VH domain comprising a CDH-H1 comprising GFTFS-N/A-RW-I/V-Y (SEQ ID NO:18); a CDR-H2 comprising GIKTKP-N/A/T-I/R-YAT-E/Q-YADSVKG (SEQ ID NO:19); and a CDR-H3 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20).

2. The antibody of claim 1, wherein

the VL domain comprises a CDR-L1, CDR-L2, and CDR-L3, each comprising a sequence set forth in Figure 3 and

the VH domain comprises a CDR-H1, CDR-H2, and CDR-H3, each comprising a sequence set forth in Figure 3.

3. The antibody of claim 1, wherein

the VL domain comprises any one of SEQ ID NOS:3-8 and

the VH domain comprises any one of SEQ ID NOS: 11-14.

4. The antibody of claim 1, wherein

the VL domain comprises SEQ ID NO:8 and

the VH domain comprises SEQ ID NO:14.

5. An anti-α5β1 antibody comprising:

a VL domain comprising a CDR-L1 comprising TL-S/T-S/P/T-Q/N-H-F/S-T/I-Y-K/T-I-G/D/S (SEQ ID NO: 15); a CDR-L2 comprising L/I-N/T-S-D/H/S-G/S-S/L/T-H/Y-N/K/Q/I-K/T-G/A-D/S/V (SEQ ID NO: 16); a CDR-L3 comprising G/A-S/A/Y-S/Y-Y-S/A/Y-S/Y/T-GY-V/I (SEQ ID NO: 17); and

a VH domain comprising a CDH-H1 comprising GFTFS-N/A-RW-I/V-Y (SEQ ID NO: 18); a CDR-H2 comprising GIKTKP-N/A/T-I/R-YAT-E/Q-YADSVKG (SEQ ID NO:

19); and a CDR-H3 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20) or is a variant comprising one or more alterations in one or more of the CDR domains.

6. The antibody of claim 5, wherein the antibody is a variant comprising one or more alterations in one or more of the CDR domains.

7. The antibody of claim *5* or claim 6, wherein said variant comprises one alteration in one of the CDR domains.

8. The antibody of claim 7, wherein said alteration is a conservative substitution.

9. The antibody of claim 8, wherein said alteration is an N to Q substitution.

10. The antibody of claim 6 or claim 7, wherein the alteration results in an improvement in affinity for $\alpha 5\beta 1$.

11. An anti-$\alpha 5\beta 1$ antibody comprising: a VL domain comprising a CDR-L3 comprising G/A-S/A/Y-S/Y-Y-S/A/Y-S/Y/T-GY-V/I (SEQ ID NO: 17); and a VH domain comprising a CDR-H3 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20).

12. The antibody of claim 11, wherein the VL domain comprises a CDR-LI comprising TL-S/T-S/P/T-Q/N-H-F/S-T/I-Y-K/T-I-G/D/S (SEQ ID NO: 15); a CDR-L2 comprising L/I-N/T-S-D/H/S-G/S-S/L/T-H/Y-N/K/Q/I-K/T-G/A-D/S/V (SEQ ID NO: 16); and the VH domain comprises a CDH-H1 comprising GFTFS-N/A-RW-I/V-Y (SEQ ID NO: 18); a CDR-H2 comprising GIKTKP-N/A/T-I/R-YAT-E/Q-YADSVKG (SEQ ID NO: 19); or is a variant having one or more alterations in one or more of the CDR domains.

13. An anti-$\alpha 5\beta 1$ antibody comprising a VL domain and a VH domain, wherein the VH domain comprises a CDH-HI comprising GFTFS-N/A-RW-I/V-Y (SEQ ID NO: 18); a CDR-H2 comprising GIKTKP-N/A/T-I/R-YAT-E/Q-YADSVKG (SEQ ID NO: 19); and a CDR-H3 comprising L/V-TG-M/K-R/K-YFDY (SEQ ID NO:20).

14. The antibody of claim 13, wherein the VH domain comprises a CDH-H1 comprising GFTFSARWIY; a CDR-H2 comprising GIKTKPAIYATEYADSVKG; and a CDR-H3 comprising LTGMKYFDY.

15. An anti-$\alpha 5\beta 1$ antibody comprising a VL domain and a VH domain, wherein the VH domain comprises SEQ ID NO: 14.

16. An anti-α5β1 antibody comprising

a VL domain comprising a CDR-L1 comprising SEQ ID NO: 21, a CDR-L2 comprising residues 49-61 of SEQ ID NO: 8, and a CDR-L3 comprising SEQ ID NO: 30; and

a VH domain comprising a CDR-HI comprising residues 26-35 of SEQ ID NO:14, a CDR-H2 comprising residues 50-65 of SEQ ID NO:14, and a CDR-H3 comprising residues 95-102 of SEQ ID NO:14.

17. The antibody of claim 16, wherein

the VL domain comprises SEQ ID NO: 8 and

the VH domain comprises SEQ ID NO: 14.

18. The antibody of any one of claims 1 to17, which is a human, humanized, chimeric, bispecifc or multispecific antibody.

19. The antibody of any one of claims 1 to18, which is an antibody fragment that binds α5β1.

20. The antibody of any one of claims 1 to18, which is a full length IgG1 antibody.

21. The antibody according to claim 20, wherein the antibody comprises an Fc portion comprising a N297A substitution.

22. An isolated nucleic acid molecule encoding the antibody of any one of claims 1 to 21.

23. A host cell comprising the nucleic acid molecule of claim 22.

24. A method of producing an anti-α5β1 antibody comprising culturing the host cell of claim 23 so that the antibody is produced.

25. An immunoconjugate comprising the antibody of any one of claims 1 to 21 and a cytotoxic agent.

26. A pharmaceutical composition comprising the antibody of any one of claims 1 to 21 and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition of claim 26, further comprising a VEGF antagonist.

28. The pharmaceutical compostion of claim 27, wherein the VEGF antagonist is an anti-VEGF antibody.

29. The pharmaceutical compostion of claim 28, wherein the anti-VEGF antibody is bevacizumab.

30. The antibody of any one of claims 1 to 21 further comprising a detectable label.

31. The antibody of claim 30, wherein the detectable label is a member selected from the group consisting of: a radioisotope, a fluorescent dye, and an enzyme.

32. A method of detecting α5β1 protein in a sample suspected of containing the α5β1 protein, the method comprising

(a) contacting the antibody of claim 30 or claim 31 with the sample; and

(b) detecting formation of a complex between the the anti-α5β1 antibody and the α5β1 protein.

33. The method of claim 32, wherein the sample is from a patient diagnosed with a disease involving abnormal angiogenesis , abnormal vascular permeability, and/or vascular leakage.

34. Use of the antibody of any one of claims 1 to 21 in the manufacture of a medicament for treating an individual having a disease or disorder involving abnormal angiogenesis and/or vascular permeability or leakage.

35. The use of claim 34, wherein the disease or disorder is a member selected from the group consisting of: cancer, an ocular disease, and an autoimmune disease.

36. The use of claim 35, wherein the cancer is a selected from the group consisting of colorectal cancer, lung cancer, breast cancer, renal cell cancer, and glioblastoma.

37. The use of claim 34, wherein the disease or disorder is a member selected from the group consisting of retinopathy, age-related macular degeneration, corneal neovascularization, corneal graft neovascularization, retinal neovascularization, and neovascular glaucoma.

38. The use of any one of claims 34 to 37, wherein an effective amount of a VEGF antagonist is to be further administered to the individual.

39. The use of claim 38, wherein the VEGF antagonist is an anti-VEGF antibody.

40. The use of claim 39, wherein the anti-VEGF antibody is bevacizumab.

41. The use of any one of claims 38 to 40, wherein the VEGF antagonist is to be administered prior to the anti-α5β1 antibody.

42. The use of any one of claims 38 to 40, wherein the VEGF antagonist and the anti-α5β1 antibody are to be administered simultaneously.

43. The use of any one of claims 38 to 40, wherein the individualis first to be treated with the VEGF antagonist until the individual is unresponsive to VEGF antagonist treatment and then the individual is to be treated with the anti-α5β1 antibody.

44. The use of any one of claims 34 to 43, wherein a therapeutic agent selected from the group consisting of an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent and a cytotoxic agent is to be further administered.

45. Use of the antibody of any one of claims 1 to 21 in the manufacture of a medicament for inhibiting angiogenesis.

46. A kit for detecting α5β1 in a subject treated with a VEGF antagonist, said kit comprising the antibody of any one of claims 1 to 21.