CLAIMS

1. An anti-alpha5beta1 antibody comprising

a VL domain comprising a CDR-L1 comprising TLSSQHSTYTIG (SEQ ID NO:21); a CDR-L2 comprising LNSDSSHNKGS (residues 50-60 of SEQ ID NO:8); a CDR-L3 comprising AAYYAYGYV (SEQ ID NO:30); and

a VH domain comprising a CDR-H1 comprising GFTFSARWIY (residues 26-35 of SEQ ID NO:14); a CDR-H2 comprising GIKTKPAIYATEYADSVKG (residues 50-68 of SEQ ID NO:14); and a CDR-H3 comprising LTGMKYFDY (residues 101-109 of SEQ ID NO:14).

2. An anti-alpha5beta1 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; a CDR-L3 comprising SEQ ID NO: 30; and

a VH domain comprising a CDR-H1 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.

3. The anti-α5β1 antibody of claim 1 or claim 2, wherein the VL domain comprises an amino acid sequence shown in SEQ ID NO: 8 and the VH domain comprises an amino acid sequence shown in SEQ ID NO: 14.

4. The anti-alpha5beta1 antibody of any one of claims 1-3, which is a human, humanized, chimeric, bispecific or multi specific antibody.

5. The anti-alpha5beta1 antibody of any one of claims 1-3, which is an antibody fragment that binds alpha5beta1.

6. The anti-alpha5beta1 antibody of any one of claims 1-3, which is a full length IgG1 antibody.

7. The anti-alpha5beta1 antibody according to claim 5, wherein the antibody comprises an Fc portion comprising a N297A substitution.

8. An isolated nucleic acid molecule encoding the anti-alpha5beta1 antibody of any one of claims 1-7.

9. A host cell comprising the nucleic acid of claim 8.

10. A method of producing an anti-alpha5beta1 antibody comprising culturing the host cell of claim 9 so that the antibody is produced.

11. An immunoconjugate comprising the anti-alpha5beta1 antibody of any one of claims 1-7 and a cytotoxic agent.

12. A pharmaceutical composition comprising the anti-alpha5beta1 antibody of any one of claims 1-7 and 11 and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12, further comprising a VEGF antagonist.

14. The pharmaceutical composition of claim 13, wherein the VEGF antagonist is an anti-VEGF antibody.

15. The pharmaceutical composition of claim 14, wherein the anti-VEGF antibody is bevacizumab.

16. The anti-alpha5beta1 antibody of any one of claims 1-7 further comprising a detectable label.

17. The anti-alpha5beta1 antibody of claim 16, wherein the detectable label is a member selected from the group consisting of: a radioisotope, a fluorescent dye, and an enzyme.

18. The anti-alpha5beta1 antibody of any one of claims 1-7 for use as a medicament.

19. The anti-alpha5beta1 antibody of any one of claims 1-7 for use in treating an individual having a disease or disorder involving abnormal angiogenesis and/or vascular permeability or leakage.

20. The antibody of claim 19, wherein the disease is cancer, ocular disease, or autoimmune disease.

21. The anti-alpha5beta1 antibody of any one of claims 1-7 for use in inhibiting angiogenesis.

22. A method of detecting alpha5beta1 protein in a sample suspected of containing the alpha5beta1 protein, the method comprising

(a) contacting the antibody of any one of claims 16 or 17 with the sample; and

(b) detecting formation of a complex between the anti-alpha5beta1 antibody and the alpha5beta1protein.

23. The method of claim 22, wherein the sample is from a patient diagnosed with a disease involving abnormal angiogenesis, abnormal vascular permeability, and/or vascular leakage.

24. Use of an anti-alpha5beta1 antibody of any one of claims 1-7 in the manufacture of a medicament for treating an individual having a disease or disorder involving abnormal angiogenesis and/or vascular permeability or leakage.

25. The use of claim 24, wherein the disease or disorder is a member selected from the group consisting of: cancer, an ocular disease, and an autoimmune disease.

26. The anti-alpha5beta1 antibody of claim 20 or the use of claim 25, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, breast cancer, renal cell cancer, and glioblastoma.

27. The anti-alpha5beta1 antibody of claim 20 or the use of claim 25, 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.

28. The anti-alpha5beta1 antibody of claim 20 or the use of claim 25, wherein an effective amount of a VEGF antagonist is to be administered to the individual.

29. The anti-alpha5beta1 antibody or use of claim 28, wherein the VEGF antagonist is an anti-VEGF antibody.

30. The anti-alpha5beta1 antibody or use of claim 29, wherein the anti-VEGF antibody is bevacizumab.

31. The anti-alpha5beta1 antibody or use of claim 28, wherein the VEGF antagonist is to be administered prior to the anti-alpha5beta1 antibody.

32. The anti-alpha5beta1 antibody or use of claim 28, wherein the VEGF antagonist and the anti-alpha5beta1 antibody are to be administered simultaneously.

33. The anti-alpha5beta1 antibody or use of claim 28, where the individual is to be first 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-alpha5beta1 antibody.

34. The anti-alpha5beta1 antibody or use of claim 28, wherein said antibody is to be administered with a therapeutic agent selected from the group consisting of an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent and a cytotoxic agent.

35. A kit for detecting alpha5beta1 in a subject who has been treated with a VEGF antagonist, said kit comprising

(a) an anti-alpha5beta1 antibody of any one of claims 1-7 and 16-17; and
(b) instructions for use.

36. Use of an anti-alpha5beta1 antibody any one of claims 1-7 and 11 in the manufacture of a medicament for inhibiting angiogenesis.

CLAIMS

1. An anti-alpha5beta1 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 CDR-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 anti-alpha5beta1 antibody of claim 1, wherein

the VL domain comprises a CDR-L1, CDR-L2, and CDR-13, 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 anti-alpha5beta1 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. An anti-alpha5beta1 antibody comprising

a VL domain comprising a CDR-L1 comprising TLSSQHSTYTIG (SEQ ID NO:21); a CDR-L2 comprising LNSDSSHNKGS (residues 50-60 of SEQ ID NO:8); a CDR-L3 comprising AAYYAYGYV (SEQ ID NO:30): and

a VH domain comprising a CDR-H1 comprising GFTFSARWIY (residues 26-35 of SEQ ID NO:14); a CDR-H2 comprising GIKTKPAIYATEYADSVKG (residues 50-68 of SEQ ID NO:14); and a CDR-H3 comprising LTGMKYFDY (residues 101-109 of SEQ ID NO:14).

5. An anti-alpha5beta1 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; a CDR-L3 comprising SEQ ID NO: 30; and

a VH domain comprising a CDR-H1 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.

6. An anti-alpha5beta1 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 CDR-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 having one or more alterations in one or more of the CDR domains.

7. The anti-alpha5beta1 antibody of claim 6, wherein the anti-α5β1 antibody is a variant having one or more alterations in one or more of the CDR domains.

8. The anti-alpha5beta1 antibody of claim 8, wherein said variant has one alteration in one of the CDR domains.

9. The anti-alpha5beta1 antibody of claim 8, wherein said alteration is a conservative substitution.

10. The anti-alpha5beta1 antibody of claim 8, wherein said alteration is an N to Q substitution.

11. The anti-alpha5beta1 antibody of claim 7, wherein the alteration results in an improvement in affinity for α5β1.

12. An anti-alpha5beta1 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).

13. The anti-alpha5beta1 antibody of claim 12, wherein the anti-α5β1antibody comprises 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); and a VH domain comprising a CDR-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.

14. The anti-alpha5beta1 antibody of claim 12, wherein the VH domain comprises SEQ ID NO:14.

15. An anti-alpha5beta1 antibody comprising a VL domain and a VH domain, wherein the VH domain comprising a CDR-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).

16. The anti-alpha5beta1 antibody of claim 15, wherein the VH domain comprises a CDR-H1 comprising GFTFSARWIY; a CDR-H2 comprising GIKTKPAIYATEYADSVKG; and a CDR-H3 comprising LTGMKYFDY.

17. The anti-alpha5beta1 antibody of any one of claims 1-16, which is a human, humanized, chimeric, bispecific or multi specific antibody.

18. The anti-alpha5beta1 antibody of any one of claims 1-16, which is an antibody fragment that binds alpha5beta1.

~~19. The anti-alpha5beta1 antibody of any one of claims 1-16, which is a full length IgG1 antibody.~~

20. The anti-alpha5beta1 antibody according to claim 19, wherein the antibody comprises an Fc portion comprising a N297A substitution.

21. An isolated nucleic acid molecule encoding the anti-alpha5beta1 antibody of any one of claims 1-20.

22. A host cell comprising the nucleic acid of claim 21.

23. A method of producing an anti-alpha5beta1 antibody comprising culturing the host cell of claim 22 so that the antibody is produced.

24. An immunoconjugate comprising the anti-alpha5beta1 antibody of any one of claims 1-16 and a cytotoxic agent.

25. A pharmaceutical composition comprising the anti-alpha5beta1 antibody of any one of claims 1-16 and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, further comprising a VEGF antagonist.

27. The pharmaceutical composition of claim 26, wherein the VEGF antagonist is an anti-VEGF antibody.

28. The pharmaceutical composition of claim 27, wherein the anti-VEGF antibody is bevacizumab.

29. The anti-alpha5beta1 antibody of any one of claims 1-16 further comprising a detectable label.

30. The anti-alpha5beta1 antibody of claim 29, wherein the detectable label is a member selected from the group consisting of: a radioisotope, a fluorescent dye, and an enzyme.

31. The anti-alpha5beta1 antibody of any one of claims 1-16 for use as a medicament.

32. The anti-alpha5beta1 antibody of any one of claims 1-16 for use in treating an individual having a disease or disorder involving abnormal angiogenesis and/or vascular permeability or leakage.

33. The antibody of claim 32, wherein the disease is cancer, ocular disease, or autoimmune disease.

34. The anti-alpha5beta1 antibody of any of claims 1-16 for use in inhibiting angiogenesis.

35. A method of detecting alpha5beta1 protein in a sample suspected of containing the alpha5beta1 protein, the method comprising

(a) contacting the antibody of any one of claims 29 or 30 with the sample; and

(b) detecting formation of a complex between the anti-alpha5beta1 antibody and the alpha5beta1protein.

36. The method of claim 35, wherein the sample is from a patient diagnosed with a disease involving abnormal angiogenesis, abnormal vascular permeability, and/or vascular leakage.

37. Use of an anti-alpha5beta1 antibody of any one of claims 1-16 in the manufacture of a medicament for treating an individual having a disease or disorder involving abnormal angiogenesis and/or vascular permeability or leakage.

38. The use of claim 37, wherein the disease or disorder is a member selected from the group consisting of: cancer, an ocular disease, and an autoimmune disease.

39. The anti-alpha5beta1 antibody of claim 33 or the use of claim 38, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, breast cancer, renal cell cancer, and glioblastoma.

40. The anti-alpha5beta1 antibody of claim 32 or the use of claim 37, 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.

41. The anti-alpha5beta1 antibody of claim 32 or the use of claim 37, wherein an effective amount of a VEGF antagonist is to be administered to the individual.

42. The anti-alpha5beta1 antibody or use of claim 41, wherein the VEGF antagonist is an anti-VEGF antibody.

43. The anti-alpha5beta1 antibody or use of claim 42, wherein the anti-VEGF antibody is bevacizumab.

44. The anti-alpha5beta1 antibody or use of claim 41, wherein the VEGF antagonist is to be administered prior to the anti-alpha5beta1 antibody.

45. The anti-alpha5beta1 antibody or use of claim 41, wherein the VEGF antagonist and the anti-alpha5beta1 antibody are to be administered simultaneously.

46. The anti-alpha5beta1 antibody or use of claim 41, where the individual is to be first 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-alpha5beta1 antibody.

47. The anti-alpha5beta1 antibody or use of claim 41, wherein said antibody is to be administered with a therapeutic agent selected from the group consisting of an anti-neoplastic agent, a chemotherapeutic agent, a growth inhibitory agent and a cytotoxic agent.

48. A kit for detecting alpha5beta1 in a subject who has been treated with a VEGF antagonist, said kit comprising

(a) an anti-alpha5beta1 antibody of any of claims 1-16; and

(b) instructions for use.

49. Use of an anti-alpha5beta1 antibody of any one of claims 1-16 in the manufacture of a medicament for inhibiting angiogenesis.