WHAT IS CLAIMED IS:

1. An isolated antibody that specifically binds to a non-ligand binding membrane proximal region of an extracellular domain of human Notch1 receptor and inhibits tumor growth.

2. The antibody of claim 1, wherein the antibody specifically binds to a non-ligand binding membrane proximal region of an extracellular domain of at least one additional Notch receptor.

3. The antibody of claims 1 or 2, wherein the antibody is an antagonist of Notch1.

4. The antibody according to any one of claims 1-3, wherein the antibody inhibits activation of Notch1.

5. The antibody according to any one of claims 1-4, wherein the antibody inhibits cleavage within the membrane proximal region.

6. The antibody according to any one of claims 1-5, wherein the antibody inhibits cleavage at the S2 site within the membrane proximal region.

7. The antibody according to any one of claims 1-6, wherein the antibody inhibits release of the intracellular domain (ICD) of Notch1.

8. The antibody according to any one of claims 1-7, wherein the antibody is an IgA, IgD, IgE, IgG or IgM antibody.

9. The antibody according to any one of claims 1-7, wherein the antibody is an IgG1 antibody.

10. The antibody according to any one of claims 1-7, wherein the antibody is an IgG2 antibody.

11. The antibody according to any one of claims 1-10, wherein the antibody is a monoclonal antibody.

12. The antibody according to any one of claims 1-11, wherein the antibody is a chimeric antibody.

13. The antibody according to any one of claims 1-12, wherein the antibody is a humanized antibody.

14. The antibody according to any one of claims 1-12, wherein the antibody is a human antibody.

15. The antibody according to any one of claims 1-14, wherein the antibody is an antibody fragment.

16. The antibody according to any one of claims 1-15, wherein the antibody is a monovalent antibody.

17. The antibody according to any one of claims 1-16, wherein the non-ligand binding membrane proximal region of the Notch1 receptor comprises SEQ ID NO:2.

18. The antibody according to any one of claims 1-17, wherein the antibody comprises a heavy chain CDR1 comprising RGYWIE (SEQ ID NO:15), a heavy chain CDR2 comprising QILPGTGRTNYNEKFKG (SEQ ID NO:16), and a heavy chain CDR3 comprising FDGNYGYYAMDY (SEQ ID NO:17).

19. The antibody of claim 18, wherein the antibody further comprises a light chain CDR1 comprising RSSTGAVTTSNYAN (SEQ ID NO:18), a light chain CDR2 comprising GTNNRAP(SEQ ID NO:19), and a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20).

20. The antibody according to any one of claims 1-17, wherein the antibody comprises a light chain CDR1 comprising RSSTGAVTTSNYAN (SEQ ID NO:18), a light chain CDR2 comprising GTNNRAP (SEQ ID NO:19), and a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20).

21. An isolated antibody that specifically binds to a non-ligand binding membrane proximal region of an extracellular domain of human Notch1, wherein the antibody comprises a heavy chain CDR1 comprising RGYWIE (SEQ ID NO:15), a heavy chain CDR2 comprising QILPGTGRTNYNEKFKG (SEQ ID NO:16), and/or a heavy chain CDR3 comprising FDGNYGYYAMDY (SEQ ID NO:17).

22. The antibody of claim 21, wherein the antibody further comprises a light chain CDR1 comprising RSSTGAVTTSNYAN (SEQ ID NO:18), a light chain CDR2 comprising GTNNRAP(SEQ ID NO:19), and/or a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20).

23. An isolated antibody that specifically binds a non-ligand binding membrane proximal region of an extracellular domain of human Notch1, wherein the antibody comprises a light chain CDR1

comprising RSSTGAVTTSNYAN (SEQ ID NO:18), a light chain CDR2 comprising GTNNRAP(SEQ ID NO:19), and/or a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20).

24. An isolated antibody that specifically binds a non-ligand binding membrane proximal region of an extracellular domain of human Notch1, wherein the antibody comprises:
(a) a heavy chain CDR1 comprising RGYWIE (SEQ ID NO:15), a heavy chain CDR2 comprising QILPGTGRTNYNEKFKG (SEQ ID NO:16), and a heavy chain CDR3 comprising FDGNYGYYAMDY (SEQ ID NO:17); and/or
(b) a light chain CDR1 comprising RSSTGAVTTSNYAN (SEQ ID NO:18), a light chain CDR2 comprising GTNNRAP(SEQ ID NO:19), and a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20).

25. An isolated antibody that specifically binds a non-ligand binding membrane proximal region of an extracellular domain of human Notch1, wherein the antibody comprises a heavy chain variable region comprising: (a) a heavy chain CDR1 comprising RGYWIE (SEQ ID NO:15), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (b) a heavy chain CDR2 comprising QILPGTGRTNYNEKFKG (SEQ ID NO:16), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and (c) a heavy chain CDR3 comprising FDGNYGYYAMDY (SEQ ID NO:17), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions.

26. The antibody of claim 25, wherein the antibody further comprises a light chain variable region comprising: (a) a light chain CDR1 comprising RSSTGAVTTSNYAN (SEQ ID NO:18), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (b) a light chain CDR2 comprising GTNNRAP(SEQ ID NO:19), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and/or (c) a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions.

27. An isolated antibody that specifically binds a non-ligand binding membrane proximal region of an extracellular domain of human Notch1, wherein the antibody comprises a light chain variable region comprising: (a) a light chain CDR1 comprising RSSTGAVTTSNYAN (SEQ ID NO:18), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; (b) a light chain CDR2 comprising GTNNRAP(SEQ ID NO:19), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions; and/or (c) a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20), or a variant thereof comprising 1, 2, 3, or 4 amino acid substitutions.

28. The antibody according to any one of claims 25-27, wherein the amino acid substitutions are conservative amino acid substitutions.

29. An isolated antibody which specifically binds to a non-ligand binding membrane proximal region of an extracellular domain of human Notch1, wherein the antibody binds to the same epitope within the membrane proximal region as the epitope to which antibody 52M51 produced by the hybridoma cell line deposited as ATCC Patent Deposit PTA-9405 binds.

30. An isolated antibody which specifically binds to a non-ligand binding membrane proximal region of an extracellular domain of human Notch1 and inhibits formation of the Notch1 ICD, wherein the antibody inhibits tumor growth.

31. An isolated antibody that competes with the antibody according to any one of claims 1-30 for specific binding to the non-ligand binding membrane proximal region of an extracellular domain of human Notch1.

32. An isolated antibody that competes with the antibody according to any one of claims 1-30 for specific binding to a non-ligand binding membrane proximal region of an extracellular domain of human Notch1 in a competitive binding assay.

33. An isolated antibody that competes with antibody 52M51 for specific binding to the non-ligand binding membrane proximal region of an extracellular domain of human Notch1.

34. An isolated antibody that specifically binds to the non-ligand binding membrane proximal region of an extracellular domain of human Notch1, wherein the antibody comprises: (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:14 or SEQ ID NO:24; and/or (b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:8, SEQ ID NO:28, or SEQ ID NO:32.

35. The antibody of claim 34, wherein the heavy chain variable region has at least 95% sequence identity to SEQ ID NO:14 or SEQ ID NO:24; and/or (b) the light chain variable region has at least 95% sequence identity to SEQ ID NO:8, SEQ ID NO:28, or SEQ ID NO:32.

36. An isolated polypeptide comprising:

(a) a polypeptide having the amino acid sequence of SEQ ID NO:14 or SEQ ID NO:24; and/or

(b) a polypeptide having the amino acid sequence of SEQ ID NO:8, SEQ ID NO:28, or SEQ ID NO:32.

37. The polypeptide of claim 36, wherein the polypeptide is an antibody.

38. The polypeptide of claim 36, wherein the polypeptide comprises a polypeptide having the amino acid sequence of SEQ ID NO:14 and a polypeptide having the amino acid sequence of SEQ ID NO:8.

39. The polypeptide of claim 36, wherein the polypeptide comprises a polypeptide having the amino acid sequence of SEQ ID NO:24 and a polypeptide having the amino acid sequence of SEQ ID NO:28.

40. The polypeptide of claim 36, wherein the polypeptide comprises a polypeptide having the amino acid sequence of SEQ ID NO:24 and a polypeptide having the amino acid sequence of SEQ ID NO:32.

41. An antibody comprising the same heavy and light chain variable regions as a polypeptide encoded by a plasmid on deposit as ATCC Patent Deposit Designation PTA-9549.

42. An antibody produced by the hybridoma cell line deposited on deposit as ATCC Patent Deposit Designation PTA-9405.

43. An antibody that specifically binds human Notch1 comprising the polypeptide of claims 36 or 37.

44. An antibody that specifically binds human Notch1 comprising:

a polypeptide comprising SEQ ID NO:14 or SEQ ID NO:24; and

a polypeptide comprising SEQ ID NO:8, SEQ ID NO:28 or SEQ ID NO:32.

45. A pharmaceutical composition comprising the antibody or polypeptide according to any one of claims 1-44 and a pharmaceutically acceptable carrier.

46. A pharmaceutical composition comprising the antibody or polypeptide according to any one of claims 1 - 44 and at least one additional anti-cancer agent.

47. An isolated polynucleotide molecule comprising a polynucleotide that encodes the antibody or polypeptide according to any one of claims 1 - 44.

48. An expression vector comprising the polynucleotide molecule of claim 47.

49. A host cell comprising the expression vector of claim 48.

50. A host cell comprising the polynucleotide molecule of claim 47.

51. A hydridoma cell line on deposit as ATCC Patent Deposit Designation PTA-9405.

52. A cell line producing the antibody according to any one of claims 1 - 44.

53. A method of inhibiting activity of Notch1 in a cell, comprising contacting the cell with the antibody or polypeptide according to any one of claims 1 - 44.

54. The method of claim 53, wherein the cell is a tumor cell.

55. A method of inhibiting growth of a tumor in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or polypeptide according to any one of claims 1 - 44.

56. A method of reducing tumorigenicity of a tumor that comprises cancer stem cells in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or polypeptide according to any one of claims 1 - 44, wherein the frequency or number of cancer stem cells in the tumor is reduced by administration of the antibody or polypeptide.

57. The method of claims 55 or 56, wherein the tumor or tumor cell is selected from the group consisting of a breast tumor, colorectal tumor, hepatic tumor, renal tumor, lung tumor, pancreatic tumor, ovarian tumor, prostate tumor, and head and neck tumor.

58. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the antibody or polypeptide according to any one of claims 1 - 44.

59. The method of claim 58, wherein the cancer is selected from the group consisting of a breast cancer, colorectal cancer, hepatic cancer, kidney cancer, liver cancer, lung cancer, pancreatic cancer, gastrointestinal cancer, melanoma, ovarian cancer, prostate cancer, cervical cancer, bladder cancer, glioblastoma, and head and neck cancer.

60. The method of any one of claims 55 - 59, wherein the method further comprises administering to the subject at least one additional anti-cancer/therapeutic agent.

61. The method of claim 60, wherein the additional anti-cancer agent is selected from the group consisting of taxol, irinotecan, gemcitabine, and oxaliplaitin.

62. The method of claim 60, wherein the anti-cancer agent is an additional antibody therapeutic.

63. The method of claim 62, wherein the additional antibody therapeutic comprises an antibody that specifically binds a second Notch receptor.

64. The method of claim 62, wherein the additional antibody therapeutic comprises an antibody that specifically binds VEGF.

65. The method of claim 62, wherein the additional antibody therapeutic comprises an antibody that specifically binds a Notch receptor ligand.

66. The method of claim 65, wherein the NOTCH receptor ligand is DLL4.

67. The method of claim 65, wherein the NOTCH receptor ligand is JAG1.

68. The method according to any one of claims 55 - 67, wherein the antibody is conjugated to a cytotoxic moiety.

69. The method according to any one of claims 55 – 68, wherein the antibody is administered with radiation therapy.

70. The method according to any one of claims 55 - 59, wherein the antibody is administered with chemotherapy.

71. A method of inhibiting growth of a tumor in a subject, the method comprising administering to the subject a therapeutically effective amount of an antibody that specifically binds to a non-ligand binding membrane proximal region of an extracellular domain of human Notch1, wherein binding inhibits activity of Notch1.

72. The method of claim 71, wherein the tumor is selected from the group consisting of a breast tumor, colorectal tumor, hepatic tumor, renal tumor, lung tumor, pancreatic tumor, ovarian tumor, prostate tumor, and head and neck tumor.

73. The method according to claims 71 or 72, wherein the subject is a human.

74. The method according to any one of claims 71 - 73, wherein the antibody is an antagonist of Notch1.

75. The method according to any one of claims 71 - 73, wherein the antibody is an IgG1 antibody.

76. The method according to any one of claims 71 - 74, wherein the antibody is an IgG2 antibody.

77. The method according to any one of claims 71 - 76, wherein the antibody is a monoclonal antibody.

78. The method according to any one of claims 71 - 77, wherein the antibody is a chimeric antibody.

79. The method according to any one of claims 71 - 78, wherein the antibody is a humanized antibody.

80. The method according to any one of claims 71 - 78, wherein the antibody is a human antibody.

81. The method according to any one of claims 71 - 80, wherein the antibody is an antibody fragment.

82. The method according to any one of the claims 71 - 81, wherein the antibody is conjugated to a cytotoxic agent.

83. The method according to any one of the claims 71 - 82, which further comprises administering at least one additional therapeutic agent appropriate for effecting combination therapy.

84. A method of reducing the tumorigenicity of a tumor that comprises cancer stem cells by reducing the frequency or number of cancer stem cells in the tumor, said method comprising contacting the tumor with an effective amount of an antibody that inhibits the activity of Notch1.

CLAIMS

1. An isolated antibody that specifically binds human Notch1, which comprises:
   (a) a heavy chain CDR1 comprising RGYWIE (SEQ ID NO:15); a heavy chain CDR2 comprising QILPGTGRTNYNEKFKG (SEQ ID NO:16); and a heavy chain CDR3 comprising FDGNYGYYAMDY (SEQ ID NO:17); and
   (b) a light chain CDR1 comprising RSSTGAVTTSNYAN (SEQ ID NO:18); a light chain CDR2 comprising GTNNRAP (SEQ ID NO:19); and a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20).

2. The antibody of claim 1, which binds to a non-ligand binding membrane proximal region of an extracellular domain of human Notch1 receptor.

3. The antibody of claim 2, wherein the non-ligand binding membrane proximal region of an extracellular domain of human Notch1 receptor comprises SEQ ID NO:2.

4. An isolated antibody that specifically binds human Notch1, wherein the antibody comprises:
   (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:24 or SEQ ID NO:14; and
   (b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:28, SEQ ID NO:32, or SEQ ID NO:8.

5. The antibody of claim 4, which comprises:
   (a) a heavy chain variable region comprising SEQ ID NO:24; and
   (b) a light chain variable region comprising SEQ ID NO:28.

6. The antibody of claim 4, which comprises:
   (a) a heavy chain variable region comprising SEQ ID NO:24; and
   (b) a light chain variable region comprising SEQ ID NO:32.

7. The antibody of claim 4, which comprises:
   (a) a heavy chain variable region comprising SEQ ID NO:14; and
   (b) a light chain variable region comprising SEQ ID NO:8.

8. The antibody of claim 1, which is 52M51-H4L3.

9. An isolated antibody comprising heavy and light chain variable regions identical in sequence to the heavy and light chain variable regions encoded by the plasmid on deposit as ATCC Patent Deposit Designation PTA-9549.

10. An antibody that competes for specific binding to human Notch1 with a second antibody in a competitive binding assay, wherein the second antibody comprises:
    (a) a heavy chain CDR1 comprising RGYWIE (SEQ ID NO:15); a heavy chain CDR2 comprising QILPGTGRTNYNEKFKG (SEQ ID NO:16); and a heavy chain CDR3 comprising FDGNYGYYAMDY (SEQ ID NO:17); and
    (b) a light chain CDR1 comprising RSSTGAVTTSNYAN (SEQ ID NO:18); a light chain CDR2 comprising GTNNRAP (SEQ ID NO:19); and a light chain CDR3 comprising ALWYSNHWVFGGGTKL (SEQ ID NO:20).

11. An antibody that competes for specific binding to human Notch1 with a second antibody in a competitive binding assay, wherein the second antibody comprises:
    (a) a heavy chain variable region comprising SEQ ID NO:24 and a light chain variable region comprising SEQ ID NO:28;
    (b) a heavy chain variable region comprising SEQ ID NO:24 and a light chain variable region comprising SEQ ID NO:32; or
    (c) a heavy chain variable region comprising SEQ ID NO:14 and a light chain variable region comprising SEQ ID NO:8.

12. An antibody that competes for specific binding to human Notch1 with antibody 52M51 or 52M51-H4L3.

13. The antibody of any one of claims 1 to 12, which is a recombinant antibody, a monoclonal antibody, a chimeric antibody, a humanized antibody, a human antibody, an antibody fragment, a bispecific antibody, a monospecific antibody, a monovalent antibody, an IgG1 antibody, or an IgG2 antibody.

14. The antibody of claim 1 encoded by the polynucleotide deposited with the ATCC as PTA-9549.

15. The antibody of any one of claims 1 to 14, which is conjugated to a cytotoxic agent.

16. An isolated cell producing the antibody of any one of claims 1 to 14.

17. A pharmaceutical composition comprising the antibody of any one of claims 1 to 14 and a pharmaceutically acceptable vehicle.

18. An isolated polynucleotide encoding the antibody of any one of claims 1 to 14.

19. A vector comprising the polynucleotide of claim 18.

20. An isolated cell comprising the polynucleotide of claim 18.

21. An isolated cell comprising the vector of claim 19.

22. Use of the antibody of any one of claims 1 to 14, in the manufacture of a medicament for the treatment of cancer.

23. Use of the antibody of any one of claims 1 to 14, in the manufacture of a medicament for inhibiting tumor growth.

24. The use of claim 22 or claim 23, wherein the treatment of cancer or inhibiting tumor growth comprises use of the antibody in combination with at least one additional anti-cancer or therapeutic agent.

25. The use of claim 24, wherein the additional therapeutic agent is a chemotherapeutic agent.

26. The use of claim 24, wherein the additional therapeutic agent is a second antibody.

27. The antibody of any one of claims 1-15, for use in the treatment of cancer.

28. The antibody of any one of claims 1-15, for use in inhibiting tumor growth.