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.

CLAIMS

1. An isolated monoclonal antibody that specifically binds a non-ligand binding membrane proximal region of an extracellular domain of human Notch 1, comprising:

   (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 according to Claim 1, wherein the antibody comprises:

   (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:24 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:28 or SEQ ID NO:32; or
   (b) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:14 and a light chain variable region having at least 90% sequence identity to SEQ ID NO:8.

3. The antibody according to Claim 1 or Claim 2, wherein the antibody is 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.

4. The antibody according to Claim 1, which comprises the same heavy and light chain variable regions as a polypeptide encoded by a plasmid on deposit as ATCC Patent Deposit Designation PTA-9549.

5. The antibody according to any one of Claims 1 to 3, comprising:

   (a) 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 or SEQ ID NO:32; or
   (b) 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.

6. The antibody according to Claim 5, comprising 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.

7. The antibody according to any one of Claims 1 to 3, comprising a polypeptide having the amino acid sequence of SEQ ID NO:22 and a polypeptide having the amino acid sequence of SEQ ID NO:26 or 30.

8. The antibody encoded by the polynucleotide deposited with the ATCC as PTA-9549.

9. The antibody according to any one of Claims 1 to 3 encoded by a polynucleotide comprising SEQ ID NO:21 and SEQ ID NO:25 or 29.

10. An isolated polynucleotide molecule comprising a polynucleotide that encodes the antibody according to any one of Claims 1 to 9.

11. A host cell:

    (a) producing the antibody according to any one of Claims 1 to 9; or
    (b) comprising the polynucleotide molecule according to Claim 10.

12. A pharmaceutical composition comprising the antibody according to any one of Claims 1 to 9 and a pharmaceutically acceptable carrier.

13. The antibody according to any one of Claims 1 to 9 for use in the treatment of a disease.

14. The antibody according to any one of Claims 1 to 9 for use in the treatment of cancer.

15. Use of the antibody according to any one of Claims 1 to 9 for the manufacture of a medicament for the treatment

16. The antibody according to any one of Claims 1 to 9 for use according to Claim 14 or the use according to Claim 15, wherein the treatment reduces the tumorigenicity of a tumor and/or reduces the frequency of cancer stem cells in a tumor.

17. The antibody according to any one of Claims 1 to 9 for use according to Claim 14 or Claim 16 or the use according to Claim 15 or Claim 16, wherein the cancer is selected from the group consisting of 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.

18. The antibody according to any one of Claims 1 to 9 for use according to any one of Claims 14, 16 or 17 or the use according to any one of Claims 15 to 17, wherein the treatment comprises administering the antibody, and further comprises administering to the subject an additional treatment for cancer;
preferably wherein the additional treatment for cancer is radiation therapy, chemotherapy, or an additional antibody therapeutic.