Claims

What is claimed is:

1. An isolated antibody, or an antigen binding portion thereof, that specifically binds to human Notch-1, wherein the antibody or antigen binding portion binds to at least a first epitope and a second epitope, wherein the first epitope resides within the Lin-A domain of human Notch-1, and the second epitope resides within the HD-C domain of human Notch-1.

2. The antibody or the antigen binding portion of claim 1, wherein the antibody or the antigen binding portion binds to both the first epitope and the second epitope, and that the first epitope and the second epitope are the only major epitopes that the antibody or the antigen binding portion binds to.

3. The antibody or the antigen binding portion of claim 2 , wherein the first epitope is a major epitope comprising 1 to 4 amino acid residues selected from 1463V, 1465S, 1466L and 1467Q.

4. The antibody or the antigen binding portion of any of claims 1, 2 and 3, wherein the second epitope is a major epitope comprising of 1 to 5 amino acid residues selected from 1705G, 1706A, 1707L, 1709S and 1710L.

5. The antibody or the antigen binding portion of claim 3 or claim 4, wherein a non conservative substitution of any of the amino acid residues of the first epitope results in a loss of more than 80% of the antibody or the antigen binding portion's binding affinity to human Notch-1.

6. The antibody or the antigen binding portion of any of claims 1 to 5, wherein the antibody or the antigen binding portion is humanized, human, or chimeric.

7. The antibody or the antigen binding portion of any of claims 1-5, wherein the antibody or the antigen binding portion is a mouse antibody.

8. The antibody or the antigen binding portion of claim 6, wherein said antibody or the antigen binding portion binds to human Notch-1 with a K_D of $1x\ 10^{-4}$ M or less.

9. An isolated monoclonal antibody, or an antigen binding portion thereof, that specifically binds to human Notch-1, comprising

(i) a heavy chain variable region CDR1 comprising the amino acid sequence shown in SEQ ID NO:18, or a variant thereof in which 1-4 residues of SEQ ID NO: 18 are modified;

(ii) a heavy chain variable region CDR2 comprising the amino acid sequence shown in SEQ ID NO:19, or a variant thereof in which 1-4 residues of SEQ ID NO: 19 are modified; and

(iii) a heavy chain variable region CDR3 having the amino acid sequence shown in SEQ ID NO:20, or a variant thereof in which 1-4 residues of SEQ ID NO: 20 are modified.

10. The antibody or antigen binding portion of claim 9, wherein any of the modifications of heavy chain variable region CDR1, CDR2 and CDR3 is a conservative substitution of the amino acid residue thereof.

11. The antibody or the antigen binding portion of claim 9, wherein none of the heavy chain variable region CDR1, CDR2 and CDR3 is modified.

12. An isolated monoclonal antibody, or an antigen binding portion thereof, that specifically binds to human Notch-1, comprising

(i) a light chain variable region CDR1 comprising the amino acid sequence shown in SEQ ID NO:12, or a variant thereof in which 1-4 residues of SEQ ID NO:12 are modified;

(ii) a light chain variable region CDR2 comprising the amino acid sequence shown in SEQ ID NO:13, or a variant thereof in which 1-4 residues of SEQ ID NO:13 are modified; and

(iii) a light chain variable region CDR3 comprising the amino acid sequence shown in SEQ ID NO:14, or a variant thereof in which 1-4 residues of SEQ ID NO: 14 are modified.

13. The antibody or the antigen binding portion of claim 12, wherein any of the modification of the light chain variable region CDR1, CDR2 and CDR3 is a conservative substitution of the amino acid residues thereof.

14. The antibody or the antigen binding portion of claim 12, wherein none of the light chain variable region CDR1, CDR2 and CDR3 is modified.

15. An isolated antibody, or an antigen binding portion thereof, that specifically binds to human Notch-1, comprising:

(i) a heavy chain variable region CDR1 comprising SEQ ID NO: 18,

(ii) a heavy chain variable region CDR2 comprising SEQ ID NO: 19,

(iii) a heavy chain variable region CDR3 comprising SEQ ID NO: 20,

(iv) a light chain variable region CDR1 comprising SEQ ID NO: 12,

(v) a light chain variable region CDR2 comprising SEQ ID NO: 13, and

(vi) a light chain variable region CDR3 comprising SEQ ID NO: 14,

wherein 1-4 amino residues of each of the light chain CDR and the heavy chain CDR may be modified.

16. The antibody or the antigen binding portion of claim 15, wherein any of the modification of the light chain CDRs and the heavy chain CDRs is a conservative substitution of the amino acid residues thereof.

17. The antibody or the antigen binding portion of claim 15, wherein none of the light chain CDRs and the heavy chain CDRs is modified.

18. The antibody or the antigen binding portion of any of claims 8 to17, wherein the antibody or the antigen binding portion is a mouse antibody or the antigen binding portion of a mouse antibody.

19. The antibody or the antigen binding portion of any of claims 8-17, wherein the antibody or the antigen binding portion is humanized, human, or chimeric.

20. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion binds to human Notch-1 with an equilibrium dissociation constant K_D of less than 1×10^{-5}M.

21. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion binds to human Notch-1 with an equilibrium dissociation constant K_D of less than 2×10^{-6}M.

22. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion binds to human Notch-1 with an equilibrium dissociation constant K_D of less than 1×10^{-6}M.

23. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion binds to human Notch-1 with an equilibrium dissociation constant K_D of less than 2×10^{-6}M.

24. The antibody of any of claims 8-17, which is a human full length antibody of subclass IgG_1, IgG_2, IgG_3 or IgG_4.

25. The antibody of any of claims 8-17, wherein the antibody is a humanized antibody of subclass IgG_1, IgG_2, IgG_3 or IgG_4.

26. The antibody of any of claims 8-17, wherein the antibody is a chimeric antibody of subclass IgG_1, IgG_2, IgG_3 or IgG_4. .

27. A pharmaceutical composition comprising the antibody or the antigen binding portion of any of claims 1-26.

28. A cell line that recombinantly produces the antibody or the antigen binding portion of any of claims 1-26.

29. An oligonucleotide encoding either the heavy chain or the light chain of the antibody or the antigen binding portion of any of claims 1-26.

30. An antibody or the antigen binding portion thereof of any of claims 1-26, or pharmaceutical composition thereof, for the use in the treatment of cancer.

Claims

What is claimed is:

1. An isolated antibody, or an antigen binding portion thereof, that specifically binds to human Notch-1, wherein the antibody or antigen binding portion binds to at least a first epitope and a second epitope, wherein the first epitope resides within the Lin-A domain of human Notch-1, and the second epitope resides within the HD-C domain of human Notch-1.

2. The antibody or the antigen binding portion of claim 1, wherein the antibody or the antigen binding portion binds to both the first epitope and the second epitope, wherein the first epitope and the second epitope are the only major epitopes that the antibody or the antigen binding portion binds to.

3. The antibody or the antigen binding portion of claim 2 , wherein the first epitope is a major epitope comprising 1 to 4 amino acid residues selected from 1463V, 1465S, 1466L and 1467Q.

4. The antibody or the antigen binding portion of any one of claims 1 to 3, wherein the second epitope is a major epitope comprising of 1 to 5 amino acid residues selected from 1705G, 1706A, 1707L, 1709S and 1710L.

5. The antibody or the antigen binding portion of claim 3 or 4, wherein a non conservative substitution of any of the amino acid residues of the first epitope results in a loss of more than 80% of the antibody or the antigen binding portion's binding affinity to human Notch-1.

6. The antibody or the antigen binding portion of any of claims 1 to 5, wherein the antibody or the antigen binding portion is humanized, human, or chimeric.

7. The antibody or the antigen binding portion of any of claims 1-5, wherein the antibody or the antigen binding portion is a mouse antibody.

8. The antibody or the antigen binding portion of claim 6, wherein said antibody or the antigen binding portion binds to human Notch-1 with a K_D of 1×10^{-4} M or less.

9. An isolated monoclonal antibody, or an antigen binding portion thereof, that specifically binds to human Notch-1, comprising

(i) a heavy chain variable region CDR1 comprising the amino acid sequence shown in SEQ ID NO:18, or a variant thereof in which 1-4 residues of SEQ ID NO: 18 are modified;

(ii) a heavy chain variable region CDR2 comprising the amino acid sequence shown in SEQ ID NO:19, or a variant thereof in which 1-4 residues of SEQ ID NO: 19 are modified; and

(iii) a heavy chain variable region CDR3 having the amino acid sequence shown in SEQ ID NO:20, or a variant thereof in which 1-4 residues of SEQ ID NO: 20 are modified.

10. The antibody or antigen binding portion of claim 9, wherein any of the modifications of heavy chain variable region CDR1, CDR2 and CDR3 is a conservative substitution of the amino acid residue thereof.

11. The antibody or the antigen binding portion of claim 9, wherein none of the heavy chain variable region CDR1, CDR2 and CDR3 are modified.

12. An isolated monoclonal antibody, or an antigen binding portion thereof, that specifically binds to human Notch-1, comprising

(i) a light chain variable region CDR1 comprising the amino acid sequence shown in SEQ ID NO:12, or a variant thereof in which 1-4 residues of SEQ ID NO:12 are modified;

(ii) a light chain variable region CDR2 comprising the amino acid sequence shown in SEQ ID NO:13, or a variant thereof in which 1-4 residues of SEQ ID NO:13 are modified; and

(iii) a light chain variable region CDR3 comprising the amino acid sequence shown in SEQ ID NO:14, or a variant thereof in which 1-4 residues of SEQ ID NO: 14 are modified.

13. The antibody or the antigen binding portion of claim 12, wherein any of the modifications of the light chain variable region CDR1, CDR2 and CDR3 is a conservative substitution of the amino acid residues thereof.

14. The antibody or the antigen binding portion of claim 12, wherein none of the light chain variable region CDR1, CDR2 and CDR3 are modified.

15. An isolated antibody, or an antigen binding portion thereof, that specifically binds to

human Notch-1, comprising:

(i) a heavy chain variable region CDR1 comprising SEQ ID NO: 18,

(ii) a heavy chain variable region CDR2 comprising SEQ ID NO: 19,

(iii) a heavy chain variable region CDR3 comprising SEQ ID NO: 20,

(iv) a light chain variable region CDR1 comprising SEQ ID NO: 12,

(v) a light chain variable region CDR2 comprising SEQ ID NO: 13, and

(vi) a light chain variable region CDR3 comprising SEQ ID NO: 14,

wherein 1-4 amino residues of each of the light chain CDR and the heavy chain CDR may be modified.

16. The antibody or the antigen binding portion of claim 15, wherein any of the modifications of the light chain CDRs and the heavy chain CDRs is a conservative substitution of the amino acid residues thereof.

17. The antibody or the antigen binding portion of claim 15, wherein none of the light chain CDRs or the heavy chain CDRs are modified.

18. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion is a mouse antibody or the antigen binding portion of a mouse antibody.

19. The antibody or the antigen binding portion of any of claims 8-17, wherein the antibody or the antigen binding portion is humanized, human, or chimeric.

20. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion binds to human Notch-1 with an equilibrium dissociation constant K_D of less than 1×10^{-5}M.

21. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion binds to human Notch-1 with an equilibrium dissociation constant K_D of less than 2×10^{-6}M.

22. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion binds to human Notch-1 with an equilibrium dissociation constant K_D of less than 1×10^{-6}M.

23. The antibody or the antigen binding portion of any of claims 8 to 17, wherein the antibody or the antigen binding portion binds to human Notch-1 with an equilibrium dissociation constant K_D of less than 2×10^{-7}M.

24. The antibody of any of claims 8-17, wherein the antibody is a human full length antibody of subclass IgG1, IgG2, IgG3 or IgG4.

25. The antibody of any of claims 8-17, wherein the antibody is a humanized antibody of subclass IgG1, IgG2, IgG3 or IgG4.

26. The antibody of any of claims 8-17, wherein the antibody is a chimeric antibody of subclass IgG1, IgG2, IgG3 or IgG4.

27. A pharmaceutical composition comprising the antibody or the antigen binding portion of any of claims 1-26.

28. A cell line that recombinantly produces the antibody or the antigen binding portion of any of claims 1-26.

29. An oligonucleotide encoding either the heavy chain or the light chain of the antibody or the antigen binding portion of any of claims 1-26.

30. An antibody or the antigen binding portion thereof of any of claims 1-26, or a pharmaceutical composition thereof, for the use in the treatment of cancer.