cleavage. Further, because the cleavage site is in a heavy chain HVR, even if amino acid change(s) would reduce cleavage, it was not known whether such changes could be made without significantly reducing the antibody's affinity for Jagged1. The inventors found, surprisingly, that mutation of the amino acid at position 101 in HVR-H3 reduced cleavage with only a slight loss of affinity.

Disclosed is an isolated antibody that binds to human Jagged1 is provided, wherein the antibody comprises an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 55 or 59, wherein X is any amino acid other than S. In one aspect, there is provided an isolated antibody that binds to human Jagged1, wherein the antibody comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 35 or 78; an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28 or 36; an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 55 or 59, wherein X is any amino acid other than S or H; an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16 or 40. In some embodiments, the antibody comprises at least one, at least two, at least three, at least four, or five HVRs selected from HVR-H1 comprising the amino acid sequence of SEQ ID NO: 35 or 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28 or 36; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16 or 40. In some embodiments, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 55; or (b) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 59; or (c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 59. In any of the embodiments described herein, the antibody may comprise (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 40; or (b) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16; or (c) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16.

In some embodiments, an isolated antibody that binds to Jagged1 comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 55; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 40; or (b) HVR-H1 comprising the amino acid sequence of SEQ

ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 59; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16; or (c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 59; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16.

In some embodiments, an isolated antibody that binds to Jagged1 comprises a VH sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 54, 58, or 62. In some embodiments, an isolated antibody that binds to Jagged1 comprises a VL sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 10, 26, or 34. In some embodiments, the antibody comprises (a) a VH sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 54 and a VL sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 34; or (b) a VH sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 58 and a VL sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 10; or (c) a VH sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 62 and a VL sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 26.

In one aspect, an isolated antibody that binds to human Jagged1 is provided, comprising (a) a VH sequence of SEQ ID NO: 54, wherein X is any amino acid other than S or H, and a VL sequence of SEQ ID NO: 34; or (b) a VH sequence of SEQ ID NO: 58, wherein X is any amino acid other than S or H, and a VL sequence of SEQ ID NO: 10; or (c) a VH sequence of SEQ ID NO: 62, wherein X is any amino acid other than S or H, and a VL sequence of SEQ ID NO: 26. In some embodiments, the antibody comprises a VH sequence of SEQ ID NO: 54 and a VL sequence of SEQ ID NO: 34. In some embodiments, the heavy chain comprises the amino acid sequence of SEQ ID NO: 56 and the light chain comprises the amino acid sequence of SEQ ID NO: 53. In some embodiments, the heavy chain comprises the amino acid sequence of SEQ ID NO: 57 and the light chain comprises the amino acid sequence of SEQ ID NO: 53.

In any of the embodiments described herein, X may be any amino acid other than S or H. In any of the embodiments described herein, X may be selected from A, D, E, G, I, K, L, N, Q, R T, and V. In any of the embodiments described herein, X may be T.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to human Jagged1, wherein the antibody comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO: 35 or 78; an HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28 or 36; an HVR-H3 comprising the amino acid sequence of SEQ ID NO: 55 or 59, wherein X is any amino acid other than S or H; an HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16 or 40.

2. The isolated antibody of claim 1, wherein the antibody comprises:

a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 55; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 40; or

b) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 59; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16; or

c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 59; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16.

3. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a VH sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 54, 58, or 62.

4. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a VL sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 10, 26, or 34.

5. The isolated antibody of any one of the preceding claims, wherein the antibody comprises:

a) a VH sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 54 and a VL sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 34; or

b) a VH sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 58 and a VL sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 10; or

c) a VH sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 62 and a VL sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 26.

6. An isolated antibody that binds human Jagged1, comprising:

a) a VH sequence of SEQ ID NO: 54, wherein X is any amino acid other than S or H, and a VL sequence of SEQ ID NO: 34; or

b) a VH sequence of SEQ ID NO: 58, wherein X is any amino acid other than S or H, and a VL sequence of SEQ ID NO: 10; or

c) a VH sequence of SEQ ID NO: 62, wherein X is any amino acid other than S or H, and a VL sequence of SEQ ID NO: 26.

7. The isolated antibody of claim 6, wherein the antibody comprises a VH sequence of SEQ ID NO: 54 and a VL sequence of SEQ ID NO: 34.

8. The isolated antibody of claim 7, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 56 and the light chain comprises the amino acid sequence of SEQ ID NO: 53.

9. The isolated antibody of claim 7, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 57 and the light chain comprises the amino acid sequence of SEQ ID NO: 53.

10. The isolated antibody of any one of the preceding claims, wherein X is selected from A, D, E, G, I, K, L, N, Q, R T, and V.

11. The isolated antibody of any one of the preceding claims, wherein X is T.

12. An isolated antibody that binds human Jagged1, comprising:

a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 37; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid

sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 40; or

b) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 36; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16; or

c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 78; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 38; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 16.

13. The isolated antibody of claim 12, wherein the antibody comprises:

a) a VH sequence of SEQ ID NO: 33 and a VL sequence of SEQ ID NO: 34; or

b) a VH sequence of SEQ ID NO: 65 and a VL sequence of SEQ ID NO: 10; or

c) a VH sequence of SEQ ID NO: 66 and a VL sequence of SEQ ID NO: 26.

14. The isolated antibody of claim 13, wherein the antibody comprises a VH sequence of SEQ ID NO: 33 and a VL sequence of SEQ ID NO: 34.

15. The antibody of any one of the preceding claims, which is a full length IgG1 antibody.

16. The antibody of claim 15, wherein the antibody substantially lacks effector function.

17. The antibody of claim 15, wherein the heavy chain comprises a N297G or N297A mutation.

18. The isolated antibody of claim 14, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 51 and the light chain comprises the amino acid sequence of SEQ ID NO: 53.

19. The isolated antibody of claim 14, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 52 and the light chain comprises the amino acid sequence of SEQ ID NO: 53.

20. The antibody of claim 13, wherein the antibody comprises:

a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 69 and a light chain comprising the amino acid sequence of SEQ ID NO: 75; or

b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 70 and a light chain comprising the amino acid sequence of SEQ ID NO: 76; or

c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 79 and a light chain comprising the amino acid sequence of SEQ ID NO: 75; or

d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 80 and a light chain comprising the amino acid sequence of SEQ ID NO: 76.

21. The antibody of any one of the preceding claims, wherein the antibody is an antagonist of Jagged1-mediated signaling.

22. The antibody of any one of the preceding claims, wherein the antibody does not bind human Jagged2.

23. The antibody of any one of the preceding claims, wherein the antibody does not bind human DLL4.

24. The antibody of any one of the preceding claims, wherein the antibody does not bind human DLL1.

25. The antibody of any one of the preceding claims, wherein the antibody does not bind murine Jagged2, murine DLL4, and/or murine DLL1.

26. The antibody of any one of the preceding claims, wherein the antibody reduces tumor growth in a mouse xenograft model without causing weight loss.

27. The antibody of claim 26, wherein the mouse xenograft model is a liver cancer xenograft model.

28. The antibody of claim 26 or claim 27, wherein tumor growth is reduced by at least 50, at least 60, at least 70, at least 80, or at least 90 AUC/day TGI%.

29. An isolated nucleic acid encoding the antibody of any one of the preceding claims.

30. A host cell comprising the isolated nucleic acid of claim 29.

31. A method of producing an antibody comprising culturing the host cell of claim 30 so that the antibody is produced.

32. An immunoconjugate comprising the antibody of any one of claims 1 to 28 and a cytotoxic agent.

33. A pharmaceutical formulation comprising the antibody of any one of the claims 1 to 28 and a pharmaceutically acceptable carrier.

34. A pharmaceutical formulation comprising the immunoconjugate of claim 32 and a pharmaceutically acceptable carrier.

35. The antibody of any one of claims 1 to 28 or the immunoconjugate of claim 32 for use as a medicament.

36. The antibody of any one of claims 1 to 28 or the immunoconjugate of claim 32 for use in treating cancer.

37. The antibody of any one of claims 1 to 28 or the immunoconjugate of claim 32 for reducing cancer cell growth.

38. Use of the antibody of any one of claims 1 to 28 or the immunoconjugate of claim 33 in the manufacture of a medicament for treating cancer.

39. The use of claim 38, wherein the medicament is for reducing cancer cell growth.

40. Use of the antibody of any one of claims 1 to 28 or the immunoconjugate of claim 33 in the manufacture of a medicament for treating diseases associated with goblet cell metaplasia (e.g., in lung) and/or excess mucus.

41. The use of claim 40, wherein the medicament is for treating a disease associated with goblet cell metaplasia.

42. The use of claim 41, wherein the medicament is for treating asthma, cystic fibrosis, chronic obstructive pulmonary disease, or Barrett's esophagus.

43. The use of claim 38, wherein the cancer is selected from breast cancer, lung cancer, brain cancer, cervical cancer, colon cancer, liver cancer, bile duct cancer, pancreatic cancer, skin cancer, B-cell malignancies, and T-cell malignancies.

44. The isolated antibody of any one of claims 1 to 28 conjugated to a label.

45. The isolated antibody of claim 44, wherein the label is a positron emitter.

46. The isolated antibody of claim 45, wherein the positron emitter is ^{89}Zr.

47. A method of detecting human Jagged1 in a biological sample comprising contacting the biological sample with the antibody of any one of claims 1 to 28 and 44 to 46 under conditions permissive for binding of the antibody to a naturally occurring human Jagged1, and detecting whether a complex is formed between the antibody and a naturally occurring human Jagged1 in the biological sample.

48. The method of claim 47, wherein the biological sample is selected from breast cancer, lung cancer, brain cancer, cervical cancer, colon cancer, liver cancer, bile duct cancer, pancreatic cancer, skin cancer, B-cell malignancies, and T-cell malignancies.