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; 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

sequence of SEQ ID NO: 33 and a light chain variable region comprising the sequence of SEQ ID NO: 34, wherein the antibody is not antibody A, antibody A-1, or antibody A-2.

In another aspect, an isolated nucleic acid encoding an isolated antibody described above is provided. In a further aspect, a host cell comprising the isolated nucleic acid described above is provided. In a further aspect, a method of producing an antibody is provided, comprising culturing the host cell described above so that the antibody is produced.

In another aspect, an immunoconjugate is provided, comprising any of the antibodies described above and a cytotoxic agent.

In another aspect, a pharmaceutical formulation is provided, comprising any of the antibodies described above and a pharmaceutically acceptable carrier. In another aspect, a pharmaceutical formulation is provided, comprising an immunoconjugate described above and a pharmaceutically acceptable carrier.

In another aspect, any of the antibodies or immunoconjugates described above is provided for use as a medicament. In another aspect, any of the antibodies or immunoconjugates described above is provided for use in treating a cancer. In another aspect, any of the antibodies or immunoconjugates described above is provided for use in reducing cancer cell growth.

In one embodiment, a method of inhibiting Jagged1-mediated signaling is provided. In one embodiment, a method of inhibiting Jagged1-mediated signaling *in vitro* is provided. In one embodiment, a method of inhibiting Jagged1-mediated signaling *in vivo* is provided.

Disclosed is a use of any of the antibodies or immunoconjugates described above in the manufacture of a medicament. In another aspect, there is provided a use of the antibody described above or the immunoconjugate described above in the manufacture of a medicament for treating cancer. In another aspect, there is provided a use of the antibody described above or the immunoconjugate described above in the manufacture of a medicament for treating diseases associated with goblet cell metaplasia (e.g., in lung) and/or excess mucus. In one embodiment, a method of treating an individual having a cancer comprising administering to the individual an effective amount of an antibody of any of the above embodiments is provided. In one embodiment, the cancer is selected from the group consisting of: 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.

The present inventors discovered that treatment with Jagged1-antibody biases cell fate in the airways away from a secretory cell (including goblet cell) fate and toward a ciliated cell fate. Jagged1 signaling is important for maintaining the secretory cell fate, and inhibition of Jagged1 signaling prevented goblet cell metaplasia. The present inventors also showed that the club cell-to-ciliated cell conversion is direct and did not involve cell division (data not shown). This transdifferentiation of one cell type to another occurred in the adult lung and is distinct from cell fate choices that involve progenitor cell division, such as after damage or during development. Goblet cell metaplasia or excess mucus is a hallmark of several airway diseases, such as asthma, cystic fibrosis, COPD and Barrett's esophagus. These Jagged inhibition results provide the basis for therapeutic applications involving use of Jagged1 or Jagged2 inhibitors for prevention or reversal of goblet cell metaplasia and for treatment of conditions

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; 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, 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, 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, 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 any amino acid other than S or H.

11. 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.

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

13. 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.

14. The isolated antibody of claim 13, 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.

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

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

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

18. The antibody of claim 16, wherein the heavy chain comprises a N297G or N297A mutation.

19. The isolated antibody of claim 15, 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.

20. The isolated antibody of claim 15, 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.

21. The antibody of claim 14, 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.

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

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

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

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

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

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

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

29. The antibody of claim 27 or claim 28, 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%.

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

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

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

33. An immunoconjugate comprising the antibody of any one of claims 1 to 29 and a cytotoxic agent.

34. A pharmaceutical formulation comprising the antibody of any one of the claims 1 to 29 and a pharmaceutically acceptable carrier.

35. A pharmaceutical formulation comprising the immunoconjugate of claim 33 and a pharmaceutically acceptable carrier.

36. The antibody of any one of claims 1 to 29 or the immunoconjugate of claim 33 for use as a medicament.

37. The antibody of any one of claims 1 to 29 or the immunoconjugate of claim 33 for use in treating cancer.

38. The antibody of any one of claims 1 to 29 or the immunoconjugate of claim 33 for reducing cancer cell growth.

39. Use of the antibody of any one of claims 1 to 29 or the immunoconjugate of claim 33 in the manufacture of a medicament for treating cancer.

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

41. Use of the antibody of any one of claims 1 to 29 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.

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

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

44. The use of claim 39, 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.

45. The isolated antibody of any one of claims 1 to 29 conjugated to a label.

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

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

48. 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 29 and 45 to 47 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.

49. The method of claim 48, 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.