expression. Thus, KGF subfamily members, including FGF7 (KGF), FGF10, and FGF22, bind only to FGFRIIIb (Zhang et al., *op. cit.*) and are expressed in mesenchymal tissues so may be paracrine effectors of epithelial cells (Ornitz et al., 1996, *op. cit.*). In contrast, the FGF4 subfamily members FGF4-6 bind to FGFR2IIIc and are expressed in both epithelial and mesenchymal lineages so may have either autocrine or paracrine functions. Because of the expression patterns of the isoforms of FGFR2 and their ligands, FGFR2 plays a role in epithelial-mesynchymal interactions (Finch et al., Dev. Dyn. 203:223, 1995), so it is not surprising that knock-out of FGFR2IIIb in mice leads to severe embryonic defects and lethality (De Moerlooze et al., Development 127:483, 2000).

[0004] KGF (FGF7) and KGFR (FGFR2IIIb) are overexpressed in many pancreatic cancers (Ishiwata et al., Am. J. Pathol. 153: 213, 1998), and their coexpression correlates with poor prognosis (Cho et al., Am. J. Pathol. 170:1964, 2007). Somatic mutations of the FGFR2 gene were found in 12% of a large panel of endometrial (uterine) carcinomas, and in several tested cases were required for tumor cell survival (Dutt et al., Proc. Natl. Acad. Sci. USA 105:8713, 2008). In two tumors the FGFR2 mutation was found to be the same S252W substitution associated with Apert syndrome. Amplification and overexpression of FGFR2 is associated with the undifferentiated, diffuse type of gastric cancer, which has a particularly poor prognosis, and inhibition of the FGFR2 activity by small molecule compounds potently inhibited proliferation of such cancer cells (Kunii et al., Cancer Res. 68:2340, 2008; Nakamura et al., Gastroenterol. 131:1530, 2006).

SUMMARY OF THE INVENTION

[0005] In once aspect, the present invention refers to a composition comprising a plurality of anti-FGFR2IIIb antibodies, wherein each anti-FGFR2IIIb antibody comprises heavy chain and light chain variable regions, wherein the heavy chain variable region comprises: (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6; (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8; and the light chain variable region comprises: (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9; (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10; and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 11; wherein at least 95% of the anti-FGFR2IIIb antibodies in the composition are afucosylated. In one aspect, the present invention refers to a host cell comprising nucleic acid encoding anti-FGFR2IIIb antibodies disclosed herein, wherein the host cell lacks a functional alpha-1,6-fucosyltransferase gene (FUT8) gene. In another ~~aspect~~example, ~~the present invention refers to~~disclosed herein is a composition comprising a plurality of afucosylated anti-FGFR2IIIb antibodies, wherein the anti-FGFR2IIIb antibodies compete for binding to FGFR2IIIb with an antibody comprising a heavy chain variable region comprising the amino acid

sequence of SEQ ID NO: 4 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 5. In yet another ~~aspect~~example, disclosed herein is ~~the present invention refers to~~ a host cell comprising nucleic acid encoding the anti-FGFR2IIIb antibody as disclosed herein, wherein the host cell lacks a functional alpha-1,6-fucosyltransferase gene (FUT8) gene. In yet another aspect, the present invention refers to a method for making afucosylated anti-FGFR2IIIb antibodies, said method comprising culturing the host cell as disclosed herein under conditions suitable for expressing the nucleic acid encoding the anti-FGFR2IIIb antibody. In a further aspect, the present invention refers to a method for making afucosylated anti-FGFR2IIIb antibodies, comprising culturing the host cell as disclosed herein under conditions suitable for producing afucosylated anti-FGFR2IIIb antibodies. In one aspect, the present invention refers to a pharmaceutical composition comprising the composition as disclosed herein and a pharmaceutically acceptable carrier. In another aspect, the present invention refers to use of a composition as disclosed herein or of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in an individual in need thereof. In one aspect, the present invention refers to a pharmaceutical composition for treating cancer comprising an effective amount of anti-FGFR2IIIb antibodies as disclosed herein and a pharmaceutically acceptable carrier. In a further ~~aspect~~example, ~~the present invention refers to~~ disclosed herein is a pharmaceutical composition for treating cancer in an individual comprising an effective amount of an anti-FGFR2IIIb antibody as disclosed herein and a pharmaceutically acceptable carrier. In some examples, an anti-FGFR2IIIb antibody is provided, wherein the heavy chain variable region comprises: (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6; (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8; and the light chain variable region comprises: (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9; (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10; and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 11; wherein the antibody is afucosylated. In some examples, the antibody lack fucose at Asn297. In some examples, compositions comprising a plurality of anti-FGFR2IIIb antibodies are provided, wherein the heavy chain variable region of each anti-FGFR2IIIb antibody in the composition comprises: (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6; (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8; and the light chain variable region of each anti-FGFR2IIIb antibody in the composition comprises: (iv) HVR-L1

CLAIMS

1. A composition comprising a plurality of anti-FGFR2IIIb antibodies, wherein each anti-FGFR2IIIb antibody comprises heavy chain and light chain variable regions, wherein the heavy chain variable region comprises:

(i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6;

(ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and

(iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8;

and the light chain variable region comprises:

(iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9;

(v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10; and

(vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 11;

wherein at least 95% of the anti-FGFR2IIIb antibodies in the composition are afucosylated.

2. The composition of claim 1, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 4.

3. The composition of claim 1 or claim 2, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 5.

4. The composition of claim 1, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 4 and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 5.

5. The composition of any one of claims 1 to 4, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 2.

6. The composition of any one of claims 1 to 5, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 3.

7. The composition of claim 1, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 2 and the light chain comprises the amino acid sequence of SEQ ID NO: 3.

8. A composition comprising a plurality of afucosylated anti-FGFR2IIIb antibodies, wherein the anti-FGFR2IIIb antibodies compete for binding to FGFR2IIIb with an antibody

comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 5.

9. The composition of any one of claims 1 to 8, wherein the antibodies are monoclonal antibodies.

10. The composition of any one of claims 1 to 9, wherein the antibodies are chimeric antibodies.

11. The composition of any one of claims 1 to 10, wherein the antibodies are humanized antibodies.

12. The composition of any one of claims 1 to 11, wherein the antibodies lack fucose at Asn297.

13. The composition of any one of claims 1 to 12, wherein the antibodies comprise a κ light chain constant region.

14. The composition of any one of claims 1 to 13, wherein the antibodies comprise an IgG1 heavy chain constant region.

15. The composition of any one of claims 1 to 14, wherein the afucosylated antibodies have enhanced ADCC activity *in vitro* compared to a fucosylated anti-FGFR2IIIb antibody having the same amino acid sequence.

16. The composition of claim 15, wherein the afucosylated anti-FGFR2IIIb antibodies cause specific lysis that is at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 60, at least 65, at least 70, or at least 75 percentage points greater than specific lysis with the fucosylated anti-FGFR2IIIb antibody.

17. The composition of claim 15 or claim 16, wherein ADCC activity is determined using Ba/F3 cells expressing FGFR2IIIb as target cells and isolated human PBMCs as effector cells.

18. The composition of any one of claims 1 to 17, wherein the afucosylated antibodies have enhanced affinity for Fc gamma RIIIA compared to a fucosylated anti-FGFR2IIIb antibody having the same amino acid sequence.

19. The composition of claim 18, wherein the afucosylated anti-FGFR2IIIb antibodies bind to Fc gamma RIIIA with at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 7-fold, at least 10-fold, at least 12-fold, at least 15-fold, at least 17-fold, or at least 20-fold greater affinity than the fucosylated anti-FGFR2IIIb antibody.

20. The composition of claim 18 and claim 19, wherein affinity for Fc gamma RIIIA is determined using surface plasmon resonance.

21. The composition of any one of claims 18 to 20, wherein Fc gamma RIIIA is selected from Fc gamma RIIIA(V158) and Fc gamma RIIIA(F158).

22. The composition of claim 21, wherein Fc gamma RIIIA is Fc gamma RIIIA(V158).

23. The composition of any one of claims 1 to 22, wherein the afucosylated anti-FGFR2IIIb antibodies bind FGFR2IIIb but do not bind to FGFR2IIIc.

24. A host cell comprising nucleic acid encoding the anti-FGFR2IIIb antibody of any one of claims 1 to 23, wherein the host cell lacks a functional alpha-1,6-fucosyltransferase gene (FUT8) gene.

25. The host cell of claim 24, which is a CHO cell.

26. A method for making afucosylated anti-FGFR2IIIb antibodies, said method comprising culturing the host cell of claim 24 of claim 25 under conditions suitable for expressing the nucleic acid encoding the anti-FGFR2IIIb antibody.

27. A method for making afucosylated anti-FGFR2IIIb antibodies, comprising culturing the host cell of claim 24 or claim 25 under conditions suitable for producing afucosylated anti-FGFR2IIIb antibodies.

28. The method of claim 26 or 27, further comprising recovering the anti-FGFR2IIIb antibody produced by the host cell.

29. The method of any one of claims 26 to 28, wherein at least 95% of the anti-FGFR2IIIb antibodies produced by the host cell are afucosylated.

30. The method of claim 29, wherein fucose is undetectable in the anti-FGFR2IIIb antibodies produced by the host cell.

31. The method of claim 29 or claim 30, wherein fucose is detected by a method comprising HPLC, capillary electrophoresis, or MALDI-TOF mass spectrometry.

32. A pharmaceutical composition comprising the composition of any one of claims 1 to 23 and a pharmaceutically acceptable carrier.

33. Use of a composition of any one of claims 1-23 or of a pharmaceutical composition of claim 32 in the manufacture of a medicament for treating cancer in an individual in need thereof.

34. The use of claim 33, wherein the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, or esophageal cancer.

35. The use of claim 34, wherein the cancer is gastric cancer.

36. The use of any one of claims 33 to 35, wherein the cancer overexpresses FGFR2IIIb.

37. The use of claim 36, wherein FGFR2IIIb expression is determined by immunohistochemistry (IHC).

38. The use of claim 36 or claim 37, wherein the cancer does not comprise FGFR2 gene amplification.

39. The use of any one of claims 33 to 38, wherein the cancer comprises an FGFR2 gene amplification.

40. A pharmaceutical composition for treating cancer comprising an effective amount of an anti-FGFR2IIIb antibody of any one of claims 1 to 23 and a pharmaceutically acceptable carrier.

41. The pharmaceutical composition of claim 40, wherein the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, and esophageal cancer.

42. The pharmaceutical composition of claim 41, wherein the cancer is gastric cancer.

43. The pharmaceutical composition of any one of claims 40 to 42, wherein the cancer overexpresses FGFR2IIIb.

44. The pharmaceutical composition of claim 43, wherein FGFR2IIIb expression is determined by immunohistochemistry (IHC).

45. The pharmaceutical composition of claim 43 or claim 44, wherein the cancer does not comprise FGFR2 gene amplification.

46. The pharmaceutical composition of any one of claims 40 to 43, wherein the cancer comprises an FGFR2 gene amplification.

CLAIMS

1. A composition comprising a plurality of anti-FGFR2IIIb antibodies, wherein each anti-FGFR2IIIb antibody comprises heavy chain and light chain variable regions, wherein the heavy chain variable region comprises:

(i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6;

(ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and

(iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8;

and the light chain variable region comprises:

(iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9;

(v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10; and

(vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 11;

wherein at least 95% of the anti-FGFR2IIIb antibodies in the composition are afucosylated.

2. The composition of claim 1, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 4.

3. The composition of claim 1 or claim 2, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 5.

4. The composition of claim 1, wherein the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 4 and the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 5.

5. The composition of any one of claims 1 to 4, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 2.

6. The composition of any one of claims 1 to 5, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 3.

7. The composition of claim 1, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 2 and the light chain comprises the amino acid sequence of SEQ ID NO: 3.

8. The composition of any one of claims 1 to 7, wherein the antibodies are monoclonal antibodies.

9. The composition of any one of claims 1 to 8, wherein the antibodies are chimeric antibodies.

10. The composition of any one of claims 1 to 9, wherein the antibodies are humanized antibodies.

11. The composition of any one of claims 1 to 10, wherein the antibodies lack fucose at Asn297.

12. The composition of any one of claims 1 to 11, wherein the antibodies comprise a κ light chain constant region.

13. The composition of any one of claims 1 to 12, wherein the antibodies comprise an IgG1 heavy chain constant region.

14. The composition of any one of claims 1 to 13, wherein the afucosylated antibodies have enhanced ADCC activity *in vitro* compared to a fucosylated anti-FGFR2IIIb antibody having the same amino acid sequence.

15. The composition of claim 14, wherein the afucosylated anti-FGFR2IIIb antibodies cause specific lysis that is at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 60, at least 65, at least 70, or at least 75 percentage points greater than specific lysis with the fucosylated anti-FGFR2IIIb antibody.

16. The composition of claim 14 or claim 15, wherein ADCC activity is determined using Ba/F3 cells expressing FGFR2IIIb as target cells and isolated human PBMCs as effector cells.

17. The composition of any one of claims 1 to 16, wherein the afucosylated antibodies have enhanced affinity for Fc gamma RIIIA compared to a fucosylated anti-FGFR2IIIb antibody having the same amino acid sequence.

18. The composition of claim 17, wherein the afucosylated anti-FGFR2IIIb antibodies bind to Fc gamma RIIIA with at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 7-fold, at least 10-fold, at least 12-fold, at least 15-fold, at least 17-fold, or at least 20-fold greater affinity than the fucosylated anti-FGFR2IIIb antibody.

19. The composition of claim 17 or claim 18, wherein affinity for Fc gamma RIIIA is determined using surface plasmon resonance.

20. The composition of any one of claims 17 to 19, wherein Fc gamma RIIIA is selected from Fc gamma RIIIA(V158) and Fc gamma RIIIA(F158).

21. The composition of claim 20, wherein Fc gamma RIIIA is Fc gamma RIIIA(V158).

22. The composition of any one of claims 1 to 21, wherein the afucosylated anti-FGFR2IIIb antibodies bind FGFR2IIIb but do not bind to FGFR2IIIc.

23. A host cell comprising nucleic acid encoding anti-FGFR2IIIb antibodies of any one of claims 1 to 22, wherein the host cell lacks a functional alpha-1,6-fucosyltransferase gene (FUT8) gene.

24. The host cell of claim 23, which is a CHO cell.

25. A method for making afucosylated anti-FGFR2IIIb antibodies, said method comprising culturing the host cell of claim 23 or claim 24 under conditions suitable for expressing nucleic acid encoding anti-FGFR2IIIb antibodies.

26. A method for making afucosylated anti-FGFR2IIIb antibodies, comprising culturing the host cell of claim 23 or claim 24 under conditions suitable for producing afucosylated anti-FGFR2IIIb antibodies.

27. The method of claim 25 or 26, further comprising recovering the anti-FGFR2IIIb antibody produced by the host cell.

28. The method of any one of claims 25 to 27, wherein at least 95% of the anti-FGFR2IIIb antibodies produced by the host cell are afucosylated.

29. The method of claim 28, wherein fucose is undetectable in the anti-FGFR2IIIb antibodies produced by the host cell.

30. The method of claim 28 or claim 29, wherein fucose is assayed by a method comprising HPLC, capillary electrophoresis, or MALDI-TOF mass spectrometry.

31. A pharmaceutical composition comprising the composition of any one of claims 1 to 22 and a pharmaceutically acceptable carrier.

32. Use of a composition of any one of claims 1-22 or of a pharmaceutical composition of claim 31 in the manufacture of a medicament for treating cancer in an individual in need thereof.

33. The use of claim 32, wherein the cancer is a solid tumor.

34. The use of claim 32 or 33, wherein the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, or esophageal cancer.

35. The use of claim 34, wherein the cancer is gastric cancer.

36. The use of any one of claims 32 to 35, wherein the cancer overexpresses FGFR2IIIb.

37. The use of claim 36, wherein FGFR2IIIb expression is determined by immunohistochemistry (IHC).

38. The use of claim 36 or claim 37, wherein the cancer does not comprise FGFR2 gene amplification.

39. The use of any one of claims 32 to 37, wherein the cancer comprises an FGFR2 gene amplification.

40. The use of any one of claims 32 to 38, wherein the treatment further comprises administering at least one additional therapeutic agent selected from a platinum agent, paclitaxel, ABRAXANE®, docetaxel, gemcitabine, capecitabine, irinotecan, epirubicin, FOLFOX, FOLFIRI, leucovorin, fluorouracil, mitomycin C, and doxorubicin hydrochloride.

41. The use of claim 40, wherein the at least one additional therapeutic agent is a platinum agent and the platinum agent is selected from cisplatin, oxaliplatin, and carboplatin.

42. The use of claim 40, wherein the additional therapeutic agent is paclitaxel.

43. The use of claim 40, wherein the additional therapeutic agent is cisplatin and/or 5-FU.

44. The use of claim 40, wherein the additional therapeutic agent is FOLFOX.

45. A pharmaceutical composition for treating cancer comprising an effective amount of anti-FGFR2IIIb antibodies of any one of claims 1 to 22 and a pharmaceutically acceptable carrier.

46. The pharmaceutical composition of claim 45, wherein the cancer is a solid tumor.

47. The pharmaceutical composition of claim 45 or claim 46, wherein the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, and esophageal cancer.

48. The pharmaceutical composition of claim 47, wherein the cancer is gastric cancer.

49. The pharmaceutical composition of any one of claims 45 to 48, wherein the cancer overexpresses FGFR2IIIb.

50. The pharmaceutical composition of claim 49, wherein FGFR2IIIb expression is determined by immunohistochemistry (IHC).

51. The pharmaceutical composition of claim 49 or claim 50, wherein the cancer does not comprise FGFR2 gene amplification.

52. The pharmaceutical composition of any one of claims 45 to 51, wherein the cancer comprises an FGFR2 gene amplification.