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 another aspect, the present invention refers to 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, 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 a further aspect, the present invention refers to 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 ~~embodiments~~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 ~~embodiments~~examples, the antibody lack fucose at Asn297. In some examples~~embodiments~~, 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

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 antibodies in the composition are afucosylated. In some examplesembodiments, the composition may be a supernatant from an antibody-producing cell line. In some examplesembodiments, the composition may be a buffered composition. In some examplesembodiments, the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 4. In some examplesembodiments, the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 5. In some examplesembodiments, 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. In some examplesembodiments, the heavy chain comprises the amino acid sequence of SEQ ID NO: 2. In some examplesembodiments, the light chain comprises the amino acid sequence of SEQ ID NO: 3. In some examplesembodiments, 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. In some examplesembodiments, a composition comprising a plurality of afucosylated anti-FGFR2IIIb antibodies is provided, wherein the antibodies compete for binding to FGFR2IIIb with an antibody comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 4 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 5.

[0006] In some examplesembodiments, the antibodies are monoclonal antibodies. In some examplesembodiments, the antibodies are chimeric antibodies. In some examplesembodiments, the antibodies are humanized antibodies. In any of the examples embodiments described herein, the antibodies may comprise a κ light chain constant region. In any of the examples embodiments described herein, the antibodies may comprise an IgG1 heavy chain constant region.

[0007] In some examplesembodiments, the antibodies have enhanced ADCC activity *in vitro* compared to fucosylated anti-FGFR2IIIb antibodies having the same amino acid sequence. In some examplesembodiments, 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 fucosylated anti-FGFR2IIIb antibodies. In some examplesembodiments, ADCC activity is determined using Ba/F3 cells expressing FGFR2IIIb as target cells and isolated human PBMCs as effector cells.

[0008] In some examplesembodiments, the antibodies have enhanced affinity for Fc gamma RIIIA compared to fucosylated anti-FGFR2IIIb antibodies having the same amino acid sequence. In some examplesembodiments, 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 fucosylated anti-FGFR2IIIb antibodies. In some examplesembodiments, affinity for Fc gamma RIIIA is determined using surface plasmon resonance. In some examplesembodiments, Fc gamma RIIIA is selected from Fc gamma RIIIA(V158) and Fc gamma RIIIA(F158). In some examplesembodiments, Fc gamma RIIIA is Fc gamma RIIIA(V158).

[0009] In any of the examples embodiments described herein, the antibodies may bind FGFR2IIIb but not FGFR2IIIc.

[0010] In any of the examples embodiments described herein, a composition comprising a plurality of afucosylated anti-FGFR2IIIb antibodies comprises at least 95% afucosylated antibodies. In any of the examples embodiments described herein, a composition comprising a plurality of afucosylated anti-FGFR2IIIb antibodies may have undetectable fucosylation. In some examplesembodiments, the presence of fucose may be determined by a method comprising high performance liquid chromatography (HPLC), capillary electrophoresis, or MALDI-TOF mass spectrometry.

[0011] In some examplesembodiments, host cells are provided that comprise nucleic acid encoding an anti-FGFR2IIIb antibody described herein, wherein the host cell lacks a functional alpha-1,6-fucosyltransferase gene (FUT8) gene. In some examplesembodiments, the host cell is a CHO cell.

[0012] In some examplesembodiments, methods for making afucosylated anti-FGFR2IIIb antibodies are provided. In some examplesembodiments, a method comprises culturing a host cell under conditions suitable for expressing nucleic acid encoding the anti-FGFR2IIIb antibody, wherein the host cell lacks a functional alpha-1,6-fucosyltransferase gene (FUT8) gene. In some examplesembodiments, a method for making afucosylated anti-FGFR2IIIb antibodies comprises culturing the host cell under conditions suitable for producing the afucosylated anti-FGFR2IIIb antibody. In some examplesembodiments, the method further comprises recovering the anti-FGFR2IIIb antibody produced by the host cell. In some examplesembodiments, less than 5% of the anti-FGFR2IIIb antibodies produced by the host cell comprise fucose. In some examplesembodiments, at least 95% of the anti-FGFR2IIIb antibodies produced by the host cell lack fucose (i.e., are afucosylated). In some examplesembodiments, fucose is undetectable in the anti-FGFR2IIIb antibodies produced by the host cell. In some examplesembodiments, presence of fucose is detected by a method comprising HPLC, capillary electrophoresis, or MALDI-TOF mass spectrometry.

[0013] In some examplesembodiments, pharmaceutical compositions are provided, wherein the pharmaceutical composition comprises afucosylated anti-FGFR2IIIb antibodies described herein and a pharmaceutically acceptable carrier.

[0014] In some examples~~embodiments~~, methods of treating cancer are provided. In some ~~embodiments~~examples, a method comprises administering an effective amount of a pharmaceutical composition comprising afucosylated anti-FGFR2IIIb antibodies described herein and a pharmaceutically acceptable carrier. In some ~~embodiments~~examples, the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, and esophageal cancer. In some ~~embodiments~~examples, the cancer is gastric cancer. In some ~~embodiments~~examples, the cancer comprises an FGFR2 gene amplification. In some ~~embodiments~~examples, FGFR2 amplification comprises FGFR2:CEN10 (chromosome 10 centromere) ratio of >3. In some ~~embodiments~~examples, the cancer overexpresses FGFR2IIIb. In some ~~embodiments~~examples, a cancer comprising FGFR2 amplification overexpresses FGFR2IIIb to a greater extent than FGFR2IIIc. In some ~~embodiments~~examples, a cancer comprising FGFR2 amplification expresses FGFR2IIIb at a normalized level that is more than 2-fold, 3-fold, 5-fold, or 10-fold greater than the normalized level of FGFR2IIIc expression. In some ~~embodiments~~examples, the expression levels are normalized to GUSB. In some ~~embodiments~~examples, the cancer overexpresses FGFR2IIIb but does not comprise FGFR2 gene amplification. In some ~~embodiments~~examples, expression or overexpression of FGFR2IIIb is determined by IHC. In some ~~embodiments~~examples, 1+, 2+ or 3+ staining of tumor cells by IHC indicates FGFR2IIIb overexpression. In some ~~embodiments~~examples, 2+ or 3+ staining in tumor cells by IHC indicates FGFR2IIIb overexpression. In some ~~embodiments~~examples, the IHC staining is scored as described in Example 6.

[0015] In some ~~embodiments~~examples, a method of treating cancer 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. In some ~~embodiments~~examples, the platinum agent is selected from cisplatin, oxaliplatin, and carboplatin. In some ~~embodiments~~examples, a method of treating cancer further comprises administering paclitaxel. In some ~~embodiments~~examples, a method of treating cancer further comprises administering cisplatin and/or 5-FU.

[0016] In some ~~embodiments~~examples, uses of a pharmaceutical composition comprising afucosylated anti-FGFR2IIIb antibodies described herein and a pharmaceutically acceptable carrier are provided. In some ~~embodiments~~examples, such use is for treating cancer in an individual with cancer. In some ~~embodiments~~examples, the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, or esophageal cancer. In some ~~embodiments~~examples, the cancer is gastric cancer. In some ~~embodiments~~examples, the cancer comprises an FGFR2 gene amplification. In some ~~embodiments~~examples, FGFR2 amplification

comprises FGFR2:CEN10 (chromosome 10 centromere) ratio of >3. In some ~~embodiments~~examples, the cancer overexpresses FGFR2IIIb. In some

~~embodiments~~examples, a cancer comprising FGFR2 amplification overexpresses FGFR2IIIb to a greater extent than FGFR2IIIc. In some ~~embodiments~~examples, a cancer comprising FGFR2 amplification expresses FGFR2IIIb at a normalized level that is more than 2-fold, 3-fold, 5-fold, or 10-fold greater than the normalized level of FGFR2IIIc expression. In some ~~embodiments~~examples, the expression levels are normalized to GUSB. In some ~~embodiments~~examples, the cancer overexpresses FGFR2IIIb but does not comprise FGFR2 gene amplification. In some ~~embodiments~~examples, expression or overexpression of FGFR2IIIb is determined by IHC. In some ~~embodiments~~examples, 1+, 2+ or 3+ staining of tumor cells by IHC indicates FGFR2IIIb overexpression. In some ~~embodiments~~examples, 2+ or 3+ staining in tumor cells by IHC indicates FGFR2IIIb overexpression. In some ~~embodiments~~examples, the IHC staining is scored as described in Example 6.

[0017] In some ~~embodiments~~examples, pharmaceutical compositions for treating cancer are provided, wherein the pharmaceutical composition comprises afucosylated anti-FGFR2IIIb antibodies described herein and a pharmaceutically acceptable carrier. In some ~~embodiments~~examples, the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, or esophageal cancer. In some ~~embodiments~~examples, the cancer is gastric cancer. In some ~~embodiments~~examples, the cancer comprises an FGFR2 gene amplification. In some ~~embodiments~~examples, FGFR2 amplification comprises FGFR2:CEN10 (chromosome 10 centromere) ratio of >3. In some ~~embodiments~~examples, the cancer overexpresses FGFR2IIIb. In some ~~embodiments~~examples, a cancer comprising FGFR2 amplification overexpresses FGFR2IIIb to a greater extent than FGFR2IIIc. In some ~~embodiments~~examples, a cancer comprising FGFR2 amplification expresses FGFR2IIIb at a normalized level that is more than 2-fold, 3-fold, 5-fold, or 10-fold greater than the normalized level of FGFR2IIIc expression. In some ~~embodiments~~examples, the expression levels are normalized to GUSB. In some ~~embodiments~~examples, the cancer overexpresses FGFR2IIIb but does not comprise FGFR2 gene amplification. In some ~~embodiments~~examples, expression or overexpression of FGFR2IIIb is determined by IHC. In some ~~embodiments~~examples, 1+, 2+ or 3+ staining of tumor cells by IHC indicates FGFR2IIIb overexpression. In some ~~embodiments~~examples, 2+ or 3+ staining in tumor cells by IHC indicates FGFR2IIIb overexpression. In some ~~embodiments~~examples, the IHC staining is scored as described in Example 6.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] Figure 1A to 1C shows ADCC activity of afucosylated αFGFR2bA and fucosylated αFGFR2bF against FGFR2IIIb-expressing Ba/F3 cells, as discussed in Example 3. In the legends, "αFGFR2bF / FGFR2b" indicates that fucosylated αFGFR2bF antibody was tested against FGFR2IIIb-expressing Ba/F3 target cells.

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. A method of treating cancer in an individual comprising administering to an individual with cancer an effective amount of a pharmaceutical composition of claim 32.~~

~~34. The method of claim 33, wherein the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, and esophageal cancer.~~

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

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

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

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

~~39. The method of any one of claims 33 to 37, wherein the cancer comprises an FGFR2 gene amplification.~~

~~40. The method of any one of claims 33 to 39, wherein the method 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 method of claim 40, wherein the platinum agent is selected from cisplatin, oxaliplatin, and carboplatin.~~

~~42. The method of claim 41, wherein the additional therapeutic agent is paclitaxel.~~

~~43. The method of claim 41, wherein the additional therapeutic agent is cisplatin and/or 5-FU.~~

~~44.~~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.

~~45.~~34. The use of claim ~~44~~33, wherein the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, or esophageal cancer.

~~46.~~35. The use of claim ~~45~~34, wherein the cancer is gastric cancer.

~~47.~~36. The use of any one of claims ~~44~~33 to ~~46~~35, wherein the cancer overexpresses FGFR2IIIb.

~~48.~~37. The use of claim ~~47~~36, wherein FGFR2IIIb expression is determined by immunohistochemistry (IHC).

~~49.~~38. The use of claim ~~47~~36 or claim ~~48~~37, wherein the cancer does not comprise FGFR2 gene amplification.

~~50.~~39. The use of any one of claims ~~42~~33 to ~~48~~38, wherein the cancer comprises an FGFR2 gene amplification.

~~51.~~40. A pharmaceutical composition for treating cancer ~~in an individual~~ comprising an effective amount of an anti-FGFR2IIIb antibody of any one of claims 1 to 23 and a pharmaceutically acceptable carrier.

~~52.~~41. The pharmaceutical composition of claim ~~51~~40, wherein the cancer is selected from gastric cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, and esophageal cancer.

~~53.~~42. The pharmaceutical composition of claim ~~52~~41, wherein the cancer is gastric cancer.

~~54.~~43. The pharmaceutical composition of any one of claims ~~51~~40 to ~~53~~42, wherein the cancer overexpresses FGFR2IIIb.

~~55.~~44. The pharmaceutical composition of claim ~~54~~43, wherein FGFR2IIIb expression is determined by immunohistochemistry (IHC).

~~56.~~45. The pharmaceutical composition of claim ~~54~~43 or claim ~~55~~44, wherein the cancer does not comprise FGFR2 gene amplification.

~~57.~~46. The pharmaceutical composition of any one of claims ~~51~~40 to ~~54~~43, wherein the cancer comprises an FGFR2 gene amplification.