patients to conventional chemotherapy (8). Overexpression of mutationally activated FGFR3 is sufficient to induce oncogenic transformation in hematopoietic cells and fibroblasts (11-14, 15), transgenic mouse models (16), and murine bone marrow transplantation models (16, 17). Accordingly, FGFR3 has been proposed as a potential therapeutic target in multiple myeloma. Indeed, several small-molecule inhibitors targeting FGFRs, although not selective for FGFR3 and having cross-inhibitory activity toward certain other kinases, have demonstrated cytotoxicity against FGFR3-positive myeloma cells in culture and in mouse models (18-22).

FGFR3 overexpression has been documented also in a high fraction of bladder cancers (23, 24). Furthermore, somatic activating mutations in FGFR3 have been identified in 60-70% of papillary and 16-20% of muscle-invasive bladder carcinomas (24, 25). In cell culture experiments, RNA interference (11, 26) or an FGFR3 single-chain Fv antibody fragment inhibited bladder cancer cell proliferation (27). A recent study demonstrated that an FGFR3 antibody-toxin conjugate attenuates xenograft growth of a bladder cancer cell line through FGFR3-mediated toxin delivery into tumors (28). However, it remains unclear whether FGFR3 signaling is indeed an oncogenic driver of in vivo growth of bladder tumors. Moreover, the therapeutic potential for targeting FGFR3 in bladder cancer has not been defined on the basis of in vivo models. Publications relating to FGFR3 and anti-FGFR3 antibodies include U.S. Patent Publication no. 2005/0147612; Rauchenberger et al, J Biol Chem 278 (40):38194-38205 (2003); WO2006/048877; Martinez-Torrecuadrada et al, (2008) Mol Cancer Ther 7(4): 862-873; WO2007/144893; Trudel et al. (2006) 107(10): 4039-4046; Martinez-Torrecuadrada et al (2005) Clin Cancer Res 11 (17): 6280-6290; Gomez-Roman et al (2005) Clin Cancer Res 11:459-465; Direnzo, R et al (2007) Proceedings of AACR Annual Meeting, Abstract No. 2080; WO2010/002862.

It is clear that there continues to be a need for agents that have clinical attributes that are optimal for development as therapeutic agents. The invention described herein meets this need and provides other benefits.

All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

SUMMARY ~~OF THE INVENTION~~

The ~~invention~~disclosure is based in part on the identification of a variety of FGFR3 binding agents (such as antibodies, and fragments thereof). FGFR3 presents an important and advantageous therapeutic target, and the ~~invention~~disclosure provides compositions and methods based on binding of the agents to FGFR3. FGFR3 binding agents of the ~~invention~~disclosure, as described

herein, provide important therapeutic and diagnostic agents for use in targeting pathological conditions associated with expression and/or activity of the FGFR3 signaling pathways. Accordingly, the ~~invention~~disclosure provides methods, compositions, kits, and articles of manufacture related to FGFR3 binding.

In one aspect, there is provided an isolated anti-FGFR3 antagonist antibody, wherein the antibody comprises HVR-L1 comprising sequence RASQDVDTSLA (SEQ ID NO:87), HVR-L2 comprising sequence SASFLYS (SEQ ID NO:88), HVR-L3 comprising sequence QQSTGHPQT (SEQ ID NO:89), HVR-H1 comprising sequence GFTFTSTGIS (SEQ ID NO:84), HVR-H2 comprising sequence GRIYPTSGSTNYADSVKG (SEQ ID NO:85); and HVR-H3 comprising sequence ARTYGIYDLYVDYTEYVMDY (SEQ ID NO:86).

The present ~~invention~~disclosure provides antibodies that bind to FGFR3. In one ~~aspect~~embodiment, the ~~invention~~disclosure features an isolated antibody that binds an FGFR3. In some embodiments, the antibody binds a FGFR3 IIIb isoform and/or a FGFR3 IIIc isoform. In some embodiments, the antibody binds a mutated FGFR3 (e.g., one or more of FGFR3 IIIb R248C, S249C, G372C, Y375C, K652E, and/or one or more of FGFR3 IIIc R248C, S249C, G370C, Y373C, K650E). In some embodiments, the antibody binds monomeric FGFR3 (e.g., monomeric FGFR3 IIIb and/or IIIc isoforms). In some embodiments, the antibody promotes formation of monomeric FGFR3, such as by stabilizing the monomeric FGFR3 form relative to the dimeric FGFR3 form.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an isolated anti-FGFR3 antibody, wherein a full length IgG form of the antibody binds human FGFR3 with a Kd of 1 x 10^{-7} or stronger. As is well-established in the art, binding affinity of a ligand to its receptor can be determined using any of a variety of assays, and expressed in terms of a variety of quantitative values. Accordingly, in one embodiment, the binding affinity is expressed as Kd values and reflects intrinsic binding affinity (e.g., with minimized avidity effects). Generally and preferably, binding affinity is measured *in vitro*, whether in a cell-free or cell-associated setting. Any of a number of assays known in the art, including those described herein, can be used to obtain binding affinity measurements, including, for example, Biacore, radioimmunoassay (RIA), and ELISA. In some embodiments, the full length IgG form of the antibody binds human FGFR3 with a Kd of 1 x 10^{-8} or stronger, with a Kd of 1 x 10^{-9} or stronger, or with a Kd of 1 x 10^{-10} or stronger.

Generally, the anti-FGFR3 antibodies of the present ~~invention~~disclosure are antagonist antibodies. Thus, in one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit FGFR3 activity (e.g.,

FGFR3-IIIb and/or FGFR3-IIIc activity). In some embodiments, the anti-FGFR3 antibody (generally in bivalent form) does not possess substantial FGFR3 agonist function. In some embodiments, the anti-FGFR3 antagonist antibody (generally in bivalent form) possesses little or no FGFR3 agonist function. In one embodiment, an antibody of the ~~invention~~disclosure (generally in bivalent form) does not exhibit an FGFR3 agonist activity level that is above background level that is of statistical significance.

In one ~~aspect~~embodiment, binding of the antibody to a FGFR3 may inhibit dimerization of the receptor with another unit of the receptor, whereby activation of the receptor is inhibited (due, at least in part, to a lack of receptor dimerization). Inhibition can be direct or indirect.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides anti-FGFR3 antibodies that do not possess substantial apoptotic activity (e.g., does not induce apoptosis of a cell, e.g., a transitional cell carcinoma cell or a multiple myeloma cell, such as a multiple myeloma cell comprising a FGFR3 translocation, such as a t(4;14) translocation). In some embodiments, the anti-FGFR3 antibody possesses little or no apoptotic function. In some embodiment, the FGFR3 antibodies do not exhibit apoptotic function that is above background level that is of statistical significance.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides anti-FGFR3 antibodies that do not induce substantial FGFR3 down-regulation. In some embodiments, the anti-FGFR3 antibody induces little or no receptor down-regulation. In some embodiment, the FGFR3 antibodies do not induce receptor down-regulation that is above background level that is of statistical significance.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides anti-FGFR3 antibodies that possess effector function. In one embodiment, the effector function comprises antibody-dependent cell-mediated cytotoxicity (ADCC). In one embodiment, the anti-FGFR3 antibody (in some embodiments, a naked anti-FGFR3 antibody) is capable of killing a cell, in some embodiments, a multiple myeloma cells (e.g., multiple myeloma cells comprising a translocation, e.g., a t(4;14) translocation). In some embodiments, the anti-FGFR3 antibody is capable of killing a cell that expresses about 10,000 FGFR3 molecules per cell or more (such as about 11,000, about 12,000, about 13,000, about 14,000, about 15,000, about 16,000, about 17,000, about 18,000 or more FGFR3 molecules per cell). In other embodiments, the cell expresses about 2000, about 3000, about 4000, about 5000, about 6000, about 7000, about 8000, or more FGFR3 molecules per cell.

In one ~~aspect~~embodiment, the anti-FGFR3 antibody of the ~~invention~~disclosure inhibits constitutive FGFR3 activity. In some embodiments, constitutive FGFR3 activity is ligand-dependent FGFR3 constitutive activity. In some embodiments, constitutive FGFR3 activity is ligand-independent constitutive FGFR3 activity.

In one ~~aspect~~embodiment, the anti-FGFR3 antibody inhibits FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{R248C}. As used herein the term "comprising a mutation corresponding to FGFR3-IIIb^{R248C}" is understood to encompass FGFR3-IIIb^{R248C} and FGFR3-IIIc^{R248C}, as well as additional FGFR3 forms comprising an R to C mutation at a

position corresponding to FGFR3-IIIb R248. One of ordinary skill in the art understands how to align FGFR3 sequences in order identify corresponding residues between respective FGFR3 sequences, e.g., aligning a FGFR3- IIIc sequence with a FGFR3- IIIb sequence to identify the position in FGFR3 corresponding R248 position in FGFR3-IIIb. In some embodiments, the anti-FGFR3 antibody inhibits FGFR3-IIIb^{R248C} and/or FGFR3-IIIc^{R248C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{K652E}. For convenience, the term "comprising a mutation corresponding to FGFR3-IIIb ^{K652E}" is understood to encompass FGFR3-IIIb ^{K652E} and FGFR3-IIIc ^{K650E}, as well as additional FGFR3 forms comprising an K to E mutation at a position corresponding to FGFR3-IIIb K652. One of ordinary skill in the art understands how to align FGFR3 sequences in order identify corresponding residues between respective FGFR3 sequences, e.g., aligning a FGFR3- IIIc sequence with a FGFR3- IIIb sequence to identify the position in FGFR3 corresponding K652 position in FGFR3-IIIb. In some embodiments, the anti-FGFR3 antibody inhibits FGFR3-IIIb ^{K652E} and/or FGFR3-IIIc ^{K650E}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{S249C}. For convenience, the term "comprising a mutation corresponding to FGFR3-IIIb^{S249C} " is understood to encompass FGFR3-IIIb ^{S249C} and FGFR3-IIIc ^{S249C}, as well as additional FGFR3 forms comprising an S to C mutation at a position corresponding to FGFR3-IIIb S249. In some embodiments, the anti-FGFR3 antibody inhibits FGFR3-IIIb^{S249C} and/or FGFR3-IIIc ^{S249C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{G372C}. For convenience, the term "comprising a mutation corresponding to FGFR3-IIIb^{G372C} " is understood to encompass FGFR3-IIIb ^{G372C} and FGFR3-IIIc ^{G370C}, as well as additional FGFR3 forms comprising a G to C mutation at a position corresponding to FGFR3-IIIb G372. In some embodiments, the anti-FGFR3 antibody inhibits FGFR3-IIIb^{G372C} and/or FGFR3-IIIc ^{G370C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{Y375C}. For convenience, the term "comprising a mutation corresponding to FGFR3-IIIb^{Y375C} " is understood to encompass FGFR3-IIIb^{Y375C} and FGFR3-IIIc^{Y373C}, as well as additional FGFR3 forms comprising an S to C mutation at a position corresponding to FGFR3-IIIb S249. In some embodiments, the anti-FGFR3 antibody inhibits FGFR3-IIIb^{Y375C} and/or FGFR3-IIIc^{Y373C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit (a) FGFR3-IIIb^{K652E} and (b) one or more of FGFR3-IIIb^{R248C}, FGFR3-IIIb^{Y375C}, FGFR3 -IIIb^{S249C}, and FGFR3IIIb ^{G372C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit (a) FGFR3-IIIc^{K650E} and (b) one or more of FGFR3-IIIc^{R248C}, FGFR3-IIIc^{Y373C}, FGFR3 -IIIc^{S249C}, and FGFR3IIIc ^{G370C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit (a) FGFR3-IIIb^{R248C} and (b) one or more of FGFR3-IIIb^{K652E}, FGFR3-IIIb^{Y375C}, FGFR3-IIIb^{S249C}, and FGFR3-IIIb^{G372C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit (a) FGFR3-IIIc^{R248C} and (b) one or more of FGFR3-IIIc^{K650E}, FGFR3-IIIc^{Y373C}, FGFR3-IIIc^{S249C}, and FGFR3-IIIc^{G370C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit (a) FGFR3-IIIb^{G372C} and (b) one or more of FGFR3-IIIb^{K652E}, FGFR3-IIIb^{Y375C}, FGFR3-IIIb^{S249C}, and FGFR3-IIIb^{R248C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit (a) FGFR3-IIIc^{G370C} and (b) one or more of FGFR3-IIIc^{K650E}, FGFR3-IIIc^{Y373C}, FGFR3-IIIc^{S249C}, and FGFR3-IIIc^{R248C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit FGFR3-IIIb^{R248C}, FGFR3-IIIb^{K652E}, FGFR3-IIIb^{Y375C}, FGFR3-IIIb ^{S249C}, and FGFR3-IIIb ^{G372C}.

In one ~~aspect~~embodiment, the anti-FGFR3 antibodies inhibit FGFR3-IIIc^{R248C}, FGFR3-IIIc^{K650E}, FGFR3-IIIc^{Y373C}, FGFR3-IIIc ^{S249C}, and FGFR3-IIIc ^{G370C}.

Disclosed is~~In one aspect, the invention provides~~ an isolated anti-FGFR3 antibody comprising:

(a) at least one, two, three, four, or five hypervariable region (HVR) sequences selected from:

(i) HVR-L1 comprising sequence A1-A11, wherein A1-A11 is RASQDVDTSLA (SEQ ID NO:87),

(ii) HVR-L2 comprising sequence B1-B7, wherein B1-B7 is SASFLYS (SEQ ID NO:88),

(iii) HVR-L3 comprising sequence C1-C9, wherein C1-C9 is QQSTGHPQT (SEQ ID NO:89),

(iv) HVR-H1 comprising sequence D1-D10, wherein D1-D10 is GFTFTSTGIS (SEQ ID NO:84),

(v) HVR-H2 comprising sequence E1-E18, wherein E1-E18 is GRIYPTSGSTNYADSVKG (SEQ ID NO:85), and

(vi) HVR-H3 comprising sequence F1-F20, wherein F1-F20 is ARTYGIYDLYVDYTEYVMDY (SEQ ID NO:86); and

(b) at least one variant HVR, where the variant HVR sequence comprises modification of at least one residue (at least two residues, at least three or more residues) of the sequence depicted in SEQ ID NOS:1-18, 48-131 and 140-145. The modification desirably is a substitution, insertion, or deletion.

In some embodiments, a HVR-L1 variant comprises 1-6 (1, 2, 3, 4, 5, or 6) substitutions in any combination of the following positions: A5 (V or D), A6 (V or I), A7 (D, E or S), A8 (T or I), A9 (A or S) and A10 (V or L). In some embodiments, a HVR-L2 variant comprises 1-2 (1 or 2) substitutions in any combination of the following positions: B1 (S or G), B4 (F or S or T) and B6 (A or Y). In some embodiments, a HVR-L3 variant comprises 1-6 (1, 2, 3, 4, 5, or 6) substitutions in any combination of the following positions: C3 (G or S or T), C4 (T or Y or A), C5 (G or S or T or A), C6 (A or H or D or T or N), C7 (Q or P or S), and C8 (S or Y or L or P or Q). In some embodiment, a HVR- H1 variant comprises 1-3 (1, 2, or 3) substitutions in any combination of the following positions: D3 (S or T), D5 (W or Y or S or T), D6 (S or G or T). In some embodiment, a HVR- H2 variant comprises 1-6 (1, 2, 3, 4, 5, or 6) substitutions in any combination of the following positions: E2 (R or S), E6 (Y or A or L or S or T), E7 (A or Q or D or G or Y or S or N or F), E8 (A or D or G), E9 (T or S), E10 (K or F or T or S), E11 (Y or H or N or I).

Disclosed is~~In one aspect, the invention provides~~ an isolated anti-FGFR3 antibody comprising:

(a) at least one, two, three, four, or five hypervariable region (HVR) sequences selected from:

(i) HVR-L1 comprising sequence $RASQX_1X_2X_3X_4X_5$ X_6A, wherein X_1 is V or D, X_2 is V or I, X_3 is D, E or S, X_4 is T or I, X_5 is A or S, and X_6 is V or L (SEQ ID NO:146),

(ii) HVR-L2 comprising sequence X_1ASFLX_2S wherein X_1 is S or G and X_2 is A or Y (SEQ ID NO:147),

(iii) HVR-L3 comprising sequence $QQX_1X_2X_3X_4X_5X_6T$, wherein X_1 is G, S or T, X_2 is T, Y or A, X_3 is G, S, T, or A, X_4 is A, H, D, T, or N, X_5 is Q, P or S, X_6 is S, Y, L, P or Q (SEQ ID NO:148),

(iv) HVR-H1 comprising sequence $GFX_1FX_2X_3TGIS$, wherein X_1 is S or T, X_2 is W, Y, S or T, X_3 is S, G, or T (SEQ ID NO:149),

(v) HVR-H2 comprising sequence $GRIYPX_1X_2X_3X_4X_5X_6YADSVKG$, wherein X_1 is Y, A, L, S, or T, X_2 is A, Q, D, G, Y, S, N or F, X_3 is A, D, or G, X_4 is T or S, X_5 is K, F, T, or S, X_6 is Y, H, N or I (SEQ ID NO:150), and

(vi) HVR-H3 comprising sequence ARTYGIYDLYVDYTEYVMDY (SEQ ID NO:151).

In some embodiments, HVR-L1 comprises sequence $RASQX_1VX_2X_3X_4VA$, wherein X_1 is V or D, X_2 is D, E or S, X_3 is T or I, X_4 is A or S (SEQ ID NO:152). In some embodiments, HVR-L3 comprises sequence $QQX_1X_2X_3X_4X_5X_6T$, wherein X_1 is S, G, or T, X_2 is Y, T, or A, X_3 is T or G, X_4 is T, H or N, X_5 is P or S, X_6 is P, Q, Y, or L (SEQ ID NO:153). In some embodiments, HVR-H2 comprises sequence

GRIYPX$_1$X$_2$GSTX$_3$YADSVKG, wherein X$_1$ is T or L, X$_2$ is N, Y, S, G, A, or Q; X$_3$ is N or H (SEQ ID NO:154).

Also disclosed is~~In another aspect, the invention features~~ an isolated anti-FGFR3 antibody that comprises one, two, three, four, five, or six HVRs, where each HVR comprises, consists, or consists essentially of a sequence selected from SEQ ID NOS:1-18, 48-131 and 140-145, and where SEQ ID NO:1, 7, 13, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120, 126 or 143 corresponds to an HVR-H1, SEQ ID NO:2, 8, 14, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127 or 144 corresponds to an HVR-H2, SEQ ID NO:3, 9, 15, 50, 56, 62, 68, 74, 80, 86, 92, 98, 104, 110, 116, 122, 128 or 145 corresponds to an HVR-H3, SEQ ID NO:4, 10, 16, 51, 57, 63, 69, 75, 81, 87, 93, 99, 105, 111, 117, 123, 129 or 140 corresponds to an HVR-L1, SEQ ID NO:5, 11, 17, 52, 58, 64, 70, 76, 82, 88, 94, 100, 106, 112, 118, 124, 130 or 141 corresponds to an HVR-L2, and SEQ ID NO:6, 12, 18, 53, 59, 65, 71, 77, 83, 89, 95, 101, 107, 113, 119, 125, 131 or 142 corresponds to an HVR-L3.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising a HVR-H1 comprising the sequence of SEQ ID NO:1, 7, 13, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120, 126 or 143.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising a HVR-H2 comprising the sequence of SEQ ID NO:2, 8, 14, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127 or 144.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising a HVR-H3 comprising the sequence of SEQ ID NO:3, 9, 15, 50, 56, 62, 68, 74, 80, 86, 92, 98, 104, 110, 116, 122, 128 or 145.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising a HVR-L1 region comprising the sequence of SEQ ID NO:4, 10, 16, 51, 57, 63, 69, 75, 81, 87, 93, 99, 105, 111, 117, 123, 129 or 140.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising a HVR-L2 region comprising the sequence of SEQ ID NO:5, 11, 17, 52, 58, 64, 70, 76, 82, 88, 94, 100, 106, 112, 118, 124, 130 or 141.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising a HVR-L3 region comprising the sequence of SEQ ID NO:6, 12, 18, 53, 59, 65, 71, 77, 83, 89, 95, 101, 107, 113, 119, 125, 131 or 142.

In one ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, wherein each, in order, comprises SEQ ID NO:1,

2, 3, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, contains SEQ ID NO: 4, 5, 6.

In another ~~aspect~~embodiment, an-anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, wherein each, in order, comprises SEQ ID NO:7, 8, 9, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 10, 11, 12.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:13, 14, 15, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO:16, 17, 18.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO: 48, 49, 50, and/or a light chain variable region HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 51, 52, 53.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO: 54, 55, 56, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 57, 58, 59.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:60, 61, 62, 63, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 63, 64, 65.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:66, 67, 68, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 69, 70, 71.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:72, 73, 74, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 75, 76, 77.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:78, 79 80, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO:81, 82, 83.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO: 84, 85, 86, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO:87, 88, 89.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO: 90, 91, 92, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO:93, 94, 95.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO: 96, 97, 98, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 99, 100, 101.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO: 102, 103, 104, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 105, 106, 107.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:108, 109, 110, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 111, 112, 113.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:114, 115, 116, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO:117, 118, 119.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:120, 121, 122, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO: 123, 124, 125.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:126, 127, 128, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO:129, 130, 131.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising HVR-H1, HVR-H2, HVR-H3, where each, in order, comprises SEQ ID NO:140,

141, 142, and/or a light chain variable region comprising HVR-L1, HVR-L2, and HVR-L3, where each, in order, comprises SEQ ID NO:143, 144, 145.

The amino acid sequences of SEQ ID NOs:1-18, 48-131 and 140-145 are numbered with respect to individual HVR (i.e., H1, H2 or H3) as indicated in Figure 1, the numbering being consistent with the Kabat numbering system as described below.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises comprises a heavy chain variable region comprising SEQ ID NO:132 and a light chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a light chain variable region comprising SEQ ID NO: 133, and a heavy chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising SEQ ID NO:132 and a light chain variable region comprising SEQ ID NO:133.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising SEQ ID NO:134 and a light chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a light chain variable region comprising SEQ ID NO: 135, and a heavy chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a light chain variable region comprising SEQ ID NO: 139, and a heavy chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising SEQ ID NO:134 and a light chain variable region comprising SEQ ID NO:135.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising SEQ ID NO:136 and a light chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a light chain variable region comprising SEQ ID NO: 137, and a heavy chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising SEQ ID NO:136 and a light chain variable region comprising SEQ ID NO:137.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising SEQ ID NO:138 and a light chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a light chain variable region comprising SEQ ID NO: 139, and a heavy chain variable region.

In another ~~aspect~~embodiment, an anti-FGFR3 antibody comprises a heavy chain variable region comprising SEQ ID NO:138 and a light chain variable region comprising SEQ ID NO:139.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising: at least one, two, three, four, five, and/or six hypervariable region (HVR) sequences selected from the group consisting of:

(a) HVR-L1 comprising sequence SASSSVSYMH (SEQ ID NO:155), SASSSVSYMH (SEQ ID NO:156) or LASQTIGTWLA (SEQ ID NO:157),

(b) HVR-L2 comprising sequence TWIYDTSILAS (SEQ ID NO:158), RWIYDTSKLAS (SEQ ID NO:159), or LLIYAATSLAD (SEQ ID NO:160),

(c) HVR-L3 comprising sequence QQWTSNPLT (SEQ ID NO:161), QQWSSYPPT (SEQ ID NO:162), or QQLYSPPWT (SEQ ID NO:163),

(d) HVR-H1 comprising sequence GYSFTDYNMY (SEQ ID NO:164), GYVFTHYNMY (SEQ ID NO:165), or GYAFTSYNMY (SEQ ID NO:166),

(e) HVR-H2 comprising sequence WIGYIEPYNGGTSYNQKFKG (SEQ ID NO:167), WIGYIEPYNGGTSYNQKFKG (SEQ ID NO:168), or WIGYIDPYIGGTSYNQKFKG (SEQ ID NO:169), and

(f) HVR-H3 comprising sequence ASPNYYDSSPFAY (SEQ ID NO:170), ARGQGPDFDV (SEQ ID NO:171), or ARWGDYDVGAMDY (SEQ ID NO:172).

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti- FGFR3 antibody comprising: at least one, two, three, four, five, and/or six hypervariable region (HVR) sequences selected from the group consisting of:

(a) HVR-L1 comprising sequence SASSSVSYMH (SEQ ID NO:155),

(b) HVR-L2 comprising sequence TWIYDTSILAS (SEQ ID NO:158),

(c) HVR-L3 comprising sequence QQWTSNPLT (SEQ ID NO:161),

(d) HVR-H1 comprising sequence GYSFTDYNMY (SEQ ID NO:164),

(e) HVR-H2 comprising sequence WIGYIEPYNGGTSYNQKFKG (SEQ ID NO:167), and

(f) HVR-H3 comprising sequence ASPNYYDSSPFAY (SEQ ID NO:170).

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti- FGFR3 antibody comprising: at least one, two, three, four, five, and/or six hypervariable region (HVR) sequences selected from the group consisting of:

(a) HVR-L1 comprising sequence SASSSVSYMH (SEQ ID NO:156),

(b) HVR-L2 comprising sequence RWIYDTSKLAS (SEQ ID NO:159),

(c) HVR-L3 comprising sequence QQWSSYPPT (SEQ ID NO:162),

(d) HVR-H1 comprising sequence GYVFTHYNMY (SEQ ID NO:165),

(e) HVR-H2 comprising sequence WIGYIEPYNGGTSYNQKFKG (SEQ ID NO:168), and

(f) HVR-H3 comprising sequence ARGQGPDFDV (SEQ ID NO:171).

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti- FGFR3 antibody comprising: at least one, two, three, four, five, and/or six hypervariable region (HVR) sequences selected from the group consisting of:

(a) HVR-L1 comprising sequence LASQTIGTWLA (SEQ ID NO:157),

(b) HVR-L2 comprising sequence LLIYAATSLAD (SEQ ID NO:160),

(c) HVR-L3 comprising sequence QQLYSPPWT (SEQ ID NO:163),

(d) HVR-H1 comprising sequence GYAFTSYNMY (SEQ ID NO:166),

(e) HVR-H2 comprising sequence WIGYIDPYIGGTSYNQKFKG (SEQ ID NO:169), and

(f) HVR-H3 comprising sequence ARWGDYDVGAMDY (SEQ ID NO:172).

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising (a) a light chain comprising (i) HVR-L1 comprising sequence SASSSVSYMH (SEQ ID NO:155); (ii) HVR-L2 comprising sequence TWIYDTSILAS (SEQ ID NO:158); and (iii) HVR-L3 comprising sequence QQWTSNPLT (SEQ ID NO:161) ; and/or (b) a heavy chain comprising (i) HVR-H1 comprising sequence GYSFTDYNMY (SEQ ID NO:164); (ii) HVR-H2 comprising sequence WIGYIEPYNGGTSYNQKFKG (SEQ ID NO:167); and (iii) HVR-H3 comprising sequence ASPNYYDSSPFAY (SEQ ID NO:170).

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising (a) a light chain comprising (i) HVR-L1 comprising sequence SASSSVSYMH (SEQ ID NO:156); (ii) HVR-L2 comprising sequence RWIYDTSKLAS (SEQ ID NO:159); and (iii) HVR-L3 comprising sequence QQWSSYPPT (SEQ ID NO:162) ; and/or (b) a heavy chain comprising (i) HVR-H1 comprising sequence GYVFTHYNMY (SEQ ID NO:165); (ii) HVR-H2 comprising sequence WIGYIEPYNGGTSYNQKFKG (SEQ ID NO:168); and (iii) HVR-H3 comprising sequence ARGQGPDFDV (SEQ ID NO:171).

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody comprising (a) a light chain comprising (i) HVR-L1 comprising sequence LASQTIGTWLA (SEQ ID NO:157); (ii) HVR-L2 comprising sequence LLIYAATSLAD (SEQ ID NO:160); and (iii) HVR-L3 comprising sequence QQLYSPPWT (SEQ ID NO:163) ; and/or (b) a heavy chain comprising (i) HVR-H1 comprising sequence GYAFTSYNMY (SEQ ID NO:166); (ii) HVR-H2 comprising sequence WIGYIDPYIGGTSYNQKFKG (SEQ ID NO:169); and (iii) HVR-H3 comprising sequence ARWGDYDVGAMDY (SEQ ID NO:172). Some embodiments of

antibodies of the ~~invention~~disclosure comprise a light chain variable domain of humanized 4D5 antibody (huMAb4D5-8) (HERCEPTIN®, Genentech, Inc., South San Francisco, CA, USA) (also referred to in U.S. Pat. No. 6,407,213 and Lee et al., J. Mol. Biol. (2004), 340(5):1073-1093) as depicted in SEQ ID NO:173 below.

1 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val ***Asn*** Thr Ala
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
Ser ***Arg*** Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln ***His*** Tyr Thr Thr Pro Pro Thr
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys 107 (SEQ ID NO:173)
(HVR residues are underlined)

In one embodiment, the huMAb4D5-8 light chain variable domain sequence is modified at one or more of positions 30, 66, and 91 (Asn, Arg, and His as indicated in bold/italics above, respectively). In a particular embodiment, the modified huMAb4D5-8 sequence comprises Ser in position 30, Gly in position 66, and/or Ser in position 91. Accordingly, in one embodiment, an antibody of the ~~invention~~disclosure comprises a light chain variable domain comprising the sequence depicted in SEQ ID NO:174 below:

1 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val ***Ser*** Thr Ala
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln ***Ser*** Tyr Thr Thr Pro Pro Thr
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys 107 (SEQ ID NO:174)
(HVR residues are underlined)

Substituted residues with respect to huMAb4D5-8 are indicated in bold/italics.

Antibodies of the ~~invention~~disclosure can comprise any suitable framework variable domain sequence, provided binding activity to FGFR3 is substantially retained. For example, in some embodiments, antibodies of the ~~invention~~disclosure comprise a human subgroup III heavy chain framework consensus sequence. In one embodiment of these antibodies, the framework consensus sequence comprises a substitution at position 71, 73, and/or 78. In some embodiments of these antibodies, position 71 is A, 73 is T and/or 78 is A. In one

embodiment, these antibodies comprise heavy chain variable domain framework sequences of huMAb4D5-8 (HERCEPTIN®, Genentech, Inc., South San Francisco, CA, USA) (also referred to in U.S. Patent Nos. 6,407,213 & 5,821,337, and Lee et al., J. Mol. Biol. (2004), 340(5):1073-1093). In one embodiment, these antibodies further comprise a human κI light chain framework consensus sequence. In a particular embodiment, these antibodies comprise light chain HVR sequences of huMAb4D5-8 as described in U.S. Patent Nos. 6,407,213 & 5,821,337.) In one embodiment, these antibodies comprise light chain variable domain sequences of huMAb4D5-8 (HERCEPTIN®, Genentech, Inc., South San Francisco, CA, USA) (also referred to in U.S. Patent Nos. 6,407,213 & 5,821,337, and Lee et al., J. Mol. Biol. (2004), 340(5):1073-1093).

In one embodiment, an antibody of the ~~invention~~disclosure comprises a heavy chain variable domain, wherein the framework sequence comprises the sequence of SEQ ID NOS:19 and 203-205, 20 and 206-208, 21 and 209-211, 22 and 212-214 , 23 and 215-217, 24 and 218-220, 25 and 221-223, 26 and 224-226, 27 and 227-229, 28 and 230-232, 29 and 233-235, 30 and 236-238, 31 and 239-241, 32 and 242-244, 33 and 245-247, 34 and 248-250, 35 and 251-253, 36 and 254-256, and/or 37 and 257-259, and HVR H1, H2, and H3 sequences are SEQ ID NOS:13, 14 and/or 15, respectively. In another embodiment, the framework sequence comprises the sequence of SEQ ID NOS: 19 and 203-205, 20 and 206-208, 21 and 209-211, 22 and 212-214 , 23 and 215-217, 24 and 218-220, 25 and 221-223, 26 and 224-226, 27 and 227-229, 28 and 230-232, 29 and 233-235, 30 and 236-238, 31 and 239-241, 32 and 242-244, 33 and 245-247, 34 and 248-250, 35 and 251-253, 36 and 254-256, and/or 37 and 257-259, and HVR H1, H2, and H3 sequences are SEQ ID NOS:48, 49and/or 50, respectively. In yet another embodiment, the framework sequence comprises the sequence of SEQ ID NOS: 19 and 203-205, 20 and 206-208, 21 and 209-211, 22 and 212-214 , 23 and 215-217, 24 and 218-220, 25 and 221-223, 26 and 224-226, 27 and 227-229, 28 and 230-232, 29 and 233-235, 30 and 236-238, 31 and 239-241, 32 and 242-244, 33 and 245-247, 34 and 248-250, 35 and 251-253, 36 and 254-256, and/or 37 and 257-259, and HVR H1, H2, and H3 sequences are SEQ ID NOS:84, 85, and/or 86, respectively. In a further embodiment, the framework sequence comprises the sequence of SEQ ID NOS: 19 and 203-205, 20 and 206-208, 21 and 209-211, 22 and 212-214 , 23 and 215-217, 24 and 218-220, 25 and 221-223, 26 and 224-226, 27 and 227-229, 28 and 230-232, 29 and 233-235, 30 and 236-238, 31 and 239-241, 32 and 242-244, 33 and 245-247, 34 and 248-250, 35 and 251-253, 36 and 254-256, and/or 37

and 257-259, and HVR H1, H2, and H3 sequences are SEQ ID NOS:108, 109, and/or 110, respectively.

In a particular embodiment, an antibody of the ~~invention~~disclosure comprises a light chain variable domain, wherein the framework sequence comprises the sequence of SEQ ID NOS:38 and 260-262, 39 and 263-265, 40 and 266-268, and/or 41 and 269-271, and HVR L1, L2, and L3 sequences are SEQ ID NOS:16, 17, and/or 18, respectively. In another embodiment, an antibody of the ~~invention~~disclosure comprises a light chain variable domain, wherein the framework sequence comprises the sequence of SEQ ID NOS: 38 and 260-262, 39 and 263-265, 40 and 266-268, and/or 41 and 269-271, and HVR L1, L2, and L3 sequences are SEQ ID NOS:51, 52 and/or 53, respectively. In an additional embodiment, an antibody of the ~~invention~~disclosure comprises a light chain variable domain, wherein the framework sequence comprises the sequence of SEQ ID NOS: 38 and 260-262, 39 and 263-265, 40 and 266-268, and/or 41 and 269-271, and HVR L1, L2, and L3 sequences are SEQ ID NOS:87, 88and/or 89, respectively. In yet another embodiment, an antibody of the ~~invention~~disclosure comprises a light chain variable domain, wherein the framework sequence comprises the sequence of SEQ ID NOS: 38 and 260-262, 39 and 263-265, 40 and 266-268, and/or 41 and 269-271, and HVR L1, L2, and L3 sequences are SEQ ID NOS:111, 112, and/or 113, respectively.

In another ~~aspect~~embodiment, an antibody of the ~~invention~~disclosure comprises a heavy chain variable domain comprising the sequence of SEQ ID NO:132 and/or a light chain variable domain comprising the sequence of SEQ ID NO:133. In another ~~aspect~~embodiment, an antibody of the ~~invention~~disclosure comprises a heavy chain variable domain comprising the sequence of SEQ ID NO:134 and/or a light chain variable domain comprising the sequence of SEQ ID NO:135. In another ~~aspect~~embodiment, an antibody of the ~~invention~~disclosure comprises a heavy chain variable domain comprising the sequence of SEQ ID NO:136 and/or a light chain variable domain comprising the sequence of SEQ ID NO:137. In another ~~aspect~~embodiment, an antibody of the ~~invention~~disclosure comprises a heavy chain variable domain comprising the sequence of SEQ ID NO:138 and/or a light chain variable domain comprising the sequence of SEQ ID NO:139.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody that binds a polypeptide comprising, consisting essentially of or consisting of the following amino acid sequence: LAVPAANTVRFRCPA (SEQ ID NO:179) and/or SDVEFHCKVYSDAQP (SEQ ID NO:180).

In some embodiments, the antibody binds a polypeptide comprising, consisting essentially of or consisting of amino acid numbers 164-178 and/or 269-283 of the mature human FGFR3 amino acid sequence.

In one embodiment, an anti-FGFR3 antibody of the ~~invention~~disclosure specifically binds an amino acid sequence having at least 50%, 60%, 70%, 80%, 90%, 95%, 98% sequence identity or similarity with the sequence LAVPAANTVRFRCPA (SEQ ID NO:179) and/or SDVEFHCKVYSDAQP (SEQ ID NO:180).

In one ~~aspect~~embodiment, the anti-FGFR3 antibody of the present ~~invention~~disclosure binds to at least one, two, three, four, or any number up to all of residues 154, 155, 158, 159, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 177, 202, 205, 207, 210, 212, 214, 216, 217, 241, 246, 247, 248, 278, 279, 280, 281, 282, 283, 314, 315, 316, 317 and/or 318 of FGFR3 IIIb polypeptide, or equivalent residues of FGFR3 IIIc polypeptide. One of ordinary skill in the art understands how to align FGFR3 sequences in order identify corresponding residues between respective FGFR3 sequences. Combinations of two or more residues can include any of residues 154, 155, 158, 159, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 177, 202, 205, 207, 210, 212, 214, 216, 217, 241, 246, 247, 248, 278, 279, 280, 281, 282, 283, 314, 315, 316, 317 and/or 318 of FGFR3 IIIb polypeptide, or equivalent residues of FGFR3 IIIc polypeptide. In some embodiments, the anti-FGFR3 antibody binds to at least one, two, three, four, or any number up to all of residues 158, 159, 169, 170, 171, 173, 175, 205, 207, and/or 315 of FGFR3 IIIb polypeptide, or equivalent residues of FGFR3 IIIc polypeptide. In some embodiments, the anti-FGFR3 antibody binds to at least one, two three, four, or any number up to all of residues 158, 170, 171, 173, 175, and/or 315 of FGFR3 IIIb polypeptide, or equivalent residues of FGFR3 IIIc polypeptide.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti- FGFR3 antibody that competes with any of the above-mentioned antibodies for binding to FGFR3. In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti- FGFR3 antibody that binds to the same or a similar epitope on FGFR3 as any of the above-mentioned antibodies.

As is known in the art, and as described in greater detail hereinbelow, the amino acid position/boundary delineating a hypervariable region of an antibody can vary, depending on the context and the various definitions known in the art (as described below). Some positions within a variable domain may be viewed as hybrid hypervariable positions in that these positions can be deemed to be within a hypervariable region under one set of criteria while being deemed to be outside a hypervariable region under a different set of criteria. One or more of these positions can also be found in extended hypervariable regions (as further defined below).

In some embodiments, the antibody is a monoclonal antibody. In other embodiments, the antibody is a polyclonal antibody. In some embodiments, the antibody is selected from

the group consisting of a chimeric antibody, an affinity matured antibody, a humanized antibody, and a human antibody. In certain embodiments, the antibody is an antibody fragment. In some embodiments, the antibody is a Fab, Fab', Fab'-SH, $F(ab')_2$, or scFv.

In some embodiment, the FGFR3 antibody is a one-armed antibody (i.e., the heavy chain variable domain and the light chain variable domain form a single antigen binding arm) comprising an Fc region, wherein the Fc region comprises a first and a second Fc polypeptide, wherein the first and second Fc polypeptides are present in a complex and form a Fc region that increases stability of said antibody fragment compared to a Fab molecule comprising said antigen binding arm. See, e.g., WO2006/015371.

In one embodiment, the antibody is a chimeric antibody, for example, an antibody comprising antigen binding sequences from a non-human donor grafted to a heterologous non-human, human, or humanized sequence (e.g., framework and/or constant domain sequences). In one embodiment, the non-human donor is a mouse. In a further embodiment, an antigen binding sequence is synthetic, e.g., obtained by mutagenesis (e.g., phage display screening, etc.). In a particular embodiment, a chimeric antibody of the ~~invention~~disclosure has murine V regions and a human C region. In one embodiment, the murine light chain V region is fused to a human kappa light chain. In another embodiment, the murine heavy chain V region is fused to a human IgG1 C region.

Humanized antibodies of the ~~invention~~disclosure include those that have amino acid substitutions in the framework region (FR) and affinity maturation variants with changes in the grafted CDRs. The substituted amino acids in the CDR or FR are not limited to those present in the donor or recipient antibody. In other embodiments, the antibodies of the ~~invention~~disclosure further comprise changes in amino acid residues in the Fc region that lead to improved effector function including enhanced CDC and/or ADCC function and B-cell killing. Other antibodies of the ~~invention~~disclosure include those having specific changes that improve stability. In other embodiments, the antibodies of the ~~invention~~disclosure comprise changes in amino acid residues in the Fc region that lead to decreased effector function, e.g., decreased CDC and/or ADCC function and/or decreased B-cell killing. In some embodiments, the antibodies of the ~~invention~~disclosure are characterized by decreased binding (such as absence of binding) to human complement factor C1q and/or human Fc receptor on natural killer (NK) cells. In some embodiments, the antibodies of the ~~invention~~disclosure are characterized by decreased binding (such as the absence of binding) to human FcγRI, FcγRIIA, and/or FcγRIIIA. In some embodiments, the antibodies of the ~~invention~~disclosure are of the IgG class (e.g., IgG1 or IgG4) and

comprise at least one mutation in E233, L234, G236, D265, D270, N297, E318, K320, K322, A327, A330, P331, and/or P329 (numbering according to the EU index). In some embodiments, the antibodies comprise the mutations L234A/L235A or D265A/N297A.

Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. For example, antibodies with a mature carbohydrate structure that lacks fucose attached to an Fc region of the antibody are described in US Pat Appl No US 2003/0157108 (Presta, L.). See also US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Antibodies with a bisecting N-acetylglucosamine (GlcNAc) in the carbohydrate attached to an Fc region of the antibody are referenced in WO 2003/011878, Jean-Mairet *et al.* and US Patent No. 6,602,684, Umana *et al.* Antibodies with at least one galactose residue in the oligosaccharide attached to an Fc region of the antibody are reported in WO 1997/30087, Patel *et al.* See, also, WO 1998/58964 (Raju, S.) and WO 1999/22764 (Raju, S.) concerning antibodies with altered carbohydrate attached to the Fc region thereof. See also US 2005/0123546 (Umana *et al.*) on antigen-binding molecules with modified glycosylation.In one ~~aspect~~embodiment, the ~~invention~~disclosure provides FGFR3 binding polypeptides comprising any of the antigen binding sequences provided herein, wherein the FGFR3 binding polypeptides specifically bind to a FGFR3, e.g., a human and/or cyno and/or mouse FGFR3.

The antibodies of the ~~invention~~disclosure bind (such as specifically bind) FGFR3 (e.g. FGFR3-IIIb and/or FGFR3-IIIc), and in some embodiments, may modulate (e.g. inhibit) one or more ~~aspects~~embodiments of FGFR3 signaling (such as FGFR3 phosphorylation) and/or disruption of any biologically relevant FGFR3 and/or FGFR3 ligand biological pathway, and/or treatment and/or prevention of a tumor, cell proliferative disorder or a cancer; and/or treatment or prevention of a disorder associated with FGFR3 expression and/or activity (such as increased FGFR3 expression and/or activity). In some embodiments, the FGFR3 antibody specifically binds to a polypeptide consisting of or consisting essentially of a FGFR3 (e.g., a human or mouse FGFR3). In some embodiments, the antibody specifically binds FGFR3 with a Kd of 1×10^{-7} M or stronger.

In some embodiments, the anti-FGFR3 antibody of the ~~invention~~disclosure is not an anti-FGFR3 antibody described in U.S. Patent Publication no. 2005/0147612 (e.g., antibody MSPRO2, MSPRO12, MSPRO59, MSPRO11, MSPRO21, MSPRO24, MSPRO26, MSPRO28, MSPRO29, MSPRO43, MSPRO55), antibody described in Rauchenberger et al, J Biol Chem 278 (40):38194-38205 (2003); an antibody described in PCT Publication No. WO2006/048877 (e.g., antibody PRO-001), an antibody described in Martinez-Torrecuadrada et al, Mol Cancer Ther (2008) 7(4): 862-873 (e.g., scFvαFGFR3 3C), an

antibody described in Direnzo, R et al (2007) Proceedings of AACR Annual Meeting, Abstract No. 2080 (e.g., D11), or an antibody described in WO 2010/002862 (e.g., antibodies 15D8, 27H2, 4E7, 2G4, 20B4).

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides compositions comprising one or more antibodies of the ~~invention~~disclosure and a carrier. In one embodiment, the carrier is pharmaceutically acceptable.

In another aspect, there is provided a polynucleotide encoding an antibody as defined above.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides nucleic acids encoding a FGFR3 antibody of the ~~invention~~disclosure.

In yet another ~~aspect~~embodiment, the ~~invention~~disclosure provides vectors comprising a nucleic acid of the ~~invention~~disclosure.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides compositions comprising one or more nucleic acids of the ~~invention~~disclosure and a carrier. In one embodiment, the carrier is pharmaceutically acceptable.

In another aspect, there is provided a host cell comprising a vector comprising the polynucleotide as defined above.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides host cells comprising a nucleic acid or a vector of the ~~invention~~disclosure. A vector can be of any type, for example, a recombinant vector such as an expression vector. Any of a variety of host cells can be used. In one embodiment, a host cell is a prokaryotic cell, for example, *E. coli*. In another embodiment, a host cell is a eukaryotic cell, for example a mammalian cell such as Chinese Hamster Ovary (CHO) cell.

In another aspect, there is provided a method for making an anti-FGFR3 antagonist antibody, said method comprising culturing a host cell comprising polynucleotide encoding the antibody as defined above so that the polynucleotide is expressed, and optionally, recovering the antibody from the culture.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides methods of making an antibody of the ~~invention~~disclosure. For example, the ~~invention~~disclosure provides methods of making an anti-FGFR3 antibody (which, as defined herein includes full length antibody and fragments thereof), said method comprising expressing in a suitable host cell a recombinant vector of the ~~invention~~disclosure encoding the antibody, and recovering the antibody. In some embodiments, the method comprises culturing a host cell comprising nucleic acid encoding the antibody so that the nucleic acid is expressed. In some embodiments, the method further comprises recovering the antibody from the host cell culture. In some embodiments, the antibody is recovered from the host cell culture medium. In some embodiments, the method further comprises combining the recovered antibody with a pharmaceutically acceptable carrier, excipient, or carrier to prepare a pharmaceutical formulation comprising the humanized antibody.

In another aspect, there is provided a pharmaceutical formulation comprising the antibody as defined above and a pharmaceutically acceptable carrier.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an article of manufacture comprising a container; and a composition contained within the container, wherein the composition comprises one or more FGFR3 antibodies of the ~~invention~~disclosure. In one embodiment, the composition comprises a nucleic acid of the ~~invention~~disclosure. In another embodiment, a composition comprising an antibody further comprises a carrier, which in some embodiments is pharmaceutically acceptable. In one embodiment, an article of manufacture of the

~~invention~~disclosure further comprises instructions for administering the composition (e.g., the antibody) to an individual (such as instructions for any of the methods described herein).

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a kit comprising a first container comprising a composition comprising one or more anti-FGFR3 antibodies of the ~~invention~~disclosure; and a second container comprising a buffer. In one embodiment, the buffer is pharmaceutically acceptable. In one embodiment, a composition comprising an antibody further comprises a carrier, which in some embodiments is pharmaceutically acceptable. In another embodiment, a kit further comprises instructions for administering the composition (e.g., the antibody) to an individual.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody of the ~~invention~~disclosure for use as a medicament.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody of the ~~invention~~disclosure for use in treating or preventing a disorder, such as a pathological condition associated with FGFR3 activation and/or expression (in some embodiments, over-expression). In some embodiments, the disorder is a cancer, a tumor, and/or a cell proliferative disorder. In some embodiments, the cancer, a tumor, and/or a cell proliferative disorder is multiple myeloma or bladder cancer (e.g., transitional cell carcinoma), breast cancer or liver cancer.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody of the ~~invention~~disclosure for use in treating or preventing a disorder such as a skeletal disorder. In some embodiments, the disorder is achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody of the ~~invention~~disclosure for use in reducing cell proliferation.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody of the ~~invention~~disclosure for use in killing a cell. In some embodiments, the cell is a multiple myeloma cell. In some embodiments, the cell is killed by ADCC. In some embodiments, the antibody is a naked antibody. In some embodiments, the cell over-expresses FGFR3.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides an anti-FGFR3 antibody of the ~~invention~~disclosure for use in depleting cells, such as multiple myeloma cells. In some embodiments, the cell is killed by ADCC. In some embodiments, the antibody is a naked antibody. In some embodiments, the cell over-expresses FGFR3.

In one aspect, there is provided the use of the anti-FGFR3 antagonist antibody as defined above in preparation of a medicament for inhibiting cell proliferation and/or depleting cancer cells.

In one aspect, there is provided the use of the anti-FGFR3 antagonist antibody as defined above in preparation of a medicament for treating cancer.

In one aspect, there is provided the use of the anti-FGFR3 antagonist antibody as defined above in the preparation of a medicament for treating a skeletal disorder.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an anti-FGFR3 antibody of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disorder, such as a pathological condition associated with FGFR3 activation and/or expression (in some embodiments, over-expression). In some embodiments, the

disorder is a cancer, a tumor, and/or a cell proliferative disorder. In some embodiments, the cancer, a tumor, and/or a cell proliferative disorder is multiple myeloma or bladder cancer (e.g., transitional cell carcinoma), breast cancer or liver cancer. In some embodiments, the disorder is a skeletal disorder, e.g., achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides use of a nucleic acid of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disorder, such as a pathological condition associated with FGFR3 activation and/or expression (in some embodiments, over-expression). In some embodiments, the disorder is a cancer, a tumor, and/or a cell proliferative disorder. In some embodiments, the cancer, a tumor, and/or a cell proliferative disorder is multiple myeloma or bladder cancer (e.g., transitional cell carcinoma), breast cancer or liver cancer. In some embodiments, the disorder is a skeletal disorder, e.g., achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an expression vector of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disorder, such as a pathological condition associated with FGFR3 activation and/or expression (in some embodiments, over-expression). In some embodiments, the disorder is a cancer, a tumor, and/or a cell proliferative disorder. In some embodiments, the cancer, a tumor, and/or a cell proliferative disorder is multiple myeloma or bladder cancer (e.g., transitional cell carcinoma), breast cancer or liver cancer. In some embodiments, the disorder is a skeletal disorder, e.g., achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

In yet another ~~aspect~~embodiment, the ~~invention~~disclosure provides use of a host cell of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disorder, such as a pathological condition associated with FGFR3 activation and/or expression (in some embodiments, over-expression). In some embodiments, the disorder is a cancer, a tumor, and/or a cell proliferative disorder. In some embodiments, the cancer, a tumor, and/or a cell proliferative disorder is multiple myeloma or bladder cancer (e.g., transitional cell carcinoma), breast cancer or liver cancer. In some embodiments, the disorder is a skeletal disorder, e.g., achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an article of manufacture of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic

treatment of a disorder, such as a pathological condition associated with FGFR3 activation and/or expression (in some embodiments, over-expression). In some embodiments, the disorder is a cancer, a tumor, and/or a cell proliferative disorder. In some embodiments, the cancer, a tumor, and/or a cell proliferative disorder is multiple myeloma or bladder cancer (e.g., transitional cell carcinoma), breast cancer or liver cancer. In some embodiments, the disorder is a skeletal disorder, e.g., achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

In one ~~aspect~~embodiment, the ~~invention~~disclosure also provides use of a kit of the ~~invention~~disclosure in the preparation of a medicament for the therapeutic and/or prophylactic treatment of a disorder, such as a pathological condition associated with FGFR3 activation and/or expression (in some embodiments, over-expression). In some embodiments, the disorder is a cancer, a tumor, and/or a cell proliferative disorder. In some embodiments, the cancer, a tumor, and/or a cell proliferative disorder is multiple myeloma or bladder cancer (e.g., transitional cell carcinoma) , breast cancer or liver cancer. In some embodiments, the disorder is a skeletal disorder, e.g., achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an anti-FGFR3 antibody of the ~~invention~~disclosure in the preparation of a medicament for inhibition of cell proliferation.In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an anti-FGFR3 antibody of the ~~invention~~disclosure in the preparation of a medicament for cell killing. In some embodiments, the cell is a multiple myeloma cell. In some embodiments, the cell is killed by ADCC. In some embodiments, the antibody is a naked antibody. In some embodiments, the cell over-expresses FGFR3.

In a further ~~aspect~~embodiment, the ~~invention~~disclosure provides use of an anti-FGFR3 antibody of the ~~invention~~disclosure in the preparation of a medicament for depleting cells, such as multiple myeloma cells. In some embodiments, the cell is killed by ADCC. In some embodiments, the antibody is a naked antibody. In some embodiments, the cell over-expresses FGFR3.

The ~~invention~~disclosure provides methods and compositions useful for modulating disorders associated with expression and/or signaling of FGFR3, such as increased expression and/or signaling or undesired expression and/or signaling.

Methods of the ~~invention~~disclosure can be used to affect any suitable pathological state. Exemplary disorders are described herein, and include a cancer selected from the group consisting of non-small cell lung cancer, ovarian cancer, thyroid cancer, testicular cancer, endometrial cancer, head and neck cancer, brain cancer (e.g., neuroblastoma or meningioma), skin cancer (e.g., melanoma, basal cell carcinoma, or squamous cell carcinoma), bladder

cancer (e.g., transitional cell carcinoma), breast carcinoma, gastric cancer, colorectal cancer (CRC), hepatocellular carcinoma, cervical cancer, lung cancer, pancreatic cancer, prostate cancer, and hematologic malignancies (e.g., T-cell acute lymphoblastic leukemia (T-ALL), B-cell acute lymphoblastic leukemia (B-ALL), acute myelogenous leukemia (AML), B-cell malignancies, Hodgkin lymphoma, and multiple myeloma). In some embodiments, the disorder is invasive transitional cell carcinoma. In some embodiments, the disorder is multiple myeloma. Additional exemplary disorders include skeletal disorders, such as achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

In certain embodiments, the cancer expresses FGFR3, amplified FGFR3, translocated FGFR3, and/or mutated FGFR3. In certain embodiments, the cancer expresses activated FGFR3. In certain embodiments, the cancer expresses translocated FGFR3 (e.g., a t(4;14) translocation). In certain embodiments, the cancer expresses constitutive FGFR3. In some embodiments, the constitutive FGFR3 comprises a mutation in the tyrosine kinase domain and/or the juxtamembrane domain and/or a ligand-binding domain. In certain embodiments, the cancer expresses ligand-independent FGFR3. In some embodiments, the cancer expresses ligand-dependent FGFR3.

In some embodiments, the cancer expresses FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{S248C}. In some embodiments, the cancer expressed FGFR3-IIIb ^{S248C} and/or FGFR3-IIIc^{S248C}.

In some embodiments, the cancer expresses FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{K652E}. In some embodiments, the cancer expressed FGFR3-IIIb ^{K652E} and/or FGFR3-IIIc ^{K650E}.

FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{S249C}. In some embodiments, the cancer expresses FGFR3-IIIb^{S249C} and/or FGFR3-IIIc ^{S249C}.

In one ~~aspect~~embodiment, the cancer expresses FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{G372C}. In some embodiments, the cancer expresses FGFR3-IIIb^{G372C} and/or FGFR3-IIIc ^{G370C}.

In one ~~aspect~~embodiment, the cancer expresses FGFR3 comprising a mutation corresponding to FGFR3-IIIb^{Y375C}. In some embodiments, the cancer expresses FGFR3-IIIb^{Y375C} and/or FGFR3-IIIc^{Y373C}.

In some embodiments, the cancer expresses (a) FGFR3-IIIb^{K652E} and (b) one or more of FGFR3-IIIb^{R248C}, FGFR3-IIIb^{Y375C}, FGFR3 -IIIb^{S249C}, and FGFR3IIIb ^{G372C}.

In some embodiments, the cancer expresses (a) FGFR3-IIIb^{R248C} and (b) one or more of FGFR3-IIIb^{K652E}, FGFR3-IIIb^{Y375C}, FGFR3-IIIb^{S249C}, and FGFR3-IIIb^{G372C}.

In some embodiments, the cancer expresses (a) FGFR3-IIIb^{G372C} and (b) one or more of FGFR3-IIIb^{K652E}, FGFR3-IIIb^{Y375C}, FGFR3-IIIb^{S249C}, and FGFR3-IIIb^{R248C}.

In some embodiments, the cancer expresses FGFR3-IIIb^{R248C}, FGFR3-IIIb^{K652E}, FGFR3-IIIb^{Y375C}, FGFR3-IIIb ^{S249C}, and FGFR3-IIIb ^{G372C}.

In certain embodiments, the cancer expresses increased levels of phospho-FGFR3, phospho-FRS2 and/or phospho-MAPK relative to a control sample (e.g., a sample of normal tissue) or level.

In some embodiments, the cancer expresses (e.g., on the cell surface) about 10,000 FGFR3 molecules per cell or more (such as 11,000, 12,000, 13,000, 14,000, 15,000, 16,000, 17,000, 18,000 or more FGFR3 receptors). In some embodiments, the cancer expresses about 13000 FGFR3 molecules. In other embodiments, the cancer expresses about 5000, 6000, 7000, 8000, or more FGFR3 molecules. In some embodiments, the cancer expresses less than about 4000, 3000, 2000, 1000, or fewer FGFR3 molecules. In some embodiments, the cancer expresses less than about 1000 FGFR3 molecules.

In one embodiment, a cell that is targeted in a method of the ~~invention~~disclosure is a cancer cell. For example, a cancer cell can be one selected from the group consisting of a breast cancer cell, a colorectal cancer cell, a lung cancer cell (e.g., a non-small cell lung cancer cell), a thyroid cancer cell, a multiple myeloma cell, a testicular cancer cell, a papillary carcinoma cell, a colon cancer cell, a pancreatic cancer cell, an ovarian cancer cell, a cervical cancer cell, a central nervous system cancer cell, an osteogenic sarcoma cell, a renal carcinoma cell, a hepatocellular carcinoma cell, a bladder cancer cell (e.g., a transitional cell carcinoma cell), a gastric carcinoma cell, a head and neck squamous carcinoma cell, a melanoma cell, a leukemia cell, a multiple myeloma cell (e.g. a multiple myeloma cell comprising a t(4:14) FGFR3 translocation)and a colon adenoma cell. In one embodiment, a cell that is targeted in a method of the ~~invention~~disclosure is a hyperproliferative and/or hyperplastic cell. In another embodiment, a cell that is targeted in a method of the ~~invention~~disclosure is a dysplastic cell. In yet another embodiment, a cell that is targeted in a method of the ~~invention~~disclosure is a metastatic cell.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods for inhibiting cell proliferation in a subject, the method comprising administering to the subject an effective amount of an anti-FGFR3 antibody to reduce cell proliferation.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods for killing a cell in a subject, the method comprising administering to the subject an effective amount of an anti-FGFR3

antibody to kill a cell. In some embodiments, the cell is a multiple myeloma cell. In some embodiments, the cell is killed by ADCC. In some embodiments, the antibody is a naked antibody. In some embodiments, the cell over-expresses FGFR3.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods for depleting cells (such as multiple myeloma cells) in a subject, the method comprising administering to the subject an effective amount of an anti-FGFR3 antibody to kill a cell. In some embodiments, the cell is killed by ADCC. In some embodiments, the antibody is a naked antibody. In some embodiments, the cell over-expresses FGFR3.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods for treating or preventing a skeletal disorder. In some embodiments, the disorder is achondroplasia, hypochondroplasia, dwarfism, thantophoric dysplasia (TD; clinical forms TD1 and TDII), or craniosynostosis syndrome.

Methods of the ~~invention~~disclosure can further comprise additional treatment steps. For example, in one embodiment, a method further comprises a step wherein a targeted cell and/or tissue (e.g., a cancer cell) is exposed to radiation treatment or a chemotherapeutic agent.

In one ~~aspect~~embodiment, the ~~invention~~disclosure provides methods comprising administration of an effective amount of an anti-FGFR3 antibody in combination with an effective amount of another therapeutic agent (such as an anti-angiogenesis agent, another antibody, a chemotherapeutic agent, a cytotoxic agent, an immunosuppressive agent, a prodrug, a cytokine, cytotoxic radiotherapy, a corticosteroid, an anti-emetic, a cancer vaccine, an analgesic, or a growth inhibitory agent). For example, anti-FGFR3 antibodies are used in combinations with an anti-cancer agent or an anti-angiogenic agent to treat various neoplastic or non-neoplastic conditions. In particular examples, the anti-FGFR3 antibodies are used in combination with velcade, revlimid, tamoxifen, letrozole, exemestane, anastrozole, irinotecan, cetuximab, fulvestrant, vinorelbine, bevacizumab, vincristine, cisplatin, gemcitabine, methotrexate, vinblastine, carboplatin, paclitaxel, docetaxel, pemetrexed, 5-fluorouracil, doxorubicin, bortezomib, lenalidomide, dexamethasone, melphalin, prednisone, vincristine, and/or thalidomide.

Depending on the specific cancer indication to be treated, the combination therapy of the ~~invention~~disclosure can be combined with additional therapeutic agents, such as chemotherapeutic agents, or additional therapies such as radiotherapy or surgery. Many known chemotherapeutic agents can be used in the combination therapy of the ~~invention~~disclosure. Preferably those chemotherapeutic agents that are standard for the treatment of the specific indications

will be used. Dosage or frequency of each therapeutic agent to be used in the combination is preferably the same as, or less than, the dosage or frequency of the corresponding agent when used without the other agent(s).

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides any of the anti-FGFR3 antibodies described herein, wherein the anti-FGFR3 antibody comprises a detectable label.

In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a complex of any of the anti-FGFR3 antibodies described herein and FGFR3. In some embodiments, the complex is *in vivo* or *in vitro*. In some embodiments, the complex comprises a cancer cell. In some embodiments, the anti-FGFR3 antibody is detectably labeled.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES 1A, 1B and1C: Heavy chain and light chain HVR loop sequences of anti-FGFR3 antibodies. The figures show the heavy chain HVR sequences, H1, H2, and H3, and light chain HVR sequences, L1, L2, and L3. Sequence numbering is as follows:

Clone 184.6 (HVR-H1 is SEQ ID NO:1; HVR-H2 is SEQ ID NO:2; HVR-H3 is SEQ ID NO:3; HVR-L1 is SEQ ID NO:4; HVR-L2 is SEQ ID NO:5; HVR-L3 is SEQ ID NO:6);

Clone 184.6.1 (HVR-H1 is SEQ ID NO:7; HVR-H2 is SEQ ID NO:8; HVR-H3 is SEQ ID NO:9; HVR-L1 is SEQ ID NO:10; HVR-L2 is SEQ ID NO:11; HVR-L3 is SEQ ID NO:12)

Clone 184.6.58 (HVR-H1 is SEQ ID NO:13; HVR-H2 is SEQ ID NO:14; HVR-H3 is SEQ ID NO:15; HVR-L1 is SEQ ID NO:16; HVR-L2 is SEQ ID NO:17; HVR-L3 is SEQ ID NO:18)

Clone 184.6.62 (HVR-H1 is SEQ ID NO:48; HVR-H2 is SEQ ID NO:49; HVR-H3 is SEQ ID NO:50; HVR-L1 is SEQ ID NO:51; HVR-L2 is SEQ ID NO:52; HVR-L3 is SEQ ID NO:53)

Clone 184.6.21 (HVR-H1 is SEQ ID NO:54; HVR-H2 is SEQ ID NO:55; HVR-H3 is SEQ ID NO:56; HVR-L1 is SEQ ID NO:57; HVR-L2 is SEQ ID NO:58; HVR-L3 is SEQ ID NO:59)

Clone 184.6.49 (HVR-H1 is SEQ ID NO:60; HVR-H2 is SEQ ID NO:61; HVR-H3 is SEQ ID NO:62; HVR-L1 is SEQ ID NO:63; HVR-L2 is SEQ ID NO:64; HVR-L3 is SEQ ID NO:65)

Clone 184.6.51 (HVR-H1 is SEQ ID NO:66; HVR-H2 is SEQ ID NO:67; HVR-H3 is SEQ ID NO:68; HVR-L1 is SEQ ID NO:69; HVR-L2 is SEQ ID NO:70; HVR-L3 is SEQ ID NO:71)