ANTI-FGFR3 ANTIBODIES AND ANTIGEN-BINDING FRAGMENTS AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to U.S. Provisional Application No. 63/383,686, filed November 14, 2022, and U.S. Provisional Application No. 63/587,538, filed October 3, 2023, the disclosure of both of which is herein incorporated by reference in its entirety.

SEQUENCE LISTING

[002] The instant application contains a Sequence Listing which has been submitted electronically in XML file format and is hereby incorporated by reference in its entirety. Said XML copy, created on November 3, 2023, is named 250298_000563_SL.xml and is 265,438 bytes in size.

FIELD OF THE INVENTION

[003] The present invention relates to antibodies and antigen-binding fragments thereof that bind specifically to FGFR3 and method for treating conditions such as cancer.

BACKGROUND OF THE INVENTION

[004] Several cancer genomic analysis studies have identified FGFR3 as a common mutation exclusive to non-inflamed bladder tumors. FGFR3 mutations including fusions are enriched in the luminal papillary (LumP) subclass of MIBC (30-40%), characterized by low immune cell infiltration.

[005] CD73 or ecto-5'-nucleotidase (ecto5'-NT, EC 3.1.3.5), is a cell surface enzyme that catalyzes the dephosphorylation of extracellular AMP to adenosine. It is broadly expressed in many types of cancer and has been associated with a pro-metastatic phenotype in melanoma and breast cancer. Adenosine activates immunoregulatory responses through specific receptors, which protect tissues from damage caused by excessive inflammation. Extracellular adenosine level is kept low under physiological conditions, but it increases during inflammation and cell death. In T-cells, the high-affinity adenosine receptor A2A (A2AR) is activated by adenosine to increase the cytoplasmic cyclic AMP level. This suppresses T-cell functions such as proliferation and cytokine secretion.

[006] Erdafitinib is a pan-FGFR tyrosine kinase inhibitor (TKI) approved to treat FGFR3-altered bladder cancer. Rapidly rising resistant mutations and the toxicity associated with TKI (hyperphosphatemia, ocular toxicity) presents a challenge in treating cancer by targeting FGFR3. In addition, the antibody B-701 (Vofatamab) has been investigated for use in the treatment of metastatic urothelial carcinoma (MUCC) and as targeted alpha therapy. Necchi *et al.*, The Journal of Urology, Vol. 201, No. 4S Supplement, 2019, e840, abstract: PD47-08; Storozhuk et al., FGFR3 Targeted Alpha Therapeutic [^{225}AC]-FPI-1966 Induces Regression in Preclinical Bladder Xenograft Model (Fusion Pharmaceuticals, Inc. (2020)).

SUMMARY OF THE INVENTION

[007] The present invention provides an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 (*e.g.*, monomeric or dimeric FGFR3b; optionally with the proviso that FGFR3 is not FGFR3c) or an antigenic fragment thereof (optionally in association with a further therapeutic agent, such as, for example, an FGFR inhibitor, erdafitinib, pemigatinib, infigratinib, rogaratinib, dexamethasone, alkylating drug, altretamine, trabectedin or busulfan, a nitrosourea, carmustine, lomustine, a cytotoxic antibiotic, an anthracycline, doxorubicin, valrubicin, bleomycin or dactinomycin, an antimetabolite drug, methotrexate, floxuridine, clofarabine, pralatrexate, a vinca alkaloid, vinblastine, vinorelbine, vincristine, vindesine, a photodynamic drug, porfimer sodium, aminolevulinic acid, a platinum drug, cisplatin, phenanthriplatin, a taxane, paclitaxel, docetaxel, a topoisomerase inhibitor, irinotecan, topotecan, etoposide, teniposide, ziv-aflibercept, an anti-cancer antibody, rituximab, trastuzumab, cetuximab, cemiplimab, pembrolizumab, panitumumab and bevacizumab) comprising: a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 2, 22, 42, 62, 82, 102, 122, 140, 159, 169, 179, 199 or 219, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 10, 30, 50, 70, 90, 110, 130, 148, 187, 207, or 227 or an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 as such an antibody or fragment or that competes with such an antibody or fragment for binding to FGFR3. In an embodiment of the invention, the antibody or antigen-binding fragment comprises (a) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 2, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR

that comprises the amino acid sequence set forth in SEQ ID NO: 10, (b) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 22, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 30, (c) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 42, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 50, (d) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 62, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 70, (e) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 82, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 90, (f) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 102, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 110, and/or (g) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 122, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 130, (h) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 140, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 148, (i) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 159, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 148, (j) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid

sequence set forth in SEQ ID NO: 169, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 148, (k) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 179, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 187, (l) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 199, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 207, and/or (m) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 219, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 227. In an embodiment of the invention, the antibody or antigen-binding fragment comprises: (a) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 4, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 6, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 8, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 16; (b) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 24, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 26, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 28, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 32, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 36; (c) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 44, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 46, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 48, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 52, an LCDR2 that

comprises the amino acid sequence set forth in SEQ ID NO: 54, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 56; (d) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 64, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 66, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 68, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 72, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 74, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 76; (e) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 84, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 86, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 88, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 92, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 94, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 96; (f) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 104, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 106, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 108, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 112, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 114, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 116; (g) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 124, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 126, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 128, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 132, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 134; (h) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 142, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 144, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 146, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an

LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153; (i) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 161, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 163, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 165, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153; (j) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 171, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 173, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 175, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153; (k) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 181, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 183, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 185, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 189, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 191, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 193; (l) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 201, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 203, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 205, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 209, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 211, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 213; and/or (m) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 221, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 223, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 225, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 32, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in

SEQ ID NO: 76. In an embodiment of the invention, the antibody or antigen-binding fragment comprises a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 2, 22, 42, 62, 82, 102, 122, 140, 159, 169, 179, 199 or 219, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10, 30, 50, 70, 90, 110, 130, 148, 187, 207, or 227. In an embodiment of the invention, the antibody or antigen-binding fragment comprises (a) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 2, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; (b) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 22, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 30; (c) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 42, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 50; (d) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 62, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 70; (e) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 82, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; (f) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 102, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 110; (g) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 122, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 130; (h) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 140, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148; (i) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 159, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148; (j) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 169, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148; (k) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 179, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 187; (l) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 199, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 207; and/or (m) a heavy chain variable region that comprises the amino

acid sequence set forth in SEQ ID NO: 219, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 227. In an embodiment of the invention, the antibody or antigen-binding fragment comprises (a) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 18, 38, 58, 78, 98, 118, 136, 155, 167, 177, 195, 215 or 229, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 20, 40, 60, 80, 100, 120, 138, 157, 197, 217, 231; *e.g.*, which comprises (a) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 18, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 20; (b) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 38, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 40; (c) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 58, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 60; (d) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 78, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 80; (e) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 98, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 100; (f) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 118, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 120; (g) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 136, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 138; (h) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 155, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157; (i) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 167, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157; (j) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 177, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157; (k) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 195, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 197; (l) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 215, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 217; and/or (m) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 229, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 231. In an embodiment of the

invention, the antibody or antigen-binding fragment thereof binds to one or more epitopes of FGFR3 selected from: a. an epitope comprising the sequence GPTVWVK (SEQ ID NO: 260) and/or an epitope comprising the sequence TQR; b. an epitope comprising the sequence ADVR (SEQ ID NO: 258) and/or an epitope comprising the sequence IGVAEK (SEQ ID NO: 259); c. an epitope comprising the sequence HCKVY (SEQ ID NO: 261), and/or an epitope comprising the sequence KSWISE (SEQ ID NO: 262), and/or an epitope comprising the sequence ADVR (SEQ ID NO: 263); e. an epitope comprised within or overlapping with the sequence GPTVWVK (SEQ ID NO: 260) and/or an epitope comprised within or overlapping with the sequence TQR; f. an epitope comprised within or overlapping with the sequence ADVR (SEQ ID NO: 258) and/or an epitope comprised within or overlapping with the sequence IGVAEK (SEQ ID NO: 259); and g. an epitope comprised within or overlapping with the sequence HCKVY (SEQ ID NO: 261), and/or an epitope comprised within or overlapping with the sequence KSWISE (SEQ ID NO: 262), and/or an epitope comprised within or overlapping with the sequence ADVR (SEQ ID NO: 263). In an embodiment of the invention, the antibody or antigen-binding fragment thereof binds to one or more epitopes of FGFR3 selected from: a. an epitope consisting of the sequence GPTVWVK (SEQ ID NO: 260) and/or an epitope consisting of the sequence IGVAEK (SEQ ID NO: 259); b. an epitope consisting of the sequence ADVR (SEQ ID NO: 258) and/or an epitope consisting of the sequence IGVAEK (SEQ ID NO: 259); and c. an epitope consisting of the sequence HCKVY (SEQ ID NO: 261), and/or an epitope consisting of the sequence KSWISE (SEQ ID NO: 262), and/or an epitope consisting of the sequence ADVR (SEQ ID NO: 263). In an embodiment of the invention, the antibody or antigen-binding fragment thereof binds to one or more epitopes of FGFR3 selected from: a. an epitope comprising the sequence SCPPPGGGPMGPTVWVKDGTGLVPSER (SEQ ID NO: 245) and/or an epitope comprising the sequence YSCRQRLTQRVL (SEQ ID NO: 246); b. an epitope comprising the sequence LLAVPAAN (SEQ ID NO: 247), and/or an epitope comprising the sequence VLERSPHRPILQAG (SEQ ID NO: 248) and/or an epitope comprising the sequence YVTVLKSWISE (SEQ ID NO: 249) and/or or an epitope comprising the sequence ADVRLR (SEQ ID NO: 250) and/or an epitope comprising the sequence LCRATNFIGVAEKAFW (SEQ ID NO: 251); c. an epitope comprising the sequence GQQEQLVFGSGDAVE (SEQ ID NO: 252) and/or an epitope comprising the sequence VLVGPQRL (SEQ ID NO: 253); d. an epitope comprising the sequence VLERSPHRPILQAG (SEQ ID NO: 254) and/or an epitope comprising the sequence HCKVYSDAQP (SEQ ID NO: 255) and/or an epitope comprising the sequence YVTVLKSWISESVEADVRLR (SEQ ID NO:

256) and/or an epitope comprising the sequence LCRATNFIGVAEKAF (SEQ ID NO: 257); e. an epitope comprised within or overlapping with the sequence SCPPPGGGPMGPTVWVKDGTGLVPSER (SEQ ID NO: 245) and/or an epitope comprised within or overlapping with the sequence YSCRQRLTQRVL (SEQ ID NO: 246); f. an epitope comprised within or overlapping with the sequence LLAVPAAN (SEQ ID NO: 247), and/or an epitope comprised within or overlapping with the sequence VLERSPHRPILQAG (SEQ ID NO: 248) and/or an epitope comprised within or overlapping with the sequence YVTVLKSWISE (SEQ ID NO: 249) and/or or an epitope comprised within or overlapping with the sequence ADVRLR (SEQ ID NO: 250) and/or an epitope comprised within or overlapping with the sequence LCRATNFIGVAEKAFW (SEQ ID NO: 251); g. an epitope comprised within or overlapping with the sequence GQQEQLVFGSGDAVE (SEQ ID NO: 252) and/or an epitope comprised within or overlapping with the sequence VLVGPQRL (SEQ ID NO: 253); and h. an epitope comprised within or overlapping with the sequence VLERSPHRPILQAG (SEQ ID NO: 254) and/or an epitope comprised within or overlapping with the sequence HCKVYSDAQP (SEQ ID NO: 255) and/or an epitope comprised within or overlapping with the sequence YVTVLKSWISESVEADVRLR (SEQ ID NO: 256) and/or an epitope comprised within or overlapping with the sequence LCRATNFIGVAEKAF (SEQ ID NO: 257). In an embodiment of the invention, the antibody or antigen-binding fragment thereof binds to one or more epitopes of FGFR3 selected from: a. an epitope consisting of the sequence SCPPPGGGPMGPTVWVKDGTGLVPSER (SEQ ID NO: 245) and/or an epitope consisting of the sequence YSCRQRLTQRVL (SEQ ID NO: 246); b. an epitope consisting of the sequence LLAVPAAN (SEQ ID NO: 247), and/or an epitope consisting of the sequence VLERSPHRPILQAG (SEQ ID NO: 248) and/or an epitope consisting of the sequence YVTVLKSWISE (SEQ ID NO: 249) and/or or an epitope consisting of the sequence ADVRLR (SEQ ID NO: 250) and/or an epitope consisting of the sequence LCRATNFIGVAEKAFW (SEQ ID NO: 251); c. an epitope consisting of the sequence GQQEQLVFGSGDAVE (SEQ ID NO: 252) and/or an epitope consisting of the sequence VLVGPQRL (SEQ ID NO: 253); and d. an epitope consisting of the sequence VLERSPHRPILQAG (SEQ ID NO: 254) and/or an epitope consisting of the sequence HCKVYSDAQP (SEQ ID NO: 255) and/or an epitope consisting of the sequence YVTVLKSWISESVEADVRLR (SEQ ID NO: 256) and/or an epitope consisting of the sequence LCRATNFIGVAEKAF (SEQ ID NO: 257).

[008] Also provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof that binds to the same FGFR3

epitope as or competes for binding to FGFR3 with an antibody or antigen-binding fragment described herein.

[009] For example, the present invention provides an antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof that is characterized by one or more of the following: Binds (*e.g.*, in a surface plasmon resonance assay) to monomeric human FGFR3b (*e.g.*, tagged, for example, at the C-terminus, with myc-myc-His_6) at 25°C with an affinity (K_D) of about 16 nM or greater affinity (*e.g.*, about 16 nM, 12 nM, 10 nM, 7nM, 5nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.22 nM, 0.2 nM, 0.19 nM, 0.14 nM, 0.1 nM); Binds (*e.g.*, in a surface plasmon resonance assay) to monomeric Cynomolgous monkey FGFR3b (*e.g.*, tagged, for example, at the C-terminus, with myc-myc-His_6) at 25°C with an affinity (K_D) of about 20 nM or greater affinity (*e.g.*, about 20nM, 16nM, 15nM, 10nM, 8nM, 5nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.9 nM, 0.65 nM, 0.3 nM, 0.28 nM, 0.2 nM, 0.15 nM, 0.1 nM); Binds (*e.g.*, in a surface plasmon resonance assay) monomeric murine FGFR3b (*e.g.*, tagged, for example, at the C-terminus, with myc-myc-His_6) at 25°C with an affinity (K_D) of about 70 nM or greater affinity (*e.g.*, about 70nM, 20nM, 17nM, 12nM, 10nM, 9nM, 8nM, 0.1 nM); Does not bind significantly to monomeric human FGFR3c (*e.g.*, tagged, for example, at the C-terminus, with myc-myc-His_6) at 25°C (*e.g.*, in a surface plasmon resonance assay); Binds (*e.g.*, in a surface plasmon resonance assay) dimeric human FGFR3b (*e.g.*, tagged, for example, at the C-terminus, with a mouse Fc (mFc)) 25°C with an affinity of about 0.6 nM of greater affinity (*e.g.*, about 0.58 nM, 0.17 nM, 0.11 nM, 0.04 nM, 0.03 nM, 0.02 nM, 0.01 nM, 0.023 nM, 0.061 nM, 0.031 nM, 0.016 nM, 0.034 nM, 0.027 nM); Blocks about 68% or more binding of FGF1 acidic to human FGFR3b-mFc at 200 nM antibody (3.g., 90% or 05%); Binds to monomeric Cynomolgous and monomeric mouse FGFR3b with a K_D that is within about 0.1 nM of the K_D for binding to monomeric or dimeric human FGFR3b; Blocks binding of 4 nM human FGFR3b-mFc to human FGF1 acidic protein with an IC_{50} of about 15 nM or a lower concentration (*e.g.*, IC_{50} of about 1, 2 or 3 nM); Competes for binding to hFGFR3b.mmH with another anti-FGFR3 antibody as set forth in Table 3-1 herein; Blocks intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express wild-type or S249C mutant human fibroblast growth factor receptor 3b that has been stimulated with human heparin, *e.g.*, at about 5 micrograms/ml, and human FGF1 ligand, *e.g.*, at about 1 nM, with an IC_{50} of about 18 nM or a lower concentration (*e.g.*, about 0.51 nM, 0.5 nM, 0.61 nM, 0.6 nM, or 0.012 nM); Blocks intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express S249C mutant

human fibroblast growth factor receptor 3b that has been stimulated with human heparin, *e.g.*, at about 5 micrograms/ml, and human FGF1 ligand, *e.g.*, at about 1 nM, with an IC_{50} that is lower than for blocking intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express wild-type human fibroblast growth factor receptor 3b that has been stimulated with human FGF1 ligand, *e.g.*, at about 1 nM, and human heparin, *e.g.*, at about 5 micrograms/ml; Blocks dimerization of FGFR3 (*e.g.*, wild-type or S249C mutant), *e.g.*, with stronger inhibition than that of REGN6331, for example, as measured in a non-reducing SDS-PAGE assay; Reduces tumor size (*e.g.*, bladder cancer tumor expressing FGFR3 (*e.g.*, S249C mutant)) in a subject administered the antibody or fragment; Reduces CD73 expression in a tumor (*e.g.*, bladder cancer tumor expressing FGFR3 (*e.g.*, S249C mutant)) in a subject administered the antibody or fragment; Inhibits FGF1/heparin stimulation induced phosphorylation of MAPK, *e.g.*, in a BaF3 cell expressing wild-type FGFR3 (*e.g.*, S249C mutant); Inhibits proliferation of UMUC14 bladder cancer cells expressing endogenous FGFR3 S249C mutation (*e.g.*, in a cancer cell spheroid proliferation assay); Inhibits tumor growth in a mouse (*e.g.*, SCID mouse) xenograft model of bladder cancer cell line UMUC14 expressing FGFR3 (*e.g.*, S249C mutation); inhibits CD73-dependent, adenosine-mediated inhibition of immune cell activation; increases the ratio of CD8/CD4 and/or CD8+/T_{reg} in tumor tissue having tumor cells expressing FGFR3 (*e.g.*, S249C mutant); Inhibits FGF3-mediated activation of CD73 expression and/or enzymatic activity (e.g., adenosine production) (e.g., on a tumor cell expressing FGFR3 (e.g., S249C mutant)); Inhibits FGFR3-dependent, adenosine-mediated immune cell suppression; Inhibits growth of BaF3 cells expressing the FGFR3 double mutant S249C and V557M, or S249C and V557L, wherein the antibody or antigen-binding fragment comprises immunoglobulin chains including any of the amino acid sequences as set forth herein.

[010] The present invention also provides a complex comprising such an antibody or antigen-binding fragment thereof bound to FGFR3 or an antigenic fragment thereof is also part of the present invention.

[011] A pharmaceutical formulation comprising an anti-FGFR3 antibody or fragment as set forth herein and a pharmaceutically acceptable carrier is also within the scope of the present invention.

[012] The present further provides an isolated polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82,

84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229 and 231; as well as an isolated polynucleotide that encodes any one or more of said polypeptides, *e.g.*, comprising a nucleotide sequence selected from that set forth in SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228 and 230. The present invention also includes a vector that comprises a polynucleotide as set forth herein. The present invention also provides host cell (*e.g.*, a eukaryotic or mammalian cell, such as a CHO cell) that comprises a polynucleotide set forth herein.

[013] The present invention also provides a method for making an anti-FGFR3 antibody or fragment as set forth herein including the steps of introducing a polynucleotide that encodes the chains of the antibody or fragment into a host cell (*e.g.*, CHO cell) and incubating the host cell that comprises the polynucleotide in a culture medium under conditions favorable to expression of the chains and, optionally, isolation of the antibody or fragment from the host cell and/or culture medium.

[014] The present invention further provides a method for administering an anti-FGFR3 antibody or fragment as set forth herein to a subject comprising introducing (*e.g.*, by injection, for example, intramuscular, intravenous or subcutaneous injection) the antibody or fragment into the body of the subject.

[015] The present invention also provides a method for treating or preventing an FGFR3-mediated condition (*e.g.*, cancer (*e.g.*, mediated by cancer cells expressing an FGFR3 S249C mutation), bladder cancer, brain cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, head & neck cancer, kidney cancer, lung cancer, multiple myeloma, ovarian cancer, pancreatic cancer, urothelial cancer, achondroplasia, crouzon syndrome with acanthosis nigricans, epidermal nevus, hypochondroplasia; lacrimo-auriculo-dento-digital (LADD) syndrome, muenke syndrome, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) and/or thanatophoric dysplasia), in

a subject in need thereof, comprising administering a therapeutically effective amount of an anti-FGFR3 antibody or fragment to the subject.

[016] The present invention provides a method for reducing metastasis (*e.g.*, CD73-dependent or adenosine-dependent) of a tumor cell expressing FGFR3 (*e.g.*, S249C mutant), reducing the concentration of adenosine in a tumor expressing FGFR3 (*e.g.*, S249C mutant), reducing CD73-dependent catalysis of AMP to adenosine by a tumor expressing FGFR3 (*e.g.*, S249C mutant), and/or inhibiting adenosine-mediated suppression of T-cell function in a tumor expressing FGFR3 (*e.g.*, S249C mutant), in the body of a subject in need thereof (e.g., a subject with cancer such as bladder cancer) comprising administering a therapeutically effective amount of the anti-FGFR3 antibody or fragment to the subject.

BRIEF DESCRIPTION OF THE FIGURES

[017] **Figure 1.** BaF3/FGFR3 WT (top, left and right panels) and BaF3/FGFR3_S249C (bottom, left and right panels) cells were treated with a titration of H4H30063P (left, top and bottom panels) or H4H30102P2 (right, top and bottom panels), alongside a comparator antibody (REGN6331) and isotype matched negative controls (REGN1945, REGN1932) in the presence of 1nM FGF1 and 5 µg/ml heparin. CellTiter-Glo, which measures ATP levels, was used to determine cell growth.

[018] **Figure 2**. Non-reducing and reducing SDS-PAGE analysis of FGFR3 dimerization in the presence of various concentrations of H4H30063P or COMP6331 (REGN6331). The mobility of the FGFR3 dimer and monomer are indicated.

[019] **Figure 3**. Western blot analysis of phosphorylated MAPK, from *in vitro* BaF3/hFGFR3b WT (wild-type), in the presence of no antibody (-), 100 nM control antibody (Con Ig; REGN6331) or 100 nM H4H30063P either with or without FGF1 & Heparin stimulation.

[020] **Figure 4**. Proliferation of UMUC14 bladder cancer cells treated with a range of concentrations (Log_{10} scale) of control antibody (IgG control), H4H30063P, H4H30071P or REGN6331 relative to that of untreated cells.

[021] **Figure 5**. UMUC14 tumor size (mm^3) in xenograft SCID mice treated with control antibody (10 mg/kg), H4H30063P (3 mg/kg or 10 mg/kg) or REGN6331 (3 mg/kg or 10 mg/kg) over time.

[022] **Figure 6**. Western blot analysis of CD73 protein expression in *in vitro* UMUC14 cells treated with control antibody (Con) or H4H30063P (FGFR3 Ab) or AZD4547 (FGFR TKI) at 1 nM, 10 nM and 100 nM concentrations.

[023] **Figure 7**. Western blot analysis of CD73 protein expression in *in vivo* UMUC14 cells from xenograft mice treated with control antibody (Con) or H4H30063P (FGFR3 Ab).

[024] **Figure 8**. Quantitation of Western blot band intensity of CD73/Actin from the blot in Figure 7.

[025] **Figure 9**. Western blot analysis of expression of CD73 protein in cell line expressing empty vector (EV), Wild-type FGFR3 (FGFR3), FGFR3-TACC3 mutant, FGFR3 S249C mutant or FGFR3 Y375C mutant.

[026] **Figure 10 (A-C).** Western blot analysis of expression of CD73 protein in tumor cells from xenograft SCID mice expressing (A) empty vector (EV) or (B) FGFR3 S249C mutant or (C) FGFR3-TACC3 mutant.

[027] **Figure 11 (A-B)**. Western blot analysis of expression of CD73 protein level in Fadu S249C tumor cells in xenograft mice treated with control antibody, H4H30063P antibody or AZD4547 (B) and graphical quantitation of band intensity (B).

[028] **Figure 12 (A-B)**. FGFR3 antibody inhibits proliferation of BaF3 cell expressing TKI resistant mutations V557L/M.

[029] **Figure 13**. HDX epitope mapping results for anti-FGFR3b H4H30117P2, H4H30063P.

[030] **Figure 14**. HDX epitope mapping results for anti-FGFR3b H4H30045P and H4H30108P2.

[031] **Figure 15**. HDX protection by FGFR3 antibodies. Regions with above 20% and 25% HDX protection are shown.

[032] **Figure 16 (A-B)**. HDX epitope mapping results of FGFR3 antibodies.

[033] **Figure 17**. HDX epitope mapping results for H4H30063P. Figure discloses SEQ ID NO: 238.

[034] **Figure 18**. HDX epitope mapping results for H4H30108P2. Figure discloses SEQ ID NO: 238.

[035] **Figure 19**. HDX epitope mapping results for H4H30117P2. Figure discloses SEQ ID NO: 238.

[036] **Figure 20**. HDX epitope mapping results for H4H30045P. Figure discloses SEQ ID NO: 238.

[037] **Figure 21**. Exemplary Hydrogen-Deuterium Exchange Mass Spectrometry experimental process.

DETAILED DESCRIPTION OF THE INVENTION

[038] The present invention provides anti-FGFR3 antibodies that exhibit *in vitro* and *in vivo* properties that are superior. In some embodiments, antibodies of the present invention exhibit greater binding to human monomeric FGFR3b while not exhibiting such binding to FGFR3c. This property facilitates a more targeted approach to treating cancer, *i.e.*, the ability to inhibit the b-isoform but not the c-isoform. In contrast, the Bioclin Therapeutics anti-FGFR3 antibody, B-701, was observed to exhibit binding to FGFR3c. The anti-FGFR3 antibodies herein also exhibited superior biological activities, relative to B-701, including for example, greater inhibition of FGFR3b dimerization, *in vitro* cancer cell proliferation and tumor growth in a mouse xenograft model.

FGFR3

[039] The term "FGFR3" refers to monomeric or dimeric human FGFR3b to which the antibodies and antigen-binding fragments thereof of the present invention bind specifically.

[040] The fibroblast growth factor receptor 3 (FGFR3) belongs to a family of structurally related tyrosine kinase receptors including four different genes (FGFR1–4). These receptors have three glycosylated extracellular immunoglobulin-like domains (Ig-like), a transmembrane domain and a split intracellular tyrosine-kinase domain. Ligand binding induces FGFR dimerization, resulting in autophosphorylation of the kinase domain and interaction with and phosphorylation of effector signaling proteins. Alternative mRNA splicing mechanisms generate many different receptor isoforms, which differ in ligand specificity. The isoforms FGFR3b and FGFR3c result from a mutually exclusive splicing event, in which the second half of the third Ig-like domain is encoded by either the 151 nucleotides of exon 8 or the 145 nucleotides of exon 9. These two isoforms have different tissue distributions: for example, FGFR3b is the main form in epithelial cells whereas FGFR3c is the predominant form in chondrocytes.

[041] Mutations of FGFR3 are associated with autosomal dominant dwarfism and craniosynostosis syndromes such as hypochondroplasia, achondroplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), thanatophoric

dysplasia, Crouzon syndrome with *acanthosis nigricans* and Muenke coronal craniosynostosis. Reports have demonstrated that these mutations lead to constitutive activation of the receptor.

[042] In addition, there is an oncogenic role for FGFR3 in human cancer. Indeed, somatic activating mutations in FGFR3 have been reported in multiple myeloma and, more recently, in two epithelial malignancies, *i.e.*, bladder- and cervix carcinomas. FGFR3 is a driver in muscle invasive bladder cancer (MIBC). See Cappellen *et al.*, Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas Nat Genet 1999 23: 18–20; Chesi *et al.*, Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3 Nat Genet 1997 16: 260–264; and Richelda *et al.* A novel translocation t(4;14)(p16.3;q32.3) in multiple myeloma involves the fibroblast growth-factor receptor 3 gene Blood 1997 90: 4062–4070. FGFR3 mutations are rare in multiple myeloma and cervix carcinomas, whereas their high incidence in bladder carcinomas (74% of non-invasive papillary tumors) suggests that the constitutive activation of FGFR3 is an important event for bladder tumorigenesis. See Fracchiolla *et al.*, FGFR3 gene mutations associated with human skeletal disorders occur rarely in multiple myeloma Blood 1998 92: 2987–2989; Wu *et al.*, Somatic mutations of fibroblast growth factor receptor 3 (FGFR3) are uncommon in carcinomas of the uterine cervix Oncogene 2000 19: 5543–5546; Billerey *et al.* Frequent FGFR3 mutations in papillary non-invasive bladder (pTa) tumors Am J Pathol 2001 158: 1955–1959; and Van Rhijn *et al.*, The fibroblast growth factor receptor 3 (FGFR3) mutation is a strong indicator of superficial bladder cancer with low recurrence rate Cancer Res 2001 61: 1265–1268. Many mutations identified in bladder tumours are identical to the activating mutations responsible for thanatophoric dysplasia, a lethal form of dwarfism. See Cappellen *et al.*, Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas Nat Genet 1999 23: 18–20; Billerey *et al.*, Frequent FGFR3 mutations in papillary non-invasive bladder (pTa) tumors Am J Pathol 2001 158: 1955–1959; Van Rhijn *et al.*, The fibroblast growth factor receptor 3 (FGFR3) mutation is a strong indicator of superficial bladder cancer with low recurrence rate Cancer Res 2001 61: 1265–1268; and Sibley *et al.*, Loss of heterozygosity at 4p16.3 and mutation of FGFR3 in transitional cell carcinoma Oncogene 2001 20: 686–691. Two of the 117 FGFR3 mutations identified by these groups, the A393E and K652Q mutations, do not correspond to thanatophoric dysplasia mutations. The A393E mutation is identical to a mutation associated with a craniosynostosis syndrome (Crouzon syndrome with *acanthosis nigricans*) and the K652Q mutation is identical to a mutation associated with hypochondroplasia.

[043] In an embodiment of the invention, the human FGFR3c isoform comprises the amino acid sequence:

ESLGTEQRVVGRAAEVPGPEPGQQEQLVFGSGDAVELSCPPPGGGPMGPTVWVKDGTGLVPSERVLVGPQRLQVLNASHE
DSGAYSCRQRLTQRVLCHFSVRVTDAPSSGDDEDGEDEAEDTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNP
TPSISWLKNGREFRGEHRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSPHRPILQAGLPAN
QTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLKTAGANTTDKELEVLSLHNVTFEDAGEYTCLAG
NSIGFSHHSAWLVVLPAEEELVEADEAGSVYAG

(SEQ ID NO: 232)

[044] In an embodiment of the invention, the human FGFR3b isoform comprises the amino acid sequence:

ESLGTEQRVVGRAAEVPGPEPGQQEQLVFGSGDAVELSCPPPGGGPMGPTVWVKDGTGLVPSERVLVGPQRLQVLNASHE
DSGAYSCRQRLTQRVLCHFSVRVTDAPSSGDDEDGEDEAEDTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNP
TPSISWLKNGREFRGEHRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSPHRPILQAGLPAN
QTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLKSWISESVEADVRLRLANVSERDGGEYLCRATN
FIGVAEKAFWLSVHGPRAAEEELVEADEAGSVYAG

(SEQ ID NO: 233)

[045] In an embodiment of the invention, an FGFR3 referred to herein comprises one or more of the following mutations: S249C, R248C, G372C, Y375C, K650E, or FGFR3-TACC3. See Singh *et al.*, Transforming fusions of FGFR and TACC genes in human glioblastoma. Science (New York, NY) 2012;337:1231–1235. Tomlinson et al., Knockdown by shRNA identifies S249C mutant FGFR3 as a potential therapeutic target in bladder cancer, Oncogene 2007 Aug 30 26(40):5889-99; Otsuka et al., Constitutively Active FGFR3 with Lys650Glu Mutation Enhances Bortezomib Sensitivity in Plasma Cell Malignancy, Anticancer Research January 2011, 31 (1) 113-122.

Antigen-binding proteins

[046] The present invention provides antigen-binding proteins, such as antibodies (*e.g.*, human antibodies, monoclonal antibodies and recombinant antibodies) and antigen-binding fragments thereof, that specifically bind to FGFR3 protein (*e.g.*, monomeric or dimeric FGFR3b) or an antigenic fragment thereof (*e.g.*, the extracellular domain of FGFR3). In an embodiment of the invention, the FGFR3 is an activating mutant (e.g., as discussed herein). Antigen-binding proteins that bind to the same epitope on FGFR3 as, or compete for binding to FGFR3 with, any of the antigen-binding proteins set forth herein (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2;

H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2), are also part of the present invention.

[047] The term "antibody", as used herein, refers to immunoglobulin molecules comprising four polypeptide chains, two heavy chains (HCs) and two light chains (LCs), inter-connected by disulfide bonds (*e.g.*, IgG). In an embodiment of the invention, each antibody heavy chain (HC) comprises a heavy chain variable region ("HCVR" or "V_H") (*e.g.*, SEQ ID NO: 2 or a variant thereof) and a heavy chain constant region; and each antibody light chain (LC) comprises a light chain variable region ("LCVR or "V_L") (*e.g.*, SEQ ID NO: 10 or a variant thereof) and a light chain constant region (CL). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR).

[048] In an embodiment of the invention, an anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, comprises a heavy chain constant domain, *e.g.*, of the type IgA (*e.g.*, IgA1 or IgA2), IgD, IgE, IgG (*e.g.*, IgG1, IgG2, IgG3 and IgG4 (*e.g.*, comprising a S228P and/or S108P mutation)) or IgM. In an embodiment of the invention, an antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, comprises a light chain constant domain, *e.g.*, of the type kappa or lambda. In an embodiment of the invention, a V_H as set forth herein is linked to a human heavy chain constant domain (*e.g.*, IgG) and a V_L as set forth herein is linked to a human light chain constant domain (*e.g.*, kappa). The present invention includes antigen-binding proteins comprising the variable domains set forth herein (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2), which are linked to a heavy and/or light chain constant domain, *e.g.*, as set forth herein.

[049] In an embodiment of the invention, the assignment of amino acids to each framework or CDR domain is in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat *et al.*; National Institutes of Health, Bethesda, Md.; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32:1-75; Kabat *et al.*, (1977) J. Biol. Chem. 252:6609-6616; Chothia *et al.*, (1987) J Mol. Biol. 196:901-917 or Chothia *et al.*, (1989) Nature 342:878-883. Thus, the present invention includes antibodies and antigen-binding fragments including the CDRs of a V_H and the CDRs of a V_L, which V_H and V_L comprise amino acid sequences as set forth herein (or a variant thereof), wherein the CDRs are as defined, for example, according to Kabat and/or Chothia.

[050] An FGFR3 binding protein described herein may be an antigen-binding fragment of an antibody. The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody, as used herein, refers to an immunoglobulin molecule that binds antigen but that does not include all of the sequences of a full antibody (preferably, the full antibody is an IgG). Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; and (vi) dAb fragments; consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, one-armed antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies and small modular immunopharmaceuticals (SMIPs), are also encompassed within the expression "antigen-binding fragment," as used herein.

[051] "Isolated" antigen-binding proteins (*e.g.*, antibodies or antigen-binding fragments thereof), polypeptides, polynucleotides and vectors, are at least partially free of other biological molecules from the cells or cell culture from which they are produced. Such biological molecules include nucleic acids, proteins, other antibodies or antigen-binding fragments, lipids, carbohydrates, or other material such as cellular debris and growth medium. An isolated antigen-binding protein may further be at least partially free of expression system components such as biological molecules from a host cell or of the growth medium thereof. Generally, the term "isolated" is not intended to refer to a complete absence of such biological molecules (*e.g.*, minor or insignificant amounts of impurity may remain) or to an absence of water, buffers, or salts or to components of a pharmaceutical formulation that includes the antigen-binding proteins (*e.g.*, antibodies or antigen-binding fragments).

[052] The amino acid sequences of polypeptide of the present invention and the nucleotide sequences of polynucleotides of the present invention are set forth below in Tables A and B, respectively.

Table A. Amino Acid Sequences of Exemplary Immunoglobulin Chains of the Present Invention

	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3	HC*	LC
H4H30063P (REGN15684)	2	4	6	8	10	12	14	16	18	20
H4H30066P	22	24	26	28	30	32	34	36	38	40

H4H30071P	42	44	46	48	50	52	54	56	58	60
H4H30089P2	62	64	66	68	70	72	74	76	78	80
H4H30093P2	82	84	86	88	90	92	94	96	98	100
H4H30102P2	102	104	106	108	110	112	114	116	118	120
H4H30076P	122	124	126	128	130	132	34	134	136	138
H4H30105P2	140	142	144	146	148	150	14	153	155	157
H4H30108P2	159	161	163	165	148	150	14	153	167	157
H4H30117P2	169	171	173	175	148	150	14	153	177	157
H4H30045P	179	181	183	185	187	189	191	193	195	197
H4H30061P	199	201	203	205	207	209	211	213	215	217
H4H30095P2	219	221	223	225	227	32	34	76	229	231

*In an embodiment of the invention, the heavy chain lacks the C-terminal Lysine.

Table B. Nucleotide Sequences of Exemplary Polynucleotides Encoding Immunoglobulin Chains of the Present Invention

	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3	HC*	LC
H4H30063P (REGN15684)	1	3	5	7	9	11	13	15	17	19
H4H30066P	21	23	25	27	29	31	33	35	37	39
H4H30071P	41	43	45	47	49	51	53	55	57	59
H4H30089P2	61	63	65	67	69	71	73	75	77	79
H4H30093P2	81	83	85	87	89	91	93	95	97	99
H4H30102P2	101	103	105	107	109	111	113	115	117	119
H4H30076P	121	123	125	127	129	131	33	133	135	137
H4H30105P2	139	141	143	145	147	149	151	152	154	156
H4H30108P2	158	160	162	164	147	149	151	152	166	156
H4H30117P2	168	170	172	174	147	149	151	152	176	156
H4H30045P	178	180	182	184	186	188	190	192	194	196
H4H30061P	198	200	202	204	206	208	210	212	214	216
H4H30095P2	218	220	222	224	226	31	33	75	228	230

*In an embodiment of the invention, the heavy chain lacks a codon encoding the C-terminal Lysine.

[053] Sequences of immunoglobulin chains of anti-FGFR3 antibodies and antigen-binding fragments of the present invention are set forth below. Thus, the present invention includes any antibody or antigen-binding fragment thereof that includes a HCVR and LCVR having amino acid sequences as set forth below or an HCVR and LCVR having the HCDRs and LCDRs thereof, respectively.

H4H30063P

HCVR Nucleotide Sequence

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGA
CTCCATTAATAGTTACTTCTGGAGCTGGATCCGGCAGTTGCCAGGGAAGGAACTGGAGTGGATTGGCCATATCTATTCTA
GTGGGAGTACCAGATACAACCCCTCCCTCCAGAGTCGAGTCACCATATCAATAGACACGTCCAAGAACCAGTTCTCCCTG
AAGCTGAGTTCTGTGACCGCTGCGGACACGGCCGTATATTACTGTGCGAGGGGCGCCAGCGCAGTTGACTACTGGGGCCA
GGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 1)

HCVR Amino Acid Sequence

QVQLQESGPGLVKPSETLSLTCTVSGDSINSYFWSWIRQLPGKELEWIGHIYSSGSTRYNPSLQSRVTISIDTSKNQFSL
KLSSVTAADTAVYYCARGASAVDYWGQGTLVTVSS

(SEQ ID NO: 2)

HCDR1 Nucleotide Sequence

GGT GAC TCC ATT AAT AGT TAC TTC

(SEQ ID NO: 3)

HCDR1 Amino Acid Sequence

G D S I N S Y F

(SEQ ID NO: 4)

HCDR2 Nucleotide Sequence

ATC TAT TCT AGT GGG AGT ACC

(SEQ ID NO: 5)

HCDR2 Amino Acid Sequence

I Y S S G S T

(SEQ ID NO: 6)

HCDR3 Nucleotide Sequence

GCG AGG GGC GCC AGC GCA GTT GAC TAC

(SEQ ID NO: 7)

HCDR3 Amino Acid Sequence

A R G A S A V D Y

(SEQ ID NO: 8)

LCVR Nucleotide Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGACCAGTCA
GAGTATTAGCAGCGGCTATTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCA
GAAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGACTTTGTAGTGTATTACTGTCAACAATATGGTAGCTCACCATACACTTTTGGCCAGGGGACCAAGCTGGAGAT
CAAA

(SEQ ID NO: 9)

LCVR Amino Acid Sequence

EIVLTQSPGTLSLSPGERATLSCRTSQSISSGYLAWYQQKPGQAPRLLIYGASRRATGIPDRFSGSGSGTDFTLTISRLE
PEDFVVYYCQQYGSSPYTFGQGTKLEIK

(SEQ ID NO: 10)

LCDR1 Nucleotide Sequence

CAG AGT ATT AGC AGC GGC TAT

(SEQ ID NO: 11)

LCDR1 Amino Acid Sequence

Q S I S S G Y

(SEQ ID NO: 12)

LCDR2 Nucleotide Sequence

GGT GCA TCC

(SEQ ID NO: 13)

LCDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 14)

LCDR3 Nucleotide Sequence

CAA CAA TAT GGT AGC TCA CCA TAC ACT

(SEQ ID NO: 15)

LCDR3 Amino Acid Sequence

Q Q Y G S S P Y T

(SEQ ID NO: 16)

Heavy Chain Nucleotide Sequence

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGA
CTCCATTAATAGTTACTTCTGGAGCTGGATCCGGCAGTTGCCAGGGAAGGAACTGGAGTGGATTGGCCATATCTATTCTA
GTGGGAGTACCAGATACAACCCCTCCCTCCAGAGTCGAGTCACCATATCAATAGACACGTCCAAGAACCAGTTCTCCCTG
AAGCTGAGTTCTGTGACCGCTGCGGACACGGCCGTATATTACTGTGCGAGGGGCGCCAGCGCAGTTGACTACTGGGGCCA
GGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCT
CCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCC
CTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTG
AGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCCA
AAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGA
GGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCC
CCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCG
TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC
CTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCT
GCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 17)

Heavy Chain Amino Acid Sequence

QVQLQESGPGLVKPSETLSLTCTVSGDSINSYFWSWIRQLPGKELEWIGHIYSSGSTRYNPSLQSRVTISIDTSKNQFSL
KLSSVTAADTAVYYCARGASAVDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

(SEQ ID NO: 18)

Light Chain Nucleotide Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGACCAGTCA
GAGTATTAGCAGCGGCTATTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCA
GAAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGACTTTGTAGTGTATTACTGTCAACAATATGGTAGCTCACCATACACTTTTGGCCAGGGGACCAAGCTGGAGAT
CAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTA
CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG

(SEQ ID NO: 19)

Light Chain Amino Acid Sequence

EIVLTQSPGTLSLSPGERATLSCRTSQSISSGYLAWYQQKPGQAPRLLIYGASRRATGIPDRFSGSGSGTDFTLTISRLE
PEDFVVYYCQQYGSSPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 20)

H4H30066P

HCVR Nucleotide Sequence

CAGGTGCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGTTTCCGGATA
CACCCTCACTGAATTATCCATGCACTGGGTGCGACAAGCTCCTGGAAAAGGGCTTGAGTGGATGGGAGGTTTTGATCCTG
AAGATGGTGAAATAATCTACGCACAGAAGTTCCAGGGCAGAGTCACCATGACCGAGGACACATCTACAGACACAGCCTAC
ATGGACCTGAGCAGTCTGACATCTGAAGACACGGCCGTGTATTACTGTGCAACGGAGAAGCAGCAACTGGTACGAAAATA
CTACTTCTACTACGGTTTGGCCGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 21)

HCVR Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGEIIYAQKFQGRVTMTEDTSTDTAY
MDLSSLTSEDTAVYYCATEKQQLVRKYYFYYGLAVWGQGTTVTVSS

(SEQ ID NO: 22)

HCDR1 Nucleotide Sequence

GGA TAC ACC CTC ACT GAA TTA TCC

(SEQ ID NO: 23)

HCDR1 Amino Acid Sequence

G Y T L T E L S

(SEQ ID NO: 24)

HCDR2 Nucleotide Sequence

TTT GAT CCT GAA GAT GGT GAA ATA

(SEQ ID NO: 25)

HCDR2 Amino Acid Sequence

F D P E D G E I

(SEQ ID NO: 26)

HCDR3 Nucleotide Sequence

GCA ACG GAG AAG CAG CAA CTG GTA CGA AAA TAC TAC TTC TAC TAC GGT TTG GCC GTC

(SEQ ID NO: 27)

HCDR3 Amino Acid Sequence

A T E K Q Q L V R K Y Y F Y Y G L A V

(SEQ ID NO: 28)

LCVR Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGTCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTCCCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAA
A

(SEQ ID NO: 29)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKVPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSPPFTFGPGTKVDIK

(SEQ ID NO: 30)

LCDR1 Nucleotide Sequence

CAG AGC ATT AGC AGT TAT

(SEQ ID NO: 31)

LCDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 32)

LCDR2 Nucleotide Sequence

GCT GCA TCC

(SEQ ID NO: 33)

LCDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 34)

LCDR3 Nucleotide Sequence

CAA CAG AGT TAC AGT CCC CCA TTC ACT

(SEQ ID NO: 35)

LCDR3 Amino Acid Sequence

Q Q S Y S P P F T

(SEQ ID NO: 36)

Heavy Chain Nucleotide Sequence

CAGGTGCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGTTTCCGGATA
CACCCTCACTGAATTATCCATGCACTGGGTGCGACAAGCTCCTGGAAAAGGGCTTGAGTGGATGGGAGGTTTTGATCCTG
AAGATGGTGAAATAATCTACGCACAGAAGTTCCAGGGCAGAGTCACCATGACCGAGGACACATCTACAGACACAGCCTAC
ATGGACCTGAGCAGTCTGACATCTGAAGACACGGCCGTGTATTACTGTGCAACGGAGAAGCAGCAACTGGTACGAAAATA
CTACTTCTACTACGGTTTGGCCGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC
GAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGG
ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACA
AGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTC

CTGGGGGGACCATCAGTCTTCCTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTG
CGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCA
AGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
AACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGG
GCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCC
TGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACG
CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAA
TGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAAT
GA

(SEQ ID NO: 37)

Heavy Chain Amino Acid

QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGEIIYAQKFQGRVTMTEDTSTDTAY
MDLSSLTSEDTAVYYCATEKQQLVRKYYFYYGLAVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEF
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

(SEQ ID NO: 38)

Light Chain Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGTCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTCCCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAA
ACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GTTAG

(SEQ ID NO: 39)

Light Chain Amino Acid

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKVPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSPPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 40)

H4H30071P

HCVR Nucleotide Sequence

CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGGGA
CAGTGTCTCTAGGAACAGTGCTGCTTGGAACTGGATCAGGCAGTCCCCATCGAGTGGCCTTGAGTGGCTGGGAAGGACAT
ACTACAGGTCCAAGTGGTTTTATGATTATGCAATATCTGTGAAAAGTCGAATAACCGTCAACCCAGACACATCCAAGAAC
CAATTCTCCCTTCACCTGAACTCTGTGACTCCCGAAGACACGGCTGTCTATTACTGTGCGAGAGGCTACGGTGGCTACGA
GGACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 41)

HCVR Amino Acid Sequence

QVQLQQSGPGLVKPSQTLSLTCAISGDSVSRNSAAWNWIRQSPSSGLEWLGRTYYRSKWFYDYAISVKSRITVNPDTSKN
QFSLHLNSVTPEDTAVYYCARGYGGYEDYFDYWGQGTLVTVSS

(SEQ ID NO: 42)

HCDR1 Nucleotide Sequence

GGG GAC AGT GTC TCT AGG AAC AGT GCT GCT

(SEQ ID NO: 43)

HCDR1 Amino Acid Sequence

G D S V S R N S A A

(SEQ ID NO: 44)

HCDR2 Nucleotide Sequence

ACA TAC TAC AGG TCC AAG TGG TTT TAT

(SEQ ID NO: 45)

HCDR2 Amino Acid Sequence

T Y Y R S K W F Y

(SEQ ID NO: 46)

HCDR3 Nucleotide Sequence

GCG AGA GGC TAC GGT GGC TAC GAG GAC TAC TTT GAC TAC

(SEQ ID NO: 47)

HCDR3 Amino Acid Sequence

A R G Y G G Y E D Y F D Y

(SEQ ID NO: 48)

LCVR Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA
GGGTATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTT
TGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTACTTTTGTCAACAGGGTAGCAGTTTCCCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAA
A

(SEQ ID NO: 49)

LCVR Amino Acid Sequence

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYFCQQGSSFPYTFGQGTKLEIK

(SEQ ID NO: 50)

LCDR1 Nucleotide Sequence

CAG GGT ATT AGC AGC TGG

(SEQ ID NO: 51)

LCDR1 Amino Acid Sequence

Q G I S S W

(SEQ ID NO: 52)

LCDR2 Nucleotide Sequence

GGT GCA TCC

(SEQ ID NO: 53)

LCDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 54)

LCDR3 Nucleotide Sequence

CAA CAG GGT AGC AGT TTC CCG TAC ACT

(SEQ ID NO: 55)

LCDR3 Amino Acid Sequence

Q Q G S S F P Y T

(SEQ ID NO: 56)

Heavy Chain Nucleotide Sequence

CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCACTCACCTGTGCCATCTCCGGGGA
CAGTGTCTCTAGGAACAGTGCTGCTTGGAACTGGATCAGGCAGTCCCCATCGAGTGGCCTTGAGTGGCTGGGAAGGACAT
ACTACAGGTCCAAGTGGTTTTATGATTATGCAATATCTGTGAAAAGTCGAATAACCGTCAACCCAGACACATCCAAGAAC
CAATTCTCCCTTCACCTGAACTCTGTGACTCCCGAAGACACGGCTGTCTATTACTGTGCGAGAGGCTACGGTGGCTACGA
GGACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCC
TGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTC
CCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCA
ACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGA
CCATCAGTCTTCCTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGT
GGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGC
CGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAG
GAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCG
AGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAG
GCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG
CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTC
ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 57)

Heavy Chain Amino Acid

QVQLQQSGPGLVKPSQTLSLTCAISGDSVSRNSAAWNWIRQSPSSGLEWLGRTYYRSKWFYDYAISVKSRITVNPDTSKN
QFSLHLNSVTPEDTAVYYCARGYGGYEDYFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV
TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV

LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

(SEQ ID NO: 58)

Light Chain Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA
GGGTATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTT
TGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTACTTTTGTCAACAGGGTAGCAGTTTCCCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAA
ACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GTTAG

(SEQ ID NO: 59)

Light Chain Amino Acid

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYGASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYFCQQGSSFPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 60)

H4H30089P2

HCVR Nucleotide Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGAGGGTCCCTGAGACTCTCCTGTATAGTCTCTGGATT
CATCTTCAGTAGTTATGAAATGAGCTGGCTCCGCCAGGCTCCAGGGAAGGGCCTGGAGTGGATTTCATATATTAGTAGTA
GTGGTCGTGTCATATACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAGCGCCAAGAATTCACTGTAT
CTGGAAATGAATAGTCTGAGAGCCGAAGACACGGCTATATATTATTGTACGAGAAAGTGGGATAGTAGTGGCCCATTTGA
CTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 61)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCIVSGFIFSSYEMSWLRQAPGKGLEWISYISSSGRVIYYADSVKGRFTISRDSAKNSLY
LEMNSLRAEDTAIYYCTRKWDSSGPFDFWGQGTLVTVSS

(SEQ ID NO: 62)

HCDR1 Nucleotide Sequence

GGA TTC ATC TTC AGT AGT TAT GAA

(SEQ ID NO: 63)

HCDR1 Amino Acid Sequence

G F I F S S Y E

(SEQ ID NO: 64)

HCDR2 Nucleotide Sequence

ATT AGT AGT AGT GGT CGT GTC ATA

(SEQ ID NO: 65)

HCDR2 Amino Acid Sequence

I S S S G R V I

(SEQ ID NO: 66)

HCDR3 Nucleotide Sequence

ACG AGA AAG TGG GAT AGT AGT GGC CCA TTT GAC TTC

(SEQ ID NO: 67)

HCDR3 Amino Acid Sequence

T R K W D S S G P F D F

(SEQ ID NO: 68)

LCVR Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT
TAAA

(SEQ ID NO: 69)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 70)

LCDR1 Nucleotide Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 71)

LCDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 72)

LCDR2 Nucleotide Sequence

GCT GCA TCC

(SEQ ID NO: 73)

LCDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 74)

LCDR3 Nucleotide Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 75)

LCDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 76)

Heavy Chain Nucleotide Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGAGGGTCCCTGAGACTCTCCTGTATAGTCTCTGGATT
CATCTTCAGTAGTTATGAAATGAGCTGGCTCCGCCAGGCTCCAGGGAAGGGCCTGGAGTGGATTTCATATATTAGTAGTA
GTGGTCGTGTCATATACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAGCGCCAAGAATTCACTGTAT
CTGGAAATGAATAGTCTGAGAGCCGAAGACACGGCTATATATTATTGTACGAGAAAGTGGGATAGTAGTGGCCCATTTGA
CTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCT

CCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG
AACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT
GGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTC
CTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCA
GGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC
AGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGT
GTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGAT
GCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 77)

Heavy Chain Amino Acid

EVQLVESGGGLVQPGGSLRLSCIVSGFIFSSYEMSWLRQAPGKGLEWISYISSSGRVIYYADSVKGRFTISRDSAKNSLY
LEMNSLRAEDTAIYYCTRKWDSSGPFDFWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

(SEQ ID NO: 78)

Light Chain Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT
TAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTA
CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG

(SEQ ID NO: 79)

Light Chain Amino Acid

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 80)

H4H30093P2

HCVR Nucleotide Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTAAGACTCTCCTGTGCAGCCTCTGGATT
CACCTTCAATGACTACCCAATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTTTCATACATTACTAGCA
GTAGTGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACTG
TATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAGGTTGTAGTGGCTACGATTGG
GGGCTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 81)

HCVR Amino Acid Sequence

QVQLVESGGGLVKPGGSLRLSCAASGFTFNDYPMSWIRQAPGKGLEWVSYITSSSGSTIYYADSVKGRFTISRDNAKNSL
YLQMNSLRAEDTAVYYCAREVVVATIGGYYGMDVWGQGTTVTVSS

(SEQ ID NO: 82)

HCDR1 Nucleotide Sequence

GGA TTC ACC TTC AAT GAC TAC CCA

(SEQ ID NO: 83)

HCDR1 Amino Acid Sequence

G F T F N D Y P

(SEQ ID NO: 84)

HCDR2 Nucleotide Sequence

ATT ACT AGC AGT AGT GGT AGT ACC ATA

(SEQ ID NO: 85)

HCDR2 Amino Acid Sequence

I T S S S G S T I

(SEQ ID NO: 86)

HCDR3 Nucleotide Sequence

GCG AGA GAG GTT GTA GTG GCT ACG ATT GGG GGC TAC TAC GGT ATG GAC GTC

(SEQ ID NO: 87)

HCDR3 Amino Acid Sequence

A R E V V V A T I G G Y Y G M D V

(SEQ ID NO: 88)

LCVR Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT
TAAA

(SEQ ID NO: 89)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 90)

LCDR1 Nucleotide Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 91)

LCDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 92)

LCDR2 Nucleotide Sequence

GCT GCA TCC

(SEQ ID NO: 93)

LCDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 94)

LCDR3 Nucleotide Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 95)

LCDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 96)

Heavy Chain Nucleotide Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTAAGACTCTCCTGTGCAGCCTCTGGATT
CACCTTCAATGACTACCCAATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTTTCATACATTACTAGCA
GTAGTGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACTG
TATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAGGTTGTAGTGGCTACGATTGG
GGGCTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCT
TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA
CCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT
CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGC
CCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTG
GGGGGACCATCAGTCTTCCTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGT
GGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGA
CAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAAC
GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA
GCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGG
TCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGT
CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 97)

Heavy Chain Amino Acid

QVQLVESGGGLVKPGGSLRLSCAASGFTFNDYPMSWIRQAPGKGLEWVSYITSSSGSTIYYADSVKGRFTISRDNAKNSL
YLQMNSLRAEDTAVYYCAREVVVATIGGYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE

PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFL
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

(SEQ ID NO: 98)

Light Chain Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT
TAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTA
CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG

(SEQ ID NO: 99)

Light Chain Amino Acid

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 100)

H4H30102P2

HCVR Nucleotide Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTACAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATT
CACCTTCAGTAGTTATGAAATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAATA
GTGGTTCTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCGAGACCTCACTGTAT
CTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGAGGGATGGGGCGCATATTGTGCTGG
TGATTGCTATTCTGGTTTTGATATTTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

(SEQ ID NO: 101)

HCVR Amino Acid Sequence

EVQLVESGGDLVQPGGSLRLSCAASGFTFSSYEMNWVRQAPGKGLEWVSYISNSGSTIYYADSVKGRFTISRDNAETSLY

LQMNSLRAEDTAVYYCAREGWGAYCAGDCYSGFDIWGQGTMVTVSS

(SEQ ID NO: 102)

HCDR1 Nucleotide Sequence

GGA TTC ACC TTC AGT AGT TAT GAA

(SEQ ID NO: 103)

HCDR1 Amino Acid Sequence

G F T F S S Y E

(SEQ ID NO: 104)

HCDR2 Nucleotide Sequence

ATT AGT AAT AGT GGT TCT ACC ATA

(SEQ ID NO: 105)

HCDR2 Amino Acid Sequence

I S N S G S T I

(SEQ ID NO: 106)

HCDR3 Nucleotide Sequence

GCG AGA GAG GGA TGG GGC GCA TAT TGT GCT GGT GAT TGC TAT TCT GGT TTT GAT ATT

(SEQ ID NO: 107)

HCDR3 Amino Acid Sequence

A R E G W G A Y C A G D C Y S G F D I

(SEQ ID NO: 108)

LCVR Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT
TAAA

(SEQ ID NO: 109)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 110)

LCDR1 Nucleotide Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 111)

LCDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 112)

LCDR2 Nucleotide Sequence

GCT GCA TCC

(SEQ ID NO: 113)

LCDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 114)

LCDR3 Nucleotide Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 115)

LCDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 116)

Heavy Chain Nucleotide Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTACAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATT
CACCTTCAGTAGTTATGAAATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAATA
GTGGTTCTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCGAGACCTCACTGTAT

CTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGAGGGATGGGGCGCATATTGTGCTGG
TGATTGCTATTCTGGTTTTGATATTTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCCACCAAGGGCCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC
GAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGG
ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACA
AGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTC
CTGGGGGGACCATCAGTCTTCCTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTG
CGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCA
AGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
AACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGG
GCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCC
TGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACG
CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAA
TGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAAT
GA

(SEQ ID NO: 117)

Heavy Chain Amino Acid

EVQLVESGGDLVQPGGSLRLSCAASGFTFSSYEMNWVRQAPGKGLEWVSYISNSGSTIYYADSVKGRFTISRDNAETSLY
LQMNSLRAEDTAVYYCAREGWGAYCAGDCYSGFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP
EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEF
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

(SEQ ID NO: 118)

Light Chain Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT
TAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTA
CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG

(SEQ ID NO: 119)

Light Chain Amino Acid

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 120)

H4H30076P

HCVR Nucleotide Sequence

GAGGTGCAGCTGGTGGAGTCTGGAGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGGTT
CACCGTCAGTAGCAACTACATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATTTATAGCG
GTGGTCACACATACTACTCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGACACAATTCCAAGAACACTCTGTATCTT
CAAATGAACAGCCTGAGAGGTGGGGACACGGCCGTGTATTACTGTGCGAGAGGGTATACCAGTGGCTGGTACGGATTTGA
CTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 121)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSIIYSGGHTYYSDSVKGRFTISRHNSKNTLYL
QMNSLRGGDTAVYYCARGYTSGWYGFDFWGQGTLVTVSS

(SEQ ID NO: 122)

HCDR1 Nucleotide Sequence

GGG TTC ACC GTC AGT AGC AAC TAC

(SEQ ID NO: 123)

HCDR1 Amino Acid Sequence

G F T V S S N Y

(SEQ ID NO: 124)

HCDR2 Nucleotide Sequence

ATT TAT AGC GGT GGT CAC ACA

(SEQ ID NO: 125)

HCDR2 Amino Acid Sequence

I Y S G G H T

(SEQ ID NO: 126)

HCDR3 Nucleotide Sequence

GCG AGA GGG TAT ACC AGT GGC TGG TAC GGA TTT GAC TTC

(SEQ ID NO: 127)

HCDR3 Amino Acid Sequence

A R G Y T S G W Y G F D F

(SEQ ID NO: 128)

LCVR Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA
GGGTATTAGCACCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGATTCAGCGGCACTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTATTGTCAGCAGACTAACAGTTTCCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAA
A

(SEQ ID NO: 129)

LCVR Amino Acid Sequence

DIQMTQSPSSVSASVGDRVTITCRASQGISTWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGTGSGTDFTLTISSLQP
EDFATYYCQQTNSFPWTFGQGTKVEIK

(SEQ ID NO: 130)

LCDR1 Nucleotide Sequence

CAG GGT ATT AGC ACC TGG

(SEQ ID NO: 131)

LCDR1 Amino Acid Sequence

Q G I S T W

(SEQ ID NO: 132)

LCDR2 Nucleotide Sequence

GCT GCA TCC

(SEQ ID NO: 33)

LCDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 34)

LCDR3 Nucleotide Sequence

CAG CAG ACT AAC AGT TTC CCG TGG ACG

(SEQ ID NO: 133)

LCDR3 Amino Acid Sequence

Q Q T N S F P W T

(SEQ ID NO: 134)

Heavy Chain Nucleotide Sequence

GAGGTGCAGCTGGTGGAGTCTGGAGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGGTT
CACCGTCAGTAGCAACTACATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATTTATAGCG
GTGGTCACACATACTACTCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGACACAATTCCAAGAACACTCTGTATCTT
CAAATGAACAGCCTGAGAGGTGGGGACACGGCCGTGTATTACTGTGCGAGAGGGTATACCAGTGGCTGGTACGGATTTGA
CTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCT
CCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG
AACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT
GGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTC
CTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCA
GGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC
AGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGT
GTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGAT
GCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 135)

Heavy Chain Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSIIYSGGHTYYSDSVKGRFTISRHNSKNTLYL
QMNSLRGGDTAVYYCARGYTSGWYGFDFWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 136)

Light Chain Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCA
GGGTATTAGCACCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGATTCAGCGGCACTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTATTGTCAGCAGACTAACAGTTTCCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAA
ACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GTTAG

(SEQ ID NO: 137)

Light Chain Amino Acid Sequence

DIQMTQSPSSVSASVGDRVTITCRASQGISTWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGTGSGTDFTLTISSLQP
EDFATYYCQQTNSFPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 138)

H4H30105P2

HCVR Nucleotide Sequence

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTCTGGATA
CAGCTTTACCAGCTACTGGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTG
GTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATGTCAGCCGACAAGTCCATCAGGATCGCCTAC
CTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTATTGTGCGAGACTTGATTATAGCGGCAGCTGGTTTGA
CTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 139)

HCVR Amino Acid Sequence

EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIAWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTMSADKSIRIAY
LQWSSLKASDTAMYYCARLDYSGSWFDYWGQGTLVTVSS

(SEQ ID NO: 140)

HCDR1 Nucleotide Sequence

GGA TAC AGC TTT ACC AGC TAC TGG

(SEQ ID NO: 141)

HCDR1 Amino Acid Sequence

G Y S F T S Y W

(SEQ ID NO: 142)

HCDR2 Nucleotide Sequence

ATC TAT CCT GGT GAC TCT GAT ACC

(SEQ ID NO: 143)

HCDR2 Amino Acid Sequence

I Y P G D S D T

(SEQ ID NO: 144)

HCDR3 Nucleotide Sequence

GCG AGA CTT GAT TAT AGC GGC AGC TGG TTT GAC TAC

(SEQ ID NO: 145)

HCDR3 Amino Acid Sequence

A R L D Y S G S W F D Y

(SEQ ID NO: 146)

LCVR Nucleotide Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGAGCCACCTTGTCATGTAGAGCAAGTCA
GTCAGTCTCTAGCTCTTATCTCGCCTGGTACCAGCAGAAGCCGGGACAGGCCCCTAGACTGCTGATCTACGGGGCAAGTT
CCAGGGCCACCGGAATCCCCGACCGGTTCAGTGGAAGCGGAAGCGGAACCGATTTTACTTTGACGATTTCTAGACTGGAG
CCAGAGGATTTCGCCGTTTACTATTGTCAACAGTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAAT
CAAG

(SEQ ID NO: 147)

LCVR Amino Acid Sequence

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLE
PEDFAVYYCQQYGSSPWTFGQGTKVEIK

(SEQ ID NO: 148)

LCDR1 Nucleotide Sequence

CAG TCA GTC TCT AGC TCT TAT

(SEQ ID NO: 149)

LCDR1 Amino Acid Sequence

Q S V S S S Y

(SEQ ID NO: 150)

LCDR2 Nucleotide Sequence

GGG GCA AGT

(SEQ ID NO: 151)

LCDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 14)

LCDR3 Nucleotide Sequence

CAA CAG TAC GGA AGC AGC CCG TGG ACG

(SEQ ID NO: 152)

LCDR3 Amino Acid Sequence

Q Q Y G S S P W T

(SEQ ID NO: 153)

Heavy Chain Nucleotide Sequence

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTCTGGATA
CAGCTTTACCAGCTACTGGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTG

GTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATGTCAGCCGACAAGTCCATCAGGATCGCCTAC
CTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTATTGTGCGAGACTTGATTATAGCGGCAGCTGGTTTGA
CTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCT
CCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG
AACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT
GGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTC
CTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCA
GGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC
AGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGT
GTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGAT
GCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 154)

Heavy Chain Amino Acid Sequence

EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIAWVRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTMSADKSIRIAY
LQWSSLKASDTAMYYCARLDYSGSWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 155)

Light Chain Nucleotide Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGAGCCACCTTGTCATGTAGAGCAAGTCA
GTCAGTCTCTAGCTCTTATCTCGCCTGGTACCAGCAGAAGCCGGGACAGGCCCCTAGACTGCTGATCTACGGGGCAAGTT
CCAGGGCCACCGGAATCCCCGACCGGTTCAGTGGAAGCGGAAGCGGAACCGATTTTACTTTGACGATTTCTAGACTGGAG
CCAGAGGATTTCGCCGTTTACTATTGTCAACAGTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAAT
CAAGCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTA
CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG

(SEQ ID NO: 156)

Light Chain Amino Acid Sequence

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLE
PEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 157)

H4H30108P2

HCVR Nucleotide Sequence

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATA
CACCTTCAACAGTTATGATGTCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATGGATGAACCCTC
ACAGTGGTAACACAGGCTACGCACAGAAGTTCCAGGGCAGAGTCACTATGACCAGGGACACCTCCACAAGCACAAGCTAT
ATGGAGTTGAGCAGCCTGACATCTGAGGACACGGCCGTATATTACTGTGCGAGAGGCCCTTTTTCTCTACTTTCAGCTGA
ATTCTTCCAGCACTGGGGCCAGGGCACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 158)

HCVR Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYDVNWVRQATGQGLEWMGWMNPHSGNTGYAQKFQGRVTMTRDTSTSTSY
MELSSLTSEDTAVYYCARGPFSLLSAEFFQHWGQGTLVTVSS

(SEQ ID NO: 159)

HCDR1 Nucleotide Sequence

GGA TAC ACC TTC AAC AGT TAT GAT

(SEQ ID NO: 160)

HCDR1 Amino Acid Sequence

G Y T F N S Y D

(SEQ ID NO: 161)

HCDR2 Nucleotide Sequence

ATG AAC CCT CAC AGT GGT AAC ACA

(SEQ ID NO: 162)

HCDR2 Amino Acid Sequence

M N P H S G N T

(SEQ ID NO: 163)

HCDR3 Nucleotide Sequence

GCG AGA GGC CCT TTT TCT CTA CTT TCA GCT GAA TTC TTC CAG CAC

(SEQ ID NO: 164)

HCDR3 Amino Acid Sequence

A R G P F S L L S A E F F Q H

(SEQ ID NO: 165)

LCVR Nucleotide Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGAGCCACCTTGTCATGTAGAGCAAGTCA
GTCAGTCTCTAGCTCTTATCTCGCCTGGTACCAGCAGAAGCCGGGACAGGCCCCTAGACTGCTGATCTACGGGGCAAGTT
CCAGGGCCACCGGAATCCCCGACCGGTTCAGTGGAAGCGGAAGCGGAACCGATTTTACTTTGACGATTTCTAGACTGGAG
CCAGAGGATTTCGCCGTTTACTATTGTCAACAGTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAAT
CAAG

(SEQ ID NO: 147)

LCVR Amino Acid Sequence

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLE
PEDFAVYYCQQYGSSPWTFGQGTKVEIK

(SEQ ID NO: 148)

LCDR1 Nucleotide Sequence

CAG TCA GTC TCT AGC TCT TAT

(SEQ ID NO: 149)

LCDR1 Amino Acid Sequence

Q S V S S S Y

(SEQ ID NO: 150)

LCDR2 Nucleotide Sequence

GGG GCA AGT

(SEQ ID NO: 151)

LCDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 14)

LCDR3 Nucleotide Sequence

CAA CAG TAC GGA AGC AGC CCG TGG ACG

(SEQ ID NO: 152)

LCDR3 Amino Acid Sequence

Q Q Y G S S P W T

(SEQ ID NO: 153)

Heavy Chain Nucleotide Sequence

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATA
CACCTTCAACAGTTATGATGTCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATGGATGAACCCTC
ACAGTGGTAACACAGGCTACGCACAGAAGTTCCAGGGCAGAGTCACTATGACCAGGGACACCTCCACAAGCACAAGCTAT
ATGGAGTTGAGCAGCCTGACATCTGAGGACACGGCCGTATATTACTGTGCGAGAGGCCCTTTTTCTCTACTTTCAGCTGA
ATTCTTCCAGCACTGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGG
CGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG
GTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCT
CAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACA
CCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCA
TCAGTCTTCCTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGA
CGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
GGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAG
TACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
GCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTG
GACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 166)

Heavy Chain Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYDVNWVRQATGQGLEWMGWMNPHSGNTGYAQKFQGRVTMTRDTSTSTSY
MELSSLTSEDTAVYYCARGPFSLLSAEFFQHWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 167)

Light Chain Nucleotide Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGAGCCACCTTGTCATGTAGAGCAAGTCA
GTCAGTCTCTAGCTCTTATCTCGCCTGGTACCAGCAGAAGCCGGGACAGGCCCCTAGACTGCTGATCTACGGGGCAAGTT
CCAGGGCCACCGGAATCCCCGACCGGTTCAGTGGAAGCGGAAGCGGAACCGATTTTACTTTGACGATTTCTAGACTGGAG
CCAGAGGATTTCGCCGTTTACTATTGTCAACAGTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAAT
CAAGCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTA
CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG

(SEQ ID NO: 156)

Light Chain Amino Acid Sequence

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLE
PEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 157)

H4H30117P2

HCVR Nucleotide Sequence

CAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGA
CACCTTCAGTAACTATGTTATCGGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTA
TCTTTGGTACAACAAACTACGCACAGCAGTTCCAGGGCAGAGTCACGATTACCACGGACGAATCCACGAGCACGGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATGGGAACTACGGTGACTACTTTGA
CTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 168)

HCVR Amino Acid Sequence

QVQLVQSGAEVKKPGSSVKVSCKASGDTFSNYVIGWVRQAPGQGLEWMGGIIPIFGTTNYAQQFQGRVTITTDESTSTAY
MELSSLRSEDTAVYYCARDGNYGDYFDYWGQGTLVTVSS
(SEQ ID NO: 169)

HCDR1 Nucleotide Sequence

GGA GAC ACC TTC AGT AAC TAT GTT
(SEQ ID NO: 170)

HCDR1 Amino Acid Sequence

G D T F S N Y V
(SEQ ID NO: 171)

HCDR2 Nucleotide Sequence

ATC ATC CCT ATC TTT GGT ACA ACA
(SEQ ID NO: 172)

HCDR2 Amino Acid Sequence

I I P I F G T T
(SEQ ID NO: 173)

HCDR3 Nucleotide Sequence

GCG AGA GAT GGG AAC TAC GGT GAC TAC TTT GAC TAC
(SEQ ID NO: 174)

HCDR3 Amino Acid Sequence

A R D G N Y G D Y F D Y
(SEQ ID NO: 175)

LCVR Nucleotide Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGAGCCACCTTGTCATGTAGAGCAAGTCA
GTCAGTCTCTAGCTCTTATCTCGCCTGGTACCAGCAGAAGCCGGGACAGGCCCCTAGACTGCTGATCTACGGGGCAAGTT
CCAGGGCCACCGGAATCCCCGACCGGTTCAGTGGAAGCGGAAGCGGAACCGATTTTACTTTGACGATTTCTAGACTGGAG
CCAGAGGATTTCGCCGTTTACTATTGTCAACAGTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAAT
CAAG

(SEQ ID NO: 147)

LCVR Amino Acid Sequence

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLE
PEDFAVYYCQQYGSSPWTFGQGTKVEIK

(SEQ ID NO: 148)

LCDR1 Nucleotide Sequence

CAG TCA GTC TCT AGC TCT TAT

(SEQ ID NO: 149)

LCDR1 Amino Acid Sequence

Q S V S S S Y

(SEQ ID NO: 150)

LCDR2 Nucleotide Sequence

GGG GCA AGT

(SEQ ID NO: 151)

LCDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 14)

LCDR3 Nucleotide Sequence

CAA CAG TAC GGA AGC AGC CCG TGG ACG

(SEQ ID NO: 152)

LCDR3 Amino Acid Sequence

Q Q Y G S S P W T

(SEQ ID NO: 153)

Heavy Chain Nucleotide Sequence

CAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGA
CACCTTCAGTAACTATGTTATCGGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTA

TCTTTGGTACAACAAACTACGCACAGCAGTTCCAGGGCAGAGTCACGATTACCACGGACGAATCCACGAGCACGGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATGGGAACTACGGTGACTACTTTGA
CTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCT
CCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG
AACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT
GGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTC
CTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCA
GGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC
AGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGT
GTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGAT
GCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 176)

Heavy Chain Amino Acid Sequence

QVQLVQSGAEVKKPGSSVKVSCKASGDTFSNYVIGWVRQAPGQGLEWMGGIIPIFGTTNYAQQFQGRVTITTDESTSTAY
MELSSLRSEDTAVYYCARDGNYGDYFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 177)

Light Chain Nucleotide Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGAGCCACCTTGTCATGTAGAGCAAGTCA
GTCAGTCTCTAGCTCTTATCTCGCCTGGTACCAGCAGAAGCCGGGACAGGCCCCTAGACTGCTGATCTACGGGGCAAGTT
CCAGGGCCACCGGAATCCCCGACCGGTTCAGTGGAAGCGGAAGCGGAACCGATTTTACTTTGACGATTTCTAGACTGGAG
CCAGAGGATTTCGCCGTTTACTATTGTCAACAGTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAAT
CAAGCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTA
CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG

(SEQ ID NO: 156)

Light Chain Amino Acid Sequence

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLE
PEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 157)

H4H30045P

HCVR Nucleotide Sequence

CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGACTTCTGGTTA
CAGATTCGTCAACTATGGTTTCAGCTGGGTGCGCCAGGCCCCTGGACAAGGCCTTGAATGGATGGGATGGATCAGCCCTT
ATAATGGTAACACAAACTATATACAGAATCTCCAGGACAGAATCACCATGACCACAGACACCTCTACGAACACAGCCTAC
ATGGAACTGACGAACCTGAGATCTGACGACACGGCCGTATATTACTGTGCGACCTTAACTGGGGTTCACTTTGACTACTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 178)

HCVR Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKTSGYRFVNYGFSWVRQAPGQGLEWMGWISPYNGNTNYIQNLQDRITMTTDTSTNTAY
MELTNLRSDDTAVYYCATLTGVHFDYWGQGTLVTVSS

(SEQ ID NO: 179)

HCDR1 Nucleotide Sequence

GGT TAC AGA TTC GTC AAC TAT GGT

(SEQ ID NO: 180)

HCDR1 Amino Acid Sequence

G Y R F V N Y G

(SEQ ID NO: 181)

HCDR2 Nucleotide Sequence

ATC AGC CCT TAT AAT GGT AAC ACA

(SEQ ID NO: 182)

HCDR2 Amino Acid Sequence

I S P Y N G N T

(SEQ ID NO: 183)

HCDR3 Nucleotide Sequence

GCG ACC TTA ACT GGG GTT CAC TTT GAC TAC

(SEQ ID NO: 184)

HCDR3 Amino Acid Sequence

A T L T G V H F D Y

(SEQ ID NO: 185)

LCVR Nucleotide Sequence

GCCATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAATCTCCTGATCTTTGAAACATCTCGTT
TACAAAGTGGGGTCCCTTCGAGGTTCAGCGGCAGTGGTTCTGGCACAGATTTCACTCTCACCATCAACAGCCTTCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAAGATTACAATTACCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAA
A

(SEQ ID NO: 186)

LCVR Amino Acid Sequence

AIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPNLLIFETSRLQSGVPSRFSGSGSGTDFTLTINSLQP
EDFATYYCLQDYNYPWTFGQGTKVEIK

(SEQ ID NO: 187)

LCDR1 Nucleotide Sequence

CAG GGC ATT AGA AAT GAT

(SEQ ID NO: 188)

LCDR1 Amino Acid Sequence

Q G I R N D

(SEQ ID NO: 189)

LCDR2 Nucleotide Sequence

GAA ACA TCT

(SEQ ID NO: 190)

LCDR2 Amino Acid Sequence

E T S

(SEQ ID NO: 191)

LCDR3 Nucleotide Sequence

CTA CAA GAT TAC AAT TAC CCG TGG ACG

(SEQ ID NO: 192)

LCDR3 Amino Acid Sequence

L Q D Y N Y P W T

(SEQ ID NO: 193)

Heavy Chain Nucleotide Sequence

CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGACTTCTGGTTA
CAGATTCGTCAACTATGGTTTCAGCTGGGTGCGCCAGGCCCCTGGACAAGGCCTTGAATGGATGGGATGGATCAGCCCTT
ATAATGGTAACACAAACTATATACAGAATCTCCAGGACAGAATCACCATGACCACAGACACCTCTACGAACACAGCCTAC
ATGGAACTGACGAACCTGAGATCTGACGACACGGCCGTATATTACTGTGCGACCTTAACTGGGGTTCACTTTGACTACTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA
GCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA
GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC
CGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGA
GAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTC
CCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGA
CCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCA
ACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTC
TCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACAC
CCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACA
TCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
TTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGA
GGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 194)

Heavy Chain Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKTSGYRFVNYGFSWVRQAPGQGLEWMGWISPYNGNTNYIQNLQDRITMTTDTSTNTAY
MELTNLRSDDTAVYYCATLTGVHFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 195)

Light Chain Nucleotide Sequence

GCCATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAATCTCCTGATCTTTGAAACATCTCGTT
TACAAAGTGGGGTCCCTTCGAGGTTCAGCGGCAGTGGTTCTGGCACAGATTTCACTCTCACCATCAACAGCCTTCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAAGATTACAATTACCCGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAA
ACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GTTAG

(SEQ ID NO: 196)

Light Chain Amino Acid Sequence

AIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPNLLIFETSRLQSGVPSRFSGSGSGTDFTLTINSLQP
EDFATYYCLQDYNYPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 197)

H4H30061P

HCVR Nucleotide Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGCCCAGCCTGGGGGGTCCCTGAAACTCTCTTGTGAAGCCTCTGGATT
CACGTTCAGTGATTCTGCAATGCACTGGGTCCGCCAGGCTTCCGGAAAAGGGCTGGAGTGGGTTGGTCGTATTAGAAGCA
AAGCTAATAGTTACGCGACAGGATATGCTGCGTCGGTGAAAGGCAGGTTCACCATCTCCAGAGATGATTCAAAGAACATG
GCGTTTCTGGAAATGAACAGCCTGAAAACCGAAGACACGGCCGTATATTACTGTCTCCGACAAACTTACGGTGACCCCTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 198)

HCVR Amino Acid Sequence

EVQLVESGGGLAQPGGSLKLSCEASGFTFSDSAMHWVRQASGKGLEWVGRIRSKANSYATGYAASVKGRFTISRDDSKNM
AFLEMNSLKTEDTAVYYCLRQTYGDPWGQGTLVTVSS

(SEQ ID NO: 199)

HCDR1 Nucleotide Sequence

GGA TTC ACG TTC AGT GAT TCT GCA

(SEQ ID NO: 200)

HCDR1 Amino Acid Sequence

G F T F S D S A

(SEQ ID NO: 201)

HCDR2 Nucleotide Sequence

ATT AGA AGC AAA GCT AAT AGT TAC GCG ACA

(SEQ ID NO: 202)

HCDR2 Amino Acid Sequence

I R S K A N S Y A T

(SEQ ID NO: 203)

HCDR3 Nucleotide Sequence

CTC CGA CAA ACT TAC GGT GAC CCC

(SEQ ID NO: 204)

HCDR3 Amino Acid Sequence

L R Q T Y G D P

(SEQ ID NO: 205)

LCVR Nucleotide Sequence

GATGTTGTGATGACTCAGTCTCCACTCTCCCTGTCCGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAGTCT
AAGCCTCGTATACAGTGATGGAAACAACTACTTGAATTGGTTTCAGCAGAGGCCAGGCCAATCTCCAAGGCGCCTACTTT
ATAAAGTTTTTAACCGGGACTCTGGGGTCCCAGACAGATTCAGCGGCAGTGGGTCAGGCACTGATTTCACACTGAAAATC
AGCAGGGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGGAACACACTGGCCGTGGACGTTCGGCCAAGGGAC
CAAGGTGGAAATCAAA

(SEQ ID NO: 206)

LCVR Amino Acid Sequence

DVVMTQSPLSLSVTLGQPASISCRSSLSLVYSDGNNYLNWFQQRPGQSPRRLLYKVFNRDSGVPDRFSGSGSGTDFTLKI
SRVEAEDVGVYYCMQGTHWPWTFGQGTKVEIK

(SEQ ID NO: 207)

LCDR1 Nucleotide Sequence

CTA AGC CTC GTA TAC AGT GAT GGA AAC AAC TAC

(SEQ ID NO: 208)

LCDR1 Amino Acid Sequence

L S L V Y S D G N N Y

(SEQ ID NO: 209)

LCDR2 Nucleotide Sequence

AAA GTT TTT

(SEQ ID NO: 210)

LCDR2 Amino Acid Sequence

K V F

(SEQ ID NO: 211)

LCDR3 Nucleotide Sequence

ATG CAA GGA ACA CAC TGG CCG TGG ACG

(SEQ ID NO: 212)

LCDR3 Amino Acid Sequence

M Q G T H W P W T

(SEQ ID NO: 213)

Heavy Chain Nucleotide Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGCCCAGCCTGGGGGGTCCCTGAAACTCTCTTGTGAAGCCTCTGGATT
CACGTTCAGTGATTCTGCAATGCACTGGGTCCGCCAGGCTTCCGGAAAAGGGCTGGAGTGGGTTGGTCGTATTAGAAGCA

AAGCTAATAGTTACGCGACAGGATATGCTGCGTCGGTGAAAGGCAGGTTCACCATCTCCAGAGATGATTCAAAGAACATG
GCGTTTCTGGAAATGAACAGCCTGAAAACCGAAGACACGGCCGTATATTACTGTCTCCGACAAACTTACGGTGACCCCTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA
GCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA
GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC
CGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGA
GAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTC
CCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGA
CCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCA
ACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTC
TCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACAC
CCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACA
TCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
TTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGA
GGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 214)

Heavy Chain Amino Acid Sequence

EVQLVESGGGLAQPGGSLKLSCEASGFTFSDSAMHWVRQASGKGLEWVGRIRSKANSYATGYAASVKGRFTISRDDSKNM
AFLEMNSLKTEDTAVYYCLRQTYGDPWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 215)

Light Chain Nucleotide Sequence

GATGTTGTGATGACTCAGTCTCCACTCTCCCTGTCCGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAGTCT
AAGCCTCGTATACAGTGATGGAAACAACTACTTGAATTGGTTTCAGCAGAGGCCAGGCCAATCTCCAAGGCGCCTACTTT
ATAAAGTTTTTAACCGGGACTCTGGGGTCCCAGACAGATTCAGCGGCAGTGGGTCAGGCACTGATTTCACACTGAAAATC
AGCAGGGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGGAACACACTGGCCGTGGACGTTCGGCCAAGGGAC
CAAGGTGGAAATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA
CTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAA
TCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCT
TCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 216)

Light Chain Amino Acid Sequence

DVVMTQSPLSLSVTLGQPASISCRSSLSLVYSDGNNYLNWFQQRPGQSPRRLLYKVFNRDSGVPDRFSGSGSGTDFTLKI
SRVEAEDVGVYYCMQGTHWPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 217)

H4H30095P2

HCVR Nucleotide Sequence

CAGGTTCAGCTGGTGCAGTCTGGAGTTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTA
CACCTTTAAGTTTTATGGTATCAGTTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGCTGGATCAGTGTTT
ACAATGGTAAAACAAAGTATGCACAGAAGCTCCAGGGCAGAGTCACCATGACAACAGACACATCCACGAGCACAGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTTTTGTGCGAGAGATGGGGACTATGAGAGTAGTGGTTA
TCCGTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 218)

HCVR Amino Acid Sequence

QVQLVQSGVEVKKPGASVKVSCKASGYTFKFYGISWVRQAPGQGLEWMGWISVYNGKTKYAQKLQGRVTMTTDTSTSTAY
MELRSLRSDDTAVYFCARDGDYESSGYPFDYWGQGTLVTVSS

(SEQ ID NO: 219)

HCDR1 Nucleotide Sequence

GGT TAC ACC TTT AAG TTT TAT GGT

(SEQ ID NO: 220)

HCDR1 Amino Acid Sequence

G Y T F K F Y G

(SEQ ID NO: 221)

HCDR2 Nucleotide Sequence

ATC AGT GTT TAC AAT GGT AAA ACA

(SEQ ID NO: 222)

HCDR2 Amino Acid Sequence

I S V Y N G K T

(SEQ ID NO: 223)

HCDR3 Nucleotide Sequence

GCG AGA GAT GGG GAC TAT GAG AGT AGT GGT TAT CCG TTT GAC TAC

(SEQ ID NO: 224)

HCDR3 Amino Acid Sequence

A R D G D Y E S S G Y P F D Y

(SEQ ID NO: 225)

LCVR Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT
TAAA

(SEQ ID NO: 226)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 227)

LCDR1 Nucleotide Sequence

CAG AGC ATT AGC AGT TAT

(SEQ ID NO: 31)

LCDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 32)

LCDR2 Nucleotide Sequence

GCT GCA TCC

(SEQ ID NO: 33)

LCDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 34)

LCDR3 Nucleotide Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 75)

LCDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 76)

Heavy Chain Nucleotide Sequence

CAGGTTCAGCTGGTGCAGTCTGGAGTTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTA
CACCTTTAAGTTTTATGGTATCAGTTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGCTGGATCAGTGTTT
ACAATGGTAAAACAAAGTATGCACAGAAGCTCCAGGGCAGAGTCACCATGACAACAGACACATCCACGAGCACAGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTTTTGTGCGAGAGATGGGGACTATGAGAGTAGTGGTTA
TCCGTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGG
CGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG
GTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCT
CAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACA
CCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCA
TCAGTCTTCCTGTTCCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGA
CGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
GGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAG
TACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
GCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTG
GACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 228)

Heavy Chain Amino Acid Sequence

QVQLVQSGVEVKKPGASVKVSCKASGYTFKFYGISWVRQAPGQGLEWMGWISVYNGKTKYAQKLQGRVTMTTDTSTSTAY
MELRSLRSDDTAVYFCARDGDYESSGYPFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 229)

Light Chain Nucleotide Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA
GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT
TAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTA
CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGTTAG

(SEQ ID NO: 230)

Light Chain Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 231)

[054] The present invention provides an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 (*e.g.*, monomeric or dimeric human FGFR3b) or an antigenic fragment thereof comprising: a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 2, 22, 42, 62, 82, 102, 122, 140, 159, 169, 179, 199 or 219 (*e.g.*, fused to an IgG4 Fc having a S108P mutation), and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 10, 30, 50, 70, 90, 110, 130, 148, 187, 207, or 227.

[055] The present invention also provides an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 (*e.g.*, monomeric or dimeric human FGFR3b) or an antigenic fragment thereof comprising: (a) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 2, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 10, (b) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 22, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 30, (c) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 42, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 50, (d) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 62, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 70, (e) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 82, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 90, (f) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 102 (*e.g.*, fused to an IgG4 Fc having a S108P mutation), and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 110, and/or (g) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 122, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 130, (h) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 140, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid

sequence set forth in SEQ ID NO: 148, (i) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 159, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 148, (j) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 169, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 148, (k) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 179, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 187, (l) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 199, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 207, and/or (m) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 219, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 227.

[056] The present invention also provides an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 (*e.g.*, monomeric or dimeric human FGFR3b) or an antigenic fragment thereof comprising: (a) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 4, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 6, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 8, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 16; (b) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 24, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 26, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 28, and

a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 32, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 36; (c) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 44, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 46, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 48, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 52, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 54, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 56; (d) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 64, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 66, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 68, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 72, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 74, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 76; (e) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 84, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 86, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 88, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 92, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 94, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 96; (f) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 104, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 106, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 108 (*e.g.*, fused to an IgG4 Fc having a S108P mutation), and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 112, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 114, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 116; and/or (g) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 124, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 126, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 128, and a light

chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 132, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 134; (h) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 142, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 144, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 146, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153; (i) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 161, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 163, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 165, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153; (j) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 171, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 173, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 175, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153; (k) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 181, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 183, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 185, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 189, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 191, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 193; (l) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 201, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 203, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 205, and a light chain variable region that comprises an

LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 209, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 211, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 213; and/or (m) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 221, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 223, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 225, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 32, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 76.

[057] The present invention further provides an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 2, 22, 42, 62, 82, 102 (*e.g.*, fused to an IgG4 Fc having a S108P mutation), 122, 140, 159, 169, 179, 199 or 219, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10, 30, 50, 70, 90, 110, 130, 148, 187, 207, or 227.

[058] In addition, the present invention provides an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 (*e.g.*, monomeric or dimeric human FGFR3b) or an antigenic fragment thereof comprising: (a) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 2, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10; (b) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 22, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 30; (c) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 42, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 50; (d) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 62, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 70; (e) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 82, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; (f) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 102, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 110; *e.g.*, wherein the heavy chain variable region is fused to an IgG4 Fc having a S108P mutation; (g) a

heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 122, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 130; (h) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 140, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148; (i) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 159, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148; (j) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 169, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148; (k) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 179, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 187; (l) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 199, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 207; and/or (m) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 219, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 227.

[059] The present invention provides an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 (*e.g.*, monomeric or dimeric human FGFR3b) or an antigenic fragment thereof comprising (a) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 18, 38, 58, 78, 98, 118,136, 155, 167, 177, 195, 215 or 229, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 20, 40, 60, 80, 100, 120,138, 157, 197, 217, or 231.

[060] The present invention also provides an isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising:

(a) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 18, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 20; (b) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 38, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 40; (c) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 58, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 60; (d) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 78, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 80; (e) a heavy chain variable region that comprises the

amino acid sequence set forth in SEQ ID NO: 98, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 100; (f) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 118, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 120; and/or (g) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 136, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 138; (h) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 155, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157; (i) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 167, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157; (j) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 177, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157; (k) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 195, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 197; (l) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 215, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 217; and/or (m) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 229, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 231.

[061] In an embodiment of the invention an anti-FGFR3 antigen-binding protein, such as an antibody or antigen-binding fragment thereof, has one or more of the following characteristics:

- Binds (*e.g.*, in a surface plasmon resonance assay) to monomeric human FGFR3b (*e.g.*, tagged, for example, at the C-terminus, with myc-myc-His_6) at 25°C with an affinity (K_D) of about 16 nM or greater affinity (*e.g.*, about 16 nM, 12 nM, 10 nM, 7nM, 5nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.22 nM, 0.2 nM, 0.19 nM, 0.14 nM, 0.1 nM);
- Binds (*e.g.*, in a surface plasmon resonance assay) to monomeric Cynomolgous monkey FGFR3b (*e.g.*, tagged, for example, at the C-terminus, with myc-myc-His_6) at 25°C with an affinity (K_D) of about 20 nM or greater affinity (*e.g.*, about 20nM, 16nM, 15nM, 10nM, 8nM, 5nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.9 nM, 0.65 nM, 0.3 nM, 0.28 nM, 0.2 nM, 0.15 nM, 0.1 nM);
- Binds (*e.g.*, in a surface plasmon resonance assay) monomeric murine FGFR3b (*e.g.*, tagged, for example, at the C-terminus, with myc-myc-His_6) at 25°C with an affinity (K_D)

of about 70 nM or greater affinity (*e.g.*, about 70nM, 20nM, 17nM, 12nM, 10nM, 9nM, 8nM, 0.1 nM);

- Does not bind significantly to monomeric human FGFR3c (*e.g.*, tagged, for example, at the C-terminus, with myc-myc-His_6) at 25°C (*e.g.*, in a surface plasmon resonance assay);
- Binds (*e.g.*, in a surface plasmon resonance assay) dimeric human FGFR3b (*e.g.*, tagged, for example, at the C-terminus, with a mouse Fc (mFc)) at 25°C with an affinity of about 0.6 nM of greater affinity (*e.g.*, about 0.58 nM, 0.17 nM, 0.11 nM, 0.04 nM, 0.03 nM, 0.02 nM, 0.01 nM, 0.023 nM, 0.061 nM, 0.031 nM, 0.016 nM, 0.034 nM, 0.027 nM);
- Blocks about 68% or more binding of FGF1 acidic to human FGFR3b-mFc at 200 nM antibody (*e.g.*, 90% or 05%);
- Binds to monomeric Cynomolgous and monomeric mouse FGFR3b with a K_D that is within about 0.1 nM of the K_D for binding to monomeric or dimeric human FGFR3b;
- Blocks binding of 4 nM human FGFR3b-mFc to human FGF1 acidic protein with an IC_{50} of about 15 nM or a lower concentration (*e.g.*, IC_{50} of about 1, 2 or 3 nM);
- Competes for binding to hFGFR3b.mmH with another anti-FGFR3 antibody as set forth in Table 3-1 herein;
- Blocks intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express wild-type or S249C mutant human fibroblast growth factor receptor 3b that has been stimulated with human heparin, *e.g.*, at about 5 micrograms/ml, and human FGF1 ligand, *e.g.*, at about 1 nM, with an IC_{50} of about 18 nM or a lower concentration (*e.g.*, about 0.51 nM, 0.5 nM, 0.61 nM, 0.6 nM, or 0.012 nM);
- Blocks intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express S249C mutant human fibroblast growth factor receptor 3b that has been stimulated with human heparin, *e.g.*, at about 5 micrograms/ml, and human FGF1 ligand, *e.g.*, at about 1 nM, with an IC_{50} that is lower than for blocking intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express wild-type human fibroblast growth factor receptor 3b that has been stimulated with human FGF1 ligand, *e.g.*, at about 1 nM, and human heparin, *e.g.*, at about 5 micrograms/ml;

- Blocks dimerization of FGFR3 (*e.g.*, wild-type or S249C mutant), *e.g.*, with stronger inhibition than that of REGN6331, for example, as measured in a non-reducing SDS-PAGE assay;
- Reduces tumor size (*e.g.*, bladder cancer tumor expressing FGFR3 (*e.g.*, S249C mutant)) in a subject administered the antibody or fragment;
- Reduces CD73 expression in a tumor (*e.g.*, bladder cancer tumor expressing FGFR3 (*e.g.*, S249C mutant)) in a subject administered the antibody or fragment;
- Inhibits FGF1/heparin stimulation induced phosphorylation of MAPK, *e.g.*, in a BaF3 cell expressing wild-type FGFR3 (*e.g.*, S249C mutant);
- Inhibits proliferation of UMUC14 bladder cancer cells expressing endogenous FGFR3 S249C mutation (*e.g.*, in a cancer cell spheroid proliferation assay);
- Inhibits tumor growth in a mouse (*e.g.*, SCID mouse) xenograft model of bladder cancer cell line UMUC14 expressing FGFR3 (*e.g.*, S249C mutation);
- Inhibits CD73-dependent, adenosine-mediated inhibition of immune cell activation;
- Increases the ratio of CD8/CD4 and/or CD8+/T_{reg} in tumor tissue having tumor cells expressing FGFR3 (*e.g.*, S249C mutant);
- Inhibits FGF3-mediated activation of CD73 expression and/or enzymatic activity (e.g., adenosine production) (e.g., on a tumor cell expressing FGFR3 (e.g., S249C mutant));
- Inhibits FGFR3-dependent, adenosine-mediated immune cell suppression;
- Inhibits growth of BaF3 cells expressing the FGFR3 double mutant S249C and V557M, or S249C and V557L, wherein the antibody or antigen-binding fragment comprises immunoglobulin chains including any of the amino acid sequences as set forth herein.

[062] The present invention includes monoclonal anti-FGFR3 antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2), as well as monoclonal compositions comprising a plurality of isolated monoclonal antigen-binding proteins. The term "monoclonal antibody" or “mAb”, as used herein, refers to a member of a population of substantially homogeneous antibodies, i.e., the antibody molecules comprising the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. A "plurality" of such monoclonal antibodies

and fragments in a composition refers to a concentration of identical (i.e., as discussed above, in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts) antibodies and fragments which is above that which would normally occur in nature, *e.g.*, in the blood of a host organism such as a mouse or a human.

[063] In an embodiment of the invention, an anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment comprises a heavy chain constant domain, *e.g.*, of the type IgA (*e.g.*, IgA1 or IgA2), IgD, IgE, IgG (*e.g.*, IgG1, IgG2, IgG3 and IgG4 (*e.g.*, comprising a S228P and/or S108P mutation)) or IgM. In an embodiment of the invention, an antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, comprises a light chain constant domain, *e.g.*, of the type kappa or lambda. The present invention includes antigen-binding proteins comprising the V_H and V_L variable domains set forth herein (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2) which are linked to a heavy and/or light chain constant domain, *e.g.*, as set forth above.

[064] The term "human" antigen-binding protein, such as an antibody or antigen-binding fragment, as used herein, includes antibodies and fragments having human amino acid sequence; for example, variable and constant regions derived from human germline immunoglobulin sequences whether in a human cell or grafted into a non-human cell, *e.g.*, a mouse cell. See *e.g.*, US8502018, US6596541 or US5789215. The human antibodies and antigen-binding fragments of the invention may, in an embodiment of the invention, include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, having mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation *in vivo*), for example in the CDRs and, in particular, CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (*e.g.*, mouse) have been grafted onto human FR sequences. The term includes antibodies recombinantly produced in a non-human mammal or in cells of a non-human mammal. The term is not intended to include antibodies isolated from or generated in a human subject. The present invention includes human antigen-binding proteins (*e.g.*, antibodies or antigen-binding fragments thereof such as H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2).

[065] The present invention includes anti-FGFR3 chimeric antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, and methods of use thereof. As used herein, a "chimeric antibody" is an antibody having the variable domain from a first antibody and the constant domain from a second antibody, where the first and second antibodies are from different species. (see *e.g.*, US4816567; and Morrison *et al.*, (1984) Proc. Natl. Acad. Sci. USA 81: 6851-6855). The present invention includes chimeric antibodies comprising the variable domains which are set forth herein (*e.g.*, from H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2) and a non-human constant domain.

[066] The term “recombinant” antigen-binding proteins, such as antibodies or antigen-binding fragments thereof, refers to such molecules created, expressed, isolated or obtained by technologies or methods known in the art as recombinant DNA technology which include, *e.g.*, DNA splicing and transgenic expression. The term includes antibodies expressed in a non-human mammal (including transgenic non-human mammals, *e.g.*, transgenic mice), or a host cell (*e.g.*, Chinese hamster ovary (CHO) cell) or cellular expression system or isolated from a recombinant combinatorial human antibody library. The present invention includes recombinant antigen-binding proteins, such as antibodies and antigen-binding fragments as set forth herein (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2).

[067] An antigen-binding fragment of an antibody will, in an embodiment of the invention, comprise less than a full antibody but still binds specifically to antigen, *e.g.*, FGFR3, *e.g.*, including at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one (*e.g.*, 3) CDR(s), which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H - V_H, V_H - V_L or V_L - V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H and/or V_L domain which are bound non-covalently.

[068] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an

antigen-binding fragment of an antibody of the present invention include: (i) V_H -CH1; (ii) V_H -CH2; (iii) V_H -CH3; (iv) V_H-CH1-CH2; (v) V_H -CH1-CH2-CH3; (vi) V_H -CH2-CH3; (vii) V_H -CL; (viii) V_L -CH1; (ix) V_L -CH2; (x) V_L -CH3; (xi) V_L -CH1-CH2; (xii) VL-CH1-CH2-CH3; (xiii) V_L -CH2-CH3; and (xiv) V_L -CL. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)). The present invention includes an antigen-binding fragment of an antigen-binding protein such as an antibody set forth herein, for example, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2.

[069] Antigen-binding proteins (*e.g.*, antibodies and antigen-binding fragments) may be monospecific or multi-specific (*e.g.*, bispecific). Multispecific antigen-binding proteins are discussed further herein. The present invention includes monospecific as well as multispecific (*e.g.*, bispecific) antigen-binding fragments comprising one or more variable domains from an antigen-binding protein that is specifically set forth herein (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2).

[070] In some embodiments, an antigen-binding fragment described herein may be an scFv. An scFv (single chain fragment variable) has variable regions of heavy (V_H) and light (V_L) domains (in either order), which, preferably, are joined together by a flexible linker (e.g., peptide linker). The length of the flexible linker used to link both of the V regions may be important for yielding the correct folding of the polypeptide chain. Previously, it has been estimated that the peptide linker must span 3.5 nm (35 Å) between the carboxy terminus of the variable domain and the amino terminus of the other domain without affecting the ability of the domains to fold and form an intact antigen-binding site (Huston et al., Protein engineering of single-chain Fv analogs and fusion proteins. Methods in Enzymology. 1991;203:46–88). In an embodiment, the linker comprises an amino acid sequence of such length to separate the variable domains

by about 3.5 nm. In an embodiment, an anti-FGFR3 scFv comprises the arrangement of variable regions as follows LCVR-HCVR or HCVR-LCVR, wherein the HCVR and LCVR are optionally connected by a linker.

[071] In some embodiments, an antigen-binding fragment described herein may be a Fab.

[072] In some embodiments, an antigen-binding fragment described herein may be a bivalent antibody.

[073] In some embodiments, an anti-FGFR3 antibody described herein comprises a monovalent or "one-armed" antibody. The monovalent or "one-armed" antibodies as used herein refer to immunoglobulin proteins comprising a single variable domain. For example, the one-armed antibody may comprise a single variable domain within a Fab wherein the Fab is linked to at least one Fc fragment. In certain embodiments, the one-armed antibody comprises: (i) a heavy chain comprising a heavy chain constant region and a heavy chain variable region, (ii) a light chain comprising a light chain constant region and a light chain variable region, and (iii) a polypeptide comprising a Fc fragment or a truncated heavy chain. In certain embodiments, the Fc fragment or a truncated heavy chain comprised in the separate polypeptide is a "dummy Fc," which refers to an Fc fragment that is not linked to an antigen binding domain. The one-armed antibodies described herein may comprise any of the HCVR/LCVR pairs or CDR amino acid sequences as set forth in Table 1-1 herein. One-armed antibodies comprising a full-length heavy chain, a full-length light chain and an additional Fc domain polypeptide can be constructed using standard methodologies (see e.g., WO2010151792, which is incorporated herein by reference in its entirety), wherein the heavy chain constant region differs from the Fc domain polypeptide by at least two amino acids (e.g., H95R and Y96F according to the IMGT exon numbering system; or H435R and Y436F according to the EU numbering system). Such modifications are useful in purification of the monovalent antibodies (see WO2010151792).

[074] The term "specifically binds" or "binds specifically" refers to those antigen-binding proteins (*e.g.*, antibodies or antigen-binding fragments thereof) having a binding affinity to an antigen, such as human FGFR3 protein (*e.g.*, FGFR3b isoform), mouse FGFR3 protein (*e.g.*, FGFR3b isoform) or cynomolgous monkey FGFR3 protein (*e.g.*, FGFR3b isoform), expressed as K_D, of at least about 10^{-9} M (*e.g.*, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 nM), as measured by real-time, label free bio-layer interferometry assay, for example, at 25°C or 37°C, *e.g.*, an Octet® HTX biosensor, or by surface plasmon resonance, *e.g.*, BIACORE™, or by solution-affinity ELISA. The present invention includes antigen-binding proteins that specifically bind to FGFR3 protein (*e.g.*, FGFR3b isoform). "Anti-FGFR3" refers to an antigen-

binding protein (or other molecule), for example an antibody or antigen-binding fragment thereof, that binds specifically to FGFR3 (*e.g.*, FGFR3b isoform).

[075] The present invention includes antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, that bind to the same epitope as an antigen-binding protein of the present invention (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2).

[076] An antigen is a molecule, such as a peptide (*e.g.*, FGFR3 or a fragment thereof (an antigenic fragment)), to which, for example, an antibody or antigen-binding fragment thereof binds. The specific region on an antigen that an antibody recognizes and binds to is called the epitope. Antigen-binding proteins (*e.g.*, antibodies) of the present invention that specifically bind to such antigens are part of the present invention.

[077] The term "epitope" refers to an antigenic determinant (*e.g.*, on FGFR3b) that interacts with a specific antigen-binding site of an antigen-binding protein, *e.g.*, a variable region of an antibody, known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope" may also refer to a site on an antigen to which B and/or T cells respond and/or to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may be linear or conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics. Epitopes to which antigen-binding proteins of the present invention bind may be included in fragments of FGFR3, *e.g.*, human FGFR3b, for example the extracellular domain thereof. Antigen-binding proteins (*e.g.*, antibodies) of the present invention that bind to such epitopes are part of the present invention.

[078] Methods for determining the epitope of an antigen-binding protein, *e.g.*, antibody or fragment or polypeptide, include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol. Biol. 248: 443-63), peptide cleavage analysis, crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction

and chemical modification of antigens can be employed (Tomer (2000) Prot. Sci. 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antigen-binding protein (*e.g.*, antibody or fragment or polypeptide) interacts is hydrogen/deuterium exchange detected by mass spectrometry. See, *e.g.*, Ehring (1999) Analytical Biochemistry 267: 252-259; Engen and Smith (2001) Anal. Chem. 73: 256A-265A.

[079] The present invention includes antigen-binding proteins that compete for binding to FGFR3, *e.g.*, an FGFR3b epitope as discussed herein, with an antigen-binding protein of the present invention, *e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2. The term "competes" as used herein, refers to an antigen-binding protein (*e.g.*, antibody or antigen-binding fragment thereof) that binds to an antigen (*e.g.*, FGFR3) and inhibits or blocks the binding of another antigen-binding protein (*e.g.*, antibody or antigen-binding fragment thereof) to the antigen. Unless otherwise stated, the term also includes competition between two antigen-binding proteins *e.g.*, antibodies, in both orientations, i.e., a first antibody that binds antigen and blocks binding by a second antibody and vice versa. Thus, in an embodiment of the invention, competition occurs in one such orientation. In certain embodiments, the first antigen-binding protein (*e.g.*, antibody) and second antigen-binding protein (*e.g.*, antibody) may bind to the same epitope. Alternatively, the first and second antigen-binding proteins (*e.g.*, antibodies) may bind to different, but, for example, overlapping or non-overlapping epitopes, wherein binding of one inhibits or blocks the binding of the second antibody, *e.g.*, via steric hindrance. Competition between antigen-binding proteins (*e.g.*, antibodies) may be measured by methods known in the art, for example, by a real-time, label-free bio-layer interferometry assay. Also, binding competition between anti- FGFR3 antigen-binding proteins (*e.g.*, monoclonal antibodies (mAbs)) can be determined using a real time, label-free bio-layer interferometry assay on an Octet RED384 biosensor (Pall ForteBio Corp.).

[080] Typically, an antibody or antigen-binding fragment of the invention which is modified in some way retains the ability to specifically bind to FGFR3 (*e.g.*, FGFR3b), *e.g.*, retains at least 10% of its FGFR3 binding activity (when compared to the parental antibody) when that activity is expressed on a molar basis. Preferably, an antibody or antigen-binding fragment of the invention retains at least 20%, 50%, 70%, 80%, 90%, 95% or 100% or more of the FGFR3 binding affinity as the parental antibody. It is also intended that an antibody or antigen-binding fragment of the invention may include conservative or non-conservative amino acid

substitutions (referred to as "conservative variants" or "function conserved variants" of the antibody) that do not substantially alter its biologic activity.

[081] A "variant" of a polypeptide, such as an immunoglobulin chain (*e.g.*, an H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2 V_H, V_L, HC or LC or CDR thereof comprising the amino acid sequence specifically set forth herein), refers to a polypeptide comprising an amino acid sequence that is at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) identical or similar to a referenced amino acid sequence that is set forth herein (*e.g.*, any of SEQ ID NOs: 2, 10, 18, 20, 22, 30, 38, 40, 42, 50, 58, 60, 62, 70, 78, 80, 82, 90, 98, 100, 102, 110, 118, 120, 122, 130, 136, 138, 140, 148, 155, 157, 159, 167, 169, 177, 179, 187, 195, 197, 199, 207, 215, 217, 219, 227, 229 or 231); when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences (*e.g.*, expect threshold: 10; word size: 3; max matches in a query range: 0; BLOSUM 62 matrix; gap costs: existence 11, extension 1; conditional compositional score matrix adjustment).

[082] Moreover, a variant of a polypeptide may include a polypeptide such as an immunoglobulin chain (*e.g.*, an H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2 V_H, V_L, HC or LC or CDR thereof) which may include the amino acid sequence of the reference polypeptide whose amino acid sequence is specifically set forth herein but for one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) mutations, *e.g.*, one or more missense mutations (*e.g.*, conservative substitutions), non-sense mutations, deletions, or insertions. See Table A. For example, the present invention includes anti-FGFR3 antigen-binding proteins which include an immunoglobulin light chain (or V_L) variant comprising the amino acid sequence set forth in SEQ ID NO: 10 but having one or more of such mutations and/or an immunoglobulin heavy chain (or V_H) variant comprising the amino acid sequence set forth in SEQ ID NO: 2 but having one or more of such mutations. In an embodiment of the invention, an anti-FGFR3 antigen-binding protein includes an immunoglobulin light chain variant comprising CDR-L1, CDR-L2 and CDR-L3 wherein one or more (*e.g.*, 1 or 2 or 3) of such CDRs has one or more of such mutations (*e.g.*, conservative substitutions) and/or an immunoglobulin heavy chain variant comprising CDR-H1, CDR-H2

and CDR-H3 wherein one or more (*e.g.*, 1 or 2 or 3) of such CDRs has one or more of such mutations (*e.g.*, conservative substitutions).

[083] The following references relate to BLAST algorithms often used for sequence analysis: BLAST ALGORITHMS: Altschul *et al.* (2005) FEBS J. 272(20): 5101-5109; Altschul, S. F., *et al.*, (1990) J. Mol. Biol. 215:403-410; Gish, W., *et al.*, (1993) Nature Genet. 3:266-272; Madden, T. L., *et al.*, (1996) Meth. Enzymol. 266:131-141; Altschul, S. F., *et al.*, (1997) Nucleic Acids Res. 25:3389-3402; Zhang, J., *et al.*, (1997) Genome Res. 7:649-656; Wootton, J. C., *et al.*, (1993) Comput. Chem. 17:149-163; Hancock, J. M. *et al.*, (1994) Comput. Appl. Biosci. 10:67-70; ALIGNMENT SCORING SYSTEMS: Dayhoff, M. O., *et al.*, "A model of evolutionary change in proteins." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3. M. O. Dayhoff (ed.), pp. 345-352, Natl. Biomed. Res. Found., Washington, D.C.; Schwartz, R. M., *et al.*, "Matrices for detecting distant relationships." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3." M. O. Dayhoff (ed.), pp. 353-358, Natl. Biomed. Res. Found., Washington, D.C.; Altschul, S. F., (1991) J. Mol. Biol. 219:555-565; States, D. J., *et al.*, (1991) Methods 3:66-70; Henikoff, S., *et al.*, (1992) Proc. Natl. Acad. Sci. USA 89:10915-10919; Altschul, S. F., *et al.*, (1993) J. Mol. Evol. 36:290-300; ALIGNMENT STATISTICS: Karlin, S., *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268; Karlin, S., *et al.*, (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877; Dembo, A., *et al.*, (1994) Ann. Prob. 22:2022-2039; and Altschul, S. F. "Evaluating the statistical significance of multiple distinct local alignments." in Theoretical and Computational Methods in Genome Research (S. Suhai, ed.), (1997) pp. 1-14, Plenum, N.Y.

[084] A "conservatively modified variant" or a "conservative substitution", *e.g.*, of an immunoglobulin chain set forth herein, refers to a variant wherein there is one or more substitutions of amino acids in a polypeptide with other amino acids having similar characteristics (*e.g.*, charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, *etc.*). Such changes can frequently be made without significantly disrupting the biological activity of the antibody or fragment. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, *e.g.*, Watson *et al.* (1987) Molecular Biology of the Gene, The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to significantly disrupt biological activity. The present invention includes anti-FGFR3 antigen-binding proteins comprising such conservatively modified variant immunoglobulin chains.

[085] Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443-45.

[086] "H4H30063P" ("REGN15684"); "H4H30066P"; "H4H30071P"; "H4H30089P2"; "H4H30093P2"; "H4H30102P2"; "H4H30076P"; "H4H30105P2"; "H4H30108P2"; "H4H30117P2"; "H4H30045P"; "H4H30061P"; and "H4H30095P2" unless otherwise stated, refer to anti-FGFR3 antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof (including multispecific antigen-binding proteins), comprising an immunoglobulin heavy chain variable region (V_H) and an immunoglobulin light chain variable region (V_L) comprising the amino acid sequence pair specifically set forth in SEQ ID NOs: 2 & 10; 22 & 30; 42 & 50; 62 & 70; 82 & 90; 102 & 110; 122 & 130; 140 & 148; 159 & 148; 169 & 148; 179 & 187; 199 & 207; and 219 & 227 (or a variant of any of said sequences), as set forth in Table A; or comprising an immunoglobulin heavy chain (HC) and an immunoglobulin light chain (LC) comprising the amino acid sequence pair specifically set forth in SEQ ID NOs: 18 & 20; 38 & 40; 58 & 60; 78 & 80; 98 & 100; 118 & 120; 136 & 138; 155 & 157; 167 & 157; 177 & 157; 195 & 197; 215 & 217; or 229 & 231 (or a variant of any of said sequences), as set forth in Table A; or that comprise a heavy chain or V_H that comprises the CDRs thereof (CDR-H1 (or a variant thereof), CDR-H2 (or a variant thereof) and CDR-H3 (or a variant thereof)) and/or a light chain or V_L that comprises the CDRs thereof (CDR-L1 (or a variant thereof), CDR-L2 (or a variant thereof) and CDR-L3 (or a variant thereof)). In an embodiment of the invention, the V_H is linked to an IgG constant heavy chain domain, for example, human IgG constant heavy chain domain (*e.g.*, IgG1 or IgG4 (*e.g.*, comprising the S228P and/or S108P mutation)) and/or the V_L is linked to a light chain constant domain, for example a human light chain constant domain (*e.g.*, lambda or kappa constant light chain domain). Polynucleotides encoding one or more of any such immunoglobulin chains (*e.g.*, V_H, V_L, HC and/or LC) forms part of the present invention.

[087] Antibodies and antigen-binding fragments of the present invention (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2;

H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2) comprise immunoglobulin chains including the amino acid sequences specifically set forth herein (and variants thereof) as well as cellular and *in vitro* post-translational modifications to the antibody or fragment. For example, the present invention includes antibodies and antigen-binding fragments thereof that specifically bind to FGFR3 comprising heavy and/or light chain amino acid sequences set forth herein as well as antibodies and fragments wherein one or more asparagine, serine and/or threonine residues is glycosylated, one or more asparagine residues is deamidated, one or more residues (*e.g.*, Met, Trp and/or His) is oxidized, the N-terminal glutamine is pyroglutamate (pyroE) and/or the C-terminal lysine or other amino acid is missing.

[088] The present invention provides a vessel (*e.g.*, a plastic or glass vial, *e.g.*, with a cap or a chromatography column, hollow bore needle or a syringe cylinder) comprising an anti-FGFR3 antigen-binding protein of the present invention, *e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2.

[089] The present invention also provides an injection device comprising one or more antigen-binding proteins (*e.g.,* antibody or antigen-binding fragment) that bind specifically to FGFR3, *e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2, or a pharmaceutical formulation thereof. The injection device may be packaged into a kit. An injection device is a device that introduces a substance into the body of a subject via a parenteral route, *e.g.*, intraocular, intravitreal, intramuscular, subcutaneous or intravenous. For example, an injection device may be a syringe or an auto-injector (*e.g.*, pre-filled with the pharmaceutical formulation) which, for example, includes a cylinder or barrel for holding fluid to be injected (*e.g.*, comprising the antibody or fragment or a pharmaceutical formulation thereof), a needle for piecing skin, blood vessels or other tissue for injection of the fluid; and a plunger for pushing the fluid out of the cylinder and through the needle bore and into the body of the subject.

Post-translational Modifications

[090] The anti-FGFR3 antibodies and antigen-binding fragments of the present invention may be modified after translation, *e.g.*, glycosylated.

[091] For example, antibodies and antigen-binding fragments of the present invention may be glycosylated (*e.g.*, N-glycosylated and/or O-glycosylated) or aglycosylated. Typically, antibodies and antigen-binding fragments are glycosylated at the conserved residue N297 of the IgG Fc domain. Some antibodies and fragments include one or more additional glycyosylation sites in a variable region. In an embodiment of the invention, the glycosylation site is in the following context: $FN_{297}S$ or $YN_{297}S$.

[092] In an embodiment of the invention, said glycosylation is any one or more of three different N-glycan types: high mannose, complex and/or hybrid that are found on IgGs with their respective linkage. Complex and hybrid types exist with core fucosylation, addition of a fucose residue to the innermost N-acetylglucosamine, and without core fucosylation.

[093] In an embodiment of the invention, an antibody or fragment of the present invention is afucosylated. Some IgG1 antibodies rely on the Fc-mediated immune effector function, antibody-dependent cellular cytotoxicity (ADCC), as the major mode of action to deplete tumor cells. This effector function is modulated by the N-linked glycosylation in the Fc region of the antibody. In particular, absence of core fucose on the Fc N-glycan has been shown to increase IgG1 Fc binding affinity to the FcγRIIIa present on immune effector cells such as natural killer cells and lead to enhanced ADCC activity.

[094] The antibodies and antigen-binding fragments of the present invention may also be post-translationally modified in other ways including, for example: Glu or Gln cyclization at N-terminus; Loss of positive N-terminal charge; Lys variants at C-terminus; Deamidation (Asn to Asp); Isomerization (Asp to isoAsp); Deamidation (Gln to Glu); Oxidation (Cys, His, Met, Tyr, Trp); and/or Disulfide bond heterogeneity (Shuffling, thioether and trisulfide formation).

Polynucleotides and Methods of Making

[095] A polynucleotide includes DNA and RNA. The present invention includes any polynucleotide of the present invention, for example, encoding an immunoglobulin V_H, V_L, CDR-H, CDR-L, HC or LC of H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; and/or H4H30093P2, optionally, which is operably linked to a promoter or other expression control sequence. For example, the present invention provides any polynucleotide (*e.g.*, DNA) that includes a nucleotide sequence set forth in SEQ ID NO: 1; 3; 5; 7; 9; 11; 13; 15; 17; 19; 21; 23; 25; 27; 29; 31; 33; 35; 37; 39; 41; 43; 45; 47; 49; 51; 53; 55; 57; 59; 61; 63; 65; 67; 69; 71; 73; 75; 77; 79; 81; 83; 85; 87; 89; 91; 93; 95; 97; 99; 101;

103; 105; 107; 109; 111; 113; 115; 117; 119; 121; 123; 125; 127; 129; 131; 133; 135; 137; 139; 141; 143; 145; 147; 149; 151; 152; 154; 156; 158; 160; 162; 164; 166; 168; 170; 172; 174; 176; 178; 180; 182; 184; 186; 188; 190; 192; 194; 196; 198; 200; 202; 204; 206; 208; 210; 212; 214; 216; 218; 220; 222; 224; 226; 228; or 230. In an embodiment of the invention, a polynucleotide of the present invention is fused to a secretion signal sequence. Polypeptides encoded by such polynucleotides are also within the scope of the present invention.

[096] In general, a "promoter" or "promoter sequence" is a DNA regulatory region capable of binding an RNA polymerase in a cell (*e.g.*, directly or through other promoter-bound proteins or substances) and initiating transcription of a coding sequence. A promoter may be operably linked to other expression control sequences, including enhancer and repressor sequences and/or with a polynucleotide of the invention. Promoters which may be used to control gene expression include, but are not limited to, cytomegalovirus (CMV) promoter (U.S. Pat. Nos. 5,385,839 and 5,168,062), the SV40 early promoter region (Benoist *et al.*, (1981) Nature 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, (1980) Cell 22:787-797), the herpes thymidine kinase promoter (Wagner *et al.*, (1981) Proc. Natl. Acad. Sci. USA 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster *et al.*, (1982) Nature 296:39-42); prokaryotic expression vectors such as the beta-lactamase promoter (VIIIa-Komaroff *et al.*, (1978) Proc. Natl. Acad. Sci. USA 75:3727-3731), or the tac promoter (DeBoer *et al.*, (1983) Proc. Natl. Acad. Sci. USA 80:21-25); see also "Useful proteins from recombinant bacteria" in Scientific American (1980) 242:74-94; and promoter elements from yeast or other fungi such as the Gal4 promoter, the ADC (alcohol dehydrogenase) promoter, PGK (phosphoglycerol kinase) promoter or the alkaline phosphatase promoter.

[097] A polynucleotide encoding a polypeptide is "operably linked" to a promoter or other expression control sequence when, in a cell or other expression system, the sequence directs RNA polymerase mediated transcription of the coding sequence into RNA, preferably mRNA, which then may be RNA spliced (if it contains introns) and, optionally, translated into a protein encoded by the coding sequence.

[098] The present invention includes a polynucleotide comprising the following polynucleotide pairs encoding a V_H and V_L:

SEQ ID NO: 1 and SEQ ID NO: 9;

SEQ ID NO: 21 and SEQ ID NO: 29;

SEQ ID NO: 41 and SEQ ID NO: 49;
SEQ ID NO: 61 and SEQ ID NO: 69;
SEQ ID NO: 81 and SEQ ID NO: 89;
SEQ ID NO: 101 and SEQ ID NO: 109;
SEQ ID NO: 121 and SEQ ID NO: 129;
SEQ ID NO: 139 and SEQ ID NO:147;
SEQ ID NO: 158 and SEQ ID NO:147;
SEQ ID NO: 168 and SEQ ID NO: 147;
SEQ ID NO: 178 and SEQ ID NO: 186;
SEQ ID NO: 198 and SEQ ID NO: 206; and/or
SEQ ID NO: 218 and SEQ ID NO: 226;
or two separate polynucleotides, each including one of the sequences
SEQ ID NO: 1 and SEQ ID NO: 9;
SEQ ID NO: 21 and SEQ ID NO: 29;
SEQ ID NO: 41 and SEQ ID NO: 49;
SEQ ID NO: 61 and SEQ ID NO: 69;
SEQ ID NO: 81 and SEQ ID NO: 89;
SEQ ID NO: 101 and SEQ ID NO: 109
SEQ ID NO: 121 and SEQ ID NO: 129;
SEQ ID NO: 139 and SEQ ID NO:147;
SEQ ID NO: 158 and SEQ ID NO:147;
SEQ ID NO: 168 and SEQ ID NO: 147;
SEQ ID NO: 178 and SEQ ID NO: 186;
SEQ ID NO: 198 and SEQ ID NO: 206; or
SEQ ID NO: 218 and SEQ ID NO: 226.

[099] The present invention includes a polynucleotide comprising the following polynucleotide sets which encode a CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and CDR-L3:
SEQ ID NOs: 3, 5, 7, 11, 13 and 15;
SEQ ID NOs: 23, 25, 27, 31, 33 and 35;
SEQ ID NOs: 43, 45, 47, 51, 53 and 55;
SEQ ID NOs: 63, 65, 67, 71, 73 and 75;
SEQ ID NOs: 83, 85, 87, 91, 93 and 95;
SEQ ID NOs: 103, 105, 107, 111, 113 and 115;

SEQ ID NOs: 123, 125, 127, 131, 33 and 133;
SEQ ID NOs: 141, 143, 415, 149, 151 and 152;
SEQ ID NOs: 160, 162, 164, 149, 151 and 152;
SEQ ID NOs: 170, 172, 174, 149, 151 and 152;
SEQ ID NOs: 180, 182, 184, 188, 190 and 192;
SEQ ID NOs: 200, 202, 204, 208, 210 and 212; and/or
SEQ ID NOs: 220, 222, 224, 31, 33 and 75;
or two separate polynucleotides, each including one of the sequences
SEQ ID NOs: 3, 5 and 7; and 11, 13 and 15;
SEQ ID NOs: 23, 25 and 27; and 31, 33 and 35;
SEQ ID NOs: 43, 45 and 47; and 51, 53 and 55;
SEQ ID NOs: 63, 65 and 67; and 71, 73 and 75;
SEQ ID NOs: 83, 85 and 87; and 91, 93 and 95;
SEQ ID NOs: 103, 105 and 107; and 111, 113 and 115;
SEQ ID NOs: 123, 125, and 127; 131, 33 and 133;
SEQ ID NOs: 141, 143, and 415; 149, 151 and 152;
SEQ ID NOs: 160, 162, and 164; 149, 151 and 152;
SEQ ID NOs: 170, 172, and 174; 149, 151 and 152;
SEQ ID NOs: 180, 182, and184; 188, 190 and 192;
SEQ ID NOs: 200, 202, and 204; 208, 210 and 212; or
SEQ ID NOs: 220, 222, and 224; 31, 33 and 75.

[100] The present invention includes a polynucleotide comprising the following polynucleotide pairs encoding a HC and LC:
SEQ ID NO: 17 and SEQ ID NO: 19;
SEQ ID NO: 37 and SEQ ID NO: 39;
SEQ ID NO: 57 and SEQ ID NO: 59;
SEQ ID NO: 77 and SEQ ID NO: 79;
SEQ ID NO: 97 and SEQ ID NO: 99;
SEQ ID NO: 117 and SEQ ID NO: 119;
SEQ ID NO: 135 and SEQ ID NO: 137;
SEQ ID NO: 154 and SEQ ID NO: 156;
SEQ ID NO: 166 and SEQ ID NO: 156;
SEQ ID NO: 176 and SEQ ID NO: 156;

SEQ ID NO: 194 and SEQ ID NO: 196;
SEQ ID NO: 214 and SEQ ID NO: 216; and/or
SEQ ID NO: 228 and SEQ ID NO: 230;
or two separate polynucleotides, each including one of the sequences
SEQ ID NO: 17 and SEQ ID NO: 19;
SEQ ID NO: 37 and SEQ ID NO: 39;
SEQ ID NO: 57 and SEQ ID NO: 59;
SEQ ID NO: 77 and SEQ ID NO: 79;
SEQ ID NO: 97 and SEQ ID NO: 99;
SEQ ID NO: 117 and SEQ ID NO: 119;
SEQ ID NO: 135 and SEQ ID NO: 137;
SEQ ID NO: 154 and SEQ ID NO: 156;
SEQ ID NO: 166 and SEQ ID NO: 156;
SEQ ID NO: 176 and SEQ ID NO: 156;
SEQ ID NO: 194 and SEQ ID NO: 196;
SEQ ID NO: 214 and SEQ ID NO: 216; and/or
SEQ ID NO: 228 and SEQ ID NO: 230.

[101] Host cells including the two separate polynucleotides as discussed above, each integrated into chromosomal DNA of the host cell at different loci or ectopic, wherein such polynucleotide are maintained in separate genetic elements, are within the scope of the present invention.

[102] The present invention includes polynucleotides encoding immunoglobulin polypeptide chains which are variants of those whose nucleotide sequence is specifically set forth herein. A "variant" of a polynucleotide refers to a polynucleotide comprising a nucleotide sequence that is at least about 70-99.9% (*e.g.*, 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, 99.9%) identical to a referenced nucleotide sequence that is set forth herein; when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences (*e.g.*, expect threshold: 10; word size: 28; max matches in a query range: 0; match/mismatch scores: 1, -2; gap costs: linear). In an embodiment of the invention, a variant of a nucleotide sequence specifically set forth herein comprises one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12) point mutations, insertions (*e.g.*, in frame insertions) or deletions (*e.g.*, in frame

deletions) of one or more nucleotides. Such mutations may, in an embodiment of the invention, be missense or nonsense mutations. In an embodiment of the invention, such a variant polynucleotide encodes an immunoglobulin polypeptide chain which can be incorporated into an anti-FGFR3 antigen-binding protein, i.e., such that the protein retains specific binding to FGFR3.

[103] Eukaryotic and prokaryotic host cells, including mammalian cells, may be used as hosts for expression of an anti-FGFR3 antigen-binding protein (*e.g.*, antibody or antigen-binding fragment thereof). Such host cells are well known in the art and many are available from the American Type Culture Collection (ATCC). These host cells include, *inter alia*, Chinese hamster ovary (CHO) cells, NSO, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), A549 cells, 3T3 cells, HEK-293 cells and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Other cell lines that may be used are insect cell lines (*e.g.*, *Spodoptera frugiperda* or *Trichoplusia ni*), amphibian cells, bacterial cells, plant cells and fungal cells. Fungal cells include yeast and filamentous fungus cells including, for example, *Pichia*, *Pichia pastoris*, *Pichia finlandica*, *Pichia trehalophila*, *Pichia koclamae*, *Pichia membranaefaciens*, *Pichia minuta* (*Ogataea minuta*, *Pichia lindneri*), *Pichia opuntiae*, *Pichia thermotolerans*, *Pichia salictaria*, *Pichia guercuum*, *Pichia pijperi*, *Pichia stiptis*, *Pichia methanolica*, *Pichia* sp., *Saccharomyces cerevisiae*, *Saccharomyces* sp., *Hansenula polymorpha*, *Kluyveromyces* sp., *Kluyveromyces lactis*, *Candida albicans*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus oryzae*, *Trichoderma reesei*, *Chrysosporium lucknowense*, *Fusarium* sp., *Fusarium gramineum*, *Fusarium venenatum*, *Physcomitrella patens* and *Neurospora crassa*. The present invention includes an isolated host cell (*e.g.*, a CHO cell or any type of host cell set forth above) comprising an antigen-binding protein, a V_H, V_L, HC, LC or CDRs thereof (or variant thereof), such as H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2; and/or a polynucleotide encoding one or more immunoglobulin chains thereof (*e.g.*, as discussed herein). In an embodiment of the invention, a host cell includes two separate polynucleotides, one encoding a V_H and the other encoding a V_L; or one encoding a HC and the other encoding a LC.

[104] The present invention also includes a cell which is expressing FGFR3 or an antigenic fragment or fusion thereof (*e.g.*, His_6 (SEQ ID NO: 235), Fc (*e.g.*, mouse Fc (mFc)), myc, or

mycmycHis6 (mmh)) which is bound by an antigen-binding protein of the present invention (*e.g.*, an antibody or antigen-binding fragment thereof), for example, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2, for example, wherein the cell is in the body of a subject or is *in vitro*. In addition, the present invention also provides a complex comprising an anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof, as discussed herein complexed with FGFR3 polypeptide or an antigenic fragment thereof or fusion thereof and/or with a secondary antibody or antigen-binding fragment thereof (*e.g.*, detectably labeled secondary antibody) that binds specifically to the anti-FGFR3 antibody or fragment. In an embodiment of the invention, the complex is *in vitro* (*e.g.*, is immobilized to a solid substrate) or is in the body of a subject.

[105] In an embodiment of the invention, a myc tag has the amino acid sequence EQKLISEEDLGG (SEQ ID NO: 234), a His_6 (SEQ ID NO: 235) or hexahis (SEQ ID NO: 235) or hexahistidine (SEQ ID NO: 235) tag has the amino acid sequence HHHHHH (SEQ ID NO: 235), an mmh tag has the amino acid sequence EQKLISEEDLGGEQKLISEEDLHHHHHH (SEQ ID NO: 236) and a mouse Fc tag has the amino acid sequence EPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHRE DYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMP EDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK (SEQ ID NO: 237).

[106] Recombinant anti-FGFR3 antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments, disclosed herein may also be produced in an *E. coli*/T7 expression system. In this embodiment, polynucleotides encoding the anti-FGFR3 antibody immunoglobulin molecules of the invention (*e.g.*, HC, LC, V_H and/or V_L or CDRs thereof of (H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2)) may be inserted into a pET-based plasmid and expressed in the *E. coli*/T7 system. For example, the present invention includes methods for expressing an antibody or antigen-binding fragment thereof or immunoglobulin chain thereof in a host cell (*e.g.*, bacterial host cell such as *E. coli* such as BL21 or BL21DE3) comprising expressing T7 RNA polymerase in the cell which also includes a polynucleotide encoding an immunoglobulin chain (*e.g.*, including the nucleotide sequence in any one or more of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17 or 19; or a variant thereof) that is operably linked to a T7 promoter. For example, in an embodiment of the

invention, a bacterial host cell, such as an *E. coli*, includes a polynucleotide encoding the T7 RNA polymerase gene operably linked to a *lac* promoter and expression of the polymerase and the chain is induced by incubation of the host cell with IPTG (isopropyl-beta-D-thiogalactopyranoside). See US4952496 and US5693489 or Studier & Moffatt, Use of bacteriophage T7 RNA polymerase to direct selective high-level expression of cloned genes, J. Mol. Biol. 1986 May 5;189(1): 113-30.

[107] There are several methods by which to produce recombinant antibodies which are known in the art. One example of a method for recombinant production of antibodies is disclosed in US4816567.

[108] Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors. Methods of transforming cells are well known in the art. See, for example, U.S. Pat. Nos. 4399216; 4912040; 4740461 and 4959455. Thus, the present invention includes recombinant methods for making an anti-FGFR3 (*e.g.*, monomeric or dimeric FGFR3b) antigen-binding protein, such as an antibody or antigen-binding fragment thereof of the present invention, or an immunoglobulin chain thereof, comprising (i) introducing, into a host cell, one or more polynucleotides (*e.g.*, including the nucleotide sequence in any one or more of SEQ ID NOs: 1, 9, 17 and/or 19; or a variant thereof) encoding light and/or heavy immunoglobulin chains of the antigen-binding protein, *e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2, for example, wherein the polynucleotide is in a vector; and/or integrates into the host cell chromosome and/or is operably linked to a promoter; (ii) culturing the host cell (*e.g.*, CHO or *Pichia* or *Pichia pastoris*) under conditions favorable to expression of the polynucleotide and, (iii) optionally, isolating the antigen-binding protein (*e.g.*, antibody or antigen-binding fragment) or chain from the host cell and/or medium in which the host cell is grown. When making an antigen-binding protein (*e.g.*, antibody or antigen-binding fragment) comprising more than one immunoglobulin chain, *e.g.*, an antibody that comprises two heavy immunoglobulin chains and two light immunoglobulin chains, co-expression of the chains in a single host cell leads to association of

the chains, *e.g.*, in the cell or on the cell surface or outside the cell if such chains are secreted, so as to form the antigen-binding protein (*e.g.*, antibody or antigen-binding fragment). The methods of the present invention include those wherein only a heavy immunoglobulin chain or only a light immunoglobulin chain or both (*e.g.*, any of those discussed herein including mature fragments and/or variable domains thereof) are expressed in a cell. Such single chains are useful, for example, as intermediates in the expression of an antibody or antigen-binding fragment that includes such a chain. For example, the present invention also includes anti-FGFR3 antigen-binding proteins, such as antibodies and antigen-binding fragments thereof which are the product of the production methods set forth herein, and, optionally, the purification methods set forth herein.

[109] In an embodiment of the invention, a method for making an anti-FGFR3 (*e.g.*, monomeric or dimeric FGFR3b) antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof, includes a method of purifying the antigen-binding protein, *e.g.*, by column chromatography, precipitation and/or filtration. As discussed, the product of such a method also forms part of the present invention.

Preparation of Human Antibodies

[110] The anti-FGFR3 (*e.g.*, monomeric or dimeric FGFR3b) antibodies and antigen-binding fragments of the present invention (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2) can be fully human antibodies and fragments. Methods for generating monoclonal antibodies, including fully human monoclonal antibodies are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human FGFR3.

[111] Using VELOCIMMUNE™ technology, for example, or any other similar known method for generating fully human monoclonal antibodies, high affinity chimeric antibodies to FGFR3 are initially isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, ligand blocking activity, selectivity, epitope, *etc.* If necessary, mouse constant regions are replaced with a desired human constant region, for example wild-type or modified IgG1 or IgG4, to generate a fully human anti-FGFR3 antibody. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region. In certain instances, fully human

anti-FGFR3 antibodies are isolated directly from antigen-positive B cells. See, for example, US6596541, Regeneron Pharmaceuticals, VELOCIMMUNE®.

Anti-FGFR3 Antibodies Comprising Fc Variants

[112] According to certain embodiments of the present invention, anti-FGFR3 (*e.g.*, monomeric or dimeric FGFR3b) antibodies and antigen-binding fragments (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2) are provided comprising an Fc domain comprising one or more mutations which enhance or diminish antibody binding to the FcRn receptor, *e.g.*, at acidic pH as compared to neutral pH (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2). For example, the present invention includes anti-FGFR3 antibodies comprising a mutation in the CH2 or a CH3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (*e.g.*, in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal.

[113] Non-limiting examples of such Fc modifications include, *e.g.*, a modification at position:

- 250 (*e.g.*, E or Q);
- 250 and 428 (*e.g.*, L or F);
- 252 (*e.g.*, L/Y/F/W or T),
- 254 (*e.g.*, S or T), and/or
- 256 (*e.g.*, S/R/Q/E/D or T);

and/or a modification at position:

- 428 and/or 433 (*e.g.*, H/L/R/S/P/Q or K), and/or
- 434 (*e.g.*, A, W, H/F or Y);

and/or a modification at position:

- 250 and/or 428;

and/or a modification at position:

- 307 or 308 (*e.g.*, 308F, V308F), and/or
- 434.

[114] In an embodiment of the invention, the modification comprises:

- a 428L (*e.g.*, M428L) and 434S (*e.g.*, N434S) modification;

- a 428L, 259I (*e.g.*, V259I), and 308F (*e.g.*, V308F) modification;
- a 433K (*e.g.*, H433K) and a 434 (*e.g.*, 434Y) modification;
- a 252, 254, and 256 (*e.g.*, 252Y, 254T, and 256E) modification;
- a 250Q and 428L modification (*e.g.*, T250Q and M428L); and/or
- a 307 and/or 308 modification (*e.g.*, 308F or 308P).

[115] For example, the present invention includes anti-FGFR3 antibodies comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of:

- 250Q and 248L (*e.g.*, T250Q and M248L);
- 252Y, 254T and 256E (*e.g.*, M252Y, S254T and T256E);
- 257I and 311I (e.g., P257I and Q311I);
- 257I and 434H (*e.g.*, P257I and N434H);
- 376V and 434H (*e.g.*, D376V and N434H);
- 307A, 380A and 434A (*e.g.*, T307A, E380A and N434A);
- 428L and 434S (*e.g.*, M428L and N434S); and
- 433K and 434F (*e.g.*, H433K and N434F).

[116] In yet another embodiment, the modification comprises a 265A (*e.g.*, D265A) and/or a 297A (*e.g.*, N297A) modification.

[117] In an embodiment of the invention, the heavy chain constant domain is gamma-4 comprising an S228P and/or S108P mutation. See Angal *et al.*, A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody, Mol Immunol. 1993 Jan;30(1):105-108.

[118] All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present invention.

[119] The anti-FGFR3 antibodies of the present invention may comprise a modified Fc domain having reduced effector function. As used herein, a "modified Fc domain having reduced effector function" means any Fc portion of an immunoglobulin that has been modified, mutated, truncated, *etc.*, relative to a wild-type, naturally occurring Fc domain such that a molecule comprising the modified Fc exhibits a reduction in the severity or extent of at least one effect selected from the group consisting of cell killing (*e.g.*, ADCC and/or CDC), complement activation, phagocytosis and opsonization, relative to a comparator molecule comprising the wild-type, naturally occurring version of the Fc portion. In certain

embodiments, a "modified Fc domain having reduced effector function" is an Fc domain with reduced or attenuated binding to an Fc receptor (*e.g.*, FcγR).

[120] In certain embodiments of the present invention, the modified Fc domain is a variant IgG1 Fc or a variant IgG4 Fc comprising a substitution in the hinge region. For example, a modified Fc for use in the context of the present invention may comprise a variant IgG1 Fc wherein at least one amino acid of the IgG1 Fc hinge region is replaced with the corresponding amino acid from the IgG2 Fc hinge region. Alternatively, a modified Fc for use in the context of the present invention may comprise a variant IgG4 Fc wherein at least one amino acid of the IgG4 Fc hinge region is replaced with the corresponding amino acid from the IgG2 Fc hinge region. Non-limiting, exemplary modified Fc regions that can be used in the context of the present invention are set forth in US Patent Application Publication No. 2014/0243504, the disclosure of which is hereby incorporated by reference in its entirety, as well as any functionally equivalent variants of the modified Fc regions set forth therein.

[121] The present disclosure also includes antigen-binding proteins, antibodies or antigen-binding fragments, comprising a HCVR set forth herein and a chimeric heavy chain constant (CH) region, wherein the chimeric CH region comprises segments derived from the CH regions of more than one immunoglobulin isotype. For example, the antibodies of the disclosure may comprise a chimeric CH region comprising part or all of a CH2 domain derived from a human IgG1, human IgG2 or human IgG4 molecule, combined with part or all of a CH3 domain derived from a human IgG1, human IgG2 or human IgG4 molecule. According to certain embodiments, the antibodies of the disclosure comprise a chimeric CH region having a chimeric hinge region. For example, a chimeric hinge may comprise an “upper hinge” amino acid sequence (amino acid residues from positions 216 to 227 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a “lower hinge” sequence (amino acid residues from positions 228 to 236 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. According to certain embodiments, the chimeric hinge region comprises amino acid residues derived from a human IgG1 or a human IgG4 upper hinge and amino acid residues derived from a human IgG2 lower hinge. An antibody comprising a chimeric CH region as described herein may, in certain embodiments, exhibit modified Fc effector functions without adversely affecting the therapeutic or pharmacokinetic properties of the antibody. (See, *e.g.,* WO2014/022540).

[122] Other modified Fc domains and Fc modifications that can be used in the context of the present invention include any of the modifications as set forth in US2014/0171623;

US8697396; US2014/0134162; WO2014/043361, the disclosures of which are hereby incorporated by reference in their entireties. Methods of constructing antibodies or other antigen-binding fusion proteins comprising a modified Fc domain as described herein are known in the art.

[123] In some cases, the anti-FGFR3 antibodies may comprise one or more mutations in a framework region, e.g., in the CH1 domain, CH2 domain, CH3 domain, hinge region, or a combination thereof. In some embodiments, the one or more mutations are to stabilize the antibody and/or to increase half-life. In some embodiments, the one or more mutations are to modulate Fc receptor interactions, to reduce or eliminate Fc effector functions such as FcyR, antibody-dependent cell-mediated cytotoxicity (ADCC), or complement-dependent cytotoxicity (CDC). In additional embodiments, the one or more mutations are to modulate glycosylation.

[124] In some embodiments, one, two or more mutations (e.g., amino acid substitutions) are introduced into the Fc region of an antibody described herein (e.g., in a CH2 domain (residues 231-340 of human IgG1) and/or CH3 domain (residues 341-447 of human IgG1) and/or the hinge region, with numbering according to the Kabat numbering system (e.g., the EU index in Kabat)) to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding and/or antigen-dependent cellular cytotoxicity. In some embodiments, one, two or more mutations (e.g., amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (e.g., increased or decreased) as described in, e.g., U.S. Patent No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain can be altered to, e.g., facilitate assembly of the light and heavy chains, or to alter (e.g., increase or decrease) the stability of the antibody or to facilitate linker conjugation.

[125] In some embodiments, one, two or more amino acid mutations (i.e., substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to alter (e.g., decrease or increase) half-life of the antibody *in vivo*. See, e.g., PCT Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Pat. Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (e.g., decrease or increase) the half-life of an antibody *in vivo*. In some embodiments, the Fc region comprises a mutation at residue position L234, L235, or a combination thereof. In some embodiments, the mutations comprise L234 and L235. In some embodiments, the mutations comprise L234A and L235A.

Immunoconjugates

[126] The invention encompasses anti-FGFR3 (*e.g.*, monomeric or dimeric FGFR3b) antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, conjugated to another moiety, *e.g.*, a therapeutic moiety (an "immunoconjugate") (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2). In an embodiment of the invention, an anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, is conjugated to any of the further therapeutic agents set forth herein. As used herein, the term "immunoconjugate" refers to an antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment, which is chemically or biologically linked to another antigen-binding protein, a drug, a radioactive agent, a reporter moiety, an enzyme, a peptide, a protein or a therapeutic agent.

Treatment and Administration

[127] The present invention provides methods for treating or preventing an FGFR3-mediated condition, in a subject, comprising administering a therapeutically effective amount of anti-FGFR3 (*e.g.*, monomeric or dimeric FGFR3b) antigen-binding protein (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2) to the subject; optionally, in association with a further therapeutic agent.

[128] An FGFR3-mediated condition is any condition that is mediated at least in part by the activity of FGFR3, for example, tyrosine kinase activity of FGFR3 or activity of molecules downstream of FGFR3 (*e.g.*, CD73 or the MEK pathway in a tumor cell expressing FGFR3).

[129] An FGFR3-mediated condition can also include T-cell suppression mediated by a tumor cell expressing FGFR3, *e.g.*, adenosine-mediated suppression of T-cells via the A2A receptor, for example, wherein the CD73 catalyzes conversion of AMP to adenosine. CD73 (NT5E, ecto-5′-nucleotidase) is a glycosylphosphatidylinositol- (GPI-) anchored cell-surface enzyme that plays a crucial role in the purinergic signaling pathway by dephosphorylating AMP (adenosine monophosphate) into adenosine. Extracellular adenosine itself is involved in tumor immunoescape and invasion of tumor cells, while nonenzymatic functions of CD73 are related to cell adhesion and migration of tumor cells.

[130] FGFR3-mediated conditions include, for example,

- cancer,
- bladder cancer,
- brain cancer,
- breast cancer,
- cervical cancer,
- colorectal cancer,
- endometrial cancer,
- gastric cancer,
- head & neck cancer
- kidney cancer,
- lung cancer,
- multiple myeloma,
- ovarian cancer,
- pancreatic cancer,
- urothelial cancer,
- achondroplasia,
- crouzon syndrome with acanthosis nigricans,
- epidermal nevus,
- hypochondroplasia;
- lacrimo-auriculo-dento-digital (LADD) syndrome,
- muenke syndrome,
- severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), and/or
- thanatophoric dysplasia.

[131] Achondroplasia is a form of short-limbed dwarfism. Crouzon syndrome with acanthosis nigricans is a condition that causes premature joining of the bones of the skull (craniosynostosis), leading to a misshapen head and distinctive facial features, and a skin abnormality called acanthosis nigricans that is characterized by thick, dark, velvety skin in body folds and creases. Epidermal nevus is abnormal skin growths that are composed of skin cells called keratinocytes. Hypochondroplasia is a form of short-limbed dwarfism that is milder than achondroplasia. Lacrimo-auriculo-dento-digital (LADD) syndrome is an extremely rare genetic disorder characterized by abnormalities affecting the lacrimal and salivary glands and

ducts, ears, teeth and fingers and toes. The most common findings involve malformations in the network of structures of the eye that secrete tears and drain them from the eyes (lacrimal apparatus) and abnormalities of the forearms and fingers. Specific symptoms may vary greatly from person to person. LADD syndrome may occur sporadically or be inherited in an autosomal dominant pattern. Muenke syndrome is a condition that causes craniosynostosis, leading to a misshapen head and distinctive facial features. Additional signs and symptoms can include hearing loss, subtle hand and foot abnormalities, and developmental delay. SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans) is characterized by short-limb dwarfism (achondroplasia); profound developmental delay; and thick, dark, velvety skin. Thanatophoric dysplasia is a severe skeletal disorder characterized by extremely short limbs and folds of extra (redundant) skin on the arms and legs. Other features of this condition include a narrow chest, short ribs, underdeveloped lungs, and an enlarged head with a large forehead and prominent, wide-spaced eyes. Bladder cancer includes non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC).

[132] An effective or therapeutically effective amount of anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, for treating or preventing an FGFR3-mediated condition refers to the amount of the antigen-binding protein sufficient to alleviate one or more signs and/or symptoms of the disease or condition in the treated subject, whether by inducing the regression or elimination of such signs and/or symptoms or by inhibiting the progression of such signs and/or symptoms. In an embodiment of the invention, an effective or therapeutically effective amount of anti-FGFR3 antigen-binding protein is about 2-30 mg/kg. This dose may be administered, for example, about once a month. The dose amount may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. In certain embodiments, the initial dose may be followed by administration of a second or a plurality of subsequent doses of antigen-binding protein in an amount that can be approximately the same or less or more than that of the initial dose, wherein the subsequent doses are separated by days or weeks or months.

[133] The present invention provides methods for administering an anti-FGFR3 (*e.g.*, monomeric or dimeric FGFR3b) antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2) to a subject, comprising introducing the protein or a

pharmaceutical formulation thereof into the body of the subject. For example, in an embodiment of the invention, the method comprises piercing the body of the subject, *e.g.*, with a needle of a syringe, and injecting the antigen-binding protein or a pharmaceutical formulation thereof into the body of the subject, *e.g.*, into the eye, vein, artery, muscular tissue or subcutis of the subject.

[134] As used herein, the term "subject" refers to a mammal (*e.g.*, rat, mouse, cat, dog, cow, sheep, horse, goat, rabbit), preferably a human, for example, in need of prevention and/or treatment of an FGFR3-mediated condition. The subject may have an FGFR3-mediated condition or be predisposed to developing such a condition. In an embodiment of the invention, the subject has an FGFR3 genotype selected from: S249C, R248C, G372C, Y375C, K650E and/or FGFR3-TACC3 (*e.g.*, heterozygous or homozygous).

Combinations and Pharmaceutical Formulation

[135] The present invention provides compositions that include anti-FGFR3 (*e.g.*, monomeric or dimeric FGFR3b) antigen-binding proteins, such as antibodies or antigen-binding fragments (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2), in association with one or more ingredients; as well as methods of use thereof and methods of making such compositions. Pharmaceutic formulations comprising an anti-FGFR3 antigen-binding protein and a pharmaceutically acceptable carrier or excipient are part of the present invention.

[136] To prepare pharmaceutical formulations of the anti-FGFR3 antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2), antigen-binding protein is admixed with a pharmaceutically acceptable carrier or excipient. See, *e.g.*, Remington's Pharmaceutical Sciences and U.S. Pharmacopeia: National Formulary, Mack Publishing Company, Easton, Pa. (1984); Hardman, *et al.* (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y.; Gennaro (2000) Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y.; Avis, *et al.* (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) Pharmaceutical Dosage Forms: Disperse

Systems, Marcel Dekker, NY; Weiner and Kotkoskie (2000) Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y. In an embodiment of the invention, the pharmaceutical formulation is sterile. Such compositions are part of the present invention.

[137] Pharmaceutical formulations of the present invention include an anti-FGFR3 antigen-binding protein (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2) and a pharmaceutically acceptable carrier including, for example, water and buffering agents.

[138] The scope of the present invention includes desiccated, *e.g.*, freeze-dried, compositions comprising an anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2), or a pharmaceutical formulation thereof that includes a pharmaceutically acceptable carrier but substantially lacks water.

[139] In a further embodiment of the invention, a further therapeutic agent that is administered to a subject in association with an anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2), disclosed herein is administered to the subject in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (Nov. 1, 2002)).

[140] The mode of administration of an anti-FGFR3 antigen-binding protein or composition thereof can vary. Routes of administration include parenteral, non-parenteral, oral, rectal, transmucosal, intestinal, parenteral; intramuscular, subcutaneous, intradermal, intramedullary, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, intraocular, inhalation, insufflation, topical, cutaneous, intraocular, intravitreal, transdermal or intra-arterial.

[141] The present invention provides a vessel (*e.g.*, a plastic or glass vial, *e.g.*, with a cap or a chromatography column, hollow bore needle or a syringe cylinder) comprising any of the anti-FGFR3 antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments thereof (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or

H4H30093P2), or a pharmaceutical formulation comprising a pharmaceutically acceptable carrier thereof.

[142] The present invention includes combinations including an anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention (*e.g.*, H4H30063P; H4H30089P2; H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2), in association with one or more further therapeutic agents. The anti-FGFR3 antigen-binding protein and the further therapeutic agent can be in a single composition or in separate compositions. For example, in an embodiment of the invention, the further therapeutic agent is cancer therapeutic agent. In an embodiment of the invention, the further therapeutic agent is

- an FGFR inhibitor (*e.g.*, erdafitinib)
- pemigatinib,
- infigratinib,
- rogaratinib,
- dexamethasone
- alkylating drug (*e.g.*, altretamine, trabectedin or busulfan),
- a nitrosourea (*e.g.*, carmustine or lomustine),
- a cytotoxic antibiotic (*e.g.*, an anthracycline, doxorubicin, valrubicin, bleomycin or dactinomycin),
- an antimetabolite drug (*e.g.*, methotrexate, floxuridine, clofarabine or pralatrexate),
- a vinca alkaloid (*e.g.*, vinblastine, vinorelbine, vincristine or vindesine),
- a photodynamic drug (*e.g.*, porfimer sodium or aminolevulinic acid),
- a platinum drug (cisplatin or phenanthriplatin),
- a taxane (*e.g.*, paclitaxel or docetaxel),
- a topoisomerase inhibitor (*e.g.*, irinotecan, topotecan, etoposide or teniposide),
- ziv-aflibercept
- an anti-cancer antibody (*e.g.*, rituximab, trastuzumab, cetuximab, cemiplimab, pembrolizumab, panitumumab or bevacizumab).

[143] As discussed herein, the present invention includes methods for treating or preventing an FGFR3-mediated condition in a subject in need of said treatment or prevention by administering an anti-FGFR3 antigen-binding protein, *e.g.*, H4H30063P; H4H30089P2;

H4H30071P; H4H30066P; H4H30102P2; H4H30076P; H4H30105P2; H4H30108P2; H4H30117P2; H4H30045P; H4H30061P; H4H30095P2; or H4H30093P2, which may be in association with a further therapeutic agent.

[144] The term "in association with" indicates that components, an anti-FGFR3 antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention, along with another agent such as methotrexate, can be formulated into a single composition, *e.g.*, for simultaneous delivery, or formulated separately into two or more compositions (*e.g.*, a kit including each component). Components administered in association with each another can be administered to a subject at a different time than when the other component is administered; for example, each administration may be given non-simultaneously (*e.g.*, separately or sequentially) at intervals over a given period of time. Separate components administered in association with each another may also be administered sequentially, though essentially simultaneously, during the same administration session. Moreover, the separate components administered in association with each another may be administered to a subject by the same or by a different route.

EXAMPLES

Example 1: Binding Kinetics

[145] Biacore binding kinetics of anti-FGFR3 antibodies, in an antibody capture format, to monomeric human FGFR3b, cynomolgus FGFR3b, murine FGFR3b, human FGFR3c, and dimeric human FGFR3b ecto domain recombinant proteins at 25ºC were analyzed.

[146] Equilibrium dissociation constants (K_D values) for human FGFR3b expressed with a C-terminal myc-myc-hexahistidine tag (hFGFR3b.mmH, REGN3152) or cynomolgus FGFR3b expressed with a C-terminal myc-myc-hexahistidine tag (mfFGFR3b.mmH, REGN3521), or murine FGFR3b expressed with a C-terminal myc-myc-hexahistidine tag (mFGFR3b.mmH, REGN3215) or human FGFR3c expressed with a C-terminal myc-myc-hexahistidine tag (hFGFR3c.mmH, REGN3155) or human FGFR3b expressed with an C-terminal murine Fc tag (hFGFR3b.mFc, REGN3153) binding to purified anti-FGFR3 antibodies were determined using a real-time surface plasmon resonance biosensor technology using a Biacore 3000 or Biacore 4000 instrument. The CM5 Biacore sensor surface was derivatized by amine coupling with a monoclonal mouse anti-human Fc monoclonal antibody (REGN2567). All Biacore binding studies were performed in a buffer composed of 0.01M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.05% v/v Surfactant P20 (HBS-EP running buffer). Different concentrations of

monomeric proteins prepared in HBS-EP running buffer (ranging from 90 nM to 3.33 nM in 3-fold serial dilutions) or dimeric protein (hFGFR3b.mFc, REGN3153) prepared in HBS-EP running buffer (ranging from 30 to 10 nM in 3-fold serial dilution) were injected over the captured anti-FGFR3 antibodies at a flow rate of 30 µL/minute. Antibody-reagent association was monitored for 5 minutes while dissociation in HBS-EP running buffer was monitored for 10 minutes. At the end of each cycle, the anti-FGFR3 antibody capture surface was regenerated using a 10 sec injection of 20 mM phosphoric acid. All binding kinetics experiments were performed at 25°C.

[147] The specific SPR-Biacore sensorgrams were obtained by a double referencing procedure. The double referencing was performed by first subtracting the signal of each injection over a reference surface (anti-hFc) from the signal over the experimental surface (anti-hFc-captured anti-FGFR3 antibodies) thereby removing contributions from refractive index changes. In addition, running buffer injections were performed to allow subtraction of the signal changes resulting from the dissociation of captured antibodies from the coupled anti-hFc surface. Kinetic association (k_a) and dissociation (k_d) rate constants were determined by fitting the real-time sensorgrams to a 1:1 binding model using Scrubber v2.0c curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives (t½) were calculated from the kinetic rate constants as:

$$K_D\ (M) = \frac{kd}{ka}, \quad \text{and} \quad t½\ (min) = \frac{\ln(2)}{60 * kd}$$

[148] Monomeric kinetics results are presented in Tables 1-1 through 1-4. Dimeric kinetic results are presented in Table 1-5.

[149] REGN3152 (human FGFR3b expressed with a C-terminal myc-myc-hexahistidine tag (hFGFR3b.mmH))

ESLGTEQRVVGRAAEVPGPEPGQQEQLVFGSGDAVELSCPPPGGGPMGPTVWVKDGTGLVPSERVLVGPQRLQVLNASHE
DSGAYSCRQRLTQRVLCHFSVRVTDAPSSGDDEDGEDEAEDTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNP
TPSISWLKNGREFRGEHRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSPHRPILQAGLPAN
QTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLKSWISESVEADVRLRLANVSERDGGEYLCRATN
FIGVAEKAFWLSVHGPRAAEEELVEADEAGSVYAGEQKLISEEDLGGEQKLISEEDLHHHHHH (SEQ ID NO: 238)

[150] REGN3153 (human FGFR3b expressed with a C-terminal murine Fc tag (hFGFR3b.mFc))

ESLGTEQRVVGRAAEVPGPEPGQQEQLVFGSGDAVELSCPPPGGGPMGPTVWVKDGTGLVPSERVLVGPQRLQVLNASHE
DSGAYSCRQRLTQRVLCHFSVRVTDAPSSGDDEDGEDEAEDTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNP
TPSISWLKNGREFRGEHRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSPHRPILQAGLPAN
QTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLKSWISESVEADVRLRLANVSERDGGEYLCRATN
FIGVAEKAFWLSVHGPRAAEEELVEADEAGSVYAGEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIV
TCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKP
KGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVE
RNSYSCSVVHEGLHNHHTTKSFSRTPGK (SEQ ID NO: 239)

[151] REGN3215 (murine FGFR3b expressed with a C-terminal myc-myc-hexahistidine tag (mFGFR3b.mmH))

EPPGPEQRVVRRAAEVPGPEPSQQEQVAFGSGDTVELSCHPPGGAPTGPTVWAKDGTGLVASHRILVGPQRLQVLNASHE
DAGVYSCQHRLTRRVLCHFSVRVTDAPSSGDDEDGEDVAEDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSI
SWLKNGKEFRGEHRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSPHRPILQAGLPANQTAI
LGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLKSWISENVEADARLRLANVSERDGGEYLCRATNFIGV
AEKAFWLRVHGPQAAEEELMETDEAGSVYAGEQKLISEEDLGGEQKLISEEDLHHHHHH (SEQ ID NO: 240)

[152] REGN3155 (human FGFR3c expressed with a C-terminal myc-myc-hexahistidine tag (hFGFR3c.mmH))

ESLGTEQRVVGRAAEVPGPEPGQQEQLVFGSGDAVELSCPPPGGGPMGPTVWVKDGTGLVPSERVLVGPQRLQVLNASHE
DSGAYSCRQRLTQRVLCHFSVRVTDAPSSGDDEDGEDEAEDTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNP
TPSISWLKNGREFRGEHRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLERSPHRPILQAGLPAN
QTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLKTAGANTTDKELEVLSLHNVTFEDAGEYTCLAG
NSIGFSHHSAWLVVLPAEEELVEADEAGSVYAGEQKLISEEDLGGEQKLISEEDLHHHHHH (SEQ ID NO: 241)

REGN3521 (mf FGFR3b ecto (R357G)(E23-G377;R357G).mmH)

ESLGTEQRVVGRVAEVSGPEPSQQEQLVFGSGDAVELSCPPPGGGPMGPTVWVKDGAGLVPSERVLVGPQ
RLQVLNASHEDSGAYSCRQRLTQLVLCHFSVRVTDAPSSGDDEDGEDEAEDTGVDTGAPYWTRPERMDKKL
LAVPAANTVRFRCPAAGNPTPSISWLKNGKEFRGEHRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFG
SIRQTYTLDVLERSPHRPILQAGLPANQTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVL
KSWISESVEADVRLRLANVSERDGGEYLCRATNFIGVAEKAFWLSVHGPRAAEEELVEADEAGSVYAGE
QKLISEEDLGGEQKLISEEDLHHHHHH (SEQ ID NO: 242)

Table 1-1. Kinetic and Equilibrium Binding Parameters of Monomeric Human FGFR3b to Surface-captured anti-FGFR3 Antibodies at 25°C

	mAb Capture (RU)	90nM hFGFR3b.mmH Bind (RU)	ka (1/Ms)	kd (1/s)	KD (M)	t1/2 (min)
H4H30045P	584.3 ± 7.5	124.1	3.85E+05	6.24E-03	1.62E-08	1.9
H4H30061P	561.3 ± 8.2	249.2	1.73E+05	8.74E-05	5.06E-10	132.2
H4H30063P	577.0 ± 5.6	240.5	1.72E+05	3.83E-05	2.22E-10	301.9
H4H30066P	486.8 ± 2.9	224.5	4.96E+05	6.35E-04	1.28E-09	18.2
H4H30071P	515.2 ± 7.9	253.0	2.16E+05	2.96E-05	1.37E-10	390.5
H4H30076P	436.8 ± 13.8	198.0	2.36E+05	4.39E-05	1.86E-10	263.3
H4H30089P2	479.7 ± 3.5	152.1	2.76E+05	2.82E-03	1.02E-08	4.1
H4H30093P2	496.4 ± 5.2	217.0	4.06E+05	2.09E-03	5.14E-09	5.5
H4H30095P2	506.5 ± 1.1	239.4	6.98E+05	5.00E-03	7.16E-09	2.3
H4H30102P2	438.3 ± 2.7	134.8	1.68E+05	2.43E-04	1.44E-09	47.5
H4H30105P2	467.9 ± 0.3	157.7	4.38E+05	5.11E-03	1.17E-08	2.3
H4H30108P2	544.3 ± 3.1	227.2	1.76E+05	1.59E-04	9.05E-10	72.6
H4H30117P2	412.2 ± 0.8	177.5	6.56E+05	6.30E-03	9.60E-09	1.8
COMP6331	145.4 ± 3.4	58.38	8.83E+05	6.16E-04	6.97E-10	18.76

* See V_H and V_L set forth in WO2016/134234

REGN6331 Heavy Chain

EVQLVESGGGLVQPGGSLRLSCAASGFTFTSTGISWVRQAPGKGLEWVGRIYPTSGSTNYADSVKGRFTISADTSKNTAY
LQMNSLRAEDTAVYYCARTYGIYDLYVDYTEYVMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 243)

REGN6331 Light Chain

DIQMTQSPSSLSASVGDRVTITCRASQDVDTSLAWYKQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGTDFTLTISSLQP
EDFATYYCQQSTGHPQTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 244)

Table 1-2. Kinetic and Equilibrium Binding Parameters of Monomeric Cynomolgus FGFR3b to Surface-captured anti-FGFR3 Antibodies at 25°C

Ab PID #	mAb Capture (RU)	90nM mfFGFR3b.mmH Bind (RU)	ka (1/Ms)	kd (1/s)	KD (M)	t1/2 (min)
H4H30045P	587.4 ± 1.6	71.9	4.29E+05	8.82E-03	2.06E-08	1.3
H4H30061P	555.8 ± 4.2	197.3	1.51E+05	9.83E-05	6.50E-10	117.5
H4H30063P	574.1 ± 4.8	212.5	1.53E+05	4.21E-05	2.75E-10	274.7
H4H30066P	487.2 ± 3.8	203.2	3.91E+05	7.79E-04	1.99E-09	14.8
H4H30071P	507.6 ± 6.8	233.1	1.80E+05	2.22E-05	1.23E-10	520.3
H4H30076P	437.5 ± 6.9	179.7	2.00E+05	3.30E-05	1.65E-10	350.2
H4H30089P2	486.8 ± 4.6	147.3	2.16E+05	2.21E-03	1.03E-08	5.2
H4H30093P2	499.6 ± 3.1	3.4	NB*	NB*	NB*	NB*
H4H30095P2	509.2 ± 1.7	205.9	5.27E+05	4.37E-03	8.29E-09	2.6
H4H30102P2	442.5 ± 2.0	125.9	1.31E+05	2.30E-04	1.75E-09	50.2
H4H30105P2	468.6 ± 2.4	67.8	5.47E+05	8.02E-03	1.47E-08	1.4
H4H30108P2	543.7 ± 3.1	211.5	1.49E+05	1.36E-04	9.09E-10	85.2
H4H30117P2	413.8 ± 1.4	147.6	5.50E+05	8.70E-03	1.58E-08	1.3
COMP6331	NT**	NT**	NT**	NT**	NT**	NT**

*NB = Non-Binding

**NT = Not Tested

Table 1-3. Kinetic and Equilibrium Binding Parameters of Monomeric Murine FGFR3b to Surface-captured anti-FGFR3 Antibodies at 25°C

Ab PID #	mAb Capture (RU)	90nM mFGFR3b.mmH Bind (RU)	ka (1/Ms)	kd (1/s)	KD (M)	t1/2 (min)
H4H30045P	586.0 ± 2.6	2.4	NB**	NB**	NB**	NB**
H4H30061P	561.0 ± 1.5	-8.5	NB**	NB**	NB**	NB**
H4H30063P	570.0 ± 6.5	259.2	2.04E+05	2.78E-05	1.37E-10	415.5
H4H30066P	486.0 ± 2.9	64.6	2.88E+05	4.87E-03	1.69E-08	2.4
H4H30071P	511.0 ± 3.2	174.3	2.20E+05	1.69E-03	7.65E-09	6.9
H4H30076P	438.1 ± 14.9	201.1	2.56E+05	3.61E-05	1.41E-10	319.7
H4H30089P2	484.0 ± 7.0	60.0	2.81E+05	2.38E-03	8.45E-09	4.9
H4H30093P2	503.8 ± 4.9	11.2	1.36E+05	9.67E-03	7.09E-08	1.2
H4H30095P2	NA*	NA*	NA*	NA*	NA*	NA*
H4H30102P2	NA*	NA*	NA*	NA*	NA*	NA*
H4H30105P2	469.9 ± 0.9	8.3	1.49E+05	1.22E-03	8.19E-09	9.5
H4H30108P2	541.4 ± 3.4	121.1	1.62E+05	1.99E-03	1.23E-08	5.8
H4H30117P2	414.0 ± 1.0	0.9	NB**	NB**	NB**	NB**
COMP6331	NT***	NT***	NT***	NT***	NT***	NT***

* NA: Not Acquired. Technical issue prevented data acquisition and analysis.

**NB = Non-Binding

***NT: Not Tested

Table 1-4. Kinetic and Equilibrium Binding Parameters of Monomeric Human FGFR3c to Surface-captured anti-FGFR3 Antibodies at 25°C

Ab PID #	mAb Capture (RU)	90nM hFGFR3c.mmH Bind (RU)	ka (1/Ms)	kd (1/s)	KD (M)	t1/2 (min)
H4H30045P	583.4 ± 1.4	77.1	3.81E+05	7.46E-03	1.96E-08	1.5
H4H30061P	555.4 ± 4.1	203.8	1.51E+05	7.92E-05	5.26E-10	145.8
H4H30063P	577.8 ± 1.9	-19.6	NB*	NB*	NB*	NB*
H4H30066P	485.8 ± 2.4	0.5	NB*	NB*	NB*	NB*
H4H30071P	519.0 ± 0.5	-4.8	NB*	NB*	NB*	NB*
H4H30076P	435.7 ± 9.9	-9.7	NB*	NB*	NB*	NB*
H4H30089P2	484.6 ± 5.0	-6.7	NB*	NB*	NB*	NB*
H4H30093P2	503.2 ± 4.1	182.1	3.63E+05	3.34E-03	9.20E-09	3.5
H4H30095P2	508.5 ± 0.9	221.8	5.75E+05	4.54E-03	7.88E-09	2.5
H4H30102P2	448.0 ± 0.7	-11.7	NB*	NB*	NB*	NB*
H4H30105P2	469.7 ± 0.8	130.6	3.87E+05	6.52E-03	1.68E-08	1.8
H4H30108P2	541.2 ± 1.9	-2.5	NB*	NB*	NB*	NB*
H4H30117P2	413.7 ± 0.6	165.5	5.95E+05	7.32E-03	1.23E-08	1.6
COMP6331	141.5 ± 3.2	39.56	5.44E+05	1.32E-03	2.42E-09	8.77

*NB = Non-Binding

Table 1-5. Kinetic and Equilibrium Binding Parameters of Dimeric Human FGFR3b to Surface-captured anti-FGFR3 Antibodies at 25°C

Ab PID #	mAb Capture (RU)	30nM hFGFR3b.mFc Bind (RU)	ka (1/Ms)	kd (1/s)	KD (M)	t1/2 (min)
H4H30045P	573.0 ± 4.6	265.5	2.77E+05	1.61E-04	5.81E-10	71.8
H4H30061P	544.3 ± 4.8	259.7	2.31E+05	≤ 1E-5	4.33E-11	≥ 1155
H4H30063P	567.0 ± 7.1	296.1	4.42E+05	≤ 1E-5	2.26E-11	≥ 1155
H4H30066P	484.6 ± 2.2	282.3	6.32E+05	≤ 1E-5	1.58E-11	≥ 1155
H4H30071P	502.2 ± 2.5	235.8	3.22E+05	≤ 1E-5	3.10E-11	≥ 1155
H4H30076P	435.0 ± 2.6	204.1	4.07E+05	≤ 1E-5	2.46E-11	≥ 1155
H4H30089P2	485.6 ± 4.1	213.9	3.12E+05	1.90E-05	6.10E-11	607.9
H4H30093P2	497.8 ± 8.2	316.9	5.85E+05	1.55E-05	2.65E-11	744.7
H4H30095P2	504.5 ± 2.0	404.9	8.67E+05	9.88E-05	1.14E-10	117.0
H4H30102P2	443.7 ± 1.7	131.4	2.97E+05	≤ 1E-5	3.37E-11	≥ 1155
H4H30105P2	NA*	NA*	NA*	NA*	NA*	NA*
H4H30108P2	532.1 ± 3.5	213.0	3.11E+05	≤ 1E-5	3.22E-11	≥ 1155

H4H30117P2	411.4 ± 1.5	337.0	7.87E+05	1.33E-04	1.69E-10	87.0
COMP6331	NT**	NT**	NT**	NT**	NT**	NT**

*NA = Not Acquired. Technical issue prevented data acquisition and analysis

**NT = Not Tested

Example 2: Blocking Assays

[153] Anti-FGFR3 antibodies blocking dimeric human FGFR3b or FGFR3c binding to human FGF acidic or FGF basic by ELISA was analyzed.

Table 2-1. Reagents used

Reagent	Source	Identification
hFGF acidic	R&D Systems	231-BC-025/CF
hFGF basic	Biolegend	571508
hFGFR3c-hFc	R&D Systems	766-FR-050
hFGFR3b-mFc		REGN3153
Human IgG1 negative control antibody (specific for cat allergy antigen - Fel d1)		REGN1932
Human IgG4 negative control antibody (specific for cat allergy antigen - Fel d1)		REGN1945
anti-FGFR3-hIgG1 comparator		REGN6331
Peroxidase AffiniPure Goat Anti-Human IgG, Fcγ fragment specific	Jackson ImmunoResearch	109-035-098
Peroxidase AffiniPure Goat Anti-Mouse IgG	Jackson ImmunoResearch	115-035-164

(subclasses 1+2a+2b+3), Fcγ Fragment Specific		
1X PBS	Irvine Scientific	9236
1X PBST (0.05% tween-20 in PBS)	Sigma	P3563
BSA: albumin solution from bovine serum, 30%	Sigma	A8577-1L
Heparin	Sigma	H4784-1G
3-3', 5-5'-tetramethylbenzidine (TMB) Substrate Reagent Set — Substrate Reagent A	BD Biosciences	51-2606KC
3-3', 5-5'-tetramethylbenzidine (TMB) Substrate Reagent Set — Substrate Reagent B	BD Biosciences	51-2607KC
2N Sulfuric Acid	VWR	BDH7500-1
Reacti-Bind 96-well plates	ThermoFisher Scientific	P15041
96-well deep well plates	VWR	82006-448, 82007-292
96-Well Polypropylene storage microplates	Fisher Scientific	Fisher 12-565-369
Aquamax Plate Washer 2000	Molecular Devices	Aquamax 2000

VICTOR™ X5 Multilabel Plate Reader	PerkinElmer	Model #2030
GraphPad Prism	GraphPad Software	Version 9

[154] An ELISA-based blocking assay was developed to determine the ability of anti-FGFR3 antibodies to block the binding of human fibroblast growth factor receptor 3 isoform b (hFGFR3b) or human fibroblast growth factor receptor 3 isoform c (hFGFR3c) to human fibroblast growth factor acidic (hFGF acidic) or basic (hFGF basic) ligands.

[155] The human FGFR3b recombinant protein used in the experiments had the hFGFR3b extracellular domain (amino acids E23-G377) expressed with the Fc portion of the mouse IgG2a at the C-terminus (amino acids E98-K330) (hFGFR3b-mFc, accession # NM_001163213.1). The hFGFR3c and hFGF acidic proteins were purchased commercially. The human FGFR3c protein had the hFGFR3c extracellular domain (amino acids Glu23-Gly375) expressed with Fc portion of the human IgG1 at the C-terminus (amino acids Pro100-Lys330) (hFGFR3c-hFc, accession # P22607) and the hFGF acidic protein was expressed with amino acids Ala2-Asp155 (accession # P05230.1). The hFGF basic protein was purchased commercially. It was expressed with amino acids Ala144-Ser288 (accession # NM_002006).

[156] In the blocking assay, a 96-well microtiter plate was coated with either hFGF acidic or hFGF basic proteins at 2 mg/ml in PBS + 10 mg/ml heparin overnight at 4°C. Nonspecific binding sites were subsequently blocked using a 0.5% (w/v) solution of BSA + 10 μg/ml heparin in PBS. In other 96-well microtiter plates, a fixed amount of 4 nM hFGFR3b-mFc, 0.4 nM or 7 nM hFGFR3c-hFc was bound for one hour with anti-FGFR3, anti-FGFR3 comparator, or irrelevant human IgG1 or IgG4 isotype antibody at dilutions from 3.4 pM to 200 nM in PBS + 0.5% BSA + 10 μg/ml heparin. The fixed concentration of hFGFR3b or hFGFR3c proteins was selected to be near the concentration that generated 50% of the maximal binding (EC_{50} value) to plate-adhered hFGF acidic or hFGF basic protein. The antibody complexes with 4 nM hFGFR3b-mFc or 0.4 nM hFGFR3c-hFc were transferred to microtiter plates coated with hFGF acidic protein. In parallel, antibody complexes with 7 nM hFGFR3c-hFc were added to the microtiter plates coated with hFGF basic protein. After a 1 hour incubation at room temperature, plates were washed, and plate-bound hFGFR3b-mFc or hFGFR3c-hFc proteins

were detected with horseradish peroxidase (HRP) conjugated goat anti-mouse or goat anti-human Fcγ fragment specific antibodies. The plates were then developed using TMB substrate solution (BD Biosciences) according to the manufacturer's recommended procedure and absorbance at 450 nm was measured on a Victor X5 plate reader.

[157] Binding data were analyzed using a sigmoidal (four-parameter logistic) dose-response model using GraphPad Prism software. The calculated IC_{50} value, defined as the concentration of antibody required to block 50% of hFGFR3b-mFc or hFGFR3c-hFc binding to plate-coated hFGF acidic or hFGF basic protein, was used as an indicator of blocking potency. Percent blocking of FGFR3 antibody at a given concentration was calculated based on the formula shown below.

$$\% \text{ Blocking} = 100 - \left(\frac{[\text{Experimental Signal}_{(\text{highest Ab conc})} - \text{Background Signal}_{(\text{buffer})}}{[\text{Maximum Signal}_{(\text{hFGFR3b-mFc or hFGF3c-hFc})} - \text{Background Signal}_{(\text{buffer})}} \right) X100$$

[158] Antibodies that blocked binding more than 50% at the highest concentration tested were classified as blockers and IC_{50} values were reported.

[159] The ability of anti-FGFR3 antibodies to block human FGFR3b binding to hFGF acidic protein or hFGFR3c binding to hFGF acidic or hFGF basic proteins was evaluated using a sandwich ELISA-based blocking assay. In this assay, a fixed concentration of the hFGFR3b-mFc or hFGFR3c-hFc was pre-incubated with a wide concentration range of anti-FGFR3 antibodies before binding to plate immobilized hFGF acidic or basic proteins, and the plate-bound hFGFR3b-mFc or hFGFR3c-hFc was detected with HRP-conjugated goat anti-mouse or goat anti-human Fcγ fragment specific antibodies, respectively. Six anti-FGFR3 antibodies were evaluated for inhibition of hFGFR3b-mFc binding to hFGF acidic protein. Antibody H4H30093P2, which also binds hFGFR3c, was additionally tested for inhibition of hFGFR3c-hFc binding to hFGF acidic or hFGF basic proteins. The IC_{50} values and maximum blocking at the highest tested concentrations of the FGFR3 antibodies are summarized in Table 2-2.

[160] All six anti-FGFR3 antibodies (H4H30063P, H4H30066P, H4H30071P, H4H30089P2, H4H30093P2 and H4H30102P2) displayed concentration-dependent blocking of hFGFR3b-mFc binding to hFGF acidic protein with the extent of block ranging from 68% to 95% at the highest antibody concentration tested (200 nM). The IC_{50} values for these blocking antibodies ranged from 2 nM to 15 nM. Antibody H4H30093P2 displayed less than 50% blocking of the binding of hFGFR3c to hFGF acidic or hFGF basic at the highest antibody concentration

tested and was classified as a non-blocker for hFGFR3c. The anti-FGFR3 comparator antibody blocked the binding of hFGFR3b to hFGF acidic with an IC_{50} of 1.5 nM, and binding of hFGFR3c binding to hFGF acidic or hFGF basic with an IC_{50} of 0.1 nM and 8.9 nM, respectively. The human IgG1 or IgG4 isotype control antibodies did not block in any assays.

Table 2-2. IC_{50} values and maximum blocking at the highest tested concentrations of the FGFR3 antibodies

Antibody	Antibody blocking 4nM hFGFR3b-mFc binding to hFGF acidic protein		Antibody blocking 0.4nM hFGFR3c-hFc binding to hFGF acidic protein		Antibody blocking 7nM hFGFR3c-hFc binding to hFGF basic protein	
	IC_{50}, M	% Blocking at 200 nM mAb	IC_{50}, M	% Blocking at 200 nM mAb	IC_{50}, M	% Blocking at 200 nM mAb
H4H30063P	2.0E-09	95	ND	ND	ND	ND
H4H30066P	3.2E-09	90	ND	ND	ND	ND
H4H30071P	3.6E-09	88	ND	ND	ND	ND
H4H30089P2	1.5E-08	68	ND	ND	ND	ND
H4H30093P2	2.5E-09	91	Nbl	-7	Nbl	-15
H4H30102P2	2.5E-09	92	ND	ND	ND	ND
hIgG4 isotype control	Nbl	14	Nbl	16	Nbl	-5
anti-FGFR3-hIgG1 comparator (*)	1.5E-09	99	1.0 E-10	86	8.9E-09	87
hIgG1 isotype control (*)	Nbl	-7	Nbl	14	Nbl	-20

Nbl: Non-blocking, % blocking is less than or equal to 50

ND: Not determined

(*) anti-FGFR3-hIgG1 comparator and hIgG1 isotype control were tested in a separate experiment for blocking of hFGFR3b binding to hFGF acidic protein or hFGFR3c binding to hFGF basic protein

Example 3: Octet cross-competition analysis of anti-FGFR3 antibodies

[161] Binding competition between anti-FGFR3 monoclonal antibodies that had been previously determined to bind to hFGFR3b.mmH was determined using a real time, label-free bio-layer interferometry (BLI) assay on an Octet HTX biosensor (ForteBio Corp., A Division of Pall Life Sciences). The entire experiment was performed at 25°C in buffer comprised of 0.01 M HEPES pH7.4, 0.15 M NaCl, 3 mM EDTA, 0.05% v/v Surfactant P20, 0.1 mg/mL BSA (Octet HBS-EP buffer) with the plate shaking at a speed of 1000rpm. To assess whether two antibodies were able to compete with one another for binding to hFGFR3b ecto domain expressed with a C-terminal myc-myc-histidine tag (hFGFR3b.mmH, REGN3152) approximately 0.2 nm of hFGFR3b.mmH was first captured onto anti-penta-His antibody coated Octet biosensors (Fortebio Inc, # 18-5079) by submerging the biosensors for 23 seconds into wells containing a 20 µg/mL solution of hFGFR3b.mmH. The antigen-captured biosensors were then saturated with the first anti-FGFR3 monoclonal antibody (subsequently referred to as mAb-1) by immersion into wells containing a 50 µg/mL solution of mAb-1 for 5 minutes. The biosensors were then subsequently submerged into wells containing a 50 µg/mL solution of a second anti-FGFR3 monoclonal antibody (subsequently referred to as mAb-2) for 3 minutes. The real-time binding response was monitored during the course of the experiment and the binding response at the end of every step was recorded. The response of mAb-2 binding to hFGFR3b.mmH pre-complexed with mAb-1 was compared and the competitive or non-competitive property of an anti-FGFR3 monoclonal antibody toward another antibody was determined using a 50% inhibition threshold. Table 3-1 summarizes cross-competing antibodies which competed binding to hFGFR3b.mmH independent of the order of the sequential binding of mAb-1 and mAb-2.

Table 3-1. Cross-competition of anti-FGFR3 antibodies for binding to hFGFR3b.mmH.

First mAb (mAb-1) captured using AHC Octet Biosensors	mAb-2 Antibodies Shown to Compete with mAb-1

H4H30045P	H4H30045P
	H4H30095P2
H4H30061P	H4H30093P2
	H4H30061P
H4H30063P	H4H30063P
	H4H30076P
H4H30066P	H4H30089P2
	H4H30108P2
	H4H30071P
	H4H30102P2
	H4H30066P
H4H30071P	H4H30089P2
	H4H30108P2
	H4H30071P
	H4H30102P2
	H4H30066P
H4H30076P	H4H30063P
	H4H30076P
	H4H30089P2
H4H30089P2	H4H30076P
	H4H30089P2
	H4H30108P2
	H4H30071P
	H4H30102P2
	H4H30066P
H4H30093P2	H4H30093P2
	H4H30061P
H4H30095P2	H4H30045P
	H4H30095P2
	H4H30105P2
	H4H30117P2
H4H30102P2	H4H30089P2
	H4H30108P2
	H4H30071P
	H4H30102P2
	H4H30066P
H4H30105P2	H4H30095P2
	H4H30105P2
	H4H30117P2
H4H30108P2	H4H30089P2
	H4H30108P2
	H4H30071P

	H4H30102P2
	H4H30066P
H4H30117P2	H4H30095P2
	H4H30105P2
	H4H30117P2

Example 4: Characterization of FGFR3 antibodies in cell growth assays using engineered BaF3 cells overexpressing human FGFR3 WT or FGFR3-S249C mutant receptor.

[162] The ability of anti-FGFR3 antibodies to block FGFR3 signaling was evaluated using a proliferation assay using an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express human fibroblast growth factor receptor 3b wild-type or mutant S249C.

[163] FGFR3 antigen binding molecules and the controls tested in this experiment are as shown in Table 4-1.

Table 4-1. FGFR3b Binding Molecules and Controls

mAb Identifier	Description
H4H30063P	FGFR3b mAb, hIgG4^{P}
H4H30102P2	FGFR3b mAb, hIgG4^{P}
REGN6331	Relates to FGFR3b mAb, hIgG1 (mAb 184.6.1 N54S, Genentech)
REGN1932	Anti-FelD1, Isotype control, hIgG1
REGN1945	Anti-FelD1, Isotype control, hIgG4^{P}

Cell Lines:

- BAF3/FGFR3b (ACL11991): IL-3 dependent murine pro B cell line, engineered to stably express full length human FGFR3b, (accession number NP_001156685.1, amino acids M1-T808). Cells are maintained in RPMI 1640 + 10% FBS + P/S/G + 1ng/ml mouse IL-3 + 500 ug/ml Neomycin; 37°C 5% CO_2.
- BAF3/FGFR3b_S249C (ACL11986): IL-3 dependent murine pro B cell line, engineered to stably express full length human FGFR3b, (accession number NP_001156685.1, amino acids M1-T808, S249C). Cells are maintained in RPMI 1640 + 10% FBS + P/S/G + 1 ng/ml mouse IL-3 + 500 ug/ml Neomycin; 37°C 5% CO_2.

[164] The FGFR3 receptor is a member of the receptor tyrosine kinase (RTK) family, which regulates cell proliferation, survival, differentiation and migration of multicellular organisms. The activation of the wild-type (WT) receptor occurs via binding of its soluble ligand, *e.g.*, FGF1, which drives the homo-dimerization and autophosphorylation of FGFR3, leading eventually to the activation of a plethora of intracellular signaling cascades such as Ras/MAPK, PLCγ1/PKC, PI3-kinase/Akt, and STAT pathways (Xie *et al.*, FGF/FGFR signaling in health and disease, Signal Transduction and Targeted Therapy (2020) 5:181). Mutations in FGFR3, leading to aberrant FGFR3 activation, have been associated with numerous types of human malignancies. The mutation, S249C, leads to constitutive, ligand independent, FGFR3 activation (Tomlinson *et al.*, Knockdown by shRNA identifies S249C mutant FGFR3 as a potential therapeutic target in bladder cancer, Oncogene. 2007 August 30; 26(40): 5889–5899).

[165] To study the blocking effects of anti-FGFR3b antibodies on signaling, a proliferation assay was deployed using an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express human fibroblast growth factor receptor 3b wild-type or mutant S249C (FGFR3b – accession number NP_001156685.1, amino acids M1-T808) (Kong *et al.*, Ba/F3 transformation assays, Oncotarget, 2017, Vol. 8, (No. 22), pp: 35488-35489)). Engineered BaF3/FGFR3b cells were stimulated with ligand (human FGF1) in the presence of titrated antibodies and cell growth was evaluated using CellTiter-Glo which measures ATP, a product of viable, proliferating cells.

[166] Engineered BaF3/hFGFR (WT or S249C) cells grown in culture medium (RPMI1640 + 10% FBS + Penicillin/Streptomycin/L-Glutamine + 1 ng/mL mouse IL-3 + 500 ug/mL Neomycin) were washed and plated in IL-3-free culture media containing 5 ug/ml heparin and 1 nM human FGF1. Cells were plated out at 10^5 cells/well into 96-well white tissue culture plates, followed by the addition of 1:4 serially diluted antibodies, ranging from 1.5 pM to 100 nM including a no antibody containing control (plotted at 0.4 pM). After addition of antibodies, the 96-well white microtiter plates were incubated at 37°C/5% CO_2 for 72 h followed by the addition of an equal volume of CellTiter-Glo™ (Promega) reagent to lyse cells and detect luciferase activity. The emitted light was captured in Relative Light Units (RLU) on a multi-label plate reader Envision (PerkinElmer). EC_{50} values of the antibodies were determined from a 4-parameter logistic equation over a 10-point dose response curve (the 10th point containing no antibody) using GraphPad Prism software.

[167] Anti-FGFR3b antibodies, H4H30063P and H4H30102P2, were tested alongside comparator antibody, REGN6331, and isotype matched negative controls in the presence of 1 nM FGF1 and 5 ug/ml heparin (see Table 4-2 and Figure 1).

[168] Anti-FGFR3b antibodies, H4H30063P and H4H30102P2, and their corresponding matched isotype control, REGN1945, were tested alongside comparator antibody REGN6331 and isotype matched control, REGN1932, in the presence of 1 nM FGF1 + 5 ug/ml heparin. It was observed that, in experiments using BaF3/hFGFR3b WT cell lines, antibodies H4H30063P and REGN6331 exhibited a similar level of maximal inhibition of proliferation, whereas antibody H4H30102P2 did not reach the same level of maximum inhibition. The degree of ligand mediated growth in BaF3/FGFR3_S249C cells was minimal due to the S249C mutation leading to constitutive FGFR3b activity. Nonetheless, ligand addition led to slight enhancement of proliferation, which can be inhibited to similar maximum levels by antibodies H4H30063P and REGN6331, while H4H30102P2 led to minimal inhibition with non-calculatable IC_{50} values.

Table 4-2: Maximum Inhibition and Potency values of Antibodies

	Max Blocking (%)[a]		IC50 [M]	
MABM Identifier	**BAF3/FGFR3b**	**BAF3/FGFR3b_S249C**	**BAF3/FGFR3b**	**BAF3/FGFR3b_S249C**
H4H30063P	98.01	93.36	6.06E-10	5.08E-10
H4H30102P2	41.07	34.55	1.86E-08	NC
REGN6331	97.60	109.56	5.79E-11	1.22E-11
REGN1945	ND	ND	ND	ND
REGN1932	NC	NC	NC	NC

[a] Maximal Blocking is given as the mean maximum blocking detected within the tested dose range.

Abbreviations: ND: Not Determined; NC: Not Calculated; a potency value could not be determined by PRISM

$$\text{Blocking} = 100 - \left(\frac{\text{Mean RLU at 100nM mAb - RLU No Ligand}}{\text{Mean RLU at 0nM mAb - RLU No Ligand}} \times 100 \right)$$

Example 5: Characterization of mechanism of action of FGFR3 antibodies

[169] Assays evaluating the following were performed: (1) Inhibition of FGFR3 S249C dimerization using bladder cancer cell line UMUC14 with endogenous FGFR3 S249C mutation; and (2) Inhibition of FGF1/heparin induced downstream signaling in BaF3 cell expressing wild-type FGFR3.

Cell Lines:

- UMUC14 (Sigma-Aldrich): Cells are maintained in MEM + 1% Non-Essential Amino Acids (NEAA) 10% FBS + P/S; 37°C 5% CO_2.
- BAF3/FGFR3b (ACL11991): IL-3 dependent murine pro B cell line, engineered to stably express full length human FGFR3b, (accession number NP_001156685.1, amino acids M1-T808). Cells are maintained in RPMI 1640 + 10% FBS + P/S/G + 1 ng/ml mouse IL-3 + 500 ug/ml Neomycin; 37°C 5% CO_2

Reagents:

- rhFGF Acidic, R&D Systems, cat 232-FA, reconstituted at 100 mg/ml in PBS/0.1% BSA
- Heparin sodium salt from porcine intestinal mucosa, Sigma Aldrich, cat H3393-100KU, reconstituted at 50 mg/ml in H_2O
- FGFR3 (B-9), Santa Cruz Biotechnology, cat sc-13121
- ECL Anti-Mouse IgG Horseradish Peroxidase Linked Whole Antibody (from sheep) GPR, cat NXA934V,
- SuperSignal West Pico PLUS Chemiluminescent Substrate, Thermo Scientific, cat 34578,
- Cell Lysis Buffer(10x), Cell Signaling Technology, cat 9803.
- Phospho-p44/42 MAPK(Erk1/2). Cell Signaling Technology, cat 4370.
- p44/42 MAPK(Erk1/2). Cell Signaling Technology, cat 4695.
- Goat anti-rabbit IgG (H+L), HRP-linked Antibody. Seracare, Cat no 5450-0010

[170] For the receptor dimerization assay, UMUC14 bladder cancer cells were seeded in 6 well tissue culture plate (Corning) in complete medium (MEM medium with 10% FBS, 1% Non Essential Amino Acids, Pen/Strep) and cultured overnight at 37°C 5% CO_2. Cells were then serum starved overnight in starvation medium (MEM medium with 0.5% FBS, Pen/Strep) followed by antibody treatment for 3 hrs at indicated dose. Cells were washed with pre-chilled PBS and collected in lysis buffer containing protease inhibitors. Equal amount of cell lysate were analyzed by either reducing or non-reducing SDS-PAGE. Blots were blocked in 0.5% Tween 20 in Tris buffered saline (TBS) containing 5% non-fat dry milk followed by overnight incubation with anti-FGFR3 primary antibody (Santa Cruz). After washing 3x with TBST and

incubation with secondary antibody, membranes were developed with SuperSignal West Pico or Femto substrate and luminescence images were captured with a C300 imager (Azure Biosystems).

[171] To test the effects of anti-FGFR3 antibody on ligand-induced signaling, an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express wild-type human fibroblast growth factor receptor 3b was used. Engineered BaF3/FGFR3b cells were incubated overnight in starvation medium (RPMI1640 + Penicillin/Streptomycin/L-Glutamine + 1 ng/mL mouse IL-3). After starvation, cells were either untreated or pretreated with 100 nM antibodies for 3 hrs followed by ligand (human 100 ng/ml FGF1 and 10 mg/ml heparin) stimulation for 10 min at 37°C. See Figure 3. Cells were lysed in lysis buffer and equal amount of cell lysates were analyzed by SDS-PAGE. Blots were incubated with pMAPK or MAPK antibody overnight followed by incubation with anti-rabbit HRP 2nd antibody. Membranes were developed with SuperSignal West Pico or Femto substrate and luminescence images were captured with a C300 imager (Azure Biosystems).

[172] Antibody H4H30063P exhibited dose dependent inhibition of FGFR3 S249C dimerization and stronger inhibition of receptor dimerization than comparator antibody REGN6331. See Figure 2. In addition, H4H30063P decreased FGF1/Hep stimulation-dependent phosphorylation of MAPK. See Figure 3.

Example 6: Characterization of FGFR3 antibodies in cancer cell spheroid proliferation assays using bladder cancer cell line UMUC14 with endogenous FGFR3 S249C mutation.

[173] Anti-FGFR3 antibody-mediated inhibition of cancer cell proliferation was evaluated.

Cell Lines

- UMUC14 (Sigma-Aldrich): Cells are maintained in MEM + 1% Non-Essential Amino Acids (NEAA) 10% FBS + P/S; 37°C 5% CO_2.

Reagents

Corning Spheroid Microplate 96 Well, Corning, cat# 4520

CellTiter-Glo 3D Cell Viability Assay, Promega, cat# G9682

[174] 7500 UMUC14 bladder cancer cells were seeded in U-bottom low attachment 96-well spheroid plate (Corning) in culture medium (MEM medium with 10% FBS, 1% Non-Essential Amino Acids, Pen/Strep). Cells were cultured for 48 hours at 37°C 5% CO_2 to allow tumor spheroid formation. Tumor spheroids were treated with antibodies at concentration ranging from 100 nM to 15.2 pM with 1:3 serial dilution as indicated in the figure. Cells were cultured for 5-6 days, and then subjected to CellTiter-Glo 3D viability assays (Promega) following the manufacturer's protocol. Luminescence signal was read on SpectraMax M3 plate reader. Cell proliferation was expressed as percentages of untreated controls. Data were analyzed using GrasphPad Prism software using three parameter nonlinear curve fit.
[175] H4H30063P exhibited stronger inhibition of proliferation than antibody H4H30071P and comparator antibody REGN6331. See Figure 4.

Example 7: *In vivo* characterization of FGFR3 antibodies in tumor growth inhibition assays using xenograft model of bladder cancer cell line UMUC14 with endogenous FGFR3 S249C mutation.
[176] Inhibition of bladder cancer cell line growth in a mouse xenograft model exposed to anti-FGFR3 antibody was evaluated in this example.

Cell Lines

- UMUC14 (Sigma-Aldrich): Cells are maintained in MEM + 1% Non-Essential Amino Acids (NEAA)+10% FBS + P/S; 37°C 5% CO_2.

Reagents
Matrigel Basement Membrane Matrix. Corning, cat# 354234, lot: 8085009

[177] Tumor cells (5 × 10^6 UMUC14 in 50% Matrigel, 100 ul) were implanted subcutaneously into the right flank of 6 to 8-week-old female SCID mice (Jackson Laboratory). Once tumors were established (~200 mm^3 in volume), mice were randomized into treatment groups (n = 10 mice per group) and injected intraperitoneally twice per week with anti-FGFR3 antibodies or isotype control at 3 or 10 mg/kg. Tumor volume was expressed in mm^3 using the formula: V = 0.5 x a x b^2 where a and b were the long and short diameters of the tumor, respectively. All data were analyzed using GraphPad Prism and tumor sizes were graph as mean ± SEM.

[178] H4H30063P exhibited stronger tumor growth inhibition than comparator antibody REGN6331 in UMUC14 xenograft model with endogenous expression of FGFR3 S249C mutation. See Figure 5.

Example 8: Effect of FGFR3 oncogenic signaling on CD73 expression.

[179] The effects of FGFR3 mutations and inhibitors of FGFR3 on the expression of CD73 was evaluated.

Cell Lines:

- UMUC14 (Sigma-Aldrich): Cells are maintained in MEM + 1% Non-Essential Amino Acids (NEAA) 10% FBS + P/S; 37°C 5% CO_2
- Fadu EV and S249C Cells are maintained in MEM + 10% FBS + Pen/Strep + 400 ug/ml Neomycin; 37°C 5% CO_2

Reagents:

- FGFR-3 (B-9), Santa Cruz Biotechnology, Cat# sc-13121
- NTSE/CD73(D7F9A) Rabbit mAb; Cell Signaling Technology. Cat# 13160
- Goat anti-rabbit IgG (H+L), HRP-conjugated, Seracare, Cat# 5450-0010
- Peroxidase Anti-Mouse IgG(H+L), Vector Laboratories, Cat# PI-2000
- SuperSignal West Pico PLUS chemiluminescent substrate, Thermo Scientific, Cat# 34578
- SuperSignal West Femto Maximum Substrate, Thermo Scientific, Cat#34096
- Cell Lysis Buffer(10x), Cell Signaling Technology, Cat# 9803
- RIPA buffer, Sigma Aldrich, Cat# R0278
- Matrigel, Corning, Cat# 354234

[180] To investigate the effect of anti-FGFR3 antibody or tyrosine kinase inhibitor (AZD4547; commercially available) on CD73 expression, UMUC14 bladder cancer cells were seeded in 6 well tissue culture plate (Corning) in complete medium (MEM medium with 10% FBS, 1% Non-Essential Amino Acids, Pen/Strep) and cultured overnight at 37°C 5% CO_2. Cells were then treated with antibodies or inhibitors at indicated concentration (100 nM, 10 nM or 1 nM) for 48 hrs. Cells were washed with pre-chilled PBS and collected in lysis buffer containing protease and phosphatase inhibitors. Equal amount of cell lysates were analyzed by SDS-PAGE. Blots

were blocked in 0.5% Tween 20 in Tris buffered saline (TBS) containing 5% non-fat dry milk followed by overnight incubation with anti-CD73 primary antibody (Cell Signaling Technology). After washing 3x with TBST and incubation with secondary antibody, membranes were developed with SuperSignal West Pico or Femto substrate and luminescence images were captured with a C300 imager (Azure Biosystems).

[181] To test the effect of FGFR3 oncogenic signaling on CD73 expression *in vivo*, 3×10^6 Fadu cells expressing FGFR3 oncogenic mutation (S249C or FGFR3-TACC3) or empty vector control (EV) were implanted subcutaneously into the right flank of 6 to 8-week-old female SCID mice (Jackson Laboratory). ~16 day post implantation, tumors were collected, snap frozen and lysed in RIPA buffer. Equal amount of tumor lysates were analyzed by SDS-PAGE and blotted with anti-CD73 and anti-FGFR3 antibodies as described above.

[182] To test the effect of anti-FGFR3 inhibitory antibody or tyrosine kinase inhibitor (AZD4547) on CD73 expression *in vivo*, tumor cells (5×10^6 UMUC14, 3×10^6 Fadu EV or S249C, in 50% Matrigel) were implanted subcutaneously into the right flank of 6 to 8-week-old female SCID mice (Jackson Laboratory). Once tumors were established (~200 mm^3 in volume), mice were randomized into treatment groups (n =5-6 mice per group) and injected intraperitoneally once with anti-FGFR3 antibodies (15 mg/kg) or isotype control. Tyrosine kinase inhibitor AZD4547 (25mg/kg) was administered once daily by oral gavage for 3 days. Tumors were collected 4 days post treatment initiation. Tumors were collected, snap frozen and lysed in RIPA buffer. Equal amount of tumor lysates were analyzed by SDS-PAGE and blotted with anti-CD73 and anti-FGFR3 antibodies as described above. Membranes were developed with SuperSignal West Pico or Femto substrate and luminescence images were captured with a C300 imager (Azure Biosystems). Intensity of each CD73 and actin band was quantitated using Image J (NIH), and the ratio of CD73/actin for each sample were graphed using Prism Graphpad.

[183] *Downregulation of CD73 protein level in response to FGFR3 inhibition in UMUC14 cells in vitro*. As shown in Figure 6, both anti-FGFR3 inhibitory antibody and the pan-FGFR tyrosine kinase inhibitor (AZD4547) demonstrated dose dependent downregulation of CD73 expression. CD73 band intensity on the blot decreased as molar concentration of each agent increased from 1 nM to 100 nM.

[184] *Downregulation of CD73 protein level in response to FGFR3 inhibition in UMUC14 cells in vivo*. CD73 band intensity decreased with increasing anti-FGFR3 antibody concentration in

the blot. See Figure 7. The band intensity of CD73/actin is graphically summarized in Figure 8.

[185] *FGFR3 activation is sufficient to induce CD73 expression.* As demonstrated in the blot of Figure 9, *in vitro* cells expressing constitutively active FGFR3 mutants without ligand-induced activation exhibited increased expression of CD73 relative to control and wild-type FGFR3.

[186] *Upregulation of CD73 expression in Fadu tumors engineered to express FGFR3 S249C mutant or FGFR3-TACC3 fusion.* Expression of CD73 in Fadu tumors expressing empty vector (EV; Figure 10 (A)) exhibited little or no activation of CD73 expression, whereas tumors expressing S249C (Figure 10 (B)) or FGFR-TACC3 (Figure 10 (C)) FGFR3 mutants exhibited increased CD73 expression.

[187] *Downregulation of CD73 protein level in response to FGFR3 inhibition in Fadu S249C tumors in vivo.* Mice having FADU tumors, expressing FGFR3 S249C mutants, treated with one dose intraperitoneal injection of FGFR3 mAb (15 mg/kg) or daily gavage of AZD4547 (25 mg/kg) exhibited decreased expression of CD73 relative to mice treated with control. The CD73 band intensity in blot shown in Figure 11 (A) was quantitated in the graph of Figure 11 (B).

Example 9: Antibody inhibition of proliferation of BaF3 cell expressing TKI resistant mutations.

[188] IL-3 dependent murine pro B cell line BaF3 cells were engineered to stably express full length human FGFR3b S249C, V557L, V557M, S249C/V557L, S249C/V557M (accession number for WT FGFR3b NP_001156685.1, amino acids M1-T808). Cells were maintained in RPMI 1640 + 10% FBS + P/S/G + 1ng/ml mouse IL-3 + 500ug/ml Neomycin; 37°C 5% CO_2. For proliferation assays, cells were washed with IL-3-free culture media and plated at 10^5 cells/well into 96-well black wall tissue culture plates. Cells were treated with 1:3 serially diluted antibody as indicated in the presence or absence of 5µg/ml heparin and 1nM human FGF1. After addition of antibodies, cells were incubated at 37°C/5% CO_2 for 72 h followed by the addition of an equal volume of CellTiter-Glo™ (Promega) reagent to lyse cells and detect luciferase activity. Luminescence signal was quantitated with Envision plate reader (PerkinElmer). EC50 values of the antibodies were determined using GraphPad Prism software.

[189] Acquired resistance to FGFR TKIs has been reported and it is frequently associated with secondary mutations in the kinase domain (Facchinetti F et al AACR 2023, abstract 3458, Chell V et al Oncogene 2013). One of the resistance mutation hotspots that appears to drive disease progression is the gatekeeper mutation V555M/L. To test the efficacy of the FGFR3 antibodies in the context of TKI resistance mutations, BaF3 cell lines were generated expressing FGFR3 S249C with or without the gatekeeper mutation V557M or V557L. The pan-FGFR TKIs AZD4547 and erdafitinib potently inhibited the growth of BaF3 cells expressing FGFR3 S249C (IC50 9.9 nM and 1.2 nM, respectively), but were ineffective in cells expressing FGFR3 that contains V557M/L mutation alone or both the S249C and V557M/L mutations. In contrast, FGFR3 antibody H4H30063P was able to strongly inhibit the growth of BaF3 cells expressing the double mutant FGFR3 (S249C plus V557M or L). The IC50 values for H4H30063P against S249C, S249C/V557M, and S249C/V557L were 1.36 nM, 3.9 nM, and 4.3 nM, respectively. See Figure 12.

Example 10: Hydrogen/Deuterium Exchange (HDX) Epitope Mapping.

[190] HDX experiment was performed using a customized HDX automation system (NovaBioAssays, MA) coupled to a Q Exactive HF mass spectrometer (Thermo Fisher Scientific, MA). Figure 21 shows an exemplary HDX-Mass Spectrometry experimental process.

[191] To initiate deuterium exchange, 10 µL of protein sample (hFGFR3b.mmh alone or hFGFR3b.mmh in mixture with H4H30117P2, H4H30063P, H4H30045P, or H4H30108P2 at 2:1 ratio) was diluted with 90 µL PBS-D2O buffer (10mM, pH 7.4 at 25°C). After 5 or 10 min, deuterium exchange was quenched by adding 100 µL quenching buffer (0.5 M TCEP, 4 M guanidine hydrochloride, pH 2.08) followed by 90 seconds incubation at 20 °C. The quenched samples were digested by online pepsin/protease XIII column at room temperature (NovaBioAssays, MA) with 100 µL/min 0.1% formic acid in water. Peptic peptides were trapped by an ACQUITY UPLC Peptide BEH C18 VanGuard Pre-column (2.0 x 5 mm, Waters, MA) and further separated by an ACQUITY UPLC Peptide BEH C18 column (2.0 x 50 mm, Waters, MA) at -5 °C, using a 15-min gradient with 0.1% formic acid in water and 0.1% formic acid in acetonitrile as mobile phases at 200 µL/min. Eluted peptides were analyzed by the Q Exactive HF mass spectrometry in LC-MS/MS or LC-MS mode.

[192] Deuterium uptake percentage (D%) of individual peptides was calculated. Differences in deuterium uptake were calculated as ΔD% = D% of hFGFR3b-antibody - D% of hFGFR3b.

Differences were considered significant if |ΔD| > 5% (averaged from 2 replicates). Mass spectra of peptides showing significant differences were confirmed manually.

[193] HDX epitope mapping results for anti-FGFR3b antibodies H4H30117P2, H4H30063P are shown in Figure 13. HDX epitope mapping results for anti-FGFR3b antibodies H4H30045P and H4H30108P2 are shown in Figure 14. HDX protection of FGFR3 by anti-FGFR3b antibodies H4H30063P Fab and H4H30117P2 scFv are shown in Figure 15. HDX epitope mapping of FGFR3 antibodies is shown in Figure 16 (A-B). As shown in the structures, the epitopes comprise segments of peptides, forming a continuous surface patch for interaction. The epitopes are likely conformational epitopes.

[194] HDX epitope mapping results for H4H30063P are shown in Figure 17. HDX epitope mapping results for H4H30108P2 are shown in Figure 18. HDX epitope mapping results for H4H30117P2 are shown in Figure 19. HDX epitope mapping results for H4H30045P are shown in Figure 20.

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[195] All references cited herein are incorporated by reference to the same extent as if each individual publication, database entry (*e.g.*, Genbank sequences or GeneID entries), patent application, or patent, was specifically and individually indicated to be incorporated by reference. This statement of incorporation by reference is intended by Applicants to relate to each and every individual publication, database entry (*e.g.*, Genbank sequences or GeneID entries), patent application, or patent, each of which is clearly identified in even if such citation is not immediately adjacent to a dedicated statement of incorporation by reference. The inclusion of dedicated statements of incorporation by reference, if any, within the specification does not in any way weaken this general statement of incorporation by reference. Citation of the references herein is not intended as an admission that the reference is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

We claim:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising: a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 2, 22, 42, 62, 82 ,102, 122, 140, 159, 169, 179, 199 or 219 and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 10, 30, 50, 70, 90, 110, 130, 148, 187, 207, or 227.

2. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising:
(a) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 2, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 10,
(b) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 22, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 30,
(c) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 42, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 50,
(d) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 62, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 70,
(e) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 82, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 90,

(f) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 102, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 110,
(g) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 122, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 130,
(h) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 140, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 148,
(i) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 159, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 148,
(j) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 169, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 148,
(k) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 179, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 187,
(l) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 199, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 207,
and/or
(m) a heavy chain variable region (HCVR) that comprises the HCDR1, HCDR2 and HCDR3 of a HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 219, and a light chain variable region (LCVR) that comprises the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 227.

3. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising:

(a) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 4, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 6, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 8, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 16;

(b) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 24, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 26, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 28, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 32, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 36;

(c) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 44, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 46, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 48, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 52, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 54, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 56;

(d) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 64, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 66, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 68, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 72, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 74, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 76;

(e) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 84, an HCDR2 that comprises the amino acid sequence set

forth in SEQ ID NO: 86, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 88, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 92, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 94, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 96;

(f) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 104, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 106, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 108, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 112, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 114, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 116,

(g) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 124, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 126, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 128, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 132, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 134;

(h) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 142, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 144, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 146, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153;

(i) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 161, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 163, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 165, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153;

(j) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 171, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 173, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 175, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 150, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 14, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 153;
(k) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 181, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 183, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 185, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 189, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 191, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 193;
(l) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 201, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 203, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 205, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 209, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 211, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 213;
and/or
(m) a heavy chain variable region that comprises an HCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 221, an HCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 223, and an HCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 225, and a light chain variable region that comprises an LCDR1 that comprises the amino acid sequence set forth in SEQ ID NO: 32, an LCDR2 that comprises the amino acid sequence set forth in SEQ ID NO: 34, and an LCDR3 that comprises the amino acid sequence set forth in SEQ ID NO: 76.

4. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 2, 22, 42, 62, 82, 102, 122, 140, 159, 169, 179,

199 or 219, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10, 30, 50, 70, 90, 110, 130, 148, 187, 207, or 227.

5. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising:
(a) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 2, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
(b) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 22, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 30;
(c) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 42, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 50;
(d) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 62, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 70;
(e) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 82, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90;
(f) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 102, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 110;
(g) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 122, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 130;
(h) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 140, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148;
(i) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 159, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148;

(j) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 169, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 148;
(k) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 179, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 187;
(l) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 199, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 207;
and/or
(m) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 219, and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 227.

6. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising (a) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 18, 38, 58, 78, 98, 118, 136, 155, 167, 177, 195, 215 or 229, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 20, 40, 60, 80, 100, 120, 138, 157, 197, 217, or 231.

7. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof comprising:
(a) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 18, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 20;
(b) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 38, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 40;
(c) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 58, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 60;
(d) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 78, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 80;
(e) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 98, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 100;

(f) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 118, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 120;
(g) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 136, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 138;
(h) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 155, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157;
(i) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 167, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157;
(j) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 177, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 157;
(k) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 195, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 197;
(l) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 215, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 217;
and/or
(m) a heavy chain that comprises the amino acid sequence set forth in SEQ ID NO: 229, and a light chain that comprises the amino acid sequence set forth in SEQ ID NO: 231.

8. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof, wherein the antibody or antigen-binding fragment binds to the same FGFR3 epitope as or competes for binding to FGFR3 with the antibody or antigen-binding fragment of any one of claims 1-7.

9. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to one or more epitopes of FGFR3 selected from:

a. an epitope comprising the sequence GPTVWVK (SEQ ID NO: 260) and/or an epitope comprising the sequence TQR;

b. an epitope comprising the sequence ADVR (SEQ ID NO: 258) and/or an epitope comprising the sequence IGVAEK (SEQ ID NO: 259);

c. an epitope comprising the sequence HCKVY (SEQ ID NO: 261), and/or an epitope comprising the sequence KSWISE (SEQ ID NO: 262), and/or an epitope comprising the sequence ADVR (SEQ ID NO: 258);

d. an epitope comprised within or overlapping with the sequence GPTVWVK (SEQ ID NO: 260) and/or an epitope comprised within or overlapping with the sequence TQR;

e. an epitope comprised within or overlapping with the sequence ADVR (SEQ ID NO: 258) and/or an epitope comprised within or overlapping with the sequence IGVAEK (SEQ ID NO: 259); and

f. an epitope comprised within or overlapping with the sequence HCKVY (SEQ ID NO: 261), and/or an epitope comprised within or overlapping with the sequence KSWISE (SEQ ID NO: 262), and/or an epitope comprised within or overlapping with the sequence ADVR (SEQ ID NO: 258).

10. The antibody or antigen-binding fragment of claim 9, wherein the antibody or antigen-binding fragment thereof binds to one or more epitopes of FGFR3 selected from:

a. an epitope consisting of the sequence GPTVWVK (SEQ ID NO: 260) and/or an epitope consisting of the sequence TQR;

b. an epitope consisting of the sequence ADVR (SEQ ID NO: 258) and/or an epitope consisting of the sequence IGVAEK (SEQ ID NO: 259); and

c. an epitope consisting of the sequence HCKVY (SEQ ID NO: 261), and/or an epitope consisting of the sequence KSWISE (SEQ ID NO: 262), and/or an epitope consisting of the sequence ADVR (SEQ ID NO: 258).

11. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to one or more epitopes of FGFR3 selected from:

a. an epitope comprising the sequence SCPPPGGGPMGPTVWVKDGTGLVPSER (SEQ ID NO: 245) and/or an epitope comprising the sequence YSCRQRLTQRVL (SEQ ID NO: 246);

b. an epitope comprising the sequence LLAVPAAN (SEQ ID NO: 247), and/or an epitope comprising the sequence VLERSPHRPILQAG (SEQ ID NO: 248) and/or an epitope comprising the sequence YVTVLKSWISE (SEQ ID NO: 249) and/or or an epitope comprising the sequence ADVRLR (SEQ ID NO: 250) and/or an epitope comprising the sequence LCRATNFIGVAEKAFW (SEQ ID NO: 251);

c. an epitope comprising the sequence GQQEQLVFGSGDAVE (SEQ ID NO: 252) and/or an epitope comprising the sequence VLVGPQRL (SEQ ID NO: 253);

d. an epitope comprising the sequence VLERSPHRPILQAG (SEQ ID NO: 254) and/or an epitope comprising the sequence HCKVYSDAQP (SEQ ID NO: 255) and/or an epitope comprising the sequence YVTVLKSWISESVEADVRLR (SEQ ID NO: 256) and/or an epitope comprising the sequence LCRATNFIGVAEKAF (SEQ ID NO: 257);

e. an epitope comprised within or overlapping with the sequence SCPPPGGGPMGPTVWVKDGTGLVPSER (SEQ ID NO: 245) and/or an epitope comprised within or overlapping with the sequence YSCRQRLTQRVL (SEQ ID NO: 246);

f. an epitope comprised within or overlapping with the sequence LLAVPAAN (SEQ ID NO: 247), and/or an epitope comprised within or overlapping with the sequence VLERSPHRPILQAG (SEQ ID NO: 248) and/or an epitope comprised within or overlapping with the sequence YVTVLKSWISE (SEQ ID NO: 249) and/or or an epitope comprised within or overlapping with the sequence ADVRLR (SEQ ID NO: 250) and/or an epitope comprised within or overlapping with the sequence LCRATNFIGVAEKAFW (SEQ ID NO: 251);

g. an epitope comprised within or overlapping with the sequence GQQEQLVFGSGDAVE (SEQ ID NO: 252) and/or an epitope comprised within or overlapping with the sequence VLVGPQRL (SEQ ID NO: 253); and

h. an epitope comprised within or overlapping with the sequence VLERSPHRPILQAG (SEQ ID NO: 254) and/or an epitope comprised within or overlapping with the sequence HCKVYSDAQP (SEQ ID NO: 255) and/or an epitope comprised within or overlapping with the sequence YVTVLKSWISESVEADVRLR (SEQ ID NO: 256) and/or an epitope comprised within or overlapping with the sequence LCRATNFIGVAEKAF (SEQ ID NO: 257).

12. The antibody or antigen-binding fragment of claim 11, wherein the antibody or antigen-binding fragment thereof binds to one or more epitopes of FGFR3 selected from:

a. an epitope consisting of the sequence SCPPPGGGPMGPTVWVKDGTGLVPSER (SEQ ID NO: 245) and/or an epitope consisting of the sequence YSCRQRLTQRVL (SEQ ID NO: 246);

b. an epitope consisting of the sequence LLAVPAAN (SEQ ID NO: 247), and/or an epitope consisting of the sequence VLERSPHRPILQAG (SEQ ID NO: 248) and/or an epitope consisting of the sequence YVTVLKSWISE (SEQ ID NO: 249) and/or or an epitope consisting of the sequence ADVRLR (SEQ ID NO: 250) and/or an epitope consisting of the sequence LCRATNFIGVAEKAFW (SEQ ID NO: 251);

c. an epitope consisting of the sequence GQQEQLVFGSGDAVE (SEQ ID NO: 252) and/or an epitope consisting of the sequence VLVGPQRL (SEQ ID NO: 253); and

d. an epitope consisting of the sequence VLERSPHRPILQAG (SEQ ID NO: 254) and/or an epitope consisting of the sequence HCKVYSDAQP (SEQ ID NO: 255) and/or an epitope consisting of the sequence YVTVLKSWISESVEADVRLR (SEQ ID NO: 256) and/or an epitope consisting of the sequence LCRATNFIGVAEKAF (SEQ ID NO: 257).

13. The antibody or antigen-binding fragment of any one of claims 1-12 wherein FGFR3 is monomeric or dimeric FGFR3b.

14. An isolated antibody or antigen-binding fragment thereof that specifically binds to FGFR3 or an antigenic fragment thereof that is characterized by one or more of the following:

- Binds to monomeric human FGFR3b tagged the C-terminus, with myc-myc-His_6 at 25°C with an affinity (K_D) of about 16 nM or greater affinity in a surface plasmon resonance assay;
- Binds to monomeric Cynomolgous monkey FGFR3b tagged at the C-terminus with myc-myc-His_6 at 25°C with an affinity (K_D) of about 20 nM or greater affinity in a surface plasmon resonance assay;
- Binds to monomeric murine FGFR3b tagged at the C-terminus with myc-myc-His_6 at 25°C with an affinity (K_D) of about 70 nM or greater affinity in a surface plasmon resonance assay;
- Does not bind significantly to monomeric human FGFR3c tagged at the C-terminus with myc-myc-His_6 at 25°C in a surface plasmon resonance assay;
- Binds to dimeric human FGFR3b tagged at the C-terminus, with a mouse Fc at 25°C with an affinity of about 0.6 nM of greater affinity in a surface plasmon resonance assay;
- Blocks about 68% or more binding of FGF1 acidic to human FGFR3b-mFc at 200 nM antibody;
- Binds to monomeric Cynomolgous and monomeric mouse FGFR3b with a K_D that is within about 0.1 nM of the K_D for binding to monomeric or dimeric human FGFR3b at 25°C in a surface plasmon resonance assay;

- Blocks binding of 4 nM human FGFR3b-mFc to human FGF1 acidic protein with an IC_{50} of about 15 nM or a lower concentration;
- Blocks intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express wild-type or a S249C mutant human fibroblast growth factor receptor 3b that has been stimulated with human heparin at about 5 micrograms/ml, and human FGF1 ligand at about 1 nM, with an IC_{50} of about 18 nM or a lower concentration;
- Blocks intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express a S249C mutant human fibroblast growth factor receptor 3b that has been stimulated with human heparin at about 5 micrograms/ml and human FGF1 ligand at about 1 nM, with an IC_{50} that is lower than for blocking intracellular signaling in an engineered IL-3-dependent Ba/F3 murine hematopoietic cell line genetically modified to stably express wild-type human fibroblast growth factor receptor 3b that has been stimulated with human FGF1 ligand at about 1 nM and human heparin at about 5 micrograms/ml;
- Blocks dimerization of FGFR3 or a S249C mutant thereof with stronger inhibition than that of REGN6331 as measured in a non-reducing SDS-PAGE assay;
- Reduces tumor size of a bladder cancer tumor expressing FGFR3 or a S249C mutant thereof in a subject administered the antibody or fragment;
- Reduces CD73 expression in a bladder cancer tumor expressing FGFR3 or a S249C mutant thereof in a subject administered the antibody or fragment;
- Inhibits FGF1/heparin stimulation induced phosphorylation of MAPK in a BaF3 cell expressing wild-type FGFR3 or a S249C mutant thereof;
- Inhibits proliferation of UMUC14 bladder cancer cells expressing endogenous FGFR3 or a S249C mutation thereof in a cancer cell spheroid proliferation assay;
- Inhibits tumor growth in a SCID mouse xenograft model of bladder cancer cell line UMUC14 expressing FGFR3 or a S249C mutation thereof;
- Inhibits CD73-dependent, adenosine-mediated inhibition of immune cell activation;
- Increases the ratio of CD8/CD4 and/or CD8+/T_{reg} in tumor tissue having tumor cells expressing FGFR3 or a S249C mutant thereof;
- Inhibits FGF3-mediated activation of CD73 expression and/or adenosine production on a tumor cell expressing FGFR3 or a S249C mutant thereof;

- Inhibits FGFR3-dependent, adenosine-mediated immune cell suppression; or
- Inhibits growth of BaF3 cells expressing the FGFR3 double mutant S249C and V557M, or S249C and V557L.

15. A complex comprising an antibody or antigen-binding fragment thereof of any one of claims 1-14 bound to FGFR3 or an antigenic fragment thereof.

16. A pharmaceutical formulation comprising the antibody or antigen-binding fragment of any one of claims 1-14, and a pharmaceutically acceptable carrier.

17. An isolated polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229 and 231.

18. An isolated polynucleotide that encodes any one or more of the polypeptides of claim 17.

19. The polynucleotide of claim 18 that comprises a nucleotide sequence selected from that set forth in SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228 and 230.

20. A vector that comprises a polynucleotide of any one of claims 18-19.

21. A host cell that comprises the polynucleotide of any one of claims 18-19.

22. A method for making an antibody or antigen-binding fragment of any one of claims 1-14 comprising introducing a polynucleotide that encodes the chains of the antibody or antigen-binding fragment into a host cell and incubating the host cell that comprises the polynucleotide in a culture medium under conditions favorable to expression of the chains and, optionally, isolation of the antibody or antigen-binding fragment from the host cell and/or culture medium.

23. A method for administering the antibody or antigen-binding fragment of any one of claims 1-14 to a subject comprising introducing the antibody or antigen-binding fragment into the body of the subject.

24. The method of claim 23 wherein the antibody or antigen-binding fragment is introduced into the body by injection.

25. The method of claim 24 wherein the injection is intramuscular, intravenous or subcutaneous.

26. A method for treating or preventing an FGFR3-mediated condition, in a subject in need thereof, comprising administering a therapeutically effective amount of the antibody or antigen-binding fragment of any one of claims 1-14 to the subject.

27. The method of claim 26 wherein the FGFR3-mediated condition is cancer, bladder cancer, brain cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, head & neck cancer, kidney cancer, lung cancer, multiple myeloma, ovarian cancer, pancreatic cancer, urothelial cancer, achondroplasia, crouzon syndrome with acanthosis nigricans, epidermal nevus, hypochondroplasia; lacrimo-auriculo-dento-digital (LADD) syndrome, muenke syndrome, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) and/or thanatophoric dysplasia.

28. The method of any one of claims 23-27 wherein the subject is administered a further therapeutic agent.

29. The method of claim 28 wherein the further therapeutic agent is one or more selected from: an FGFR inhibitor, erdafitinib, pemigatinib, infigratinib, rogaratinib, dexamethasone,

alkylating drug, altretamine, trabectedin or busulfan, a nitrosourea, carmustine, lomustine, a cytotoxic antibiotic, an anthracycline, doxorubicin, valrubicin, bleomycin or dactinomycin, an antimetabolite drug, methotrexate, floxuridine, clofarabine, pralatrexate, a vinca alkaloid, vinblastine, vinorelbine, vincristine, vindesine, a photodynamic drug, porfimer sodium, aminolevulinic acid, a platinum drug, cisplatin, phenanthriplatin, a taxane, paclitaxel, docetaxel, a topoisomerase inhibitor, irinotecan, topotecan, etoposide, teniposide, ziv-aflibercept, an anti-cancer antibody, rituximab, trastuzumab, cetuximab, cemiplimab, pembrolizumab, panitumumab and bevacizumab.

30. A method for
- reducing metastasis of a tumor cell expressing FGFR3,
- reducing the concentration of adenosine in a tumor expressing FGFR3,
- reducing CD73-dependent catalysis of AMP to adenosine by a tumor expressing FGFR3,
- inhibiting adenosine-mediated suppression of T-cell function in a tumor expressing FGFR3,
in the body of a subject in need thereof comprising administering a therapeutically effective amount of the antibody or antigen-binding fragment of any one of claims 1-14 to the subject.

31. The method of claim 30 wherein the metastasis is CD73-dependent or adenosine-dependent.