

FGFR3 ANTIBODIES AND METHODS OF USE

RELATED APPLICATION

[001] This application claims the benefit of priority of U.S. Provisional Application No. 63/068,575, filed August 21, 2020, the content of which is incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[001] This disclosure relates to compositions of anti-fibroblast growth factor receptor 3 (anti-FGFR3) antigen-binding proteins or antigen-binding fragments thereof, such as antibodies and fragments thereof, and methods of using the same.

BACKGROUND

[002] Fibroblast growth factor receptor 3 (FGFR3) is a protein involved, in part, in the negative regulation of bone development, being highly expressed in growth plate chondrocytes (Sarabipour et al. Biochim Biophys Acta. 1858(7 Pt A): 1436–1442. 2016). FGFR3 is a single-pass membrane receptor tyrosine kinase with 3 Ig-like domains (D1-D3). Binding of FGFR3 to an FGFR3-ligand, such as FGF18, triggers ligand-dependent receptor dimerization which leads to tyrosine kinase activation and downstream signal transduction. This signaling cascade regulates, among other things, chondrocyte proliferation and differentiation.

[003] FGFR3 is a member of the fibroblast growth factor receptor family, which also includes FGFR1, FGFR2, and FGFR4. Each member of the receptor family is a single-pass membrane receptor tyrosine kinase and shares the feature of 3 Ig-like domains. Moreover, each member of the receptor family possesses a high degree of homology with the other members. Strategies to develop FGFR3-specific inhibitors have proven challenging for this reason. Nonetheless, it is important to develop FGFR3-specific inhibitors that do not cross-react with other fibroblast growth factor receptor family members to avoid unwanted side effects in the treatment of an FGFR3-mediate disease or disorder.

[004] Accordingly, there is a need in the art to identify antigen-binding proteins or antigen-binding fragments thereof, that achieve effective inhibition of FGFR3 activity.

Such antigen-binding proteins or antigen-binding fragments thereof may be useful in the treatment of FGFR3-mediated diseases and disorders.

SUMMARY

[005] Disclosed herein are anti-FGFR3 antigen-binding proteins or antigen-binding fragments thereof, such as antibodies and antigen-binding fragments thereof. The antigen-binding proteins or antigen-binding fragments thereof, such as anti-FGFR3 antibodies and antigen-binding fragments thereof of the disclosure are suitable for treating FGFR3-mediated diseases and disorders.

[006] In one aspect, the disclosure provides an antigen-binding protein or antigen-binding fragment thereof that specifically binds to fibroblast growth factor receptor 3 (FGFR3), comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain, wherein: (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GX¹TFTDX²E (SEQ ID NO: 157), wherein X¹ comprises or consists of Y or D and X² comprises or consists of F or Y; a CDR-H2 sequence comprising the amino acid sequence of IDPETGX³T (SEQ ID NO: 158), wherein X³ comprises or consists of G or S; or CDR-H2 sequence comprising the amino acid sequence of INPNNGX⁴T (SEQ ID NO: 159), wherein X⁴ comprises or consists of G or V; or CDR-H2 sequence comprising the amino acid sequence of VX⁵PETGGT (SEQ ID NO: 160), wherein X⁵ comprises or consists of D or E; a CDR-H3 sequence comprising the amino acid sequence of TRX⁶YX⁷GYX⁸X⁹X¹⁰X¹¹DY (SEQ ID NO: 161), wherein X⁶ comprises or consists of T or N, X⁷ comprises D or E, X⁸ comprises or consists of S or P, X⁹ comprises or consists of Q, R, or Y, X¹⁰ comprises or consists of T or A, X¹¹ comprises or consists of F or M; and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QS X¹²LYS X¹³N X¹⁴KNY (SEQ ID NO: 162), wherein X¹² comprises or consists of L or V, X¹³ comprises or consists of N, D, or S, and X¹⁴ comprises or consists of Q or N; a CDR-L2 sequence comprising the amino acid sequence of X¹⁵AS (SEQ ID NO: 163), wherein X¹⁵ comprises or consists of W, Y, or F; a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75), LQYDNLLWT (SEQ ID NO: 81), or HQYLSX¹⁶YT (SEQ ID NO: 290) wherein X¹⁶ comprises or consists of P or S; (b) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82); a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and

83); a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGAMDY (SEQ ID NO: 78); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85); a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86); a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87); (c) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82); a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83); a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGSMDF (SEQ ID NO: 84); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85); a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86); a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87); (d) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTVTDYY (SEQ ID NO: 88); a CDR-H2 sequence comprising the amino acid sequence of INPNNGVT (SEQ ID NO: 89); a CDR-H3 sequence comprising the amino acid sequence of AREEDFDGFDY (SEQ ID NO: 90); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVSTG (SEQ ID NO: 91); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98 and 104); a CDR-L3 sequence comprising the amino acid sequence of QQHYSTPLT (SEQ ID NO: 93); (e) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFSDFE (SEQ ID NO: 94); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101); a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSTX¹⁷DY (SEQ ID NO: 308), wherein X¹⁷ comprises M or F; and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSX¹⁸NQKNY (SEQ ID NO: 309), wherein X¹⁸ comprises S or D; a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98 and 104); a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105); or (f) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFTDFE (SEQ ID NO: 100); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101); a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSTX¹⁷DY (SEQ ID NO: 308), wherein X¹⁷ comprises M or F; and the VL

domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSX¹⁸NQKNY (SEQ ID NO: 309), wherein X¹⁸ comprises S or D; a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98 and 104); a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105).

[007] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), GDTFTDYE (SEQ ID NO: 295), or GYTFTDFE (SEQ ID NO: 296); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101), VDPETGGT (SEQ ID NO: 297), IDPETGST (SEQ ID NO: 298), or VEPETGGT (SEQ ID NO: 299); a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPYAMDY (SEQ ID NO: 72), TRTYEGYPYAMDY (SEQ ID NO: 300), or TRTYDGYPYAFDY (SEQ ID NO: 301); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLLYSNNQKNY (SEQ ID NO: 73), QSVLYSNNQKNY (SEQ ID NO: 302), or QSVLYSDNQKNY (SEQ ID NO: 306); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104), YAS (SEQ ID NO: 303), or FAS (SEQ ID NO: 304); a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75); (b) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82); a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83); a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGAMDY (SEQ ID NO: 78); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85); a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86); a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87); (c) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82); a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83); a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGSMDF (SEQ ID NO: 84); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85); a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and

86); a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87); (d) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTVTDYY (SEQ ID NO: 88); a CDR-H2 sequence comprising the amino acid sequence of INPNNGVT (SEQ ID NO: 89); a CDR-H3 sequence comprising the amino acid sequence of AREEDFDGFDY (SEQ ID NO: 90); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVSTG (SEQ ID NO: 91); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104); a CDR-L3 sequence comprising the amino acid sequence of QQHYSTPLT (SEQ ID NO: 93); (e) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFSDFE (SEQ ID NO: 94); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101); a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTMDY (SEQ ID NO: 96) or TRNYDGYSQTFDY (SEQ ID NO: 305); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NOs: 97 and 103) or QSVLYSDNQKNY (SEQ ID NO: 306); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104); a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105); or (f) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFTDFE (SEQ ID NO: 100); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101); a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSRTMDY (SEQ ID NO: 102) or TRNYDGYSRTFDY (SEQ ID NO: 307); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NOs: 97 and 103) or QSVLYSDNQKNY (SEQ ID NO: 306); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104); a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105).

[008] In certain embodiments, (a) the VH domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 6, SEQ ID NO: 18, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 10, SEQ ID NO: 110, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 57, and SEQ ID NO: 58; and the VL domain comprises the amino acid sequence selected from the group

consisting of: SEQ ID NO: 7, SEQ ID NO: 19, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 60, and SEQ ID NO: 61; (b) the VH domain comprises the amino acid sequence of SEQ ID NO: 8; and the VL domain comprises the amino acid sequence of SEQ ID NO: 9; (c) the VH domain comprises the amino acid sequence of SEQ ID NO: 10; and the VL domain comprises the amino acid sequence of SEQ ID NO: 11; (d) the VH domain comprises the amino acid sequence of SEQ ID NO: 12; and the VL domain comprises the amino acid sequence of SEQ ID NO: 13; (e) the VH domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 14, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, and SEQ ID NO: 23; and the VL domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 15, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, and SEQ ID NO: 27; (f) the VH domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 16, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, and SEQ ID NO: 31; the VL domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 17, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, and SEQ ID NO: 35.

[009] In certain embodiments, the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 63 or 65, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67 or 69.

[010] In certain embodiments, the VH domain is at least about 90% identical or at least about 95% identical to the amino acid sequence of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, or SEQ ID NO: 122, and wherein the VL domain is at least about 90% identical or at least about 95% identical to the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27,

SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, or SEQ ID NO: 132.

[011] In certain embodiments, the antigen binding protein or fragment thereof of comprises an antibody heavy chain at least about 90% identical or at least about 95% identical to the amino acid sequence of SEQ ID NO: 63 or 65, and an antibody light chain at least about 90% identical or at least about 95% identical to the amino acid sequence of SEQ ID NO: 67 or 69.

[012] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NO: 71), and a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPYAMDY (SEQ ID NO: 72); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLLYSNNQKNY (SEQ ID NO: 73), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NO: 74), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75). In some embodiments thereof, the VH domain comprises the amino acid sequence of SEQ ID NO: 6, and the VL domain comprises the amino acid sequence of SEQ ID NO: 7.

[013] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NO: 76), a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NO: 77), and a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGAMDY (SEQ ID NO: 78); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NO: 79), a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NO: 80), and a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NO: 81).

[014] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 8, and the VL domain comprises the amino acid sequence of SEQ ID NO: 9.

[015] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NO: 82), a CDR-

H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NO: 83), and a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGSMDF (SEQ ID NO: 84); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NO: 85), a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NO: 86), and a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NO: 87).

[016] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 10, and the VL domain comprises the amino acid sequence of SEQ ID NO: 11.

[017] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTVTDYY (SEQ ID NO: 88), a CDR-H2 sequence comprising the amino acid sequence of INPNNGVT (SEQ ID NO: 89), and a CDR-H3 sequence comprising the amino acid sequence of AREEDFDGFDY (SEQ ID NO: 90); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVSTG (SEQ ID NO: 91), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NO: 92), and a CDR-L3 sequence comprising the amino acid sequence of QQHYSTPLT (SEQ ID NO: 93).

[018] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 12, and the VL domain comprises the amino acid sequence of SEQ ID NO: 13.

[019] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFSDFE (SEQ ID NO: 94), a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NO: 95), and a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTMDY (SEQ ID NO: 96); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NO: 97), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NO: 98), and a CDR-L3 sequence comprising the amino acid sequence of HQYLSSYT (SEQ ID NO: 99).

[020] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 14, and the VL domain comprises the amino acid sequence of SEQ ID NO: 15.

[021] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFTDFE (SEQ ID NO: 100), a CDR-

H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NO: 101), and a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSRTMDY (SEQ ID NO: 102); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NO: 103), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NO: 104), and a CDR-L3 sequence comprising the amino acid sequence of HQYLSSYT (SEQ ID NO: 105).

[022] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 16, and the VL domain comprises the amino acid sequence of SEQ ID NO: 17.

[023] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), a CDR-H2 sequence comprising the amino acid sequence of VDPETGGT (SEQ ID NO: 297), and a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPYAFDY (SEQ ID NO: 301); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSNNKNY (SEQ ID NO: 302), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, 104), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75).

[024] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 57, and the VL domain comprises the amino acid sequence of SEQ ID NO: 19 or 59.

[025] In certain embodiments, the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 63, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67.

[026] In certain embodiments, (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), a CDR-H2 sequence comprising the amino acid sequence of VDPETGGT (SEQ ID NO: 297), and a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPYAFDY (SEQ ID NO: 301); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSDNQKNY (SEQ ID NO: 306), a CDR-L2 sequence comprising the amino acid sequence of FAS (SEQ ID NO: 304), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75).

[027] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 57, and the VL domain comprises the amino acid sequence of SEQ ID NO: 61.

[028] In certain embodiments, the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 65, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67.

[029] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds a human FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO: 133.

[030] In certain embodiments, the antigen binding protein or antigen-binding fragment thereof binds a human FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO: 134.

[031] In certain embodiments, the antigen binding protein or antigen-binding fragment thereof binds a region of human FGFR3 polypeptide comprising the amino acids D143 through L163 of SEQ ID NO: 133.

[032] In certain embodiments, the antigen binding protein or antigen-binding fragment thereof binds a region of human FGFR3 polypeptide comprising the amino acids D143 through N170 of SEQ ID NO: 133.

[033] In certain embodiments, the antigen binding protein or antigen-binding fragment thereof binds a region of human FGFR3 polypeptide comprising the amino acids D143 through D160 and G197 through L213 of SEQ ID NO: 133.

[034] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is a chimeric or humanized antibody or antigen-binding binding fragment thereof.

[035] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is a human antibody or antigen-binding binding fragment thereof.

[036] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is a monoclonal antibody or antigen-binding binding fragment thereof.

[037] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof comprises one or more full-length antibody heavy chains comprising an Fc region.

[038] In certain embodiments, the Fc region is a human IgG1 Fc region.

[039] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof comprises an antibody F(ab), F(ab')₂, Fab'-SH, Fv, or scFv fragment.

[040] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof comprises an antibody F(ab) fragment.

[041] In certain embodiments, the antibody F(ab) fragment comprises SEQ ID NO: 56 and the first about 100 amino acids of SEQ ID NO: 54.

[042] In certain embodiments, the antibody F(ab) fragment comprises SEQ ID NO: 57 and the first about 100 amino acids of SEQ ID NO: 54.

[043] In certain embodiments, the antibody F(ab) fragment comprises SEQ ID NO: 58 and the first about 100 amino acids of SEQ ID NO: 54.

[044] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 141 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 142.

[045] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 143 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 144.

[046] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 145 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 146.

[047] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 147 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 148.

[048] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 149 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 150.

[049] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 151 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 152.

[050] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[051] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[052] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[053] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[054] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[055] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[056] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[057] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[058] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[059] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof comprises cross-reactivity to mouse and cynomolgus FGFR3.

[060] In certain embodiments, the antigen binding or antigen-binding binding fragment thereof protein does not bind to one or more of FGFR1, FGFR2, and FGFR4.

[061] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof does not bind to each of FGFR1, FGFR2, and FGFR4.

[062] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds to each of FGFR1, FGFR2, and FGFR4 with an affinity of 100 μ M or greater.

[063] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds human FGFR3 with an equilibrium dissociation constant (KD) of 10 nM or less.

[064] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds human FGFR3 with an off rate (Kd) of 10^{-4} or greater.

[065] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof inhibits ligand-induced FGFR3 dimerization with IC₅₀ of 5 µg/ml or less.

[066] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof inhibits FGFR3 receptor activation and downstream signaling with IC₅₀ of 5 µg/ml or less.

[067] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof inhibits the activity of an FGFR3^{G380R} mutant.

[068] In certain embodiments, the antigen binding protein or antigen-binding fragment thereof is capable of penetrating a bone growth plate.

[069] In certain embodiments, the antigen binding protein or antigen-binding fragment thereof is capable of decreasing binding of FGFR3 and its ligand in a bone growth plate.

[070] In another aspect, the disclosure provides a pharmaceutical composition comprising the antigen binding protein or antigen-binding fragment thereof recited above, and a pharmaceutically acceptable carrier.

[071] In another aspect, the disclosure provides an isolated nucleic acid molecule encoding the antigen binding protein or antigen-binding fragment thereof recited above.

[072] In another aspect, the disclosure provides an expression vector comprising the nucleic acid molecule recited above.

[073] In another aspect, the disclosure provides a host cell comprising the expression vector recited above.

[074] In another aspect, the disclosure provides a method for treating a FGFR3-mediated disease or disorder in a subject, comprising administering to a subject in need thereof the antigen binding protein or antigen-binding fragment thereof recited above.

[075] In certain embodiments, the FGFR3-mediated disease or disorder is achondroplasia.

[076] In certain embodiments, the achondroplasia is FGFR3^{G380R+} achondroplasia.

[077] In certain embodiments, the subject suffering from achondroplasia comprises one or more symptoms selected from the group consisting of shortened proximal limbs, brachydactyly, large head with prominent forehead frontal bossing, small midface with a flattened nasal bridge, spinal kyphosis, spinal lordosis, varus, valgus, ear infections, sleep apnea, and hydrocephalus.

[078] In certain embodiments, the FGFR3-mediated disease or disorder is cancer.

[079] In certain embodiments, the cancer is bladder cancer melanoma, urothelial cancer, and endometrial cancer.

[080] In one aspect, the disclosure provides a method for treating achondroplasia in a subject, comprising administering to a subject in need thereof an antigen-binding protein fragment that specifically binds to FGFR3, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4.

[081] In one aspect, the disclosure provides a method for inhibiting one or both of FGFR3 activity and expression in a bone growth plate of a subject, comprising administering to a subject an antigen-binding protein fragment that specifically binds to FGFR3, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4.

[082] In one aspect, the disclosure provides an antigen-binding protein or antigen-binding fragment thereof that specifically binds to fibroblast growth factor receptor 3 (FGFR3), comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain, wherein the antigen binding protein binds a human FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO: 134.

[083] In certain embodiments, the antigen binding protein binds a region of human FGFR3 polypeptide comprising the amino acids D143 through L163 of SEQ ID NO: 133.

[084] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds a region of human FGFR3 polypeptide comprising the amino acids D143 through N170 of SEQ ID NO: 133.

[085] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds a region of human FGFR3 polypeptide comprising the amino acids D143 through D160 and G197 through L213 of SEQ ID NO: 133.

[086] In one aspect, the disclosure provides an antigen-binding protein or antigen-binding fragment thereof with binding specificity to a fibroblast growth factor receptor 3 (FGFR3) epitope, comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain, wherein the antigen binding protein or antigen-binding binding fragment thereof competes for binding to FGFR3 with an antibody comprising VH / VL domain amino acid sequence pairs selected from the group consisting of: SEQ ID NO: 6 / SEQ ID NO: 7, SEQ ID NO: 8 / SEQ ID NO: 9, SEQ ID NO: 10 / SEQ ID NO: 11, SEQ ID NO: 12 / SEQ ID NO: 13, SEQ ID NO: 14 / SEQ ID NO: 15, and SEQ ID NO: 16 / SEQ ID NO: 17.

[087] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is a chimeric or humanized antibody or antigen-binding binding fragment thereof.

[088] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is a human antibody or antigen-binding binding fragment thereof.

[089] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is a monoclonal antibody or antigen-binding binding fragment thereof.

[090] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof comprises one or more full-length antibody heavy chains comprising an Fc region.

[091] In certain embodiments, the Fc region is a human IgG1 Fc region.

[092] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof comprises an antibody F(ab), F(ab')₂, Fab'-SH, Fv, or scFv fragment.

[093] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof comprises an antibody F(ab) fragment.

[094] In certain embodiments, the antibody F(ab) fragment comprises SEQ ID NO: 56 and the first about 100 amino acids of SEQ ID NO: 54.

[095] In certain embodiments, the antibody F(ab) fragment comprises a heavy chain comprising SEQ ID NO: 57 and the first about 100 amino acids of SEQ ID NO: 54.

[096] In certain embodiments, the antibody F(ab) fragment comprises a heavy chain comprising SEQ ID NO: 58 and the first about 100 amino acids of SEQ ID NO: 54.

[097] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 141, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 254, 263, 272, or 281, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 142.

[098] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 143, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 255, 264, 273, or 282, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 144.

[099] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 145, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 256, 265, 274, or 283, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 146.

[0100] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 147, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 257, 266, 275, or 284, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 148.

[0101] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 149, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 258, 267, 276, or 285, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 150.

[0102] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 151, 169, 178, 187, 196, 205, 214, 223, 232, 241, 250, 259, 268, 277, or 286, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 152.

[0103] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[0104] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[0105] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[0106] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[0107] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[0108] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[0109] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[0110] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217,

226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[0111] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[0112] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof comprises has cross-reactivity to mouse and cynomolgus FGFR3.

[0113] In certain embodiments, the antigen binding or antigen-binding binding fragment thereof protein does not bind to one or more of FGFR1, FGFR2, and FGFR4.

[0114] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof does not bind to each of FGFR1, FGFR2, and FGFR4.

[0115] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds to each of FGFR1, FGFR2, and FGFR4 with an affinity equilibrium dissociation constant (KD) of 100 μ M or greater.

[0116] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds human FGFR3 with an equilibrium dissociation constant (KD) of 10 nM or less.

[0117] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof binds human FGFR3 with an off rate (Kd) of 10^{-4} or greater.

[0118] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof inhibits ligand-induced FGFR3 dimerization with IC₅₀ of 5 μ g/ml or less.

[0119] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof inhibits FGFR3 receptor activation and downstream signaling with IC₅₀ of 5 μ g/ml or less.

[0120] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof inhibits the activity of an FGFR3^{G380R} mutant.

[0121] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is capable of penetrating a bone growth plate.

[0122] In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is capable of decreasing the binding of FGFR3 with its ligand in a bone growth plate. In certain embodiments, the antigen binding protein or antigen-binding binding fragment thereof is capable of decreasing the kinase activity of FGFR3 in a bone growth plate.

[0123] Also provided is a pharmaceutical composition comprising the antigen binding protein or antigen-binding fragment thereof as described herein. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable carrier.

[0124] Also provided is an isolated nucleic acid molecule encoding the antigen binding protein or antigen-binding fragment thereof as described herein. Also provided is an expression cassette comprising said nucleic acid molecule. Also provided is an expression vector comprising the isolated nucleic acid molecule. Further provided is a host cell comprising the expression vector, the expression cassette or the nucleic acid molecule.

[0125] Further provided is a method for treating a FGFR3-mediated disease or disorder in a subject. In certain embodiments, the method comprises administering to a subject in need thereof the antigen binding protein or antigen-binding fragment thereof as described herein. In certain embodiments, the FGFR3-mediated disease or disorder is achondroplasia. In certain embodiments, the achondroplasia is FGFR3^{G380R}+ achondroplasia.

[0126] In certain embodiments, the FGFR3-mediated disease or disorder is cancer.

[0127] In certain embodiments, the cancer is bladder cancer melanoma, urothelial cancer, and endometrial cancer.

[0128] Also provided is a method for treating achondroplasia in a subject. In certain embodiments, the method comprises administering to a subject in need thereof an antigen-binding protein fragment that specifically binds to FGFR3, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4.

[0129] Also provided is a method for inhibiting one or both of FGFR3 activity and expression in a bone growth plate of a subject. In certain embodiments, the method comprises administering to a subject an antigen-binding protein fragment that specifically binds to FGFR3, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4.

[0130] In certain embodiments, the subject is a child. In certain embodiments, the child is an infant. In certain embodiments, the infant is a newborn.

[0131] Also provided is a method for preventing or alleviating one or more symptoms of achondroplasia in a subject. In certain embodiments, the method comprises administering to the subject an antigen-binding protein or an antigen-binding protein fragment thereof that specifically binds to FGFR3, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4.

BRIEF DESCRIPTION OF THE DRAWINGS

[0132] The foregoing and other features and advantages of the present disclosure will be more fully understood from the following detailed description of illustrative embodiments taken in conjunction with the accompanying drawings. The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided to the Office upon request and payment of the necessary fee.

[0133] **Fig. 1** schematically depicts fibroblast growth factor receptor 3 (FGFR3) isoform IIIc.

[0134] **Fig. 2** depicts heat maps generated with hydrogen deuterium exchange (HDX) mass spectrometry used to determine the epitopes on FGFR3 for select antibodies by measuring the amide hydrogen deuterium exchange on FGFR3.

[0135] **Fig. 3** depicts fluorescent images from internalization assays to detect internalization of anti-FGFR3 antibodies in KMS-11 cells.

[0136] **Fig. 4** graphically depicts the average amount of anti-FGFR3 antibody internalization relative to the total amount of antibody.

[0137] **Fig. 5A – Fig. 5C** graphically depict inhibition of FGFR3 dimerization by anti-FGFR3 antibody KC18 (**Fig. 5A**), KE58 (**Fig. 5B**), KE94 (**Fig. 5C**). Inhibition was evaluated by a chemiluminescent assay in U2OS cells co-expressing fusion protein

of β -galactosidase-prolink (PK) and FGFR3 (FGFR3-PK) and β -galactosidase-enzyme acceptor (EA) and FGFR3 (FGFR3-EA).

[0138] **Fig. 6** depicts an alignment of anti-FGFR3 antibodies KC18, KE63, and KE94.

[0139] **Fig. 7** depicts an alignment of anti-FGFR3 antibody KC18_Hu18 with variants. Mutations of Hu18 residues are highlighted green or red.

[0140] **Fig. 8A – Fig. 8C** depict graphs demonstrating IC₅₀ values for the inhibition of Erk phosphorylation by humanized anti-FGFR3 antibodies Hu18 (**Fig. 8A**), Hu44 (**Fig. 8B**), and Hu46 (**Fig. 8C**). Inhibition of Erk phosphorylation was determined by a homogenous time-resolved fluorescence (HTRF) assay.

[0141] **Fig. 9A – Fig. 9B** graphically depict relative Erk phosphorylation inhibition by anti-FGFR3 antibodies KC18 (**Fig. 9A**), KE63 (**Fig. 9B**), and KE94 (**Fig. 9B**) and their corresponding Fab fragments.

[0142] **Fig. 10A – Fig. 10C** graphically depict relative Erk phosphorylation inhibition by anti-FGFR3 antibody KC18 in different formats. **Fig. 10A** depicts inhibition effect of KC18 as a full-length antibody (KC18), a Fab fragment (Kc18 Fab), a one-armed, monovalent antibody (MetMab), and a PEGylated Fab fragment (PEG) in WT cells. **Fig. 10B** depicts inhibition effect of KC18 as a full-length antibody (IgG), a Fab fragment, a one-armed, monovalent antibody (MetMab), and a PEGylated Fab fragment (PEG) in Ach cells. **Fig. 10C** depicts KC18 fab fragments with half-life extension moieties using a human albumin nanobody conjugate (KC18 Fab-HLE), with and without human serum albumin (HSA) or mouse serum albumin (MSA). Erk phosphorylation was measured in an HTRF assay and compared to an isotype control (Iso).

[0143] **Fig. 11** graphically depicts inhibition of Erk phosphorylation by humanized anti-FGFR3 antibodies Hu18, Hu44, and Hu46. Inhibition of Erk phosphorylation was determined using an HTRF assay.

[0144] **Fig. 12A – Fig. 12B** graphically depict femur (**Fig. 12A**) and tibia (**Fig. 12B**) length in an achondroplasia mouse model (Ach), which is a transgenic mouse that overexpresses the mouse FGFR3 protein with the G380R mutation under the collagen II promoter. Mice were administered the KC18 fab fragment subcutaneously from 3 days of age to 20 days of age.

[0145] *Fig. 13A – Fig. 13B* graphically depict vertebrae (*Fig. 13A*) and skull (*Fig. 13B*) length in the Ach mouse model. For skull measurements, NL = nasal length; FL = frontal length; and PL = parietal length.

[0146] *Fig. 14* graphically depicts brain volume in the WT and Ach mouse model treated by saline or KC18 fab fragment.

[0147] *Fig. 15A* graphically depicts Kyphosis Index in the WT and Ach mouse model treated by saline or KC18 fab fragment. *Fig. 15B* depicts the calculation of Kyphotic Index using a mouse model.

[0148] *Fig. 16A* graphically depicts femur growth plate (GP) volume in Ach mouse model treated by vehicle or KC18 fab fragment. *Fig. 16B* depicts femur diameter in Ach mouse model treated by vehicle or KC18 fab fragment.

[0149] *Fig. 17* graphically depicts increased secondary ossification center in tibia in Ach mouse model compared to those treated with vehicle.

DETAILED DESCRIPTION

[0150] Antigen-binding proteins or antigen-binding fragments thereof are provided. Methods of inhibiting one or more FGFR3 activities, and methods of treating FGFR3-mediated diseases and disorders are also provided.

[0151] Generally, nomenclature used in connection with cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art. The methods and techniques provided herein are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclature used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0152] Unless otherwise defined herein, scientific and technical terms used herein have the meanings that are commonly understood by those of ordinary skill in the

art. In the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of “or” means “and/or” unless stated otherwise. The use of the term “including,” as well as other forms, such as “includes” and “included,” is not limiting.

[0153] So that the disclosure may be more readily understood, certain terms are first defined.

Fibroblast Growth Factor Receptor 3 (FGFR3)

[0154] As used herein, the term “FGFR3” or “fibroblast growth factor receptor 3” or “CD333” refers to the FGFR3 protein encoded by the *FGFR3* gene. FGFR3 belongs to a family of fibroblast growth factor receptors that also includes FGFR1, FGFR2, and FGFR4. Like the other fibroblast growth factor receptor family members, FGFR3 is a single-pass membrane receptor tyrosine kinase with 3 Ig-like domains (D1, D2, and D3). Ligand dependent receptor dimerization leads to tyrosine kinase activation and downstream signal transduction. FGFR3 undergoes alternative splicing leading to several isoforms, including isoform IIIb and isoform IIIc. IIIb and IIIc arise from alternative splicing of exons 8 and 9. IIIb and IIIc have identical Ig1 (D1) and Ig2 (D2) domains, but vary in the Ig3 (D3) domain. It is FGFR3 IIIc that is the major FGFR3 isoform in chondrocytes and mediates the anabolic effects of the FGFR3 ligand, FGF18, in articular cartilage. The structure and function of FGFR3 is described in further detail in Olsen et al. (PNAS. 101(4): 935-940. 2004), incorporated herein by reference in its entirety for all purposes.

[0155] The human FGFR3 isoform IIIc amino acid sequence is recited below.

MGAPACALALCVAVAIVAGASSES LGTEQRVVGRAAEVPGPEPGQQEQLVFGS
GDAVELSCPPPGGGPMGPTVWVKDGTGLVPSEVLVGPQRLQVLNASHEDSGA
YSCRQRLTQRVLCHF SVRVTDAPSSGDDDEGEDEAEDTGVD TGAPYWTRPERM
DKKLLAVPAANTVRFRC PAAGNPTPSISWLKNGREFRGEHRIGGIKLRHQWWSL
VMESVVP SDRGN YTCVVENKFGSIRQTYTLDV LERSPHRPILQAGLPANQTAVL
GSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDPGTPYVTVLKTAGANTTDK
ELEVLSLHNVT FEDAGEYTCLAGNSIGFSHHS AWLVVLP AEEELVEADEAGSVY
AGILSYGVGF FLFILVVA AVTLCRLRSPPKKGLGSPTVHKISRFP LKRQVSLESNA
SMSSNTPLVRIARLSSGEGPTLANVSELELPADPKWELSRARLT LGKPLGEGCFG

QVVM AE AIGIDKDRAAKPVTVAVKMLKDDATDKDLSDLVSEMEMMKMIGKH
 KNIINLLGACTQGGPLYVLVEYAAKGNLREFLRARRPPGLDYSFDTCKPPEEQLT
 FKDLVSCAYQVARGMEYLASQKCIHRDLAARNVLVTEDNVMKIADFG LARDV
 HNL DYYKKT TNGRLPVK WMAPEALFDRVYTHQSDVWSFGVLLWEIFTLGGSP
 YPGIPVEELFKLLKEGHRMDK PANCTHDLYMIMREC WHAAPSQRPTFKQLVED
 LDRVLTVTSTDEYLDLSAPFEQYSPGGQDTPSSSSSGDDSVFAHDLLPPAPPSSG
 GSRT (SEQ ID NO: 135)

[0156] Mutations in FGFR3 can lead to certain undesired conditions. A G380R mutation in the transmembrane domain of FGFR3 is associated with 98% of all achondroplasia cases. FGFR3 with a G380R mutation can be referred to as FGFR3^{G380R}, and the sequence of the human FGFR3^{G380R} isoform IIIc is recited below.

MGAPACALALCVAVAIVAGASSES LGTEQRVVGRAAEVPGPEPGQQEQLVFGS
 GDAVELSCPPPGGGPMGPTVWVKDGTGLVPSE RVLVGPQRLQVLNASHEDSGA
 YSCRQRLTQRVLCHF SVRVT DAPSSGDDDEGEDEAEDTGVD TGAPYWTRPERM
 DKLLAVPAANTVRFRCPAAGNPTPSISWLKNGREFRGEHRIGGIKLRHQQWSL
 VMESVVP SDRGNYTCVVENKFGSIRQTYTLDVLERSPHRPILQAGLPANQTAVL
 GSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGPYVTVLKTAGANTTDK
 ELEVLSLHNVT FEDAGEYTCLAGNSIGFSHHS AWLVVLPAAEELVEADEAGSVY
 AGILSYRVGFFLFILVVA AVTLCRLRSPPKKGLGSPTVHKISRFP LKRQVSLESNA
 SMSSNTPLVRIARLSSGEGPTLANVSELELPADPKWELSRARLT LGKPLGEGCFG
 QVVM AE AIGIDKDRAAKPVTVAVKMLKDDATDKDLSDLVSEMEMMKMIGKH
 KNIINLLGACTQGGPLYVLVEYAAKGNLREFLRARRPPGLDYSFDTCKPPEEQLT
 FKDLVSCAYQVARGMEYLASQKCIHRDLAARNVLVTEDNVMKIADFG LARDV
 HNL DYYKKT TNGRLPVK WMAPEALFDRVYTHQSDVWSFGVLLWEIFTLGGSP
 YPGIPVEELFKLLKEGHRMDK PANCTHDLYMIMREC WHAAPSQRPTFKQLVED
 LDRVLTVTSTDEYLDLSAPFEQYSPGGQDTPSSSSSGDDSVFAHDLLPPAPPSSG
 GSRT (SEQ ID NO: 133)

Antigen-binding proteins

[0157] As used herein, the term “antibody” or “antigen-binding protein” refers to an immunoglobulin molecule that specifically binds to, or is immunologically reactive with an antigen or epitope (e.g., a FGFR3 antigen or epitope), and includes both polyclonal and monoclonal antibodies, as well as functional antibody fragments thereof, including

but not limited to fragment antigen-binding (Fab) fragments, F(ab')₂ fragments, Fab' fragments, Fv fragments, recombinant IgG (rIgG) fragments, single chain variable fragments (scFv) and single domain antibodies (e.g., sdAb, sdFv, nanobody) fragments. The term “antibody” includes genetically engineered or otherwise modified forms of immunoglobulins, such as intrabodies, peptibodies, chimeric antibodies, fully human antibodies, humanized antibodies, mediotope-enabled antibodies, heteroconjugate antibodies (e.g., bispecific antibodies, diabodies, triabodies, tetrabodies, tandem di-scFv, tandem tri-scFv) and the like. Unless otherwise stated, the term “antibody” should be understood to encompass functional antibody fragments thereof. As used herein, the term “functional antibody fragment” refers to an antibody fragment having at least 80%, at least 85%, at least 90%, or at least 95% affinity as the antibody of interest from which the fragment is derived from.

[0158] As used herein, the term “complementarity determining region” or “CDR” refers to sequences of amino acids within antibody variable regions, which confer antigen specificity and binding affinity. In general, there are three CDRs in each heavy chain variable region (CDR-H1, CDR-H2, CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, CDR-L3). “Framework regions” or “FR” are known in the art to refer to the non-CDR portions of the variable regions of the heavy and light chains. In general, there are four FRs in each heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each light chain variable region (FR-L1, FR-L2, FR-L3, and FR-L4).

[0159] The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (“Kabat” numbering scheme), Al-Lazikani et al., (1997) JMB 273, 927-948 (“Chothia” numbering scheme), MacCallum et al., J. Mol. Biol. 262:732-745 (1996), “Antibody-antigen interactions: Contact analysis and binding site topography,” J. Mol. Biol. 262, 732-745. (“Contact” numbering scheme), Lefranc M P et al., “IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains,” Dev Comp Immunol, 2003 January; 27(1):55-77 (“IMGT” numbering scheme), and Honegger A and Pluckthun A, “Yet another numbering scheme for immunoglobulin

variable domains: an automatic modeling and analysis tool,” J Mol Biol, 2001 Jun. 8; 309(3):657-70, (AHO numbering scheme).

[0160] The boundaries of a given CDR or FR may vary depending on the scheme used for identification. For example, the Kabat scheme is based structural alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, “30a,” and deletions appearing in some antibodies. The two schemes place certain insertions and deletions (“indels”) at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme.

[0161] A “CDR” or “complementary determining region,” or individual specified CDRs (e.g., “CDR-H1,” “CDR-H2,” “CDR-H3”), of a given antibody or region thereof, such as a variable region thereof, should be understood to encompass a (or the specific) complementary determining region as defined by any of the known schemes. Likewise, an “FR” or “framework region,” or individual specified FRs (e.g., “FR-H1,” “FR-H2”) of a given antibody or region thereof, such as a variable region thereof, should be understood to encompass a (or the specific) framework region as defined by any of the known schemes. In some instances, the scheme for identification of a particular CDR or FR is specified, such as the CDR as defined by the IMGT, Kabat, Chothia, AbM, or Contact method. In other cases, the particular amino acid sequence of a CDR or FR is given. Unless otherwise specified, all particular CDR amino acid sequences mentioned in the disclosure are IMGT CDRs. However, alternative CDRs defined by other schemes are also encompassed by the present disclosure, such as those determined by abYsis Key Annotation (Website: abysis.org/abysis/sequence_input/key_annotation/key_annotation.cgi).

[0162] As used herein, the term “specifically binds,” “specifically binding,” “binding specificity” or “specifically recognized” refers that an antigen binding protein or antigen-binding fragment thereof that exhibits appreciable affinity for an antigen (e.g., an FGFR3 antigen) and does not exhibit significant cross reactivity to a target that is not an FGFR3 protein. As used herein, the term “affinity” refers to the strength of the interaction between an antigen binding protein or antigen-binding fragment thereof antigen binding site and the epitope to which it binds. As readily understood by those skilled in the art, an

antigen binding protein affinity may be reported as a dissociation constant (KD) in molarity (M). The antigen binding protein or antigen-binding fragment thereof of the disclosure have KD values in the range of about 10^{-6} M to about 10^{-12} M (i.e., low micromolar to picomolar range), about 10^{-7} M to 10^{-11} M, about 10^{-8} M to about 10^{-10} M, about 10^{-9} M. In certain embodiments, the antigen binding protein or antigen-binding fragment thereof has a binding affinity of about 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M. In certain embodiments, the antigen binding protein or antigen-binding fragment thereof has a binding affinity of about 10^{-7} M to about 10^{-9} M (nanomolar range).

[0163] Specific binding can be determined according to any art-recognized means for determining such binding. In some embodiments, specific binding is determined by competitive binding assays (e.g. ELISA) or Biacore assays. In certain embodiments, the assay is conducted at about 20°C, 25°C, 30°C, or 37°C.

Anti-FGFR3 antigen-binding proteins

[0164] In one aspect, the disclosure provides antigen binding proteins and antigen-binding fragments thereof with binding specificity to FGFR3.

[0165] Exemplary anti-FGFR3 antigen binding protein and antigen-binding fragment thereof CDRs are recited below in Table 1 and Table 4. Exemplary anti-FGFR3 antigen binding protein and antigen-binding fragment thereof variable heavy (VH) and variable light (VL) domains are recited below in Table 3, Table 8, Table 9, and Table 13. Exemplary anti-FGFR3 antigen binding protein full length heavy and light chains are recited below in Table 14.

[0166] Table 1. Antibody Heavy chain and Light chain CDR regions

HEAVY Chain			
VH Chain ID	HCDR1-IMGT	HCDR2-IMGT	HCDR3-IMGT
KC18_VH	GDFTDFE (SEQ ID NO: 70)	IDPETGGT (SEQ ID NO: 71)	TRTYDGYPYAMDY (SEQ ID NO: 72)
KE35_VH	GYTFTDYN (SEQ ID NO: 76)	INPNNGGT (SEQ ID NO: 77)	ARERDYDGAMDY (SEQ ID NO: 78)
KE42_VH	GYTFTDYN (SEQ ID NO: 82)	INPNNGGT (SEQ ID NO: 83)	ARERDYDGSMDY (SEQ ID NO: 84)
KE58_VH	GYTVTDYY (SEQ ID NO: 88)	INPNNGVT (SEQ ID NO: 89)	AREEDFDGFDY (SEQ ID NO: 90)
KE63_VH	GSTFSDFE (SEQ ID NO: 94)	IDPETGGT (SEQ ID NO: 95)	TRNYDGYSTMDY (SEQ ID NO: 96)
KE94_VH	GSTFTDFE	IDPETGGT	TRNYDGYSTMDY

	(SEQ ID NO: 100)	(SEQ ID NO: 101)	(SEQ ID NO: 102)
KC18 Hu18 VH	GDFTDFE (SEQ ID NO: 70)	VDPETGGT (SEQ ID NO: 297)	TRTYDGYPYAFDY (SEQ ID NO: 301)
KC18Hrw1	GDFTDFE (SEQ ID NO: 70)	IDPETGST (SEQ ID NO: 298)	TRTYDGYPYAMDY (SEQ ID NO: 72)
KC18Hrw2	GDFTDYE (SEQ ID NO: 295)	IDPETGST (SEQ ID NO: 298)	TRTYDGYPYAMDY (SEQ ID NO: 72)
KC18Hrw3	GDFTDYE (SEQ ID NO: 295)	IDPETGST (SEQ ID NO: 298)	TRTYDGYPYAMDY (SEQ ID NO: 72)
KC18HV1-69rw2	GDFTDFE (SEQ ID NO: 70)	VDPETGGT (SEQ ID NO: 297)	TRTYDGYPYAMDY (SEQ ID NO: 72)
KC18HV1-69rw3	GDFTDFE (SEQ ID NO: 70)	VDPETGGT (SEQ ID NO: 297)	TRTYEGYPYAMDY (SEQ ID NO: 300)
KC18HV1-69rw4	GDFTDFE (SEQ ID NO: 70)	VDPETGGT (SEQ ID NO: 297)	TRTYDGYPYAFDY (SEQ ID NO: 301)
KC18_CL_VH1	GDFTDFE (SEQ ID NO: 70)	IDPETGGT (SEQ ID NO: 95)	ARTYDGYPYAMDY (SEQ ID NO: 310)
KC18_CL_VH1b	GYFTDFE (SEQ ID NO: 296)	VDPETGGT (SEQ ID NO: 297)	ARTYDGYPYAMDY (SEQ ID NO: 310)
KC18_CL_VH1c	GYFTDFE (SEQ ID NO: 296)	VEPETGGT (SEQ ID NO: 299)	ARTYDGYPYAMDV (SEQ ID NO: 311)
KC18_CL_VH2	GDFTDFE (SEQ ID NO: 70)	IDPETGGT (SEQ ID NO: 95)	TRTYDGYPYAMDY (SEQ ID NO: 72)
KC18_CL_VH3	GDFTDFE (SEQ ID NO: 70)	IDPESGGT (SEQ ID NO: 312)	ARTYDGYPYAMDY (SEQ ID NO: 310)
KC18_CL_VH3b	GYFTDFE (SEQ ID NO: 296)	IDPESGGT (SEQ ID NO: 312)	ARTYDGYPYAMDY (SEQ ID NO: 310)
KC18_CL_VH3c	GYFTDFE (SEQ ID NO: 296)	IEPESGGT (SEQ ID NO: 313)	ARTYDGYPYAMDV (SEQ ID NO: 311)
KC18_CL_VH4	GDFTDFE (SEQ ID NO: 70)	IDPETGGT (SEQ ID NO: 95)	TRTYDGYPYAMDY (SEQ ID NO: 72)
KC18_VH_6	GDFTDFE (SEQ ID NO: 70)	VDPETGGT (SEQ ID NO: 297)	TRTYDGYPYAFDY (SEQ ID NO: 301)
KC18_VH_15	GDFTDFE (SEQ ID NO: 70)	VDPETGGT (SEQ ID NO: 297)	TRTYDGYPYAFDY (SEQ ID NO: 301)
KC18_VH_16	GDFTDFE (SEQ ID NO: 70)	VDPETGGT (SEQ ID NO: 297)	TRTYDGYPYAFDY (SEQ ID NO: 301)
KE63 Hu01 VH	GSTFSDFE (SEQ ID NO: 94)	IDPETGGT (SEQ ID NO: 95)	TRNYDGYSQTFDY (SEQ ID NO: 305)
KE63 Hu02 VH	GSTFSDFE (SEQ ID NO: 94)	IDPETGGT (SEQ ID NO: 95)	TRNYDGYSQTFDY (SEQ ID NO: 305)
KE63 Hu03 VH	GSTFSDFE (SEQ ID NO: 94)	IDPETGGT (SEQ ID NO: 95)	TRNYDGYSQTFDY (SEQ ID NO: 305)
KE63 Hu04 VH	GSTFSDFE (SEQ ID NO: 94)	IDPETGGT (SEQ ID NO: 95)	TRNYDGYSQTFDY (SEQ ID NO: 305)
KE94 Hu01 VH	GSTFTDFE (SEQ ID NO: 100)	IDPETGGT (SEQ ID NO: 101)	TRNYDGYSRTFDY (SEQ ID NO: 307)
KE94 Hu02 VH	GSTFTDFE (SEQ ID NO: 100)	IDPETGGT (SEQ ID NO: 101)	TRNYDGYSRTFDY (SEQ ID NO: 307)
KE94 Hu03 VH	GSTFTDFE (SEQ ID NO: 100)	IDPETGGT (SEQ ID NO: 101)	TRNYDGYSRTFDY (SEQ ID NO: 307)
KE94 Hu04 VH	GSTFTDFE (SEQ ID NO: 100)	IDPETGGT (SEQ ID NO: 101)	TRNYDGYSRTFDY (SEQ ID NO: 307)

LIGHT Chain			
VL Chain ID	LCDRI-IMGT	LCDR2-IMGT	LCDR3-IMGT

KC18_VL	QSLLYSNNQKNY (SEQ ID NO: 73)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KE35_VL	QDINKF (SEQ ID NO: 79)	YTS (SEQ ID NO: 80)	LQYDNLLWT (SEQ ID NO: 81)
KE42_VL	QDINKF (SEQ ID NO: 85)	YTS (SEQ ID NO: 86)	LQYDNLLWT (SEQ ID NO: 87)
KE58_VL	QDVSTG (SEQ ID NO: 91)	WAS (SEQ ID NO: 92)	QQHYSTPLT (SEQ ID NO: 93)
KE63_VL	QSVLYSSNQKNY (SEQ ID NO: 97)	WAS (SEQ ID NO: 98)	HQYLSSYT (SEQ ID NO: 99)
KE94_VL	QSVLYSSNQKNY (SEQ ID NO: 103)	WAS (SEQ ID NO: 104)	HQYLSSYT (SEQ ID NO: 105)
KC18_Hu18_VL	QSVLYSNNKNY (SEQ ID NO: 302)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18Lrw1	QSLLYSNNQKNY (SEQ ID NO: 73)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18Lrw2	QSVLYSNNKNY (SEQ ID NO: X)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18Lrw3	QSVLYSNNKNY (SEQ ID NO: 302)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL1	QSVLYSSNQKNY (SEQ ID NO: 97)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL1b	QSVLYSNNQKNY (SEQ ID NO: 315)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL1c	QSVLYSSNQKNY (SEQ ID NO: 97)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL1d	QSVLYSSNQKNY (SEQ ID NO: 97)	YAS (SEQ ID NO: 303)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL2	QSLLYSNNQKNY (SEQ ID NO: 73)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL3	QSLHSSNNQKNY (SEQ ID NO: 317)	WGS (SEQ ID NO: 316)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL3b	QSLLYSNNQKNY (SEQ ID NO: 73)	WGS (SEQ ID NO: 316)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL4	QSLLYSNNQKNY (SEQ ID NO: 73)	WGS (SEQ ID NO: 316)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL5	QGISYSNNQKNY (SEQ ID NO: X)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18_CL_VL6	QSLLYSNNQKNY (SEQ ID NO: 73)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18_VL_3	QSVLYSNNKNY (SEQ ID NO: 302)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KC18_VL_14	QSVLYSDNQKNY (SEQ ID NO: 306)	YAS (SEQ ID NO: 303)	QQYYSYRT (SEQ ID NO: 75)
KC18_VL_15	QSVLYSDNQKNY (SEQ ID NO: 306)	FAS (SEQ ID NO: 304)	QQYYSYRT (SEQ ID NO: 75)
KE63_Hu01_VL	QSVLYSSNQKNY (SEQ ID NO: 97)	WAS (SEQ ID NO: 98)	HQYLSSYT (SEQ ID NO: 99)
KE63_Hu02_VL	QSVLYSSNQKNY (SEQ ID NO: 97)	WAS (SEQ ID NO: 98)	HQYLSPYT (SEQ ID NO: 314)
KE63_Hu03_VL	QSVLYSDNQKNY (SEQ ID NO: 306)	YAS (SEQ ID NO: 303)	HQYLSPYT (SEQ ID NO: 314)
KE63_Hu04_VL	QSVLYSDNQKNY (SEQ ID NO: 306)	FAS (SEQ ID NO: 304)	HQYLSPYT (SEQ ID NO: 314)
KE94_Hu01_VL	QSVLYSSNQKNY (SEQ ID NO: 97)	WAS (SEQ ID NO: 104)	HQYLSSYT (SEQ ID NO: 105)
KE94_Hu02_VL	QSVLYSSNQKNY	WAS	HQYLSPYT

	(SEQ ID NO: 97)	(SEQ ID NO: 104)	(SEQ ID NO: 314)
KE94 Hu03 VL	QSVLYSDNQKNY (SEQ ID NO: 306)	YAS (SEQ ID NO: 303)	HQYLSPTY (SEQ ID NO: 314)
KE94 Hu04 VL	QSVLYSDNQKNY (SEQ ID NO: 306)	FAS (SEQ ID NO: 304)	HQYLSPTY (SEQ ID NO: 314)

[0167] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof comprise an antibody heavy chain variable (VH) domain comprising a CDR-H1 sequence, a CDR-H2 sequence, and a CDR-H3 sequence. The CDR-H1 sequence comprises the amino acid sequence of GX¹TFTDX²E (SEQ ID NO: 157), wherein X¹ comprises Y or D and X² comprises F or Y; the CDR-H2 sequence comprises the amino acid sequence of IDPETGX³T (SEQ ID NO: 158), wherein X³ comprises G or S; or CDR-H2 sequence comprising the amino acid sequence of INPNNGX⁴T (SEQ ID NO: 159), wherein X⁴ comprises G or V; or CDR-H2 sequence comprising the amino acid sequence of VX⁵PETGGT (SEQ ID NO: 160), wherein X⁵ comprises D or E; and the CDR-H3 sequence comprises the amino acid sequence of TRX⁶YX⁷GYX⁸X⁹X¹⁰X¹¹DY (SEQ ID NO: 161), wherein X⁶ comprises T or N, X⁷ comprises D or E, X⁸ comprises S or P, X⁹ comprises Q, R, or Y, X¹⁰ comprises T or A, X¹¹ comprises F or M.

[0168] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof comprise an antibody light chain variable (VL) domain comprising a CDR-L1 sequence, a CDR-L2 sequence, and a CDR-L3 sequence. The CDR-L1 sequence comprises the amino acid sequence of QS X¹²LYS X¹³N X¹⁴KNY (SEQ ID NO: 162), wherein X¹² comprises L or V, X¹³ comprises N, D, or S, and X¹⁴ comprises Q or N; the CDR-L2 sequence comprises the amino acid sequence of X¹⁵AS (SEQ ID NO: 163), wherein X¹⁵ comprises W, Y, or F; and the CDR-L3 sequence comprises the amino acid sequence of QQYYSYRT (SEQ ID NO: 75), LQYDNLLWT (SEQ ID NO: 81), or HQYLSX¹⁶YT (SEQ ID NO: 290), wherein X¹⁶ comprises P or S.

[0169] In one aspect, the disclosure provides an antigen-binding protein or fragment thereof that specifically binds to fibroblast growth factor receptor 3 (FGFR3), comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain, wherein:

[0170] (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GX¹TFTDX²E (SEQ ID NO: 157), wherein X¹ comprises Y or D and X² comprises F or Y; a CDR-H2 sequence comprising the amino acid sequence of IDPETGX³T (SEQ ID NO: 158), wherein X³ comprises G or S; or CDR-H2 sequence

comprising the amino acid sequence of INPNNGX⁴T (SEQ ID NO: 159), wherein X⁴ comprises G or V; or CDR-H2 sequence comprising the amino acid sequence of VX⁵PETGGT (SEQ ID NO: 160), wherein X⁵ comprises D or E; a CDR-H3 sequence comprising the amino acid sequence of TRX⁶YX⁷GYX⁸X⁹X¹⁰X¹¹DY (SEQ ID NO: 161), wherein X⁶ comprises T or N, X⁷ comprises D or E, X⁸ comprises S or P, X⁹ comprises Q, R, or Y, X¹⁰ comprises T or A, X¹¹ comprises F or M; and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QS X¹²LYS X¹³N X¹⁴KNY (SEQ ID NO: 162), wherein X¹² comprises L or V, X¹³ comprises N, D, or S, and X¹⁴ comprises Q or N; a CDR-L2 sequence comprising the amino acid sequence of X¹⁵AS (SEQ ID NO: 163), wherein X¹⁵ comprises W, Y, or F; a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75), LQYDNLLWT (SEQ ID NO: 81), or HQYLSX¹⁶YT (SEQ ID NO: 290) wherein X¹⁶ comprises P or S;

[0171] (b) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82); a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83); a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGAMDY (SEQ ID NO: 78); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85); a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86); a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87);

[0172] (c) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82); a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83); a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGSMDF (SEQ ID NO: 84); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85); a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86); a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87);

[0173] (d) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTVTDYY (SEQ ID NO: 88); a CDR-H2 sequence comprising the amino acid sequence of INPNNGVT (SEQ ID NO: 89); a CDR-H3 sequence comprising the amino acid sequence of AREEDFDGFDY (SEQ ID NO: 90); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVSTG (SEQ

ID NO: 91); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104); a CDR-L3 sequence comprising the amino acid sequence of QQHYSTPLT (SEQ ID NO: 93);

[0174] (e) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFSDFE (SEQ ID NO: 94); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101); a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTX¹⁷DY (SEQ ID NO: 308), wherein X¹⁷ comprises M or F; and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSX¹⁸NQKNY (SEQ ID NO: 309), wherein X¹⁸ comprises S or D; a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104); a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105); or

[0175] (f) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFTDFE (SEQ ID NO: 100); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101); a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTX¹⁷DY (SEQ ID NO: 308), wherein X¹⁷ comprises M or F; and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSX¹⁸NQKNY (SEQ ID NO: 309), wherein X¹⁸ comprises S or D; a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104); a CDR-L3 sequence comprising the amino acid sequence of HQYLSSYT (SEQ ID NOs: 99 and 105).

[0176] In certain embodiments, the antigen binding protein or fragment thereof comprises a VH domain and a VL domain, wherein:

[0177] (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), GDTFTDYE (SEQ ID NO: 295), or GYTFTDFE (SEQ ID NO: 296); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101), VDPETGGT (SEQ ID NO: 297), IDPETGST (SEQ ID NO: 298), or VEPETGGT (SEQ ID NO: 299); a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPYAMDY (SEQ ID NO: 72), TRTYEGYPYAMDY (SEQ ID NO: 300), or TRTYDGYPYAFDY (SEQ ID NO: 301); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLLYSNNQKNY (SEQ ID NO: 73), QSVLYSNNQKNY (SEQ ID NO: 302), or QSVLYSDNQKNY (SEQ ID NO: 306); a CDR-L2 sequence comprising the

amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104), YAS (SEQ ID NO: 303), or FAS (SEQ ID NO: 304); a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75);

[0178] (b) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82); a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83); a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGAMDY (SEQ ID NO: 78); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85); a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86); a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87);

[0179] (c) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82); a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83); a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGSMDF (SEQ ID NO: 84); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85); a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86); a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87);

[0180] (d) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTVTDYY (SEQ ID NO: 88); a CDR-H2 sequence comprising the amino acid sequence of INPNNGVT (SEQ ID NO: 89); a CDR-H3 sequence comprising the amino acid sequence of AREEDFDGFDY (SEQ ID NO: 90); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVSTG (SEQ ID NO: 91); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, 104); a CDR-L3 sequence comprising the amino acid sequence of QQHYSTPLT (SEQ ID NO: 93);

[0181] (e) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFSDFE (SEQ ID NO: 94); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101); a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTMDY (SEQ ID NO: 96) or TRNYDGYSQTFDY (SEQ ID NO: 305); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NOs: 97

and 103) or QSVLYSDNQKNY (SEQ ID NO: 306); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104); a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105); or

[0182] (f) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFTDFE (SEQ ID NO: 100); a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101); a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSRTMDY (SEQ ID NO: 102) or TRNYDGYSRTFDY (SEQ ID NO: 307); and the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NOs: 97 and 103) or QSVLYSDNQKNY (SEQ ID NO: 306); a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, 104); a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105).

[0183] In certain embodiments, the FGFR3 antigen binding proteins and antigen-binding fragments thereof comprise one VH domain and one VL domain recited in Table 3, 8, 9, or 13. In certain embodiments, exemplary antigen-binding proteins or antigen-binding fragments thereof are provided:

Table 1.1 Heavy chains and light chains of exemplary antigen-binding proteins or antigen-binding fragments

No.	Heavy Chain	Light Chain	No.	Heavy Chain	Light Chain
1	SEQ ID NO: 6	SEQ ID NO: 7	867	SEQ ID NO: 235	SEQ ID NO: 142
2	SEQ ID NO: 6	SEQ ID NO: 9	868	SEQ ID NO: 236	SEQ ID NO: 142
3	SEQ ID NO: 6	SEQ ID NO: 11	869	SEQ ID NO: 237	SEQ ID NO: 142
4	SEQ ID NO: 6	SEQ ID NO: 13	870	SEQ ID NO: 238	SEQ ID NO: 142
5	SEQ ID NO: 6	SEQ ID NO: 15	871	SEQ ID NO: 239	SEQ ID NO: 142
6	SEQ ID NO: 6	SEQ ID NO: 17	872	SEQ ID NO: 240	SEQ ID NO: 142
7	SEQ ID NO: 8	SEQ ID NO: 7	873	SEQ ID NO: 241	SEQ ID NO: 142
8	SEQ ID NO: 8	SEQ ID NO: 9	874	SEQ ID NO: 242	SEQ ID NO: 142
9	SEQ ID NO: 8	SEQ ID NO: 11	875	SEQ ID NO: 243	SEQ ID NO: 142
10	SEQ ID NO: 8	SEQ ID NO: 13	876	SEQ ID NO: 244	SEQ ID NO: 142
11	SEQ ID NO: 8	SEQ ID NO: 15	877	SEQ ID NO: 245	SEQ ID NO: 142
12	SEQ ID NO: 8	SEQ ID NO: 17	878	SEQ ID NO: 246	SEQ ID NO: 142
13	SEQ ID NO: 10	SEQ ID NO: 7	879	SEQ ID NO: 247	SEQ ID NO: 142
14	SEQ ID NO: 10	SEQ ID NO: 9	880	SEQ ID NO: 248	SEQ ID NO: 142
15	SEQ ID NO: 10	SEQ ID NO: 11	881	SEQ ID NO: 249	SEQ ID NO: 142
16	SEQ ID NO: 10	SEQ ID NO: 13	882	SEQ ID NO: 250	SEQ ID NO: 142
17	SEQ ID NO: 10	SEQ ID NO: 15	883	SEQ ID NO: 251	SEQ ID NO: 142
18	SEQ ID NO: 10	SEQ ID NO: 17	884	SEQ ID NO: 252	SEQ ID NO: 142
19	SEQ ID NO: 12	SEQ ID NO: 7	885	SEQ ID NO: 253	SEQ ID NO: 142
20	SEQ ID NO: 12	SEQ ID NO: 9	886	SEQ ID NO: 254	SEQ ID NO: 142
21	SEQ ID NO: 12	SEQ ID NO: 11	887	SEQ ID NO: 255	SEQ ID NO: 142
22	SEQ ID NO: 12	SEQ ID NO: 13	888	SEQ ID NO: 256	SEQ ID NO: 142
23	SEQ ID NO: 12	SEQ ID NO: 15	889	SEQ ID NO: 257	SEQ ID NO: 142
24	SEQ ID NO: 12	SEQ ID NO: 17	890	SEQ ID NO: 258	SEQ ID NO: 142
25	SEQ ID NO: 14	SEQ ID NO: 7	891	SEQ ID NO: 259	SEQ ID NO: 142
26	SEQ ID NO: 14	SEQ ID NO: 9	892	SEQ ID NO: 260	SEQ ID NO: 142
27	SEQ ID NO: 14	SEQ ID NO: 11	893	SEQ ID NO: 261	SEQ ID NO: 142
28	SEQ ID NO: 14	SEQ ID NO: 13	894	SEQ ID NO: 262	SEQ ID NO: 142
29	SEQ ID NO: 14	SEQ ID NO: 15	895	SEQ ID NO: 263	SEQ ID NO: 142

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572	SEQ ID NO: 115	SEQ ID NO: 24	1438	SEQ ID NO: 266	SEQ ID NO: 150
573	SEQ ID NO: 115	SEQ ID NO: 25	1439	SEQ ID NO: 267	SEQ ID NO: 150
574	SEQ ID NO: 115	SEQ ID NO: 26	1440	SEQ ID NO: 268	SEQ ID NO: 150
575	SEQ ID NO: 115	SEQ ID NO: 27	1441	SEQ ID NO: 269	SEQ ID NO: 150
576	SEQ ID NO: 115	SEQ ID NO: 32	1442	SEQ ID NO: 270	SEQ ID NO: 150
577	SEQ ID NO: 115	SEQ ID NO: 33	1443	SEQ ID NO: 271	SEQ ID NO: 150
578	SEQ ID NO: 115	SEQ ID NO: 34	1444	SEQ ID NO: 272	SEQ ID NO: 150
579	SEQ ID NO: 115	SEQ ID NO: 35	1445	SEQ ID NO: 273	SEQ ID NO: 150
580	SEQ ID NO: 115	SEQ ID NO: 59	1446	SEQ ID NO: 274	SEQ ID NO: 150
581	SEQ ID NO: 115	SEQ ID NO: 60	1447	SEQ ID NO: 275	SEQ ID NO: 150
582	SEQ ID NO: 115	SEQ ID NO: 61	1448	SEQ ID NO: 276	SEQ ID NO: 150
583	SEQ ID NO: 115	SEQ ID NO: 67	1449	SEQ ID NO: 277	SEQ ID NO: 150
584	SEQ ID NO: 115	SEQ ID NO: 69	1450	SEQ ID NO: 278	SEQ ID NO: 150
585	SEQ ID NO: 115	SEQ ID NO: 112	1451	SEQ ID NO: 279	SEQ ID NO: 150
586	SEQ ID NO: 115	SEQ ID NO: 113	1452	SEQ ID NO: 280	SEQ ID NO: 150
587	SEQ ID NO: 115	SEQ ID NO: 114	1453	SEQ ID NO: 281	SEQ ID NO: 150
588	SEQ ID NO: 115	SEQ ID NO: 123	1454	SEQ ID NO: 282	SEQ ID NO: 150
589	SEQ ID NO: 115	SEQ ID NO: 124	1455	SEQ ID NO: 283	SEQ ID NO: 150

590	SEQ ID NO: 115	SEQ ID NO: 125	1456	SEQ ID NO: 284	SEQ ID NO: 150
591	SEQ ID NO: 115	SEQ ID NO: 126	1457	SEQ ID NO: 285	SEQ ID NO: 150
592	SEQ ID NO: 115	SEQ ID NO: 127	1458	SEQ ID NO: 286	SEQ ID NO: 150
593	SEQ ID NO: 115	SEQ ID NO: 128	1459	SEQ ID NO: 287	SEQ ID NO: 150
594	SEQ ID NO: 115	SEQ ID NO: 129	1460	SEQ ID NO: 288	SEQ ID NO: 150
595	SEQ ID NO: 115	SEQ ID NO: 130	1461	SEQ ID NO: 289	SEQ ID NO: 150
596	SEQ ID NO: 115	SEQ ID NO: 131	1462	SEQ ID NO: 141	SEQ ID NO: 152
597	SEQ ID NO: 115	SEQ ID NO: 132	1463	SEQ ID NO: 143	SEQ ID NO: 152
598	SEQ ID NO: 116	SEQ ID NO: 19	1464	SEQ ID NO: 145	SEQ ID NO: 152
599	SEQ ID NO: 116	SEQ ID NO: 24	1465	SEQ ID NO: 147	SEQ ID NO: 152
600	SEQ ID NO: 116	SEQ ID NO: 25	1466	SEQ ID NO: 149	SEQ ID NO: 152
601	SEQ ID NO: 116	SEQ ID NO: 26	1467	SEQ ID NO: 151	SEQ ID NO: 152
602	SEQ ID NO: 116	SEQ ID NO: 27	1468	SEQ ID NO: 153	SEQ ID NO: 152
603	SEQ ID NO: 116	SEQ ID NO: 32	1469	SEQ ID NO: 155	SEQ ID NO: 152
604	SEQ ID NO: 116	SEQ ID NO: 33	1470	SEQ ID NO: 156	SEQ ID NO: 152
605	SEQ ID NO: 116	SEQ ID NO: 34	1471	SEQ ID NO: 164	SEQ ID NO: 152
606	SEQ ID NO: 116	SEQ ID NO: 35	1472	SEQ ID NO: 165	SEQ ID NO: 152
607	SEQ ID NO: 116	SEQ ID NO: 59	1473	SEQ ID NO: 166	SEQ ID NO: 152
608	SEQ ID NO: 116	SEQ ID NO: 60	1474	SEQ ID NO: 167	SEQ ID NO: 152
609	SEQ ID NO: 116	SEQ ID NO: 61	1475	SEQ ID NO: 168	SEQ ID NO: 152
610	SEQ ID NO: 116	SEQ ID NO: 67	1476	SEQ ID NO: 169	SEQ ID NO: 152
611	SEQ ID NO: 116	SEQ ID NO: 69	1477	SEQ ID NO: 170	SEQ ID NO: 152
612	SEQ ID NO: 116	SEQ ID NO: 112	1478	SEQ ID NO: 171	SEQ ID NO: 152
613	SEQ ID NO: 116	SEQ ID NO: 113	1479	SEQ ID NO: 172	SEQ ID NO: 152
614	SEQ ID NO: 116	SEQ ID NO: 114	1480	SEQ ID NO: 173	SEQ ID NO: 152
615	SEQ ID NO: 116	SEQ ID NO: 123	1481	SEQ ID NO: 174	SEQ ID NO: 152
616	SEQ ID NO: 116	SEQ ID NO: 124	1482	SEQ ID NO: 175	SEQ ID NO: 152
617	SEQ ID NO: 116	SEQ ID NO: 125	1483	SEQ ID NO: 176	SEQ ID NO: 152
618	SEQ ID NO: 116	SEQ ID NO: 126	1484	SEQ ID NO: 177	SEQ ID NO: 152
619	SEQ ID NO: 116	SEQ ID NO: 127	1485	SEQ ID NO: 178	SEQ ID NO: 152
620	SEQ ID NO: 116	SEQ ID NO: 128	1486	SEQ ID NO: 179	SEQ ID NO: 152
621	SEQ ID NO: 116	SEQ ID NO: 129	1487	SEQ ID NO: 180	SEQ ID NO: 152
622	SEQ ID NO: 116	SEQ ID NO: 130	1488	SEQ ID NO: 181	SEQ ID NO: 152
623	SEQ ID NO: 116	SEQ ID NO: 131	1489	SEQ ID NO: 182	SEQ ID NO: 152
624	SEQ ID NO: 116	SEQ ID NO: 132	1490	SEQ ID NO: 183	SEQ ID NO: 152
625	SEQ ID NO: 117	SEQ ID NO: 19	1491	SEQ ID NO: 184	SEQ ID NO: 152
626	SEQ ID NO: 117	SEQ ID NO: 24	1492	SEQ ID NO: 185	SEQ ID NO: 152
627	SEQ ID NO: 117	SEQ ID NO: 25	1493	SEQ ID NO: 186	SEQ ID NO: 152
628	SEQ ID NO: 117	SEQ ID NO: 26	1494	SEQ ID NO: 187	SEQ ID NO: 152
629	SEQ ID NO: 117	SEQ ID NO: 27	1495	SEQ ID NO: 188	SEQ ID NO: 152
630	SEQ ID NO: 117	SEQ ID NO: 32	1496	SEQ ID NO: 189	SEQ ID NO: 152
631	SEQ ID NO: 117	SEQ ID NO: 33	1497	SEQ ID NO: 190	SEQ ID NO: 152
632	SEQ ID NO: 117	SEQ ID NO: 34	1498	SEQ ID NO: 191	SEQ ID NO: 152
633	SEQ ID NO: 117	SEQ ID NO: 35	1499	SEQ ID NO: 192	SEQ ID NO: 152
634	SEQ ID NO: 117	SEQ ID NO: 59	1500	SEQ ID NO: 193	SEQ ID NO: 152
635	SEQ ID NO: 117	SEQ ID NO: 60	1501	SEQ ID NO: 194	SEQ ID NO: 152
636	SEQ ID NO: 117	SEQ ID NO: 61	1502	SEQ ID NO: 195	SEQ ID NO: 152
637	SEQ ID NO: 117	SEQ ID NO: 67	1503	SEQ ID NO: 196	SEQ ID NO: 152
638	SEQ ID NO: 117	SEQ ID NO: 69	1504	SEQ ID NO: 197	SEQ ID NO: 152
639	SEQ ID NO: 117	SEQ ID NO: 112	1505	SEQ ID NO: 198	SEQ ID NO: 152
640	SEQ ID NO: 117	SEQ ID NO: 113	1506	SEQ ID NO: 199	SEQ ID NO: 152
641	SEQ ID NO: 117	SEQ ID NO: 114	1507	SEQ ID NO: 200	SEQ ID NO: 152
642	SEQ ID NO: 117	SEQ ID NO: 123	1508	SEQ ID NO: 201	SEQ ID NO: 152
643	SEQ ID NO: 117	SEQ ID NO: 124	1509	SEQ ID NO: 202	SEQ ID NO: 152
644	SEQ ID NO: 117	SEQ ID NO: 125	1510	SEQ ID NO: 203	SEQ ID NO: 152
645	SEQ ID NO: 117	SEQ ID NO: 126	1511	SEQ ID NO: 204	SEQ ID NO: 152
646	SEQ ID NO: 117	SEQ ID NO: 127	1512	SEQ ID NO: 205	SEQ ID NO: 152
647	SEQ ID NO: 117	SEQ ID NO: 128	1513	SEQ ID NO: 206	SEQ ID NO: 152
648	SEQ ID NO: 117	SEQ ID NO: 129	1514	SEQ ID NO: 207	SEQ ID NO: 152
649	SEQ ID NO: 117	SEQ ID NO: 130	1515	SEQ ID NO: 208	SEQ ID NO: 152
650	SEQ ID NO: 117	SEQ ID NO: 131	1516	SEQ ID NO: 209	SEQ ID NO: 152
651	SEQ ID NO: 117	SEQ ID NO: 132	1517	SEQ ID NO: 210	SEQ ID NO: 152
652	SEQ ID NO: 118	SEQ ID NO: 19	1518	SEQ ID NO: 211	SEQ ID NO: 152
653	SEQ ID NO: 118	SEQ ID NO: 24	1519	SEQ ID NO: 212	SEQ ID NO: 152
654	SEQ ID NO: 118	SEQ ID NO: 25	1520	SEQ ID NO: 213	SEQ ID NO: 152
655	SEQ ID NO: 118	SEQ ID NO: 26	1521	SEQ ID NO: 214	SEQ ID NO: 152
656	SEQ ID NO: 118	SEQ ID NO: 27	1522	SEQ ID NO: 215	SEQ ID NO: 152
657	SEQ ID NO: 118	SEQ ID NO: 32	1523	SEQ ID NO: 216	SEQ ID NO: 152
658	SEQ ID NO: 118	SEQ ID NO: 33	1524	SEQ ID NO: 217	SEQ ID NO: 152
659	SEQ ID NO: 118	SEQ ID NO: 34	1525	SEQ ID NO: 218	SEQ ID NO: 152

660	SEQ ID NO: 118	SEQ ID NO: 35	1526	SEQ ID NO: 219	SEQ ID NO: 152
661	SEQ ID NO: 118	SEQ ID NO: 59	1527	SEQ ID NO: 220	SEQ ID NO: 152
662	SEQ ID NO: 118	SEQ ID NO: 60	1528	SEQ ID NO: 221	SEQ ID NO: 152
663	SEQ ID NO: 118	SEQ ID NO: 61	1529	SEQ ID NO: 222	SEQ ID NO: 152
664	SEQ ID NO: 118	SEQ ID NO: 67	1530	SEQ ID NO: 223	SEQ ID NO: 152
665	SEQ ID NO: 118	SEQ ID NO: 69	1531	SEQ ID NO: 224	SEQ ID NO: 152
666	SEQ ID NO: 118	SEQ ID NO: 112	1532	SEQ ID NO: 225	SEQ ID NO: 152
667	SEQ ID NO: 118	SEQ ID NO: 113	1533	SEQ ID NO: 226	SEQ ID NO: 152
668	SEQ ID NO: 118	SEQ ID NO: 114	1534	SEQ ID NO: 227	SEQ ID NO: 152
669	SEQ ID NO: 118	SEQ ID NO: 123	1535	SEQ ID NO: 228	SEQ ID NO: 152
670	SEQ ID NO: 118	SEQ ID NO: 124	1536	SEQ ID NO: 229	SEQ ID NO: 152
671	SEQ ID NO: 118	SEQ ID NO: 125	1537	SEQ ID NO: 230	SEQ ID NO: 152
672	SEQ ID NO: 118	SEQ ID NO: 126	1538	SEQ ID NO: 231	SEQ ID NO: 152
673	SEQ ID NO: 118	SEQ ID NO: 127	1539	SEQ ID NO: 232	SEQ ID NO: 152
674	SEQ ID NO: 118	SEQ ID NO: 128	1540	SEQ ID NO: 233	SEQ ID NO: 152
675	SEQ ID NO: 118	SEQ ID NO: 129	1541	SEQ ID NO: 234	SEQ ID NO: 152
676	SEQ ID NO: 118	SEQ ID NO: 130	1542	SEQ ID NO: 235	SEQ ID NO: 152
677	SEQ ID NO: 118	SEQ ID NO: 131	1543	SEQ ID NO: 236	SEQ ID NO: 152
678	SEQ ID NO: 118	SEQ ID NO: 132	1544	SEQ ID NO: 237	SEQ ID NO: 152
679	SEQ ID NO: 119	SEQ ID NO: 19	1545	SEQ ID NO: 238	SEQ ID NO: 152
680	SEQ ID NO: 119	SEQ ID NO: 24	1546	SEQ ID NO: 239	SEQ ID NO: 152
681	SEQ ID NO: 119	SEQ ID NO: 25	1547	SEQ ID NO: 240	SEQ ID NO: 152
682	SEQ ID NO: 119	SEQ ID NO: 26	1548	SEQ ID NO: 241	SEQ ID NO: 152
683	SEQ ID NO: 119	SEQ ID NO: 27	1549	SEQ ID NO: 242	SEQ ID NO: 152
684	SEQ ID NO: 119	SEQ ID NO: 32	1550	SEQ ID NO: 243	SEQ ID NO: 152
685	SEQ ID NO: 119	SEQ ID NO: 33	1551	SEQ ID NO: 244	SEQ ID NO: 152
686	SEQ ID NO: 119	SEQ ID NO: 34	1552	SEQ ID NO: 245	SEQ ID NO: 152
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688	SEQ ID NO: 119	SEQ ID NO: 59	1554	SEQ ID NO: 247	SEQ ID NO: 152
689	SEQ ID NO: 119	SEQ ID NO: 60	1555	SEQ ID NO: 248	SEQ ID NO: 152
690	SEQ ID NO: 119	SEQ ID NO: 61	1556	SEQ ID NO: 249	SEQ ID NO: 152
691	SEQ ID NO: 119	SEQ ID NO: 67	1557	SEQ ID NO: 250	SEQ ID NO: 152
692	SEQ ID NO: 119	SEQ ID NO: 69	1558	SEQ ID NO: 251	SEQ ID NO: 152
693	SEQ ID NO: 119	SEQ ID NO: 112	1559	SEQ ID NO: 252	SEQ ID NO: 152
694	SEQ ID NO: 119	SEQ ID NO: 113	1560	SEQ ID NO: 253	SEQ ID NO: 152
695	SEQ ID NO: 119	SEQ ID NO: 114	1561	SEQ ID NO: 254	SEQ ID NO: 152
696	SEQ ID NO: 119	SEQ ID NO: 123	1562	SEQ ID NO: 255	SEQ ID NO: 152
697	SEQ ID NO: 119	SEQ ID NO: 124	1563	SEQ ID NO: 256	SEQ ID NO: 152
698	SEQ ID NO: 119	SEQ ID NO: 125	1564	SEQ ID NO: 257	SEQ ID NO: 152
699	SEQ ID NO: 119	SEQ ID NO: 126	1565	SEQ ID NO: 258	SEQ ID NO: 152
700	SEQ ID NO: 119	SEQ ID NO: 127	1566	SEQ ID NO: 259	SEQ ID NO: 152
701	SEQ ID NO: 119	SEQ ID NO: 128	1567	SEQ ID NO: 260	SEQ ID NO: 152
702	SEQ ID NO: 119	SEQ ID NO: 129	1568	SEQ ID NO: 261	SEQ ID NO: 152
703	SEQ ID NO: 119	SEQ ID NO: 130	1569	SEQ ID NO: 262	SEQ ID NO: 152
704	SEQ ID NO: 119	SEQ ID NO: 131	1570	SEQ ID NO: 263	SEQ ID NO: 152
705	SEQ ID NO: 119	SEQ ID NO: 132	1571	SEQ ID NO: 264	SEQ ID NO: 152
706	SEQ ID NO: 120	SEQ ID NO: 19	1572	SEQ ID NO: 265	SEQ ID NO: 152
707	SEQ ID NO: 120	SEQ ID NO: 24	1573	SEQ ID NO: 266	SEQ ID NO: 152
708	SEQ ID NO: 120	SEQ ID NO: 25	1574	SEQ ID NO: 267	SEQ ID NO: 152
709	SEQ ID NO: 120	SEQ ID NO: 26	1575	SEQ ID NO: 268	SEQ ID NO: 152
710	SEQ ID NO: 120	SEQ ID NO: 27	1576	SEQ ID NO: 269	SEQ ID NO: 152
711	SEQ ID NO: 120	SEQ ID NO: 32	1577	SEQ ID NO: 270	SEQ ID NO: 152
712	SEQ ID NO: 120	SEQ ID NO: 33	1578	SEQ ID NO: 271	SEQ ID NO: 152
713	SEQ ID NO: 120	SEQ ID NO: 34	1579	SEQ ID NO: 272	SEQ ID NO: 152
714	SEQ ID NO: 120	SEQ ID NO: 35	1580	SEQ ID NO: 273	SEQ ID NO: 152
715	SEQ ID NO: 120	SEQ ID NO: 59	1581	SEQ ID NO: 274	SEQ ID NO: 152
716	SEQ ID NO: 120	SEQ ID NO: 60	1582	SEQ ID NO: 275	SEQ ID NO: 152
717	SEQ ID NO: 120	SEQ ID NO: 61	1583	SEQ ID NO: 276	SEQ ID NO: 152
718	SEQ ID NO: 120	SEQ ID NO: 67	1584	SEQ ID NO: 277	SEQ ID NO: 152
719	SEQ ID NO: 120	SEQ ID NO: 69	1585	SEQ ID NO: 278	SEQ ID NO: 152
720	SEQ ID NO: 120	SEQ ID NO: 112	1586	SEQ ID NO: 279	SEQ ID NO: 152
721	SEQ ID NO: 120	SEQ ID NO: 113	1587	SEQ ID NO: 280	SEQ ID NO: 152
722	SEQ ID NO: 120	SEQ ID NO: 114	1588	SEQ ID NO: 281	SEQ ID NO: 152
723	SEQ ID NO: 120	SEQ ID NO: 123	1589	SEQ ID NO: 282	SEQ ID NO: 152
724	SEQ ID NO: 120	SEQ ID NO: 124	1590	SEQ ID NO: 283	SEQ ID NO: 152
725	SEQ ID NO: 120	SEQ ID NO: 125	1591	SEQ ID NO: 284	SEQ ID NO: 152
726	SEQ ID NO: 120	SEQ ID NO: 126	1592	SEQ ID NO: 285	SEQ ID NO: 152
727	SEQ ID NO: 120	SEQ ID NO: 127	1593	SEQ ID NO: 286	SEQ ID NO: 152
728	SEQ ID NO: 120	SEQ ID NO: 128	1594	SEQ ID NO: 287	SEQ ID NO: 152
729	SEQ ID NO: 120	SEQ ID NO: 129	1595	SEQ ID NO: 288	SEQ ID NO: 152

730	SEQ ID NO: 120	SEQ ID NO: 130	1596	SEQ ID NO: 289	SEQ ID NO: 152
731	SEQ ID NO: 120	SEQ ID NO: 131	1597	SEQ ID NO: 141	SEQ ID NO: 154
732	SEQ ID NO: 120	SEQ ID NO: 132	1598	SEQ ID NO: 143	SEQ ID NO: 154
733	SEQ ID NO: 121	SEQ ID NO: 19	1599	SEQ ID NO: 145	SEQ ID NO: 154
734	SEQ ID NO: 121	SEQ ID NO: 24	1600	SEQ ID NO: 147	SEQ ID NO: 154
735	SEQ ID NO: 121	SEQ ID NO: 25	1601	SEQ ID NO: 149	SEQ ID NO: 154
736	SEQ ID NO: 121	SEQ ID NO: 26	1602	SEQ ID NO: 151	SEQ ID NO: 154
737	SEQ ID NO: 121	SEQ ID NO: 27	1603	SEQ ID NO: 153	SEQ ID NO: 154
738	SEQ ID NO: 121	SEQ ID NO: 32	1604	SEQ ID NO: 155	SEQ ID NO: 154
739	SEQ ID NO: 121	SEQ ID NO: 33	1605	SEQ ID NO: 156	SEQ ID NO: 154
740	SEQ ID NO: 121	SEQ ID NO: 34	1606	SEQ ID NO: 164	SEQ ID NO: 154
741	SEQ ID NO: 121	SEQ ID NO: 35	1607	SEQ ID NO: 165	SEQ ID NO: 154
742	SEQ ID NO: 121	SEQ ID NO: 59	1608	SEQ ID NO: 166	SEQ ID NO: 154
743	SEQ ID NO: 121	SEQ ID NO: 60	1609	SEQ ID NO: 167	SEQ ID NO: 154
744	SEQ ID NO: 121	SEQ ID NO: 61	1610	SEQ ID NO: 168	SEQ ID NO: 154
745	SEQ ID NO: 121	SEQ ID NO: 67	1611	SEQ ID NO: 169	SEQ ID NO: 154
746	SEQ ID NO: 121	SEQ ID NO: 69	1612	SEQ ID NO: 170	SEQ ID NO: 154
747	SEQ ID NO: 121	SEQ ID NO: 112	1613	SEQ ID NO: 171	SEQ ID NO: 154
748	SEQ ID NO: 121	SEQ ID NO: 113	1614	SEQ ID NO: 172	SEQ ID NO: 154
749	SEQ ID NO: 121	SEQ ID NO: 114	1615	SEQ ID NO: 173	SEQ ID NO: 154
750	SEQ ID NO: 121	SEQ ID NO: 123	1616	SEQ ID NO: 174	SEQ ID NO: 154
751	SEQ ID NO: 121	SEQ ID NO: 124	1617	SEQ ID NO: 175	SEQ ID NO: 154
752	SEQ ID NO: 121	SEQ ID NO: 125	1618	SEQ ID NO: 176	SEQ ID NO: 154
753	SEQ ID NO: 121	SEQ ID NO: 126	1619	SEQ ID NO: 177	SEQ ID NO: 154
754	SEQ ID NO: 121	SEQ ID NO: 127	1620	SEQ ID NO: 178	SEQ ID NO: 154
755	SEQ ID NO: 121	SEQ ID NO: 128	1621	SEQ ID NO: 179	SEQ ID NO: 154
756	SEQ ID NO: 121	SEQ ID NO: 129	1622	SEQ ID NO: 180	SEQ ID NO: 154
757	SEQ ID NO: 121	SEQ ID NO: 130	1623	SEQ ID NO: 181	SEQ ID NO: 154
758	SEQ ID NO: 121	SEQ ID NO: 131	1624	SEQ ID NO: 182	SEQ ID NO: 154
759	SEQ ID NO: 121	SEQ ID NO: 132	1625	SEQ ID NO: 183	SEQ ID NO: 154
760	SEQ ID NO: 122	SEQ ID NO: 19	1626	SEQ ID NO: 184	SEQ ID NO: 154
761	SEQ ID NO: 122	SEQ ID NO: 24	1627	SEQ ID NO: 185	SEQ ID NO: 154
762	SEQ ID NO: 122	SEQ ID NO: 25	1628	SEQ ID NO: 186	SEQ ID NO: 154
763	SEQ ID NO: 122	SEQ ID NO: 26	1629	SEQ ID NO: 187	SEQ ID NO: 154
764	SEQ ID NO: 122	SEQ ID NO: 27	1630	SEQ ID NO: 188	SEQ ID NO: 154
765	SEQ ID NO: 122	SEQ ID NO: 32	1631	SEQ ID NO: 189	SEQ ID NO: 154
766	SEQ ID NO: 122	SEQ ID NO: 33	1632	SEQ ID NO: 190	SEQ ID NO: 154
767	SEQ ID NO: 122	SEQ ID NO: 34	1633	SEQ ID NO: 191	SEQ ID NO: 154
768	SEQ ID NO: 122	SEQ ID NO: 35	1634	SEQ ID NO: 192	SEQ ID NO: 154
769	SEQ ID NO: 122	SEQ ID NO: 59	1635	SEQ ID NO: 193	SEQ ID NO: 154
770	SEQ ID NO: 122	SEQ ID NO: 60	1636	SEQ ID NO: 194	SEQ ID NO: 154
771	SEQ ID NO: 122	SEQ ID NO: 61	1637	SEQ ID NO: 195	SEQ ID NO: 154
772	SEQ ID NO: 122	SEQ ID NO: 67	1638	SEQ ID NO: 196	SEQ ID NO: 154
773	SEQ ID NO: 122	SEQ ID NO: 69	1639	SEQ ID NO: 197	SEQ ID NO: 154
774	SEQ ID NO: 122	SEQ ID NO: 112	1640	SEQ ID NO: 198	SEQ ID NO: 154
775	SEQ ID NO: 122	SEQ ID NO: 113	1641	SEQ ID NO: 199	SEQ ID NO: 154
776	SEQ ID NO: 122	SEQ ID NO: 114	1642	SEQ ID NO: 200	SEQ ID NO: 154
777	SEQ ID NO: 122	SEQ ID NO: 123	1643	SEQ ID NO: 201	SEQ ID NO: 154
778	SEQ ID NO: 122	SEQ ID NO: 124	1644	SEQ ID NO: 202	SEQ ID NO: 154
779	SEQ ID NO: 122	SEQ ID NO: 125	1645	SEQ ID NO: 203	SEQ ID NO: 154
780	SEQ ID NO: 122	SEQ ID NO: 126	1646	SEQ ID NO: 204	SEQ ID NO: 154
781	SEQ ID NO: 122	SEQ ID NO: 127	1647	SEQ ID NO: 205	SEQ ID NO: 154
782	SEQ ID NO: 122	SEQ ID NO: 128	1648	SEQ ID NO: 206	SEQ ID NO: 154
783	SEQ ID NO: 122	SEQ ID NO: 129	1649	SEQ ID NO: 207	SEQ ID NO: 154
784	SEQ ID NO: 122	SEQ ID NO: 130	1650	SEQ ID NO: 208	SEQ ID NO: 154
785	SEQ ID NO: 122	SEQ ID NO: 131	1651	SEQ ID NO: 209	SEQ ID NO: 154
786	SEQ ID NO: 122	SEQ ID NO: 132	1652	SEQ ID NO: 210	SEQ ID NO: 154
787	SEQ ID NO: 141	SEQ ID NO: 142	1653	SEQ ID NO: 211	SEQ ID NO: 154
788	SEQ ID NO: 143	SEQ ID NO: 142	1654	SEQ ID NO: 212	SEQ ID NO: 154
789	SEQ ID NO: 145	SEQ ID NO: 142	1655	SEQ ID NO: 213	SEQ ID NO: 154
790	SEQ ID NO: 147	SEQ ID NO: 142	1656	SEQ ID NO: 214	SEQ ID NO: 154
791	SEQ ID NO: 149	SEQ ID NO: 142	1657	SEQ ID NO: 215	SEQ ID NO: 154
792	SEQ ID NO: 151	SEQ ID NO: 142	1658	SEQ ID NO: 216	SEQ ID NO: 154
793	SEQ ID NO: 153	SEQ ID NO: 142	1659	SEQ ID NO: 217	SEQ ID NO: 154
794	SEQ ID NO: 155	SEQ ID NO: 142	1660	SEQ ID NO: 218	SEQ ID NO: 154
795	SEQ ID NO: 156	SEQ ID NO: 142	1661	SEQ ID NO: 219	SEQ ID NO: 154
796	SEQ ID NO: 164	SEQ ID NO: 142	1662	SEQ ID NO: 220	SEQ ID NO: 154
797	SEQ ID NO: 165	SEQ ID NO: 142	1663	SEQ ID NO: 221	SEQ ID NO: 154
798	SEQ ID NO: 166	SEQ ID NO: 142	1664	SEQ ID NO: 222	SEQ ID NO: 154
799	SEQ ID NO: 167	SEQ ID NO: 142	1665	SEQ ID NO: 223	SEQ ID NO: 154

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[0184] In certain embodiments, the anti-FGFR3 antigen binding protein or fragment thereof comprises a pair of heavy chain and light chain of Table 1.1 above.

[0185] In certain embodiments, the anti-FGFR3 antigen binding protein or fragment thereof comprises a VH domain and a VL domain, wherein:

[0186] (a) the VH domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 6, SEQ ID NO: 18, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, and SEQ ID NO: 122,; and the VL domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 7, SEQ ID NO: 19, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, and SEQ ID NO: 132;

[0187] (b) the VH domain comprises the amino acid sequence of SEQ ID NO: 8; and the VL domain comprises the amino acid sequence of SEQ ID NO: 9;

[0188] (c) the VH domain comprises the amino acid sequence of SEQ ID NO: 10; and the VL domain comprises the amino acid sequence of SEQ ID NO: 11;

[0189] (d) the VH domain comprises the amino acid sequence of SEQ ID NO: 12; and the VL domain comprises the amino acid sequence of SEQ ID NO: 13;

[0190] (e) the VH domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 14, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, and SEQ ID NO: 23; and the VL domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 15, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, and SEQ ID NO: 27;

[0191] (f) the VH domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 16, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, and SEQ ID NO: 31; the VL domain comprises the amino acid sequence selected from the group consisting of: SEQ ID NO: 17, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, and SEQ ID NO: 35.

[0192] In certain embodiments, the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 63 or 65, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67 or 69.

[0193] Variants of the anti-FGFR3 antigen binding protein or fragment thereof as described herein are also provided. In certain embodiments, the VH domain of a variant is at least about 80%, at least at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90% identical, at least about 91% identical, at least about 92% identical, at least about 93% identical, at least about 94% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, or at least about 99% identical to the amino acid sequence of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, or SEQ ID NO: 122, and the VL domain of the variant is at least about 80%, at least at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90% identical, at least about 91% identical, at least about 92% identical, at least about 93% identical, at least about 94% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, or at least about 99% identical to the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, or SEQ ID NO: 132. The amino acid sequence alignment for obtaining the identity can be any conventional amino acid sequence alignment tool, and the sequence alignment algorithms includes Needle-Wunsch algorithm, Smith-Waterman algorithm, or Karling & Altschul algorithm, but is not limited thereto; the amino acid sequence alignment tool includes BLAST (Basic Local Alignment Search Tool), BLAT (BLAST-like Alignment Tool), Grapped BLAST or FASTA, but is not limited thereto. In certain embodiments, the variant has all of the identical heavy chain CDRs and light chain CDRs

of the anti-FGFR3 antigen binding protein or fragment thereof as described herein, with modifications in the constant region on the heavy chain and/or the light chain.

[0194] In certain embodiments, the anti-FGFR3 antigen binding protein or fragment thereof comprises an antibody heavy chain at least about 80%, at least at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90% identical, at least about 91% identical, at least about 92% identical, at least about 93% identical, at least about 94% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, or at least about 99% identical to the amino acid sequence of SEQ ID NO: 63 or 65, and an antibody light chain at least about 80%, at least at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90% identical, at least about 91% identical, at least about 92% identical, at least about 93% identical, at least about 94% identical, at least about 95% identical, at least about 96% identical, at least about 97% identical, at least about 98% identical, or at least about 99% identical to the amino acid sequence of SEQ ID NO: 67 or 69.

[0195] In certain embodiments, the anti-FGFR3 antigen binding protein or fragment thereof comprises a VH domain and a VL domain, wherein: (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), a CDR-H2 sequence comprising the amino acid sequence of VDPETGGT (SEQ ID NO: 297), and a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPYAFDY (SEQ ID NO: 301); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSNNKNY (SEQ ID NO: 302), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75).

[0196] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 57, and the VL domain comprises the amino acid sequence of SEQ ID NO: 19 or 59.

[0197] In certain embodiments, the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 63, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67. In certain embodiments, the antibody heavy chain comprises

the amino acid sequence of SEQ ID NO: 65, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 69.

[0198] In certain embodiments, the anti-FGFR3 antigen binding protein or fragment thereof comprises a VH domain and a VL domain, wherein: (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), a CDR-H2 sequence comprising the amino acid sequence of VDPETGGT (SEQ ID NO: 297), and a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPPYAFDY (SEQ ID NO: 301); and (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSDNQKNY (SEQ ID NO: 306), a CDR-L2 sequence comprising the amino acid sequence of FAS (SEQ ID NO: 304), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75).

[0199] In certain embodiments, the VH domain comprises the amino acid sequence of SEQ ID NO: 57, and the VL domain comprises the amino acid sequence of SEQ ID NO: 61.

[0200] In certain embodiments, the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 65, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67.

[0201] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof of the disclosure comprise one or more sequences with at least about 80%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to any of the sequences of Table 1, Table 3, Table 4, Table 8, Table 13, or Table 14, or protein sequences encoded by the nucleic acid sequences in Table 9.

[0202] Also provided herein are human framework regions for anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof. Non-limiting examples of human framework regions are provided below.

[0203] Table 1.2 Human Framework regions of anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof

Framework type	Sequence	Note
Heavy chain	QVQLVQSGAEVKKPGASVKVSCKAS(X) _{n1} IHWVRQAPGQGLEWIGA(X) _{n2} AYNQKFQGRVTITADKSTSTAYMELSSLRSEDVAVYYC(X) _{n3} WGQGTLLTVSS	X is any naturally occurring amino acid, and n1, n2, and n3 are

	SEQ ID NO: 318	numbers at least 3, and less than 50, each X can be the same or different amino acid as the amino acid next to it
Heavy chain	QVQLVQSGAEVKKPGASVKVSCKAS(X) _{n1} IHWVRQAPGQGLEWIGA(X) _{n2} AYNQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 319	
Heavy chain	QVQLVQSGAEVKKPGASVKVSCKAS(X) _{n1} IHWVRQAPGQGLEWIGA(X) _{n2} AYNQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 320	
Heavy chain	QVQLVQSGAEVKKPGASVKVSCKAS(X) _{n1} IHWVRQAPGQGLEWIGA(X) _{n2} AYNQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 321	
Heavy chain	QVQLVQSGAEVKKPGASVKVSCKAS(X) _{n1} IHWVRQAPGQGLEWIGG(X) _{n2} AYNQKFQGRVTITADRSTSTAYMELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 322	
Heavy chain	QVQLVQSGAEVKKPGASVKVSCKAS(X) _{n1} IHWVRQAPGQGLEWIGG(X) _{n2} AYNQKFQGRVTITADRSTSTAYMELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 323	
Heavy chain	QVQLVQSGAEVKKPGASVKVSCKAS(X) _{n1} IHWVRQAPGQGLEWIGG(X) _{n2} AYNQKFQGRVTITADRSTSTAYMELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 324	
Heavy chain	QVQLVQSGAEVKKPGASVKVSCKAS(X) _{n1} IHWVRQAPGQGLEWIGG(X) _{n2} AYNQKFQGRVTITADRSTSTAYMELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 325	
Heavy chain	EVQLVQSGAEVKKPGATVKLSCKAS(X) _{n1} IHWVQQAPGKGLEWIGD(X) _{n2} AYA EK FQGRATLTADRSTDTAYMELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 326	
Heavy chain	EVQLVQSGAEVKKPGATVKLSCKAS(X) _{n1} IHWVQQAPGKGLEWIGD(X) _{n2} AYA EK FQGRATLTADRSTDTAYLELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 327	
Heavy chain	EVQLVQSGAEVKKPGATVKLSCKAS(X) _{n1} IHWVQQAPGKGLEWIGD(X) _{n2} AYA EK FQGRATLTADRSTDTAYLELSSLRSEDTAVYYC(X) _{n3} WGQGTLVTVSS SEQ ID NO: 328	
Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPGQSPKLLIY(X) _{n2} TRESGVPDRFSGSGSGTDFTLTISSLQAE DVAVYYC(X) _{n3} FGQGTKLEIK SEQ ID NO: 329	
Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPGQSPKLLIY(X) _{n2} TRESGVPDRFSGSGSGTDFTLTISSLQAE DVAVYYC(X) _{n3} FGQGTKLEIK SEQ ID NO: 330	
Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPGQSPKLLIY(X) _{n2} TRESGVPDRFSGSGSGTDFTLTISSLQAE DVAVYYC(X) _{n3} FGQGTKLEIK SEQ ID NO: 331	
Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPGQSPKLLIY(X) _{n2} TRESGVPDRFSGSGSGTDFTLTISSLQAE DVAVYYC(X) _{n3} FGQGTKLEIK SEQ ID NO: 332	

Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPG QSPKLLIY(X) _{n2} TRESGVPDFRFGSGSGTDFLTISSLQAE DVAVYYC(X) _{n3} FGQGTKLEIK SEQ ID NO: 333	
Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPG QSPKLLIY(X) _{n2} TRESGVPDFRFGSGSGTDFLTISSLQAE DVAVYYC(X) _{n3} FGQGTKLEIK SEQ ID NO: 334	
Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPG QSPKLLIY(X) _{n2} TRESGVPDFRFGSGSGTDFLTISSLQAE DVAVYYC(X) _{n3} FGQGTKLEIK SEQ ID NO: 335	
Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPG QSPKLLIY(X) _{n2} TRESGVPDFRFGSGSGTDFLTISSLQAE DVAVYYC(X) _{n3} FGQGTKLEIK SEQ ID NO: 336	
Light chain	DIVMTQSPDSLAVSLGERATINCKSS(X) _{n1} LAWYQQKPG QSPKLLIY(X) _{n2} TRESGVPDFRFGSGSGTDFLTISSVQA EDVAVYYC(X) _{n3} FGGGTKVEIK SEQ ID NO: 337	
Light chain	DIVMTQSPDSLAVSLGERATINCKSS(X) _{n1} LAWYQQKPG QSPKLLIY(X) _{n2} TRESGVPDFRFGSGSGTDFLTISSVQA EDVAVYYC(X) _{n3} FGGGTKVEIK SEQ ID NO: 338	
Light chain	DIVMTQSPDSLAVSLGERVTINCKSS(X) _{n1} LAWYQQKPG QSPKLLIY(X) _{n2} TRESGVPDFRFGSGSGTDFLTISSVQA EDVAVYYC(X) _{n3} FGGGTKLEIK SEQ ID NO: 339	

[0204] In some embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments comprise three heavy chain CDRs that bind to FGFR3, such as the three heavy chain CDRs of mouse antibody KC18, KE35, KE42, KE58, KE63, or KE94, and a human heavy chain variable region framework. In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments further comprise three light chain CDRs that bind to FGFR3, such as the three light chain CDRs of mouse antibody KC18, KE35, KE42, KE58, KE63, or KE94, and a human light chain variable region framework. In certain embodiments, the human heavy chain variable region framework comprises any one of SEQ ID NOs: 318 to 328. In certain embodiments, the human light chain variable region framework comprises any one of SEQ ID NOs: 329 to 339. In certain embodiments, the human heavy chain variable region framework comprises a sequence having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more identity to any one of SEQ ID NOs: 318 to 328. In certain embodiments, the human light chain variable region framework comprises a sequence

having at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more identity to any one of SEQ ID NOs: 329 to 339. In certain embodiments, such anti-FGFR3 antigen binding proteins and antigen-binding fragments bind human FGFR3 with an equilibrium dissociation constant (KD) of about 100 nM or less, about 90 nM or less, about 80 nM or less, about 70 nM or less, about 60 nM or less, about 50 nM or less, about 40 nM or less, about 30 nM or less, about 20 nM or less, about 10 nM or less, about 9 nM or less, about 8 nM or less, about 7 nM or less, about 6 nM or less, about 5 nM or less, about 4 nM or less, about 3 nM or less, about 2.89 nM or less, about 2 nM or less, about 1.5 or less, about 1.4 or less, about 1.23 or less, about 1.2 or less, or about 1 nM or less, about 0.8 or less, or about 0.6 or less. "X nM or less" therein includes the embodiment "less than X nM". "Less" therein can mean e.g. to about 2.8 nM, to about 1.3 nM, to about 1.1 nM, to about 0.7 nM or to about 0.5 nM. These lower limits can be used to form ranges with any of the aforementioned upper limits, such as about 3 nM or <3 nM to about 2.8 nM, about 1.5 nM or <1.5 nM to about 1.3 nM, about 1.3 nM or <1.3 nM to about 1.1 nM, about 0.9 nM or <0.9 nM to about 0.7 nM, or about 0.7 nM or <0.7 nM to about 0.5 nM. "About X" therein can mean e.g. "X±5%", "X±4%", "X±4%", "X±3%", "X±2%", "X±1%" or "X±0.5%". In certain embodiments, the nM values are as obtained by a Surface Plasmon Resonance assay, such as the Biacore assay.

[0205] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof of the disclosure are chimeric or humanized antibodies. In certain embodiments, the antigen binding protein is a humanized antibody.

[0206] In certain embodiments, the antigen binding protein is a monoclonal antibody.

[0207] In certain embodiments, the antigen binding protein comprises one or more full-length antibody heavy chains comprising an Fc region. In certain embodiments, the Fc region is a human IgG1 Fc region. In certain embodiments, the Fc region is a human IgG4 Fc region.

[0208] In certain embodiments, the antibody Fc region comprises one or more mutations that reduces Fc effector function. In certain embodiments, the one or more mutations reduces one or more of antibody dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), or complement dependent cytotoxicity

(CDC). In certain embodiments, the human IgG1 Fc region comprises a L234A and L235A mutation. In certain embodiments, the human IgG4 Fc region comprises a F234A and L235A mutation. These IgG1 and IgG4 mutations are also known as the “LALA” and “FALA” mutations, respectively, and are described in further detail in Xu et al. (Cell Immunol. 2000; 200:16–26). In certain embodiments, the human IgG4 Fc region comprises one or more stabilizing mutations, including, but limited to, mutations in the IgG4 hinge that reduce or prevent the formation of disulfide bonds and *in vivo* fab arm exchange (FAE). In certain embodiments, the human IgG4 Fc region comprises a S228P mutation. The IgG4 hinge mutation is described in further detail in Angal et al. (Mol. Immunol. 1993; 30:105–108). In certain embodiments, the human IgG4 Fc region comprises a S228P mutation and a L235A mutation. In certain embodiments, the human IgG1 Fc region comprises one or more mutations that alters antibody glycosylation. In certain embodiments, the human IgG1 Fc region comprises one or more of a S298N mutation, a T299A mutation, and a Y300S mutation. In certain embodiments, the human IgG1 Fc region comprises a S298N mutation, a T299A mutation, and a Y300S mutation. The Fc region amino acid positions referred to herein are based on EU antibody numbering.

[0209] In certain embodiments, the anti-FGFR3 antigen binding protein fragments of the disclosure comprise or consists of an antibody F(ab), F(ab')₂, Fab'-SH, Fv, or scFv fragment. In certain embodiments, the antigen binding protein fragment comprises an antibody F(ab) fragment.

[0210] The antibody F(ab) fragment can be modified with one or more serum half-life extending moieties. In certain embodiments, the antibody F(ab) fragment is conjugated to an antigen binding protein with binding specificity to serum albumin. In certain embodiments, the antigen binding protein with binding specificity to serum albumin is a nanobody. In certain embodiments, the serum albumin is human serum albumin or mouse serum albumin.

[0211] In certain embodiments, the antibody F(ab) fragment comprises a heavy chain and a light chain. In certain embodiments, the heavy chain of the F(ab) fragment comprises a heavy chain variable region disclosed herewith, and a light chain variable region disclosed herewith. In certain embodiments, the heavy chain variable region comprises or consists of any one of SEQ ID NOs: 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 28, 29, 30, 31, 56, 57, 58, 106, 107, 108, 109, 110, 111, 115, 116, 117, 118, 119, 120, 121,

or 112, or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identity to any of SEQ ID NOs: 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 28, 29, 30, 31, 56, 57, 58, 106, 107, 108, 109, 110, 111, 115, 116, 117, 118, 119, 120, 121, or 112. In certain embodiments, the light chain variable region comprises or consists of any one of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 19, 24, 25, 26, 27, 32, 33, 34, 35, 59, 60, 61, 112, 113, 114, 123, 124, 125, 126, 127, 128, 129, 130, 131, or 132, or a or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least 99% identity to any of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 19, 24, 25, 26, 27, 32, 33, 34, 35, 59, 60, 61, 112, 113, 114, 123, 124, 125, 126, 127, 128, 129, 130, 131, or 132.

[0212] In certain embodiments, the heavy chain of the F(ab) fragment comprises or consists of a heavy chain variable region disclosed herewith and a heavy chain constant region. In certain embodiments, the heavy chain constant region is derived from a human IgG1 Fc region, a human IgG2 Fc region, a human IgG3 Fc region, a human IgG4 Fc region, or a combination thereof. In certain embodiments, the heavy chain constant region is a fragment of a human IgG1 Fc region, a human IgG2 Fc region, a human IgG3 Fc region, a human IgG4 Fc region, or a combination thereof. In certain embodiments, the heavy chain constant region comprises or consists of the first 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, or 300 amino acids of a human IgG Fc region, such as the human IgG1 Fc region (SEQ ID NO: 54).

[0213] In certain embodiments, the light chain of the F(ab) fragment comprises or consists of a light chain variable region disclosed herewith, and a light chain constant region. In certain embodiments, the light chain constant region is derived from a human kappa (κ) chain, a human lambda (λ) chain, or a combination thereof. In certain embodiments, the light chain constant region comprises or consists of a part of IgG1 light constant region. In certain embodiments, the part of the IgG1 light constant region comprises or consists of the first 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, or 107 amino acids of SEQ ID NO: 55.

[0214] In certain embodiments, the F(ab) fragment comprises one or more point mutations in the C-terminus to reduce anti-Fab antibody binding.

[0215] In certain embodiments, the antigen binding protein comprises cross-reactivity to one or both of mouse and cynomolgus FGFR3. In certain embodiments, the cynomolgus FGFR3 is encoded by SEQ ID NO: 136:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCAGTGGCCATCGTGG
CCGGCGCCTCCTCGGAGTCCTTGGGGACGGAGCAGCGCGTCGTGGGGCGAG
TGGCAGAAGTGTCCGGCCCCGAGCCCAGCCAGCAGGAGCAGTTGGTCTTCG
GCAGCGGGGACGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCA
TGGGGCCCACTGTCTGGGTCAAGGATGGCGCAGGGCTGGTGCCCTCGGAGC
GTGTCCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGA
CTCTGGGGCCTACAGCTGCCGGCAGCGGCTCACACAGCTCGTACTGTGCCAC
TTCAGTGTGCGGGTGACAGATGCTCCATCCTCGGGAGATGACGAAGACGGG
GAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCCTTACTGGACT
CGGCCCCGAGCGGATGGACAAGAAGCTGCTGGCTGTGCCGGCCGCCAACACC
GTCCGCTTCCGCTGCCCGGCTGCCGGCAACCCCACTCCCTCCATCTCCTGGCT
GAAGAATGGCAAGGAGTTCCGCGGCGAGCACCGCATTGGCGGCATCAAGCT
TCGGCACCAGCAGTGGAGCCTGGTCATGGAAAGCGTGGTGCCCTCGGACCG
CGGCAACTACACCTGCGTGGTGGAGAACAAGTTTGGCAGCATCCGGCAGAC
ATACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCG
GGGCTGCCGGCCAACCAGACGGCGGTGCTGGGCAGCGATGTGGAGTTTCAC

TGCAAGGTGTACAGTGATGCGCAGCCCCACATCCAGTGGCTCAAGCACGTG
GAGGTGAATGGCAGCAAGGTGGGCCCCGACGGCACACCCTACGTACCGTG
CTCAAGACGGCGGGCGCTAATACCACCGACAAGGAGCTAGAGGTTCTGTCC
TTGCACAACGTCACCTTTGAGGACGCCGGGGAGTACACCTGCCTGGCGGGCA
ATTCTATTGGGTTTTCCCATCACTCTGCGTGGCTCGTGGTGCTGCCAGCTGAG
GAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTGTGTACGCAGGCATCCTC
AGCTACGGGGTGGGCTTCTTCCTGTTTCATCCTGGTGGTGGCGGCTGTGACGC
TCTGCCGCTGCGCAGCACCCCCAAGAAAGGCCTGGGCTCCCCACCGTGCA
CAAGATCTCCCGCTTCCCACTCAAGCGACAGGTGTCCCTGGAGTCCAACGCG
TCCATGAGCTCCAACACACCGCTGGTGCATCGCAAGGCTGTCTCAGGGG
AGGGTCCCACACTGGCCAATGTCTCCGAGCTTGAGCTGCCTGCTGACCCCAA
ATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCCTGGGGAGGG
CTGCTTTGGCCAGGTGGTCATGGCGGAGGCTATCGGCATTGACAAGGACCGG
GCCGCCAAGCCTGTCACCGTAGCCGTGAAGATGCTGAAAGATGATGCCACT
GACAAGGACCTGTCAGACCTGGTGTCTGAGATGGAGATGATGAAGATGATT
GGGAAACACAAGAACATTATCAACCTGCTGGGCGCCTGCACGCAGGGCGGG
CCCCTGTACGTGCTGGTGGAGTACGCGGCCAAGGGCAACCTGAGGGAGTTTC
TGCGGGCGCGGCGGCCCCCGGCCTGGACTACTCCTTCGACACCTGCAAGCC
GCCTGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCCTACCAGGTG
GCCCAGGCATGGAGTACCTCGCCTCCCAGAAGTGCATCCACAGGGACCTG
GCTGCTCGAAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGAC
TTCGGGCTGGCCCGCGACGTGCACAACCTTGACTACTACAAGAAGACAACC
AACGGCCGGCTGCCCCTGAAGTGGATGGCGCCTGAGGCCCTGTTTGACCGA
GTCTACACCCACCAGAGTGACGTCTGGTCCTTTGGGGTCTGCTCTGGGAGA
TCTTACGCTGGGGGGCTCTCCGTACCCCGGCATCCCTGTGGAGGAGCTCTT
CAAGCTGCTGAAGGAGGGTCACCGGATGGACAAGCCGGCCAACCTGCACACA
CGACCTGTACATGATCATGCGGGAGTGCTGGCATGCTGCGCCCTCCCAGAGG
CCCACCTTCAAGCAGCTGGTGGAGGACCTGGACCGTGTCTCACTGTGACGT
CCACCGACGAGTACCTGGACCTGTCAGCGCCCTTCGAGCAGTACTCCCCCGG
CGGCCAGGACACCCCGAGCTCCAGCTCCTCAGGGGATGACTCCGTGTTTGCC
CACGACCTGCTGCCCCCGGCCCCACCCAGCAGTGGGGGCTCGCGGACGTGA
(SEQ ID NO: 136)

In certain embodiments, the cynomolgus FGFR3 is the IIIc isoform, comprising SEQ ID NO: 138, or its mutated version comprising the G380R mutation (SEQ ID NO: 139):

MGAPACALALCVAVAIVAGASSES LGTEQRVVGRVAEVSGPEPSQQEQLVFGS
GDAVELSCPPPGGGPMGPTVWVKDGAGLVPSEVLVGPQRLQVLNASHEDSGA
YSCRQRLTQLVLCHF SVRVTDAPSSGDDDEGEDEAEDTGVDTGAPYWTRPERM
DKKLLAVPAANTVRFRCPAAGNPTPSISWLKNGKEFRGEHRIGGIKLRHQQWSL
VMESVVPSDRGNYTCVVENKFGSIRQTYTLDV LERSPHRPILQAGLPANQTAVL
GSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLKTAGANTTDK
ELEVLSLHNVT FEDAGEYTCLAGNSIGFSHSAWL VVLPAAEELVEADEAGSVY
AGILSYGVGF FILVVAAVTLCRLRSTPKKGLGSPTVHKISRFP LKRQVSLESNA
SMSSNTPLVRIARLSSGEGPTLANVSELELPADPKWELSRARLT LGKPLGEGCFG
QVVM AE AIGIDKDRAAKPVTVA VKMLKDDATDKDLSDLVSEMEMMKMIGKH
KNIINLLGACTQGGPLYVLVEYAAKGNLREFLRARRPPGLDYSFD TCKPPEEQLT
FKDLVSCAYQVARGMEY LASQKCIHRDLAARNVLVTEDNVMKIADFG LARDV
HNLDYYKKT TNGLPVK WMAPEALFDRVYTHQSDVWSFGVLLWEIFTLGGSP
YPGIPVEELFKLLKEGHRMDKPANCTHDLYMIMREC WHAAPSQRPTFKQLVED
LDRVLTVTSTDEYLDLSAPFEQYSPGGQDTPSSSSSGDDSVFAHDL LPPAPPSSG
GSRT (SEQ ID NO: 138)

MGAPACALALCVAVAIVAGASSES LGTEQRVVGRVAEVSGPEPSQQEQLVFGS
GDAVELSCPPPGGGPMGPTVWVKDGAGLVPSEVLVGPQRLQVLNASHEDSGA
YSCRQRLTQLVLCHF SVRVTDAPSSGDDDEGEDEAEDTGVDTGAPYWTRPERM
DKKLLAVPAANTVRFRCPAAGNPTPSISWLKNGKEFRGEHRIGGIKLRHQQWSL
VMESVVPSDRGNYTCVVENKFGSIRQTYTLDV LERSPHRPILQAGLPANQTAVL
GSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLKTAGANTTDK
ELEVLSLHNVT FEDAGEYTCLAGNSIGFSHSAWL VVLPAAEELVEADEAGSVY
AGILSYRVGGF FILVVAAVTLCRLRSTPKKGLGSPTVHKISRFP LKRQVSLESNA
SMSSNTPLVRIARLSSGEGPTLANVSELELPADPKWELSRARLT LGKPLGEGCFG
QVVM AE AIGIDKDRAAKPVTVA VKMLKDDATDKDLSDLVSEMEMMKMIGKH
KNIINLLGACTQGGPLYVLVEYAAKGNLREFLRARRPPGLDYSFD TCKPPEEQLT
FKDLVSCAYQVARGMEY LASQKCIHRDLAARNVLVTEDNVMKIADFG LARDV
HNLDYYKKT TNGLPVK WMAPEALFDRVYTHQSDVWSFGVLLWEIFTLGGSP

YGPVVEELFKLLKEGHRMDKPANCTHDLYMIMRECWAAPSQRPTFKQLVED
LDRVLTVTSTDEYLDLSAPFEQYSPGGQDTPSSSSSGDDSVFAHDLLPPAPPSSG
GSRT (SEQ ID NO: 139)

[0216] In certain embodiments, the antigen binding protein comprises binding specificity for FGFR3 isoform IIIb and/or isoform IIIc.

[0217] In certain embodiments, the antigen binding protein specifically binds to FGFR3, and does not bind to one or more of FGFR1, FGFR2, and FGFR4, or does not have detectable binding to one or more of FGFR1, FGFR2, and FGFR4. In certain embodiments, the antigen binding protein does not bind to each of FGFR1, FGFR2, and FGFR4, or does not have detectable binding to each of FGFR1, FGFR2, and FGFR4. In certain embodiments, the antigen binding protein binds to each of FGFR1, FGFR2, and FGFR4 with an affinity of about 100 μ M, 500 μ M, 1000 μ M, or greater. In certain embodiments, the antigen binding protein does not bind to one or more of FGFR1, FGFR2, and FGFR4 over a background measurement, as determined by a Biacore affinity analysis.

[0218] In certain embodiments, the antigen binding protein binds human FGFR3 with an equilibrium dissociation constant (KD) of about 100 nM or less, about 90 nM or less, about 80 nM or less, about 70 nM or less, about 60 nM or less, about 50 nM or less, about 40 nM or less, about 30 nM or less, about 20 nM or less, about 10 nM or less, about 9 nM or less, about 8 nM or less, about 7 nM or less, about 6 nM or less, about 5 nM or less, about 4 nM or less, about 3 nM or less, about 2.89 nM or less, about 2 nM or less, about 1.5 or less, about 1.4 or less, about 1.23 or less, about 1.2 or less, or about 1 nM or less, about 0.8 or less, or about 0.6 or less. “X nM or less” therein includes the embodiment “less than X nM”. “Less” therein can mean e.g. to about 2.8 nM, to about 1.3 nM, to about 1.1 nM, to about 0.7 nM or to about 0.5 nM. These lower limits can be used to form ranges with any of the aforementioned upper limits, such as about 3 nM or <3 nM to about 2.8 nM, about 1.5 nM or <1.5 nM to about 1.3 nM, about 1.3 nM or <1.3 nM to about 1.1 nM, about 0.9 nM or <0.9 nM to about 0.7 nM, or about 0.7 nM or <0.7 nM to about 0.5 nM. “About X” therein can mean e.g. “X $\pm$ 5%”, “X $\pm$ 4%”, “X $\pm$ 4%”, “X $\pm$ 3%”, “X $\pm$ 2%”, “X $\pm$ 1%” or “X $\pm$ 0.5%”. In certain embodiments, the nM values are as obtained by a Surface Plasmon Resonance assay, such as the Biacore assay. In certain embodiments, the Biacore assay is carried out at about 4°C, 10°C, 15°C, 20°C, 25°C, 30°C, or 37°C.

[0219] In certain embodiments, the antigen binding protein binds human FGFR3 with an off rate (Kd) of about 10^{-2} s⁻¹ or less, about 5×10^{-3} s⁻¹ or less, about 2×10^{-3} s⁻¹ or

less, about 10^{-3} s^{-1} or less, about $9 \times 10^{-4} \text{ s}^{-1}$ or less, about $8 \times 10^{-4} \text{ s}^{-1}$ or less, about $7 \times 10^{-4} \text{ s}^{-1}$ or less, about $6 \times 10^{-4} \text{ s}^{-1}$ or less, about $5 \times 10^{-4} \text{ s}^{-1}$ or less, about $4 \times 10^{-4} \text{ s}^{-1}$ or less, or about $3.5 \times 10^{-4} \text{ s}^{-1}$ or less. "Less" therein can mean e.g. to about $3 \times 10^{-4} \text{ s}^{-1}$. "About X" therein can mean e.g. " $X \pm 10\%$ ", " $X \pm 5\%$ ", " $X \pm 4\%$ ", " $X \pm 4\%$ ", " $X \pm 3\%$ ", " $X \pm 2\%$ ", " $X \pm 1\%$ " or " $X \pm 0.5\%$ ".

[0220] In certain embodiments, the antigen binding protein inhibits ligand-induced FGFR3 dimerization with IC_{50} of about $5 \mu\text{g/ml}$ or less, about $4 \mu\text{g/ml}$ or less, about $3 \mu\text{g/ml}$ or less, about $2 \mu\text{g/ml}$ or less, about $1 \mu\text{g/ml}$ or less, about $0.9 \mu\text{g/ml}$ or less, about $0.8 \mu\text{g/ml}$ or less, about $0.7 \mu\text{g/ml}$ or less, about $0.6 \mu\text{g/ml}$ or less, about $0.5 \mu\text{g/ml}$ or less, about $0.4 \mu\text{g/ml}$ or less, or about $0.3 \mu\text{g/ml}$ or less. "Less" therein can mean e.g. to about $0.25 \mu\text{g/ml}$ (or less, e.g. to about $0.2 \mu\text{g/ml}$ or about $0.1 \mu\text{g/ml}$). "About X" therein can mean e.g. " $X \pm 10\%$ ", " $X \pm 5\%$ ", " $X \pm 4\%$ ", " $X \pm 4\%$ ", " $X \pm 3\%$ ", " $X \pm 2\%$ ", " $X \pm 1\%$ " or " $X \pm 0.5\%$ ". In certain embodiments, the nM values are as obtained by a Homogenous Time-Resolved Fluorescence (HTRF) assay at about 4°C , 10°C , 15°C , 20°C , 25°C , 30°C , or 37°C .

[0221] In certain embodiments, the antigen binding protein inhibits FGFR3 receptor activation and downstream signaling with IC_{50} of about $5 \mu\text{g/ml}$ or less, about $4 \mu\text{g/ml}$ or less, about $3 \mu\text{g/ml}$ or less, about $2 \mu\text{g/ml}$ or less, about $1 \mu\text{g/ml}$ or less, about $0.9 \mu\text{g/ml}$ or less, about $0.8 \mu\text{g/ml}$ or less, about $0.7 \mu\text{g/ml}$ or less, about $0.6 \mu\text{g/ml}$ or less, about $0.5 \mu\text{g/ml}$ or less, about $0.4 \mu\text{g/ml}$ or less, or about $0.3 \mu\text{g/ml}$ or less. "Less" therein can mean e.g. to about $0.25 \mu\text{g/ml}$ (or less, e.g. to about $0.2 \mu\text{g/ml}$ or about $0.1 \mu\text{g/ml}$). "About X" therein can mean e.g. " $X \pm 10\%$ ", " $X \pm 5\%$ ", " $X \pm 4\%$ ", " $X \pm 4\%$ ", " $X \pm 3\%$ ", " $X \pm 2\%$ ", " $X \pm 1\%$ " or " $X \pm 0.5\%$ ". In certain embodiments, the nM values are as obtained by a homogenous time-resolved fluorescence (HTRF) assay.

[0222] Inhibition of FGFR3 receptor activation and downstream signaling can be determined by any means known in the art. In certain embodiments, inhibition of FGFR3 receptor activation and downstream signaling is measured by determining Erk phosphorylation. A decrease in Erk phosphorylation indicates inhibition of FGFR3 activation. Erk phosphorylation can be determined using a homogenous time-resolved fluorescence (HTRF) assay. In certain embodiments, the assay is performed in chondrocytes. In certain embodiments, the assay is performed in mouse primary rib chondrocytes.

[0223] In certain embodiments, the antigen binding protein inhibits the activity of an FGFR3^{G380R} mutant. In certain embodiments, the antigen binding protein inhibits the activity of a human FGFR3^{G380R} mutant, a mouse FGFR3^{G380R} mutant, and/or a cynomolgus FGFR3^{G380R} mutant. In certain embodiments, the human FGFR3^{G380R} mutant is represented by the amino acid sequence set forth in SEQ ID NO: 133.

[0224] In certain embodiments, the antigen binding protein or fragment thereof is capable of penetrating a bone growth plate.

[0225] In certain embodiments, the antigen binding protein or fragment thereof is capable of decreasing the binding of FGFR3 with its ligand in a bone growth plate.

Anti-FGFR3 antigen-binding protein epitopes

[0226] In one aspect, the disclosure provides an antigen-binding protein or fragment thereof with binding specificity to a fibroblast growth factor receptor 3 (FGFR3) epitope, comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain, wherein the antigen binding protein binds a human FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO: 134, recited below.

DTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSISWLKNGREF
RGEHRIGGIKLRHQWVSLVMESVVPDRGNYTCVVENKFGSIRQTYTLVDLERS
PHRPILQAGLPANQTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDG
TPYVTVLKTAGANTTDKEVLVSLHNVTTFEDAGEYTCLAGNSIGFSHHS AWLV
VLPAAEEELVE (SEQ ID NO: 134)

[0227] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof of the disclosure bind a human FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO: 134, recited above. The amino acid sequence recited above corresponds to the D2D3 region of FGFR3 isoform IIIc, specifically to amino acid D143 to E365 of FGFR3 isoform IIIc.

[0228] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof of the disclosure bind an epitope of human FGFR3 polypeptide comprising the N-terminus of the D2 region (amino acids D143 to L163) of SEQ ID NO: 133, shown above.

[0229] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof of the disclosure bind an epitope of human FGFR3

polypeptide comprising the N-terminus of the D2 region (amino acids D143 to N170) of SEQ ID NO: 133, shown above.

[0230] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof of the disclosure bind an epitope of human FGFR3 polypeptide comprising the N-terminus and middle of the D2 region (amino acids D143 to D160 and G197 to L213) of SEQ ID NO: 133, shown above.

[0231] In certain embodiments, the one or more epitopes of the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof of the disclosure are determined by hydrogen deuterium exchange (HDX) mass spectrometry. HDX is performed by measuring the amide hydrogen deuterium exchange on FGFR3 over time. HDX mass spectrometry is described in further detail in Prądzińska et al. (Amino Acids. 48: 2809–2820. 2016).

[0232] In certain embodiments, the anti-FGFR3 antigen binding proteins and antigen-binding fragments thereof of the disclosure compete with a reference binding protein for binding to the human FGFR3 polypeptide D2 region.

[0233] In one aspect, the disclosure provides an antigen-binding protein or fragment thereof with binding specificity to a fibroblast growth factor receptor 3 (FGFR3) epitope, comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain, wherein the antigen binding protein competes for binding to FGFR3 with an antibody comprising VH / VL domain amino acid sequence pairs selected from the group consisting of: SEQ ID NO: 6 / SEQ ID NO: 7, SEQ ID NO: 8 / SEQ ID NO: 9, SEQ ID NO: 10 / SEQ ID NO: 11, SEQ ID NO: 12 / SEQ ID NO: 13, SEQ ID NO: 14 / SEQ ID NO: 15, and SEQ ID NO: 16 / SEQ ID NO: 17.

Expression of Antigen-Binding Proteins

[0234] In one aspect, polynucleotides encoding the binding proteins (e.g., antigen-binding proteins and antigen-binding fragments thereof) disclosed herein are provided. Methods of making binding proteins comprising expressing these polynucleotides are also provided.

[0235] Polynucleotides encoding the binding proteins disclosed herein are typically inserted in an expression vector for introduction into host cells that may be used to produce the desired quantity of the binding proteins. Accordingly, in certain aspects,

the disclosure provides expression vectors comprising polynucleotides disclosed herein and host cells comprising these vectors and polynucleotides.

[0236] The term “vector” or “expression vector” is used herein to mean vectors used in accordance with the present disclosure as a vehicle for introducing into and expressing a desired gene in a cell. As known to those skilled in the art, such vectors may readily be selected from the group consisting of plasmids, phages, viruses and retroviruses. In general, vectors compatible with the disclosure will comprise a selection marker, appropriate restriction sites to facilitate cloning of the desired gene and the ability to enter and/or replicate in eukaryotic or prokaryotic cells.

[0237] Numerous expression vector systems may be employed for the purposes of this disclosure. For example, one class of vector utilizes DNA elements which are derived from animal viruses such as bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (RSV, MMTV or MOMLV), or SV40 virus. Others involve the use of polycistronic systems with internal ribosome binding sites. Additionally, cells which have integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow selection of transfected host cells. The marker may provide for prototrophy to an auxotrophic host, biocide resistance (e.g., antibiotics) or resistance to heavy metals such as copper. The selectable marker gene can either be directly linked to the DNA sequences to be expressed, or introduced into the same cell by co-transformation. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include signal sequences, splice signals, as well as transcriptional promoters, enhancers, and termination signals. In some embodiments, the cloned variable region genes are inserted into an expression vector along with the heavy and light chain constant region genes (e.g., human constant region genes) synthesized as discussed above.

[0238] In other embodiments, the binding proteins may be expressed using polycistronic constructs. In such expression systems, multiple gene products of interest such as heavy and light chains of antibodies may be produced from a single polycistronic construct. These systems advantageously use an internal ribosome entry site (IRES) to provide relatively high levels of polypeptides in eukaryotic host cells. Compatible IRES sequences are disclosed in U.S. Pat. No. 6,193,980, which is incorporated by reference herein in its entirety for all purposes. Those skilled in the art will appreciate that such

expression systems may be used to effectively produce the full range of polypeptides disclosed in the instant application.

[0239] More generally, once a vector or DNA sequence encoding a binding protein, e.g. an antibody or fragment thereof, has been prepared, the expression vector may be introduced into an appropriate host cell. That is, the host cells may be transformed. Introduction of the plasmid into the host cell can be accomplished by various techniques well known to those of skill in the art. These include, but are not limited to, transfection (including electrophoresis and electroporation), protoplast fusion, calcium phosphate precipitation, cell fusion with enveloped DNA, microinjection, and infection with intact virus. See, Ridgway, A. A. G. "Mammalian Expression Vectors" Chapter 24.2, pp. 470-472 Vectors, Rodriguez and Denhardt, Eds. (Butterworths, Boston, Mass. 1988). Plasmid introduction into the host can be by electroporation. The transformed cells are grown under conditions appropriate to the production of the light chains and heavy chains, and assayed for heavy and/or light chain protein synthesis. Exemplary assay techniques include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or fluorescence-activated cell sorter analysis (FACS), immunohistochemistry and the like.

[0240] As used herein, the term "transformation" shall be used in a broad sense to refer to the introduction of DNA into a recipient host cell that changes the genotype.

[0241] Along those same lines, "host cells" refers to cells that have been transformed with vectors constructed using recombinant DNA techniques and encoding at least one heterologous gene. In descriptions of processes for isolation of polypeptides from recombinant hosts, the terms "cell" and "cell culture" are used interchangeably to denote the source of antibody unless it is clearly specified otherwise. In other words, recovery of polypeptide from the "cells" may mean either from spun down whole cells, from supernatant of lysed cells culture, or from the cell culture containing both the medium and the suspended cells.

[0242] In one embodiment, a host cell line used for antibody expression is of mammalian origin. Those skilled in the art can determine particular host cell lines which are best suited for the desired gene product to be expressed therein. Exemplary host cell lines include, but are not limited to, DG44 and DUXB11 (Chinese Hamster Ovary lines, DHFR minus), HELA (human cervical carcinoma), CV-1 (monkey kidney line), COS (a derivative of CV-1 with SV40 T antigen), R1610 (Chinese hamster fibroblast)

BALBC/3T3 (mouse fibroblast), HEK (human kidney line), SP2/O (mouse myeloma), BFA-1c1BPT (bovine endothelial cells), RAJI (human lymphocyte), 293 (human kidney). In one embodiment, the cell line provides for altered glycosylation, e.g., afucosylation, of the antibody expressed therefrom (e.g., PER.C6® (Crucell) or FUT8-knock-out CHO cell lines (POTELLIGENT® cells) (Biowa, Princeton, N.J.)). In one embodiment, NS0 cells may be used. CHO cells are particularly useful. Host cell lines are typically available from commercial services, e.g., the American Tissue Culture Collection, or from authors of published literature.

[0243] *In vitro* production allows scale-up to give large amounts of the desired polypeptides. Techniques for mammalian cell cultivation under tissue culture conditions are known in the art and include homogeneous suspension culture, e.g., in an airlift reactor or in a continuous stirrer reactor, or immobilized or entrapped cell culture, e.g., in hollow fibers, microcapsules, on agarose microbeads or ceramic cartridges. If necessary and/or desired, the solutions of polypeptides can be purified by the customary chromatography methods, for example gel filtration, ion-exchange chromatography, chromatography over DEAE-cellulose and/or (immuno-) affinity chromatography.

[0244] Genes encoding the binding proteins featured in the disclosure can also be expressed in non-mammalian cells such as bacteria or yeast or plant cells. In this regard, it will be appreciated that various unicellular non-mammalian microorganisms such as bacteria can also be transformed, i.e., those capable of being grown in cultures or fermentation. Bacteria, which are susceptible to transformation, include members of the enterobacteriaceae, such as strains of *Escherichia coli* or *Salmonella*; *Bacillaceae*, such as *Bacillus subtilis*; *Pneumococcus*; *Streptococcus*, and *Haemophilus influenzae*. It will further be appreciated that, when expressed in bacteria, the binding proteins can become part of inclusion bodies. In some embodiments, the binding proteins are then isolated, purified and assembled into functional molecules. In some embodiments, the binding proteins of the disclosure are expressed in a bacterial host cell. In some embodiments, the bacterial host cell is transformed with an expression vector comprising a nucleic acid molecule encoding a binding protein of the disclosure.

[0245] In addition to prokaryotes, eukaryotic microbes may also be used. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among eukaryotic microbes, although a number of other strains are commonly available. For

expression in *Saccharomyces*, the plasmid YRp7, for example (Stinchcomb et al., *Nature*, 282:39 (1979); Kingsman et al., *Gene*, 7:141 (1979); Tschemper et al., *Gene*, 10:157 (1980)), is commonly used. This plasmid already contains the TRP1 gene which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example ATCC No. 44076 or PEP4-1 (Jones, *Genetics*, 85:12 (1977)). The presence of the *trp1* lesion as a characteristic of the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan.

Methods of Preparing/Administering Binding Proteins

[0246] Methods of preparing and administering binding proteins (e.g., antigen-binding proteins and antigen-binding fragments thereof disclosed herein) to a subject are also provided. The route of administration of the antigen binding proteins and antigen-binding fragments thereof of the current disclosure may be oral, parenteral, by inhalation or topical. The term parenteral as used herein includes intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, rectal or vaginal administration. While all these forms of administration are clearly contemplated as being within the scope of the current disclosure, a form for administration would be a solution for injection, e.g. for intravenous or intraarterial injection or drip. Usually, a suitable pharmaceutical composition for injection may comprise a buffer, a surfactant, optionally a stabilizer agent, etc. However, in other methods compatible with the teachings herein, the modified antibodies can be delivered directly to the site of the adverse cellular population thereby increasing the exposure of the diseased tissue to the therapeutic agent.

[0247] Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Other common parenteral vehicles include sodium phosphate solutions, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present such as for example, antimicrobials, antioxidants, chelating agents, and inert gases and the like. Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In such cases,

the composition must be sterile and should be fluid to the extent that syringability for injection exists. It should be stable under the conditions of manufacture and storage, and should also be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium. The proper fluidity can be maintained, for example, by the use of a coating, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[0248] Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents. Isotonic agents, for example, sugars, polyalcohols, may also be included in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0249] In any case, sterile injectable solutions can be prepared by incorporating an active compound (e.g., a modified binding protein by itself or in combination with other active agents) in a required amount in an appropriate solvent with one or a combination of ingredients enumerated, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and any required other ingredients. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation typically include vacuum drying and freeze-drying, which yield a powder of an active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparations for injections are processed, filled into containers such as ampoules, bags, bottles, syringes or vials, and sealed under aseptic conditions according to methods known in the art. Further, the preparations may be packaged and sold in the form of a kit.

[0250] Effective doses of the compositions of the present disclosure, for the treatment of a disease or disorder vary depending upon many different factors, including means of administration, target site, physiological state of the subject, whether the subject is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human, but non-human mammals including transgenic mammals can also be treated. Treatment dosages may be titrated to optimize safety and efficacy.

[0251] Binding proteins described herein can be administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring levels of binding protein or antigen in the

subject. Alternatively, binding proteins can be administered as a sustained release formulation, in which case less frequent administration is required. For antibodies, dosage and frequency vary depending on the half-life of the antibody in the patient. In general, humanized antibodies show the longest half-life, followed by chimeric antibodies and non-human antibodies.

[0252] The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, compositions containing the present binding protein are administered to a subject not already in the disease state to enhance the subject's resistance. In terms of achondroplasia, a prophylactic treatment is understood as a method of preventing or alleviating one or more symptoms of the disorder. In terms of cancer, a prophylactic treatment is understood as a method of preventing the happening of cancer, or alleviating one or more symptoms of the cancer. Such an amount is defined to be a "prophylactic effective dose." In this use, the precise amounts again depend upon the subject's state of health and general immunity. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, or until the patient shows partial or complete amelioration of disease symptoms. Thereafter, the patient can be administered a prophylactic regime.

[0253] Binding proteins described herein can optionally be administered in combination with other agents that are effective in treating the disorder or condition in need of treatment (e.g., prophylactic or therapeutic).

[0254] While the binding proteins may be administered as described immediately above, it must be emphasized that in other embodiments binding proteins may be administered to otherwise healthy subjects as a first line therapy. In such embodiments the binding proteins may be administered to subjects that have not, and are not, undergoing one or more other therapies, or subjects that have, or are undergoing one or more other therapies. As used herein, the administration of binding proteins, e.g. antibodies or fragments thereof, in conjunction or combination with an adjunct therapy means the sequential, simultaneous, coextensive, concurrent, concomitant, or contemporaneous administration or application of the therapy and the disclosed binding proteins. The administration or application of the various components of the combined therapeutic regimen may be timed to enhance the overall effectiveness of the treatment.

[0255] As previously discussed, the binding proteins of the present disclosure may be administered in a pharmaceutically effective amount for the *in vivo* treatment of mammalian disorders.

[0256] Pharmaceutical compositions in accordance with the present disclosure typically include a pharmaceutically acceptable, non-toxic, sterile carrier such as physiological saline, buffers, preservatives and the like. For the purposes of the instant application, a pharmaceutically effective amount of the binding protein that, shall be held to mean an amount sufficient to achieve effective binding to an antigen and to achieve a benefit, e.g., to ameliorate symptoms of a disease or disorder. Of course, the pharmaceutical compositions of the present disclosure may be administered in single or multiple doses to provide for a pharmaceutically effective amount of the antigen-binding protein or antigen-binding fragment thereof.

[0257] In keeping with the scope of the present disclosure, the antigen-binding protein or antigen-binding fragment thereof may be administered to a human or other animal in accordance with the methods of treatment herein in an amount sufficient to produce a therapeutic or prophylactic effect. The binding proteins of the disclosure can be administered to such human or other animal in a conventional dosage form prepared by combining the binding protein with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. The form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. In some embodiments, a cocktail comprising one or more species of binding proteins described in the current disclosure may prove to be particularly effective.

Methods of Treatment and Inhibition of FGFR3 Activity

[0258] The anti-FGFR3 antigen binding proteins or fragments thereof are useful for the treatment of FGFR3-mediated diseases or disorders. As used herein, the term “FGFR3-mediated disease or disorder” refers to any disease or disorder that is the result of aberrant FGFR3 activity. In certain embodiments, the disease or disorder is caused by FGFR3 over activity or over expression. Non-limiting examples of FGFR3-mediated diseases or disorders include achondroplasia, hypochondroplasia, and cancer.

[0259] The anti-FGFR3 antigen binding proteins or fragments thereof are useful for the reduction of FGFR3 activity. As used herein, an “FGFR3 activity” refers to any

signaling event associated with the dimerization of FGFR3 on the surface of a cell. The FGFR3 activity can be one or both of an extracellular activity and an intracellular activity. FGFR3 activities include, but are not limited to, FGFR3 dimerization, extracellular signal-regulated kinase (Erk) phosphorylation, mitogen-activated protein kinase kinase (MKK, MEK, or MAP2K) phosphorylation, FGFR3 cytoplasmic tyrosine kinase domain activity, and FGF ligand binding activity (e.g., FGF18 binding to FGFR3).

[0260] As used herein, the term “achondroplasia” refers to a genetic disorder caused by mutations in the FGFR3 gene that make the resulting protein overactive. The anti-FGFR3 antigen binding proteins or fragments thereof are useful for the reduction of one or more symptoms of achondroplasia. Achondroplasia symptoms include, but are not limited to, shortening of the proximal limbs, brachydactyly (i.e., short fingers and toes with trident hands), large head with prominent forehead frontal bossing, small midface with a flattened nasal bridge, spinal kyphosis (convex curvature) or lordosis (concave curvature), varus (i.e., bowleg) or valgus (i.e., knock knee, ear infections (due to Eustachian tube blockages)), sleep apnea (central or obstructive), and hydrocephalus. Achondroplasia may be diagnosed through the measurement of one or more of proximal limb length (e.g., femur and tibia length), finger and toe length, head circumference (e.g., skull length), and lumbar vertebrae length, although other anatomical measurements can be employed. Achondroplasia may be diagnosed through genetic testing to detect one or more mutations in the FGFR3 gene.

[0261] In one aspect, the disclosure provides a method for treating a FGFR3-mediated disease or disorder in a subject, comprising administering to a subject in need thereof the antigen binding protein or fragment thereof described herein.

[0262] As used herein, the term “subject,” “patient,” or “individual” refers to a human or non-human animal. The term “non-human animal” includes, but is not limited to, vertebrates such as non-human primates, sheep, dogs, cats, rabbits, ferrets, rodents such as mice, rats and guinea pigs, avian species (e.g., chickens), amphibians, and reptiles. In certain embodiments, the subject is a mammal such as a non-human primate, sheep, dog, cat, rabbit, ferret or rodent. In certain embodiments, the subject is a cynomolgus monkey. In certain embodiments, the subject is a human. In certain embodiments, the subject is a child. In certain embodiments, the subject is an adolescent.

[0263] In certain embodiments, the FGFR3-mediated disease or disorder is achondroplasia. In certain embodiments, the achondroplasia is FGFR3^{G380R}+

achondroplasia, meaning the subject to be treated contains the G380R mutation in its FGFR3 gene, either homozygous or heterozygous.

[0264] In certain embodiments, a subject diagnosed as having achondroplasia or risk of achondroplasia is treated with a binding protein disclosed herewith. In certain embodiments, the treatment leads to one or more effects selected from the group consisting of increased bone length (e.g., femur length and/or tibia length), increased bone diameter (e.g., femur diameter), increased growth plate volume (e.g., femur growth plate volume), increased vertebrae length, increased skull length, increased bone volume, increased skull volume, corrected vertebral abnormalities (e.g., increased Kyphosis Index), and improved bone age (e.g., more developed secondary ossification center), as compared to a control subject not receiving the treatment that is of the same development stage.

[0265] Accordingly, a method of improving one or more bone features in a subject is also provided. In certain embodiments, the method comprises administering a binding protein or an antigen-binding fragment thereof disclosed herewith to a subject in need. In certain embodiments, the improved bone feature is selected from the group consisting of bone length (e.g., femur length or tibia length), bone diameter (e.g., femur diameter), growth plate volume, vertebrae length, skull length, bone volume, skull volume, Kyphosis Index, and improved bone age.

[0266] In certain embodiments, the FGFR3-mediated disease or disorder is cancer. In certain embodiments, the cancer is selected from the group consisting of bladder cancer, melanoma, urothelial cancer, and endometrial cancer.

[0267] In another aspect, the disclosure provides a method for treating achondroplasia in a subject, comprising administering to a subject in need thereof an antigen binding protein or an antigen-binding fragment thereof with binding specificity to an FGFR3 epitope, wherein the antigen binding protein or the antigen binding fragment thereof does not bind to one or more of FGFR1, FGFR2, and FGFR4.

[0268] In another aspect, the disclosure provides a method for inhibiting one or both of FGFR3 activity and expression in a bone growth plate of a subject, comprising administering to a subject an antigen binding protein or an antigen binding fragment thereof with binding specificity to an FGFR3 epitope, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4. In certain embodiments, an FGFR3 antibody as described herewith is used.

Therapeutic and prophylactic uses

[0269] The disclosure provides therapeutic uses of its binding proteins or an antigen binding protein fragment thereof with binding specificity to an FGFR3 epitope, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4) corresponding to the methods of treatment disclosed above. For instance, the disclosure provides a binding protein or the antigen binding protein fragment thereof as described herein for use in medicine. In some embodiments, it provides a binding protein, or an antigen binding protein fragment thereof as described herein for use as an FGFR3-activity inhibiting medicament. In some embodiments, it provides a binding protein, or an antigen binding protein fragment thereof as described herein for use in treating an FGFR3-mediated disorder. Examples of such disorders are given herein. In some embodiments, it provides a binding protein, or antigen binding protein fragment thereof as described herein for use in preventing one or more symptoms of achondroplasia, as exemplified above. In some embodiments, it provides a binding protein, or antigen binding protein fragment thereof as described herein for use in preventing cancer, as exemplified above. Embodiments described herein regarding methods of treatment, administration, subjects and all other aspects relevant to therapy and prevention also apply to these uses of binding proteins.

[0270] It will be readily apparent to those skilled in the art that other suitable modifications and adaptations of the methods described herein may be made using suitable equivalents without departing from the scope of the embodiments disclosed herein. Having now described certain embodiments in detail, the same will be more clearly understood by reference to the following example, which is included for purposes of illustration only and is not intended to be limiting.

EXAMPLE**Example 1 – Generation of Anti-FGFR3 Antibodies**

[0271] Generation of immunogen

[0272] Anti-FGFR3 monoclonal antibodies were developed using 300.19 pre-B lymphoblast cells (ATCC, Manassas, VA) transformed with DNA encoding full-length human FGFR3 (see **Fig. 1**, GenBank ID NP_000133.1, FGFR3 isoform IIIc) with the mutation G380R (SEQ ID NO: 133) which was expressed on the cell surface (FGFR3^{G380R}-300.19 cell). The FGFR3^{G380R} open reading frame was subcloned into the pXL-MCS vector and transfected into 300.19 cells (Immunogen 1). Separately, DNA encoding the human FGFR3 extra cellular domain (ECD) protein (Immunogen 2) was subcloned into the pTT5 vector (Invitrogen), and was prepared using Expi293 cells (Invitrogen).

FGFR3 extra cellular domain (ECD) protein (Immunogen 2):

GGLNDIFEAQKIEWHEHHHHHHEDQVDPRLIDGKIQPEPESLGTEQRRVVGRAAE
VPGPEPGQEQQLVFGSGDAVELSCPPPGGGPMGPTVWVKDGTGLVPSERVLVG
PQRLQVLNASHEDSGAYSCRQRLTQRVLCHFVSVRVTDAPSSGDDEDEGEDEAED
TGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSISWLKNGREFR
GEHRIGGIKLRHQWQSLVMESVVPDRGNVTCVVENKFGSIRQTYTLDVLERSP
HRPILQAGLPANQTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGT
PYVTVLKTAGANTTDKEVLVSLHNVTFEDAGEYTCLAGNSIGFSHHS AWLVV
LPAAEELVEADEAGSAS (SEQ ID NO: 140)

[0273] FGFR3 expression on FGFR3^{G380R} - 300.19 cells was monitored and quantified by FACS analysis using the comparator antibody, GT184.6.1, described further in Yin et al. (Mol. Cancer Ther. 14(10): 2270-8. 2015). Anti-FGFR1 (MAB765), anti-FGFR2 (MAB6843), anti-FGFR3 (MAB766), and anti-FGFR4 (MAB6852) antibodies were used as negative controls (R&D Systems, Minneapolis, MN). The FGFR3 ECD protein was quantified using an enzyme-linked immunosorbent assay (ELISA) with the antibodies described further below.

[0274] The cells expressing FGFR3 were maintained at 37 °C under 5% CO₂ in RPMI (Gibco) supplemented with heat inactivated fetal bovine serum (FBS) (Hyclone). Cells were prepared for injection by substituting the above culture medium with phosphate buffered (Ca-Mg free) saline (CMF-PBS) supplemented with 5 mM EDTA and harvesting the cells in that buffer. The harvested cells were pelleted by centrifugation at 500 x g for 5 minutes, washed once by resuspending the pellet in CMF-PBS and centrifuging as before, counted and adjusted to the appropriate volume (such as 5 x 10⁶ cells in 0.2 ml)

for injection by resuspending the cell pellet in CMF-PBS. The FGFR3 ECD protein was used to boost antibody titers in animals before sacrificing the mouse.

[0275] Cells were maintained in RPMI medium by seeding about $3\text{--}5 \times 10^5$ cells per ml in a T75 flask and grown for approximately 24-48 hours with selection antibiotic to eliminate the cells not carrying FGFR3 plasmid. Cell surface expression of FGFR3 on cells was verified by FACS analysis prior to use as an immunogen.

[0276] Generation of anti-FGFR3 antibodies – Hybridoma Strategy

[0277] Six eight-week old female FGFR3 KO (C57BL/6^{mFGFR3}⁻) mice from the Jackson Laboratory (Bar Harbor, ME) were immunized with the FGFR3-transfected cells (Immunogen 1). Separately, wild-type Balb/c mice were immunized with the FGFR3 ECD protein described above (Immunogen 2). A group of mice were primed intraperitoneally on day 0 with FGFR3-expressing cells, FGFR3^{G380R} - 300.19 cells, in PBS without adjuvants, administered on days 14, 28, 42 and 56, followed by an intraperitoneal boost on day 77 with the FGFR3 ECD protein in PBS without adjuvants. Each injection was administered with approximately 5×10^6 cells in a volume of 200 μ l and 50 μ g protein in a volume of 100 μ l PBS. Immunizations were performed in two-week intervals and the IgG titer was evaluated by ELISA with FGFR3 ECD protein to assess immune response.

[0278] The mice were sacrificed for harvesting the spleen and placed in approximately 10 ml of pre-warmed serum-free DMEM (Hyclone) at 37 °C in a petri dish. The splenocytes were teased out of the capsule using forceps and transferred to a 15-ml conical tube. The cells were then washed three times with pre-warmed serum-free IMDM (Hyclone) and cells from multiple mice were pooled.

[0279] The fusion partner cell, F0 B lymphoblasts (ATCC, Manassas, VA), for the immunized spleen cells was established with a hypoxanthine/aminopterin/thymidine (HAT)-sensitive and IgG non-secreting myeloma cell line. Prior to the fusion, F0 B lymphoblasts were maintained in IMDM medium supplemented with 10% FBS (37 °C, 7% CO₂) ensuring that the cells were in logarithmic growth phase on the day of the fusion.

[0280] The fusion protocol was derived from Lerner (Yale J Biol Med, 1981, 54 (5) 387-402) and Gefter et al. (Somatic Cell Genet, 1977, 3 (2) 231-236). Before the fusion, the spleen cells and the logarithmic phase myeloma cells were washed three times

with serum-free IMDM and counted. For each fusion, $1-1.5 \times 10^8$ spleen cells were mixed with $2-3 \times 10^7$ myeloma cells in a 50-ml conical polypropylene tube and cells were washed once with serum-free IMDM. The ratio of spleen cells to myeloma cells was 5:1. The tubes were centrifuged at $500 \times g$ for 10 minutes to pellet the cells. After aspiration of the supernatant, the pellets were gently resuspended by tapping the bottom of the tubes. The tubes were then placed in a beaker of 37°C water. All subsequent fusion steps were carried out in the beaker of 37°C water.

[0281] Next, 1 ml of polyethylene glycol 1500 (PEG) (Roche Applied Science, Indianapolis, IN) preheated to 37°C was slowly added to the cell pellet over the course of about 1 minute, while gently rocking the tube. The cells were incubated in the PEG for one minute followed by addition of 1 ml serum-free IMDM added dropwise to the pellet over the course of 30 seconds, and then 9 ml of serum-free IMDM were added to the pellet for one minute. The tube was then centrifuged at $500 \times g$ for 10 minutes at room temperature, and the supernatant was aspirated. The pellet was resuspended in 200 ml of filtered complete hybridoma production media, IMDM (Hyclone) supplemented with 10% FBS (Hyclone), 1x non-essential amino acid (Gibco), 1 mM sodium pyruvate (Gibco), 1x pen-strep (Gibco) and 1X HAT (Sigma). The resuspended cells were then seeded in ten 96-well flat-bottom microtiter plates, in a volume of about 200 μl /well. The plates were kept in an incubator at 37°C , 7% CO_2 .

[0282] A primary hybridoma screen was designed to select hybridoma clones producing antibodies which recognized native FGFR3 epitopes. Supernatants from wells growing clones, typically on days 10-14 post-fusion, were incubated with Chinese hamster ovary (CHO) cells stably expressing FGFR3 (FGFR3-CHO). Antibody binding was detected by FACS using a fluorescently labeled goat anti-mouse secondary antibody. Clones were considered positive if labeled supernatant samples were greater than 10-fold over background in the FACS analysis. Selected positive clones were transferred to 24-well flat bottom plates and expanded for a second screen to confirm selection. Supernatants from 24-well plates were incubated with hFGFR3^{G380R} - 300.19 cells and detected by a fluorescently labeled goat anti-mouse secondary antibody. More than 4,000 hybridomas were generated and screened by FACS assay described above. Only 25 clones were confirmed specific to FGFR3. Positive clones were expanded for purified antibody production, VH and VL gene sequencing and cryo-preservation.

[0283] Generation of anti-FGFR3 antibodies – Phage-display Strategy

[0284] Three scFv phage libraries and two fab fragment phage libraries were screened, with 5 separate screening campaigns performed. A first campaign screened the scFv phage libraries against the hFGFR3 isoform IIIc dimer. 2,700 scFv antibodies were screened with only 13 antibodies identified as potential candidates. A second campaign screened fab and scFv libraries against the hFGFR3 isoform IIIc dimer. 1,940 antibodies were screened with only 13 antibodies identified as potential candidates. A third and fourth campaign screened fab and scFv libraries against the hFGFR3 isoform IIIc dimer, the hFGFR3 isoform IIIc his tagged monomer, and hFGFR3 isoform IIIc-expressing cells. 9,770 antibodies were screened with only 36 antibodies identified as potential candidates. A fifth campaign screened fab libraries against the hFGFR3 isoform IIIc monomer and mouse FGFR3 (mFGFR3) isoform IIIc monomer, and hFGFR3 isoform IIIc- and mFGFR3 isoform IIIc-expressing cells. 2,990 antibodies were screened with only 57 antibodies identified as potential candidates. Between the five screening campaigns, 17,400 antibodies were screened. Among those screened antibodies, only 48 were found to be cross-reactive between human, mouse, and cyno, and only 15 were found to block FGFR3 ligand binding.

[0285] FGFR family member proteins (human FGFR1 α IIIb, FGFR1 α IIIc, FGFR1 β IIIb, FGFR1 β IIIc, FGFR2 α IIIc, FGFR2 β IIIb, FGFR3 IIIb, FGFR3 IIIc, FGFR4; mouse FGFR3; and cynomolgus FGFR3 recombinant proteins) were purchased from R&D Systems (Minneapolis, MN) for identifying FGFR3 specific clones by ELISA. cDNA encoding the following proteins were all subcloned into the pTT5 vector (Invitrogen): partial ECD and chimeric ECD proteins of FGFR3; human D2D3 (hD2D3) and D3 (hD3) of human FGFR3; mouse D2D3 (mD2D3) and D3 (mD3) of mouse FGFR3; cynomolgus D2D3 (cyD2D3) and D3 (cyD3) of cynomolgus FGFR3; and hD1-cyD2D3 and hD1-mD2D3 recombinant proteins. Proteins were prepared by transient transfection using Lipofectamine 2000 (Invitrogen) in Expi293 cells (Invitrogen). Supernatants from the selected clones were incubated in 96-well plates coated with the recombinant FGFR proteins and detected with goat anti-mouse IgG horseradish peroxidase (Jackson ImmunoResearch, West Grove, PA) followed by chemiluminescent detection.

[0286] Cell based-binding assays for anti-FGFR3 antibodies

[0287] A cell-based binding assay was used to characterize the anti-FGFR3 antibodies generated above. Full-length human, mouse, and cynomolgus FGFR3 cDNAs were subcloned into different pcDNA 3.1 (Invitrogen) vectors and transfected into 300.19 cells (ATCC). The cDNA of FGFR3 Ig domains D2D3 was subcloned into pcDNA 3.1 and transfected into CHO (D2D3-CHO) (ATCC) cells. Full-length human FGFR3^{G380R}, mouse FGFR3, and cynomolgus FGFR3^{G380R} cDNAs were also subcloned into different pcDNA 3.1 vectors. Stable cell lines expressing FGFR3 were generated by transfection of human FGFR3^{G380R}, mouse FGFR3, and cynomolgus FGFR3^{G380R} cDNA plasmid constructs into CHO (hFGFR3^{G380R} - CHO and cyFGFR3^{G380R} - CHO) and human embryonic kidney (HEK, mFGFR3-HEK) (ATCC) cells using the Lipofectamine 2000 kit (Invitrogen). Cell lines were maintained in F-12K medium supplemented with 10% FBS for CHO cells and in DMEM supplemented with 10% FBS for HEK cells overnight, then cultured in the presence of geneticin (0.5 ml/ml) for 10-14 days. Isolated single colonies were picked and grown in separate wells until sufficient clonal cells were expanded. Stable clones resistant to geneticin and expressing high copies of FGFR3 protein were identified by FACS assay using GT184.6.1.

[0288] Cell-based antibody binding to wild-type FGFR3, mutant FGFR3, and D2D3 FGFR3 expressed on CHO and HEK cells was accessed by FACS analysis. Cells were incubated with anti-FGFR3 antibodies in 1% bovine serum albumin in PBS (BPBS). After three washes, the cells were incubated with a fluorescent-conjugated secondary antibody (Invitrogen).

[0289] The results indicated that several antibodies bind specifically to FGFR3 expressed on the cells. For example, clones KC18, KE35, KE42, KE58, KE63, and KE94, with mouse and human isotype controls as negative controls and GT184.6.1 as a positive control, were tested for binding to CHO, HEK and 300.19 cells transfected to express wild-type FGFR3, mutant FGFR3, and the ECD domain of FGFR3. All antibodies bound to the cells as described above, with similar binding profiles and titration kinetics. The negative control antibodies exhibited only background reactivities. The binding of anti-FGFR3 antibodies to mouse primary rib chondrocytes was also observed by FACS analysis.

[0290] The binding specificities of antibodies KC18, KE35, KE42, KE58, KE63, and KE94 were also tested using GT184.6.1 as positive control. Unlike GT184.6.1, which

bound to both hFGFR2 and hFGFR3, KC18, KE35, KE42, KE58, KE63, and KE94 only bound to hFGFR3, indicating high FGFR3 specificities.

[0291] Biacore affinity Analysis

[0292] The N-terminal ECD proteins of FGFR3 from human and mouse were produced with a terminal avidin tag and used in a forward format Biacore assay where proteins were immobilized on a Biacore chip and then the kinetics of antibody interaction with the proteins on the chip were determined. The proteins were immobilized on a Biacore chip for approximately 10,000 response units (RU). Then the antibodies were exposed to the chip for kinetic measurements, following the manufacturer's recommendations (GE Healthcare). Sensorgrams were fit to a 1:1 binding model and analyzed using double-reference subtraction by T200 Evaluation software (GE Healthcare). Affinities of the tested antibodies are shown in Table 2.

[0293] Table 2. anti-FGFR3 antibodies binding specificities and affinities

FGFR3 antibodies	Selectivity				Reactivity			
	FGFR1	FGFR2	FGFR3	FGFR4	hFGFR3IIIc	hFGFR3IIb	mFGFR3	cynoFGFR3
KC18	-	-	+	-	+++	+++	+++	+++
KE35	-	-	+	-	+++	+++	+++	+++
KE42	-	-	+	-	+++	+++	+++	+++
KE58	-	-	+	-	+++	+++	+++	+++
KE63	-	-	+	-	+++	+++	+++	+++
KE94	-	-	+	-	+++	+++	+++	+++
Control mAb: GT184	-	+	+	-	++	++	+++	+++

FGFR3 antibodies	Affinity (hFGFR3)			Affinity (mFGFR3)		
	Ka (M ⁻¹ s ⁻¹)	Kd (s ⁻¹)	KD (nM)	Ka	Kd	KD (nM)
KC18	7.92E+05	3.47E-04	1.4	1.74E+05	1.10E-03	6.30
KE35	4.14E+05	1.20E-03	2.89	5.71E+5	1.08E-03	1.89
KE42	4.60E+05	5.67E-04	1.23	7.39E+5	6.00E-04	0.81
KE58	1.15E+06	1.43E-03	1.2	1.67E+05	9.18E-04	5.50
KE63	8.87E+05	7.45E-04	0.8	4.36E+05	2.91E-03	6.70

KE94	9.40E+05	5.95E-04	0.6	7.05E+05	1.48E-03	2.10
Control mAb: GT184	4.23E+05	1.20E-03	2.8	4.15E+05	1.52E-03	3.7

[0294] Sequence analysis of anti-FGFR3 monoclonal antibodies

[0295] Prior to sequence analyses, the isotype of each clone was determined using the IsoStrip Mouse Monoclonal Antibody Isotyping Kit (Roche Applied Science, Indianapolis, IN). The heavy (VH) and light (VL) chain variable regions of clones were sequenced using 5'RACE (Rapid Amplification of cDNA Ends) Kit (Clontech, Mountain View, CA) as per the manufacturer's instruction. Total RNA was extracted from each hybridoma clone using the RNeasy Miniprep kit according to the manufacturer's instructions (Qiagen, Germantown, MD). Full-length first strand cDNAs containing 5'ends were generated by polymerase chain reaction (PCR) using 5'RACE kits (Clontech). The VH and VL genes were amplified by TA cloning kit (Invitrogen) with primers, 5'primer (5'RACE kit, Clontech), and 3' primer of IgG isotype specific heavy chain and 3'primer of kappa light chain.

[0296] IgG1 3' Primer: 5'- TATGCAAGGCTTACAACCACA-3' (SEQ ID NO: 1)

[0297] IgG2b 3' Primer: 5'- GTTAGGAGCTGGGCATTTGTGACACTCC – 3' (SEQ ID NO: 2)

[0298] IgG2c 3' Primer: 5'- GTTAGGTGCTGGGCATTTGCATGGAGGACAGGG – 3' (SEQ ID NO: 3)

[0299] IgG3 3' Primer: 5'- GTTTGGTGGGCATGAAGAACCCGGGG – 3' (SEQ ID NO: 4)

[0300] Kappa light chain 3'Primer: 5' – CTCATTCCTGTTGAAGCTCTTGAC – 3' (SEQ ID NO: 5)

[0301] The amplified cDNAs were cloned into pCR2.1 vectors (Invitrogen) and transformed using a TOPO-TA cloning kit (Invitrogen) as per the manufacturer's instructions. Plasmids were isolated from 2 ml of an LB culture, inoculated from a single colony and grown overnight, using QIAprep spin miniprep kit (Qiagen) and sequenced using M13 Forward and M13 Reverse primers included in the TOPO-TA cloning kit

(Invitrogen). The VH and VL gene sequences were analyzed using the IMGT V-Quest web server to identify and confirm variable region sequences. VH and VL sequences of each antibody are provided below in Table 3:

[0302] Table 3. Antibody VH and VL amino acid sequences

Antibody ID	Sequence
KC18 VH	QVQLQQSGAELVRPGASVTLSCKASGDTFTDFEIHVWKQTPVHGLEWIGDI DPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRITYDG YPYAMDYWGQGTSTVTVSS (SEQ ID NO: 6)
KC18 VL	DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSNNQKNYLAWYQQKPGQSPK LLIYWASTRESGVPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQYYSYRTF GGGKLEIK (SEQ ID NO: 7)
KE35 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWIGY INPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCARERD YDGAMDYWGQGTSTVTVSS (SEQ ID NO: 8)
KE35 VL	DIQMTQSPSSLSASLGKVTITCKASQDINKFIAWYQHKPGKGPRLLIHYTST LQPGIPSRFSGSGSGRDYFSISNLEPEDIATYYCLQYDNLWTFGGGKLEIK (SEQ ID NO: 9)
KE42 VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWIGY INPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCARER DYDGSMDFWGQGTSTVTVSS (SEQ ID NO: 10)
KE42 VL	DIQMTQSPSSLSASLGKVTITCKASQDINKFIAWYQHKPGKGPRLLIHYTST LQPGIPSRFSGSGSGRDYFSISNLEPEDIATYFCLQYDNLWTFGGGKLEIK (SEQ ID NO: 11)
KE58 VH	EVQLQQSGPDLVKPGASVKISCKASGYTVDYIMNHWVKQSHGKSLEWIGD INPNNGVTYTNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCAREED FDGFDYWGQGTTLTVSS (SEQ ID NO: 12)
KE58 VL	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTGVAWYQQKPGQSPQLLIYWA STRHTGVPDRFTGSGSGTDYILTIRSVQAEDLALYYCQHYSTPLTFGAGTK LELK (SEQ ID NO: 13)
KE63 VH	QVQLQQSGAELVRPGASVTLSCKASGSTFTDFEIHVWKQTPVHGLEWIGGID PETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNYDGY SQTMDYWGQGTSTVTVSS (SEQ ID NO: 14)
KE63 VL	NIMMTQSPSSSLAVSAGEKVTMSCKSSQSVLYSSNQKNYLAWYQQKPGQSP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCHQYLSSYT FGGKLEMK (SEQ ID NO: 15)
KE94 VH	QVQLQQSGAELVRPGASVTLSCKASGSTFTDFEIHVWKQTPVHGLEWIGAI PETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNYDGY SRTMDYWGQGTSTVTVSS (SEQ ID NO: 16)
KE94 VL	NIMMTQSPSSSLAVSAGEKVTMSCKSSQSVLYSSNQKNYLAWYQQKPGQSP KLLIYWASTRESGVPDRFTGSGSGTDFSLISSVQTEDLAVYYCHQYLSSYTF GGGTRLEMK (SEQ ID NO: 17)

[0303] The CDR regions for the VH and VL sequences recited above are provided below in Table 4:

[0304] Table 4. Antibody Heavy chain and Light chain CDR regions

HEAVY Chain			
VH Chain ID	HCDR1-IMGT	HCDR2-IMGT	HCDR3-IMGT
KC18_VH	GDTFTDFE (SEQ ID NO: 70)	IDPETGGT (SEQ ID NO: 71)	TRTYDGYPYAMDY (SEQ ID NO: 72)
KE35_VH	GYTFTDYN (SEQ ID NO: 76)	INPNNGGT (SEQ ID NO: 77)	ARERDYDGAMDY (SEQ ID NO: 78)
KE42_VH	GYTFTDYN (SEQ ID NO: 82)	INPNNGGT (SEQ ID NO: 83)	ARERDYDGSMDY (SEQ ID NO: 84)
KE58_VH	GYTVTDYY (SEQ ID NO: 88)	INPNNGVT (SEQ ID NO: 89)	AREEDFDGFDY (SEQ ID NO: 90)
KE63_VH	GSTFSDFE (SEQ ID NO: 94)	IDPETGGT (SEQ ID NO: 95)	TRNYDGYSTMDY (SEQ ID NO: 96)
KE94_VH	GSTFTDFE (SEQ ID NO: 100)	IDPETGGT (SEQ ID NO: 101)	TRNYDGYSTMDY (SEQ ID NO: 102)

LIGHT Chain			
VL Chain ID	LCDR1-IMGT	LCDR2-IMGT	LCDR3-IMGT
KC18_VL	QSLLYSNNQKNY (SEQ ID NO: 73)	WAS (SEQ ID NO: 74)	QQYYSYRT (SEQ ID NO: 75)
KE35_VL	QDINKF (SEQ ID NO: 79)	YTS (SEQ ID NO: 80)	LQYDNLLWT (SEQ ID NO: 81)
KE42_VL	QDINKF (SEQ ID NO: 85)	YTS (SEQ ID NO: 86)	LQYDNLLWT (SEQ ID NO: 87)
KE58_VL	QDVSTG (SEQ ID NO: 91)	WAS (SEQ ID NO: 92)	QQHYSTPLT (SEQ ID NO: 93)
KE63_VL	QSVLYSSNQKNY (SEQ ID NO: 97)	WAS (SEQ ID NO: 98)	HQYLSSYT (SEQ ID NO: 99)
KE94_VL	QSVLYSSNQKNY (SEQ ID NO: 103)	WAS (SEQ ID NO: 104)	HQYLSSYT (SEQ ID NO: 105)

[0305] Inhibition of FGF1 ligand binding by Anti-FGFR3 antibodies

[0306] To test if the isolated antibodies could inhibit the binding between FGF1 ligand and FGFR3, an FGF1 ligand blocking assay was conducted. For the FGFR1 ligand blocking assay, human FGFR3 cells, FGFR3-300.19 and FGFR3^{G380R}-300.19, were pre-incubated with various concentration of anti-FGFR3 antibodies and isotype controls, prior to addition of human FGF1 ligand (R&D Systems). Binding of hFGF1 to FGFR3 expressed on the cells was determined by FACS assay using biotinylated anti-FGF1 antibody followed by incubation with a streptavidin-fluorescent secondary antibody. The

anti-FGFR3 antibodies which bound to the EC domain, including KC18, KE35, KE42, KE58, KE63, and KE94, all blocked binding of FGF1 to FGFR3 on these cells.

[0307] An ELISA-based blocking assay using human and mouse FGF1 ligand was conducted. Each well of 96-well plates was coated with either human or mouse FGFR3 proteins to capture both/either anti-hFGFR3 antibody and/or FGF1 ligand, then incubated with various concentrations of anti-FGFR3 antibody and isotype controls, prior to addition of human FGF1 ligand. Binding of FGF1 ligand was determined by addition of a substrate to induce a quantifiable chemiluminescence reaction. Inhibition of FGF1 binding to human FGFR3 and mouse FGFR3 proteins by the anti-FGFR3 antibodies was detected by ELISA, respectively.

[0308] Epitope binning of anti-FGFR3 antibodies

[0309] Using a Biacore T100 (GE Healthcare, Piscataway, NJ), anti-FGFR3 antibodies were immobilized on a Biacore CM5 chip and ECD proteins of FGFR3 were injected. Competition of second anti-FGFR3 antibodies (Ab2) bound to FGFR3 protein captured by immobilized anti-FGFR3 antibodies (Ab1) were determined. The anti-FGFR3 antibodies were immobilized on a Biacore chip for approximately 100 response units (RU). Flow cell 1 remained blank for reference subtraction on each chip. The ECD FGFR3 protein and mouse anti-FGFR3 antibodies (Ab2) prepared in HBS-EP+ running buffer were injected for 3 minutes and 5 minutes at a flow rate of 50 μ l/min, respectively. The Ab1 surface was regenerated between cycles using 10 mM glycine-HCl (pH 2.0) at 50 μ l/min for 1 minutes. Sensorgrams were fit to a 1:1 binding model and analyzed using double-reference subtraction by BiaEvaluation software (GE Healthcare). It was determined that anti-FGFR3 antibodies KC18, KE35, KE42, KE58, KE63, and KE94 competed for the same region on FGFR3 around the D2 domain.

[0310] Hydrogen deuterium exchange (HDX) mass spectrometry was also used to determine the epitopes on FGFR3 for these antibodies by measuring the amide hydrogen deuterium exchange on FGFR3. HDX mass spectrometry measured amide hydrogen deuterium exchange over time and quenched at 0 °C and pH 2.5 along with protease digestion. Briefly, the antibody to be tested and antigen were mixed such that about 90% of the antibody is bound to the antigen at room temperature. Deuterium exchange was performed with a 10-fold dilution into D₂O at neutral pH. Quenching was then performed by holding the reaction mixture for 1 minute at about 0 to 1 °C to reduce

disulfide bonds. Protease digestion was performed with protease XIII and pepsin. HDX mass spectrometry is described in further detail in Prądzińska et al. (Amino Acids. 48: 2809–2820. 2016). The FGFR3 sequence used in the HDX assay is recited below, and corresponds to the D2D3 region, corresponding to D143 to E365 of FGFR3 Isoform IIIc:

DTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSISWLKNGREF
RGEHRIGGIKLRHQWVSLVMESVVPVSDRGNYTCVVENKFGSIRQTYTLDVLERS
PHRPILQAGLPANQTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDG
TPYVTVLKTAGANTTDKELEVLSLHNVTTFEDAGEYTCLAGNSIGFSHHSALWV
VLPAAEEELVE (SEQ ID NO: 134)

[0311] The results (**Fig. 2**) indicated that KE35 and KE58 bind to the N-terminus of the D2 region (D143 to L163); KE42 binds to N-terminus of the D2 region (D143 to N170); while KC18, KE94, and KE63 bind to N-terminus and middle of the D2 region (D143 to D160 and G197 to L213).

[0312] Internalization Assay

[0313] Internalization of anti-FGFR3 antibodies was evaluated in KMS-11 cells (JCRB cell bank, Japan). The KMS-11 cells were incubated with each antibody at a final concentration of 2 µg/ml for 30 minutes, 1, 2, 5, and 24 hours, then placed at 4 °C before washing the cells with PBS (Ca²⁺ and Mg²⁺). A subset of samples was washed with glycine-HCl buffer (pH 4) and fixed with 4% paraformaldehyde (Sigma). Another subset of samples was permeabilized with Triton X-100 (Sigma). The cells with immunofluorescence staining buffer, containing dye and fluorescent conjugated secondary antibody, were imaged by a PerkinElmer Opera high-throughput automated microscope and analyzed using the PerkinElmer Columbus image management system (PerkinElmer, Hopkinton, MA). Internalization of anti-FGFR3 antibodies was observed in KMS-11 cells treated with glycine-HCl and Triton X-100. The cell surface staining of each antibody was detected in a subset without treatment of glycine-HCl and Triton X-100 (**Fig. 3**). The ratio of the fluorescence signal for internalized antibody (+pH3/+TX100) to total antibody (-pH3/+TX100) then allows comparison of the degree of internalization for different antibodies (**Fig. 4**). The results indicate that the anti-FGFR3 antibodies were effectively internalized into the KMS-11 cells.

[0314] Dimerization of FGFR3 assay

[0315] Inhibition of FGFR3 dimerization by anti-FGFR3 antibodies was evaluated by a chemiluminescent assay. U2OS cells co-expressing a fusion protein of β -galactosidase-prolink (PK) and FGFR3 (FGFR3-PK) and β -galactosidase-enzyme acceptor (EA) and FGFR3 (FGFR3-EA) were developed by DiscoverRx (Fremont, CA). β -galactosidase is in an inactive form and when dimerization occurs the prolink and enzyme acceptor come together and are cleaved by the now activated β -galactosidase. The cells were pre-incubated with anti-FGFR3 antibodies at various concentrations before addition of FGF18 ligand to induce dimerization of FGFR3 proteins, then incubated at 37 °C overnight. The substrate was added to the cells and chemiluminescent signal was measured by EnVision (PerkinElmer). Blocking of FGFR3 dimerization by anti-FGFR3 antibodies was observed (**Fig. 5A – Fig. 5C**).

[0316] Humanization

[0317] Humanized variants of KC18, KE63 and KE94 clones were generated as follows: 1) Structural models of the Fv regions of these antibodies in complex with FGFR3 were generated by the Molecular Operating Environment (MOE) from the Chemical Computing Group using KC18-FGFR3 complex structure as template given their high sequence similarity with KC18 (**Fig. 6**); 2) The VH and VL sequences were searched against the human germline sequence, and the most similar human germline Fv sequence and J region were identified. CDRs from KC18, KE63 and KE94 were then grafted onto the framework of the closest human germline genes; 3) Analysis was performed to identify amino acids that were likely to be important for the FGFR3 binding properties of the antibodies. Selected Vernier zone and key contact residues were mutated back to mouse residues after examination within the structural models; and 4) Potential liability sites were removed.

[0318] Heavy chain of KC18_Hrw1-3 and _HV1.69rw2-4, and light chain of KC18_Lrw1-3 were designed by the method described above. Further analysis to introduce back-mutations, stabilizing mutations and to eliminate other unwanted motifs, additional heavy and light chains of KC18 variants were identified KC18_VH1, VH1b-c, VH2-3, VH3b-c and VH4, and KC18_VL1, VL1b-d, VL2, VL3, VL3b, VL4, VL5 and VL6, respectively. Heavy chains KE63 VH1-6 and light chains KE63_VL1-4 were designed. Particularly, initial KE63 (KE63_VH1 and KE63_VL1) humanized constructs were designed, then further modifications to the heavy and light chain were designed

(KE63_VH2-6 and KE63_VL2-4) to introduce back-mutations, stabilizing mutations and to eliminate other unwanted motifs. Similar methods were also used to design KE94 humanized constructs KE94_VH1-6. Notably, KE63 and KE94 share the same set of VL designs, namely KE63_VL1-4 here. Tables 5, 6, and 7 indicate the strategy used to pair the heavy and light chain variants for KC18, KE63 and KE94, respectively, including the human and mouse germline identity percentage.

[0319] Table 5. Human and mouse germline identity percentage of the designed KC18 variants

KC18			Lrw1	Lrw2	Lrw3	VL1	VL1d	VL1c	
	Human		93.07%	96.04%	95.05%	95.05%	93.07%	94.06%	
	Mouse		88.12%	87.13%	86.14%	88.12%	88.12%	89.11%	
Hrw1	83.67%	74.49%	KC18_Hu1	KC18_Hu7	KC18_Hu13				
Hrw2	84.73%	75.51%	KC18_Hu2	KC18_Hu8	KC18_Hu14				
Hrw3	84.69%	75.51%	KC18_Hu3	KC18_Hu9	KC18_Hu15				
HV1.69rw2	83.67%	72.45%	KC18_Hu4	KC18_Hu10	KC18_Hu16				
HV1.69rw3	83.67%	72.45%	KC18_Hu5	KC18_Hu11	KC18_Hu17				
HV1.69rw4	83.67%	72.45%	KC18_Hu6	KC18_Hu12	KC18_Hu18				
VH1	80.61%	75.51%				KC18_Hu19		KC18_Hu23	
VH1b	84.69%	73.47%							
VH1c	82.65%	73.47%					KC18_Hu38		
VH2	77.55%	78.57%							
VH3	84.69%	73.47%				KC18_Hu20		KC18_Hu24	
VH3b	85.71%	74.49%							
VH3c	84.69%	74.49%					KC18_Hu39		
VH4	78.57%	79.59%							
KC18			VL1b	VL2	VL3	VL3b	VL4	VL5	VL6
	Human		94.06%	90.10%	86.14%	85.15%	81.19%	81.19%	81.19%
	Mouse		87.13%	91.09%	79.21%	80.20%	86.14%	81.19%	85.15%
Hrw1	83.67%	74.49%							
Hrw2	84.73%	75.51%							
Hrw3	84.69%	75.51%							
HV1.69rw2	83.67%	72.45%							
HV1.69rw3	83.67%	72.45%							
HV1.69rw4	83.67%	72.45%							
VH1	80.61%	75.51%			KC18_Hu29				
VH1b	84.69%	73.47%	KC18_Hu40			KC18_Hu31		KC18_Hu35	
VH1c	82.65%	73.47%							
VH2	77.55%	78.57%		KC18_Hu27			KC18_Hu33		KC18_Hu37
VH3	84.69%	73.47%			KC18_Hu30				
VH3b	85.71%	74.49%	KC18_Hu41			KC18_Hu32			
VH3c	84.69%	74.49%							
VH4	78.57%	79.59%		KC18_Hu28			KC18_Hu34		

[0320] Table 6. Human and mouse germline identity percentage of the designed KE63 variants

KE63			KE63_VL1	KE63_VL2	KE63_VL3	KE63_VL4
	Human		93.07%	93.07%	91.09%	91.09%
	Mouse		90.00%	89.00%	87.00%	87.00%
KE63_VH1	83.67%	74.49%	KE63_Hu1	KE63_Hu2	KE63_Hu3	KE63_Hu4
KE63_VH2	86.73%	73.47%	KE63_Hu5	KE63_Hu6	KE63_Hu7	KE63_Hu8
KE63_VH3	85.71%	74.49%	KE63_Hu9	KE63_Hu10	KE63_Hu11	KE63_Hu12
KE63_VH4	86.73%	73.47%	KE63_Hu13	KE63_Hu14	KE63_Hu15	KE63_Hu16
KE63_VH5	82.65%	73.47%	KE63_Hu17	KE63_Hu18	KE63_Hu19	KE63_Hu20
KE63_VH6	81.63%	72.45%	KE63_Hu21	KE63_Hu22	KE63_Hu23	KE63_Hu24

[0321] Table 7. Human and mouse germline identity percentage of the designed KE94 variants

KE94			KE94_VL1	KE94_VL2	KE94_VL3	KE94_VL4
	Human		93.07%	93.07%	91.09%	91.09%
	Mouse		90.00%	89.00%	87.00%	87.00%
KE94_VH1	82.65%	77.55%	KE94_Hu1	KE94_Hu2	KE94_Hu3	KE94_Hu4
KE94_VH2	85.71%	76.53%	KE94_Hu5	KE94_Hu6	KE94_Hu7	KE94_Hu8
KE94_VH3	84.69%	77.55%	KE94_Hu9	KE94_Hu10	KE94_Hu11	KE94_Hu12
KE94_VH4	83.67%	78.57%	KE94_Hu13	KE94_Hu14	KE94_Hu15	KE94_Hu16
KE94_VH5	82.65%	77.55%	KE94_Hu17	KE94_Hu18	KE94_Hu19	KE94_Hu20
KE94_VH6	81.63%	76.53%	KE94_Hu21	KE94_Hu22	KE94_Hu23	KE94_Hu24

[0322] Amino acid sequences for the humanized variants of KC18, KE64 and KE94, without the constant regions, are depicted below in Table 8. Nucleic acid sequences for the humanized variants of KC18, KE64 and KE94, without the constant regions, are depicted below in Table 9. The heavy and light constant regions are indicated in SEQ ID NO: 54 and SEQ ID NO: 55, respectively.

[0323] Table 8. Amino acid sequences of humanized variants of KC18, KE64 and KE94

Antibody ID	Sequence
KC18_Hu18_VH	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGL EWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSED AVYYCTRTYDGPYAFDYWGQGTLVTVSS (SEQ ID NO: 18)

KC18 Hu18 VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSNNKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CQQYYSYRTFGGQTKLEIK (SEQ ID NO: 19)
KE63 Hu01 VH	QVQLVQSGAEVKKPGASVKVSCKASGSTFSDFEIHVWRQAPGQGL EWIGGIDPETGGTAYNQKFQGRVTITADRSTSTAYMELSSLRSEDTA VYYCTRNYDGYSQTFDYWGQGLTVTVSS (SEQ ID NO: 20)
KE63 Hu02 VH	QVQLVQSGAEVKKPGASVKVSCKASGSTFSDFEIHVWRQAPGQGL EWIGGIDPETGGTAYNQKFQGRVTITADRSTSTAYMELSSLRSEDTA VYYCTRNYDGYSQTFDYWGQGLTVTVSS (SEQ ID NO: 21)
KE63 Hu03 VH	QVQLVQSGAEVKKPGASVKVSCKASGSTFSDFEIHVWRQAPGQGL EWIGGIDPETGGTAYNQKFQGRVTITADRSTSTAYMELSSLRSEDTA VYYCTRNYDGYSQTFDYWGQGLTVTVSS (SEQ ID NO: 22)
KE63 Hu04 VH	QVQLVQSGAEVKKPGASVKVSCKASGSTFSDFEIHVWRQAPGQGL EWIGGIDPETGGTAYNQKFQGRVTITADRSTSTAYMELSSLRSEDTA VYYCTRNYDGYSQTFDYWGQGLTVTVSS (SEQ ID NO: 23)
KE63 Hu01 VL	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSSNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CHQYLSSYTFGQGTKLEIK (SEQ ID NO: 24)
KE63 Hu02 VL	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSSNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CHQYLSPYTFGQGTKLEIK (SEQ ID NO: 25)
KE63 Hu03 VL	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNYLAWYQQKP GQSPKLLIYYASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CHQYLSPYTFGQGTKLEIK (SEQ ID NO: 26)
KE63 Hu04 VL	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNYLAWYQQKP GQSPKLLIYFASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC HQYLSPYTFGQGTKLEIK (SEQ ID NO: 27)
KE94 Hu01 VH	QVQLVQSGAEVKKPGASVKVSCKASGSTFTDFEIHVWRQAPGQGL EWIGAIIDPETGGTAYNQKFQGRVTITADKSTSTAYMELSSLRSEDTA VYYCTRNYDGYSRTFDYWGQGLTVTVSS (SEQ ID NO: 28)
KE94 Hu02 VH	QVQLVQSGAEVKKPGASVKVSCKASGSTFTDFEIHVWRQAPGQGL EWIGAIIDPETGGTAYNQKFQGRVTITADKSTSTAYMELSSLRSEDTA VYYCTRNYDGYSRTFDYWGQGLTVTVSS (SEQ ID NO: 29)
KE94 Hu03 VH	QVQLVQSGAEVKKPGASVKVSCKASGSTFTDFEIHVWRQAPGQGL EWIGAIIDPETGGTAYNQKFQGRVTITADKSTSTAYMELSSLRSEDTA VYYCTRNYDGYSRTFDYWGQGLTVTVSS (SEQ ID NO: 30)
KE94 Hu04 VH	QVQLVQSGAEVKKPGASVKVSCKASGSTFTDFEIHVWRQAPGQGL EWIGAIIDPETGGTAYNQKFQGRVTITADKSTSTAYMELSSLRSEDTA VYYCTRNYDGYSRTFDYWGQGLTVTVSS (SEQ ID NO: 31)
KE94 Hu01 VL	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSSNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CHQYLSSYTFGQGTKLEIK (SEQ ID NO: 32)
KE94 Hu02 VL	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSSNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CHQYLSPYTFGQGTKLEIK (SEQ ID NO: 33)
KE94 Hu03 VL	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNYLAWYQQKP GQSPKLLIYYASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY CHQYLSPYTFGQGTKLEIK (SEQ ID NO: 34)
KE94 Hu04 VL	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNYLAWYQQKP GQSPKLLIYFASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC HQYLSPYTFGQGTKLEIK (SEQ ID NO: 35)
IgG1 Constant Heavy	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSIVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVMHEALHNHYTQ KSLSLSPG (SEQ ID NO: 54)

IgG1 Constant Light	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC (SEQ ID NO: 55)
KC18Hrw1	QVQLVQSGAEVKKPGASVKVSCKASGDTFTDFEIHWVRQAPGQGL EWIGDIDPETGSTSYAQKFQGRATLTADRSTSTAYMELSSLRSEDTA VYYCTRTYDGYPYAMDYWGQGTLLTVSS (SEQ ID NO: 106)
KC18Hrw2	QVQLVQSGAEVKKPGASVKVSCKASGDTFTDFEIHWVRQAPGQGL EWIGDIDPETGSTSYAQKFQGRATLTADRSTSTAYMELSSLRSEDTA VYYCTRTYDGYPYAMDYWGQGTLLTVSS (SEQ ID NO: 107)
KC18Hrw3	QVQLVQSGAEVKKPGASVKVSCKASGDTFTDFEIHWVRQAPGQGL EWIGDIDPETGSTSYAQKFQGRATLTADRSTSTAYMELSSLRSEDTA VYYCTRTYDGYPYAMDYWGQGTSTVTVSS (SEQ ID NO: 108)
KC18HV1-69rw2	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGL EWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDT AVYYCTRTYDGYPYAMDYWGQGTLLTVSS (SEQ ID NO: 109)
KC18HV1-69rw3	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGL EWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDT AVYYCTRTYEGYPYAMDYWGQGTLLTVSS (SEQ ID NO: 110)
KC18HV1-69rw4	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGL EWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDT AVYYCTRTYDGYPYAFDYWGQGTLLTVSS (SEQ ID NO: 111)
KC18Lrw1	DIVMTQSPDSLAVSLGERATINCKSSQSLLYSNNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISIVQAEDVAVYY CQQYYSYRTFGGGTKVEIK (SEQ ID NO: 112)
KC18Lrw2	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSNNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISIVQAEDVAVYY CQQYYSYRTFGGGTKVEIK (SEQ ID NO: 113)
KC18Lrw3	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSNNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISIVQAEDVAVYY CQQYYSYRTFGGGTKVEIK (SEQ ID NO: 114)
KC18_CL_VH1	QVQLVQSGAEVVKPGATVKISCKASGDTFTDFEIHVVQAPGKGL EWIGDIDPETGGTAYNEKFQGRATLTADRSTSTAYMELSSLRSEDT AVYYCARTYDGYPYAMDYWGQGTITVTVSS (SEQ ID NO: 115)
KC18_CL_VH1b	QVQLVQSGAEVVKPGATVKISCKASGYTFTDFEIHVVQAPGKGL EWIGDVPETGGTAYAEKFQGRATITADRSTSTAYMELSSLRSEDT AVYYCARTYDGYPYAMDYWGQGTITVTVSS (SEQ ID NO: 116)
KC18_CL_VH1c	QVQLVQSGAEVVKPGATVKISCKASGYTFTDFEIHVVQAPGKGL EWIGDVEPETGGTAYAEKFQGRATITADRSTSTAYMELSSLRSEDA AVYYCARTYDGYPYAMDVWGQGTITVTVSS (SEQ ID NO: 117)
KC18_CL_VH2	QVQLVQSGAEVVKPGATVKLSCKASGDTFTDFEIHVVQAPGKGL EWIGDIDPETGGTAYNEKFQGRATLTADRSTSTAYMELSSLRSEDT AVYYCTRTYDGYPYAMDYWGQGTITVTVSS (SEQ ID NO: 118)
KC18_CL_VH3	QVQLVQSGAEVVKPGASVKVSCKASGDTFTDFEIHVVQAPGQGL EWIGDIDPESGGTAYNQKFQGRVTMTADRSISTAYMELSSLRSDDT AVYYCARTYDGYPYAMDYWGQGTITVTVSS (SEQ ID NO: 119)
KC18_CL_VH3b	QVQLVQSGAEVVKPGASVKVSCKASGYTFTDFEIHVVQAPGQGL EWIGDIDPESGGTAYNQKFQGRVTMTADRSISTAYMELSSLRSDDT AVYYCARTYDGYPYAMDYWGQGTITVTVSS (SEQ ID NO: 120)
KC18_CL_VH3c	QVQLVQSGAEVVKPGASVKVSCKASGYTFTDFEIHVVQAPGQGL EWIGDIEPESGGTAYNQKFQGRVTMTADRSISTAYMELSSLRSDDA AVYYCARTYDGYPYAMDVWGQGTITVTVSS (SEQ ID NO: 121)
KC18_CL_VH4	QVQLVQSGAEVVKPGASVKLSCKASGDTFTDFEIHVVQAPGQGL EWIGDIDPETGGTAYNQKFQGRATLTADRSSSTAYMELSSLRSDDT AVYYCTRTYDGYPYAMDYWGQGTITVTVSS (SEQ ID NO: 122)
KC18_CL_VL1	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSNNQKNYLAWYQQKP GQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISIVQAEDVAVYY CQQYYSYRTFGGGTKLEIK (SEQ ID NO: 123)

KC18_CL_VL1b	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSNNQKNYLAWYQQKP GQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYY CQQYYSYRTFGGGTKLEIK (SEQ ID NO: 124)
KC18_CL_VL1c	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSNNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYY CQQYYSYRTFGGGTKLEIK (SEQ ID NO: 125)
KC18_CL_VL1d	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSNNQKNYLAWYQQKP GQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYY CQQYYSYRTFGGGTKLEIK (SEQ ID NO: 126)
KC18_CL_VL2	DIVMTQSPSSLAVSLGERVTMNCKSSQSLLYSNNQKNYLAWYQQK PGQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVY YCQQYYSYRTFGGGTKLEIK (SEQ ID NO: 127)
KC18_CL_VL3	DIVMTQSPSLPVTVGEPVSISCRSSQSLLHSNNQKNYLAWYLQKPG QSPQLLIYWGSTRASGVPDRFSGSGSGTDFTLTKISRVEAEDVGYYC QQYYSYRTFGGGTKLEIK (SEQ ID NO: 128)
KC18_CL_VL3b	DIVMTQSPSLPVTVGEPVSISCRSSQSLLYSNNQKNYLAWYLQKPG QSPQLLIYWGSTRASGVPDRFSGSGSGTDFTLTKISRVEAEDVGYYC QQYYSYRTFGGGTKLEIK (SEQ ID NO: 129)
KC18_CL_VL4	DIVMTQSPSLAVTVGEKVSISCRSSQSLLYSNNQKNYLAWYQQKP GQSPKLLIYWGSTRESGVPDRFSGSGSGTDFTLTISRVEAEDVGYYC CQQYYSYRTFGGGTKLEIK (SEQ ID NO: 130)
KC18_CL_VL5	DIQMTQSPSSLSVSVGDRVTMTCRASQGISYNNQKNYLAWYQQK PGKSPKLLIYWASTRQSGVPSRFSGSGSGTDFTLTISSVQAEDVAVY YCQQYYSYRTFGGGTKLEIK (SEQ ID NO: 131)
KC18_CL_VL6	DIQMTQSPSSLSVSVGDRVTMTCRSSQSLLYSNNQKNYLAWYQQK PGKSPKLLIYWASTRQSGVPSRFSGSGSGTDFTLTISSVQAEDVAVY YCQQYYSYRTFGGGTKLEIK (SEQ ID NO: 132)

[0324] Table 9. Nucleic acid sequences of humanized variants of KC18, KE64 and KE94 (HC: heavy chain; LC: light chain)

Antibody ID	Sequence
KC18 Hu18 HC	GAGGTACAACCTGTCCAGTCAGGTGCGGAGGTTAAAAAACCGGG GGCCACAGTTAAACTGAGCTGCAAGGCTAGCGGTGATACTTTA CCGATTTTGAGATACTGGGTTCAGCAGGCTCCGGGGAAAGGG CTTGAATGGATTGGTGATGTTGACCCGAAACGGGCGGAACCGC GTATGCAGAGAAGTTCAAGGTAGGGCAACGCTCACTGCGGACA GAAGCACAGACACGGCATAACATGGAGCTTAGTTCTCTCCGCTCT GAGGATACCGCTGTTTATTATTGTAAGTAACCTATGATGGATAT CCATACGCATTGATTATTGGGGGCAAGGGACTCTTGTCACAGT CAGCTCCGCTTCAACCAAGGGACCTTCTGTCTTCTCTGGCCCC TTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGGTGCC TTGTGAAAGATTACTTCCAGAGCCTGTACCGTCAGCTGGAATT CAGGCGCTCTGACTAGCGGAGTGACACCTTCCCCGCTGTGCTTC AGTCCTCCGACTCTACTCTCTGAGCAGCGTGGTGACCGTGCCGT CCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAATCAT AGCCTTCTAATAACCAAGGTGGACAAGAAGGTGGAACCCAAATCA TGTGACAAGACCCACACCTGTCCGCCCTGTCCGGCACCCGAAC GCTGGGTGGCCCTTCCGTGTTCTTTTCCCTCCAAAGCCGAAGGA CACTCTTATGATTTCTCGCACTCCCGAAGTGACTTGCGTCGTGGT GGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTGGTACG TGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCGAGAGA GGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCTGACCG TGCTGCACCAGGACTGGCTTAACGGAAAGGAGTACAAGTGCAA AGTGTCAAACAAGGCACTGCCCCGCTCCGATCGAAAAGACCATT GCAAAGCTAAGGGCCAGCCAGAGAAACCCCAAGTCTATACCCTT CCACCCAGCCGGGACGAGCTGACCAAAAACAGGTGTCACTCAC

	TTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTGCAATG GGAGTCCAATGGTCAGCCAGAGAACAACCTACAAAACCCCCCTC CCGTGCTGGACAGCGACGGGTCTTTCTTTCTCTACTCAAAGCTGA CCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTTTCTGTT CAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAAAGTCA CTGAGCCTGTCTCCCGGA (SEQ ID NO: 36)
KC18 Hu18 LC	GACATAGTGATGACTCAATCCCCAGATTCACTCGCCGTATCACTC GGAGAAAAGAGCCACAATTAATTGTAAGAGTAGTCAGTCAGTCCT TTACTCTAATAACAACAAAAATTACCTGGCCTGGTACCAACAGA AACCAGGTCAATCTCCTAAACTGCTTATCTACTGGGCTAGTACCC GAGAATCAGGAGTTCCTCGATAGGTTTTCTGGGTCTGGGAGCGGC ACCGACTTCACACTCACAATCTCTAGCGTACAGGCTGAAGATGT AGCGGTGTATTACTGCCAACAGTATTATTCATACAGGACCTTCG GTGGTGGCACCAGTAAAGTAGAAATCAAACGCACGTGTGGCAGCCCT TCTGTGTTTATCTTCCCACCTCCGACGAGCAGCTCAAGTCCGGT ACCGCCTCTGTCTGCTGCTGCTGAACAATTTCTACCCAAGAGAG GCCAAGGTGCAGTGGAAAGGTGGACAACGCACGTGCAAAGCGGTA ATTACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCAC CTACTCACTGTCATCCACCCTGACTCTCTCAAAGGCTGACTACGA AAAGCACAAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTT CTAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 37)
KE63 Hu01 HC	CAGGTACAGTTGGTACAGTCAGGAGCGGAGGTTAAAAAACAG GGGCGTCTGTGAAAGTCTCATGTAAAGCGAGCGGAAGCACGTTT AGCGATTTTCGAGATTCACTGGGTGAGACAAGCACCCGGTCAGGG CCTGGAATGGATTGGAGGGATCGACCCGGAACAGGGGTACA GCATATAACCAAAAAGTTTCAGGGACGGGTCACTATAACGGCTGA CAGGAGCACGTCAACTGCGTATATGGAATTGTCCAGTTTGAGGT CAGAAGATACGGCAGTCTACTACTGCACAAGAAATTATGATGGA TACTCTCAAACGTTTGATTATTTGGGGTCAGGGGACCTTGTAAC AGTCAGTCTCAGCTTCAACCAAGGGACCTTCTGTCTTCTCTGGC CCCTTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGGT GCCTTGTGAAAGATTACTTCCCAGAGCCTGTCACCGTCAGCTGG AATTCAGGCGCTCTGACTAGCGGAGTGCACACCTTCCCCGCTGT GCTTCAGTCTCCTCGGACTCTACTCTCTGAGCAGCGTGGTGACCGT GCCGTCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAA TCATAAGCCTTCTAATACCAAGGTGGACAAGAAGGTGGAACCCA AATCATGTGACAAGACCCACACCTGTCCGCCCTGTCCGGCACCC GAACGTCTGGGTGGCCCTTCCGTGTTCTTTTCCCTCAAAGCCG AAGGACACTCTTATGATTTCTCGCACTCCCAGAGTGAAGTGGTGC GTGGTGGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTG GTACGTGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCG AGAGAGGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCCT GACCGTGTGCAACAGGACTGGCTTAACGGAAAGGAGTACAAGT GCAAAGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAGACC ATTAGCAAAGCTAAGGGCCAGCCAGAGAACCCCAAGTCTATAC CCTTCCACCCAGCCGGGACGAGCTGACCAAAAAACAGGTGTCAC TCACTTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTG AATGGGAGTCCAATGGTCAGCCAGAGAACAATAACAAAACAC CCCTCCCGTGTGACAGCGACGGGTCTTCTTCTCTACTCAAA GCTGACCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTTT CCTGTTCAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAA AGTCACTGAGCCTGTCTCCCGGA (SEQ ID NO: 38)
KE63 Hu02 HC	CAGGTACAGTTGGTACAGTCAGGAGCGGAGGTTAAAAAACAG GGGCGTCTGTGAAAGTCTCATGTAAAGCGAGCGGAAGCACGTTT AGCGATTTTCGAGATTCACTGGGTGAGACAAGCACCCGGTCAGGG CCTGGAATGGATTGGAGGGATCGACCCGGAACAGGGGTACA GCATATAACCAAAAAGTTTCAGGGACGGGTCACTATAACGGCTGA CAGGAGCACGTCAACTGCGTATATGGAATTGTCCAGTTTGAGGT

	CAGAAGATACGGCAGTCTACTACTGCACAAGAAATTATGATGGA TACTCTCAAACGTTTGATTATTGGGGTCAGGGGACCTTGTAAC AGTCAGCTCAGCTTCAACCAAGGGACCTTCTGTCTTCTCTGGC CCCTTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGGT GCCTTGTGAAAGATTACTTCCCAGAGCCTGTCACCGTCAGCTGG AATTCAGGCGCTCTGACTAGCGGAGTGCACACCTTCCCCGCTGT GCTTCAGTCCTCCGGACTCTACTCTCTGAGCAGCGTGGTGACCGT GCCGTCCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAA TCATAAGCCTTCTAATACCAAGGTGGACAAGAAGGTGGAACCCA AATCATGTGACAAGACCCACACCTGTCCGCCCTGTCCGGCACCC GAACTGCTGGGTGGCCCTTCCGTGTTCTTTTCCCTCCAAAGCCG AAGGACACTCTTATGATTTCTCGCACTCCCGAAGTGACTTGCGTC GTGGTGGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTG GTACGTGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCG AGAGAGGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCCT GACCGTGCTGCACCAGGACTGGCTTAACGAAAAGGAGTACAAGT GCAAAGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAGACC ATTAGCAAAGCTAAGGGCCAGCCAGAGAACCCCAAGTCTATAC CCTTCCACCCAGCCGGGACGAGCTGACCAAAAAACAGGTGTCAC TCACTTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTCG AATGGGAGTCCAATGGTCAGCCAGAGAACAATAACAAAAACCAC CCCTCCCGTGCTGGACAGCGACGGGTCTTTCTTCTCTACTCAA GCTGACCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTTT CCTGTTCAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAA AGTCACTGAGCCTGTCTCCCGGA (SEQ ID NO: 39)
KE63 Hu03 HC	CAGGTACAGTTGGTACAGTCAGGAGCGGAGGTTAAAAAACAG GGGCGTCTGTGAAAGTCTCATGTAAAGCGAGCGGAAGCACGTTT AGCGATTTTCGAGATTCAGTGGGTGAGACAAGCACCCGGTCAGGG CCTGGAATGGATTGGAGGGATCGACCCGGAACAGGGGGTACA GCATATAACCAAAAGTTTCAGGGACGGGTCACTATAACGGCTGA CAGGAGCACGTCAACTGCGTATATGGAATTGTCCAGTTTGAGGT CAGAAGATACGGCAGTCTACTACTGCACAAGAAATTATGATGGA TACTCTCAAACGTTTGATTATTGGGGTCAGGGGACCCCTGGTAAC AGTCAGCTCAGCTTCAACCAAGGGACCTTCTGTCTTCTCTGGC CCCTTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGGT GCCTTGTGAAAGATTACTTCCCAGAGCCTGTCACCGTCAGCTGG AATTCAGGCGCTCTGACTAGCGGAGTGCACACCTTCCCCGCTGT GCTTCAGTCCTCCGGACTCTACTCTCTGAGCAGCGTGGTGACCGT GCCGTCCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAA TCATAAGCCTTCTAATACCAAGGTGGACAAGAAGGTGGAACCCA AATCATGTGACAAGACCCACACCTGTCCGCCCTGTCCGGCACCC GAACTGCTGGGTGGCCCTTCCGTGTTCTTTTCCCTCCAAAGCCG AAGGACACTCTTATGATTTCTCGCACTCCCGAAGTGACTTGCGTC GTGGTGGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTG GTACGTGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCG AGAGAGGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCCT GACCGTGCTGCACCAGGACTGGCTTAACGAAAAGGAGTACAAGT GCAAAGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAGACC ATTAGCAAAGCTAAGGGCCAGCCAGAGAACCCCAAGTCTATAC CCTTCCACCCAGCCGGGACGAGCTGACCAAAAAACAGGTGTCAC TCACTTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTCG AATGGGAGTCCAATGGTCAGCCAGAGAACAATAACAAAAACCAC CCCTCCCGTGCTGGACAGCGACGGGTCTTTCTTCTCTACTCAA GCTGACCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTTT CCTGTTCAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAA AGTCACTGAGCCTGTCTCCCGGA (SEQ ID NO: 40)
KE63 Hu04 HC	CAGGTACAGTTGGTACAGTCAGGAGCGGAGGTTAAAAAACAG GGGCGTCTGTGAAAGTCTCATGTAAAGCGAGCGGAAGCACGTTT AGCGATTTTCGAGATTCAGTGGGTGAGACAAGCACCCGGTCAGGG

	CCTGGAATGGATTGGAGGGATCGACCCGAAACAGGGGGTACAGCATATAACCAAAAAGTTTCAGGGACGGGTCCTATAACGGCTGACAGGACACGTCAACTGCGTATATGGAATTGTCCAGTTTGAGGT CAGAAGATACGGCAGTCTACTACTGCACAAGAAATTATGATGGA TACTCTCAAACGTTTGATTATTGGGGTCAGGGGACCTTGGAAC AGTCAGCTCAGCTTCAACCAAGGGACCTTCTGTCTTCTCTGGC CCCTTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGT GCCTTGTGAAAGATTACTTCCCAGAGCCTGTACCCGTGAGCTGG AATTCAGGCGCTCTGACTAGCGGAGTGCACACCTTCCCCGTGT GCTTCAGTCTCCGGACTCTACTCTCTGAGCAGCGTGGTGACCGT GCCGTCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAA TCATAAGCCTTCTAATACCAAGGTGGACAAGAAGGTGGAACCA AATCATGTGACAAGACCCACACCTGTCCGCCCTGTCCGCAACC GAACTGCTGGGTGGCCCTTCCGTGTCTCTTTTCCCTCCAAAGCCG AAGGACACTCTTATGATTTCTCGCACTCCCGAAGTGACTTGCGTC GTGGTGGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTG GTACGTGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCG AGAGAGGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCTT GACCGTGTGCACCAGGACTGGCTTAACGGAAGGAGTACAAGT GCAAAAGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAGACC ATTAGCAAAGCTAAGGGCCAGCCAGAGAACCCCAAGTCTATAC CTTTCCACCCAGCCGGGACGAGCTGACCAAAAAACAGGTGTCAC TCACTTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTG AATGGGAGTCCAATGGTCAGCCAGAGAACAATAACAAAACAC CCCTCCCGTGTGGACAGCGACGGGTCTTCTTCTCTACTCAA GCTGACCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTT CCTGTTCAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAA AGTCACTGAGCCTGTCTCCCGA (SEQ ID NO: 41)
KE63 Hu01 LC	GATATAGTTATGACACAGAGCCCTGACTCTCTGGCTGTGAGTTTGGCGAGCGAGTAACCATTAAATTGTAAGAGTTCTCAATCCGTCTCTACTCAAGCAACCAGAAAAATTACCTCGCGTGGTACCAGCAAA AACCAGGACAGAGCCCCAACTCTTGATCTATTGGGCGTCCACC CGAGAGAGTGGCGTGCCAGATCGGTTTTAGGTTCTGGATCTGG TACCGACTTACCCCTTACAATCTCAAGCCTGCAAGCAGAGGATG TCGCAGTTTATTATTGCCATCAGTACCTGAGCAGTACACATTCG GACAAGGAACGAACTGGAATCAAACGCACTGTGGCAGCCCC TTCTGTGTTTATCTTCCCACCCTCCGACGAGCAGCTCAAGTCCGG TACCGCTCTGTCTGTCTGCTGCTGAACAATTCTACCCAGAGA GGCCAAGGTGCAGTGGAAAGGTGGACAACGCACTGCAAAAGCGGT AATTCACAAGAGTCAGTACCCGAACAAGACTCAAAGGACAGCA CCTACTCACTGTATCCACCCTGACTCTCTCAAAGGTGACTACG AAAAGCACAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTT TCTAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 42)
KE63 Hu02 LC	GACATAGTAATGACCCAAAGTCCAGATTCTTTGGCCGTATCTTTGGTGAGCGCGTTACCATCAACTGTAAGTCTTCCAGTCTGTGTTG TACTCATCTAATCAAAAAAACTACCTCGCTTGGTACCAGCAGAA GCCAGGTCAAAGCCCGAACTGCTTATTATTGGGCGTCTACGC GAGAGTCTGGGGTCCCCGATCGGTTTTAGGGTCAAGGCTCTGGC ACTGATTTTACTCTGACTATTTATCCCTCCAAGCCGAAGACGTG GCAGTGTATTACTGCCACCAGTATTTGAGCCCTTACACGTTTGGG CAGGGGACTAACTTGAAATCAAGCGCACTGTGGCAGCCCCCTT TGTGTTTATCTTCCCACCCTCCGACGAGCAGCTCAAGTCCGGTAC CGCTCTGTCTGTCTGCTGCTGAACAATTTCTACCCAAGAGAGGC CAAGGTGCAGTGGAAAGGTGGACAACGCACTGCAAGCGGTAAT TCACAAGAGTCAGTACCCGAACAAGACTCAAAGGACAGCACCT ACTCACTGTATCCACCCTGACTCTCTCAAAGGCTGACTACGAA AAGCACAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTTC

	TAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 43)
KE63 Hu03 LC	GATATTGTGATGACTCAGTCACCTGACAGTCTGGCGGTTTCTTTG GGCGAAAGAGTGACTATAAATTGCAAAAGCAGCCAGTCAGTTCT CTATTCCGACAATCAAAAGAACTATCTCGCATGGTATCAGCAGA AGCCAGGGCAATCCCCAAAATTGCTTATATACTATGCATCAACG CGCGAAAGCGGTGTACCCGATCGGTTTTAGGAAGTGCGAGTGG GACCGACTTTACGCTGACAATCTCTTCCCTTCAAGCGGAGGATGT CGCGGTTTATTATTGTCATCAGTATCTGAGTCCTTACACCTTTGG TCAAGGGACGAAGTTGGAGATCAAACGCACTGTGGCAGCCCTT CTGTGTTTATCTTCCACCTCCGACGAGCAGCTCAAGTCCGGTA CCGCCTCTGTCGTCTGCCTGCTGAACAATTTCTACCAAGAGAGG CCAAGGTGCAGTGGAAGGTGGACAACGCACTGCAAAGCGGTAA TTCACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCACCT ACTCACTGTCATCCACCCTGACTCTCTCAAAGGCTGACTACGAA AAGCACAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTTC TAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 44)
KE63 Hu04 LC	GACATCGTAATGACCCAGTCCCCCGATAGTCTGGCTGTGTCTTTG GGCGAGAGGGTAACGATAAACTGTAAATCAAGTCAGTCAGTGCT TTACTCAGATAAACCAGAAAGAACTATCTTGCGTGGTATCAGCAAA AGCCCGGACAGTCTCCAAAACCTTCTTATATATTTGCTTCTACCA GAGAATCAGGTGTACAGACCGCTTTTCTGGAAGCGGCTCTGGT ACTGACTTTACCCTGACAATTAGTAGCTTGCAAGCTGAAGATGTT GCGGTATATTATTGTCACCAATACTTGAGTCCCTATACTTTTGGC CAAGGGACAAAACCTGGAAATAAAGCGCACTGTGGCAGCCCTTC TGTGTTTATCTTCCACCTCCGACGAGCAGCTCAAGTCCGGTAC CGCCTCTGTCGTCTGCCTGCTGAACAATTTCTACCAAGAGAGGC CAAGGTGCAGTGGAAGGTGGACAACGCACTGCAAAGCGGTAAT TCACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCACCT ACTCACTGTCATCCACCCTGACTCTCTCAAAGGCTGACTACGAA AAGCACAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTTC TAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 45)
KE94 Hu01 HC	CAGGTTGAGCTGGTACAATCTGGCGCGGAAGTCAAAAAGCCAGG CGCAAGTGTTAAAGTGTCTTGCAAGGCTTCAGGATCTACCTTTAC AGATTTTGAAATCCACTGGGTAAGACAAGCACCTGGCCAGGGGC TGGAATGGATTGGTGCCATAGACCCTGAGACGGGAGGAACCGC ATATAACCAGAAATTCCAAGGTCGAGTACTATTACTGCGGACA AGTCAACATCAACTGCCTATATGGAGCTGTCTTCTTTGAGGTGAG AGGATACAGCAGTTTACTACTGCACTAGAAATTACGATGGTTAT TCACGGACCTTCGATTATTGGGGTCAAGGCACTCTGGTGACCGT GAGTTCCGCTTCAACCAAGGGACCTTCTGTCTTTCCTCTGGCCCC TTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGGTGCC TTGTGAAAGATTACTTCCAGAGCCTGTACCGTCAGCTGGAATT CAGGCGCTCTGACTAGCGGAGTGCACACCTTCCCCGCTGTGCTTC AGTCCTCCGGACTCTACTCTCTGAGCAGCGTGGTGACCGTGCCGT CCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAATCATA AGCCTTCTAATACCAAGGTGGACAAGAAGGTGGAACCCAAATCA TGTGACAAGACCCACACCTGTCCGCCCTGTCCGGCACCCGAAC GCTGGGTGGCCCTTCCGTGTTCTTTTCCCTCAAAGCCGAAGGA CACTCTTATGATTTCTCGCACTCCCGAAGTGACTTGCCTCGTGGT GGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTGGTACG TGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCGAGAGA GGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCTGACCG TGCTGCACCAGGACTGGCTTAACGGAAGGAGTACAAGTGCAA AGTGTCAAACAAGGCACTGCCCCGCTCCGATCGAAAAGACCATTA GCAAAGCTAAGGGCCAGCCAGAGAACCCCAAGTCTATACCTT CCACCCAGCCGGGACGAGCTGACCAAAAACCAGGTGTCACTCAC

	TTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTGCAATG GGAGTCCAATGGTCAGCCAGAGAACAACCTACAAAACCCCCCTC CCGTGCTGGACAGCGACGGGTCTTTCTTTCTCTACTCAAAGCTGA CCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTTTCTGTT CAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAAAGTCA CTGAGCCTGTCTCCCGGA (SEQ ID NO: 46)
KE94 Hu02 HC	CAGGTTCACTGGTACAATCTGGCGCGGAAGTCAAAAAGCCAGG CGCAAGTGTTAAAGTGTCTTGCAAGGCTTCAGGATCTACCTTTAC AGATTTTGAAATCCACTGGGTAAGACAAGCACCTGGCCAGGGGC TGGAATGGATTGGTGCCATAGACCCTGAGACGGGAGGAACCGC ATATAACCAGAAATTCCAAGGTCGAGTGACTATTACTGCGGACA AGTCAACATCAACTGCCTATATGGAGCTGTCTTTTGAGGTGAG AGGATACAGCAGTTTACTACTGCACTAGAAATTACGATGGTTAT TCACGGACCTTCGATTATTGGGGTCAAGGCACTCTGGTGACCGT GAGTTCGCTTCAACCAAGGGACCTTCTGTCTTTCTCTGGCCCC TTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGGTGCC TTGTGAAAGATTACTTCCCAGAGCCTGTACCGTCAGCTGGAATT CAGGCGCTCTGACTAGCGGAGTGACACCTTCCCCGCTGTGCTTC AGTCCTCCGGACTCTACTCTCTGAGCAGCGTGGTGACCGTGCCGT CCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAATCATA AGCCTTCTAATACCAAGGTGGACAAGAAGGTGGAACCCAAATCA TGTGACAAGACCCACACCTGTCCGCCCTGTCCGGCACCCGAAC GCTGGGTGGCCCTTCCGTGTTCTTTTCCCTCCAAAGCCGAAGGA CACTCTTATGATTTCTCGCACTCCCGAAGTGACTTGCGTCGTGGT GGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTGGTACG TGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCGAGAGA GGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCTGACCG TGCTGCACCAGGACTGGCTTAACGGAAAGGAGTACAAGTGCAA AGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAGACCATT GCAAAGCTAAGGGCCAGCCAGAGAACCCCAAGTCTATACCTT CCACCCAGCCGGGACGAGCTGACCAAAAACAGGTGTCACCTAC TTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTGCAATG GGAGTCCAATGGTCAGCCAGAGAACAACCTACAAAACCCCCCTC CCGTGCTGGACAGCGACGGGTCTTTCTTTCTCTACTCAAAGCTGA CCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTTTCTGTT CAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAAAGTCA CTGAGCCTGTCTCCCGGA (SEQ ID NO: 47)
KE94 Hu03 HC	CAGGTTCACTGGTACAATCTGGCGCGGAAGTCAAAAAGCCAGG CGCAAGTGTTAAAGTGTCTTGCAAGGCTTCAGGATCTACCTTTAC AGATTTTGAAATCCACTGGGTAAGACAAGCACCTGGCCAGGGGC TGGAATGGATTGGTGCCATAGACCCTGAGACGGGAGGAACCGC ATATAACCAGAAATTCCAAGGTCGAGTGACTATTACTGCGGACA AGTCAACATCAACTGCCTATATGGAGCTGTCTTTTGAGGTGAG AGGATACAGCAGTTTACTACTGCACTAGAAATTACGATGGTTAT TCACGGACCTTCGATTATTGGGGTCAAGGCACTCTGGTGACCGT GAGTTCGCTTCAACCAAGGGACCTTCTGTCTTTCTCTGGCCCC TTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGGTGCC TTGTGAAAGATTACTTCCCAGAGCCTGTACCGTCAGCTGGAATT CAGGCGCTCTGACTAGCGGAGTGACACCTTCCCCGCTGTGCTTC AGTCCTCCGGACTCTACTCTCTGAGCAGCGTGGTGACCGTGCCGT CCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAATCATA AGCCTTCTAATACCAAGGTGGACAAGAAGGTGGAACCCAAATCA TGTGACAAGACCCACACCTGTCCGCCCTGTCCGGCACCCGAAC GCTGGGTGGCCCTTCCGTGTTCTTTTCCCTCCAAAGCCGAAGGA CACTCTTATGATTTCTCGCACTCCCGAAGTGACTTGCGTCGTGGT GGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTGGTACG TGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCGAGAGA GGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCTGACCG TGCTGCACCAGGACTGGCTTAACGGAAAGGAGTACAAGTGCAA

	AGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAAGACCATT GCAAAGCTAAGGGCCAGCCCAGAGAACCCCAAGTCTATACCCTT CCACCCAGCCGGGACGAGCTGACCAAAAACCAGGTGTCAC TTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTCGAATG GGAGTCCAATGGTCAGCCAGAGAACAACCTACAAAACCAACCCCTC CCGTGCTGGACAGCGACGGGTCTTTCTTTCTACTCAAAGCTGA CCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTTTCTGTT CAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAAAGTCA CTGAGCCTGTCTCCCGGA (SEQ ID NO: 48)
KE94 Hu04 HC	CAGGTTTCAGCTGGTACAATCTGGCGCGAAGTCAAAAAGCCAGG CGCAAGTGTTAAAGTGTCTTGCAAGGCTTCAGGATCTACCTTTAC AGATTTTGAAATCCACTGGGTAAGACAAGCACCTGGCCAGGGGC TGGAATGGATTGGTGCCATAGACCCTGAGACGGGAGGAACCGC ATATAACCAGAAAATTCCAAGGTCGAGTGACTATTACTGCCGACA AGTCAACATCAACTGCCTATATGGAGCTGTCTTTGAGGTGAG AGGATACAGCAGTTTACTACTGCACTAGAAATTACGATGGTTAT TCACGGACCTTCGATTATTGGGGTCAAGGCACTCTGGTGACCGT GAGTTCGGCTTCAACCAAGGGACCTTCTGTCTTCTCTGGCCCC TTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCACTCGGGTGCC TTGTGAAAGATTACTTCCCAGAGCCTGTACCGTCAGCTGGAATT CAGGCGCTCTGACTAGCGGAGTGACACCTTCCCCGCTGTGCTTC AGTCCTCCGGACTCTACTCTCTGAGCAGCGTGGTGACCGTGCCGT CCTCTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAATCATA AGCCTTCTAATACCAAGGTGGACAAGAAGGTGGAACCCAAATCA TGTGACAAGACCCACACCTGTCCGCCCTGTCCGGCACCCGAAT GCTGGGTGGCCCTTCCGTGTTCTTTTCCCTCCAAGGCCGAAGGA CACTCTTATGATTTCTCGCACTCCCGAAGTGACTTGCGTCGTGGT GGATGTGTCCCATGAGGATCCAGAGGTCAAGTTCAACTGGTACG TGGACGGTGTGGAAGTCCACAACGCCAAGACTAAGCCGAGAGA GGAACAGTACAATTCAACCTATCGGGTGGTGAGCGTCTGACCG TGCTGCACCAGGACTGGCTTAACGGAAAGGAGTACAAGTGCAA AGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAAGACCATT GCAAAGCTAAGGGCCAGCCCAGAGAACCCCAAGTCTATACCCTT CCACCCAGCCGGGACGAGCTGACCAAAAACCAGGTGTCAC TTGTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTCGAATG GGAGTCCAATGGTCAGCCAGAGAACAACCTACAAAACCAACCCCTC CCGTGCTGGACAGCGACGGGTCTTTCTTTCTACTCAAAGCTGA CCGTGGATAAGTCTCGCTGGCAGCAAGGGAATGTGTTTTCTGTT CAGTGATGCATGAGGCCCTTCATAATCATTACACCCAAAAGTCA CTGAGCCTGTCTCCCGGA (SEQ ID NO: 49)
KE94 Hu01 LC	GATATAGTTATGACACAGAGCCCTGACTCTCTGGCTGTGAGTTG GGCGAGCGAGTAACCATTAATTGTAAGAGTTCTCAATCCGTCCT CTACTCAAGCAACCAGAAAAATTACCTCGCGTGGTACCAGCAAA AACCAGGACAGAGCCCCAACTCTTGATCTATTGGGCGTCCACC CGAGAGAGTGGCGTGCCAGATCGGTTTTAGGTTCTGGATCTGG TACCGACTTCACCTTACAATCTCAAGCCTGCAAGCAGAGGATG TCGCAGTTTATTATTGCCATCAGTACCTGAGCAGCTACACATTG GACAAGGAACGAACTGGAAATCAAACGCACTGTGGCAGCCCC TTCTGTGTTTATCTTCCACCTCCGACGAGCAGCTCAAGTCCGG TACCGCCTCTGTCTGCTGCTGCTGAACAATTTCTACCCAAGAGA GGCCAAGGTGCAGTGGAAGGTGGACAACGCACTGCAAAAGCGGT AATTACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCA CCTACTCACTGTCATCCACCCTGACTCTCTCAAAGGCTGACTACG AAAAGCACAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTT TCTAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 50)
KE94 Hu02 LC	GACATAGTAATGACCCAAAGTCCAGATTCTTTGGCCGTATCTTTG GGTGAGCGCGTTACCATCAACTGTAAGTCTTCCAGTCTGTGTTG TACTCATCTAATCAAAAAAACTACCTCGCTTGGTACCAGCAGAA

	GCCAGGTCAAAGCCCGAACTGCTTATTTATTGGGCGTCTACGC GAGAGTCTGGGGTCCCCGATCGGTTTTTCAGGGTCAGGCTCTGGC ACTGATTTTACTCTGACTATTTTCATCCCTCCAAGCCGAAGACGTG GCAGTGTATTACTGCCACCAGTATTTGAGCCCTTACACGTTTGGG CAGGGGACTAAACTTGAAATCAAGCGCACTGTGGCAGCCCCCTTC TGTGTTTATCTTCCCACCCTCCGACGAGCAGCTCAAGTCCGGTAC CGCCTCTGTCGTCTGCCTGCTGAACAATTTCTACCCAAGAGAGGC CAAGGTGCAGTGGAAGGTGGACAACGCACTGCAAAGCGGTAAT TCACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCACCT ACTCACTGTATCCACCCTGACTCTCTCAAAGGCTGACTACGAA AAGCACAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTTC TAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 51)
KE94 Hu03 LC	GATATTGTGATGACTCAGTCACCTGACAGTCTGGCGGTTTCTTTG GGCGAAAGAGTGACTATAAATTGCAAAGCAGCCAGTCAGTTCT CTATTCCGACAATCAAAAAGAACTATCTCGCATGGTATCAGCAGA AGCCAGGGCAATCCCCAAAATTGCTTATATACTATGCATCAACG CGCGAAAGCGGTGTACCCGATCGGTTTTTCAGGAAGTGGCAGTGG GACCGACTTTACGCTGACAATCTTCCCTTCAAGCGGAGGATGT CGCGGTTTATTATTGTCATCAGTATCTGAGTCCTTACACCTTTGG TCAAGGGACGAAGTTGGAGATCAAACGCACTGTGGCAGCCCCCTT CTGTGTTTATCTTCCCACCCTCCGACGAGCAGCTCAAGTCCGGTA CCGCCTCTGTCGTCTGCCTGCTGAACAATTTCTACCCAAGAGAGG CCAAGGTGCAGTGGAAGGTGGACAACGCACTGCAAAGCGGTAA TTCACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCACCT ACTCACTGTATCCACCCTGACTCTCTCAAAGGCTGACTACGAA AAGCACAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTTC TAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 52)
KE94 Hu04 LC	GACATCGTAATGACCCAGTCCCCGATAGTCTGGCTGTGTCTTTG GGCGAGAGGGTAACGATAAACTGTAAATCAAGTCAGTCAGTGCT TTACTCAGATAACCAGAAGAACTATCTTGCCTGGTATCAGCAAA AGCCCCGACAGTCTCCAAAACCTTCTATATATTTTCGCTTCTACCA GAGAATCAGGTGTACCAGACCGCTTTTCTGGAAGCGGCTCTGGT ACTGACTTTACCCTGACAATTAGTAGCTTGCAAGCTGAAGATGTT GCGGTATATTATGTACCAATACTTGAGTCCCTATACTTTTGGC CAAGGGACAAAACCTGGAATAAAAGCGCACTGTGGCAGCCCCCTTC TGTGTTTATCTTCCCACCCTCCGACGAGCAGCTCAAGTCCGGTAC CGCCTCTGTCGTCTGCCTGCTGAACAATTTCTACCCAAGAGAGGC CAAGGTGCAGTGGAAGGTGGACAACGCACTGCAAAGCGGTAAT TCACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCACCT ACTCACTGTATCCACCCTGACTCTCTCAAAGGCTGACTACGAA AAGCACAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTTC TAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 53)

[0325] Affinities of the humanized KC18 antibodies to human and mouse FGFR3 were determined and are shown in Table 10 below. The affinities of these humanized antibodies are comparable to the parental KC18 antibody.

[0326] Table 10. Affinities to human and mouse FGFR3 of the humanized KC18 antibodies

	hFGFR3	mFGFR3
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KC18 Variants	ka	kd	KD	ka	kd	KD
Hu7	1.96E+05	1.06E-3	5.41E-09	1.98E+05	1.26E-3	6.36E-09
Hu10	2.78E+05	1.32E-3	4.73E-09	2.86E+05	1.47E-3	5.15E-09
Hu12	3.27E+05	5.27E-04	1.61E-09	3.37E+05	5.83E-04	1.73E-09
Hu13	1.89E+05	8.57E-04	4.52E-09	1.93E+05	1.02E-3	5.28E-09
Hu16	2.76E+05	1.04E-3	3.76E-09	2.78E+05	1.18E-3	4.23E-09
Hu18	3.34E+05	4.17E-04	1.25E-09	3.37E+05	4.79E-04	1.42E-09
Hu19	2.25E+05	6.75E-04	2.99E-09	2.35E+05	8.85E-04	3.78E-09
Hu23	2.41E+05	6.48E-04	2.68E-09	2.54E+05	8.50E-04	3.35E-09
Hu27	2.14E+05	8.34E-04	3.90E-09	2.20E+05	1.01E-3	4.60E-09
Hu28	2.13E+05	9.49E-04	4.46E-09	2.10E+05	1.14E-3	5.41E-09
Hu33	1.66E+05	1.14E-3	6.89E-09	1.68E+05	1.54E-3	9.15E-09
Hu34	1.55E+05	1.06E-3	6.85E-09	1.64E+05	1.34E-3	8.14E-09
KC18	2.13E+05	5.80E-04	2.73E-09	2.20E+05	8.32E-04	3.78E-09

[0327] Humanized antibodies KC18_Hu42 to KC18_49 were designed based on the sequence of KC_Hu18 to further remove liability sites, such as oxidation sites in FRWH3 and CDRH3, a deamidation site in CDRL1, and an oxidation site in CDRL2 (Table 11). At the end, two additional variants each for VH and VL were designed, which resulted in 8 more variants (KC18_Hu42-49) in addition to KC18_Hu18 (Table 12).

[0328] Table 11. Liability motifs in KC18_Hu18. The IMGT definition was used. Liability residues are underlined in the sequences.

Liability Motif	Modification	Region	Sequence	Involved in binding	Proposed mutations
W	Oxidation	HFW2	IHWVQQAPGKGLE <u>W</u> IGD (SEQ ID NO: 340)	No	Y
M	Oxidation	HFW3	AYA EK FQGRATLTADRSTD TAY <u>M</u> ELSSLRSEDTAVYYC (SEQ ID NO: 341)	No	L
W	Oxidation	HFW4	<u>W</u> GQGTLVTVSS (SEQ ID NO: 342)	No	Y
NNN	Deamidation	LCDR1	QSVLYSN <u>N</u> NNKNY (SEQ ID NO: 302)	Yes	DNQ
W	Oxidation	LCDR2	<u>W</u> AS (SEQ ID NO: 74)	Yes	Y and F

[0329] A sequence alignment of Hu18 and the newly designed variants (Hu42-49) is shown in **Fig. 7**. Mutations of Hu18 residues are underlined.

[0330] Table 12. Human and mouse germline identity percentage of the designed KC18 variants.

KC18			KC18_VL_3 (SEQ ID NO: 59)	KC18_VL_14 (SEQ ID NO: 60)	KC18_VL_15 (SEQ ID NO: 61)
	Human		95.05%	92.08%	92.08%
	Mouse		86.14%	87.13%	87.13%
KC18_VH_6 (SEQ ID NO: 56)	83.67%	72.45%	KC18_Hu18	KC18_Hu42	KC18_Hu43
KC18_VH_15 (SEQ ID NO: 57)	82.65%	71.43%	KC18_Hu44	KC18_Hu45	KC18_Hu46
KC18_VH_16 (SEQ ID NO: 58)	81.63%	70.41%	KC18_Hu47	KC18_Hu48	KC18_Hu49

[0331] Table 13. Designed KC18 variant amino acid sequences.

Antibody ID	Sequence
KC18_VH_6	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGLEWIG DVDPETGGTAYAEKFGGRATLTADRSTDTAYMELSSLRSEDVAVYYCTR TYDGYPYAFDYWGQGLTLTVSS (SEQ ID NO: 56)
KC18_VH_15	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGLEWIG DVDPETGGTAYAEKFGGRATLTADRSTDTAYLELSSLRSEDVAVYYCTR YDGYPYAFDYWGQGLTLTVSS (SEQ ID NO: 57)
KC18_VH_16	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGLEWIG DVDPETGGTAYAEKFGGRATLTADRSTDTAYLELSSLRSEDVAVYYCTR YDGYPYAFDYWGQGLTLTVSS (SEQ ID NO: 58)
KC18_VL_3	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSNNNKYNLAWYQQKPGQSP KLLIYWASTRESGVPDRFSGSGSGTDFTLTISVQAEDVAVYYCQYYYSY RTFGGGTKVEIK (SEQ ID NO: 59)
KC18_VL_14	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNLAWYQQKPGQSP KLLIYASTRESGVPDRFSGSGSGTDFTLTISVQAEDVAVYYCQYYYSY RTFGGGTKLEIK (SEQ ID NO: 60)
KC18_VL_15	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNLAWYQQKPGQSP KLLIYFASTRESGVPDRFSGSGSGTDFTLTISVQAEDVAVYYCQYYYSY RTFGGGTKLEIK (SEQ ID NO: 61)

[0332] Table 14. Designed KC18 variant sequences.

Antibody ID	Sequence
KC18_Hu44 Heavy chain nucleic acids (with constant region)	GAGGTTCAAGTTGGTGCAAAGTGGGGCCGAGGTTAAAAAACCGGTGC AACCGTGAAACTGTCCTGCAAGGCGAGTGGTGATACATTTACAGATTT TGAAATTCATTGGGTACAGCAGGCACCCGAAAGGGATTGGAATGGAT AGGAGATGTGGACCCGAGACTGGCGGAACCGCGTACGCGGAGAAAT TTCAGGGCAGAGCCACTTTGACGGCGGATAGAAGTACGGATACTGCCT ACCTTGAAGTGAAGTTCCTTGGGTCCGAAGATACGGCAGTTTACTATTG TACTCGCACGTATGATGGCTACCCATACGCTTTCGATTATTGGGGACAA GGCACTCTCGTGACCGTATCTTCAGCTTCAACCAAGGGACCTTCTGTCT TTCCTCTGGCCCTTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCAC TCGGGTGCCTTGTGAAAGATTACTTCCAGAGCCTGTCACCGTCAGCTG GAATTCAGGCGCTCTGACTAGCGGAGTGCACACCTTCCCGCTGTGCTT CAGTCCTCCGACTCTACTCTGAGCAGCGTGGTGACCGTGCCGTCCT CTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAATCATAAGCCTTC

	TAATACCAAGGTGGACAAGAAGGTGGAACCCAAATCATGTGACAAGA CCCACACCTGTCCGCCCTGTCCGGCACCCGAAGTGTGGGTGGCCCTTC CGTGTTCCTTTTCCCTCCAAAGCCGAAGGACACTCTTATGATTTCTCGC ACTCCCGAAGTGACTTGCCTCGTGGTGGATGTGTCCCATGAGGATCCA GAGGTCAAGTTCAACTGGTACGTGGACGGTGTGGAAGTCCACAACGCC AAGACTAAGCCGAGAGAGGAACAGTACAATTCAACCTATCGGGTGGT GAGCGTCCTGACCGTGCTGCACCAGGACTGGCTTAACGGAAAGGAGTA CAAGTGCAAAAGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAGA CCATTAGCAAAGCTAAGGGCCAGCCAGAGAACCCCAAGTCTATACCC TTCCACCCAGCCGGGACGAGCTGACCAAAAACAGGTGCACTCACTT GTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTGCAATGGGAGT CCAATGGTCAGCCAGAGAACAATAACAAAACACCCCTCCCGTGTGG ACAGCGACGGGTCTTTCTTTCTACTCAAAAGCTGACCGTGGATAAGTC TCGCTGGCAGCAAGGGAATGTGTTTTCTGTTCAGTGATGCATGAGGC CCTTCATAATCATTACACCCAAAAGTCACTGAGCCTGTCTCCCGGA (SEQ ID NO: 62)
KC18 Hu44 Heavy Chain amino acids (with constant region)	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVPETGGTAYAEKFGGRATLTADRSTDTAYLELSSLRSEDVAVYYCTRT YDGYPYAFDYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHPKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTKISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 63)
KC18 Hu46 Heavy Chain nucleic acids (with constant region)	GAGGTTCAAGTTGGTGCAAGTGGGGCCGAGGTTAAAAAACAGGTGC AACCGTGAAACTGTCTGCAAGGCGAGTGGTGATACATTTACAGATTT TGAAATTCATTGGGTACAGCAGGCACCCGAAAGGGATTGGAATGGAT AGGAGATGTGGACCCGGAGACTGGCGGAACCGCGTACGCGGAGAAAT TTCAGGGCAGAGCCACTTTGACGGCGGATAGAAGTACGGATACTGCCT ACCTTGAAGTGAAGTTCCTTGCCTGCGGATACGGCAGTTTACTATTG TACTCGCACGTATGATGGCTACCCATACGCTTTTCGATTATTGGGGACAA GGCACTCTCGTGACCGTATCTTCAGCTTCAACCAAGGGACCTTCTGTCT TTCTCTGGCCCCCTCAAGCAAGAGCACTTCCGGAGGGACTGCCGCAC TCGGGTGCCTTGTGAAAGATTACTTCCAGAGCCTGTACCGTCAAGTGT GAATTCAGGCGCTCTGACTAGCGGAGTGCACACCTTCCCCGCTGTGCTT CAGTCTCCGGACTCTACTCTGAGCAGCGTGGTGACCGTGCCGTCTCT CTTCTCTGGGGACCCAGACTTATATCTGCAACGTCAATCATAAGCCTTC TAATACCAAGGTGGACAAGAAGGTGGAACCCAAATCATGTGACAAGA CCCACACCTGTCCGCCCTGTCCGGCACCCGAAGTGTGGGTGGCCCTTC CGTGTTCCTTTTCCCTCCAAAGCCGAAGGACACTCTTATGATTTCTCGC ACTCCCGAAGTGACTTGCCTCGTGGTGGATGTGTCCCATGAGGATCCA GAGGTCAAGTTCAACTGGTACGTGGACGGTGTGGAAGTCCACAACGCC AAGACTAAGCCGAGAGAGGAACAGTACAATTCAACCTATCGGGTGGT GAGCGTCCTGACCGTGCTGCACCAGGACTGGCTTAACGGAAAGGAGTA CAAGTGCAAAAGTGTCAAACAAGGCACTGCCCGCTCCGATCGAAAAGA CCATTAGCAAAGCTAAGGGCCAGCCAGAGAACCCCAAGTCTATACCC TTCCACCCAGCCGGGACGAGCTGACCAAAAACAGGTGCACTCACTT GTCTCGTGAAGGGTTTCTACCCCTCAGACATCGCCGTGCAATGGGAGT CCAATGGTCAGCCAGAGAACAATAACAAAACACCCCTCCCGTGTGG ACAGCGACGGGTCTTTCTTTCTACTCAAAAGCTGACCGTGGATAAGTC TCGCTGGCAGCAAGGGAATGTGTTTTCTGTTCAGTGATGCATGAGGC CCTTCATAATCATTACACCCAAAAGTCACTGAGCCTGTCTCCCGGA (SEQ ID NO: 64)
KC18 Hu46 Heavy Chain amino acids	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVPETGGTAYAEKFGGRATLTADRSTDTAYLELSSLRSEDVAVYYCTRT YDGYPYAFDYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT

(with constant region)	YICNVNHNKPSNTKVDDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSEFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 65)
KC18 Hu44 Light Chain nucleic acids (with constant region)	GACATTGTAATGACACAATCTCCCGACTCTCTGCAGTCAGCTTGGGTGAACGAGCAACTATAAATTGTAAGCAGCCAGTCTGTAAGTCTACTCTATAACAACAAGAACTACCTCGCATGGTATCAGCAGAAACCGGGGCAAAGTCCTAAACTTTTGATCTATTGGGCAAGTACCAGGGAGAGCGGAGTACCCGACAGATTACGCGGGTCTGGATCAGGCACCGATTTTACTCTCACCATTCTTCAGTTCAAGCTGAAGACGTCGAGTCTACTACTGCCAGCAGTATTACAGTTACCGAACTTTTGGCGGTGGAACAAAAGTGGAAATAAAGCGACTGTGGCAGCCCCCTTCTGTGTTATCTTCCACCCTCCGACGAGCAGCTCAAGTCCGGTACCGCCTCTGTCGCTGCTGCTGAACAATTTCTACCCAAGAGAGGCCAAGGTGCAGTGAAGGTGGACAACGCACTGCAAAAGCGGTAAATTCACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCACTACTCACTGTCATCCACCCTGACTCTCTCAAAGGCTGACTACGAAAAACACAAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTTCTAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 66)
KC18 Hu44 Light Chain amino acids (with constant region)	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSNNKNYLAWYQQKPGQSPKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISVVQAEDEVAVYYCQQYYSYRTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 67)
KC18 Hu46 Light Chain nucleic acids (with constant region)	GACATAGTTATGACCCAGTCTCCAGACTCCCTCGCAGTTTCTCTCGGCGAGAGAGTAACAATCAACTGTAAAGTCATCACAGTCCGTACTCTACTCTGACAACCAAAAAGAATTATTTGGCTTGGTATCAGCAAAAGCCAGGACAAAACCCCAAACTTCTTATCTATTTTGGCAGCACTAGGGAGTCCGGGGTACCGACCGCTTTAGTGGCTCAGGTTCTGGGACAGACTTTACACTGACCATTCTAGCGTACAGGCTGAAGACGTTGCACTACTACTGCCAGCAATACATTCTTACAGAACGTTTGGCGGGGGCACAAAAGTGGAGATCAAACGCACTGTGGCAGCCCCCTTCTGTGTTATCTTCCACCCTCCGACGAGCAGCTCAAGTCCGGTACCGCCTCTGTCGCTGCTGCTGAACAATTTCTACCCAAGAGAGGCCAAGGTGCAGTGAAGGTGGACAACGCACTGCAAAAGCGTAATTCACAAGAGTCAGTCACCGAACAAGACTCAAAGGACAGCACCTACTCACTGTCATCCACCCTGACTCTCTCAAAGGCTGACTACGAAAAAGCACAAAAGTGTATGCTTGTGAAGTCACTCATCAGGGCCTTTCTAGCCCTGTGACCAAGAGCTTCAACAGAGGCGAATGC (SEQ ID NO: 68)
KC18 Hu46 Light Chain amino acids (with constant region)	DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNYLAWYQQKPGQSPKLLIYFASTRESGVDPDRFSGSGSGTDFTLTISVVQAEDEVAVYYCQQYYSYRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 69)

[0333] Table 15. Humanized Anti-FGFR3 Fab fragment heavy chain amino acid sequences.

Antibody ID	Sequence
Fab Heavy chain	QVQLQQSGAELVRPGASVTLSCKASGDTFTDFEIHVWKQTPVHGLEWIGDIDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRTYDGYPYANDYWGQTSVTSSASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHNKPSNTKVDDKKVEPKSC (SEQ ID NO: 141)

	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWIGYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCARERDYDGAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (SEQ ID NO: 143) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWIGYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCARERDYDGSMDFWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (SEQ ID NO: 145) EVQLQQSGPDLVKPGASVKISCKASGYTFTDYNMHWVKQSHGKSLEWIGDINPNNGVTYTNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCAREEDFDGFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (SEQ ID NO: 147) QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVWKQTPVHGLEWIGIDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNYDGYSQTMIDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (SEQ ID NO: 149) QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVWKQTPVHGLEWIGIDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNYDGYSRTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (SEQ ID NO: 151) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKLEWIGDVPETGGTAYAEKQFGRATLTADRSTDTAYMELSSLRSEDTAVYYCTRITYDGYPYAFDYWGQGTTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (SEQ ID NO: 153) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKLEWIGDVPETGGTAYAEKQFGRATLTADRSTDTAYLELSSLRSEDTAVYYCTRITYDGYPYAFDYWGQGTTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (SEQ ID NO: 155) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKLEYIGDVPETGGTAYAEKQFGRATLTADRSTDTAYLELSSLRSEDTAVYYCTRITYDGYPYAFDYWGQGTTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (SEQ ID NO: 156) QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHVWKQTPVHGLEWIGIDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRITYDGYPYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 164) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWIGYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCARERDYDGAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 165)
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EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHVVKQSHGKSLQWIGYINPNNGGTNYNQFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCARRDYDGSMDFWGQGTSTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 166) EVQLQQSGPDLVKPGASVKISCKASGYTVDYYMNWVKQSHGKSLEWIGDINPNNGVTTYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCAREDFDGFYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 167) QVQLQQSGAELVRPGASVTLCKASGSTFSDFEIHWVKQTPVHGLEWIGIDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNYDGYSQTMDYWGQGTSTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 168) QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVVKQTPVHGLEWIGIDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNYDGYSRTMDYWGQGTSTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 169) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDYAVYYCTRITYDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 170) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDYAVYYCTRITYDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 171) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDYAVYYCTRITYDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS (SEQ ID NO: 172) QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHVVKQTPVHGLEWIGIDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRITYDGYPYAMDYWGQGTSTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 173) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHVVKQSHGKSLQWIGYINPNNGGTNYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCARRDYDYGAMDYWGQGTSTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 174) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHVVKQSHGKSLQWIGYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCARRDYDGSMDFWGQGTSTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
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	VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 175) EVQLQQSGPDLVKPGASVKISCKASGYTVDYIMNWVKQSHGKSLEWIG DINPNNGVTTYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPK (SEQ ID NO: 176) QVQLQQSGAELVRPGASVTLSCASGSTFSDFEIHWVKQTPVHGLEWIGG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTM DYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 177) QVQLQQSGAELVRPGASVTLSCASGSTFTDFEIHVWKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 178) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSED TAVYYCTR TYDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 179) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYLESSLRSED TAVYYCTR YDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 180) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEYIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYLESSLRSED TAVYYCTR YDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 181) QVQLQQSGAELVRPGASVTLSCASGDTFTDFEIHVWKQTPVHGLEWIGD IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTR DGYPYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 182) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 183) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLQWI GYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPK (SEQ ID NO: 184) EVQLQQSGPDLVKPGASVKISCKASGYTVDYIMNWVKQSHGKSLEWIG DINPNNGVTTYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE
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	EDFDGFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHNKPSNTKVDKKVEP (SEQ ID NO: 185) QVQLQQSGAELVRPGASVTLCKASGSTFSDFEIHVWKQTPVHGLEWIGG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHNKPSNTKVDKKVEP (SEQ ID NO: 186) QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVWKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHNKPSNTKVDKKVEP (SEQ ID NO: 187) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDATVYYCTR TYDGYPYAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEP (SEQ ID NO: 188) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDATVYYCTR YDGYPYAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEP (SEQ ID NO: 189) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDATVYYCTR YDGYPYAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEP (SEQ ID NO: 190) QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHVWKQTPVHGLEWIGD IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTR DGYPYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEP (SEQ ID NO: 191) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEP (SEQ ID NO: 192) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLQWI GYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEP (SEQ ID NO: 193) EVQLQQSGPDLVKPGASVKISCKASGYTFTDYYMNWVKQSHGKSLEWIG DINPNNGVTYNYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHNKPSNTKVDKKVEP (SEQ ID NO: 194)
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QVQLQQSGAELVRPGASVTLSCASGSTFSDFEIHWVKQTPVHGLEWIG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHHKPSNTKVDKKVE (SEQ ID NO: 195) QVQLQQSGAELVRPGASVTLSCASGSTFTDFEIHWWKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHHKPSNTKVDKKVE (SEQ ID NO: 196) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDYAVYYCTR TYDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHHKPSNTKVDKKVE (SEQ ID NO: 197) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDYAVYYCTR TYDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHHKPSNTKVDKKVE (SEQ ID NO: 198) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEYIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDYAVYYCTR TYDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHHKPSNTKVDKKVE (SEQ ID NO: 199) QVQLQQSGAELVRPGASVTLSCASGDTFTDFEIHWWKQTPVHGLEWIGD IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTR TYDGYPYAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHHKPSNTKVDKKV (SEQ ID NO: 200) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHHKPSNTKVDKKV (SEQ ID NO: 201) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLQWI GYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHHKPSNTKVDKKV (SEQ ID NO: 202) EVQLQQSGPDLVKPGASVKISCKASGYTFTDYNMHWVKQSHGKSLEWIG DINPNNGGVTYNYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHHKPSNTKVDKKV (SEQ ID NO: 203) QVQLQQSGAELVRPGASVTLSCASGSTFSDFEIHWVKQTPVHGLEWIG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHHKPSNTKVDKKV (SEQ ID NO: 204)

QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVWKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSTRMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHNKPSNTKVDKKV (SEQ ID NO: 205) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDATVYYCTR TYDGYPYAFDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHNKPSNTKVDKKV (SEQ ID NO: 206) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDATVYYCTR YDGYPYAFDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ YICNVNHNKPSNTKVDKKV (SEQ ID NO: 207) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDATVYYCTR YDGYPYAFDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ YICNVNHNKPSNTKVDKKV (SEQ ID NO: 208) QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHVWKQTPVHGLEWIGD IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTR DGYPYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ YICNVNHNKPSNTKVDKK (SEQ ID NO: 209) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHNKPSNTKVDKK (SEQ ID NO: 210) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHNKPSNTKVDKK (SEQ ID NO: 211) EVQLQQSGPDLVKPGASVKISCKASGYTFTDYNMHWVKQSHGKSLEWIG DINPNNGVTYNYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYIC NVNHNKPSNTKVDKK (SEQ ID NO: 212) QVQLQQSGAELVRPGASVTLCKASGSTFDFEIHVWKQTPVHGLEWIGG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSTRMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHNKPSNTKVDKK (SEQ ID NO: 213) QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVWKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSTRMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHNKPSNTKVDKK (SEQ ID NO: 214)
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	EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDATVYYCTR TYDGYPYAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDDK (SEQ ID NO: 215) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDATVYYCTR YDGYPYAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDDK (SEQ ID NO: 216) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDATVYYCTR YDGYPYAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDDK (SEQ ID NO: 217) QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHVWVQTPVHGLEWIG IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTR DGYPYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDDK (SEQ ID NO: 218) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHVWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDDK (SEQ ID NO: 219) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHVWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDDK (SEQ ID NO: 220) EVQLQQSGPDLVKPGASVKISCKASGYTFTDYNMNVWVKQSHGKSLEWIG DINPNNGVTYTNQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHKPSNTKVDDK (SEQ ID NO: 221) QVQLQQSGAELVRPGASVTLCKASGSTFSDFEIHVWVQTPVHGLEWIG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTM DYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHKPSNTKVDDK (SEQ ID NO: 222) QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVWVQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHKPSNTKVDDK (SEQ ID NO: 223) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDATVYYCTR TYDGYPYAFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
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	VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVVDK (SEQ ID NO: 224) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGLEWIG DVPETGGTAYAEKFGGRATLTADRSTDTAYLELSSLRSEDVAVYYCTRT YDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVVDK (SEQ ID NO: 225) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGLEYIG DVPETGGTAYAEKFGGRATLTADRSTDTAYLELSSLRSEDVAVYYCTRT YDGYPYAFDYYGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVVDK (SEQ ID NO: 226) QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHVVQKTPVHGLEWIGD IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRTY DGYPYAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDDKKVEPKSCDKTHTCP (SEQ ID NO: 227) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDDKKVEPKSCDKTHTCP (SEQ ID NO: 228) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLQWI GYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDDKKVEPKSCDKTHTCP (SEQ ID NO: 229) EVQLQQSGPDLVKPGASVKISCKASGYTVTDYYMNWVKQSHGKSLEWIG DINPNNGVTYNYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDDKKVEPKSCDKTHTCP (SEQ ID NO: 230) QVQLQQSGAELVRPGASVTLCKASGSTFSDFEIHVVQKTPVHGLEWIGG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDDKKVEPKSCDKTHTCP (SEQ ID NO: 231) QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVVQKTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDDKKVEPKSCDKTHTCP (SEQ ID NO: 232) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGLEWIG DVPETGGTAYAEKFGGRATLTADRSTDTAYMELSSLRSEDVAVYYCTR TYDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDDKKVEPKSCDKTHTCP (SEQ ID NO: 233) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVVQAPGKGLEWIG DVPETGGTAYAEKFGGRATLTADRSTDTAYLELSSLRSEDVAVYYCTRT
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YDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID NO: 234) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEYIG DVDPETGGTAYAEKFQGRATLTADRSTDYAYLELSSLRSEDYAVYYCTRT YDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID NO: 235) QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHWWKQTPVHGLEWIGD IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRTY DGYPYANDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 236) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 237) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSQWI GYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 238) EVQLQQSGPDLVKPGASVKISCKASGYTVDYIMNWVKQSHGKSLEWIG DINPNNGVTTYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 239) QVQLQQSGAELVRPGASVTLCKASGSTFSDFEIHWWKQTPVHGLEWIGG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTM DYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 240) QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHWWKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 241) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDYAYMELSSLRSEDYAVYYCTR TYDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 242) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDYAYLELSSLRSEDYAVYYCTRT YDGYPYAFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 243)

EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEYIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDNAVYYCTRT YDGYPYAFDYYGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTC (SEQ ID NO: 244)
QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHWWKQTPVHGLEWIG IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRTY DGYPYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 245)
EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 246)
EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLQWI GYINPNNGGTNYNQKFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 247)
EVQLQQSGPDLVKPGASVKISCKASGYTVDYIMNHWVKQSHGKSLEWIG DINPNNGVTYNYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 248)
QVQLQQSGAELVRPGASVTLCKASGSTFDFEIHWWKQTPVHGLEWIG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTM DYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 249)
QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHWWKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 250)
EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDNAVYYCTR TYDGYPYAFDYYGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 251)
EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEWIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDNAVYYCTR YDGYPYAFDYYGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 252)
EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEYIG DVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDNAVYYCTR YDGYPYAFDYYGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 253)

QVQLQQSGAELVRPGASVTLSCKASGDTFTDFEIHVWKQTPVHGLEWIG IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRTY DGYPYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 254) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 255) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLQWI GYINPNNGGTNYNQKFKDKATLTVNKSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 256) EVQLQQSGPDLVKPGASVKISCKASGYTFTDYYMNWVKQSHGKSLEWIG DINPNNGVTTYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 257) QVQLQQSGAELVRPGASVTLSCKASGSTFSDFEIHVWKQTPVHGLEWIG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTM DYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 258) QVQLQQSGAELVRPGASVTLSCKASGSTFTDFEIHVWKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 259) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSED TAVYYCTR TYDGYPYAFDYWGQGT LTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 260) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSED TAVYYCTR YDGYPYAFDYWGQGT LTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ YICNVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 261) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEYIG DVDPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSED TAVYYCTR YDGYPYAFDYWGQGT LTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQ YICNVNHKPSNTKVDKKVEPKSCDKTH (SEQ ID NO: 262) QVQLQQSGAELVRPGASVTLSCKASGDTFTDFEIHVWKQTPVHGLEWIGD IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRTY DGYPYAMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
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KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 263)
EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 264)
EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLQWI GYINPNNGGTNYNQNFKD KATLTVNKSSSTAYMELRSLTSEDSAVYYCA RERDYGSMDFWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 265)
EVQLQQSGPDLVKPGASVKISCKASGYTFTDYNMHWVKQSHGKSLEWIG DINPNNGVTTYNQKFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 266)
QVQLQQSGAELVRPGASVTLCKASGSTFSDFEIHVVKQTPVHGLEWIGG IDPETGGTAYNQKFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTM DYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 267)
QVQLQQSGAELVRPGASVTLCKASGSTFTDFEIHVVKQTPVHGLEWIGA IDPETGGTAYNQKFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 268)
EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTD TAYMELSSLRSED TAVYYCTR TYDGYPYAFDYWGQGT LTVVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 269)
EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTD TAYLESSLRSED TAVYYCTR YDGYPYAFDYWGQGT LTVVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 270)
EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKLEYIG DVDPETGGTAYAEKFQGRATLTADRSTD TAYLESSLRSED TAVYYCTR YDGYPYAFDYWGQGT LTVVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHNKPSNTKVDKKVEPKSCDKT (SEQ ID NO: 271)
QVQLQQSGAELVRPGASVTLCKASGDTFTDFEIHVVKQTPVHGLEWIGD IDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTR YDGYPYAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHNKPSNTKVDKKVEPKSCDK (SEQ ID NO: 272)
EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLEWI GYINPNNGGTRYNQKFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCA

	RERDYDGAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 273) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHVVKQSHGKSLQWIGYINPNNGGTNYNQFKDKATLTVNKSSSTAYMELRSLTSEDSAVYYCARRERDYDGSMDFWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 274) EVQLQQSGPDLVKPGASVKISCKASGYTFTDYMNWVKQSHGKSLEWIGDINPNNGVTTYNQFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCAREDFDGFYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 275) QVQLQQSGAELVRPGASVTLSCASGSTFSDFEIHVVKQTPVHGLEWIGIDPETGGTAYNQFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNYDGYSTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 276) QVQLQQSGAELVRPGASVTLSCASGSTFTDFEIHVVKQTPVHGLEWIGIDPETGGTAYNQFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNYDGYSTMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 277) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYMELSSLRSEDATVYYCTRNYDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 278) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEWIGDVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDATVYYCTRNYDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 279) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHVWVQAPGKGLEYIGDVPETGGTAYAEKFQGRATLTADRSTDTAYLELSSLRSEDATVYYCTRNYDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 280) QVQLQQSGAELVRPGASVTLSCASGDTFTDFEIHVVKQTPVHGLEWIGIDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTRNYDGYPYAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 281) EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHVVKQSHGKSLQWIGYINPNNGGTNYNQFKGKATLTVNKSSSTAYMELRSLTSEDSAVYYCARRERDYDGAMDYWGQGSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSCDK (SEQ ID NO: 282)
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	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYNMHWVKQSHGKSLQWI GYINPNNGGTNYNQFKDKATLTVNKSSTTAYMELRSLTSEDSAVYYCA RERDYDGSMDFWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCD (SEQ ID NO: 283) EVQLQQSGPDLVKPGASVKISCKASGYTFTDYMNWVKQSHGKSLQWIG DINPNNGVTYNYNQFKDKATLTVDKSSSTAYMELRSLTSEDSAVYYCARE EDFDGFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCD (SEQ ID NO: 284) QVQLQQSGAELVRPGASVTLSCASGSTFSDFEIHWVKQTPVHGLEWIGG IDPETGGTAYNQFKGKAILTADRSSSTAYMELRSLTSEDSAVYYCTRNY DGYSQTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCD (SEQ ID NO: 285) QVQLQQSGAELVRPGASVTLSCASGSTFTDFEIHWWKQTPVHGLEWIGA IDPETGGTAYNQFKGKAILTAVKSSSTAYMGLRSLTSEDSAVYYCTRNY DGYSRTMDYWGQGTSTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCD (SEQ ID NO: 286) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDATAYMELSSLRSEDATVYYCTR TYDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCD (SEQ ID NO: 287) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEWIG DVDPETGGTAYAEKFQGRATLTADRSTDATAYLELSSLRSEDATVYYCTR YDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCD (SEQ ID NO: 288) EVQLVQSGAEVKKPGATVKLSCKASGDTFTDFEIHWWQAPGKGLEIYG DVDPETGGTAYAEKFQGRATLTADRSTDATAYLELSSLRSEDATVYYCTR YDGYPYAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCD (SEQ ID NO: 289)
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[0334] Table 16. Humanized Anti-FGFR3 Fab fragment light chain amino acid sequences.

Antibody ID	Sequence
Fab Light chain	DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSNNQKNYLAWYQQKPGQS PKLLIYWASTRESGVDPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQYYYSY RTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACE VTHQGLSPVTKSFNRGEC (SEQ ID NO: 142) DIQMTQSPSSLSASLGKVTITCKASQDINKFIAWYQHKGKGPRLLIHYTS TLQPGIPSRFSGSGSGRSDYSFISINLEPEDATYYCLQYDNLWTFGGGTCL

	EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 144) DIQMTQSPSSLSASLGKVTITCKASQDINKFIAWYQHKGKGPRLLIHYTS TLQPGIPSRFSGSGSRDYFSISNLEPEDIATYFCLQYDNLWTFGGGTGL EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC (SEQ ID NO: 146) DIVMTQSHKFMSTSVGDRVSITCKASQDVSTGVAWYQQKPGQSPQLLIY WASTRHTGVPDRFTGSGSGTDYILTIRSVQAEDLALYYCQHHYSTPLTFG AGTKLELKRVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC (SEQ ID NO: 148) NIMMTQSPSSLAVSAGEKVTMSCKSSQSVLYSSNQKNYLAWYQQKPGQS PKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCHQYLSS YTFGGGTGLEMKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 150) NIMMTQSPSSLAVSAGEKVTMSCKSSQSVLYSSNQKNYLAWYQQKPGQS PKLLIYWASTRESGVPDRFTGSGSGTDFSLISSVQTEDLAVYYCHQYLSS YTFGGGTRLEMKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC (SEQ ID NO: 152) DIVMTQSPDSLAVSLGERATINCKSSQSVLYSNNKNYLAWYQQKPGQSP KLLIYWASTRESGVPDRFSGSGTDFTLTISVQAEDVAVYYCQYYYSY RTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC (SEQ ID NO: 67) DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNYLAWYQQKPGQSP KLLIYFASTRESGVPDRFSGSGTDFTLTISVQAEDVAVYYCQYYYSYR TFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC (SEQ ID NO: 69) DIVMTQSPDSLAVSLGERVTINCKSSQSVLYSDNQKNYLAWYQQKPGQSP KLLIYYASTRESGVPDRFSGSGTDFTLTISVQAEDVAVYYCQYYYSYR TFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC (SEQ ID NO: 154)
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[0335] In certain embodiments, an anti-FGFR3 F(ab) fragment of the present application comprises a heavy chain of Table 15, and a light chain in Table 16.

[0336] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 141, 164, 173, 182, 191, 200, 209,

218, 227, 236, 245, 254, 263, 272, or 281, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 142.

[0337] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 143, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 255, 264, 273, or 282, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 144.

[0338] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 145, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 256, 265, 274, or 283 and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 146.

[0339] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 147, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 257, 266, 275, or 284, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 148.

[0340] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 149, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 258, 267, 276, or 285, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 150.

[0341] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 151, 169, 178, 187, 196, 205, 214, 223, 232, 241, 250, 259, 268, 277, or 286, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 152.

[0342] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[0343] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[0344] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[0345] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[0346] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[0347] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[0348] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

[0349] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

[0350] In certain embodiments, the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

[0351] *In vitro* analysis

[0352] Antibodies were screened for binding and specificity to FGFR3. Activity was assessed using a Homogenous Time-Resolved Fluorescence (HTRF) assay to evaluate

the level of inhibition on Erk phosphorylation using mouse primary rib chondrocytes. Briefly, primary mouse rib chondrocyte cells isolated from the achondroplasia mouse model were pretreated for 2 hours with anti-FGFR3 antibodies with a concentration ranging from 0.016 µg/ml to 100 µg/ml. Cells were then stimulated with FGF18 for 5 minutes. The reaction was then stopped, total Erk was measured using the HTRF assay, and Phospho-Erk (Thr202/Tyr204) was measured in a separate HTRF assay. The percent inhibition of Erk phosphorylation was measured by taking the ratio of Phospho-Erk over total Erk and multiplying by 100. Particularly, mouse antibodies KC18, KE63, and KE94 and their corresponding Fab fragments were tested in the HTRF assay, all of which inhibited Erk phosphorylation (**Fig. 9A** and **Fig. 9B**).

[0353] To determine the effects of different mouse antibody formats on inhibition of Erk phosphorylation, KC18 mouse antibody in various formats, including full-length antibody (IgG), Fab, a one-armed, monovalent antibody (MetMab), and pegylated (PEG) Fab fragment were tested in the HTRF assay and compared to isotype control (Iso). Also, KC18 Fab with half-life extension using a human albumin nanobody (KC18 Fab-HLE) was tested, with and without human serum albumin (HSA) or mouse serum albumin (MSA).

[0354] The full-length KC18 mouse antibody has a heavy chain of SEQ ID NO: 291 (with mIgG2a Fc sequence), and a light chain of SEQ ID NO: 292. The KC18 mouse Fab antibody has a heavy chain of SEQ ID NO: 293, and a light chain of SEQ ID NO: 294.

QVQLQQSGAELVRPGASVTLSCKASGDTFTDFEIHVVKQTPVHGLEWIG
DIDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTR
TYDGYPYAMDYWGQGTSTVTVSSAKTTAPSVYPLAPVCGD TTGSSVTLG
CLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWP
SQSITCNVAHPASSTKVDDKKIEPRGPTIKPCPPCKCPAPPVAGPSVFIFPPKI
KDVLMISLSPIVTCVVVDVSEDDPDVQISWVFNNEVHTAQTQTHREDY
NSTLRVVSALPIQHQQDWMSGKEFKCKVNNKGLPSSIERTISKPKGSVRAP
QVYVLPPEEEMTKKQVTLCMVTD FMPEDIYVEWTNNGKTELNYKNT
EPVLDSG SYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFS
RTPGK (SEQ ID NO: 291)

DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSNNQKNYLAWYQQKPGQS
PKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQQYYYS
YRTFGGGTKLEIKRADAAPTIVSIFPPSSEQLTSGGASVVCFLNNFYPKDIN
VKWKIDGSERQNGVLNSWTDQDSKDYSTYSMSSTLTTLTKDEYERHNSYT
CEATHKTSTSPIVKSFNRNEC (SEQ ID NO: 292)

QVQLQQSGAELVRPGASVTLSCKASGDTFTDFEIHVVKQTPVHGLEWIG
DIDPETGGTAYNQKFRGRAMLTADRSSSTAYMELRSLTSEDSAVYYCTR
TYDGYPYAMDYWGQGTSTVTVSSAKTTAPSVYPLAPVCGDITGSSVTLG
CLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWP
SQSITCNVAHPASSTKVDKKI (SEQ ID NO: 293)

DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSNNQKNYLAWYQQKPGQS
PKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQQYYYS
YRTFGGGTKLEIKRADAAPTIVSIFPPSSEQLTSGGASVVCFLNNFYPKDIN
VKWKIDGSERQNGVLNSWTDQDSKDYSTYSMSSTLTTLTKDEYERHNSYT
CEATHKTSTSPIVKSFNRNEC (SEQ ID NO: 294)

[0355] All formats inhibited Erk phosphorylation (**Fig. 10A** to **Fig. 10C**). The antibody format referred to in **Fig. 10A** as “MetMab” is described in further detail in Merchant et al. (PNAS. 110(32): E2987-E2996. 2013).

[0356] Humanized FGFR3 antibodies, including Hu18, Hu44, and Hu46, were also tested in the HTRF assay, and found to inhibit Erk phosphorylation (**Fig. 11**). The IC₅₀s of these humanized antibodies were determined, as well (**Fig. 8A** to **Fig. 8C**, respectively).

[0357] In vivo analysis

[0358] For *in vivo* evaluation of the antibodies, an achondroplasia mouse model (Ach) was used. The achondroplasia mouse is a transgenic mouse that overexpresses the mouse FGFR3 protein having the G380R mutation under control of the collagen II promoter (Shazeeb et al., (2018) Sci Rep 8, 469). The mice were genotyped at 1 day of

age, and randomized to either a control (i.e., saline) group or an antibody dosed group. Achondroplasia mice (G380R) received a daily dose subcutaneously (SC) from 3 days of age to 20 days of age. The mice were then euthanized, and bones were collected at 21 days of age for microCT analysis. Tibias, femurs, vertebrae and skulls were used for the analysis, and lengths were measured using 3D microCT analysis. AMIRA (V6.0.1, FEI, Hillsboro, OR, USA) was used for all numerical analysis of bone lengths. The lengths of leg bones were measured using seed points along the bone, and a 3D length tool in AMIRA. The results indicated that achondroplasia (Ach) mice treated with KC18 Fab had a significantly increased tibia and femur length (**Fig. 12A** and **Fig. 12B**), a significantly increased vertebra and skull length (**Fig. 13A** and **Fig. 13B**), a significantly increased brain volume (**Fig. 14**), and corrected vertebral abnormalities as measured by Kyphosis Index (**Fig. 15A – Fig. 15B**). Ach mice treated with KC18 Fab also had several improved bone parameters, including femur growth plate volume, and femur diameter (**Fig. 16A** and **Fig. 16B**). Ach mice treated with KC18 Fab also had improved bone age as shown by more developed secondary ossification center in tibia (**Fig. 17**) compared to those treated with vehicle.

[0359] In summary, achondroplasia is the most common form of dwarfism due to activating mutations in the FGFR3 gene. FGFR3 protein is expressed in the growth plate and its function is to regulate proper growth. However, the activating mutations lead to excessive inhibition of chondrocyte proliferation and differentiation which is the main cause for the short stature and other skeletal deformities. The antibodies generated herein are specific to FGFR3 and inhibit FGFR3 activity. The mechanism of action of the antibody is to inhibit ligand binding and prevent activation of the receptor. The antibodies described herein can block ligand activation and subsequently inhibit downstream signaling measured by the decrease in Erk phosphorylation. This translates into inhibition of receptor activity. *In vivo* testing of anti-FGFR3 antibodies in the Ach mouse model demonstrated efficacy on the axial and appendicular skeleton. More specifically, a significant increase in femur and tibia length, skull length as well as lumbar length were observed.

Claims

What is claimed:

1. An antigen-binding protein or antigen-binding fragment thereof that specifically binds to fibroblast growth factor receptor 3 (FGFR3), comprising an antibody heavy chain variable (VH) domain and an antibody light chain variable (VL) domain, wherein:

(a) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GX¹TFTDX²E (SEQ ID NO: 157), wherein X¹ is Y or D and X² is F or Y;

a CDR-H2 sequence comprising the amino acid sequence of IDPETGX³T (SEQ ID NO: 158), wherein X³ is G or S; or a CDR-H2 sequence comprising the amino acid sequence of INPNNGX⁴T (SEQ ID NO: 159), wherein X⁴ is G or V; or a CDR-H2 sequence comprising the amino acid sequence of VX⁵PETGGT (SEQ ID NO: 160), wherein X⁵ is D or E;

a CDR-H3 sequence comprising the amino acid sequence of TRX⁶YX⁷GYX⁸X⁹X¹⁰X¹¹DY (SEQ ID NO: 161), wherein X⁶ is T or N, X⁷ is D or E, X⁸ is S or P, X⁹ is Q, R, or Y, X¹⁰ is T or A, X¹¹ is F or M; and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QSX¹²LYSX¹³NX¹⁴KNY (SEQ ID NO: 162), wherein X¹² is L or V, X¹³ is N, D, or S, and X¹⁴ is Q or N;

a CDR-L2 sequence comprising the amino acid sequence of X¹⁵AS (SEQ ID NO: 163), wherein X¹⁵ is W, Y, or F;

a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75), LQYDNLLWT (SEQ ID NO: 81), or HQYLSX¹⁶YT (SEQ ID NO: 290) wherein X¹⁶ is P or S;

(b) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82);

a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83);

a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGAMDY (SEQ

ID NO: 78); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85);

a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86);

a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87);

(c) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82);

a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83);

a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGSMDF (SEQ ID NO: 84); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85);

a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86);

a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87);

(d) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GYTVTDYY (SEQ ID NO: 88);

a CDR-H2 sequence comprising the amino acid sequence of INPNNGVT (SEQ ID NO: 89);

a CDR-H3 sequence comprising the amino acid sequence of AREEDFDGFDY (SEQ ID NO: 90); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QDVSTG (SEQ ID NO: 91);
a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104);
a CDR-L3 sequence comprising the amino acid sequence of QQHYSTPLT (SEQ ID NO: 93);

(e) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GSTFSDFE (SEQ ID NO: 94);
a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101);
a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTX¹⁷DY (SEQ ID NO: 308), wherein X¹⁷ is M or F; and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QSVLYSX¹⁸NQKNY (SEQ ID NO: 309), wherein X¹⁸ is S or D;
a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104);
a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105); or

(f) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GSTFTDFE (SEQ ID NO: 100);
a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101);
a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTX¹⁷DY (SEQ ID NO: 308), wherein X¹⁷ is M or F; and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QSVLYSX¹⁸NQKNY (SEQ ID NO: 309), wherein X¹⁸ is S or D;

a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104);

a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105).

2. The antigen binding protein or antigen-binding fragment thereof of claim 1, wherein:

(a) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), GDTFTDYE (SEQ ID NO: 295), or GYTFTDFE (SEQ ID NO: 296);

a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101), VDPETGGT (SEQ ID NO: 297), IDPETGST (SEQ ID NO: 298), or VEPETGGT (SEQ ID NO: 299);

a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPPYAMDY (SEQ ID NO: 72), TRTYEGYPYAMDY (SEQ ID NO: 300), or TRTYDGYPPYAFDY (SEQ ID NO: 301); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QSLLYSNNQKNY (SEQ ID NO: 73), QSVLYSNNQKNY (SEQ ID NO: 302), or QSVLYSDNQKNY (SEQ ID NO: 306);

a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, 104), YAS (SEQ ID NO: 303), or FAS (SEQ ID NO: 304);

a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75);

(b) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82);

a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83);

a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGAMDY (SEQ ID NO: 78); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85);

a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86);

a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87);

(c) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NOs: 76 and 82);

a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NOs: 77 and 83);

a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGSMDF (SEQ ID NO: 84); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NOs: 79 and 85);

a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NOs: 80 and 86);

a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NOs: 81 and 87);

(d) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GYTVTDYY (SEQ ID NO: 88);

a CDR-H2 sequence comprising the amino acid sequence of INPNNGVT (SEQ ID NO: 89);

a CDR-H3 sequence comprising the amino acid sequence of AREEDFDGFDY (SEQ ID NO: 90); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QDVSTG (SEQ ID NO: 91);

a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92,

98, and 104);

a CDR-L3 sequence comprising the amino acid sequence of QQHYSTPLT (SEQ ID NO: 93);

(e) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GSTFSDFE (SEQ ID NO: 94);

a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101);

a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTMDY (SEQ ID NO: 96) or TRNYDGYSQTFDY (SEQ ID NO: 305); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NOs: 97 and 103) or QSVLYSDNQKNY (SEQ ID NO: 306);

a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104);

a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105); or

(f) the VH domain comprises

a CDR-H1 sequence comprising the amino acid sequence of GSTFTDFE (SEQ ID NO: 100);

a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NOs: 71, 95, and 101);

a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSRTMDY (SEQ ID NO: 102) or TRNYDGYSRTFDY (SEQ ID NO: 307); and

the VL domain comprises

a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NOs: 97 and 103) or QSVLYSDNQKNY (SEQ ID NO: 306);

a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104);

a CDR-L3 sequence comprising the amino acid sequence of or HQYLSSYT (SEQ ID NOs: 99 and 105).

3. The antigen binding protein or antigen-binding fragment thereof of claim 1 or 2, wherein:

(a) the VH domain comprises an amino acid sequence selected from the group consisting of:

SEQ ID NO: 6, SEQ ID NO: 18, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 10, SEQ ID NO: 110, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, and SEQ ID NO: 122; and

the VL domain comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 7, SEQ ID NO: 19, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, and SEQ ID NO: 132;

(b) the VH domain comprises the amino acid sequence of SEQ ID NO: 8; and the VL domain comprises the amino acid sequence of SEQ ID NO: 9;

(c) the VH domain comprises the amino acid sequence of SEQ ID NO: 10; and the VL domain comprises the amino acid sequence of SEQ ID NO: 11;

(d) the VH domain comprises the amino acid sequence of SEQ ID NO: 12; and the VL domain comprises the amino acid sequence of SEQ ID NO: 13;

(e) the VH domain comprises an amino acid sequence selected from the group consisting of:

SEQ ID NO: 14, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, and SEQ ID NO: 23; and

the VL domain comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 15, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, and SEQ ID NO: 27;

(f) the VH domain comprises an amino acid sequence selected from the group consisting of:

SEQ ID NO: 16, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, and SEQ ID NO: 31;

the VL domain comprises an amino acid sequence selected from the group consisting of:

SEQ ID NO: 17, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, and SEQ ID NO: 35.

4. The antigen binding protein or antigen-binding fragment thereof of any one of any one of claims 1-3, wherein the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 63 or 65, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67 or 69.

5. The antigen binding protein or antigen-binding fragment thereof of claim 3, wherein the VH domain is at least about 90% identical or at least about 95% identical to the amino acid sequence of SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, or SEQ ID NO: 122, and

wherein the VL domain is at least about 90% identical or at least about 95% identical to the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132.

6. The antigen binding protein or fragment thereof of claim 5, comprising an antibody heavy chain at least about 90% identical or at least about 95% identical to the amino acid sequence of SEQ ID NO: 63 or 65, and an antibody light chain at least about 90% identical or at least about 95% identical to the amino acid sequence of SEQ ID NO: 67 or 69.

7. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-5, wherein:

(a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NO: 71), and a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPPYAMDY (SEQ ID NO: 72); and

(b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLLYSNNQKNY (SEQ ID NO: 73), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NO: 74), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75).

8. The antigen binding protein or antigen-binding fragment thereof of claim 7, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 6, and the VL domain comprises the amino acid sequence of SEQ ID NO: 7.

9. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-5, wherein:

(a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NO: 76), a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NO: 77), and a CDR-H3 sequence comprising the amino acid sequence of ARERDYDGAMDY (SEQ ID NO: 78); and

(b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NO: 79), a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NO: 80), and a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NO: 81).

10. The antigen binding protein or antigen-binding fragment thereof of claim 9, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 8, and the VL domain

comprises the amino acid sequence of SEQ ID NO: 9.

11. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-5, wherein:

(a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTFTDYN (SEQ ID NO: 82), a CDR-H2 sequence comprising the amino acid sequence of INPNNGGT (SEQ ID NO: 83), and a CDR-H3 sequence comprising the amino acid sequence of ARERDYGSMDF (SEQ ID NO: 84); and

(b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDINKF (SEQ ID NO: 85), a CDR-L2 sequence comprising the amino acid sequence of YTS (SEQ ID NO: 86), and a CDR-L3 sequence comprising the amino acid sequence of LQYDNLLWT (SEQ ID NO: 87).

12. The antigen binding protein or antigen-binding fragment thereof of claim 11, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 10, and the VL domain comprises the amino acid sequence of SEQ ID NO: 11.

13. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-5, wherein:

(a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GYTVTDYY (SEQ ID NO: 88), a CDR-H2 sequence comprising the amino acid sequence of INPNNGVT (SEQ ID NO: 89), and a CDR-H3 sequence comprising the amino acid sequence of AREEDFDGFDY (SEQ ID NO: 90); and

(b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QDVSTG (SEQ ID NO: 91), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NO: 92), and a CDR-L3 sequence comprising the amino acid sequence of QQHYSTPLT (SEQ ID NO: 93).

14. The antigen binding protein or antigen-binding fragment thereof of claim 13, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 12, and the VL domain comprises the amino acid sequence of SEQ ID NO: 13.

15. The antigen binding protein or antigen-binding fragment thereof of any one of claims

1-5, wherein:

- (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFSDFE (SEQ ID NO: 94), a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NO: 95), and a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSQTMDY (SEQ ID NO: 96); and
- (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NO: 97), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NO: 98), and a CDR-L3 sequence comprising the amino acid sequence of HQYLSSYT (SEQ ID NO: 99).

16. The antigen binding protein or antigen-binding fragment thereof of claim 15, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 14, and the VL domain comprises the amino acid sequence of SEQ ID NO: 15.

17. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-5, wherein:

- (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GSTFTDFE (SEQ ID NO: 100), a CDR-H2 sequence comprising the amino acid sequence of IDPETGGT (SEQ ID NO: 101), and a CDR-H3 sequence comprising the amino acid sequence of TRNYDGYSRTMDY (SEQ ID NO: 102); and
- (b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSSNQKNY (SEQ ID NO: 103), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NO: 104), and a CDR-L3 sequence comprising the amino acid sequence of HQYLSSYT (SEQ ID NO: 105).

18. The antigen binding protein or antigen-binding fragment thereof of claim 17, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 16, and the VL domain comprises the amino acid sequence of SEQ ID NO: 17.

19. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-5, wherein:

- (a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), a CDR-H2 sequence comprising the amino acid

sequence of VDPETGGT (SEQ ID NO: 297), and a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPPYAFDY (SEQ ID NO: 301); and

(b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSNNKNY (SEQ ID NO: 302), a CDR-L2 sequence comprising the amino acid sequence of WAS (SEQ ID NOs: 74, 92, 98, and 104), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75).

20. The antigen binding protein or antigen-binding fragment thereof of claim 19, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 57, and the VL domain comprises the amino acid sequence of SEQ ID NO: 19 or 59.

21. The antigen binding protein or antigen-binding fragment thereof of claim 19, wherein the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 63, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67.

22. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-5, wherein:

(a) the VH domain comprises a CDR-H1 sequence comprising the amino acid sequence of GDTFTDFE (SEQ ID NO: 70), a CDR-H2 sequence comprising the amino acid sequence of VDPETGGT (SEQ ID NO: 297), and a CDR-H3 sequence comprising the amino acid sequence of TRTYDGYPPYAFDY (SEQ ID NO: 301); and

(b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSVLYSDNQKNY (SEQ ID NO: 306), a CDR-L2 sequence comprising the amino acid sequence of FAS (SEQ ID NO: 304), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75).

23. The antigen binding protein or antigen-binding fragment thereof of claim 22, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 57, and the VL domain comprises the amino acid sequence of SEQ ID NO: 61.

24. The antigen binding protein or antigen-binding fragment thereof of claim 22, wherein

the antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 65, and the antibody light chain comprises the amino acid sequence of SEQ ID NO: 67.

25. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-24, wherein the antigen binding protein or antigen-binding binding fragment thereof binds a human FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO: 133.

26. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-24, wherein the antigen binding protein or antigen-binding fragment thereof binds a human FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO: 134.

27. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-26, wherein the antigen binding protein or antigen-binding fragment thereof binds a region of human FGFR3 polypeptide, the region comprising the amino acids D143 through L163 of SEQ ID NO: 133.

28. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-26, wherein the antigen binding protein or antigen-binding fragment thereof binds a region of human FGFR3 polypeptide, the region comprising the amino acids D143 through N170 of SEQ ID NO: 133.

29. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-26, wherein the antigen binding protein or antigen-binding fragment thereof binds a region of human FGFR3 polypeptide, the region comprising the amino acids D143 through D160, and the amino acids G197 through L213 of SEQ ID NO: 133.

30. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-29 wherein the antigen binding protein or antigen-binding binding fragment thereof is a chimeric or humanized antibody or antigen-binding binding fragment thereof.

31. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-29, wherein the antigen binding protein or antigen-binding binding fragment thereof is

a human antibody or antigen-binding binding fragment thereof.

32. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-31, wherein the antigen binding protein or antigen-binding binding fragment thereof is a monoclonal antibody or antigen-binding binding fragment thereof.

33. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-32, wherein the antigen binding protein or antigen-binding binding fragment thereof comprises one or more full-length antibody heavy chains comprising an Fc region.

34. The antigen binding protein or antigen-binding fragment thereof of claim 33, wherein the Fc region is a human IgG1 Fc region.

35. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-32, wherein the antigen binding protein or antigen-binding binding fragment thereof comprises an antibody F(ab), F(ab')₂, Fab'-SH, Fv, or scFv fragment.

36. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-32, wherein the antigen binding protein or antigen-binding binding fragment thereof comprises an antibody F(ab) fragment.

37. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment comprises SEQ ID NO: 56 and the first about 100 amino acids of SEQ ID NO: 54.

38. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment comprises a heavy chain comprising SEQ ID NO: 57 and the first about 100 amino acids of SEQ ID NO: 54.

39. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment comprises a heavy chain comprising SEQ ID NO: 58 and the first about 100 amino acids of SEQ ID NO: 54.

40. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 141, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 254, 263, 272, or 281, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 142.

41. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 143, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 255, 264, 273, or 282, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 144.

42. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 145, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 256, 265, 274, or 283, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 146.

43. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 147, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 257, 266, 275, or 284, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 148.

44. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 149, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 258, 267, 276, or 285, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 150.

45. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 151, 169, 178, 187, 196, 205, 214, 223, 232, 241, 250, 259, 268, 277, or 286, and the

antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 152.

46. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

47. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

48. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 153, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, or 287, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

49. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

50. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

51. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 155, 171, 180, 189, 198, 207, 216, 225, 234, 243, 252, 261, 270, 279, or 288, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

52. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 67.

53. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 154.

54. The antigen binding protein or antigen-binding fragment thereof of claim 36, wherein the antibody F(ab) fragment heavy chain comprises the amino acid sequence of SEQ ID NO: 156, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, or 289, and the antibody F(ab) fragment light chain comprises the amino acid sequence of SEQ ID NO: 69.

55. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-54, wherein the antigen binding protein or antigen-binding binding fragment thereof has cross-reactivity to mouse and cynomolgus FGFR3.

56. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-55, wherein the antigen binding or antigen-binding binding fragment thereof protein does not bind to one or more of FGFR1, FGFR2, and FGFR4.

57. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-56, wherein the antigen binding protein or antigen-binding binding fragment thereof does not bind to each of FGFR1, FGFR2, and FGFR4.

58. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-56, wherein the antigen binding protein or antigen-binding binding fragment thereof binds to each of FGFR1, FGFR2, and FGFR4 with an equilibrium dissociation constant (KD) of 100 μ M or greater.

59. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-58, wherein the antigen binding protein or antigen-binding binding fragment thereof binds human FGFR3 with an equilibrium dissociation constant (KD) of 10 nM or less.

60. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-59, wherein the antigen binding protein or antigen-binding binding fragment thereof binds human FGFR3 with an off rate (Kd) of 10^{-4} or greater.

61. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-60, wherein the antigen binding protein or antigen-binding binding fragment thereof inhibits ligand-induced FGFR3 dimerization with IC₅₀ of 5 μ g/ml or less.

62. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-61, wherein the antigen binding protein or antigen-binding binding fragment thereof inhibits FGFR3 receptor activation and downstream signaling with IC₅₀ of 5 μ g/ml or less.

63. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-62, wherein the antigen binding protein or antigen-binding binding fragment thereof inhibits the activity of an FGFR3^{G380R} mutant.

64. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-63, capable of penetrating a bone growth plate.

65. The antigen binding protein or antigen-binding fragment thereof of any one of claims 1-64, capable of decreasing the binding of FGFR3 with its ligand in a bone growth plate.
66. A pharmaceutical composition comprising the antigen binding protein or antigen-binding fragment thereof of any one of the preceding claims, and a pharmaceutically acceptable carrier.
67. An isolated nucleic acid molecule encoding the antigen binding protein or antigen-binding fragment thereof of any one of the preceding claims.
68. An expression vector comprising the nucleic acid molecule of claim 67.
69. A host cell comprising the expression vector of claim 68.
70. A method for treating a FGFR3-mediated disease or disorder in a subject, comprising administering to a subject in need thereof the antigen binding protein or antigen-binding fragment thereof of any one of the preceding claims.
71. The method of claim 70, wherein the FGFR3-mediated disease or disorder is achondroplasia.
72. The method of claim 71, wherein the achondroplasia is FGFR3^{G380R+} achondroplasia.
73. The method of claim 70, wherein the subject suffering from achondroplasia comprises one or more symptoms selected from the group consisting of shortened proximal limbs, brachydactyly, large head with prominent forehead frontal bossing, small midface with a flattened nasal bridge, spinal kyphosis, spinal lordosis, varus, valgus, ear infections, sleep apnea, and hydrocephalus.
74. The method of claim 70, wherein the FGFR3-mediated disease or disorder is cancer.
75. The method of claim 74, wherein the cancer is bladder cancer melanoma, urothelial cancer, and endometrial cancer.

76. A method for treating achondroplasia in a subject, comprising administering to a subject in need thereof an antigen-binding protein fragment that specifically binds to FGFR3, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4.

77. A method for inhibiting one or both of FGFR3 activity and expression in a bone growth plate of a subject, comprising administering to a subject an antigen-binding protein fragment that specifically binds to FGFR3, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4.

78. The method of any one of claims 70-77, wherein the subject is a child.

79. The method of claim 78, wherein the child is an infant.

80. The method of claim 79, wherein the infant is a newborn.

81. A method for preventing or alleviating one or more symptoms of achondroplasia in a subject, comprising administering to the subject an antigen-binding protein or an antigen-binding protein fragment thereof that specifically binds to FGFR3, wherein the antigen binding protein fragment does not bind to one or more of FGFR1, FGFR2, and FGFR4.