

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 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), QSVLYSNNNKNY (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 TRTYDGYPYAMDY (SEQ ID NO: 72); and~~

~~(b) the VL domain comprises a CDR-L1 sequence comprising the amino acid sequence of QSLYSNNQKNY (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 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).~~

~~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 composing 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 QSVLYSNNNKNY (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 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).~~

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 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 fragment thereof is a chimeric or humanized antibody or antigen-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 fragment thereof is a human antibody or antigen-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 pM 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 pg/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 pg/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 antigenbinding 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 antigenbinding 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 anti-gen-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 antigenbinding 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.~~

CLAIMS

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 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

wherein 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 NO: 74), and a CDR-L3 sequence comprising the amino acid sequence of QQYYSYRT (SEQ ID NO: 75).

2. The antigen binding protein or antigen-binding fragment thereof of claim 1, wherein the VH domain is at least about 90% identical to the amino acid sequence of SEQ ID NO: 57, and the VL domain is at least about 90% identical to the amino acid sequence of SEQ ID NO: 19.

3. The antigen binding protein or antigen-binding fragment thereof of claim 1, wherein the antibody heavy chain is at least 95% identical to the amino acid sequence of SEQ ID NO: 63, and the antibody light chain is at least 95% identical to the amino acid sequence of SEQ ID NO: 67.

4. The antigen binding protein or antigen-binding fragment thereof of claim 1, 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.

5. The antigen binding protein or antigen-binding fragment thereof of claim 1, wherein the antigen binding protein or antigen-binding binding fragment thereof comprises an Fc region.

6. The antigen binding protein or antigen-binding fragment thereof of claim 5, wherein the Fc region is a human IgG1 Fc region.

7. The antigen binding protein or antigen-binding fragment thereof of claim 1, 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.
8. The antigen binding protein or antigen-binding fragment thereof of claim 7, wherein the antibody F(ab) fragment comprises the sequence of SEQ ID NO: 56 followed by the first about 100 to about 110 amino acids of SEQ ID NO: 54.
9. The antigen binding protein or antigen-binding fragment thereof of claim 7, wherein the antibody F(ab) fragment comprises a heavy chain comprising the sequence of SEQ ID NO: 57 followed by the first about 100 to about 110 amino acids of SEQ ID NO: 54.
10. The antigen binding protein or antigen-binding fragment thereof of claim 7, wherein the antibody F(ab) fragment comprises a heavy chain comprising the sequence of SEQ ID NO: 58 followed by the first about 100 to about 110 amino acids of SEQ ID NO: 54.
11. A pharmaceutical composition comprising the antigen binding protein or antigen-binding fragment of claim 1, and a pharmaceutically acceptable carrier.
12. The antigen binding protein or antigen-binding fragment thereof of claim 1, wherein the antigen binding protein or antigen-binding binding fragment thereof comprises an antibody F(ab) fragment.
13. 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 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.
14. A pharmaceutical composition comprising the antigen binding protein or antigen-binding fragment of claim 13, and a pharmaceutically acceptable carrier.
15. An antibody F(ab) fragment, wherein the antibody F(ab) fragment comprises an antibody F(ab) fragment heavy chain comprising 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 an antibody F(ab) fragment light chain comprising the amino acid sequence of SEQ ID NO: 67.

16. A pharmaceutical composition comprising the antigen binding protein or antigen-binding fragment of claim 15, and a pharmaceutically acceptable carrier.