CLAIMS

What is claimed is:

1. An isolated antigen binding protein that induces FGF21-mediated signaling.

2. An isolated antigen binding protein that specifically binds to at least one of:

(i) β-Klotho;

(ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; and

(iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c and FGFR4 wherein the antigen binding protein induces FGF21-mediated signaling.

3. The antigen binding protein of claim 1, wherein the antigen binding protein comprises an amino acid sequence selected from the group consisting of:

(a) a light chain CDR3 comprising a sequence selected from the group consisting of:

(i) a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of L1-L18, SEQ ID NOs: 180-194;

(ii) QVWDX_1X_2SDHVV (SEQ ID NO: 276);

(iii) QQX3G$X_4X_5X_6X_7$T (SEQ ID NO: 283);

(iv) LQHNSYPLT (SEQ ID NO: 267);

(v) MQSLQTPFT (SEQ ID NO: 268);

(vi) QQYNNWPPT (SEQ ID NO: 269);

(vii) MQSIQLPRT (SEQ ID NO: 270);

(viii) QQANDFPIT (SEQ ID NO: 271);

(ix) MQALQTPCS (SEQ ID NO: 272);

(b) a heavy chain CDR3 sequence comprising a sequence selected from the group consisting of:

(i) a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3

sequence selected from the group consisting of the heavy chain CDR3 sequences of H1-H18, SEQ ID NOs:145-157;

(ii) $X_{34}X_{16}X_{17}X_{18}GX_{19}YYYX_{20}GMDV$ (SEQ ID NO: 322);

(iii) $SLIVVX_{21}VY\ X_{22}LDX_{23}$ (SEQ ID NO: 326);

(iv) IVVVPAAIQSYYYYYGMGV (SEQ ID NO: 311);

(v) DPDGDYYYYGMDV (SEQ ID NO: 312);

(vi) TYSSGWYVWDYYGMDV (SEQ ID NO: 313);

(vii) DRVLSYYAMAV (SEQ ID NO: 314);

(viii) VRIAGDYYYYYGMDV (SEQ ID NO: 315);

(ix) ENIVVIPAAIFAGWFDP (SEQ ID NO: 316); and

(x) DRAAAGLHYYYGMDV (SEQ ID NO: 317); or

(c) the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b);

wherein,

X_1 is G, S or N;

X_2 is N, S or T;

X_3 is C, Y or S;

X_4 is G or S;

X_5 is A or S;

X_6 is P or F;

X_7 is L or absent;

X_{34} is I, V or S;

X_{16} is L or V;

X_{17} is L, T or V;

X_{18} is L, V, G or T;

X_{19} is A, G or absent;

X_{20} is Y, C or D;

X_{21} is I or M;

X_{22} is A or V; and

X_{23} is H or Y;

and wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

4. The antigen binding protein of claim 1, comprising either:

(a) a light chain CDR1 sequence selected from the group consisting of:

(i) a light chain CDR1 that differs by no more than three amino acids additions, substitutions, and/or deletions from a CDR1 sequence of L1-L18, SEQ ID NOs:158-170;

(ii) RASQ $X_9X_{10}X_{11}X_{12}X_{13}X_{14}$LA (SEQ ID NO: 304);

(iii) GGNNIGSX_{15}SVH (SEQ ID NO: 307);

(iv) RSSQSLL$X_{29}X_{30}$NG$X_{31}X_{32}X_{33}$LD (SEQ ID NO: 310);

(v) RASQSVNSNLA (SEQ ID NO: 295);

(vi) RASQDIRYDLG (SEQ ID NO: 296);

(vii) RASQGISIWLA (SEQ ID NO: 297); and

(viii) KSSQSLLQSDGKTYLY (SEQ ID NO: 298);

(b) a light chain CDR2 sequence selected from the group consisting of:

(i) a light chain CDR2 that differs by no more than two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L18, SEQ ID NOs:171-179;

(ii) LGSX_{27}RAS (SEQ ID NO: 290);

(iii) GX_8SX_{28}RAT (SEQ ID NO: 294);

(iv) AASSLQS (SEQ ID NO: 284);

(v) GVSTRAT (SEQ ID NO: 285);

(vi) DDSDRPS (SEQ ID NO: 286);

(vii) EVSNRFS (SEQ ID NO: 287);

(c) a heavy chain CDR1 sequence selected from the group consisting of:

(i) a heavy chain CDR1 that differs by no more than two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H18, SEQ ID NOs:121-131; and

(ii) NARMGVX$_{39}$ (SEQ ID NO: 352);

(iii) X$_{40}$YGIH (SEQ ID NO: 355);

(iv) DLSMH (SEQ ID NO: 345);

(v) DAWMS (SEQ ID NO: 346);

(vi) TYAMS (SEQ ID NO: 347);

(vii) SYFWS (SEQ ID NO: 348);

(viii) SYYWS (SEQ ID NO: 131);

(ix) SGGYNWS (SEQ ID NO: 349);

(d) a heavy chain CDR2 selected from the group consisting of:

(i) a heavy sequence that differs by no more than three amino acid additions, substitutions, and /or deletions from a CDR2 sequence of H1-H18, SEQ ID NOs:132-144;

(ii) HIFSNDEKSYSTSLKX$_{24}$ (SEQ ID NO: 333);

(iii) X$_{25}$ISGSGVSTX$_{26}$YADSVKG (SEQ ID NO: 338);

(iv) VIWYDGSX$_{35}$KYYX$_{36}$DSVKG (SEQ ID NO: 341);

(v) X$_{37}$IYX$_{38}$SGSTX$_{41}$YNPSLKS (SEQ ID NO: 344);

(vi) GFDPEDGETIYAQKFQG (SEQ ID NO: 327);

(vii) RIKSKTDGGTTDYAAPVKG (SEQ ID NO: 328);

(viii) RIYTSGSTNYNPSLKS (SEQ ID NO: 329);

(ix) RIKSKDGGTTDYAAPVKG (SEQ ID NO: 330);

(x) RIKSKX$_{42}$DGGTTDYAAPVKG (SEQ ID NO: 483);

wherein

X$_9$ is N or S;

X$_{10}$ is V or F;

X$_{11}$ is D or S;

X$_{12}$ is G or S;

X_{13} is S, N or T;

X_{14} is S or Y;

X_{15} is E or Q;

X_{29} is Y or H;

X_{30} is Y or S;

X_{31} is F or Y;

X_{32} is T or N;

X_{33} is Y or F;

X_{27} is N or D;

X_8 is A or T;

X_{28} is S or F;

X_{39} is S or N;

X_{24} is S or N;

X_{25} is G or A;

X_{26} is H, Y or N;

X_{35} is D or I;

X_{36} is A or G;

X_{37} is N or R;

X_{38} is Y or T;

X_{41} is Y or N;

X_{42} is T or absent;

(e) the light chain CDR1 of (a) and the light chain CDR2 of (b);

(f) the light chain CDR1 of (a) and the heavy chain CDR1 of (c);

(g) the light chain CDR1 of (a) and the heavy chain CDR2 of (d);

(h) the light chain CDR1 (b) and the heavy chain CDR1 of (c);

(i) the heavy chain CDR1 of (c) and the heavy chain CDR2 of (d);

(j) the light chain CDR2 of (b) and the heavy chain CDR2 of (d);

(k) the light chain CDR1 of (a), the light chain CDR2 of (b), and the heavy chain CDR1 of (c);

(l) the light chain CDR2 of (b), the heavy CDR1 of (c), and the heavy chain CDR2 of (d);

(m) the light chain CDR1 of (a), the heavy chain CDR1 of (c), and the heavy chain CDR2 of (d); or

(n) the light chain CDR1 of (a), the light chain CDR2 of (b), the heavy chain CDR2 of (c), and the heavy chain CDR2 of (d),

wherein said antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

5. The antigen binding protein of claim 1, comprising either:

(a) a light chain variable domain comprising;

(i) a light chain CDR1 sequence selected from SEQ ID NOs:158-170;

(ii) a light chain CDR2 sequence selected from SEQ ID NOs:171-179;

(iii) a light chain CDR3 sequence selected from SEQ ID NOs:180-194; and

(b) a heavy chain variable domain comprising:

(i) a heavy chain CDR1 sequence selected from SEQ ID NOs:121-131;

(ii) a heavy chain CDR2 sequence selected from SEQ ID NOs:132-144; and

(iii) a heavy chain CDR3 sequence selected from SEQ ID NOs:145-157; or

(c) the light chain variable domain of (a) and the heavy chain variable domain of (b),

wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

6. The antigen binding protein of claim 1 comprising either:

(a) a light chain variable domain sequence selected from the group consisting of:

(i) amino acids having a sequence at least 80% identical to a light chain variable domain sequence selected from V_L1-V_L18, SEQ ID NOs:48-65;

(ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the light chain variable domain sequence of V_L1-V_L18, SEQ ID NOs:48-65;

(b) a heavy chain variable domain sequence selected from the group consisting of:

(i) a sequence of amino acids that is at least 80% identical to a heavy chain variable domain sequence of V_H1-V_H18 of SEQ ID NOs:66-84;

(ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the heavy chain variable domain sequence of V_H1-V_H18, SEQ ID NOs:66-84; or

(c) the light chain variable domain of (a) and the heavy chain variable domain of (b);

wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

7. The antigen binding protein of claim 6, comprising either:

(a) a light chain variable domain sequence selected from the group consisting of: V_L1-V_L18 of SEQ ID NOs:48-65;

(b) a heavy chain variable domain sequence selected from the group consisting of: V_H1-V_H18 of SEQ ID NOs:66-84; or

(c) the light chain variable domain of (a) and the heavy chain variable domain of (b),

wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

8. The antigen binding protein of claim 7, wherein the light chain variable domain and a heavy chain variable domain are selected from the group of combinations consisting of: V_L1V_H1, V_L2V_H2, V_L3V_H3, V_L3V_H4, V_L4V_H5, V_L5V_H6, V_L6V_H7, V_L7V_H8, V_L8V_H8, V_L9V_H9, V_L9V_H10, V_L10V_H11, V_L11V_H11, V_L12V_H12, V_L13V_H13, V_L14V_H14, V_L15V_H15, V_L16V_H16, V_L17V_H17, and V_L18V_H18, wherein the antigen binding protein specifically binds (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

9. The antigen binding protein of claim 8, further comprising:

(a) the light chain constant sequence of SEQ ID NO: 10;

(b) the light chain constant sequence of SEQ ID NO:11;

(c) the heavy chain constant sequence of SEQ ID NO: 9; or

(d) the light chain constant sequence of SEQ ID NO: 10 or SEQ ID NO:11 and the heavy chain constant sequence of SEQ ID NO: 9.

10. The antigen binding protein of claim 1, wherein the antigen binding protein is a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an $F(fab')_2$ fragment, a domain antibody, an IgD antibody, an IgE antibody, an IgM antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, an IgG4 antibody, or an IgG4 antibody having at least one mutation in the hinge region.

11. The antigen binding protein of claim 1, that, when bound to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4:

(a) binds to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, with substantially the same Kd as a reference antibody;

(b) induces FGF21-like signaling of 10 % or greater than the signaling induced by a wild-type FGF21 standard comprising the mature form of SEQ ID NO:2 as measured in an ELK-luciferase reporter assay;

(c) exhibits an EC50 of 10nM or less of FGF21-like signaling in an assay selected from the group consisting of:

(i) a FGFR1c/β–Klotho-mediated *in vitro* recombinant cell-based assay; and

(ii) an *in vitro* human adipocyte functional assay;

(d) exhibits an EC50 of less than 10nM of agonistic activity on FGFR1c in the presence of β–Klotho in an *in vitro* recombinant FGFR1c receptor mediated reporter assay; and

(e) exhibits an EC50 of greater than 1μM of agonistic activity on FGFR1c in the absence of β–Klotho in an *in vitro* recombinant FGFR1c receptor mediated reporter assay; or

(f) competes for binding with a reference antibody to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, wherein the reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group consisting of V_L1V_H1, V_L2V_H2, V_L3V_H3, V_L3V_H4, V_L4V_H5, V_L5V_H6, V_L6V_H7, V_L7V_H8, V_L8V_H8, V_L9V_H9, V_L9V_H10, V_L10V_H11, V_L11V_H11, V_L12V_H12, V_L13V_H13, V_L14V_H14, V_L15V_H15, V_L16V_H16, V_L17V_H17, and V_L18V_H18.

12. The antigen binding protein of claim 11, that, when bound to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4:

(a) lowers blood glucose in an animal model;

(b) lowers serum lipid levels in an animal model;

(c) lowers insulin levels in an animal model; or

(d) two or more of (a) and (b) and (c).

13. The antigen binding protein of claim 1, wherein the antigen binding protein comprises:

(a) a heavy chain comprising one of SEQ ID NOs:31, 32, 390-401, 404-405;

(b) a light chain comprising one of SEQ ID NO:13, 14, 385-389, 402-403; or

(c) a combination comprising a heavy chain of (a) and a light chain of (b).

14. An antigen binding protein that is capable of binding wild type human β-Klotho (SEQ ID NO:7) but which doesn't bind to a chimeric form of β-Klotho wherein the chimeric form of β-Klotho comprises a human β-Klotho framework wherein murine β-Klotho sequences replace the wild type human residues at at least one of (a) positions 1-80; (b) positions 303-522; (c) positions 852-1044; and (d) combinations thereof.

15. An antigen binding protein that is capable of binding wild type human β-Klotho (SEQ ID NO:7) at at least one of (a) positions 1-80; (b) positions 303-522; (c) positions 852-1044; and (d) combinations thereof.

16. An antigen binding protein that is capable of competing with an antigen binding protein of claims 8 or 13 for binding to human wild type β-Klotho residues at at least one of (a) positions 1-80; (b) positions 303-522; (c) positions 852-1044; and (d) combinations thereof.

17. A pharmaceutical composition comprising one or more antigen binding proteins of claim 1 in admixture with a pharmaceutically acceptable carrier thereof.

18. A pharmaceutical composition comprising the one or more antigen binding proteins of claim 11 in admixture with a pharmaceutically acceptable carrier thereof.

19. An isolated nucleic acid comprising a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of the antigen binding protein of claim 6.

20. The isolated nucleic acid of claim 19, wherein the sequence comprises:

(a) V_L1-V_L18 (SEQ ID NOs:48-65);

(b) V_H1-V_H18 (SEQ ID NOs:66-84); or

(c) one or more sequences of (a) and one or more sequences of (b).

21. An expression vector comprising the nucleic acid of claim 20.

22. An isolated cell comprising the nucleic acid of claim 21.

23. An isolated cell comprising the expression vector of claim 22.

24. A method of producing an antigen binding protein that specifically binds to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and

one of FGFR1c, FGFR2c, FGFR3c, and FGFR4, comprising incubating the host cell of claim 23 under conditions that allow it to express the antigen binding protein.

25. Use of a therapeutically effective amount of the composition of claim 17 in the manufacture of a medicament for preventing or treating a condition in a subject in need of such treatment, wherein the condition is treatable by lowering blood glucose, insulin or serum lipid levels.

26. The use of claim 25, wherein the condition is type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease or metabolic syndrome.

CLAIMS

What is claimed is:

1. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 14 and SEQ ID NO: 32.

2. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 385.

3. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 386.

4. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 387.

5. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 390

6. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 391.

7. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 392.

8. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 385 and SEQ ID NO: 386.

9. An isolated antibody that induces FGF21-mediated signaling and comprises SEQ ID NO: 387 and SEQ ID NO: 391.

10. The isolated antibody 16H7 capable of inducing FGF21-mediated signaling.

11. A pharmaceutical composition comprising one or more antigen binding proteins of claim 1 in admixture with a pharmaceutically acceptable carrier thereof.

12. A pharmaceutical composition comprising an antigen binding proteins of claims 1-10 in admixture with a pharmaceutically acceptable carrier thereof.

ABSTRACT OF INVENTION

The present disclosure provides compositions and methods relating to or derived from antigen binding proteins activate FGF21-mediated signaling. In embodiments, the antigen binding proteins specifically bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In some embodiments the antigen binding proteins induce FGF21-like signaling. In some embodiments, an antigen binding protein is a fully human, humanized, or chimeric antibodies, binding fragments and derivatives of such antibodies, and polypeptides that specifically bind to (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Other embodiments provide nucleic acids encoding such antigen binding proteins, and fragments and derivatives thereof, and polypeptides, cells comprising such polynucleotides, methods of making such antigen binding proteins, and fragments and derivatives thereof, and polypeptides, and methods of using such antigen binding proteins, fragments and derivatives thereof, and polypeptides, including methods of treating or diagnosing subjects suffering from type 2 diabetes, obesity, NASH, metabolic syndrome and related disorders or conditions.