The present disclosure provides a human (or humanized) antigen binding protein, such as a monoclonal antibody, that induces FGF21-like signaling, *e.g.*, an agonistic antibody that mimics the function of FGF21. Such an antibody is a molecule with FGF21-like activity and selectivity but with added therapeutically desirable characteristics typical for an antibody such as protein stability, lack of immunogenicity, ease of production and long half-life *in vivo*.

## SUMMARY

In one aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises a heavy and light chain comprising the amino acid sequences of SEQ ID NO: 14 and SEQ ID NO: 32.

In another aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises CDRs comprising the amino acid sequences of SEQ ID NOs: 122, 133, 148, 166, 176, and 188.

In yet another aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 50.

In yet another aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 387.

In yet another aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises a light chain comprising the amino acid sequence of SEQ ID NO: 14 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 390.

In yet another aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises a light chain comprising the amino acid sequence of SEQ ID NO: 14 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 391.

In yet another aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises a light chain comprising the amino acid sequence of SEQ ID NO: 14 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 392.

In yet another aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 385 or SEQ ID NO: 386.

In yet another aspect, there is provided an isolated antibody that induces FGF21-mediated signaling and comprises a light chain comprising the amino acid sequence of SEQ ID NO: 387 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 391.

In yet another aspect, there is provided a pharmaceutical composition comprising an antibody as disclosed herein in admixture with a pharmaceutically acceptable carrier thereof.

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

Also provided is 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.

In one example, the provided antigen binding proteins comprise 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$_1$X$_2$SDHVV (SEQ ID NO: 276); (iii) QQX3GX$_4$X$_5$X$_6$X$_7$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) VRIAGDYY YYYGMDV (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.

In another example the provided antigen binding proteins comprise 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 $X_9$ $X_{10}X_{11}X_{12}X_{13}X_{14}$LA (SEQ ID NO: 304); (iii) GGNNIGS$X_{15}$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) LGS$X_{27}$RAS (SEQ ID NO: 290); (iii) G$X_8$S$X_{28}$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) NARMGV$X_{39}$ (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.

In yet another example the provided antigen binding proteins comprise 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.

In a further example the provided antigen binding proteins comprise 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. In particular examples the provided antigen binding proteins comprise 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. In other particular embodiments, the provided antigen binding proteins 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. In still further examples the provided antigen binding proteins further comprise: (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.

The provided antigen binding proteins can take many forms and can be, for example, 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.

In another example, the provided antigen binding proteins 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) 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, with substantially the same Kd as a reference antibody; (b) induce 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) exhibit 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) exhibit 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) exhibit 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 $V_L18V_H18$. In other examples the provided antigen binding proteins can 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) lower blood glucose in an animal model; (b) lower serum lipid levels in an animal model; (c) lower insulin levels in an animal model; or (d) two or more of (a) and (b) and (c).

In specific examples the provided antigen binding proteins comprise: (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).

Also disclosed are antigen binding proteins that are 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.

Also disclosed are antigen binding proteins that are 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.

Also disclosed are antigen binding proteins that are 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.

Also disclosed is a pharmaceutical composition comprising one or more antigen binding proteins provided herein, in admixture with a pharmaceutically acceptable carrier thereof.

Also disclosed are isolated nucleic acid molecules that encode the antigen binding proteins disclosed herein. In some instances, the isolated nucleic acid molecules are operably-linked to a control sequence. In some examples, such nucleic acids comprise a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of an antigen binding protein provided herein. In particular examples the nucleic acids comprise (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).

Also provided are expression vectors and host cells transformed or transfected with the expression vectors that comprise the aforementioned isolated nucleic acid molecules that encode the antigen binding proteins disclosed herein.

Also provided are methods of preparing antigen binding proteins that specifically or selectively bind (i) β-Klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising β-Klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and comprises the step of preparing the antigen binding protein from a host cell that secretes the antigen binding protein.

Other examples provide a method of preventing or treating a condition in a subject in need of such treatment comprising administering a therapeutically effective amount of a

pharmaceutical composition provided herein to a subject, wherein the condition is treatable by lowering blood glucose, insulin or serum lipid levels. In examples, the condition is type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease or metabolic syndrome.

These and other aspects are described in greater detail herein. Each of the aspects provided can encompass various embodiments provided herein. It is therefore anticipated that each of the embodiments involving one element or combinations of elements can be included in each aspect described, and all such combinations of the above aspects and embodiments are expressly considered. Other features, objects, and advantages of the disclosed antigen binding proteins and associated methods and compositions are apparent in the detailed description that follows.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A-1B is an alignment showing the sequence homology between human FGFR1c (GenBank Accession No P11362; SEQ ID NO: 356) and murine FGFR1c (GenBank Accession No NP_034336; SEQ ID NO: 357); various features are highlighted, including the signal peptide, transmembrane sequence, heparin binding region, and a consensus sequence (SEQ ID NO: 358) is provided.

Figure 2a-2c is an alignment showing the sequence homology between human β-Klotho (GenBank Accession No NP_783864; SEQ ID NO: 359) and murine β-Klotho (GenBank Accession No NP_112457; SEQ ID NO: 360); various features are highlighted, including the transmembrane sequence and two glycosyl hydrolase domains, and a consensus sequence (SEQ ID NO: 361) is provided.

Figure 3 is a flow cytometry profile of cells stained with FGF21-Alexa 647 that were used as an immunogen to generate antigen binding proteins; the figure shows the expression level of an FGF21R (a complex comprising FGFR1c and β–Klotho) and binding to FGF21.

Figure 4 is a sequence (SEQ ID NO: 362) showing an Fc fusion protein that was used as an immunogen to generate antigen binding proteins; the immunogen comprises the extracellular domain (ECD) of human FGFR1c fused to an IgG1 Fc via a $Gly_5$ linker (SEQ ID NO: 379); the FGFR1c component is in capitals, the linker is italic and underlined and the Fc is in lower case letters.