sensitivity (Tomlinson *et al.*, 2002, Endocrinology 143: 1741-1747). In addition, these transgenic mice were reported not to become obese or diabetic on a high-fat diet (Tomlinson *et al.*, 2002, Endocrinology 143: 1741-1747). It has also been reported that FGF19 treatment prevented or reversed diabetes in mice made obese by genetic ablation of brown adipose tissue or the genetic absence of leptin (Fu *et al.*, 2004, Endocrinology 145: 2594-2603).

[0006] FGF21 acts through the interaction of FGFRs and beta klotho. FGFR1 is an abundant receptor in white adipose tissue and is most likely the main functional receptor for FGF21 in white adipose tissue. FGF21 expression is detected in the liver, thymus, adipose tissue, and islet beta-cells in the pancreas. It has been reported that the interaction of FGF21 with the beta klotho-FGFR complex stimulates glucose uptake, decreases glucagon secretion, improves insulin sensitivity and glucose clearance, promotes white adipose tissue in response to fasting, increases ketogenesis in liver in response to fasting, reduces plasma triglyceride levels, and increases energy expenditure (Iglesias *et al.*, 2012, European Journal of Endocrinology 167: 301-309).

[0007] Since FGF19 and FGF21 require both FGFRs and beta klotho for cell signaling, agents which mimic FGF19 and/or FGF21 may be desirable for their effects or glucose metabolism or lipid metabolism. However, it is not clear what features are required for an agent to confer FGF19-like or FGF21-like cell signaling activity.

## SUMMARY

[0008] The present disclosure provides proteins that bind to beta klotho, including binding proteins such as antibodies that bind to beta klotho. Such binding proteins including antibodies, may bind to a beta klotho polypeptide, a beta klotho fragment and/or a beta klotho epitope. Such binding proteins, including antibodies, may be agonists (*e.g.*, induce FGF19-like or FGF21-like signaling of a FGF receptor or activate a beta klotho/FGF receptor complex).

[0009] The present disclosure also provides binding proteins, including antibodies or fragments thereof, that (i) bind to human beta klotho, (ii) induce FGF19-like signaling and/or FGF21-like signaling, and (iii) do not compete with FGF19 and/or FGF21 for the interaction with beta klotho. In one aspect, the present disclosure refers to an antibody or antigen-binding fragment thereof that (i) binds to an epitope of human beta klotho and cynomolgus monkey beta klotho recognized by an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO:25 and a light chain variable region having the amino acid sequence

of SEQ ID NO:26; or (ii) competes for the binding to human beta klotho with an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO:25 and a light chain variable region having the amino acid sequence of SEQ ID NO:26. In another aspect, the present disclosure refers to an antibody or an antigen binding fragment thereof that binds to human beta klotho, wherein the antibody or the antigen-binding fragment thereof comprises: a heavy chain variable region (VH) comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:271, and a light chain variable region (VL) comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:276. In another aspect, the present disclosure refers to an antibody or an antigen binding fragment thereof that binds to human beta klotho, wherein the antibody or the antigen-binding fragment comprises a VH comprising the amino acid sequence of SEQ ID NO:271 and a VL comprising the amino acid sequence of SEQ ID NO:276. In yet another aspect, the present disclosure refers to an antibody that binds human beta klotho, wherein the antibody comprises a heavy chain comprising amino acids 23-472 of the amino acid sequence of SEQ ID NO:317 and a light chain comprising amino acids 23-240 of the amino acid sequence of SEQ ID NO:319. In another aspect, the present disclosure refers to an antibody or an antigen binding fragment thereof that binds to human beta klotho, wherein the antibody or antigen-binding fragment thereof comprises: (a) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:51, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:52; (b) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:77, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:78; (c) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:103, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:104; (d) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:129, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:130; (e) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:155, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:156; (f) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:181, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:182; (g) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:207, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:208; (h) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:233, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:234; or (i) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:259, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:260. In another aspect, the present disclosure refers to an isolated polynucleotide or polynucleotides encoding the antibody or the antigen-binding fragment thereof as disclosed herein. In yet another aspect, the present disclosure refers to an expression vector or vectors: (i) encoding the antibody an antigen-binding fragment thereof as disclosed herein, or (ii) comprising the polynucleotide or polynucleotides as disclosed herein. In another aspect, the present disclosure refers

to an isolated cell producing the antibody or the antigen-binding fragment thereof as disclosed herein. In another aspect, the present disclosure refers to an isolated cell comprising the polynucleotide or polynucleotides or the expression vector or vectors as disclosed herein. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or the antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein, and a pharmaceutically acceptable carrier. In another aspect, the present disclosure refers to a use of the antibody or the antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein in the manufacture of a medicament for improving glucose metabolism or improving lipid metabolism in a subject. In another aspect, the present disclosure refers to a use of the antibody or the antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein in the manufacture of a medicament for treating Type 2 diabetes, gestational diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), obesity, dyslipidemia, Type 1 diabetes, cardiovascular disease, or metabolic syndrome in a subject. In another aspect, the present disclosure refers to a use of the antibody or the antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein in the manufacture of a medicament for inducing FGF19-like signaling and/or FGF21-like signaling in a subject. In yet another aspect, the present disclosure refers to a method of making the antibody or antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein, comprising (a) culturing the cell as disclosed herein and (b) isolating the antibody or antigen-binding fragment thereof. In yet another aspect, the present disclosure refers to an antibody or the antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein for use in therapy.

[0010] In some examples, the anti-beta klotho antibodies are humanized antibodies that bind to a beta klotho polypeptide, a beta klotho fragment, or a beta klotho epitope. In certain examples, an anti-beta klotho antibody comprises a VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of a monoclonal antibody designated 5H23, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 or 1G19 as described herein, or a humanized variant thereof. In certain examples, an anti-beta klotho antibody can further comprise a VH FR1, VH FR2, VH FR3, VH FR4, VL FR1, VL FR2, VL FR3, and/or VL FR4 of a human immunoglobulin amino acid sequence or a variant thereof.

[0011] In some examples, a binding protein (*e.g.,* an anti-beta klotho antibody) comprises six CDRs or less than six CDRs. In some examples, a binding protein (*e.g.,* an anti-beta klotho antibody) comprises one, two, three, four, five, or six CDRs selected from VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3. In some examples, a binding protein (*e.g.,* an anti-beta klotho antibody) comprises one, two, three, four, five, or six CDRs selected from VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of a monoclonal antibody designated as 5H23, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 or 1G19 as described herein, or a humanized variant thereof. In some examples, a binding protein (*e.g.,* an anti-beta klotho antibody) further comprises a scaffold region or frame work region, including a VH FR1, VH FR2, VH FR3, VH FR4, VL FR1, VL FR2, VL FR3, and/or VL FR4 of a human immunoglobulin amino acid sequence or a variant thereof.

[0012] In some examples, the antibody is a humanized antibody, a monoclonal antibody, a recombinant antibody, an antigen binding fragment or any combination thereof. In some examples, the antibody is a humanized monoclonal antibody, or antigen binding fragment thereof, that binds to a beta klotho polypeptide (*e.g.,* a cell surface-expressed or soluble beta klotho), a beta klotho fragment, or a beta klotho epitope.

[0013] The present disclosure also provides binding proteins such as anti-beta klotho antibodies (i) that competitively block (*e.g.,* in a dose-dependent manner) an anti-beta klotho antibody provided herein from binding to a beta klotho polypeptide (*e.g.,* a cell surface-expressed or soluble beta klotho), a beta klotho fragment, or a beta klotho epitope and/or (ii) that bind to a beta klotho epitope that is bound by an anti-beta klotho antibody provided herein. In other examples, the binding proteins such as anti-beta klotho antibody competitively blocks (*e.g.,* in a dose-dependent manner) monoclonal antibody 5H23 or 1G19 described herein or a humanized variant thereof from binding to a beta klotho polypeptide (*e.g.,* a cell surface-expressed or soluble beta klotho), a beta klotho fragment, or a beta klotho epitope. In other examples, the binding proteins such as anti-beta klotho antibody binds to a beta klotho epitope that is bound (*e.g.,* recognized) by monoclonal antibody 5H23, or 1G19 described herein or a humanized variant thereof.

[0014] The present disclosure also provides binding proteins, including antibodies or fragments thereof, that (i) bind to an epitope of human beta klotho and cynomologous monkey beta klotho recognized by an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO:25 and a light chain variable region having the amino acid sequence of SEQ ID NO:26; or (ii) compete for the binding to human beta klotho with an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO:25 and a light chain variable region having the amino acid sequence of SEQ ID NO:26.In some examples, binding proteins, including antibodies or fragments thereof, are provided herein that bind to a region, including an epitope, of human beta klotho or cyno beta klotho. In some examples, binding proteins, including antibodies or fragments thereof, bind to a region of human beta klotho or cycno beta klotho including, for example, those that bind to: (i) a KLB2 domain of human beta klotho comprising amino acid residues 509 to 1044 of SEQ ID NO:297; (ii) a glycosyl hydrolase 1 region of a KLB2 domain of human beta klotho comprising amino acid residues 517 to 967 of SEQ ID NO:297; (iii) a region of human beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:297; or (iv) a region of cyno beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:299.

[0015] In some examples, binding proteins, including antibodies or fragments thereof, are provided herein that bind to a specific epitope of human beta klotho, including, for example, those that bind to: (i) an epitope of human beta klotho comprising at least one of amino acid residues 657, 701 and/or 703 of human beta klotho (SEQ ID NO: 297); (ii) an epitope of human beta klotho comprising at least amino acid residue 657 of SEQ ID NO: 297; (iii) an epitope of human beta klotho comprising at least amino acid residue 701 of SEQ ID NO: 297; (iv) an epitope of human beta klotho comprising at least amino acid residue 703 of SEQ ID NO: 297; (v) an epitope of human beta klotho comprising at least amino acid residues 657 and 701 of SEQ ID NO: 297; (vi) an epitope of human beta klotho comprising at least amino acid residues 657 and 703 of SEQ ID NO: 297; (vii) an epitope of human beta klotho comprising at least amino acid residues 701 and 703 of SEQ ID NO: 297; or

(viii) an epitope of human beta klotho comprising at least amino acid residues 657, 701 and 703 of SEQ ID NO: 297. Such antibodies provided above can, in some examples, induce FGF19-like signaling and/or FGF21-like signaling or activate a beta klotho/FGF receptor complex in a cell that expresses human beta klotho and an FGF receptor. Additionally, in some examples, the antibody is a monoclonal antibody, for example, a humanized, human or chimeric antibody.

[0016] In some examples, the binding proteins such as anti-beta klotho antibodies provided herein are conjugated or recombinantly linked to a diagnostic agent, detectable agent or therapeutic agent. In some examples, the therapeutic agent is a drug, including one or more drugs such as biguanides and sulphonylureas (*e.g.,* metformin tolbutamide, chlorpropamide, acetohexamide, tolazamide, glibenclamide, glyburide, and glipizide), thiazolidinediones (*e.g.,* rosiglitazone, pioglitazone), GLP-1 analogues, PPAR gamma agonists (*e.g.,* pioglitazone and rosiglitazone), dipeptidyl peptidase-4 (DPP-4) inhibitors, (*e.g.,* JANUVIN®, ONGLYZA®) bromocriptine formulations and bile acid sequestrants (*e.g.,* colesevelam), and insulin (*e.g.,* bolus and basal analogs), alpha glucosidase inhibitors (*e.g.,* acarbose, roglibose), metformin (*e.g.,* metformin hydrochloride) with or without a thiazolidinedione (TZD), SGLT-2 inhibitors, appetite suppression or weight loss drugs (*e.g.,* Meridia® / sibutramine, Xenical® / ortistat). In some examples, the detectable agent is a radioisotope, an enzyme, a fluorescent compound, a bioluminescent compound or a chemiluminescent compound.

[0017] In certain examples, compositions are provided comprising a binding protein such as an anti-beta klotho antibody described herein. Also provided herein are pharmaceutical compositions comprising a binding protein such as an beta klotho antibody as described herein.

[0018] The present disclosure also provides isolated nucleic acid molecules encoding an immunoglobulin heavy chain, an immunoglobulin light chain, VH region, VL region, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of binding proteins (*e.g.,* anti-beta klotho antibodies) that bind to a beta klotho polypeptide, a beta klotho polypeptide fragment, or a beta klotho epitope. In some examples, the nucleic acid molecule encodes a VH region, VL region, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of a monoclonal antibody designated as 5H23, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 or 1G19 as described herein, or a humanized variant thereof. In some examples, the nucleic acid molecule further encodes a scaffold region or a framework region, including VH FR1, VH FR2, VH FR3, VH FR4, VL FR1, VL FR2, VL FR3, and/or VL FR4 of a human immunoglobulin amino acid sequence or a variant thereof. Also provided herein are vectors and host cells comprising the nucleic acid molecules encoding an a binding protein such as anti-beta klotho antibody, as well as methods of producing a binding protein such as an anti-beta klotho antibody by culturing the host cells provided herein under conditions that promote the production of a binding protein such as an anti-beta klotho antibody.

[0019] The present disclosure also provides methods of treating, preventing or alleviating a disease, disorder or condition (*e.g.,* one or more symptoms) comprising administering a therapeutically effective amount of a binding protein such as an anti-beta klotho antibody provided herein to a subject, including a subject in need thereof, thereby treating, preventing or alleviating the disease, disorder or condition. In some examples, the disease, disorder or condition is caused by or otherwise associated with beta klotho, such as those related to FGF19-like and/or FGF21-like signaling in a subject. In certain examples, the disease is treatable by lowering blood glucose, insulin or serum lipid levels (*e.g.,* Type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, metabolic syndrome).

[0020] In some examples, the disease, disorder or condition is related to glucose metabolism or lipid metabolism. In some examples, the disease, disorder or condition is selected from the group of a hyperglycemic condition. (*e.g.,* diabetes, such as Type I diabetes, Type 2 diabetes, gestational diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, metabolic syndrome, or obesity).

[0021] In some examples, the methods of treating, preventing or ameliorating include methods of improving glucose metabolism and/or methods of improving lipid metabolism. In some examples, the methods of treating, preventing or ameliorating result in reduced glucose levels (*e.g.,* reduced blood glucose), increased insulin sensitivity, reduced insulin resistance, reduced glycogen, improved glucose tolerance, improved glucose tolerance, improved glucose metabolism, improved homeostasis, improved pancreatic function, reduced triglycerides, reduced cholesterol, reduced IDL, reduced LDL, reduced VLDL, decreased blood pressure, decreased internal thickening of a blood vessel and/or decreased body mass or weight gain.

[0022] The present disclosure provides methods of treating a disease, disorder or condition associated with human FGF19 and/or human FGF21, which includes any disease, disorder or condition whose onset in a subject (*e.g.,* a patient) is caused by, at least in part, the induction of FGF19-like and/or FGF21-like signaling, which is initiated *in vivo* by the formation of a complex comprising FGFR1c, FGFR2c, FGFR3c or FGFR4 and beta klotho and FGF19 or FGF21. The severity of the disease or condition can also be decreased by the induction of FGF19-like and/or FGF21-like signaling. Examples of diseases and conditions that can be treated with the binding proteins such as anti-beta klotho antibodies include type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

[0023] As such, the binding proteins such as anti-beta klotho antibodies described herein can be used to treat type 2 diabetes, obesity, dyslipidemia (*e.g.,* hypertriglyceridemia), NASH, cardiovascular disease, and/or metabolic syndrome, as well as any disease, disorder, or condition in which it is desirable to mimic or augment the *in vivo* effects of FGF19 and/or FGF21, or can be employed as a prophylactic treatment administered, for example, daily, weekly, biweekly, monthly, bimonthly, biannually, etc. to prevent or reduce the frequency and/or severity of

symptoms (*e.g.,* elevated plasma glucose levels, elevated triglycerides and cholesterol levels), including, for example, to thereby provide an improved glycemic and/or cardiovascular risk factor profile. The present disclosure provides methods of improving metabolic parameters by administering to a subject a binding protein, including an antibody or fragment thereof as described herein or an pharmaceutical composition described herein, including, for example, wherein the improvement includes a decrease in body weight, body mass index, abdominal circumference, skinfold thickness, glucose, insulin and/or triglycerides.

[0024] The present disclosure also provides methods of inducing FGF19-like or FGF21-like signaling of cells having cell surface expression of beta kloth*o an*d one or more FGF receptors, such as FGFR1, FGFR2, FGFR3, or FGFR4 comprising contacting the cells with an effective amount of a binding protein (*e.g.,* an antibody) that binds to beta klotho as described herein. In some examples, the cell is an adipocyte or hepatocyte. In other examples, the cell is a cell transfected with a gene encoding beta klotho and optionally a gene encoding an FGF receptor. Additional methods provided include using an anti-beta klotho antibody as described herein, with activity to mediate FGF19-like and/or FGF21 like signaling effects.

[0025] The present disclosure also provides methods of modulating an FGF19-like or FGF21-like signaling in a subject comprising administering an effective amount of a binding protein such as an anti-beta klotho antibody as described herein to a subject, including a subject in need thereof. In some examples, the modulating comprises FGF19-like activation. In some examples, the modulating comprises FGF21-like activation. In some examples, the modulating comprises increasing glucose metabolism (*e.g.,* reducing glucose levels such as blood glucose levels).

[0026] The present disclosure also provideds methods for detecting beta klotho in a sample comprising contacting the sample with a binding protein such as an anti-beta klotho antibody as described herein, that comprises a detectible agent. In certain examples, the sample comprises a cell expressing beta klotho on its surface.

[0027] The present disclosure also provides kits comprising a binding protein such as an anti-beta klotho antibody that binds to a beta klotho polypeptide, a beta klotho fragment or a beta klotho epitope as described herein.

## BRIEF DESCRIPTION OF THE FIGURES

[0028] Figure 1A-1B shows a sequence alignment of the heavy chain variable regions and light chain variable regions of the anti-beta klotho antibodies designated 5H23, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 and 1G19. Boundaries of CDRs are indicated by Kabat, AbM, Chothia, Contact and IMGT numbering.

[0029] Figure 2A-1 and 2A-2 shows sequence alignments of the heavy chain variable regions of the anti-beta klotho antibodies providing consensus CDR

WHAT IS CLAIMED:

1. An antibody or antigen-binding fragment thereof that (i) binds to an epitope of human beta klotho and cynomolgus monkey beta klotho recognized by an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO:25 and a light chain variable region having the amino acid sequence of SEQ ID NO:26; or (ii) competes for the binding to human beta klotho with an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO:25 and a light chain variable region having the amino acid sequence of SEQ ID NO:26.

2. The antibody or the antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof binds to an epitope comprising:

(i) at least one of amino acid residues 657, 701 and/or 703 of the human beta klotho;

(ii) at least two of amino acid residues 657, 701 and/or 703 of the human beta klotho; or

(iii) amino acid residues 657, 701 and 703 of the human beta klotho.

3. The antibody or the antigen-binding fragment thereof of claims 1 or 2, wherein the antibody or the antigen-binding fragment thereof induces FGF19-like signaling and/or FGF21-like signaling in a cell that expresses human beta klotho and an FGF receptor.

4. An antibody or an antigen-binding fragment thereof that binds to human beta klotho, wherein the antibody or the antigen-binding fragment thereof comprises: a heavy chain variable region (VH) comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:271, and a light chain variable region (VL) comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:276.

5. The antibody or the antigen-binding fragment thereof of claim 4, wherein:

(a) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:12, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:2, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:3, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:4, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:5, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:6;

(b) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:7, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:8, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:9; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:10, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:11, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:6;

(c) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:12, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:2, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:3; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:4, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:5, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:6;

(d) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:13, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:14, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:15; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:16, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:11, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:17;

(e) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:18, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:19, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:20; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:21, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:22, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:23; or

(f) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:1, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:24, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:3; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:4, the VL CDR2 comprises the amino acid

sequence of SEQ ID NO:5, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:6.

6. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VH has at least 80% sequence identity to SEQ ID NO:25.

7. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VL has at least 80% sequence identity to SEQ ID NO:26.

8. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:25 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:26.

9. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VH comprises the amino acid sequence of SEQ ID NO:25.

10. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VL comprises the amino acid sequence of SEQ ID NO:26.

11. The antibody or the antigen-binding fragment thereof of claim 4, wherein the VH comprises the amino acid sequence of SEQ ID NO:25 and the VL comprises the amino acid sequence of SEQ ID NO:26.

12. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:271 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:276.

13. The antibody or the antigen-binding fragment thereof of claim 4, 5 or 12, wherein the VH comprises the amino acid sequence of SEQ ID NO:271.

14. The antibody or the antigen-binding fragment thereof of claim 4,5 or 12, wherein the VL comprises the amino acid sequence of SEQ ID NO:276.

15. An antibody or an antigen-binding fragment thereof that binds to human beta klotho, wherein the antibody or the antigen-binding fragment comprises a VH comprising the amino acid sequence of SEQ ID NO:271 and a VL comprising the amino acid sequence of SEQ ID NO:276.

16. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the antibody comprises a heavy chain comprising amino acids 23-472 of the amino acid sequence of SEQ ID NO:317.

17. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the antibody comprises a light chain comprising amino acids 23-240 of the amino acid sequence of SEQ ID NO:319.

18. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the antibody comprises (i) a heavy chain that is 90% identical to amino acids 23-472 of the amino acid sequence of SEQ ID NO:317, and (ii) a light chain that is 90% identical to amino acids 23-240 of the amino acid sequence of SEQ ID NO:319.

19. An antibody that binds human beta klotho, wherein the antibody comprises a heavy chain comprising amino acids 23-472 of the amino acid sequence of SEQ ID NO:317 and a light chain comprising amino acids 23-240 of the amino acid sequence of SEQ ID NO:319.

20. An antibody or an antigen-binding fragment thereof that binds to human beta klotho, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:51, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:52;

(b) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:77, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:78;

(c) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:103, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:104;

(d) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:129, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:130;

(e) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:155, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:156;

(f) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:181, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:182;

(g) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:207, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:208;

(h) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:233, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:234; or

(i) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:259, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:260.

21. The antibody or an antigen-binding fragment thereof of claim 20, wherein:

(a) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:27, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:28, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:29, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:30, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:31, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:32;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:33, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:34, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:35, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:36, the VL CDR2

comprises the amino acid sequence of SEQ ID NO:37, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:32;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:38, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:28, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:29, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:30, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:31, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:32;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:39, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:40, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:41, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:42, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:37, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:43;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:44, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:45, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:46, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:47, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:48, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:49; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:27, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:50, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:29, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:30, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:31, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:32;

(b) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:53, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:54, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:55, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:56, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:57, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:58;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:59, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:60,

the VH CDR3 comprises the amino acid sequence of SEQ ID NO:61, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:62, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:63, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:58;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:64, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:54, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:55, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:56, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:57, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:58;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:65, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:66, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:67, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:68, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:63, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:69;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:70, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:71, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:72, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:73, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:74, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:75; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:53, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:76, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:55, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:56, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:57, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:58;

(c) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:79, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:80, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:81, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:82, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:83, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:84;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:85, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:86, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:87, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:88, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:89, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:84;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:90, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:80, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:81, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:82, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:83, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:84;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:91, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:92, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:93, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:94, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:89, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:95;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:96, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:97, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:98, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:99, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:100, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:101; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:79, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:102, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:81, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:82, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:83 and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:84;

(d) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:105, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:106, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:107, the VL CDR1 comprises the amino acid sequence of SEQ ID

NO:108, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:109, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:110;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:111, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:112, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:113, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:114, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:115, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:110;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:116, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:106, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:107, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:108, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:109, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:110;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:117, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:118, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:119, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:120, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:115, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:121;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:122, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:123, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:124, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:125, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:126, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:127; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:105, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:128, the VH CDR3 comprises the amino acid sequence of SEQ ID

NO:107, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:108, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:109, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:110;

(e) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:131, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:132, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:133, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:134, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:135, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:136;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:137, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:138, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:139, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:140, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:141, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:136;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:142, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:132, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:133, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:134, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:135, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:136;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:143, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:144, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:145, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:146, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:141, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:147;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:148, the VH CDR2 comprises the amino acid sequence of SEQ ID

NO:149, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:150, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:151, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:152, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:153; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:131, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:154, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:133, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:134, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:135, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:136;

(f) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:157, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:158, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:159, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:160, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:161, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:162;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:163, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:164, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:165, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:166, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:167, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:162;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:168, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:158, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:159, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:160, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:161, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:162;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:169, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:170, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:171, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:172, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:167, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:173;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:174, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:175, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:176, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:177, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:178, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:179; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:157, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:180, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:159, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:160, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:161, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:162;

(g) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:183, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:184, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:185, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:186, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:187, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:188;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:189, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:190, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:191, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:192, the VL CDR2 comprises the amino acid sequence of SEQ ID

NO:193, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:188;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:194, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:184, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:185, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:186, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:187, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:188;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:195, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:196, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:197, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:198, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:193, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:199;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:200, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:201, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:202, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:203, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:204, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:205; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:183, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:206, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:185, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:186, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:187, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:188;

(h) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:209, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:210, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:211, the VL CDR1 comprises the amino acid sequence of SEQ ID

NO:212, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:213, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:214;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:215, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:216, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:217, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:218, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:219, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:214;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:220, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:210, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:211, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:212, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:213, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:214;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:221, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:222, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:223, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:224, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:219, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:225;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:226, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:227, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:228, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:229, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:230, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:231; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:209, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:232, the VH CDR3 comprises the amino acid sequence of SEQ ID

NO:211, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:212, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:213, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:214; or

(i) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:235, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:236, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:237, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:238, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:239, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:240;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:241, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:242, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:243, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:244, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:245, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:240;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:246, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:236, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:237, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:238, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:239, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:240;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:247, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:248, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:249, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:250, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:245, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:251;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:252, the VH CDR2 comprises the amino acid sequence of SEQ ID

NO:253, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:254, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:255, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:256, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:257; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:235, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:258, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:237, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:238, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:239, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:240.

22. The antibody or the antigen-binding fragment thereof of claim 20 or 21, wherein:

(a) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:51 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:52;

(b) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:77 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:78;

(c) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:103 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:104;

(d) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:129 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:130;

(e) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:155 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:156;

(f) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:181 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:182;

(g) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:207 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:208;

(h) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:233 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:234; or

(i) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:259 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:260.

23. The antibody or the antigen-binding fragment thereof of claim 20 or 21, wherein:

(a) the VH comprises the amino acid sequence of SEQ ID NO:51 and the VL comprises the amino acid sequence of SEQ ID NO:52;

(b) the VH comprises the amino acid sequence of SEQ ID NO:77 and the VL comprises the amino acid sequence of SEQ ID NO:78;

(c) the VH comprises the amino acid sequence of SEQ ID NO:103 and the VL comprises the amino acid sequence of SEQ ID NO:104;

(d) the VH comprises the amino acid sequence of SEQ ID NO:129 and the VL comprises the amino acid sequence of SEQ ID NO:130;

(e) the VH comprises the amino acid sequence of SEQ ID NO:155 and the VL comprises the amino acid sequence of SEQ ID NO:156;

(f) the VH comprises the amino acid sequence of SEQ ID NO:181 and the VL comprises the amino acid sequence of SEQ ID NO:182;

(g) the VH comprises the amino acid sequence of SEQ ID NO:207 and the VL comprises the amino acid sequence of SEQ ID NO:208;

(h) the VH comprises the amino acid sequence of SEQ ID NO:233 and the VL comprises the amino acid sequence of SEQ ID NO:234; or

(i) the VH comprises the amino acid sequence of SEQ ID NO:259 and the VL comprises the amino acid sequence of SEQ ID NO:260.

24. The antibody or the antigen-binding fragment of claims 1-8, 12-18, and 20-22, which is a humanized antibody.

25. The antibody or the antigen-binding fragment of any one of claims 1-18 and 20-24, which is a chimeric antibody.

26. The antibody or the antigen-binding fragment thereof of any one of claims 1-15 and 20-23, wherein the antigen-binding fragment is an Fab, Fab', F(ab')2, Fv, scFv, (scFv)2, single chain antibody molecule, dual variable region antibody, or linear antibody, or wherein the antibody is a bispecific antibody.

27. An isolated polynucleotide or polynucleotides encoding the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19.

28. An expression vector or vectors: (i) encoding the antibody an antigen-binding fragment thereof of any of claims 1-18 and 20-26 or the antibody of claim 19, or (ii) comprising the polynucleotide or polynucleotides of claim 27.

29. An isolated cell producing the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19.

30. An isolated cell comprising the polynucleotide or polynucleotides of claim 27 or the expression vector or vectors of claim 28.

31. A pharmaceutical composition comprising the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19, and a pharmaceutically acceptable carrier.

32. Use of the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19 in the manufacture of a medicament for improving glucose metabolism or improving lipid metabolism in a subject.

33. Use of the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19 in the manufacture of a medicament for treating Type 2 diabetes, gestational diabetes, insulin resistance,

hyperinsulinemia, glucose intolerance, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), obesity, dyslipidemia, Type 1 diabetes, cardiovascular disease, or metabolic syndrome in a subject.

34. Use of the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19 in the manufacture of a medicament for inducing FGF19-like signaling and/or FGF21-like signaling in a subject.

35. The use of claim 32, wherein improvement in glucose metabolism or improvement of lipid metabolism in the subject results in:

(a) reduced glucose levels;
(b) increased insulin sensitivity;
(c) reduced insulin resistance;
(d) improved glucose tolerance;
(e) improved pancreatic function;
(f) reduced triglycerides;
(g) reduced cholesterol;
(h) reduced IDL, LDL, or VLDL;
(i) decreased blood pressure; or
(j) decreased body mass.

36. The use of claim 35, wherein the subject has Type 2 diabetes, gestational diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), dyslipidemia, Type 1 diabetes, cardiovascular disease, or metabolic syndrome; or wherein the subject is obese.

37. The use of any one of claims 32-36, wherein the antibody or the antigen-binding fragment is to be used in combination with one or more additional therapeutic agents.

38. The use of claim 37, wherein the one or more additional therapeutic agents is selected from the group consisting of biguanides, sulphonylureas,

thiazolidinediones, GLP-1 analogues, PPAR gamma agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, bromocriptine, bile acid sequestrants, insulin, alpha glucosidase inhibitors, metformin, SGLT-2 inhibitors, appetite suppression agents, and weight loss drugs.

39. The use of any one of claims 32-38, wherein the subject is human.

40. A method of making the antibody or antigen-binding fragment thereof of any one of claims 1 to 18 and 20-26 or the antibody of claim 19, comprising (a) culturing the cell of claim 29 or 30 and (b) isolating the antibody or antigen-binding fragment thereof.

41. The method of claim 40, further comprising formulating the antibody or antigen-binding fragment thereof as a sterile pharmaceutical composition.

42. An antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19 for use in therapy.