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 inventin refers to the subject matter as defined in the attached set of claims. ~~The present disclosure provides~~Further disclosed herein are 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.

[0010] In some ~~embodiments~~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 example~~embodiments~~, 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 example~~embodiments~~, 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 example~~embodiments~~, a binding protein (*e.g.,* an anti-beta klotho antibody) comprises six CDRs or less than six CDRs. In some example~~embodiments~~, 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 example~~embodiments~~, 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 example~~embodiments~~, 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 example~~embodiments~~, the antibody is a humanized antibody, a monoclonal antibody, a recombinant antibody, an antigen binding fragment or any combination thereof. In some example~~embodiments~~, 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 exampleembodiments, 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 exampleembodiments, 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 exampleembodiments, 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 exampleembodiments, 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 exampleembodiments, 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 embodiments, 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 example~~embodiment~~s, the antibody is a monoclonal antibody, for example, a humanized, human or chimeric antibody.

[0016] In some example~~embodiment~~s, 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 example~~aspect~~s, 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 example~~aspect~~s, the detectable agent is a radioisotope, an enzyme, a fluorescent compound, a bioluminescent compound or a chemiluminescent compound.

[0017] In certain example~~embodiment~~s, 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 exampleembodiments, 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 exampleembodiments, 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 exampleembodiments, 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 exampleembodiments, 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 exampleembodiments, the disease, disorder or condition is related to glucose metabolism or lipid metabolism. In some exampleembodiments, 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 exampleembodiments, the methods of treating, preventing or ameliorating include methods of improving glucose metabolism and/or methods of improving lipid metabolism. In some exampleembodiments, the methods of treating, preventing or

[0024] The present disclosure also provides methods of inducing FGF19-like or FGF21-like signaling of cells having cell surface expression of beta klotho *and* 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 exampleembodiments, the cell is an adipocyte or hepatocyte. In other exampleembodiments, 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 exampleembodiments, the modulating comprises FGF19-like activation. In some exampleembodiments, the modulating comprises FGF21-like activation. In some exampleembodiments, 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 exampleembodiments, 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

120. A pharmaceutical composition that comprises the antibody or fragment thereof of any one of claims 1-108, and a pharmaceutically acceptable carrier.

121. An *in vitro* method of inducing FGF19-like and/or FGF21-like signaling in cells that express beta klotho and an FGF receptor, the method comprising contacting the cells with the antibody or fragment of any one of claims 1-108.

122. An *in vitro* method for activating a beta klotho/FGF receptor complex in cells that express a beta klotho and an FGF receptor comprising contacting the cells with the antibody or fragment of any one of claims 1-108

123. The *in vitro* method of claim 121 or 122, wherein the cells express human beta klotho and a human FGF receptor IC.

124. Use of the antibody or fragment thereof of any one of Claims 1-108 or the pharmaceutical composition of claim 120 in the manufacture of a medicament ~~A method~~ for improving glucose metabolism in a subject ~~comprising administering to the subject the antibody or fragment thereof of any one of Claims 1-108 or the pharmaceutical composition of claim 120~~.

125. The ~~method~~ use of claim 124, wherein the improvement is glucose metabolism is reduced glucose levels, increased insulin sensitivity, reduced insulin resistance, reduced glucagon, improved glucose tolerance, and/or improved pancreatic function.

126. The ~~method~~ use of claim 124, wherein the subject is to be administered one or more therapeutic agents in combination with the antibody or fragment thereof, wherein the therapeutic agent is an analgesic agent, an anesthetic agent, an antibiotic, or an immunomodulatory agent.

127. The ~~method~~ use of claim 126, wherein the one or more therapeutic agents is selected from non-steroidal anti-inflammatory drugs (NSAID), propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams, salicylates or pyrazolones.

128. The ~~method~~ use of claim 126, wherein the one or more therapeutic agents is selected from biguanides and sulphonylureas, thiazolidinediones, GLP-1

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

129. The ~~method~~ use of claim 124 wherein the improvement in glucose metabolism is associated with lowered blood glucose levels.

130. A method of detecting the presence of beta klotho in a biological sample, comprising contacting the biological sample with an antibody of any one of claims 1-108 under conditions permissive for binding of the antibody to beta klotho, and detecting whether a complex is formed between the antibody and beta klotho.

131. The method of claim 130, wherein the biological sample is from a mammal having or suspected of having Type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, or metabolic syndrome.

~~132. Use of the antibody or fragment thereof of any one of claims 1-108 in the manufacture of a medicament, wherein the medicament is for use in a disease, disorder, or condition, in a subject comprising administering the antibody or fragment to the subject.~~

~~133. Use of the pharmaceutical composition of claim 120 in the manufacture of a medicament, wherein the medicament is for use in a in a disease, disorder, or condition, in a subject, the method comprising administering the pharmaceutical composition to the subject.~~

~~134~~132. Use of an antibody or fragment thereof of any one of claims 1-108 in the manufacture of a composition, wherein the composition is for use in a method for detecting the presence of beta klotho in a biological sample, the method comprising contacting the biological sample with the antibody under conditions permissive for binding of the antibody to beta klotho, and detecting whether a complex is formed between the antibody and beta klotho.

~~135~~133. An antibody or fragment thereof which binds to human beta klotho, wherein the antibody binds to a KLB2 domain of human beta klotho comprising amino acid residues 509 to 1044 of SEQ ID NO:297.

~~136~~134. An antibody or fragment thereof which binds to human beta klotho, wherein the antibody binds to 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.

~~137~~135. An antibody or fragment thereof which binds to human beta klotho, wherein the antibody binds a region of human beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:297.

~~138~~136. An antibody or fragment thereof which binds to cyno beta klotho, wherein the antibody binds a region of cyno beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:299.

~~139~~137. An antibody or fragment thereof that binds to human beta klotho, wherein the antibody binds an epitope of human beta klotho comprising at least one of amino acid residues 657, 701 and/or 703 of SEQ ID NO: 297, wherein the antibody induces FGF19-like signaling and/or FGF21-like signaling in a cell that expresses human beta klotho and an FGF receptor or wherein the antibody activates a beta klotho/FGF receptor complex in a cell that expresses human beta klotho and an FGF receptor.

~~140~~138. The antibody or fragment thereof of claim ~~139~~136, wherein the epitope of human beta klotho comprise at least amino acid residue 657 of SEQ ID NO: 297.

~~141~~139. The antibody or fragment thereof of claim ~~139~~136, wherein the epitope of human beta klotho comprise at least amino acid residue 701 of SEQ ID NO: 297.

~~142~~140. The antibody or fragment thereof of claim ~~139~~137, wherein the epitope of human beta klotho comprise at least amino acid residue 703 of SEQ ID NO: 297.

~~143~~141. The antibody or fragment thereof of claim ~~139~~137, wherein the epitope of human beta klotho comprise at least amino acid residues 657 and 701 of SEQ ID NO: 297.

~~144~~142. The antibody or fragment thereof of claim ~~139~~137, wherein the epitope of human beta klotho comprise at least amino acid residues 657 and 703 of SEQ ID NO: 297.

~~145~~143. The antibody or fragment thereof of claim ~~139~~137, wherein the epitope of human beta klotho comprise at least amino acid residues 701 and 703 of SEQ ID NO: 297.

~~146~~144. The antibody or fragment thereof of claim ~~139~~137, wherein the epitope of human beta klotho comprise at least amino acid residues 657, 701 and 703 of SEQ ID NO: 297.

~~147~~145. The antibody or fragment thereof of any one of claims ~~135~~133-~~146~~144, wherein the antibody or fragment thereof is a monoclonal antibody.

~~148~~146. The antibody or fragment thereof of any one of claims ~~135~~133-~~147~~145, wherein the antibody or fragment thereof is a humanized, human or chimeric monoclonal antibody.

~~149~~147. The antibody or fragment thereof of any one of claims ~~135~~133-~~148~~146, wherein the antibody or fragment thereof is an agonist antibody.

~~150~~148. The antibody or fragment thereof of claim ~~149~~147, wherein the agonist antibody or fragment thereof induces FGF19-like signaling and/or FGF21-like signaling of an FGF receptor.

~~151~~149. The antibody or fragment thereof of claim ~~149~~147, wherein the agonoist antibody activates a beta klotho/FGF receptor complex.

~~152~~150. A pharmaceutical composition that comprises the antibody or fragment thereof of any one of claims ~~135~~133-~~151~~149, and a pharmaceutically acceptable carrier.

~~153~~151. Use of the antibody or fragment thereof of any one of claims 1-108 and 133-149 or the pharmaphceutical composition of claim 120 or 150 in the manufacture of a medicament for ~~A method of~~ treating Type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, or metabolic syndrome in a subject ~~comprising administering to a subject the antibody or fragment thereof of any one of claims 1-108 and 135-151 or the pharmaphceutical composition of claim 120 or 152~~.

~~154~~152. Use of the antibody or fragment thereof of any one of claims 1-108 and 133-149 or the pharmaphceutical composition of claim 120 or 150 in the manufacture of a medicament for ~~A method of~~ improving metabolic parameters ~~comprising administering to a subject the antibody or fragment thereof of any one of claims 1-108 and 135-151 or the pharmaphceutical composition of claim 120 or 152~~.

~~155~~153. The ~~method~~ use of claim ~~154~~152, wherein the improvement of metabolic parameters is a decrease in body weight, body mass index, abdominal circumference, skinfold thickness, glucose, insulin and/or triglycerides.

~~156~~154. The ~~method~~ use of any one of claims ~~153~~151-~~155~~153, wherein the subject is to be administered one or more therapeutic agents in combination with the antibody or fragment thereof, wherein the therapeutic agent is an analgesic agent, an anesthetic agent, an antibiotic, or an immunomodulatory agent.

~~157~~155. The ~~method~~ use of any one of claims ~~153~~151-~~155~~153, wherein the one or more therapeutic agents is selected from non-steroidal anti-inflammatory drugs (NSAID), propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams, salicylates or pyrazolones.

~~158~~156. The ~~method~~ use of any one of claims ~~153~~151-~~155~~153, wherein the one or more therapeutic agents is selected from biguanides and sulphonylureas, thiazolidinediones, GLP-1 analogues, PPAR gamma agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, bromocriptine formulations, bile acid sequestrants, insulin, alpha glucosidase inhibitors, metformin, SGLT-2 inhibitors, appetite suppression or weight loss drugs.