BINDING PROTEINS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of United States Provisional Application Serial No. 61/931,531, filed January 24, 2014, the entire contents of which are incorporated herein by reference.

FIELD

[0002] The present disclosure relates generally to binding proteins, such as antibodies, that bind to beta klotho, including human beta klotho, and methods of their use.

BACKGROUND

[0003] Beta klotho, which belongs to the Klotho family, is a single-pass type I membrane protein. Beta klotho has an extracellular domain consisting of two internal repeats which share homology with members of the family 1 glycosidases but lack glucosidase catalytic activity. Beta klotho expression is primarily detected in the liver, pancreas and adipose tissue. Ito and colleagues have reported that beta klotho-deficient (KLB-/-) mice have elevated mRNA levels of CYP7A1 and CY8B1 and exhibit increased synthesis and excretion of bile acid (Ito *et al.*, 2005, J Clin Invest 115: 2202–2208). Beta klotho forms a complex with fibroblast growth factor (FGF) receptors and functions as a co-receptor for FGFs, including FGF19 and FGF21.

[0004] Twenty-two members of the human FGF family have been identified and four tyrosine kinase receptors that bind to FGF (FGFR1-FGFR4) have been identified. The interaction between FGF and its receptor results in FGFR dimerization, which enables the cytoplasmic domains of the receptor to transphosphorylate and become activated, which in turn leads to the phosphorylation and activation of downstream signaling molecules.

[0005] The high affinity receptor for FGF19 is FGFR4 and the binding of FGF19 to FGFR4 is facilitated by beta klotho. It has been reported that FGF19 transgenic mice have decreased adiposity, increased metabolic rate, reduced liver triglycerides, increased fatty acid oxidation, reduced glucose levels and increased insulin

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.

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

[0016] In some embodiments, 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 aspects, 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 aspects, the detectable agent is a radioisotope, an enzyme, a fluorescent compound, a bioluminescent compound or a chemiluminescent compound.

[0017] In certain embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the disease, disorder or condition is related to glucose metabolism or lipid metabolism. In some embodiments, 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 embodiments, the methods of treating, preventing or ameliorating include methods of improving glucose metabolism and/or methods of improving lipid metabolism. In some embodiments, 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 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 embodiments, the cell is an adipocyte or hepatocyte. In other *embo*diments, 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 embodiments, the modulating comprises FGF19-like activation. In some embodiments, the modulating comprises FGF21-like activation. In some embodiments, 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 embodiments, 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

sequences. Top grouping consists of antibodies designated 5H23, 1D19, 2L12, 3L3, 4P5, 5C23 and 5F7. Lower grouping consists of antibodies designated 1C17 and 1G19. Bottom grouping consists only of the antibody designated 3N20 Variable residues are presented by "X." Boundaries of CDRs are indicated by Kabat, AbM, Chothia, Contact and IMGT numbering.

[0030] Figure 2B-1 and 2B-2 shows sequence alignments of the light chain variable regions of the anti-beta klotho antibodies providing consensus CDR sequences. Top grouping consists of antibodies designated 5H23, 1D19, 2L12, 3L3, 4P5, 5C23 and 5F7. Lower grouping consists of antibodies designated 1C17 and 1G19. Bottom grouping consists only of the antibody designated 3N20. Variable residues are presented by "X." Boundaries of CDRs are indicated by Kabat, AbM, Chothia, Contact and IMGT numbering.

[0031] Figure 3A-1 and 3A-2 shows a sequence alignment of the heavy chain variable region of anti-beta klotho antibody designated 5H23 with the humanized sequences (vH1-vH9). Residues that are bolded indicate exemplary residues that have been modified from the original antibody. Residues that are bolded and underlined indicate residues altered back to a mouse residue.

[0032] Figure 3B shows a sequence alignment of the light chain variable region of anti-beta klotho antibody designated 5H23 with the humanized sequences (vL1-vL5). Residues that are bolded indicate exemplary residues that have been modified. Residues that are bolded and underlined indicate residues altered back to a mouse residue.

[0033] Figure 3C-1 and 3C-2 shows a sequence alighnment of the light chain variable region of anti-beta klotho antibody designated 5H23 with the humanized sequences (v1-39a- v1-39p). Residues that are bolded indicate exemplary residues that have been modified.

[0034] Figure 3D-1 and 3D-2 shows a sequence alignment of a light chain variable region of anti-beta klotho antibody designated 5H23 with various humanized sequences (v3-20a- v3-20j). Residues that are bolded indicate exemplary residues that have been modified.

[0035] Figure 4A-4C shows a sequence alignment between human, mouse and chimeric beta klotho polypeptides. Chimeric polypeptide chMoHu indicates mouse

KLB(M1-F506)-human KLB(S509-S1044). Chimeric polypeptide chHuMo indicates human KLB (M1-F508)-mouse KLB (P507-S1043). Residues corresponding to mouse residues are bolded and italicized.

[0036] Figure 5A-5F shows a sequence alignment between beta klotho polypeptides from various species described herein.

[0037] Figure 6 shows a three-dimentional model of the three identified binding residues (dark spheres) at the equivalent positions on human cytosolic beta-glucosidase. The structure shows the equivalent of Klotho-beta residues 521-963.

DETAILED DESCRIPTION

[0038] Binding proteins, such as antibodies that bind beta klotho, including human and/or cyno beta klotho, are provided herein. A unique property of such binding proteins, including antibodies disclosed herein, is their agonistic nature, including the ability to mimic the *in vivo* effect of FGF19 and/or FGF21 and to induce FGF19-like signaling and/or FGF21-like signaling. More remarkably and specifically, some of the binding proteins such as antibodies to beta klotho disclosed herein (i) bind to human and cyno beta klotho, (ii) do not compete for binding with FGF19 and/or FGF21, and (iii) induce FGF19-like signaling and/or FGF21-like signaling, including, for example, in several *in vitro* cell-based assays. Such assays may include (1) an ELK-luciferase reporter assay (see, *e.g.,* Example 4); (2) a recombinant FGF19 receptor mediated cell assay for ERK-phosphorylation (see, *e.g.,* Example 4); and (3) a human adipocyte assay for ERK-phosphorylation (see, *e.g.,* Example 5). Binding proteins such as anti-beta klotho antibodies, as described herein, therefore are expected to exhibit activities *in vivo* that are consistent with the natural biological function of FGF19 and/or FGF21. This property makes the disclosed binding proteins, including anti-beta klotho antibodies, viable therapeutics for the treatment of metabolic diseases (*e.g.,*Type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, metabolic syndrome) and broadly any disease, disorder, or condition in which it is desirable to mimic or augment the *in vivo* effects of FGF19 and/or FGF21.

[0039] The binding proteins, such as antibodies that bind beta klotho, that are provided herein share the common feature of competing with each other for the

bindng of beta klotho (see, *e.g.*, Example 3 describing antibodies in the 5H23 epitope bin). This competitive inhibition indicates that each antibody binds to the same region of beta klotho (*e.g.*, the same epitope), thereby asserting similar effects. The anti-beta klotho antibodies provided herein include humanized anti-beta klotho antibodies, including humanized anti-beta klotho antibodies derived from or based on 5H23, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 and/or 1G19 having CDR sequence as described in Tables 1-10 or Figures 1-3, such as anti-beta klotho antibodies, including humanized anti-beta klotho antibodies, bind to a specific domain of human beta klotho (*e.g.*, KL2 (residues S509-S1044); see Example 9). Moreover, such binding can be largely attributed to particular amino acid residues within the KL2 region (*e.g.*, H657, Y701 and R703), which comprise the epitope recognized by the anti-beta klotho antibodies described herein. Taken together, the results described herein demonstrate that the effects observed for an anti-beta klotho antibody that is derived from or based on 5H23 or an antibody in the 5H23 eptitope bin, including an antibody having one or more CDRs described in Tables 1-10 or Figures 1-3, can be extrapolated to other anti-beta klotho antibodies described herein having the same or similar eptitope specificity (*e.g.*, the same or similar CDRs). For example, the *in vitro* activities of antibodies as shown in Examples 4-7 and 9, as well as the *in vivo* effects demonstrated in Example 8 for an exemplary humanized anti-beta klotho antibody, are representative of the activites and effects of the the anti-beta klotho antibodies described herein.

[0040] In some embodiments of the present disclosure, the binding proteins such as anti-beta klotho antibodies may comprise immunoglobulin variable regions which comprise one or more complementary determining regions (CDRs) as described in Tables 1-10. In such binding proteins (*e.g.,* anti-beta klotho antibodies), the CDRs may be joined with one or more scaffold regions or framework regions, which orient(s) the CDR(s) such that the proper antigen binding properties of the CDR(s) is achieved. Such binding proteins, including anti-beta klotho antibodies as described herein, can facilitate or enhance the interaction between FGFR1c and beta klotho, and can induce FGF19-like and/or FGF21-like signaling.

General Techniques

[0041] Techniques and procedures described or referenced herein include those that are generally well understood and/or commonly employed using conventional

methodology by those skilled in the art, such as, for example, the widely utilized methodologies described in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual 3rd. edition (2001) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Current Protocols in Molecular Biology (F. M. Ausubel, *et al.* eds., (2003)); Therapeutic Monoclonal Antibodies: From Bench to Clinic, Z. An, ed, Wiley, Hoboken N.J. (2009); Monoclonal Antibodies: Methods and Protocols, M. Albitar, ed., Humana Press, Totawa, N.J. (2010); and Antibody Engineering, 2nd Ed., Vols 1 and 2, Kontermann and Dubel, eds., Springer-Verlag, Heidelberg, 2010.

TERMINOLOGY

[0042] Unless described otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. For purposes of interpreting this specification, the following description of terms will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that any description of terms set forth conflicts with any document incorporated herein by reference, the description of term set forth below shall control.

[0043] The term “beta klotho” or “beta klotho polypeptide” and similar terms refers to a polypeptide (“polypeptide,” and “protein” are used interchangeably herein) or any native beta klotho from any vertebrate source, including mammals such as primates (*e.g.,* humans, cynomolgus monkey (cyno)), dogs, and rodents (*e.g.,* mice and rats), unless otherwise indicated, and, in certain embodiments, included related beta klotho polypeptides, including SNP variants thereof. Beta klotho comprises two domains, beta klotho 1 (KLB1) and beta klotho 2 (KLB2). Each beta klotho domain comprises a glycosyl hydrolase 1 region. For example, the KLB1 domain of human beta klotho comprises amino acid residues 1-508 with the glycosyl hydrolase 1 region comprising amino acid residues 77-508, and the KLB2 domain of human beta klotho comprises amino acid residues 509-1044 with the glycosyl hydrolase 1 region comprising amino acid residues 517-967. The amino acid sequence of human beta klotho is provided below:

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  1 MKPGCAAGSP GNEWIFFSTD EITTRYRNTM SNGGLQRSVI LSALILLRAV
 51 TGFSGDGRAI WSKNPNFTPV NESQLFLYDT FPKNFFWGIG TGALQVEGSW
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  101 KKDGKGPSIW DHFIHTHLKN VSSTNGSSDS YIFLEKDLSA LDFIGVSFYQ
  151 FSISWPRLFP DGIVTVANAK GLQYYSTLLD ALVLRNIEPI VTLYHWDLPL
  201 ALQEKYGGWK NDTIIDIFND YATYCFQMFG DRVKYWITIH NPYLVAWHGY
  251 GTGMHAPGEK GNLAAVYTVG HNLIKAHSKV WHNYNTHFRP HQKGWLSITL
  301 GSHWIEPNRS ENTMDIFKCQ QSMVSVLGWF ANPIHGDGDY PEGMRKKLFS
  351 VLPIFSEAEK HEMRGTADFF AFSFGPNNFK PLNTMAKMGQ NVSLNLREAL
  401 NWIKLEYNNP RILIAENGWF TDSRVKTEDT TAIYMMKNFL SQVLQAIRLD
  451 EIRVFGYTAW SLLDGFEWQD AYTIRRGLFY VDFNSKQKER KPKSSAHYYK
  501 QIIRENGFSL KESTPDVQGQ FPCDFSWGVT ESVLKPESVA SSPQFSDPHL
  551 YVWNATGNRL LHRVEGVRLK TRPAQCTDFV NIKKQLEMLA RMKVTHYRFA
  601 LDWASVLPTG NLSAVNRQAL RYYRCVVSEG LKLGISAMVT LYYPTHAHLG
  651 LPEPLLHADG WLNPSTAEAF QAYAGLCFQE LGDLVKLWIT INEPNRLSDI
  701 YNRSGNDTYG AAHNLLVAHA LAWRLYDRQF RPSQRGAVSL SLHADWAEPA
  751 NPYADSHWRA AERFLQFEIA WFAEPLFKTG DYPAAMREYI ASKHRRGLSS
  801 SALPRLTEAE RRLLKGTVDF CALNHFTTRF VMHEQLAGSR YDSDRDIQFL
  851 QDITRLSSPT RLAVIPWGVR KLLRWVRRNY GDMDIYITAS GIDDQALEDD
  901 RLRKYYLGKY LQEVLKAYLI DKVRIKGYYA FKLAEEKSKP RFGFFTSDFK
  951 AKSSIQFYNK VISSRGFPFE NSSSRCSQTQ ENTECTVCLF LVQKKPLIFL
 1001 GCCFFSTLVL LLSIAIFQRQ KRRKFWKAKN LQHIPLKKGK RVVS
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(SEQ ID NO: 297)

[0044] An encoding nucleic acid sequence of human beta klotho is provided below:

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atgaagccaggctgtgcggcaggatctccagggaatgaatggattttcttcagcactgatga
aataaccacacgctataggaatacaatgtccaacgggggattgcaaagatctgtcatcctgt
cagcacttattctgctacgagctgttactggattctctggagatggaagagctatatggtct
aaaaatcctaatttactccggtaaatgaaagtcagctgtttctctatgacactttccctaa
aaacttttctggggtattgggactggagcattgcaagtggaagggagttggaagaaggatg
gaaaaggaccttctatatgggatcatttcatccacacacaccttaaaaatgtcagcagcacg
aatggttccagtgacagttatatttttctggaaaaagacttatcagccctggattttatagg
agtttctttttatcaattttcaatttcctggccaaggcttttccccgatggaatagtaacag
ttgccaacgcaaaaggtctgcagtactacagtactcttctggacgctctagtgcttagaaac
attgaacctatagttactttataccactgggatttgcctttggcactacaagaaaaatatgg
ggggtggaaaaatgataccataatagatatcttcaatgactatgccacatactgtttccaga
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tgtttggggaccgtgtcaaatattggattacaattcacaacccatatctagtggcttggcat
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cagtggcatcgacgaccaggctctggaggatgaccggctccggaagtactacctagggaagt
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ttcaaactggctgaagagaaatctaaacccagatttggattcttcacatctgattttaaagc
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gtagttctagatgcagtcagacccaagaaaatacagagtgcactgtctgcttattccttgtg
cagaagaaaccactgatattcctgggttgttgcttcttctccaccctggttctactcttatc
aattgccatttttcaaaggcagaagagaagaaagttttggaaagcaaaaaacttacaacaca
taccattaaagaaaggcaagagagttgttagc

(SEQ ID NO: 298)

[0045] The amino acid sequence of beta klotho from cynomolgus monkey (cyno), scientific name Macaca fascicularis, is provided below:

```
   1 MKPGCAAGSP GNEWIFFSTD EITIRYRNTM SNGGLQRSVI LSALTLLRAV
  51 TGFSGDGRAV WSKNPNFTPV NESQLFLYDT FPKNFFWGVG TGALQVEGSW
 101 KKDGKGPSIW DHFVHTHLKN VSSTNGSSDS YIFLEKDLSA LDFIGVSFYQ
 151 FSISWPRLFP DGIVTVANAK GLQYYNTLLD SLVLRNIEPI VTLYHWDLPL
 201 ALQEKYGGWK NDTIIDIFND YATYCFQTFG DRVKYWITIH NPYLVAWHGY
 251 GTGMHAPGEK GNLAAVYTVG HNLIKAHSKV WHNYNTHFRP HQKGWLSITL
 301 GSHWIEPNRS ENTMDILKCQ QSMVSVLGWF ANPIHGDGDY PEGMKKKLLS
 351 ILPLFSEAEK NEVRGTADFF AFSFGPNNFK PLNTMAKMGQ NVSLNLREAL
 401 NWIKLEYNNP RILIAENGWF TDSHVKTEDT TAIYMMKNFL SQVLQAIRLD
 451 EIRVFGYTAW SLLDGFEWQD AYTIRRGLFY VDFNSKQKER KPKSSAHYYK
 501 QIIRENGFSL KEATPDVQGQ FPCDFSWGVT ESVLKPESVA SSPQFSDPYL
 551 YVWNATGNRL LHRVEGVRLK TRPAQCTDFV NIKKQLEMLA RMKVTHYRFA
 601 LDWASVLPTG NLSAVNRQAL RYYRCVVSEG LKLGISAMVT LYYPTHAHLG
 651 LPEPLLHAGG WLNPSTVEAF QAYAGLCFQE LGDLVKLWIT INEPNRLSDI
 701 YNRSGNDTYG AAHNLLVAHA LAWRLYDRQF RPSQRGAVSL SLHADWAEPA
 751 NPYADSHWRA AERFLQFEIA WFAEPLFKTG DYPAAMREYI ASKHRRGLSS
 801 SALPRLTEAE RRLLKGTVDF CALNHFTTRF VMHEQLAGSR YDSDRDIQFL
 851 QDITRLSSPT RLAVIPWGVR KLLRWVRRNY GDMDIYITAS GIDDQALEDD
 901 RLRKYYLEKY LQEVLKAYLI DKVRIKGYYA FKLAEEKSKP RFGFFTSDFK
 951 AKSSIQFYNK MISSSGFPSE NSSSRCSQTQ KNTECTVCLF LVQKKPLIFL
1001 GCCFFSTLVL LLSITIFHRQ KRRKFWKAKN LQHIPLKKGK RVLS
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(SEQ ID NO: 299)

[0046] An encoding nucleic acid sequence of cyno beta klotho is provided below:

atgaagcctggatgtgccgccggaagccccggcaacgagtggatcttcttcagcaccgacga
gatcaccatccggtacagaaacaccatgagcaacggcggcctgcagcggagcgtgatcctgt
ctgctctgaccctgctgagagccgtgaccggcttcagcggagatggcagagccgtgtggtcc
aagaaccccaacttcacccccgtgaacgagagccagctgttcctgtacgataccttccccaa
gaacttcttctggggcgtgggcacaggcgccctgcaggtggaaggatcctggaagaaggacg
gcaagggccccagcatctgggaccactttgtgcacacccacctgaagaacgtgtccagcacc
aacggcagcagcgacagctacatctttctggaaaaggacctgagcgccctggacttcatcgg
cgtgtccttctaccagttcagcatcagctggcccagactgttccccgacggcatcgtgacag
tggccaatgccaagggcctgcagtactacaacaccctgctggacagcctggtgctgcggaac
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gagaacaccatggacatcctgaagtgccagcagagcatggtgtccgtgctgggatggttcgc
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cctgaacctgagagaggccctgaactggatcaagctggagtacaacaacccccggatcctga
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cggctacaccgcctggtcactgctggacggcttcgaatggcaggacgcctacaccatcagac
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cactactacaagcagatcatcagagagaatggcttcagcctgaaagaggccacccccgacgt
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ccctggactgggccagcgtgctgcctaccggaaatctgagcgccgtgaacagacaggccctg
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gtactaccctacccacgcccacctgggactgcctgaacctctgctgcatgctggcggctggc
tgaaccctagcaccgtggaagcctttcaggcctacgccgggctgtgcttccaggaactgggc

gacctcgtgaagctgtggatcaccatcaacgagcccaacagactgagcgacatctacaacag
aagcggcaacgacacctacggcgctgcccacaatctgctggtggctcatgccctggcttggc
ggctgtacgacagacagttccggccttctcagcggggagccgtgtctctgtctctgcatgcc
gattgggccgagcccgccaacccttacgccgactctcattggagagccgccgagcggttcct
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tgagagagtatatcgccagcaagcacagacggggcctgagcagctctgccctgcctagactg
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caccagattcgtgatgcacgagcagctggccggcagcagatacgacagcgaccgggacatcc
agtttctgcaggacatcacccggctgagcagccctacaagactggccgtgatcccttgggga
gtgcggaagctgctgagatgggtgcgcagaaactacggcgacatggatatctacatcaccgc
cagcggcatcgacgaccaggccctggaagatgaccggctgcggaagtactacctggaaaagt
acctgcaggaagtgctgaaggcctacctgatcgacaaagtgcggatcaagggctactacgcc
ttcaagctggccgaggaaaagagcaagcccagattcggcttcttcaccagcgacttcaaggc
caagagcagcatccagttctacaacaagatgatcagcagcagcggcttccccagcgagaaca
gcagctccagatgcagccagacccagaaaaacaccgagtgtaccgtgtgcctgttcctggtg
cagaagaagcccctgatcttcctgggctgctgcttctttagcaccctggtgctgctgctgtc
catcaccatcttccaccggcagaagcggagaaagttctggaaggccaaaaacctgcagcaca
tccccctgaagaaaggcaagcgggtgctgagctga

(SEQ ID NO: 300)

[0047] The amino acid sequence of beta klotho homolog from mouse, scientific name Mus musculus, is provided below:

```
  1 MKTGCAAGSP GNEWIFFSSD ERNTRSRKTM SNRALQRSAV LSAFVLLRAV
 51 TGFSGDGKAI WDKKQYVSPV NPSQLFLYDT FPKNFSWGVG TGAFQVEGSW
101 KTDGRGPSIW DRYVYSHLRG VNGTDRSTDS YIFLEKDLLA LDFLGVSFYQ
151 FSISWPRLFP NGTVAAVNAQ GLRYYRALLD SLVLRNIEPI VTLYHWDLPL
201 TLQEEYGGWK NATMIDLFND YATYCFQTFG DRVKYWITIH NPYLVAWHGF
251 GTGMHAPGEK GNLTAVYTVG HNLIKAHSKV WHNYDKNFRP HQKGWLSITL
301 GSHWIEPNRT DNMEDVINCQ HSMSSVLGWF ANPIHGDGDY PEFMKTGAMI
351 PEFSEAEKEE VRGTADFFAF SFGPNNFRPS NTVVKMGQNV SLNLRQVLNW
401 IKLEYDDPQI LISENGWFTD SYIKTEDTTA IYMMKNFLNQ VLQAIKFDEI
451 RVFGYTAWTL LDGFEWQDAY TTRRGLFYVD FNSEQKERKP KSSAHYYKQI
501 IQDNGFPLKE STPDMKGRFP CDFSWGVTES VLKPEFTVSS PQFTDPHLYV
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 551 WNVTGNRLLY RVEGVRLKTR PSQCTDYVSI KKRVEMLAKM KVTHYQFALD
 601 WTSILPTGNL SKVNRQVLRY YRCVVSEGLK LGVFPMVTLY HPTHSHLGLP
 651 LPLLSSGGWL NMNTAKAFQD YAELCFRELG DLVKLWITIN EPNRLSDMYN
 701 RTSNDTYRAA HNLMIAHAQV WHLYDRQYRP VQHGAVSLSL HCDWAEPANP
 751 FVDSHWKAAE RFLQFEIAWF ADPLFKTGDY PSVMKEYIAS KNQRGLSSSV
 801 LPRFTAKESR LVKGTVDFYA LNHFTTRFVI HKQLNTNRSV ADRDVQFLQD
 851 ITRLSSPSRL AVTPWGVRKL LAWIRRNYRD RDIYITANGI DDLALEDDQI
 901 RKYYLEKYVQ EALKAYLIDK VKIKGYYAFK LTEEKSKPRF GFFTSDFRAK
 951 SSVQFYSKLI SSSGLPAENR SPACGQPAED TDCTICSFLV EKKPLIFFGC
1001 CFISTLAVLL SITVFHHQKR RKFQKARNLQ NIPLKKGHSR VFS
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(SEQ ID NO: 301)

[0048] An encoding nucleic acid sequence of mouse beta klotho is provided below:

```
atgaagacaggctgtgcagcagggtctccggggaatgaatggattttcttcagctctgatga
aagaaacacacgctctaggaaaacaatgtccaacagggcactgcaaagatctgccgtgctgt
ctgcgtttgttctgctgcgagctgttaccggcttctccggagacgggaaagcaatatgggat
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aaacttttcctggggcgttgggaccggagcatttcaagtggaagggagttggaagacagatg
gaagaggaccctcgatctgggatcggtacgtctactcacacctgagaggtgtcaacggcaca
gacagatccactgacagttacatctttctggaaaaagacttgttggctctggatttttagg
agtttctttttatcagttctcaatctcctggccacggttgtttcccaatggaacagtagcag
cagtgaatgcgcaaggtctccggtactaccgtgcacttctggactcgctggtacttaggaat
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gggctggaaaaatgcaactatgatagatctcttcaacgactatgccacatactgcttccaga
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aatacatcgcctccaagaaccagcgagggctgtctagctcagtcctgccgcgcttcaccgcg
aaggagagcaggctggtgaagggtaccgtcgacttctacgcactgaaccacttcactacgag
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aaaccactcatcttcttcggttgctgcttcatctccactctggctgtactgctatccatcac
cgtttttcatcatcaaaagagaagaaaattccagaaagcaaggaacttacaaaatataccat
tgaagaaaggccacagcagagttttcagc

(SEQ ID NO: 302)

[0049] The amino acid sequence of beta klotho from rat, scientific name Rattus norvegicus, is provided below:

MKTGCAAGSPGNEWVFFSSDERSTRSRKTMSNGALQRSAVLSALVLLRAVTGFSG
DGKAIWDKKQYVSPVNPGQLFLYDTFPKNFSWGVGTGAFQVEGSWKADGRGPSI
WDRYVDSHLRGVNSTDRSTDSYVFLEKDLLALDFLGVSFYQFSISWPRLFPNGTVA
AVNAKGLQYYRALLDSLVLRNIEPIVTLYHWDLPLTLQEEYGGWKNATMIDLFNDYA
TYCFQTFGDRVKYWITIHNPYLVAWHGFGTGMHAPGEKGNLTAVYTVGHNLIKAHS
KVWHNYDKNFRPHQKGWLSITLGSHWIEPNRTENMEDVINCQHSMSSVLGWFAN
PIHGDGDYPEFMKTSSVIPEFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQ
NVSLNLRQVLNWIKLEYDNPRILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAIK
FDEIQVFGYTAWTLLDGFEWQDAYTTRRGLFYVDFNSEQKERKPKSSAHYYKQIIQ
DNGFPLQESTPDMKGQFPCDFSWGVTESVLKPEFTVSSPQFTDPHLYVWNVTGN
RLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFALDWTSILPTGNLSKI
NRQVLRYYRCVVSEGLKLGISPMVTLYHPTHSHLGLPMPLLSSGGWLNTNTAKAFQ
DYAGLCFKELGDLVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHAQVWHLYD
RQYRPVQHGAVSLSLHSDWAEPANPYVESHWKAAERFLQFEIAWFADPLFKTGDY
PLAMKEYIASKKQRGLSSSVLPRFTLKESRLVKGTIDFYALNHFTTRFVIHKQLNTNC
SVADRDVQFLQDITRLSSPSRLAVTPWGMRKLLGWIRRNYRDMDIYVTANGIDDLA
LEDDQIRKYYLEKYVQEALKAYLIDKVKIKGYYAFKLTEEKSKPRFGFFTSDFKAKSS
VQFYSKLISSSGFSSENRSPACGQPPEDTECAICSFLTQKKPLIFFGCCFISTLAALL
SITIFHHRKRRKFQKARNLQNIPLKKGHSRVFS (SEQ ID NO:356)

[0050] An encoding nucleic acid sequence of rat beta klotho is provided below:

ATGAAGACAGGCTGTGCAGCAGGGTCTCCAGGGAATGAATGGGTTTTCTTCAG
CTCTGATGAAAGAAGCACACGCTCTAGGAAAACAATGTCCAACGGAGCACTGC
AAAGATCTGCCGTGCTGTCTGCATTGGTTCTGCTGCGAGCTGTTACCGGCTTCT
CTGGAGACGGAAAAGCAATATGGGATAAAAAACAATACGTGAGTCCGGTAAACC
CAGGTCAGCTGTTCCTCTATGACACTTTCCCTAAAAACTTTTCCTGGGGCGTTG
GGACCGGAGCATTTCAAGTGGAAGGGAGTTGGAAGGCAGATGGAAGAGGACC
CTCGATCTGGGACCGTTATGTCGACTCACACCTGAGAGGTGTCAACAGCACAG
ACAGATCCACTGACAGTTATGTCTTTCTGGAAAAGGACTTGCTGGCTCTGGATT
TTTTAGGAGTTTCTTTTTATCAGTTCTCAATCTCCTGGCCGCGGTTGTTCCCCAA
CGGAACAGTAGCAGCTGTGAATGCAAAAGGTCTCCAGTACTACAGAGCACTTCT

GGACTCGCTGGTACTTAGGAATATCGAACCCATTGTTACCTTATACCATTGGGA
TTTGCCTTTGACGCTACAGGAAGAATATGGGGGCTGGAAAAATGCAACTATGAT
AGATCTCTTCAATGACTATGCCACATACTGCTTCCAGACCTTTGGAGACCGTGT
CAAATATTGGATTACAATTCACAACCCTTACCTCGTTGCTTGGCATGGGTTTGGC
ACAGGTATGCATGCGCCAGGAGAGAAGGGAAATTTAACAGCTGTCTACACTGT
GGGACACAACCTGATCAAGGCGCATTCGAAAGTGTGGCATAACTACGACAAAA
ACTTCCGCCCTCATCAGAAGGGTTGGCTCTCCATCACCTTGGGGTCCCATTGG
ATAGAACCAAACAGAACAGAAAACATGGAGGACGTGATCAACTGCCAGCACTC
CATGTCTTCTGTGCTCGGATGGTTTGCCAACCCCATCCACGGAGACGGCGACT
ACCCCGAGTTCATGAAGACGAGCTCCGTAATCCCTGAGTTCTCTGAGGCAGAG
AAGGAGGAGGTGCGGGGCACTGCTGACTTCTTTGCCTTTTCCTTCGGGCCCAA
CAATTTCAGGCCCTCGAACACCGTGGTAAAAATGGGACAAAATGTATCACTCAA
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GATGAAATACAAGTGTTTGGTTATACGGCTTGGACTCTCCTGGATGGCTTTGAG
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GAGCAGAAAGAGAGGAAACCCAAGTCCTCCGCTCATTACTACAAACAGATTATA
CAAGACAACGGTTTCCCTTTGCAAGAATCCACACCAGACATGAAGGGTCAGTTT
CCCTGTGACTTCTCCTGGGGAGTCACTGAGTCTGTTCTTAAGCCGGAGTTTACG
GTGTCCTCCCCACAGTTTACTGATCCTCACCTGTATGTGTGGAATGTCACTGGC
AACAGATTGCTATACCGAGTGGAAGGAGTCAGGCTAAAAACAAGACCGTCCCA
ATGCACAGATTATGTGAGCATCAAAAAACGAGTTGAAATGTTGGCCAAAATGAA
AGTCACCCACTACCAGTTTGCTCTGGACTGGACCTCTATCCTCCCTACCGGAAA
TCTGTCTAAAATTAATAGACAAGTGTTGAGGTACTATAGGTGTGTGGTGAGCGA
AGGACTGAAGCTGGGCATCTCCCCTATGGTGACGTTGTACCACCCGACCCACT
CCCATCTAGGCCTCCCCATGCCACTTCTGAGCAGTGGGGGATGGCTAAACACC
AACACAGCCAAGGCCTTCCAGGACTACGCAGGCCTGTGCTTCAAGGAGCTGGG
GGACTTGGTAAAGCTCTGGATCACCATCAATGAACCCAATAGGCTGAGTGACAT
GTACAACCGCACGAGTAACGACACCTACCGTGCGGCCCACAACCTGATGATCG
CCCATGCCCAGGTCTGGCACCTCTATGATAGGCAGTATAGGCCGGTCCAGCAC
GGGGCTGTGTCGCTGTCCTTACATTCCGACTGGGCAGAACCTGCCAACCCCTA
TGTGGAGTCTCACTGGAAGGCAGCCGAGCGCTTCCTCCAGTTTGAGATCGCCT
GGTTTGCGGATCCACTCTTCAAGACTGGTGACTACCCGCTGGCCATGAAGGAA

TACATCGCCTCCAAGAAGCAGCGAGGGCTGTCTAGCTCAGTCCTGCCGCGCTT
TACCTTGAAGGAGAGCAGGCTGGTGAAGGGGACCATCGACTTTTACGCACTGA
ACCACTTCACTACTAGATTCGTGATACACAAGCAGTTGAATACCAACTGCTCAGT
GGCAGACAGGGACGTCCAGTTCCTGCAGGACATCACCCGCCTGAGCTCGCCC
AGTCGCCTAGCCGTAACGCCCTGGGGAATGCGCAAGCTCCTTGGGTGGATCC
GGAGGAACTACAGAGACATGGATATCTACGTCACAGCCAATGGCATTGATGATC
TTGCTCTAGAGGACGATCAGATTAGAAAGTACTACTTGGAGAAGTACGTCCAGG
AGGCTCTGAAAGCATATCTGATTGACAAGGTCAAAATCAAAGGCTACTATGCAT
TCAAACTGACTGAAGAGAAATCTAAGCCTAGATTTGGATTTTTCACATCTGACTT
CAAAGCTAAATCTTCTGTACAGTTTTATAGCAAGCTGATCAGCAGCAGCGGCTT
CTCCTCTGAGAACAGAAGTCCTGCCTGTGGTCAGCCTCCAGAAGACACAGAAT
GCGCCATTTGCTCCTTCCTTACACAGAAGAAACCACTCATCTTCTTTGGTTGTTG
CTTCATCTCCACTCTGGCTGCACTGCTATCAATCACTATTTTTCATCATCGGAAG
AGAAGAAAATTCCAGAAAGCAAGGAACTTACAAAATATACCATTGAAGAAAGGG
CACAGCAGAGTTTTTAGCTAA (SEQ ID NO:357)

[0051] The amino acid sequence of beta klotho from Hamster, scientific name Cricetulus griseus, is provided below:

MKAGCAAGSPGNEWIFLSSYERNTRSKKTMSNRALQRSVVLSAFVLLRAVTGLSG
DGKAIWDKKQYVSPVNASQLFLYDTFPKNFFWGVGTGAFQVEGNWQADGRGPSI
WDRFIYTHLRDVSITEKSADSYIFLEKDLLALDFLGVSFYQFSISWPRLFPNGTVASV
NAKGLQYYNKLLDSLILRNIEPVVTLYHWDLPLALQEDYGGWKNATMIDLFNDYATY
CFQTFGDRVKYWITIHNPYLVAWHGFATGMHAPGETGNLTAVYIVGHNLIKAHSKV
WHNYDKNFRPHQKGLLSITLGSHWIEPNKTENMADTISCQHSMAFVLGWFANPIHA
DGDYPEFMKTLSTMPVFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVS
LNLRQVLNWIKLEYDNPRILISENGWFTDSDIKTEDTTAIYMMKHFLNQVLQAIQFDEI
RVFGYTAWSLLDGFEWQYAYTSRRGLFYVDFNSEQKERKPKTSAHYYKQIIQENG
FPLKESTPDMQGQFPCDFSWGVTESVLKPEFMVSSPQFTDPHLYVWNATGNRLL
QRVEGVRLKTKPSHCTDYVSIKKRVEMLAKMKVTHYQFALDWATILPTGNLSEVNR
QVLRYYRCVVSEGLKLGVSPMVTLYHPTHSHLGLPEPLLNSGGWLNTYTAKAFQD
YAGLCFQELGDLVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHAQVWRLYDR
QYRPVQHGAVSLSLHSDWVEPANPYVDSHWKAAERFLLFEIAWFADPLFKTGDYP
LAMKEYIASKNQQGLSRSVLPRFTPEESRLVKGTIDFYALNHFTTRFVIHKQLNSSR

SMADRDVQFLQDITRLSSPSRLAVMPWGARKLLGWIQRNYGDMDIYITANGIDDLA
LENDGIRKYYLEKYIQEALKAYLIDKVKIKGYYAFKLTEEKSKPRFGFFTSDFKAKSS
VEFYSKLISRSGFPSETSNPACGQPPEDTDCTICSFFTQKKSLIFFGCCFISTLAVLLS
ITIFHHRKRRFHKSKNLENIPLKEGHSRVLS (SEQ ID NO: 408

[0052] An encoding nucleic acid sequence of Hamster beta klotho is provided below:

atgtccaacagggcactgcaaagatctgtcgtgctgtcagcgtttgttctgctgcgagctgttaccggattgtctggagac
gggaaagcgatatgggataaaaaacagtacgtgagtccggtgaatgcaagtcagctgtttctctatgacactttcccta
aaaacttttctggggtgttggaactggagcatttcaagtggaagggaattggcaggcagacggaagaggaccctcg
atttgggatcgtttcatctacacacacctgagagatgtcagcatcacagagaaatccgccgacagttacatttttctgga
aaaagatttgttggctctggatttttaggagtttctttttatcagttctcaatctcctggccacggttgttccccaatggaaca
gtagcatccgtgaatgcaaaaggtctccaatactacaacaaacttctggactcgctgatacttaggaatattgagcccg
ttgttaccttataccattgggatttgcctttggcgctacaggaagactatgggggttggaaaaatgcaactatgatagatc
tcttcaatgactatgccacatactgcttccagacctttggagaccgtgtcaagtattggattacaattcacaacccttacct
ggttgcttggcatgggtttgccacaggtatgcatgcgccaggagagacgggaaatttaacagctgtctacattgtggga
cacaacctgatcaaggctcattcgaaagtgtggcataactacgacaaaaacttccgcccccatcagaagggtttgct
gtccattaccttggggtcccactggatagaaccaaacaaaacagaaaacatggccgatacaatcagctgccagca
ctctatggcttttgtgcttgggtggtttgccaaccccatccatgcagacggcgactaccctgagttcatgaaaacattgtc
caccatgccagtgttctctgaggcagagaaggaggaggtgaggggcacagctgacttctttgccttttcctttgggccc
aacaatttcaggccctcgaacactgtagtgaaaatgggacaaaatgtatcactcaacttaagacaggtgctgaactg
gattaaattagaatatgacaaccctcgaatcttgatttcggagaatggctggttcacagatagtgacataaagacaga
ggacaccacagccatctacatgatgaagcatttcctcaaccaggttcttcaagcaatacagtttgatgaaatacgagtg
tttggttacacggcctggtctctcctggatggctttgaatggcagtatgcctacacgtctcgccgaggactgttttatgtgga
ctttaatagtgaacagaaagaaaggaaacccaagacctcggcacattactacaaacagatcatacaagaaaatgg
tttccctttgaaagagtccacgccagacatgcagggtcagtttccctgtgacttctcctgggggtcaccgagtctgttctt
aagccggagtttatggtttcctccccacagtttaccgaccctcacctgtatgtgtggaatgccactggcaacagattgct
acagcgagtagaaggagtaaggctaaaaacaaaaccatcccactgcacagactatgttagcatcaaaaaacgag
ttgagatgttggccaaaatgaaagtcacccactaccagtttgctctggactgggccaccatccttcccactggcaatctg
tctgaagttaatagacaagtactaaggtactataggtgtgtggtgagcgaaggactgaagctgggcgtctctcccatg
gtgacgttgtaccaccccacccactcccatctaggcctccctgagccgcttcttaacagtgggggatggctaaacactt
acaccgccaaggccttccaggactacgcaggactgtgcttccaggaactaggggacttggtgaagctctggatcac
catcaatgagcctaataggctgagtgacatgtacaaccgcacgagtaatgacacctaccgtgcagcccataacctg

atgattgcccatgcccaggtctggcgtctctacgacaggcagtataggccagtccagcatggagctgtgtcgctgtccc
tacattctgactgggtggaacctgccaacccctatgtggactcacactggaaggcagcggagcgcttcctcctgtttga
gatcgcctggttcgctgatccgctcttcaagactggcgactatccactggccatgaaggagtacatcgcctccaagaa
ccagcaagggctgtcccgctcagtcctgccgcgcttcaccccagaggagagcaggctggtgaagggcaccatcga
cttctacgcactgaaccacttcactactaggttcgtgatacacaaacagctcaacagcagccgctctatggcagacag
ggacgtccagttcctgcaggacatcacccgcctgagctcgcccagccgcctggctgttatgccctggggagcacgca
agctgcttgggtggatccagaggaactatggggacatggacatctacatcacagccaatggcatcgatgatctggct
ctggagaatgatgggatccgaaagtactacttggagaagtacatccaggaggctctgaaagcatacctcattgacaa
agtcaaaatcaaaggctattatgcattcaaactgactgaagagaaatctaagcctagatttggatttttcacatctgactt
caaagctaagtcatctgtagagttttatagcaagttgatcagcagaagtggcttcccctctgagactagcaatcccgcat
gtggtcagcctccagaagacacagactgcaccatctgctcatttttcactcagaagaaatctctgatcttctttggttgttg
cttcatctccactctggctgtactgctgtcaatcaccatttttcatcatcgaaagagaagatttcataaatcaaagaactta
gaaaatataccattgaaggaaggccacagtagagttcttagctaa (SEQ ID NO: 409)

[0053] The amino acid sequence of beta klotho from rabbit, scientific name Oryctolagus cuniculus, is provided below:

MKPGCAAGSPGNEWVSFCTDERNRRCRETMSSGRLRRSVMLSAFILLRAVTGFP
GDGRAVWSQNPNLSPVNESQLFLYDTFPKNFFWGVGTGAFQVEGSWKKDGKGL
SVWDHFIATHLNVSSRDGSSDSYIFLEKDLSALDFLGVSFYQFSISWPRLFPDGTVA
VANAKGLQYYNRLLDSLLLRNIEPVVTLYHWDLPWALQEKYGGWKNETLIDLFNDY
ATYCFQTFGDRVKYWITIHNPYLVAWHGYGTGLHAPGEKGNVAAVYTVGHNLLKA
HSKVWHNYNRNFRPHQKGWLSITLGSHWIEPNRAESIVDILKCQQSMVSVLGWFA
NPIHGDGDYPEVMTKKLLSVLPAFSEAEKNEVRGTADFFAFSFGPNNFKPLNTMAK
MGQNVSLNLRQVLNWIKLEYGNPRILIAENGWFTDSYVQTEDTTAIYMMKNFLNQV
LQAIRLDGVRVFGYTAWSLLDGFEWQDAYNTRRGLFYVDFNSEQRERRPKSSAHY
YKQVIGENGFTLREATPDLQGQFPCDFSWGVTESVLKPESVASSPQFSDPHLYVW
NATGNRMLHRVEGVRLKTRPAQCTDFITIKKQLEMLARMKVTHFRFALDWASVLPT
GNLSEVNRQALRYYRCVVTEGLKLNISPMVTLYYPTHAHLGLPAPLLHSGGWLDPS
TAKAFRDYAGLCFRELGDLVKLWITINEPNRLSDVYNRTSNDTYQAAHNLLIAHALV
WHLYDRQYRPSQRGALSLSLHSDWAEPANPYVASHWQAAERFLQFEIAWFAEPLF
KTGDYPVAMREYIASKTRRGLSSSVLPRFSDAERRLVKGAADFYALNHFTTRFVMH
EQQNGSRYDSDRDVQFLQDITRLASPSRLAVMPWGEGKLLRWMRNNYGDLDVYI
TANGIDDQALQNDQLRQYYLEKYVQEALKAYLIDKIKIKGYYAFKLTEEKSKPRFGFF

TSDFKAKSSIQFYNKLITSNGFPSENGGPRCNQTQGNPECTVCLLLLQKKPLIFFSC
CFFCTLVLLSSITIFHRRKRRKFWKAKDLQHIPLKKGHKRVLS (SEQ ID NO: 410)

[0054] An encoding nucleic acid sequence of rabbit beta klotho is provided below:

tgaagccgtgataagacggtcccgcagttcgtggcaaatgaagccaggctgtgcggcaggatctccagggaatga
atgggtttccttctgcaccgatgaaagaaacagacgctgtagggaaacgatgtccagcggacgcctgcggagatct
gtcatgctgtcagccttcatcctgctgcgagccgtgactgggttccccggagacggaagagctgtatggtcgcaaaat
cctaatttgagtccggtaaacgaaagtcagctgtttctctatgacactttcccaaaaaacttttttctggggtgtggggactg
gagccttccaagtggaagggagttggaagaaggatgggaaaggactctctgtatgggatcatttcatcgctacacac
ctgaacgtcagcagccgcgatggctccagtgacagctacatttttttggagaaagacttatcggcgctggatttttttagg
agtctcttttttatcagttttcaatttcctggccaagactgttcccggatggcacagtagcagtcgccaatgcaaaaggtctc
cagtactataatcggctcctggactctctgctacttagaaacattgaacctgtagtcactttataccattgggatctgccttg
ggcgctacaagaaaaatacgggggtggaaaaacgagacgttgattgatttattcaatgactatgccacctactgtttc
cagacgtttggggaccgtgtcaaatactggatcaccattcacaatccctatctggtggcttggcatggctacgggacag
gtctgcatgctccgggagagaaggggaatgtggcagctgtctacactgtgggacacaacctgcttaaggctcattca
aaagtctggcacaactacaacaggaatttccgcccgcatcagaaaggctggctgtcgatcacgctgggatcccact
ggattgagccaaacagagcggaaagcatcgtggacatactcaagtgccagcagtccatggtctcggtgctgggctg
gtttgccaacccgatccacggggacggggactacccagaggtgatgacaaagaagctgctctccgtcctgcccgctt
tctcagaagcagagaagaacgaggtacgaggcaccgcagacttctttgccttttcgtttggacccaacaacttcaagc
ccttaaacaccatggctaaaatggggcagaatgtgtcactcaatctaagacaggtgctgaactggattaaactggaat
atggcaaccctcgaatcctgatcgctgagaacggctggttcacagacagttacgtgcaaacagaagacaccacag
ccatctacatgatgaagaatttcctcaaccaggttcttcaagcaataaggttggatggagtccgagtgtttggctacact
gcctggtctctcctggatggcttcgaatggcaggacgcttacaacacccgccgtggactgttttatgtggacttcaacag
cgaacagagagaaagaaggcccaagtcctcggcgcattactataaacaggtcataggagaaaacggcttcacgc
tcagagaggccaccccggatctgcaggggcagtttccctgtgacttctcctggggcgtcaccgagtctgttcttaagcc
cgagtcggtggcttcctcgccacagttcagcgaccctcacctctacgtgtggaacgccactggcaaccgaatgcttca
ccgggtggaaggggtgaggctgaaaacacggcccgctcagtgcacagatttcatcaccatcaagaaacaactcga
gatgttggcaagaatgaaagtcacccacttccggtttgctctggactgggcctcggtccttcccacgggcaacctgtcc
gaggtgaaccgacaagccctgaggtactacaggtgtgtggtcaccgaggggctgaagctcaacatctcgcccatgg
tcaccttgtactacccgacccatgcccacctgggcctgcccgcgccgctgctgcacagcgggggtggctggaccc
atccacggccaaggccttccgcgactacgcagggctgtgcttccgggagctgggggacctggtgaagctctggatc
accatcaacgagcccaaccggctgagcgacgtctacaaccgcaccagcaacgacacctaccaggccgcccaca
acctgctgatcgcgcacgcgctcgtgtggcacctgtacgaccgccagtaccggccgtcgcagcgcggggcgctgtc

gctgtccctgcactcggactgggccgagcccgccaacccctacgtggcctcgcactggcaggcggccgagcgcttc
ctgcagttcgagattgcgtggttcgccgagcccctgttcaagaccggggactacccggtggccatgagggagtacat
cgcctccaagacccggcgcgggctctccagctccgtgctgccccgcttcagcgacgccgagcggcggctggtcaa
gggcgccgccgacttctacgccctcaaccacttcaccaccaggttcgtgatgcacgagcagcagaacggcagccg
ctacgactcggacagggacgtgcagttcctgcaggacatcacccgcctggcctcacccagccgcctggccgtgatg
ccctggggcgagggcaagctgctgcggtggatgcggaacaactacggagacctggacgtctacatcacggccaat
ggcatcgacgaccaggccctgcagaacgaccagcttcgccagtactacctggagaagtacgtccaggaggctctg
aaagcatatctgatagataaaataaaaatcaaaggctattatgcattcaaactgactgaagaaaaatctaaacccag
gtttggattcttcacctctgatttcaaagccaagtcttcaatacagttttacaacaaactaattaccagcaacggcttcccg
tctgagaacggcggtcctagatgcaatcagactcaaggaaatcccgagtgcaccgtctgcttactcctcctgcagaa
gaagccgctgatattctttagctgctgcttcttctgcaccctggttctactctcatcaattaccatctttcacagacggaaga
gaagaaaattttggaaagcaaaggacttacaacacataccattaaagaaaggccacaagagagtccttagctaaa
gtgaacttatttctctctgaagagtttagaaattcactccagttccatatgctggtaacacaaaagacatacccgtattgta
cacagagtatttgagatactgtgctaaccaaggcgatgacaatcaaaacctctgccatgtggttgaatgcattttccctt
aagcggtgacaatcagcgaactcagttcttggttctaaaggaggcttcgcactgccactaggctatgagtattacctga
cgcattgctttgtcaagtttgatgagctgtttcgcatcattctctagctttctttagataccaatagctactatggtaaaagttgt
ttttaaaagtcaaactctgtaaggcttcacagcagatttaaaactattctttacactggatctgtgattttgtcactcgtagca
aggtgctttccccttttggtcctagtggctctcaaatagaaagcaaacacatcttagggtaatctacttatctatagccaat
cacagcactgacccacaactacacaaatccgttagctcttctccataaaacacctaattttgtgatcttttaagtaatctg
aaatgtaaaagtatgacttccgtaacccatctcatggaaagatcgactaaggagagccatacccagctgtgaggac
aatttagtcactaatctcaccgtactgcaacttcctcctttagagcaggcattccttaccatttttgtaagatgacatgattta
gcatctagaacccctatctgcagtttctttctatggcttacctacatttcaagaatattgaacggaaaatttcagaaagattt
ccaagttttaaattgtgtactagcattagtgcatgatgaaatctcattttctttgctccatcctgcacaggatgtgaaacatc
cctctgtccagcaagtccaagctacctatattactcacttgatagtcaccatggttatccagctgttattacttgctcatacc
caggtaacccttttttatttaatatagctccaaagtataagactagtgatgaaaaggaggtaagtcatcaaatatggaa
ggacagattaactctggcactaagtgggaatgctgcaggttttacaggaaaacaaaattcagtcagtggtttaaagca
tcctctgaggtacctggggcacaatctccacagataaggggaaagagcactgacaaagactaaacatcctaaaaa
gacgcaatgttctacttactggccatcagaataatggccaaaggaccctatacttgcttgctctctagccaagtttcgctg
cacataggtgtagaatgcagcgactgaccctggatgcgattcagaatgctgatctgagtgaactagttttttatacagca
ctttttaaagcctagaattcttccatctgaacttgggagttttgacttttttgaaattaattgtgcttaagatttattcagtgattct
aaacactggaggtagaaaactgtatacccattatgcctattaatttttcttgattagccaacatttaaataaccacaaagt
ggccagtcgttgtctttccctttcaggaatttaagtcaaaggatgctgctgcctgcgatgctggcacttcataggggtgac
agtttgtgtccctgcggttccacttcctatccagctccctgctaatggcttgggagagccctgcacccacatgggagacc
caaaagcagatcctgctgctttcagcctgctgcggccacttggagtatgaaccagtggatggaagatcaatgtctctcc

caacaattctttgaataaatttttttcaaaagtcaaaataaaattctccagctcaaaaagctttagtagaaaacgatcctac
attaaggcggttgtgattgtatcccaagtgcatctacgttacaaaccaaattgagtatgcaattcagtatgctactagact
ataaggagaaaacagccaattcaaacaaaataccaaagtcacgtgcagttaatttgctttctggttggccaaatgttttttt
ttctcttcttgccaccactgttttacatgtactttagaagaaattttgacttttttgcttcctttgagaaatcactattatcaaaggc
aattcataattacaagtggtccattgtcttaagagctcaagattatagcccttcaaacttgccaaactcctcaaatagtga
agctcctaacgaagggtttacaacatcctgttccttaggggttatatttttaagtgactgtaatttacctaacaaatttaatct
ggctatctattggtaatacatgtaatattcaggtttatcataaacccacttaaaaactaaaggttaagtggaagttgctgct
tttcaaagtaacaggcttctcaggggaaaatatcaccttagcgtccacctggtactacatctcgtgtattcactgtaaccc
atctttccgaacatgtctgatatatatggaaacaacactagtgcttagcctctggaaatgaggccaggattttgtgattaa
atgtctaatttattccaaataaactgatttacgccaata (SEQ ID NO: 411)

[0055] The amino acid sequence of beta klotho from dog, scientific name Canis lupus familiaris, is provided below:

MKPGCAAGSPGNEWIFLSTDESNTHYRKTMCNHGLQRSVILSAFILLGAVPGFSGD
GRAIWSKNPHFSPVNESQLFLYDTFPKNFFWGVGTGAFQVEGNWKTDGKGPSIW
DHFIHTHLKNVNSMNSSSDSYIFLEKDLSALDFIGVSFYQFSISWPRLFPDGIAAVAN
AKGLQYYNSLLDALVLRNIEPIVTLYHWDLPLALQEKYGGWKNETITDIFNDYATYCF
QTFGDRVKYWITIHNPYLVAWHGYGTGMHAPGEKGNLAAVYTVGHNLIKAHSKVW
HNYNTNFRPYQKGLLSITLGSHWIEPNRSENMMDILKCQQSMVSVLGWFANPIHGN
GDYPEVMKKKLLSTLPLFSEAEKNEVRGTADFFAFSFGPNNFKPQNTMAKMGQNV
SLNLREVLNWIKLEYGNPRILIAENGWFTDSHVKTEDTTAIYMMKNFLNQVLQAIRFD
EIQVFGYTAWSLLDGFEWQDAYSTRRGLFYVDFNSKQKERKPKSSAYYYKQIIQEN
GFTFKESTPDVQGQFPCDFSWGVTESVLKPKVVASSPQFSDPHLYVWNVTGNRLL
HRVEGVRLKTRPAQCTDFVSIKRQLEMLARMNVTHYRFALDWPSILPTGNLSTVNR
QALRYYRCVVSESLKLSISPMVTLYYPTHAHLGLPSPLLHSGGWLNASTARAFQDY
AGLCFQELGDLVKLWITINEPNRLSDVYSHTSSDTYRAAHNLLIAHALVWHLYDRRY
RPAQRGAVSLSLHSDWAEPANPYADSHWKAAERFLQFEIAWFAEPLFKTGDYPPA
MREYIASKNRQGLSRSTLPRFTDEERRLVKGAADFYALNHFTTRFVMHARQNGSR
YDADRDVQFLQDITCLSSPSRLAVLPWGERKVLRWIQKNYGDVDVYITASGIDDQS
LENDELRKYYLEKYIQEALKAHLIDKVKVKGYYAFKLTEEKSKPRFGFFTSEFKAKSS
VQLYNKLISNSGFPSENRSPRCSETQRNTECMVCLFLVQKKPLIFFSCCFFSTLVLL
SSITILHKRKRRKIWKAKNLQHIPLKKSKNSLQS (SEQ ID NO: 412)

[0056] An encoding nucleic acid sequence of dog beta klotho is provided below:

acaatcacaagcttttactgaagcgttgataagacaggcgagcagttagtggcaaatgaagccaggctgtgcggctg
gatctccagggaatgaatggattttcctcagcaccgatgaaagcaacacacactataggaaaacaatgtgcaacca
cgggctacagagatctgtcatcctgtcagcatttattctcctaggagctgttcctggattctctggagacggaagagctat
atggtctaaaaatcctcattttagtccggtaaatgaaagtcagctgtttctctatgacacttttcctaaaaacttttttggggc
gttgggactggagcatttcaagtggaagggaattggaagacagatggaaaaggaccctctatatgggatcatttcatc
cacacacaccttaaaaatgtcaacagcatgaatagttccagtgacagttacatttttctggaaaaagacctatcagccc
tggattttatcggagtttctttttatcaattttcaatttcctggccaaggcttttccccgatggaatagcagcagttgccaacgc
aaaaggtctccagtactacaattctcttctcgatgctctagtacttaggaacattgaacctatagttactttataccattggg
atttgcctttggcactacaagaaaaatatgggggtggaaaaatgaaaccataacggatatcttcaatgactatgcca
cctactgtttccagacgttcggggatcgtgtcaaatactggattacaattcacaatccatatctagttgcttggcatgggta
tgggacaggtatgcacgcgcctggagagaagggaaacttagcagctgtctacactgtgggacacaacctaatcaa
ggctcattcgaaagtttggcataactacaacacaaatttccgcccatatcagaagggtttgttatcaatcacgttgggat
cccattggattgaaccaaacagatcagaaaacatgatggatatactcaaatgtcaacaatccatggtttcagtgctcg
ggtggtttgccaaccccatccatgggaatggagactatccagaagtgatgaaaaagaagttgctctccactctacccc
ttttctctgaagcagagaagaatgaagtgaggggcacagctgacttctttgccttttcctttggacccaacaatttcaagc
cccagaacaccatggctaaaatgggacaaaatgtgtcactcaatttaagagaagtgctgaattggattaaactggaa
tatggcaacccccgaatcttgattgctgagaatggctggttcacagacagtcatgtgaaaacagaagataccacagc
catttacatgatgaagaatttcctcaaccaggttcttcaagcaataaggtttgacgaaatacaagtgtttggctacactgc
ttggtctctcctggatggctttgaatggcaggatgcttactccactcgccgaggattattttatgtggattttaatagtaaaca
aaaagaaagaaagcccaagtcttcggcatattactataaacagatcatacaagaaaatggttttactttcaaagagtc
caccccagatgtgcagggtcagtttccctgtgacttctcatggggtgtcaccgaatctgtccttaagcccaaagtcgtgg
cttcctccccacagttcagcgaccctcacctgtacgtgtggaatgtgacaggcaacagactgttgcaccgagtggaag
gggtgaggctgaagacacggccggctcaatgcacagattttgtcagcatcaaaagacaacttgagatgttggcgag
gatgaacgtcactcactacaggtttgctctggactggccctccatccttcccaccggcaacctgtccacggttaaccga
caagccctgaggtactacaggtgtgtggtcagcgagtcgctgaagctcagcatctccccgatggtcacgctgtactac
ccgacccacgcccacctgggcctcccctcgccgctgctgcacagcgggggctggctgaacgcgtccaccgcccgc
gccttccaggactatgccgggctgtgcttccaggagctgggggacctggtgaagctctggatcaccatcaatgagcc
caaccggctgagtgacgtctacagccacaccagcagcgacacctaccgggcagcgcacaacctgctgatcgccc
acgccctggtgtggcacctgtacgaccggcggtaccggccggcgcagcgcggggccgtgtcgctgtccctgcactc
ggactgggcggagcccgccaacccctacgccgactcgcactggaaggcggccgagcgcttcctgcagttcgaaat
cgcctggttcgccgagccgctcttcaagaccggggactacccgccggccatgagggagtacatcgcctccaagaa
caggcaggggctctcgcgctccaccctgccccgcttcaccgacgaggagaggaggctggtcaagggcgccgccg
acttctacgcgctgaaccacttcaccaccaggttcgtgatgcacgcgcgccagaacggcagccgctacgacgcgg
accgcgacgtccagttcctgcaggacatcacctgcctgagctccccagccgcctggccgtcctgccctgggggga

gcgcaaggtgctcaggtggatccagaagaactacggagacgtggacgtgtacatcacggccagtggcatcgatga
ccagtctctggaaaatgatgagctcagaaaatactacttggagaaatacatccaggaggctctgaaagcacaccta
attgataaagtcaaagtcaaaggctattatgcattcaaactgactgaagaaaaatctaaacccagatttggattcttcac
gtctgaattcaaagctaaatcctcagttcagctttacaacaaactgatcagcaacagtggcttcccttctgagaacagg
agtcctagatgcagtgagactcaaagaaacacagagtgcatggtctgcttatttcttgtgcaaaagaaaccactgatat
tctttagttgttgcttcttctctaccctggttctactttcatcgattaccattcttcataagcgaaagagaagaaaaatttggaa
agcaaagaacttacaacatataccattaaagtgaggccacagaaagttcttagtgaaactgatcctatttctgtctgcat
gatagaaagtctaaaaattcactccagtcccaaatactggtaacatagaagacaatttgaaacactagtagtaacca
aggtgatgacaatcaaggtctctgctgtgtggtccaaatgaattttccattaggtgttgacatcactgaatacagtttttag
atctgaagactaagatctagagagtaagctaggattatctgatacaatgcttcattaagtttaataagctgttatccatcat
tcttctctggcttccttctagaaataccaatagctaattatagcaacttagaaaaaagtgcaacttttgctagactccatag
cagaaatctaaaactcttaacactggatattcagtgattattctatcacttctaacaaggtgcttttccccttttagaagatat
acaatagggtaaatagtgctcctttatcatccattccagcacttttttttttccagcatagactcttaaacacattgatcctagtt
tttctcaatagaaataaaaaatcatttagaaaacatggaattttgtgaggtctctccttgcattagatctgagtttttttttaaaa
aaaagacttaacttccataacccatctcatgggaagatcacaggactaagattaaggagagttagacccatcaactg
cctgaggagacagcactcaacctcacagtacagcaaattccttgggacaaactgacagcaatcttccgcacttggat
tgttgaggcagcacacaagatcttaacatacttaggaaagttaaatattctaaaaagatgtaaagttttatttttattatcaa
gtcttcaaaggaccatattattccataagacttgctctctcctgagttccactcttctgacactatgtgtatatggggacact
caaactgcaccttgacattgcaactttggatacaattcagaatgtaaatgtttgaaggacttaaaactttctccactgcac
cttttgaagctgggattaagtaaatacgaactgggagtttgacttttttgaactctgtgcttgatttattcactgtattctaaattt
taaggaaaacctgaatgtaaacccattcataccctttctttgggttagtaaacatttaaccacccatttca (SEQ ID
NO: 413).

[0057] The amino acid sequence of human/mouse beta klotho chimeric protein (human KLB (M1-F508)-mouse KLB (P507-S1043)) is provided below:

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAVTGFSGDG
RAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSWKKDGKGPSIWDH
FIHTHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQFSISWPRLFPDGIVTVANAK
GLQYYSTLLDALVLRNIEPIVTLYHWDLPLALQEKYGGWKNDTIIDIFNDYATYCFQM
FGDRVKYWITIHNPYLVAWHGYGTGMHAPGEKGNLAAVYTVGHNLIKAHSKVWHN
YNTHFRPHQKGWLSITLGSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDG
DYPEGMRKKLFSVLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVS
LNLREALNWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLDE

IRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYKQIIRENG
FPLKESTPDMKGRFPCDFSWGVTESVLKPEFTVSSPQFTDPHLYVWNVTGNRLLY
RVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFALDWTSILPTGNLSKVNRQ
VLRYYRCVVSEGLKLGVFPMVTLYHPTHSHLGLPLPLLSSGGWLNMNTAKAFQDY
AELCFRELGDLVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHAQVWHLYDRQ
YRPVQHGAVSLSLHCDWAEPANPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPS
VMKEYIASKNQRGLSSSVLPRFTAKESRLVKGTVDFYALNHFTTRFVIHKQLNTNRS
VADRDVQFLQDITRLSSPSRLAVTPWGVRKLLAWIRRNYRDRDIYITANGIDDLALE
DDQIRKYYLEKYVQEALKAYLIDKVKIKGYYAFKLTEEKSKPRFGFFTSDFRAKSSV
QFYSKLISSSGLPAENRSPACGQPAEDTDCTICSFLVEKKPLIFFGCCFISTLAVLLSI
TVFHHQKRRKFQKARNLQNIPLKKGHSRVFS (SEQ ID NO:374).

[0058] An encoding nucleic acid sequence of human/mouse beta klotho chimeric protein is provided below:

ATGAAGCCAGGCTGTGCGGCAGGATCTCCAGGGAATGAATGGATTTTCTTCAG
CACTGATGAAATAACCACACGCTATAGGAATACAATGTCCAACGGGGGATTGCA
AAGATCTGTCATCCTGTCAGCACTTATTCTGCTACGAGCTGTTACTGGATTCTCT
GGAGATGGAAGAGCTATATGGTCTAAAAATCCTAATTTTACTCCGGTAAATGAAA
GTCAGCTGTTTCTCTATGACACTTTCCCTAAAAACTTTTTCTGGGGTATTGGGAC
TGGAGCATTGCAAGTGGAAGGGAGTTGGAAGAAGGATGGAAAAGGACCTTCTA
TATGGGATCATTTCATCCACACACACCTTAAAAATGTCAGCAGCACGAATGGTT
CCAGTGACAGTTATATTTTTCTGGAAAAAGACTTATCAGCCCTGGATTTTATAGG
AGTTTCTTTTTATCAATTTTCAATTTCCTGGCCAAGGCTTTTCCCCGATGGAATA
GTAACAGTTGCCAACGCAAAAGGTCTGCAGTACTACAGTACTCTTCTGGACGCT
CTAGTGCTTAGAAACATTGAACCTATAGTTACTTTATACCACTGGGATTTGCCTT
TGGCACTACAAGAAAAATATGGGGGGTGGAAAAATGATACCATAATAGATATCT
TCAATGACTATGCCACATACTGTTTCCAGATGTTTGGGGACCGTGTCAAATATTG
GATTACAATTCACAACCCATATCTAGTGGCTTGGCATGGGTATGGGACAGGTAT
GCATGCCCCTGGAGAGAAGGGAAATTTAGCAGCTGTCTACACTGTGGGACACA
ACTTGATCAAGGCTCACTCGAAAGTTTGGCATAACTACAACACACATTTCCGCC
CACATCAGAAGGGTTGGTTATCGATCACGTTGGGATCTCATTGGATCGAGCCAA
ACCGGTCGGAAAACACGATGGATATATTCAAATGTCAACAATCCATGGTTTCTG
TGCTTGGATGGTTTGCCAACCCTATCCATGGGGATGGCGACTATCCAGAGGGG

ATGAGAAAGAAGTTGTTCTCCGTTCTACCCATTTTCTCTGAAGCAGAGAAGCAT
GAGATGAGAGGCACAGCTGATTTCTTTGCCTTTTCTTTTGGACCCAACAACTTCA
AGCCCCTAAACACCATGGCTAAAATGGGACAAAATGTTTCACTTAATTTAAGAGA
AGCGCTGAACTGGATTAAACTGGAATACAACAACCCTCGAATCTTGATTGCTGA
GAATGGCTGGTTCACAGACAGTCGTGTGAAAACAGAAGACACCACGGCCATCT
ACATGATGAAGAATTTCCTCAGCCAGGTGCTTCAAGCAATAAGGTTAGATGAAA
TACGAGTGTTTGGTTATACTGCCTGGTCTCTCCTGGATGGCTTTGAATGGCAGG
ATGCTTACACCATCCGCCGAGGATTATTTTATGTGGATTTTAACAGTAAACAGAA
AGAGCGGAAACCTAAGTCTTCAGCACACTACTACAAACAGATCATACGAGAAAA
TGGTTTTCCTTTGAAAGAGTCCACGCCAGACATGAAGGGTCGGTTCCCCTGTGA
TTTCTCTTGGGGAGTCACTGAGTCTGTTCTTAAGCCCGAGTTTACGGTCTCCTC
CCCGCAGTTTACCGATCCTCACCTGTATGTGTGGAATGTCACTGGCAACAGATT
GCTCTACCGAGTGGAAGGGGTAAGGCTGAAAACAAGACCATCCCAGTGCACAG
ATTATGTGAGCATCAAAAAACGAGTTGAAATGTTGGCAAAAATGAAAGTCACCC
ACTACCAGTTTGCTCTGGACTGGACCTCTATCCTTCCCACTGGCAATCTGTCCA
AAGTTAACAGACAAGTGTTAAGGTACTATAGGTGTGTGGTGAGCGAAGGACTGA
AGCTGGGCGTCTTCCCCATGGTGACGTTGTACCACCCAACCCACTCCCATCTC
GGCCTCCCCCTGCCACTTCTGAGCAGTGGGGGGTGGCTAAACATGAACACAGC
CAAGGCCTTCCAGGACTACGCTGAGCTGTGCTTCCGGGAGTTGGGGGACTTGG
TGAAGCTCTGGATCACCATCAATGAGCCTAACAGGCTGAGTGACATGTACAACC
GCACGAGTAATGACACCTACCGTGCAGCCCACAACCTGATGATCGCCCATGCC
CAGGTCTGGCACCTCTATGATAGGCAGTATAGGCCGGTCCAGCATGGGGCTGT
GTCGCTGTCCTTACATTGCGACTGGGCAGAACCTGCCAACCCCTTTGTGGATTC
ACACTGGAAGGCAGCCGAGCGCTTCCTCCAGTTTGAGATCGCCTGGTTTGCAG
ATCCGCTCTTCAAGACTGGCGACTATCCATCGGTTATGAAGGAATACATCGCCT
CCAAGAACCAGCGAGGGCTGTCTAGCTCAGTCCTGCCGCGCTTCACCGCGAAG
GAGAGCAGGCTGGTGAAGGGTACCGTCGACTTCTACGCACTGAACCACTTCAC
TACGAGGTTCGTGATACACAAGCAGCTGAACACCAACCGCTCAGTTGCAGACA
GGGACGTCCAGTTCCTGCAGGACATCACCCGCCTAAGCTCGCCCAGCCGCCT
GGCTGTAACACCCTGGGGAGTGCGCAAGCTCCTTGCGTGGATCCGGAGGAAC
TACAGAGACAGGGATATCTACATCACAGCCAATGGCATCGATGACCTGGCTCTA
GAGGATGATCAGATCCGAAAGTACTACTTGGAGAAGTATGTCCAGGAGGCTCT
GAAAGCATATCTCATTGACAAGGTCAAAATCAAAGGCTACTATGCATTCAAACTG
ACTGAAGAGAAATCTAAGCCTAGATTTGGATTTTTCACCTCTGACTTCAGAGCTA

AGTCCTCTGTCCAGTTTTACAGCAAGCTGATCAGCAGCAGTGGCCTCCCCGCT
GAGAACAGAAGTCCTGCGTGTGGTCAGCCTGCGGAAGACACAGACTGCACCAT
TTGCTCATTTCTCGTGGAGAAGAAACCACTCATCTTCTTCGGTTGCTGCTTCATC
TCCACTCTGGCTGTACTGCTATCCATCACCGTTTTTCATCATCAAAAGAGAAGAA
AATTCCAGAAAGCAAGGAACTTACAAAATATACCATTGAAGAAAGGCCACAGCA
GAGTTTTCAGCTGA (SEQ ID NO:375)

[0059] The amino acid sequence of mouse/human beta klotho chimeric protein (mouse KLB (M1-F506) - human KLB(S509-S1044)) is provided below:

MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSAVLSAFVLLRAVTGFSG
DGKAIWDKKQYVSPVNPSQLFLYDTFPKNFSWGVGTGAFQVEGSWKTDGRGPSI
WDRYVYSHLRGVNGTDRSTDSYIFLEKDLLALDFLGVSFYQFSISWPRLFPNGTVA
AVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLPLTLQEEYGGWKNATMIDLFNDYA
TYCFQTFGDRVKYWITIHNPYLVAWHGFGTGMHAPGEKGNLTAVYTVGHNLIKAHS
KVWHNYDKNFRPHQKGWLSITLGSHWIEPNRTDNMEDVINCQHSMSSVLGWFAN
PIHGDGDYPEFMKTGAMIPEFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMG
QNVSLNLRQVLNWIKLEYDDPQILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAI
KFDEIRVFGYTAWTLLDGFEWQDAYTTRRGLFYVDFNSEQKERKPKSSAHYYKQII
QDNGFSLKESTPDVQGQFPCDFSWGVTESVLKPESVASSPQFSDPHLYVWNATG
NRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFALDWASVLPTGNLS
AVNRQALRYYRCVVSEGLKLGISAMVTLYYPTHAHLGLPEPLLHADGWLNPSTAEA
FQAYAGLCFQELGDLVKLWITINEPNRLSDIYNRSGNDTYGAAHNLLVAHALAWRLY
DRQFRPSQRGAVSLSLHADWAEPANPYADSHWRAAERFLQFEIAWFAEPLFKTGD
YPAAMREYIASKHRRGLSSSALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLA
GSRYDSDRDIQFLQDITRLSSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITASGIDD
QALEDDRLRKYYLGKYLQEVLKAYLIDKVRIKGYYAFKLAEEKSKPRFGFFTSDFKA
KSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGCCFFSTLV
LLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS (SEQ ID NO:376)

[0060] An encoding nucleic acid sequence of mouse/human beta klotho chimeric protein is provided below:

ATGAAGACAGGCTGTGCAGCAGGGTCTCCGGGGAATGAATGGATTTTCTTCAG
CTCTGATGAAAGAAACACACGCTCTAGGAAAACAATGTCCAACAGGGCACTGCA

AAGATCTGCCGTGCTGTCTGCGTTTGTTCTGCTGCGAGCTGTTACCGGCTTCTC
CGGAGACGGGAAAGCAATATGGGATAAAAAACAGTACGTGAGTCCGGTAAACC
CAAGTCAGCTGTTCCTCTATGACACTTTCCCTAAAAACTTTTCCTGGGGCGTTG
GGACCGGAGCATTTCAAGTGGAAGGGAGTTGGAAGACAGATGGAAGAGGACC
CTCGATCTGGGATCGGTACGTCTACTCACACCTGAGAGGTGTCAACGGCACAG
ACAGATCCACTGACAGTTACATCTTTCTGGAAAAAGACTTGTTGGCTCTGGATTT
TTTAGGAGTTTCTTTTTATCAGTTCTCAATCTCCTGGCCACGGTTGTTTCCCAAT
GGAACAGTAGCAGCAGTGAATGCGCAAGGTCTCCGGTACTACCGTGCACTTCT
GGACTCGCTGGTACTTAGGAATATCGAGCCCATTGTTACCTTGTACCATTGGGA
TTTGCCTCTGACGCTCCAGGAAGAATATGGGGGCTGGAAAAATGCAACTATGAT
AGATCTCTTCAACGACTATGCCACATACTGCTTCCAGACCTTTGGAGACCGTGT
CAAATATTGGATTACAATTCACAACCCTTACCTTGTTGCTTGGCATGGGTTTGGC
ACAGGTATGCATGCACCAGGAGAGAAGGGAAATTTAACAGCTGTCTACACTGTG
GGACACAACCTGATCAAGGCACATTCGAAAGTGTGGCATAACTACGACAAAAAC
TTCCGCCCTCATCAGAAGGGTTGGCTCTCCATCACCTTGGGGTCCCATTGGATA
GAGCCAAACAGAACAGACAACATGGAGGACGTGATCAACTGCCAGCACTCCAT
GTCCTCTGTGCTTGGATGGTTCGCCAACCCCATCCACGGGGACGGCGACTACC
CTGAGTTCATGAAGACGGGCGCCATGATCCCCGAGTTCTCTGAGGCAGAGAAG
GAGGAGGTGAGGGGCACGGCTGATTTCTTTGCCTTTTCCTTCGGGCCCAACAA
CTTCAGGCCCTCAAACACCGTGGTGAAAATGGGACAAAATGTATCACTCAACTT
AAGGCAGGTGCTGAACTGGATTAAACTGGAATACGATGACCCTCAAATCTTGAT
TTCGGAGAACGGCTGGTTCACAGATAGCTATATAAAGACAGAGGACACCACGG
CCATCTACATGATGAAGAATTTCCTAAACCAGGTTCTTCAAGCAATAAAATTTGA
TGAAATCCGCGTGTTTGGTTATACGGCCTGGACTCTCCTGGATGGCTTTGAGTG
GCAGGATGCCTATACGACCCGACGAGGGCTGTTTTATGTGGACTTTAACAGTGA
GCAGAAAGAGAGGAAACCCAAGTCCTCGGCTCATTACTACAAGCAGATCATACA
AGACAACGGCTTCTCTTTAAAAGAGTCCACGCCAGATGTGCAGGGCCAGTTTCC
CTGTGACTTCTCCTGGGGTGTCACTGAATCTGTTCTTAAGCCCGAGTCTGTGGC
TTCGTCCCCACAGTTCAGCGATCCTCATCTGTACGTGTGGAACGCCACTGGCAA
CAGACTGTTGCACCGAGTGGAAGGGGTGAGGCTGAAAACACGACCCGCTCAAT
GCACAGATTTTGTAAACATCAAAAAACAACTTGAGATGTTGGCAAGAATGAAAGT
CACCCACTACCGGTTTGCTCTGGATTGGGCCTCGGTCCTTCCCACTGGCAACC
TGTCCGCGGTGAACCGACAGGCCCTGAGGTACTACAGGTGCGTGGTCAGTGA
GGGGCTGAAGCTTGGCATCTCCGCGATGGTCACCCTGTATTATCCGACCCACG

CCCACCTAGGCCTCCCCGAGCCTCTGTTGCATGCCGACGGGTGGCTGAACCCA
TCGACGGCCGAGGCCTTCCAGGCCTACGCTGGGCTGTGCTTCCAGGAGCTGG
GGGACCTGGTGAAGCTCTGGATCACCATCAACGAGCCTAACCGGCTAAGTGAC
ATCTACAACCGCTCTGGCAACGACACCTACGGGGCGGCGCACAACCTGCTGGT
GGCCCACGCCCTGGCCTGGCGCCTCTACGACCGGCAGTTCAGGCCCTCACAG
CGCGGGGCCGTGTCGCTGTCGCTGCACGCGGACTGGGCGGAACCCGCCAAC
CCCTATGCTGACTCGCACTGGAGGGCGGCCGAGCGCTTCCTGCAGTTCGAGAT
CGCCTGGTTCGCCGAGCCGCTCTTCAAGACCGGGGACTACCCCGCGGCCATG
AGGGAATACATTGCCTCCAAGCACCGACGGGGGCTTTCCAGCTCGGCCCTGCC
GCGCCTCACCGAGGCCGAAAGGAGGCTGCTCAAGGGCACGGTCGACTTCTGC
GCGCTCAACCACTTCACCACTAGGTTCGTGATGCACGAGCAGCTGGCCGGCAG
CCGCTACGACTCGGACAGGGACATCCAGTTTCTGCAGGACATCACCCGCCTGA
GCTCCCCCACGCGCCTGGCTGTGATTCCCTGGGGGGTGCGCAAGCTGCTGCG
GTGGGTCCGGAGGAACTACGGCGACATGGACATTTACATCACCGCCAGTGGCA
TCGACGACCAGGCTCTGGAGGATGACCGGCTCCGGAAGTACTACCTAGGGAA
GTACCTTCAGGAGGTGCTGAAAGCATACCTGATTGATAAAGTCAGAATCAAAGG
CTATTATGCATTCAAACTGGCTGAAGAGAAATCTAAACCCAGATTTGGATTCTTC
ACATCTGATTTTAAAGCTAAATCCTCAATACAATTTTACAACAAAGTGATCAGCA
GCAGGGGCTTCCCTTTTGAGAACAGTAGTTCTAGATGCAGTCAGACCCAAGAAA
ATACAGAGTGCACTGTCTGCTTATTCCTTGTGCAGAAGAAACCACTGATATTCCT
GGGTTGTTGCTTCTTCTCCACCCTGGTTCTACTCTTATCAATTGCCATTTTTCAA
AGGCAGAAGAGAAGAAAGTTTTGGAAAGCAAAAAACTTACAACACATACCATTA
AAGAAAGGCAAGAGAGTTGTTAGCTAG (SEQ ID NO:377)

[0061] Related beta klotho polypeptides include allelic variants (*e.g.,* SNP variants); splice variants; fragments; derivatives; substitution, deletion, and insertion variants; fusion polypeptides; and interspecies homologs, preferably, which retain beta klotho activity and/or are sufficient to generate an anti-beta klotho immune response. As those skilled in the art will appreciate, an anti-beta klotho antibody provided herein can bind to a beta klotho polypeptide, a beta klotho polypeptide fragment, a beta klotho antigen, and/or a beta klotho epitope. An epitope may be part of a larger beta klotho antigen, which may be part of a larger beta klotho polypeptide fragment, which, in turn, may be part of a larger beta klotho polypeptide. Beta klotho may exist in a native or denatured form. Beta klotho polypeptides

described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. A beta klotho polypeptide may comprise a polypeptide having the same amino acid sequence as a corresponding beta klotho polypeptide derived from nature. Beta klotho polypeptides encompass truncated or secreted forms of a beta klotho polypeptide (*e.g.,* an extracellular domain sequence), variant forms (*e.g.,* alternatively spliced forms) and allelic variants of the polypeptide. Orthologs to the beta klotho polypeptide are also well known in the art.

[0062] The term “beta klotho” encompasses “full-length,” unprocessed beta klotho as well as any form of beta klotho that results from processing in the cell. The term also encompasses naturally occurring variants or mutations of beta klotho (*e.g.,* splice variants, allelic variants, SNP variants and isoforms). The beta klotho polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

[0063] The terms "FGF19-like signaling" and "induces FGF19-like signaling," when applied to a binding protein such an antibody that binds to beta klotho of the present disclosure, means that the binding protein (*e.g.,* antibody) mimics, or modulates, an *in vivo* biological effect induced by the binding of (i) beta klotho; (ii) FGFR1c, FGFR2c, FGFR3c, and FGFR4; or (iii) a complex comprising beta klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and induces a biological response that otherwise would result from FGF19 binding to (i) beta klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising beta klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 *in vivo*. In assessing the binding and specificity of anti-beta klotho antibody, for example, an antibody or fragment thereof, that binds to beta klotho (*e.g.,* human beta klotho), an antibody or fragment thereof is deemed to induce a biological response when the response is equal to or greater than 5%, and preferably equal to or greater than 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%, of the activity of a wild type FGF19 standard comprising the mature form of SEQ ID NO:304 (*e.g.,* the mature form of human FGF19) and has the following properties: exhibiting an efficacy level of equal to or more than 5% of an FGF19 standard, with an EC50 of equal to or less than 100 nM, *e.g.,* 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30

nM, 20 nM or 10 nM in (1) a recombinant FGF19 receptor mediated luciferase-reporter cell assay (see, *e.g.,* Example 4); (2) ERK-phosphorylation in a recombinant FGF19 receptor mediated cell assay (see, *e.g.,* Example 4); or (3) ERK-phosphorylation in human adipocytes (see, *e.g.,* Example 5).

[0064] The term "FGF19R" may refer to a multimeric receptor complex that FGF19 is known or suspected to form *in vivo*. In various embodiments, FGF19R comprises (i) an FGFR, *e.g.,* FGFR1c, FGFR2c, FGFR3c or FGFR4, and (ii) beta klotho.

[0065] The terms "FGF21-like signaling" and "induces FGF21-like signaling," when applied to a binding protein such an antibody that binds to beta klotho of the present disclosure, means that the binding protein (*e.g.,* antibody) mimics, or modulates, an *in vivo* biological effect induced by the binding of (i) beta klotho; (ii) FGFR1c, FGFR2c, FGFR3c, and FGFR4; or (iii) a complex comprising beta klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and induces a biological response that otherwise would result from FGF21 binding to (i) beta klotho; (ii) FGFR1c, FGFR2c, FGFR3c or FGFR4; or (iii) a complex comprising beta klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4 *in vivo*. In assessing the binding and specificity of anti-beta klotho antibody, for example, an antibody or fragment thereof that binds to beta klotho (*e.g.,* human beta klotho), an antibody or fragment thereof is deemed to induce a biological response when the response is equal to or greater than 5%, and preferably equal to or greater than 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%, of the activity of a wild type FGF21 standard comprising the mature form of SEQ ID NO:306 or 429 (*e.g.,* the mature form of the human FGF21 sequence) and has the following properties: exhibiting an efficacy level of equal to or more than 5% of an FGF21 standard, with an EC50 of equal to or less than 100 nM, *e.g.,* 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM or 10 nM in (1) a recombinant FGF21 receptor mediated luciferase-reporter cell assay (see, *e.g.,* Example 4); (2) ERK-phosphorylation in the recombinant FGF21 receptor mediated cell assay (see, *e.g.,* Example 4); or (3) ERK-phosphorylation in human adipocytes (see, *e.g.,* Example 5).

[0066] The term "FGF21R" may refer to a multimeric receptor complex that FGF21 is known or suspected to form *in vivo*. In various embodiments, FGF21R comprises (i) an FGFR, *e.g.,* FGFR1c, FGFR2c, FGFR3c or FGFR4, and (ii) beta klotho.

[0067] The term "binding protein" refers to a protein comprising a portion (*e.g.,* one or more binding regions such as CDRs) that binds to beta klotho, including human and/or cyno beta klotho and, optionally, a scaffold or framework portion (*e.g.,* one or more scaffold or framework regions) that allows the binding portion to adopt a conformation that promotes binding of the binding protein to a beta klotho polypeptide, fragment or epitope. Examples of such binding proteins include antibodies, such as a human antibody, a humanized antibody; a chimeric antibody; a recombinant antibody; a single chain antibody; a diabody; a triabody; a tetrabody; a Fab fragment; a F(ab') 2 fragment; an IgD antibody; an IgE antibody; an IgM antibody; an IgG1 antibody; an IgG2 antibody; an IgG3 antibody; or an IgG4 antibody, and fragments thereof. The binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, *e.g.,* Korndorfer et al., 2003, Proteins: Structure, Function, and Bioinformatics, 53(1):121-129 (2003); Roque *et al.*, Biotechnol. Prog. 20:639-654 (2004). In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronectin components as a scaffold. In the context of the present disclosure, a binding protein is said to specifically bind or selectively bind to beta klotho, for example, when the dissociation constant (K_D) is $\leq 10^{-8}$ M. The binding protein (*e.g.,*antibody) may specifically bind beta klotho with high affinity when the K_D is $\leq 10^{-9}$ M or K_D is $\leq 10^{-10}$ M. In some embodiments, the binding proteins (*e.g.,* antibodies) may bind to beta klotho or a complex comprising FGFR1c and beta klotho, including with a K_D of between about 10^{-7} M and about 10^{-12} M and in other embodiments, the binding proteins (*e.g.,* antibodies) may bind with a K_D of 1-2 x 10^{-9} M.

[0068] The term “antibody” and “immunoglobulin” or “Ig” are used inter*chan*geably herein, and is used in the broadest sense and specifically covers, for example, individual anti-beta klotho monoclonal antibodies (including agonist, anta*goni*st, neutralizing antibodies, full length or intact monoclonal antibodies), anti-beta klotho antibody compositions with polyepitopic or monoepitopic specificity, polyclonal or monovalent antibodies, multivalent antibodies, multispecific antibodies (*e.g.,*

bispecific antibodies so long as they exhibit the desired biological activity), formed from at least two intact antibodies, single chain anti-beta klotho antibodies, and fragments of anti-beta klotho antibodies, as described below. An antibody can be human, humanized, chimeric and/or affinity matured as well as an antibody from other species, for example mouse, rabbit etc. The term "antibody" is intended to include a polypeptide product of B cells within the immunoglobulin class of polypeptides that is able to bind to a specific molecular antigen and is composed of two identical pairs of polypeptide chains, wherein each pair has one heavy chain (about 50-70 kDa) and one light chain (about 25 kDa) and each amino-terminal portion of each chain includes a *vari*able region of about 100 to about 130 or more amino acids and each carboxy-terminal portion of each chain includes a constant region (See, Borrebaeck (ed.) (1995) Antibody Engineering, Second Ed., Oxford University Press.; Kuby (1997) Immunology, Third Ed., W.H. Freeman and Company, New York). In specific embodiments, the specific molecular antigen can be bound by an antibody provided herein includes a beta klotho polypeptide, beta klotho fragment or beta klotho epitope. Antibodies also include, but are not l*imit*ed to, synthetic anti*bodi*es, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bi-specific antibodies), huma*n an*tibodies, humanized antibodies*, ca*melized antibodies, chimeric antibodies, intrabodies, anti-idiotypic (anti-Id) antibodies, and functional fragments (*e.g.,* antigens-binding fragments such as beta k*lotho* binding fragments) of any of the above, which refers a portion of an antibody heavy or light chain polypeptide th*at ret*ains some or all of the binding activity of the antibody from which the fragment was derived. Non-limiting examples of functional fragments (*e.g.,* antigens-bi*nding* fragments such as beta klotho binding fragments) include single-chain Fvs (scFv) (*e.g.,* including monospecific, bispecific, etc.), Fab fragments, F(ab') fragments, F(ab)2 fragments, F(ab')2 fragments, disulfide-linked Fvs (sdFv), Fd fragments, Fv fragments, diabody, triabody, tetrabody and minibody. In particular, antibodies provided herein include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, for example, antigen binding domains or molecules that contain an antigen-binding site that binds to a beta klotho an*tige*n (*e.g.,* one or more complementarity determining regions (CDRs) of an anti-beta klotho antibody). Such antibody fragments can be found described in, for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York (1989);

Myers (ed.), Molec. Biology and Biotechnology: A Comprehensive Desk Reference, New York: VCH Publisher, Inc.; Huston et al., Cell Biophysics, 22:189-224 (1993); Plückthun and Skerra, Meth. Enzymol., 178:497-515 (1989) and in Day, E.D., Advanced Immunochemistry, Second Ed., Wiley-Liss, Inc., New York, NY (1990). The antibodies provided herein can be of any type (*e.g.,* IgG, IgE, IgM, IgD, IgA and IgY), any class (*e.g.,* IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), or any subclass (*e.g.,* IgG2a and IgG2b) of immunoglobulin molecule. Anti-beta klotho antibodies may be agonistic antibodies or antagonistic antibodies. Provided herein are agonistic antibodies to beta klotho, including antibodies that induce FGF19-like signaling and/or FGF21-like signaling. Preferred agonistic antibodies to beta klotho do not compete for the binding of FGF19 and/or FGF21 to an FGF receptor including, for example, FGFR1c, FGFR2c, FGFR3c, or FGFR4c.

[0069] The term "fibroblast growth factors" refers to a family of growth factors, including twenty-two members of the human FGF family. The FGF19 subfamily of fibroblast growth factors consists of human FGF21, FGF23 and FGF19 and mouse FGF15. The effects of FGF family members are the result of their heparin-dependent binding to one or more members of the FGF receptor tyrosine kinase (FGFR) family, which includes four members each having a tyrosine kinase domain, FGFR1, FGFR2, FGFR3 and FGFR4, as well as two splice variants each of FGFR1, FGFR2 and FGFR3. These splice variants, which occur in exon 3 of FGFR1, FGFR2 and FGFR3, are designated as "b" and "c" variants (*e.g.,* FGFR1b, FGFR2b, FGFR3c, FGFR1c, FGFR2c and FGFR3c, which are also known as FGFR1(III)b, FGFR2(III)b, FGFR3(III)c, FGFR1(III)c, FGFR2(III)c and FGFR3(III)c, respectively). For example, FGF19 targets and has effects on both adipocytes and hepatocytes. Mice treated with recombinant human FGF19 (rhFGF19), despite being on a high-fat diet, show increased metabolic rates, increased lipid oxidation, a lower respiratory quotient and weight loss. Moreover, such mice showed lower serum levels of leptin, insulin, cholesterol and triglycerides, and normal levels of blood glucose despite the high-fat diet and without appetite diminishment. In addition, obese mice that lacked leptin but included a FGF19 transgene showed weight loss, lowered cholesterol and triglycerides, and did not develop diabetes. In addition, obese, diabetic mice that lack leptin, when injected with rhFGF19, showed reversal of their metabolic characteristics in the form of weight loss and lowered blood glucose. For example,

FGF21 is expressed primarily by the liver and has metabolic effects similar to that of FGF19, such as increased metabolism via its effects on adipose tissue, weight loss, lowered blood glucose levels, and resistance to obesity and diabetes. FGF21-transgenic mice were also resistant to diet-induced obesity, and, in diabetic rodent models, FGF21 administration lowered blood glucose and triglyceride levels. FGF19 and FGF21 metabolic effects occur via their binding FGF receptors, including the FGFR1c, FGFR2c and FGFR3c receptors, and required beta klotho for the binding. for the binding. The binding of FGF19 and FGF21 to FGFR1c and FGFR2c are significant. FGF19 has also been shown to have metabolic effects distinct from FGF21, including regulating bile production by the liver via its liver-specific effects, negatively regulating bile production in response to postprandial bile-production, and liver mitogenic effects that are not observed with respect to FGF21. For example, FGF19 transgenic mice develop hepatic adenocarcinoma due to increased proliferation and dysplasia of hepatocytes, and rhFGF19-treated mice exhibit hepatocyte proliferation of hepatocytes. These additional activities of FGF19 appear to be mediated via its binding to FGFR4. FGF19 can bind FGFR4 in both a beta klotho-dependent and beta klotho-independent manner. Although FGF21 has also been shown to bind FGFR4 in a beta klotho-dependent manner, efficient signaling has not previously been observed from the binding of FGF21 to FGFR4.

[0070] Binding proteins, such as anti-beta klotho *an*tibodies, as disclosed herein can induce FGF19-like signaling, as described herein. *In vivo*, the mature form of FGF19 is the active form of the molecule. A nucleic acid sequence encoding full length FGF19 is provided below; the nucleotides encoding the signal sequence are underlined.

atgcggagcgggtgtgtggtggtccacgtatggatcctggccggcctctggctggccgtggc
cgggcgcccctcgccttctcggacgcggggccccacgtgcactacggctggggcgacccca
tccgcctgcggcacctgtacacctccggcccccacgggctctccagct*gctt*cctgcgcatc
cgtgccgacggcgtcgtggactgcgcgcggggccagagcgcgcacagtttgctggagatcaa
ggcagtcgctctgcggaccgtggccatcaagggcgtgcacagcgtgcggtacctctgcatgg
*gcgc*cgacggcaagatgcaggggctgcttcagtactcggaggaagactgtgctttcgaggag
gagatccgcccagatggctacaatgtgtaccgatccgagaagc*accg*cctcccggtctccct
gagcagtgccaaacagcggcagctgtacaagaacagaggctttcttccactctctcatttcc
tgcccatgctgcccatggtcccagaggagcctgaggacctcaggggccacttggaatctgac

atgttctcttcgcccctggagaccgacagcatggacccatttgggcttgtcaccggact*gga*
*ggcc*gtgaggagtcccagctttgagaagtaa

(SEQ ID NO:303)

[0071] The amino acid sequence of full length FGF19 is provided; the amino acids that make up the signal sequence are underlined:

mrsgcvvvhvwilaglwlavagRPLAFSDAGPH*VHYG*WGDPIRLRHLYTSGPHGLSSCFLRI
RADGVVDCARGQSAHSLLEIKAVA*LRTV*AIKGVH*SVRY*LCMGADGKMQGLLQYSEEDCAFEE
EIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESD
MFSSPLETDSMDPFGLVTGLEAVRSPSFEK

(SEQ ID NO:304)

[0072] Binding proteins, such as anti-beta klotho antibodies, as described herein can induce FGF21-like signaling, as described herein. *In vivo*, the mature form of FGF21 is the active form of the molecule. A nucleic acid sequence encoding a full length FGF21 is provided; the nucleotides encoding the signal sequence are underlined:

atg gac tcg gac gag acc ggg ttc gag cac tca gga ctg tgg gtt
tct gtg ctg gct ggt ctt ctg ctg gga gcc tgc cag gca cac ccc
atc cct gac tcc agt cct ctc *ctg* caa ttc ggg ggc caa gtc cgg
cag cgg tac ctc ta*c ac*a gat gat gcc cag cag aca gaa gcc cac
ctg gag atc agg gag g*at g*gg acg gtg ggg ggc gct gct gac cag
agc ccc gaa agt ctc ctg cag ctg aaa gcc ttg aag ccg gga gtt
att caa atc ttg gga gtc aag aca tcc agg ttc ctg tgc cag cgg
cca gat ggg gcc ctg tat gga tcg ctc cac ttt gac cct gag gcc
tgc agc ttc cgg gag ctg ctt ctt gag gac gga tac aat gtt tac
cag tcc gaa gcc cac ggc ctc ccg ctg cac ctg cca ggg aac aag
tcc cca cac cgg gac cct gca ccc cga gga cca gct cgc ttc ctg
cca cta cca ggc ctg ccc ccc gca ccc ccg gag cca ccc gga atc
ctg gcc ccc cag ccc ccc gat gtg ggc tcc tcg gac cct ctg agc
atg gtg gga cct tcc cag ggc cga agc ccc agc tac gct tcc tga

(SEQ ID NO:305).

[0073] An amino acid sequence of a full length FGF21 is provided below; the amino acids that make up the signal sequence are underlined:

m d s d e t g f e h s g l w v s v l a g l l l g a c q a H P I
P D S S P L L Q F G G Q V R Q R Y L Y T D D A Q Q T E A H L E I
R E D G T V G G A A D Q S P E S L L Q L K A L K P G V I Q I L
G V K T S R F L C Q R P D G A L Y G S L H F D P E A C S F R E
L L L E D G Y N V Y Q S E A H G L P L H L P G N K S P H R D P
A P R G P A R F L P L P G L P P A L P E P P G I L A P Q P P D
V G S S D P L S M V G P S Q G R S P S Y A S

(SEQ ID NO:306).

[0074] A nucleic acid sequence also encoding a full length FGF21 is provided; the nucleotides encoding the signal sequence are underlined:

atggactcggacgagaccgggttcgagcactcaggactgtgggtttctgtgctggctggtcttctgctgggagcc
tgccaggcaCACCCCATCCCTGACTCCAGTCCTCTCCTGCAATTCGGGGGCCAAGTCCGGCAGCGGTACCTCTAC
ACAGATGATGCCCAGCAGACAGAAGCCCACCTGGAGATCAGGGAGGATGGGACGGTGGGGGGCGCTGCTGACCAG
AGCCCCGAAAGTCTCCTGCAGCTGAAAGCCTTGAAGCCGGGAGTTATTCAAATCTTGGGAGTCAAGACATCCAGG
TTCCTGTGCCAGCGGCCAGATGGGGCCCTGTATGGATCGCTCCACTTTGACCCTGAGGCCTGCAGCTTCCGGGAG
CTGCTTCTTGAGGACGGATACAATGTTTACCAGTCCGAAGCCCACGGCCTCCCGCTGCACCTGCCAGGGAACAAG
TCCCCACACCGGGACCCTGCACCCCGAGGACCAGCTCGCTTCCTGCCACTACCAGGCCTGCCCCCCGCACTCCCG
GAGCCACCCGGAATCCTGGCCCCCCAGCCCCCCGATGTGGGCTCCTCGGACCCTCTGAGCATGGTGGGACCTTCC
CAGGGCCGAAGCCCCAGCTACGCTTCCTGA

(SEQ ID NO:428).

[0075] An amino acid sequence also encoding a full length FGF21 is provided; the amino acids encoding the signal sequence are underlined:

mdsdetgfehsglwvsvlaglllgacqaHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIR
EDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEA
CSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPE
PPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS

(SEQ ID NO:429)

[0076] Binding proteins, such as anti-beta klotho antibodies, as described herein bind to beta klotho alone or in complex with an FGF receptor, such as FGFR1c. An

encoding nucleic acid sequence of human FGFR1c (GenBank Accession Number NM 023110; also designated FGFRαIIIc) is provided below:

atgtggagctggaagtgcctcctcttctgggctgtgctggtcacagcc
acactctgcaccgctaggccgtccccgaccttgcctgaacaagcccag
ccctggggagcccctgtggaagtggagtccttcctggtccaccccggt
gacctgctgcagcttcgctgtcggctgcgggacgatgtgcagagcatc
aactggctgcgggacggggtgcagctggcggaaagcaaccgcacccg
catcacaggggaggaggtggaggtgcaggactccgtgcccgcagact
ccggcctctatgcttgcgtaaccagcagcccctcgggcagtgacacca
cctacttctccgtcaatgtttcagatgctctcccctcctcggaggatga
tgatgatgatgatgactcctcttcagaggagaaagaaacagataaca
ccaaaccaaaccgtatgcccgtagctccatattggacatcaccagaaa
agatggaaaagaaattgcatgcagtgccggctgccaagacagtgaag
ttcaaatgcccttccagtgggacaccaaacccaacactgcgctggttg
aaaaatggcaaagaattcaaacctgaccacagaattggaggctacaa
ggtccgttatgccacctggagcatcataatggactctgtggtgccctc
tgacaagggcaactacacctgcattgtggagaatgagtacggcagca
tcaaccacacataccagctggatgtcgtggagcggtcccctcaccggc
ccatcctgcaagcagggttgcccgccaacaaaacagtggccctgggt
agcaacgtggagttcatgtgtaaggtgtacagtgacccgcagccgcac
atccagtggctaaagcacatcgaggtgaatgggagcaagattggccc
agacaacctgccttatgtccagatcttgaagactgctggagttaatac
caccgacaaagagatggaggtgcttcacttaagaaatgtctcctttga
ggacgcaggggagtatacgtgcttggcgggtaactctatcggactctc
ccatcactctgcatggttgaccgttctggaagccctggaagagaggcc
ggcagtgatgacctcgcccctgtacctggagatcatcatctattgcac
aggggccttcctcatctcctgcatggtggggtcggtcatcgtctacaa
gatgaagagtggtaccaagaagagtgacttccacagccagatggctg
tgcacaagctggccaagagcatccctctgcgcagacaggtaacagtg
tctgctgactccagtgcatccatgaactctggggttcttctggttcggc
catcacggctctcctccagtgggactcccatgctagcaggggtctctg
agtatgagcttcccgaagaccctcgctgggagctgcctcgggacagac
tggtcttaggcaaacccctgggagagggctgctttgggcaggtggtgt
tggcagaggctatcgggctggacaaggacaaacccaaccgtgtgacc

aaagtggctgtgaagatgttgaagtcggacgcaacagagaaagactt
gtcagacctgatctcagaaatggagatgatgaagatgatcgggaagc
ataagaatatcatcaacctgctgggggcctgcacgcaggatggtccct
tgtatgtcatcgtggagtatgcctccaagggcaacctgcgggagtacc
tgcaggcccggaggcccccagggctggaatactgctacaaccccagc
cacaacccagaggagcagctctcctccaaggacctggtgtcctgcgcc
taccaggtggcccgaggcatggagtatctggcctccaagaagtgcata
caccgagacctggcagccaggaatgtcctggtgacagaggacaatgt
gatgaagatagcagactttggcctcgcacgggacattcaccacatcga
ctactataaaaagacaaccaacggccgactgcctgtgaagtggatgg
cacccgaggcattatttgaccggatctacacccaccagagtgatgtgt
ggtctttcggggtgctcctgtgggagatcttcactctgggcggctcccc
ataccccggtgtgcctgtggaggaacttttcaagctgctgaaggaggg
tcaccgcatggacaagcccagtaactgcaccaacgagctgtacatgat
gatgcgggactgctggcatgcagtgccctcacagagacccaccttcaa
gcagctggtggaagacctggaccgcatcgtggccttgacctccaacca
ggagtacctggacctgtccatgcccctggaccagtactcccccagctt
tcccgacacccggagctctacgtgctcctcaggggaggattccgtctt
ctctcatgagccgctgcccgaggagccctgcctgccccgacacccagc
ccagcttgccaatggcggactcaaacgccgctga.

(SEQ ID NO:307)

[0077] The amino acid sequence of human FGFR1c (GenBank Accession Number NP 075598) (also designated FGFRαIIIC) is provided below:

MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPG
DLLQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGL
YACVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNR
MPVAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEF
KPDHRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDV
VERSPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNG
SKIGPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSI
GLSHHSAWLTVLEALEERPAVMTSPLYLEIIIYCTGAFLISCMVGSVIVY
KMKSGTKKSDFHSQMAVHKLAKSIPLRRQVTVSADSSASMNSGVLLVRPS
RLSSSGTPMLAGVSEYELPEDPRWELPRDRLVLGKPLGEGCFGQVVLAEA

IGLDKDKPNRVTKVAVKMLKSDATEKDLSDLISEMEMMKMIGKHKNIIN
LLGACTQDGPLYVIVEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQLS
SKDLVSCAYQVARGMEYLASKKCIHRDLAARNVLVTEDNVMKIADFGL
ARDIHHIDYYKKTTNGRLPVKWMAPEALFDRIYTHQSDVWSFGVLLWEI
FTLGGSPYPGVPVEELFKLLKEGHRMDKPSNCTNELYMMMRDCWHAVP
SQRPTFKQLVEDLDRIVALTSNQEYLDLSMPLDQYSPSFPDTRSSTCSSG
EDSVFSHEPLPEEPCLPRHPAQLANGGLKRR.
(SEQ ID NO:308)

[0078] Binding proteins, such as anti-beta klotho antibodies, described herein may bind to beta klotho in complex with the extracellular portion of an FGF receptor such as FGFR1c. An example of an extracellular region of FGFR1c is:

MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPGDL
LQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGLYA
CVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNRMP
VAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEFKPD
HRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDVVER
SPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKI
GPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLS
HHSAWLTVLEALEERPAVMTSPLY. (SEQ ID NO:309)

[0079] An example of an extracellular region of FGFR1c (αIIIc) is:

RPSPTLPEQAQPWGAPVEVESFLVHPGDLLQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADS
GLYACVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNRMPVAPYWTSPEKMEKKLHAVPAA
KTVKFKCPSSGTPNPTLRWLKNGKEFKPDHRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLD
VVERSPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKIGPDNLPYVQILKTAGVNTTDK
EMEVLHLRNVSFEDAGEYTCLAGNSIGLSHHSAWLTVLEALEERPAVMTSPLYE.
(SEQ ID NO:427)

[0080] An example of an extracellular region of FGFR1c (βIIIc) is:

RPSPTLPEQDALPSSEDDDDDDDSSSEEKETDNTKPNPVAPYWTSPEKMEKKLHAVPAAKTV
KFKCPSSGTPNPTLRWLKNGKEFKPDHRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEY
GSINHTYQLDVVERSPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGS

KIGPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLSHHSAWLTVLE
ALEERPAVMTSPLYLE.

(SEQ ID NO: 426)

[0081] As described herein, FGFR1c proteins can also include fragments. As used herein, the terms are used interchangeably to mean a receptor, in particular and unless otherwise specified, a human receptor, that upon association with beta klotho and FGF21 induces FGF21-like signaling activity.

[0082] The term FGFR1c also includes post-translational modifications of the FGFR1c amino acid sequence, for example, possible N-linked glycosylation sites. Thus, the antigen binding proteins can bind to or be generated from proteins glycosylated at one or more of the positions.

[0083] Binding proteins, such as anti-beta klotho antibodies, as described herein bind to beta klotho alone or in complex with an FGF receptor, such as FGFR2c. An encoding nucleic acid sequence of human FGFR2c is provided below:

atggtcagctggggtcgtttcatctgcctggtcgtggtcaccatggcaaccttgtccctggc
ccggccctccttcagtttagttgaggataccacattagagccagaagagccaccaaccaaat
accaaatctctcaaccagaagtgtacgtggctgcgccaggggagtcgctagaggtgcgctgc
ctgttgaaagatgccgccgtgatcagttggactaaggatggggtgcacttggggcccaacaa
taggacagtgcttattggggagtacttgcagataaagggcgccacgcctagagactccggcc
tctatgcttgtactgccagtaggactgtagacagtgaaacttggtacttcatggtgaatgtc
acagatgccatctcatccggagatgatgaggatgacaccgatggtgcggaagattttgtcag
tgagaacagtaacaacaagagagcaccatactggaccaacacagaaaagatggaaaagcggc
tccatgctgtgcctgcggccaacactgtcaagtttcgctgcccagccgggggggaacccaatg
ccaaccatgcggtggctgaaaaacgggaaggagtttaagcaggagcatcgcattggaggcta
caaggtacgaaaccagcactggagcctcattatggaaagtgtggtcccatctgacaagggaa
attatacctgtgtagtggagaatgaatacgggtccatcaatcacacgtaccacctggatgtt
gtggagcgatcgcctcaccggcccatcctccaagccggactgccggcaaatgcctccacagt
ggtcggaggagacgtagagtttgtctgcaaggtttacagtgatgcccagccccacatccagt
ggatcaagcacgtggaaaagaacggcagtaaatacgggcccgacgggctgccctacctcaag
gttctcaaggccgccggtgttaacaccacggacaaagagattgaggttctctatattcggaa
tgtaacttttgaggacgctggggaatatacgtgcttggcgggtaattctattgggatatcct
ttcactctgcatggttgacagttctgccagcgcctggaagagaaaaggagattacagcttcc
ccagactacctggagatagccatttactgcataggggtcttcttaatcgcctgtatggtggt

aacagtcatcctgtgccgaatgaagaacacgaccaagaagccagacttcagcagccagccgg
ctgtgcacaagctgaccaaacgtatccccctgcggagacaggtaacagtttcggctgagtcc
agctcctccatgaactccaacaccccgctggtgaggataacaacacgcctctcttcaacggc
agacacccccatgctggcaggggtctccgagtatgaacttccagaggacccaaaatgggagt
ttccaagagataagctgacactgggcaagcccctgggagaaggttgctttgggcaagtggtc
atggcggaagcagtgggaattgacaaagacaagcccaaggaggcggtcaccgtggccgtgaa
gatgttgaaagatgatgccacagagaaagacctttctgatctggtgtcagagatggagatga
tgaagatgattgggaaacacaagaatatcataaatcttcttggagcctgcacacaggatggg
cctctctatgtcatagttgagtatgcctctaaaggcaacctccgagaatacctccgagcccg
gaggccacccgggatggagtactcctatgacattaaccgtgttcctgaggagcagatgacct
tcaaggacttggtgtcatgcacctaccagctggccagaggcatggagtacttggcttcccaa
aaatgtattcatcgagatttagcagccagaaatgttttggtaacagaaaacaatgtgatgaa
aatagcagactttggactcgccagagatatcaacaatatagactattacaaaaagaccacca
atgggcggcttccagtcaagtggatggctccagaagccctgtttgatagagtatacactcat
cagagtgatgtctggtccttcggggtgttaatgtgggagatcttcactttaggggctcgcc
ctacccagggattcccgtggaggaacttttaagctgctgaaggaaggacacagaatggata
agccagccaactgcaccaacgaactgtacatgatgatgagggactgttggcatgcagtgccc
tcccagagaccaacgttcaagcagttggtagaagacttggatcgaattctcactctcacaac
caatgaggaatacttggacctcagccaacctctcgaacagtattcacctagttaccctgaca
caagaagttcttgttcttcaggagatgattctgtttttctccagaccccatgccttacgaa
ccatgccttcctcagtatccacacataaacggcagtgttaaaacatga
(SEQ ID NO:310)

[0084] The amino acid sequence of human FGFR2c is provided below; the amino acids that make up the signal sequence are underlined:

<u>mvswgrficlvvvtmatlsla</u>RPSFSLVEDTTLEPEEPPTKYQISQPEVYVAAPGESLEVRC
LLKDAAVISWTKDGVHLGPNNRTVLIGEYLQIKGATPRDSGLYACTASRTVDSETWYFMVNV
TDAISSGDDEDDTDGAEDFVSENSNNKRAPYWTNTEKMEKRLHAVPAANTVKFRCPAGGNPM
PTMRWLKNGKEFKQEHRIGGYKVRNQHWSLIMESVVPSDKGNYTCVVENEYGSINHTYHLDV
VERSPHRPILQAGLPANASTVVGGDVEFVCKVYSDAQPHIQWIKHVEKNGSKYGPDGLPYLK
VLKAAGVNTTDKEIEVLYIRNVTFEDAGEYTCLAGNSIGISFHSAWLTVLPAPGREKEITAS
PDYLEIAIYCIGVFLIACMVVTVILCRMKNTTKKPDFSSQPAVHKLTKRIPLRRQVTVSAES
SSSMNSNTPLVRITTRLSSTADTPMLAGVSEYELPEDPKWEFPRDKLTLGKPLGEGCFGQVV
MAEAVGIDKDKPKEAVTVAVKMLKDDATEKDLSDLVSEMEMMKMIGKHKNIINLLGACTQDG

PLYVIVEYASKGNLREYLRARRPPGMEYSYDINRVPEEQMTFKDLVSCTYQLARGMEYLASQ
KCIHRDLAARNVLVTENNVMKIADFGLARDINNIDYYKKTTNGRLPVKWMAPEALFDRVYTH
QSDVWSFGVLMWEIFTLGGSPYPGIPVEELFKLLKEGHRMDKPANCTNELYMMMRDCWHAVP
SQRPTFKQLVEDLDRILTLTTNEEYLDLSQPLEQYSPSYPDTRSSCSSGDDSVFSPDPMPYE
PCLPQYPHINGSVKT

(SEQ ID NO:311)

[0085] Binding proteins, such as anti-beta klotho antibodies, as described herein bind to beta klotho alone or in complex with an FGF receptor, such as FGFR3c. An encoding nucleic acid sequence of human FGFR3c (GenBank Accession Number NP 000133) is provided below:

atgggcgcccctgcctgcgccctcgcgctctgcgtggccgtggccatcgtggccggcgcctc
ctcggagtccttggggacggagcagcgcgtcgtggggcgagcggcagaagtcccgggcccag
agcccggccagcaggagcagttggtcttcggcagcggggatgctgtggagctgagctgtccc
ccgcccgggggtggtcccatggggcccactgtctgggtcaaggatggcacagggctggtgcc
ctcggagcgtgtcctggtggggccccagcggctgcaggtgctgaatgcctcccacgaggact
ccggggcctacagctgccggcagcggctcacgcagcgcgtactgtgccacttcagtgtgcgg
gtgacagacgctccatcctcgggagatgacgaagacggggaggacgaggctgaggacacagg
tgtggacacaggggccccttactggacacggcccgagcggatggacaagaagctgctggccg
tgccggccgccaacaccgtccgcttccgctgcccagccgctggcaaccccactccctccatc
tcctggctgaagaacggcagggagttccgcggcgagcaccgcattggaggcatcaagctgcg
gcatcagcagtggagcctggtcatggaaagcgtggtgccctcggaccgcggcaactacacct
gcgtcgtggagaacaagtttggcagcatccggcagacgtacacgctggacgtgctggagcgc
tccccgcaccggcccatcctgcaggcggggctgccggccaaccagacggcggtgctgggcag
cgacgtggagttccactgcaaggtgtacagtgacgcacagccccacatccagtggctcaagc
acgtggaggtgaatggcagcaaggtgggcccggacggcacaccctacgttaccgtgctcaag
acggcgggcgctaacaccaccgacaaggagctagaggttctctccttgcacaacgtcacctt
tgaggacgccggggagtacacctgcctggcgggcaattctattgggttttctcatcactctg
cgtggctggtggtgctgccagccgaggaggagctggtggaggctgacgaggcgggcagtgtg
tatgcaggcatcctcagctacggggtgggcttcttcctgttcatcctggtggtggcggctgt
gacgctctgccgcctgcgcagccccccaagaaaggcctgggctcccccaccgtgcacaaga
tctcccgcttcccgctcaagcgacaggtgtccctggagtccaacgcgtccatgagctccaac
acaccactggtgcgcatcgcaaggctgtcctcaggggagggccccacgctggccaatgtctc
cgagctcgagctgcctgccgaccccaaatgggagctgtctcgggcccggctgaccctgggca

agcccctttggggagggctgcttcggccaggtggtcatggcggaggccatcggcattgacaag
gaccgggccgccaagcctgtcaccgtagccgtgaagatgctgaaagacgatgccactgacaa
ggacctgtcggacctggtgtctgagatggagatgatgaagatgatcgggaaacacaaaaaca
tcatcaacctgctgggcgcctgcacgcagggcgggcccctgtacgtgctggtggagtacgcg
gccaagggtaacctgcgggagtttctgcgggcgcggcggcccccgggcctggactactcctt
cgacacctgcaagccgcccgaggagcagctcaccttcaaggacctggtgtcctgtgcctacc
aggtggcccggggcatggagtacttggcctcccagaagtgcatccacagggacctggctgcc
cgcaatgtgctggtgaccgaggacaacgtgatgaagatcgcagacttcgggctggcccggga
cgtgcacaacctcgactactacaagaagacaaccaacggccggctgcccgtgaagtggatgg
cgcctgaggccttgtttgaccgagtctacactcaccagagtgacgtctggtcctttggggtc
ctgctctgggagatcttcacgctgggggctccccgtaccccggcatccctgtggaggagct
cttcaagctgctgaaggagggccaccgcatggacaagcccgccaactgcacacacgacctgt
acatgatcatgcgggagtgctggcatgccgcgccctcccagaggcccaccttcaagcagctg
gtggaggacctggaccgtgtccttaccgtgacgtccaccgacgagtacctggacctgtcggc
gcctttcgagcagtactccccgggtggccaggacacccccagctccagctcctcaggggacg
actccgtgtttgcccacgacctgctgcccccggccccacccagcagtgggggctcgcggacg
tga

(SEQ ID NO:312)

[0086] The amino acid sequences of human FGFR3c is provided below; the amino acids that make-up the signal sequence are underlined:

mgapacalalcvavaivagassESLGTEQRVVGRAAEVPGPEPGQQEQLVFGSGDAVELSCP
PPGGGPMGPTVWVKDGTGLVPSERVLVGPQRLQVLNASHEDSGAYSCRQRLTQRVLCHFSVR
VTDAPSSGDDEDGEDEAEDTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSI
SWLKNGREFRGEHRIGGIKLRHQQWSLVMESVVPSDRGNYTCVVENKFGSIRQTYTLDVLER
SPHRPILQAGLPANQTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDGTPYVTVLK
TAGANTTDKELEVLSLHNVTFEDAGEYTCLAGNSIGFSHHSAWLVVLPAEEELVEADEAGSV
YAGILSYGVGFFLFILVVAAVTLCRLRSPPKKGLGSPTVHKISRFPLKRQVSLESNASMSSN
TPLVRIARLSSGEGPTLANVSELELPADPKWELSRARLTLGKPLGEGCFGQVVMAEAIGIDK
DRAAKPVTVAVKMLKDDATDKDLSDLVSEMEMMKMIGKHKNIINLLGACTQGGPLYVLVEYA
AKGNLREFLRARRPPGLDYSFDTCKPPEEQLTFKDLVSCAYQVARGMEYLASQKCIHRDLAA
RNVLVTEDNVMKIADFGLARDVHNLDYYKKTTNGRLPVKWMAPEALFDRVYTHQSDVWSFGV
LLWEIFTLGGSPYPGIPVEELFKLLKEGHRMDKPANCTHDLYMIMRECWHAAPSQRPTFKQL

VEDLDRVLTVTSTDEYLDLSAPFEQYSPGGQDTPSSSSSGDDSVFAHDLLPPAPPSSGGSRT
(SEQ ID NO:313)

[0087] Binding proteins, such as anti-beta klotho antibodies, as described herein bind to beta klotho alone or in complex with an FGF receptor, such as FGFR4. An encoding nuclic acid sequence of human FGFR4 is provided below:

atgcggctgctgctggccctgttgggggtcctgctgagtgtgcctgggcctccagtcttgtc
cctggaggcctctgaggaagtggagcttgagccctgcctggctcccagcctggagcagcaag
agcaggagctgacagtagcccttgggcagcctgtgcgtctgtgctgtgggcgggctgagcgt
ggtggccactggtacaaggagggcagtcgcctggcacctgctggccgtgtacggggctggag
gggccgcctagagattgccagcttcctacctgaggatgctggccgctacctctgcctggcac
gaggctccatgatcgtcctgcagaatctcaccttgattacaggtgactccttgacctccagc
aacgatgatgaggaccccaagtcccatagggacccctcgaataggcacagttacccccagca
agcaccctactggacacacccccagcgcatggagaagaaactgcatgcagtacctgcgggga
acaccgtcaagttccgctgtccagctgcaggcaaccccacgcccaccatccgctggcttaag
gatggacaggcctttcatggggagaaccgcattggaggcattcggctgcgccatcagcactg
gagtctcgtgatggagagcgtggtgccctcggaccgcggcacatacacctgcctggtagaga
acgctgtgggcagcatccgctataactacctgctagatgtgctggagcggtccccgcaccgg
cccatcctgcaggccgggctcccggccaacaccacagccgtggtgggcagcgacgtggagct
gctgtgcaaggtgtacagcgatgcccagccccacatccagtggctgaagcacatcgtcatca
acggcagcagcttcggagccgacggtttcccctatgtgcaagtcctaaagactgcagacatc
aatagctcagaggtggaggtcctgtacctgcggaacgtgtcagccgaggacgcaggcgagta
cacctgcctcgcaggcaattccatcggcctctcctaccagtctgcctggctcacggtgctgc
cagaggaggaccccacatggaccgcagcagcgcccgaggccaggtatacggacatcatcctg
tacgcgtcgggctccctggccttggctgtgctcctgctgctggccgggctgtatcgagggca
ggcgctccacggccggcacccccgcccgcccgccactgtgcagaagctctcccgcttccctc
tggcccgacagttctccctggagtcaggctcttccggcaagtcaagctcatccctggtacga
ggcgtgcgtctctcctccagcggccccgccttgctcgccggcctcgtgagtctagatctacc
tctcgacccactatgggagttcccccgggacaggctggtgcttgggaagcccctaggcgagg
gctgctttggccaggtagtacgtgcagaggcctttggcatggaccctgcccggcctgaccaa
gccagcactgtggccgtcaagatgctcaaagacaacgcctctgacaaggacctggccgacct
ggtctcggagatggaggtgatgaagctgatcggccgacacaagaacatcatcaacctgcttg
gtgtctgcacccaggaagggcccctgtacgtgatcgtggagtgcgccgccaagggaaacctg
cgggagttcctgcgggcccggcgcccccccaggccccgacctcagccccgacggtcctcggag

cagtgaggggccgctctccttcccagtcctggtctcctgcgcctaccaggtggcccgaggca
tgcagtatctggagtcccggaagtgtatccaccgggacctggctgcccgcaatgtgctggtg
actgaggacaatgtgatgaagattgctgactttgggctggcccgcggcgtccaccacattga
ctactataagaaaaccagcaacggccgcctgcctgtgaagtggatggcgcccgaggccttgt
ttgaccgggtgtacacacaccagagtgacgtgtggtcttttgggatcctgctatgggagatc
ttcaccctcgggggctccccgtatcctggcatcccggtggaggagctgttctcgctgctgcg
ggagggacatcggatggaccgacccccacactgccccccagagctgtacgggctgatgcgtg
agtgctggcacgcagcgccctcccagaggcctaccttcaagcagctggtggaggcgctggac
aaggtcctgctggccgtctctgaggagtacctcgacctccgcctgaccttcggaccctattc
cccctctggtggggacgccagcagcacctgctcctccagcgattctgtcttcagccacgacc
ccctgccattgggatccagctccttccccttcgggtctggggtgcagacatga
(SEQ ID NO:314)

[0088] The amino acid sequence of human FGFR4 (GenBank Accession Number NP. 002002.3) is provided below; the amino acids that make-up the signal sequence are underlined:

mrlllallgvllsvpgppvlsLEASEEVELEPCLAPSLEQQEQELTVALGQPVRLCCGRAER
GGHWYKEGSRLAPAGRVRGWRGRLEIASFLPEDAGRYLCLARGSMIVLQNLTLITGDSLTSS
NDDEDPKSHRDPSNRHSYPQQAPYWTHPQRMEKKLHAVPAGNTVKFRCPAAGNPTPTIRWLK
DGQAFHGENRIGGIRLRHQHWSLVMESVVPSDRGTYTCLVENAVGSIRYNYLLDVLERSPHR
PILQAGLPANTTAVVGSDVELLCKVYSDAQPHIQWLKHIVINGSSFGADGFPYVQVLKTADI
NSSEVEVLYLRNVSAEDAGEYTCLAGNSIGLSYQSAWLTVLPEEDPTWTAAAPEARYTDIIL
YASGSLALAVLLLLAGLYRGQALHGRHPRPPATVQKLSRFPLARQFSLESGSSGKSSSSLVR
GVRLSSSGPALLAGLVSLDLPLDPLWEFPRDRLVLGKPLGEGCFGQVVRAEAFGMDPARPDQ
ASTVAVKMLKDNASDKDLADLVSEMEVMKLIGRHKNIINLLGVCTQEGPLYVIVECAAKGNL
REFLRARRPPGPDLSPDGPRSSEGPLSFPVLVSCAYQVARGMQYLESRKCIHRDLAARNVLV
TEDNVMKIADFGLARGVHHIDYYKKTSNGRLPVKWMAPEALFDRVYTHQSDVWSFGILLWEI
FTLGGSPYPGIPVEELFSLLREGHRMDRPPHCPPELYGLMRECWHAAPSQRPTFKQLVEALD
KVLLAVSEEYLDLRLTFGPYSPSGGDASSTCSSSDSVFSHDPLPLGSSSFPFGSGVQT
(SEQ ID NO:315)

[0089] An “antigen” is a predetermined antigen to which an antibody can selectively bind. A target antigen may be a polypeptide, carbohydrate, nucleic acid,

lipid, hapten or other naturally occurring or synthetic compound. Preferably, the target antigen is a polypeptide.

[0090] The term "antigen binding fragment," "antigen binding domain," "antigen binding region," and similar terms refer to that portion of an antibody which comprises the amino acid residues that interact with an antigen and confer on the binding agent its specificity and affinity for the antigen (*e.g.,* the complementarity determining regions (CDRs)).

[0091] The terms "binds" or "binding" refer to an interaction between molecules including, for example, to form a complex. Interactions can be, for example, non-covalent interactions including hydrogen bonds, ionic bonds, hydrophobic interactions, and/or van der Waals interactions. A complex can also include the binding of two or more molecules held together by covalent or non-covalent bonds, interactions or forces. The strength of the total non-covalent interactions between a single antigen-binding site on an antibody and a single epitope of a target molecule, such as beta klotho, is the affinity of the antibody or functional fragment for that epitope. The ratio of association (k1) to dissociation (k-1) of an antibody to a monovalent antigen (k1/ k-1) is the association constant K, which is a measure of affinity. The value of K varies for different complexes of antibody and antigen and depends on both k1 and k-1. The association constant K for an antibody provided herein can be determined using any method provided herein or any other method well known to those skilled in the art. The affinity at one binding site does not always reflect the true strength of the interaction between an antibody and an antigen. When complex antigens containing multiple, repeating antigenic determinants, such as a polyvalent beta klotho, come in contact with antibodies containing multiple binding sites, the interaction of antibody with antigen at one site will increase the probability of a reaction at a second site. The strength of such multiple interactions between a multivalent antibody and antigen is called the avidity. The avidity of an antibody can be a better measure of its binding capacity than is the affinity of its individual binding sites. For example, high avidity can compensate for low affinity as is sometimes found for pentameric IgM antibodies, which can have a lower affinity than IgG, but the high avidity of IgM, resulting from its multivalence, enables it to bind antigen effectively.

[0092] The terms "antibodies that specifically bind to beta klotho," "antibodies that specifically bind to a beta klotho epitope," and analogous terms are also used interchangeably herein and refer to antibodies that specifically bind to a beta klotho polypeptide, such as a beta klotho antigen, or fragment, or epitope (*e.g.,* human beta klotho such as a human beta klotho polypeptide, antigen or epitope). An antibody that specifically binds to beta klotho, (*e.g.,* human beta klotho) may bind to the extracellular domain or peptide derived from the extracellular domain of beta klotho beta klotho. An antibody that specifically binds to a beta klotho antigen (*e.g.,* human beta klotho) may be cross-reactive with related antigens (*e.g.,*cyno beta klotho). In certain embodiments, an antibody that specifically binds to a beta klotho antigen does not cross-react with other antigens. An antibody that specifically binds to a beta klotho antigen can be identified, for example, by immunoassays, Biacore, or other techniques known to those of skill in the art. An antibody binds specifically to a beta klotho antigen when it binds to a beta klotho antigen with higher affinity than to any cross reactive antigen as determined using experimental techniques, such as radioimmunoassays (RIA) and enzyme linked immunosorbent assays (ELISAs). Typically a specific or selective reaction will be at least twice background signal or noise and may be more than 10 times background. See, *e.g.,* Paul, ed., 1989, Fundamental Immunology Second Edition, Raven Press, New York at pages 332 336 for a discussion regarding antibody specificity. An antibody "which binds" an antigen of interest (*e.g.,* a target antigen such as beta klotho) is one that binds the antigen with sufficient affinity such that the antibody is useful as a therapeutic agent in targeting a cell or tissue expressing the antigen, and does not significantly cross-react with other proteins. In such embodiments, the extent of binding of the antibody to a "non-target" protein will be less than about 10% of the binding of the antibody to its particular target protein, for example, as determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA). With regard to the binding of an antibody to a target molecule, the term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is

similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term “specific binding” or “specifically binds to” or is “specific for” a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a Kd for the target of at least about 10^{-4} M, alternatively at least about 10^{-5} M, alternatively at least about 10^{-6} M, alternatively at least about 10^{-7} M, alternatively at least about 10^{-8} M, alternatively at least about 10^{-9} M, alternatively at least about 10^{-10} M, alternatively at least about 10^{-11} M, alternatively at least about 10^{-12} M, or greater. In one embodiment, the term “specific binding” refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. In certain embodiments, an antibody that binds to beta klotho has a dissociation constant (Kd) of less than or equal to 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.9 nM, 0.8 nM, 0.7 nM, 0.6 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, or 0.1 nM. The lower the K_D, the higher the affinity of the anti-beta klotho antibody. In certain embodiments, anti-beta klotho antibody binds to an epitope of beta klotho that is conserved among beta klotho from different species (*e.g.,* between human and cyno beta klotho).

[0093] The term "compete" when used in the context of anti-beta klotho antibodies (*e.g.,* agonistic antibodies and binding proteins that bind to (i) beta klotho; or (ii) a complex comprising beta klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4) that compete for the same epitope or binding site on a target means competition between as determined by an assay in which the antibody (or binding fragment) thereof under study prevents or inhibits the specific binding of a reference molecule (*e.g.,* a reference ligand, or reference antigen binding protein, such as a reference antibody) to a common antigen (*e.g.,* beta klotho or a fragment thereof). Numerous types of competitive binding assays can be used to determine if a test antibody competes with a reference antibody for binding to beta klotho (*e.g.,* human beta klotho). Examples of assays that can be employed include solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see, *e.g.,* Stahli et al., (1983) Methods in Enzymology 9:242-253); solid phase direct biotin-avidin EIA (see, *e.g.,*

Kirkland *et al.*, (1986) J. Immunol. 137:3614-3619) solid phase direct labeled assay, solid phase direct labeled sandwich assay (see, *e.g.,* Harlow and Lane, (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Press); solid phase direct label RIA using 1-125 label (see, *e.g.,* Morel *et al.*, (1988) Molec. Immunol. 25:7-15); solid phase direct biotin-avidin EIA (see, *e.g.,* Cheung, et al., (1990) Virology 176:546-552); and direct labeled RIA (Moldenhauer et al., (1990) Scand. J. Immunol. 32:77-82). Typically, such an assay involves the use of a purified antigen (*e.g.,* beta klotho such as human beta klotho) bound to a solid surface or cells bearing either of an unlabelled test antigen binding protein (*e.g.,* test anti-beta klotho antibody) or a labeled reference antigen binding protein (*e.g.,* reference anti-beta klotho antibody). Competitive inhibition may be measured by determining the amount of label bound to the solid surface or cells in the presence of the test antigen binding protein. Usually the test antigen binding protein is present in excess. Antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and/or antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference for antibodies steric hindrance to occur. Additional details regarding methods for determining competitive binding are described herein. Usually, when a competing antibodies protein is present in excess, it will inhibit specific binding of a reference antibodies to a common antigen by at least 23%, for example 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%]]. In some instance, binding is inhibited by at least 80%, 85%, 90%, 95%, 96% or 97%, 98%, 99% or more.

[0094] The term “anti-beta klotho antibody” or “an antibody that binds to beta klotho” includes an antibody that is capable of binding beta klotho with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting beta klotho. Preferably, the extent of binding of an anti-beta klotho antibody to an unrelated, non-beta klotho protein is less than about 10% of the binding of the antibody to beta klotho as measured, for example, by fluorescence activated cell sorting (FACS) analysis or an immunoassay such as a radioimmunoassay (RIA). An antibody that “specifically binds to” or is “specific for” beta klotho is Illustrated above. In certain embodiments, an antibody that binds to beta klotho, as described herein has a dissociation constant (Kd) of less than or equal to 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 0.9 nM, 0.8 nM, 0.7 nM, 0.6

nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, or 0.1 nM, and/or is greater than or equal to 0.1nM. In certain embodiments, anti-beta klotho antibody binds to an epitope of beta klotho that is conserved among beta klotho from different species (*e.g.,* between human and cyno beta klotho).

[0095] An "isolated" antibody is substantially free of cellular material or other contaminating proteins from the cell or tissue source and/or other contaminant components from which the antibody is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 25%, 20%, 15%,10%, 5%, or 1% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). In certain embodiments, when the antibody is recombinantly produced, it is substantially free of culture medium, *e.g.,* culture medium represents less than about 20%, 15%, 10%, 5%, or 1% of the volume of the protein preparation. In certain embodiments, when the antibody is produced by chemical synthesis, it is substantially free of chemical precursors or other chemicals, for example, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the antibody have less than about 30%, 25%, 20%, 15%, 10%, 5%, or 1% (by dry weight) of chemical precursors or compounds other than the antibody of interest. Contaminant components can also include, but are not limited to, materials that would interfere with therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In certain embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method (Lowry *et al.* J. Bio. Chem. 193: 265-275, 1951), such as 96%, 97%, 98%, or 99%, by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily,

however, isolated antibody will be prepared by at least one purification step. In specific embodiments, antibodies provided herein are isolated.

[0096] A 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to a H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (VH) followed by three constant domains (CH) for each of the α and γ chains and four CH domains for μ and ε isotypes. Each L chain has at the N-terminus, a variable domain (VL) followed by a constant domain (CL) at its other end. The VL is aligned with the VH and the CL is aligned with the first constant domain of the heavy chain (CH1). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a VH and VL together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, *e.g.,* Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

[0097] The term "variable region" or "variable domain" refers to a portion of the light or heavy chains of an antibody that is generally located at the amino-terminal of the light or heavy chain and has a length of about 120 to 130 amino acids in the heavy chain and about 100 to 110 amino acids in the light chain, and are used in the binding and specificity of each particular antibody for its particular antigen. The variable region of the heavy chain may be referred to as "VH." The variable region of the light chain may be referred to as "VL." The term "variable" refers to the fact that certain segments of the variable regions differ extensively in sequence among antibodies. The V region mediates antigen binding and defines specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable regions. Instead, the V regions consist of less variable (*e.g.,* relatively invariant) stretches called framework regions (FRs) of about 15-30 amino acids separated by shorter regions of greater variability (*e.g.,* extreme variability) called "hypervariable regions" that are each about 9-12 amino acids long. The variable regions of heavy and light chains each

comprise four FRs, largely adopting a β sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see, *e.g.,* Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991)). The constant regions are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). The variable regions differ extensively in sequence between different antibodies. The variability in sequence is concentrated in the CDRs while the less variable portions in the variable region are referred to as framework regions (FR). The CDRs of the light and heavy chains are primarily responsible for the interaction of the antibody with antigen. In specific embodiments, the variable region is a human variable region.

[0098] The term "variable region residue numbering as in Kabat" or "amino acid position numbering as in Kabat", and variations thereof, refers to the numbering system used for heavy chain variable regions or light chain variable regions of the compilation of antibodies in Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991). Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or CDR of the variable domain. For example, a heavy chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (*e.g.,* residues 82a, 82b, and 82c, etc, according to Kabat) after heavy chain FR residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence. The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.,* Kabat *et al.,* Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The "EU numbering system" or "EU index" is generally used when referring

to a residue in an immunoglobulin heavy chain constant region (*e.g.,* the EU index reported in Kabat *et al.*, supra). The "EU index as in Kabat" refers to the residue numbering of the human IgG 1 EU antibody. Other numbering systems have been described, including, for example, by AbM, Chothia, Contact, IMGT and AHon. Various numbers systems are illustrated in Figures 1-3.

[0099] An "intact" antibody is one comprising an antigen-binding site as well as a CL and at least heavy chain constant regions, CH1, CH2 and CH3. The constant regions may include human constant regions or amino acid sequence variants thereof. Preferably, an intact antibody has one or more effector functions.

[00100] "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include, without limitation, Fab, Fab', F(ab')2, and Fv fragments; diabodies and di-diabodies (see, *e.g.,* Holliger, P. *et al.,* (1993) Proc. Natl. Acad. Sci. 90:6444-8; Lu, D. *et al.,* (2005) J. Biol. Chem. 280:19665-72; Hudson *et al.*, Nat. Med. 9:129-134 (2003); WO 93/11161; and U.S. Patent Nos. 5,837,242 and 6,492,123); single-chain antibody molecules (see, *e.g.,* U.S. Patent Nos. 4,946,778; 5,260,203; 5,482,858 and 5,476,786); dual variable domain antibodies (see, *e.g.,* U.S. Patent No. 7,612,181); single variable domain antibodies (SdAbs) (see, *e.g.,* Woolven *et al.*, Immunogenetics 50: 98-101, 1999; Streltsov *et al.*, Proc Natl Acad Sci USA. 101:12444-12449, 2004); and multispecific antibodies formed from antibody fragments.

[00101] A "functional fragment" or "binding fragment" or "antigen binding fragment" of a therapeutic antibody will exhibit at least one if not some or all of the biological functions attributed to the intact antibody, the function comprising at least binding to the target antigen, (*e.g.,* a beta klotho binding fragment or fragment that binds to beta klotho).

[00102] The term "fusion protein" as used herein refers to a polypeptide that comprises an amino acid sequence of an antibody and an amino acid sequence of a heterologous polypeptide or protein (*e.g.,* a polypeptide or protein not normally a part of the antibody (*e.g.,* a non-anti-beta klotho antigen binding antibody)). The term "fusion" when used in relation to beta klotho or to an anti-beta klotho antibody refers to the joining of a peptide or polypeptide, or fragment, variant and/or derivative

thereof, with a heterologous peptide or polypeptide. In certain embodiments, the fusion protein retains the biological activity of the beta klotho or anti-beta klotho antibody. In certain embodiments, the fusion protein comprises a beta klotho antibody VH region, VL region, VH CDR (one, two or three VH CDRs), and/or VL CDR (one, two or three VL CDRs), wherein the fusion protein binds to a beta klotho epitope, a beta klotho fragment and/or a beta klotho polypeptide.

[00103] The term "heavy chain" when used in reference to an antibody refers to a polypeptide chain of about 50-70 kDa, wherein the amino-terminal portion includes a variable region of about 120 to 130 or more amino acids and a carboxy-terminal portion that includes a constant region. The constant region can be one of five distinct types, (*e.g.,* isotypes) referred to as alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino acid sequence of the heavy chain constant region. The distinct heavy chains differ in size: α, δ and γ contain approximately 450 amino acids, while μ and ε contain approximately 550 amino acids. When combined with a light chain, these distinct types of heavy chains give rise to five well known classes (*e.g.,* isotypes) of antibodies, IgA, IgD, IgE, IgG and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG2, IgG3 and IgG4. A heavy chain can be a human heavy chain.

[00104] The term "light chain" when used in reference to an antibody refers to a polypeptide chain of about 25 kDa, wherein the amino-terminal portion includes a variable region of about 100 to about 110 or more amino acids and a carboxy-terminal portion that includes a constant region. The approximate length of a light chain is 211 to 217 amino acids. There are two distinct types, referred to as kappa (κ) of lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. A light chain can be a human light chain.

[00105] The term "host" as used herein refers to an animal, such as a mammal (*e.g.,* a human).

[00106] The term "host cell" as used herein refers to a particular subject cell that may be transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental

influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[00107] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *e.g.,* the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts, and each monoclonal antibody will typically recognize a single epitope on the antigen. In specific embodiments, a "monoclonal antibody," as used herein, is an antibody produced by a single hybridoma or other cell, wherein the antibody binds to only a beta klotho epitope as determined, for example, by ELISA or other antigen-binding or competitive binding assay known in the art. The term "monoclonal" is not limited to any particular method for making the antibody. For example, the monoclonal antibodies useful in the present disclosure may be prepared by the hybridoma methodology first described by Kohler *et al.*, Nature, 256:495 (1975), or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, *e.g.,* U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, Nature, 352:624-628 (1991) and Marks *et al.*, J. Mol. Biol., 222:581-597 (1991), for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel *et al.*, eds., John Wiley and Sons, New York). Exemplary methods of producing monoclonal antibodies are provided in the Examples herein.

[00108] The term "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to those which are found in nature and not manipulated, modified, and/or changed (*e.g.,* isolated, purified, selected) by a human being.

[00109] The antibodies provided herein can include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as

well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Patent No. 4,816,567; and Morrison *et al.*, Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)).

[00110] "Humanized" forms of nonhuman (*e.g.,* murine) antibodies are chimeric antibodies that include human immunoglobulins (*e.g.,* recipient antibody) in which the native CDR residues are replaced by residues from the corresponding CDR of a nonhuman species (*e.g.,* donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, one or more FR region residues of the human immunoglobulin are replaced by corresponding nonhuman residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. A humanized antibody heavy or light chain can comprise substantially all of at least one or more variable regions, in which all or substantially all of the CDRs correspond to those of a nonhuman immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. In certain embodiments, the humanized antibody will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see, Jones *et al.*, Nature, 321:522-525 (1986); Riechmann *et al.*, Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992); Carter *et al.*, Proc. Natl. Acd. Sci. USA 89:4285-4289 (1992); and U.S. Patent Nos: 6,800,738 (issued Oct. 5, 2004), 6,719,971 (issued Sept. 27, 2005), 6,639,055 (issued Oct. 28, 2003), 6,407,213 (issued June 18, 2002), and 6,054,297 (issued April 25, 2000).

[00111] A "human antibody" is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries (Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks *et al.*, J. Mol. Biol., 222:581 (1991) and yeast display libraries (Chao *et al.*, Nature Protocols 1: 755-768 (2006)). Also available for the preparation of human monoclonal antibodies are methods described in Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, Alan

R. Liss, p. 77 (1985); Boerner *et al.*, J. Immunol., 147(1):86-95 (1991). See also van Dijk and van de Winkel, Curr. Opin. Pharmacol., 5: 368-74 (2001). Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, *e.g.,* mice (see, *e.g.,* Jakobovits, A., Curr. Opin. Biotechnol. 1995, 6(5):561-6; Brüggemann and Taussing, Curr. Opin. Biotechnol. 1997, 8(4):455-8; and U.S. Pat. Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). See also, for example, Li *et al.*, Proc. Natl. Acad. Sci. USA, 103:3557-3562 (2006) regarding human antibodies generated via a human B-cell hybridoma technology.

[00112] A "CDR" refers to one of three hypervariable regions (H1, H2 or H3) within the non-framework region of the immunoglobulin (Ig or antibody) VH β-sheet framework, or one of three hypervariable regions (L1, L2 or L3) within the non-framework region of the antibody VL β-sheet framework. Accordingly, CDRs are variable region sequences interspersed within the framework region sequences. CDR regions are well known to those skilled in the art and have been defined by, for example, Kabat as the regions of most hypervariability within the antibody variable (V) domains (Kabat *et al.*, J. Biol. Chem. 252:6609-6616 (1977); Kabat, Adv. Prot. Chem. 32:1-75 (1978)). CDR region sequences also have been defined structurally by Chothia as those residues that are not part of the conserved β-sheet framework, and thus are able to adapt different conformations (Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)). Both terminologies are well recognized in the art. CDR region sequences have also been defined by AbM, Contact and IMGT. CDR region sequences are illustrated in Figures 1-3. The positions of CDRs within a canonical antibody variable region have been determined by comparison of numerous structures (Al-Lazikani *et al.*, J. Mol. Biol. 273:927-948 (1997); Morea *et al.*, Methods 20:267-279 (2000)). Because the number of residues within a hypervariable region varies in different antibodies, additional residues relative to the canonical positions are conventionally numbered with a, b, c and so forth next to the residue number in the canonical variable region numbering scheme (Al-Lazikani *et al.*, supra (1997)). Such nomenclature is similarly well known to those skilled in the art.

[00113] The term "hypervariable region", "HVR", or "HV", when used herein refers to the regions of an antibody variable region that are hypervariable in sequence

and/or form structurally defined loops. Generally, antibodies comprise six hypervariable regions; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). A number of hypervariable region delineations are in use and are encompassed herein. The Kabat Complementarity Determining Regions (CDRs) are based on sequence variability and are the most commonly used (see, *e.g.,* Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). Chothia refers instead to the location of the structural loops (see, *e.g.,*Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (see, *e.g.,* Martin, in Antibody Engineering, Vol. 2, Chapter 3, Springer Verlag). The "contact" hypervariable regions are based on an analysis of the available complex crystal structures. The residues from each of these hypervariable regions or CDRs are noted below.

[00114] Recently, a universal numbering system has been developed and widely adopted, ImMunoGeneTics (IMGT) Information System® (Lafranc *et al.*, Dev. Comp. Immunol. 27(1):55-77 (2003)). IMGT is an integrated information system specializing in immunoglobulins (IG), T cell receptors (TR) and major histocompatibility complex (MHC) of human and other vertebrates. Herein, the CDRs are referred to in terms of both the amino acid sequence and the location within the light or heavy chain. As the "location" of the CDRs within the structure of the immunoglobulin variable domain is conserved between species and present in structures called loops, by using numbering systems that align variable domain sequences according to structural features, CDR and framework residues and are readily identified. This information can be used in grafting and replacement of CDR residues from immunoglobulins of one species into an acceptor framework from, typically, a human antibody. An additional numbering system (AHon) has been developed by Honegger and Plückthun, *J. Mol. Biol.* 309: 657-670 (2001).

Correspondence between the numbering system, including, for example, the Kabat numbering and the IMGT unique numbering system, is well known to one skilled in the art (see, *e.g.,* Kabat, *supra*; Chothia and Lesk, *supra*; Martin, *supra*; Lefranc *et al.*, *supra*) and is also illustrated in Figures 1-3. An Exemplary system, shown herein, combines Kabat and Chothia.

	Exemplary	IMGT	Kabat	AbM	Chothia	Contact
V_H CDR1	26-35	27-38	31-35	26-35	26-32	30-35
V_H CDR2	50-65	56-65	50-65	50-58	53-55	47-58
V_H CDR3	95-102	105-117	95-102	95-102	96-101	93-101
V_L CDR1	24-34	27-38	24-34	24-34	26-32	30-36
V_L CDR2	50-56	56-65	50-56	50-56	50-52	46-55
V_L CDR3	89-97	105-117	89-97	89-97	91-96	89-96

[00115] Hypervariable regions may comprise "extended hypervariable regions" as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2) and 89-97 or 89-96 (L3) in the VL and 26-35 or 26-35A (H1), 50-65 or 49-65 (H2) and 93-102, 94-102, or 95-102 (H3) in the VH. As used herein, the terms "HVR" and "CDR" are used interchangeably.

[00116] The term "constant region" or "constant domain" refers to a carboxy terminal portion of the light and heavy chain which is not directly involved in binding of the antibody to antigen but exhibits various effector function, such as interaction with the Fc receptor. The terms refer to the portion of an immunoglobulin molecule having a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable region, which contains the antigen binding site. The constant region may contain the CH1, CH2 and CH3 regions of the heavy chain and the CL region of the light chain.

[00117] The term "framework" or "FR" residues are those variable region residues flanking the CDRs. FR residues are present, for example, in chimeric, humanized, human, domain antibodies, diabodies, linear antibodies, and bispecific antibodies. FR residues are those variable domain residues other than the hypervariable region residues or CDR residues.

[00118] An "affinity matured" antibody is one with one or more alterations (*e.g.,* amino acid sequence variations, including changes, additions and/or deletions) in

one or more HVRs thereof which result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody which does not possess those alteration(s). Preferred affinity matured antibodies will have nanomolar or even picomolar affinities for the target antigen. Affinity matured antibodies are produced by procedures known in the art. For review, see Hudson and Souriau, Nature Medicine 9 :129-134 (2003); Hoogenboom, Nature Biotechnol. 23 : 1105-1116 (2005); Quiroz and Sinclair, Revista Ingeneria Biomedia 4 : 39-51 (2010).

[00119] A "blocking" antibody or an "antagonist" antibody is one which inhibits or reduces biological activity of the antigen it binds. For example, blocking antibodies or antagonist antibodies may substantially or completely inhibit the biological activity of the antigen.

[00120] An "agonist antibody" is an antibody that triggers a response, *e.g.,* one that mimics at least one of the functional activities of a polypeptide of interest (*e.g.,* FGF19 or FGF21). An agonist antibody includes an antibody that is a ligand mimetic, for example, wherein a ligand binds to a cell surface receptor and the binding induces cell signaling or activities via an intercellular cell signaling pathway and wherein the antibody induces a similar cell signaling or activation.

[00121] An "agonist" of beta klotho refers to a molecule that is capable of activating or otherwise increasing one or more of the biological activities of beta klotho, such as in a cell expressing beta klotho and a FGF receptor. In some embodiments, an agonist of beta klotho (*e.g.,* an agonistic antibody as described herein) may, for example, act by activating or otherwise increasing the activation and/or cell signaling pathways of a cell expressing a beta klotho protein and a FGF receptor, thereby increasing a beta klotho-mediated biological activity of the cell relative to the beta klotho-mediated biological activity in the absence of agonist. In some embodiments the antibodies provided herein are agonistic anti-beta klotho antibodies, including antibodies that induce FGF19-like signaling and/or FGF21-like signaling.

[00122] "Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (*e.g.,* a binding protein such as an antibody) and its binding partner (*e.g.,* an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.,* antibody

and antigen). The affinity of a binding molecule X for its binding partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present disclosure. Specific illustrative embodiments include the following. In one embodiment, the "K_D" or "K_D value" may be measured by assays known in the art, for example by a binding assay. The K_D may be measured in a radiolabeled antigen binding assay (RIA), for example, performed with the Fab version of an antibody of interest and its antigen (Chen, *et al.*, (1999) J. Mol Biol 293:865-881). The K_D or K_D value may also be measured by using surface plasmon resonance assays by Biacore, using, for example, a BIAcoreTM-2000 or a BIAcoreTM-3000 BIAcore, Inc., Piscataway, NJ), or by biolayer interferometry using, for example, the OctetQK384 sytem (ForteBio, Menlo Park, CA). An "on-rate" or "rate of association" or "association rate" or "kon" may can also be determined with the same surface plasmon resonance or biolayer interferometry techniques described above using, for example, a BIAcoreTM-2000 or a BIAcoreTM-3000 (BIAcore, Inc., Piscataway, NJ), or the OctetQK384 sytem (ForteBio, Menlo Park, CA).

[00123] The phrase "substantially similar" or "substantially the same" denotes a sufficiently high degree of similarity between two numeric values (*e.g.,* one associated with an antibody of the present disclosure and the other associated with a reference antibody) such that one of skill in the art would consider the difference between the two values to be of little or no biological and/or statistical significance within the context of the biological characteristic measured by the values (*e.g.,* K_D values). For example, the difference between the two values may be less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%,as a function of the value for the reference antibody.

[00124] The phrase "substantially reduced," or "substantially different", as used herein, denotes a sufficiently high degree of difference between two numeric values (*e.g.,* one associated with an antibody of the present disclosure and the other associated with a reference antibody) such that one of skill in the art would consider

the difference between the two values to be of statistical significance within the context of the biological characteristic measured by the values. For example, the difference between said two values may be preferably greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50% as a function of the value for the reference antibody.

[00125] Antibody "effector functions" refer to those biological activities attributable to the Fc region (*e.g.,* a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.,* B cell receptor); and B cell activation.

[00126] The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including, for example, native sequence Fc regions, recombinant Fc regions, and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is often defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue.

[00127] A "functional Fc region" possesses an "effector function" of a native sequence Fc region. Exemplary "effector functions" include C1q binding; complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.,* B cell receptor; BCR), etc. Such effector functions generally require the Fc region to be combined with a binding region or binding domain (*e.g.,* an antibody variable region or domain) and can be assessed using various assays as disclosed.

[00128] A “native sequence Fc region” comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature, and not manipulated, modified, and/or changed (*e.g.,* isolated, purified, selected, including or combining with other sequences such as variable region sequences) by a human. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

[00129] A “variant Fc region” comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, (*e.g.,* substituting, addition, or deletion) preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, for example, from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and more preferably at least about 90% homology therewith, for example, at least about 95% homology therewith. For example, a variant with two amino acid changes to alanine at two positions in the human IgG1 Fc sequence are shown bolded in the amino acid sequence provided below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP**A**L**A**GGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK

(SEQ ID NO:316)

Such a variant sequence may be used in humanized heavy chain constructs such as shown below for a humanized 5H23-vH3 (see, *e.g.,* Example 7) designated 5H23(vH3)-hIgG1(E233A)(L235A) as provided below; the amino acids that make up the signal sequence are underlined and the variable region sequence is bolded:

mdmrvpaqllglllwlrgarc**QVQLQQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQA**
PGQGLEWIGWIYPGDGSTKYNEKFKGKATITRDTSASTAYMELSSLRSEDTAVYFCARSDYY
GSRSFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
HTCPPCPAPALAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO:317)

[00130] A “light chain constant region” includes kappa and lambda constant regions. An exemplary kappa constant region is provided below:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK
DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
(SEQ ID NO: 318)
Such a kappa constant region sequence may be used in humanized light chain constructs such as shown below for a humanized 5H23-vL2 (see, *e.g.,* Example 7) as provided below; the amino acids that make up the signal sequence are underlined and the variable region sequence is bolded:
mdmrvpaqllglllwlrgarc**DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYVYMHWY**
QQKPGQPPKLLIYLASYLESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQHSRDLTFPF
GGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
(SEQ ID NO: 319)

[00131] The term “variant” when used in relation to beta klotho or to an anti-beta klotho antibody may refer to a peptide or polypeptide comprising one or more (such as, for example, about 1 to about 25, about 1 to about 20, about 1 to about 15, about 1 to about 10, or about 1 to about 5) amino acid sequence substitutions, deletions, and/or additions as compared to a native or unmodified beta klotho sequence. For example, a beta klotho variant may result from one or more (such as, for example, about 1 to about 25, about 1 to about 20, about 1 to about 15, about 1 to about 10, or

about 1 to about 5) changes to an amino acid sequence of a native beta klotho. Also by way of example, a variant of an anti-beta klotho antibody may result from one or more (such as, for example, about 1 to about 25, about 1 to about 20, about 1 to about 15, about 1 to about 10, or about 1 to about 5) changes to an amino acid sequence of a native or previously unmodified anti-beta klotho antibody. Variants may be naturally occurring, such as allelic or splice variants, or may be artificially constructed. Polypeptide variants may be prepared from the corresponding nucleic acid molecules encoding the variants. In specific embodiments, the beta klotho variant or anti-beta klotho antibody variant at least retains beta klotho or anti-beta klotho antibody functional activity, respectively. In specific embodiments, an anti-beta klotho antibody variant binds beta klotho and/or is antagonistic to beta klotho activity. In specific embodiments, an anti-beta klotho antibody variant binds beta klotho and/or is agonistic to beta klotho activity. In certain embodiments, the variant is encoded by a single nucleotide polymorphism (SNP) variant of a nucleic acid molecule that encodes beta klotho or anti-beta klotho antibody VH or VL regions or subregions, such as one or more CDRs.

[00132] The term "vector" refers to a substance that is used to carry or include a nucleic acid sequences, including for example, in order to introduce a nucleic acid sequence into a host cell. Vectors applicable for use include, for example, expression vectors, plasmids, phage vectors, viral vectors, episomes and artificial chromosomes, which can include selection sequences or markers operable for stable integration into a host cell's chromosome. Additionally, the vectors can include one or more selectable marker genes and appropriate expression control sequences. Selectable marker genes that can be included, for example, provide resistance to antibiotics or toxins, complement auxotrophic deficiencies, or supply critical nutrients not in the culture media. Expression control sequences can include constitutive and inducible promoters, transcription enhancers, transcription terminators, and the like which are well known in the art. When two or more nucleic acid molecules are to be co-expressed (*e.g.* both an antibody heavy and light chain or an antibody VH and VL) both nucleic acid molecules can be inserted, for example, into a single expression vector or in separate expression vectors. For single vector expression, the encoding nucleic acids can be operationally linked to one common expression control sequence or linked to different expression control sequences,

such as one inducible promoter and one constitutive promoter. The introduction of nucleic acid molecules into a host cell can be confirmed using methods well known in the art. Such methods include, for example, nucleic acid analysis such as Northern blots or polymerase chain reaction (PCR) amplification of mRNA, or immunoblotting for expression of gene products, or other suitable analytical methods to test the expression of an introduced nucleic acid sequence or its corresponding gene product. It is understood by those skilled in the art that the nucleic acid molecules are expressed in a sufficient amount to produce a desired product (*e.g.* an anti-beta klotho antibody as described herein), and it is further understood that expression levels can be optimized to obtain sufficient expression using methods well known in the art.

[00133] "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (*e.g.,* Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies "arm" the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is known (see, *e.g.,* Table 3, page 464, Ravetch and Kinet, Annu. Rev. Immunol. 9:457-92 (1991)). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, (see, *e.g.,* US Patent No. 5,500,362 or 5,821,337) may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, for example, in a animal model (*see*, *e.g.,* Clynes *et al.* (USA) 95:652-656 (1998)). Antibodies with little or no ADCC activity may be selected for use.

[00134] "Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one that binds an IgG antibody (*e.g.,* a gamma receptor) and includes receptors of the FcγRI, FcγRII and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have

similar amino acid sequences that differ primarily in the cytoplasmic domains thereof (see, *e.g.,* review Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are known (see, *e.g.,* Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991); Capel *et al.*, Immunomethods 4:25-34 (1994); and de Haas *et al.*, J. Lab. Clin. Med. 126:330-41 (1995)). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (see, *e.g.,* Guyer *et al.*, J. Immunol. 117:587 (1976) and Kim *et al.*, J. Immunol. 24:249 (1994)). Antibody variants with improved or diminished binding to FcRs have been described (see, *e.g.,* in WO 2000/42072; U.S. Patent Nos. 7,183,387, 7,332,581 and 7.335,742; Shields *et al.* J. Biol. Chem. 9(2):6591-6604 (2001)).

[00135] "Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, (see, *e.g.,* Gazzano-Santoro *et al.*, J. Immunol. Methods 202:163 (1996)), may be performed. Polypeptide variants with altered Fc region amino acid sequences (polypeptides with a variant Fc region) and increased or decreased C1q binding capability have been described, (see, *e.g.,* US Patent No. 6,194,551, WO 1999/51642, Idusogie *et al.* J. Immunol. 164: 4178-4184 (2000)). Antibodies with little or no CDC activity may be selected for use.

[00136] A beta klotho polypeptide "extracellular domain" or "ECD" refers to a form of the beta klotho polypeptide that is essentially free of the transmembrane and cytoplasmic domains. For example, a beta klotho polypeptide ECD may have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, may have less than 0.5% of such domains. The term "identity" refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. "Percent identity" means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) must be addressed by a particular mathematical model or

computer program (*e.g.,* an "algorithm"). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in Computational Molecular Biology, (Lesk, A. M., ed.), (1988) New York: Oxford University Press; Biocomputing Informatics and Genome Projects, (Smith, D. W., ed.), 1993, New York: Academic Press; Computer Analysis of Sequence Data, Part I, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., (1987) Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo *et al.*, (1988) SIAM J. Applied Math. 48:1073.

[00137] In calculating percent identity, the sequences being compared may be aligned in a way that gives the largest match between the sequences. Computer program may be used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., (1984) Nucl. Acid Res. 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences may be aligned for optimal matching of their respective amino acid or nucleotide (the "matched span", as determined by the algorithm). A gap opening penalty (which is calculated as 3.times. the average diagonal, wherein the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see, Dayhoff *et al.*, (1978) Atlas of Protein Sequence and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff *et al.*, (1992) Proc. Natl. Acad. Sci. U.S.A. 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

[00138] Examplary parameters for determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following: (i) Algorithm: Needleman *et al.*, 1970, J. Mol. Biol. 48:443-453; (ii) Comparison matrix: BLOSUM 62 from Henikoff *et al.*, 1992, supra; (iii) Gap Penalty: 12 (but with no penalty for end gaps) (iv) Gap Length Penalty: 4; and (v) Threshold of Similarity: 0.

[00139] Certain alignment schemes for aligning two amino acid sequences may result in matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (*e.g.,* the GAP program) can be adjusted if so desired to result in an alignment that spans a number of amino acids, for example, at least 50 contiguous amino acids of the target polypeptide.

[00140] "Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[00141] A "modification" of an amino acid residue/position refers to a change of a primary amino acid sequence as compared to a starting amino acid sequence, wherein the change results from a sequence alteration involving said amino acid residue/positions. For example, typical modifications include substitution of the residue with another amino acid (*e.g.,* a conservative or non-conservative substitution), insertion of one or more (*e.g.,* generally fewer than 5, 4 or 3) amino acids adjacent to said residue/position, and/or deletion of said residue/position.

[00142] An "epitope" is the site on the surface of an antigen molecule to which a single antibody molecule binds, such as a localized region on the surface of an antigen, such as a beta klotho polypeptide, a beta klotho polypeptide fragment or a beta klotho epitope, that is capable of being bound to one or more antigen binding regions of an antibody, and that has antigenic or immunogenic activity in an animal, such as a mammal (*e.g.,* a human), that is capable of eliciting an immune response. An epitope having immunogenic activity is a portion of a polypeptide that elicits an

antibody response in an animal. An epitope having antigenic activity is a portion of a polypeptide to which an antibody binds as determined by any method well known in the art, including, for example, by an immunoassay. Antigenic epitopes need not necessarily be immunogenic. Epitopes often consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics. The term, "epitope" specifically includes linear epitopes and conformational epitopes. A region of a polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide. The epitope may or may not be a three-dimensional surface feature of the antigen. In certain embodiments, a beta klotho epitope is a three-dimensional surface feature of a beta klotho polypeptide. In other embodiments, a beta klotho epitope is linear feature of a beta klotho polypeptide. Generally an antigen has several or many different epitopes and may react with many different antibodies.

[00143] An antibody binds "an epitope" or "essentially the same epitope" or "the same epitope" as a reference antibody, when the two antibodies recognize identical, overlapping or adjacent epitopes in a three-dimensional space. The most widely used and rapid methods for determining whether two antibodies bind to identical, overlapping or adjacent epitopes in a three-dimensional space are competition assays, which can be configured in a number of different formats, for example, using either labeled antigen or labeled antibody. In some assays, the antigen is immobilized on a 96-well plate, or expressed on a cell surface, and the ability of unlabeled antibodies to block the binding of labeled antibodies is measured using radioactive, fluorescent or enzyme labels.

[00144] "Epitope mapping" is the process of identifying the binding sites, or epitopes, of antibodies on their target antigens. Antibody epitopes may be linear epitopes or conformational epitopes. Linear epitopes are formed by a continuous sequence of amino acids in a protein. Conformational epitopes are formed of amino acids that are discontinuous in the protein sequence, but which are brought together upon folding of the protein into its three-dimensional structure. Induced epitopes are formed when the three dimensional structure of the protein is in an altered confirmation, such as following activation or binding of another protein or ligand (*e.g.,*

the binding of beta klotho to an FCF receptor such as FGRFR1c, FGFR2c, FGFR3c, or FGFR4c.

[00145] "Epitope binning" is the process of grouping antibodies based on the epitopes they recognize. More particularly, epitope binning comprises methods and systems for discriminating the epitope recognition properties of different antibodies, using competition assays combined with computational processes for clustering antibodies based on their epitope recognition properties and identifying antibodies having distinct binding specificities.

[00146] A "beta klotho-mediated disease" and "beta klotho-mediated disorder" and "beta klotho-mediated condition" are used interchangeably and refer to any disease, disorder or condition that is completely or partially caused by or is the result of beta klotho or the interaction of a beta klotho with an FGF receptor such as FGFR1c, FGFR2c, FGFR3c, or FGFR4 and/or alternatively any disease, disorder, or condition in which it is desirable to mimic or augment the *in vivo* effects of FGF19 and/or FGF21.

[00147] The term "therapeutically effective amount" as used herein refers to the amount of an agent (*e.g.,* an antibody described herein or any other agent described herein) that is sufficient to reduce and/or ameliorate the severity and/or duration of a given disease, disorder or condition, and/or a symptom related thereto. A therapeutically effective amount of a agent, including a therapeutic agent, can be an amount necessary for (i) reduction or amelioration of the advancement or progression of a given disease, disorder, or condition, (ii) reduction or amelioration of the recurrence, development or onset of a given disease, disorder or conditions, and/or (iii) to improve or enhance the prophylactic or therapeutic effect of another therapy (*e.g.,* a therapy other than the administration of an antibody provided herein). A "therapeutically effective amount" of a substance/molecule/agent of the present disclosure (*e.g.,* an anti-beta klotho antibody) may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the substance/molecule/agent, to elicit a desired response in the individual. A therapeutically effective amount encompasses an amount in which any toxic or detrimental effects of the substance/molecule/agent are outweighed by the therapeutically beneficial effects. In certain embodiments, the term "therapeutically

effective amount" refers to an amount of an antibody or other agent (*e.g.,* or drug) effective to "treat" a disease, disorder, or condition, in a subject or mammal.

[00148] An "effective amount" is generally an amount sufficient to reduce the severity and/or frequency of symptoms, eliminate the symptoms and/or underlying cause, prevent the occurrence of symptoms and/or their underlying cause, and/or improve or remediate the damage that results from or is associated with a disease, disorder, or condition, including, for example, diabetes, obesity, dyslipidemia, cardiovascular disease, metabolic syndrome or broadly any disease, disorder, or condition in which it is desirable to mimic or augment the *in vivo* effects of FGF19 and/or FGF21. In some embodiments, the effective amount is a therapeutically effective amount or a prophylactically effective amount. A "therapeutically effective amount" is an amount sufficient to remedy a disease, disorder, or condition (*e.g.,* Type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, metabolic syndrome or broadly any disease, disorder, or condition in which it is desirable to mimic or augment the in vivo effects of FGF19 and/or FGF21) or symptoms, particularly a disease, disorder, or condition, or symptoms associated with such a disease, disorder, or condition, or otherwise prevent, hinder, retard or reverse the progression of the disease, disorder, or condition, or any other undesirable symptom associated with such a disease, disorder, or condition, in any way whatsoever. A "prophylactically effective amount" is an amount of a pharmaceutical composition that, when administered to a subject, will have the intended prophylactic effect, *e.g.,* preventing or delaying the onset (or reoccurrence) of diabetes, obesity or dyslipidemia, or reducing the likelihood of the onset (or reoccurrence) of a disease, disorder, or condition or associated symptom(s), including, for example, diabetes, obesity, dyslipidemia, cardiovascular disease, metabolic syndrome or broadly any disease, disorder, or condition in which it is desirable to mimic or augment the in vivo effects of FGF19 and/or FGF21) or associated symptoms. The full therapeutic or prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically or prophylactically effective amount may be administered in one or more administrations.

[00149] A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic

result. Typically, but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of a disease, disorder, or condition, a prophylactically effective amount may be less than a therapeutically effective amount.

[00150] "Chronic" administration refers to administration of the agent(s) in a continuous mode (*e.g.,* for a period of time such as days, weeks, months or years) as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

[00151] Administration "in combination with" one or more further therapeutic agents includes simultaneous (*e.g.,* concurrent) and consecutive administration in any order. The term "in combination" in the context of the administration of other therapies (*e.g.,* other agents) includes the use of more than one therapy (*e.g.,* one agent). The use of the term "in combination" does not restrict the order in which therapies are administered to a subject. A first therapy (*e.g.,* agent) can be administered before (*e.g.,* 1 minute, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks), concurrently, or after (*e.g.,* 1 minute, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks) the administration of a second therapy (*e.g.,* agent) to a subject which had, has, or is susceptible to a beta klotho-mediated disease.

[00152] Any additional therapy (*e.g.,* agent) can be administered in any order with the other additional therapies (*e.g.,* agents). In certain embodiments, the antibodies can be administered in combination with one or more therapies such as agents (*e.g.,* therapies, including agents, that are not the antibodies that are currently administered) to prevent, treat, manage, and/or ameliorate a beta klotho-mediated disease. Non-limiting examples of therapies (*e.g.,* agents) that can be administered in combination with an antibody include, for example, analgesic agents, anesthetic agents, antibiotics, or immunomodulatory agents or any other agent listed in the U.S. Pharmacopoeia and/or Physician's Desk Reference. Examples of agents useful in

combination therapy include, but are not limited to, the following: non-steroidal anti-inflammatory drug (NSAID) such as aspirin, ibuprofen, and other propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, fuirofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone). Other combinations include cyclooxygenase-2 (COX-2) inhibitors. Other agents for combination include steroids such as prednisolone, prednisone, methylprednisolone, betamethasone, dexamethasone, or hydrocortisone. Such a combination may be especially advantageous, since one or more side-effects of the steroid can be reduced or even eliminated by tapering the steroid dose required when treating patients in combination with the present antibodies. Additional examples of agents for combinations include cytokine suppressive anti-inflammatory drug(s) (CSAIDs); antibodies to or antagonists of other human cytokines or growth factors, for example, TNF, LT, IL-1β, IL-2, IL-6, IL-7, IL-8, IL-15, IL-16, IL-18, EMAP-II, GM-CSF, FGF, or PDGF. Combinations of agents may include TNF antagonists like chimeric, humanized or human TNF antibodies, REMICADE, anti-TNF antibody fragments (*e.g.,* CDP870), and soluble p55 or p75 TNF receptors, derivatives thereof, p75TNFRIgG (ENBREL®) or p55TNFR1gG (LENERCEPT®), soluble IL-13 receptor (sIL-13), and also TNFα converting enzyme (TACE) inhibitors; similarly IL-1 inhibitors (*e.g.,* Interleukin-1-converting enzyme inhibitors) may be effective. Other combinations include Interleukin 11, anti-P7s and p-selectin glycoprotein ligand (PSGL). Other examples of agents useful in combination therapy include interferon-β1a (AVONEX); interferon-β1b (BETASERON®); copaxone; hyperbaric oxygen; intravenous immunoglobulin; clabribine; and antibodies to or antagonists of other human cytokines or growth factors (*e.g.,* antibodies to CD40 ligand and CD80).

[00153] "Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight ((*e.g.,* less than about 10 amino acid residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™. The term "carrier" can also refer to a diluent, adjuvant (*e.g.,* Freund's adjuvant (complete or incomplete)), excipient, or vehicle with which the therapeutic is administered. Such carriers, including pharmaceutical carriers, can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a exemplary carrier when a composition (*e.g., a* pharmaceutical composition) is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable excipients (*e.g.,* pharmaceutical excipients) include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral compositions, including formulations, can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA. Compositions, including pharmaceutical compounds, may contain a prophylactically or therapeutically effective amount of an anti-beta klotho antibody, for example, in

isolated or purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the subject (*e.g.,* patient). The formulation should suit the mode of administration.

[00154] The term "pharmaceutically acceptable" as used herein means being approved by a regulatory agency of the Federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia or other generally recognized Pharmacopeia for use in animals, and more particularly in humans.

[00155] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of the active ingredient (*e.g.,* an anti-beta klotho antibody) to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. Such formulation may be sterile.

[00156] A "sterile" formulation is aseptic or free from all living microorganisms and their spores.

[00157] "Polyclonal antibodies" as used herein refers to an antibody population generated in an immunogenic response to a protein having many epitopes and thus includes a variety of different antibodies directed to the same and to different epitopes within the protein. Methods for producing polyclonal antibodies are known in the art (See, *e.g.,* Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel *et al.*, eds., John Wiley and Sons, New York).

[00158] An "isolated nucleic acid" is a nucleic acid, for example, an RNA, DNA, or a mixed polymer, which is substantially separated from other genome DNA sequences as well as proteins or complexes such as ribosomes and polymerases, which naturally accompany a native sequence. An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. In a specific embodiment, one or more nucleic acid molecules encoding an antibody as described herein are isolated or purified. The term embraces nucleic acid sequences that have been removed from their naturally

occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogues or analogues biologically synthesized by heterologous systems. A substantially pure molecule may include isolated forms of the molecule.

[00159] "Polynucleotide," or "nucleic acid," as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase or by a synthetic reaction. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. "Oligonucleotide," as used herein, generally refers to short, generally single-stranded, generally synthetic polynucleotides that are generally, but not necessarily, less than about 200 nucleotides in length. The terms "oligonucleotide" and "polynucleotide" are not mutually exclusive. The description above for polynucleotides is equally and fully applicable to oligonucleotides. A cell that produces an anti-beta klotho antibody of the present disclosure may include a parent hybridoma cell, as well as bacterial and eukaryotic host cells into which nucleic acid encoding the antibodies have been introduced. Suitable host cells are disclosed below.

[00160] Unless specified otherwise, the left-hand end of any single-stranded polynucleotide sequence disclosed herein is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA transcript that are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences;" sequence regions on the DNA strand having the same sequence as the RNA transcript that are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences."

[00161] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

[00162] The terms "prevent," "preventing," and "prevention" refer to the total or partial inhibition of the development, recurrence, onset or spread of a beta klotho-mediated disease and/or symptom related thereto, resulting from the administration of a therapy or combination of therapies provided herein (*e.g.,* a combination of prophylactic or therapeutic agents, such as an antibody provided herein).

[00163] The term "prophylactic agent" refers to any agent that can totally or partially inhibit the development, recurrence, onset or spread of a beta klotho-mediated disease and/or symptom related thereto in a subject. In certain embodiments, the term "prophylactic agent" refers to an anti-beta klotho antibody as described herein. In certain other embodiments, the term "prophylactic agent" refers to an agent other than an anti-beta klotho antibody as described herein. In certain embodiments, a prophylactic agent is an agent which is known to be useful to or has been or is currently being used to prevent a beta klotho-mediated disease, disorder, or condition, and/or a symptom related thereto or impede the onset, development, progression and/or severity of a beta klotho-mediated disease, disorder, or condition, and/or a symptom related thereto. In specific embodiments, the prophylactic agent is a humanized anti-beta klotho antibody, such as a humanized anti-beta klotho monoclonal antibody.

[00164] In certain embodiments, a "prophylactically effective serum titer" is the serum titer in a subject, preferably a human, that totally or partially inhibits the development, recurrence, onset or spread of a beta klotho-mediated disease, disorder, or condition, and/or symptom related thereto in the subject.

[00165] In certain embodiments, a "therapeutically effective serum titer" is the serum titer in a subject, preferably a human, that reduces the severity, the duration and/or the symptoms associated with a beta klotho-mediated disease, disorder, or condition, in the subject.

[00166] The term "recombinant antibody" refers to an antibody that is prepared, expressed, created or isolated by recombinant means. Recombinant antibodies can be antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial antibody library, antibodies isolated from an animal (*e.g.,* a mouse or cow) that is transgenic and/or transchromosomal for human immunoglobulin genes (see, *e.g.,* Taylor, L. D. *et al.*

(1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of immunoglobulin gene sequences to other DNA sequences. Such recombinant antibodies can have variable and constant regions, including those derived from human germline immunoglobulin sequences (See Kabat, E. A. *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). In certain embodiments, however, such recombinant antibodies may be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[00167] The term "serum titer" refers to an average serum titer in a subject from multiple samples (*e.g.,* at one time present or multiple time points) or in a population of least 10, such as at least 20, or at least 40 subjects, up to about 100, 1000 or more.

[00168] The term "side effects" encompasses unwanted and/or adverse effects of a therapy (*e.g.,* a prophylactic or therapeutic agent). Unwanted effects are not necessarily adverse. An adverse effect from a therapy (*e.g.,* a prophylactic or therapeutic agent) might be harmful or uncomfortable or risky. Examples of side effects include, diarrhea, cough, gastroenteritis, wheezing, nausea, vomiting, anorexia, abdominal cramping, fever, pain, loss of body weight, dehydration, alopecia, dyspenea, insomnia, dizziness, mucositis, nerve and muscle effects, fatigue, dry mouth, and loss of appetite, rashes or swellings at the site of administration, flu-like symptoms such as fever, chills and fatigue, digestive tract problems and allergic reactions. Additional undesired effects experienced by patients are numerous and known in the art. Many are described in the Physician's Desk Reference (68th ed., 2014).

[00169] The terms "subject" and "patient" may be used interchangeably. As used herein, in certain embodiments, a subject is a mammal, such as a non-primate (*e.g.,* cows, pigs, horses, cats, dogs, rats, etc.) or a primate (*e.g.,* monkey and human). In specific embodiments, the subject is a human. In one embodiment, the subject is a

mammal (*e.g.,* a human) having a beta klotho-mediated disease, disorder or condition. In another embodiment, the subject is a mammal (*e.g.,* a human) at risk of developing a beta klotho-mediated disease, disorder, or condition.

[00170] "Substantially all" refers to refers to at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or about 100%.

[00171] The term "therapeutic agent" refers to any agent that can be used in treating, preventing or alleviating a disease, disorder or condition, including in the treatment, prevention or alleviation of one or more symptoms of a beta klotho-mediated disease, disorder, or condition and/or a symptom related thereto. In certain embodiments, a therapeutic agent refers to an anti-beta klotho antibody as described herein. In certain other embodiments, a therapeutic agent refers to an agent other than an antibody provided herein. In certain embodiments, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, prevention or alleviation of one or more symptoms of a beta klotho-mediated disease, disorder, or condition, or a symptom related thereto.

[00172] The combination of therapies (*e.g.,* use of agents, including therapeutic agents) can be more effective than the additive effects of any two or more single therapy (*e.g.,* synergistic). A synergetic effect is unexpected and can not be predicted. For example, a synergistic effect of a combination of therapeutic agents permits the use of lower dosages of one or more of the agents and/or less frequent administration of the agents to a subject with a beta klotho-mediated disease. The ability to utilize lower dosages of therapeutic therapies and/or to administer the therapies less frequently reduces the toxicity associated with the administration of the therapies to a subject without reducing the efficacy of the therapies in the prevention, treatment or alleviation of one or more symptom of a beta klotho-mediated disease. In addition, a synergistic effect can result in improved efficacy of therapies in the prevention, treatment or alleviation of one or more symptom of a beta klotho-mediated disease. Finally, synergistic effect of a combination of therapies (*e.g.,* therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of any single therapy.

[00173] The term "therapy" refers to any protocol, method and/or agent that can be used in the prevention, management, treatment and/or amelioration of a beta klotho-mediated disease, disorder, or conditions. In certain embodiments, the terms "therapies" and "therapy" refer to a biological therapy, supportive therapy, and/or other therapies useful in the prevention, management, treatment and/or amelioration of a beta klotho-mediated disease, disorder or condition, known to one of skill in the art such as medical personnel.

[00174] The term "detectable probe" refers to a composition that provides a detectable signal. The term includes, without limitation, any fluorophore, chromophore, radiolabel, enzyme, antibody or antibody fragment, and the like, that provide a detectable signal via its activity.

[00175] The term "diagnostic agent" refers to a substance administered to a subject that aids in the diagnosis of a disease, disorder, or conditions. Such substances can be used to reveal, pinpoint, and/or define the localization of a disease causing process. In certain embodiments, a diagnostic agent includes a substance that is conjugated to an anti-beta klotho antibody as described herein, that when administered to a subject or contacted to a sample from a subject aids in the diagnosis a beta klotho-mediated disease.

[00176] The term "detectable agent" refers to a substance that can be used to ascertain the existence or presence of a desired molecule, such as an anti-beta klotho antibody as described herein, in a sample or subject. A detectable agent can be a substance that is capable of being visualized or a substance that is otherwise able to be determined and/or measured (*e.g.,* by quantitation).

[00177] The term "encode" or grammatical equivalents thereof as it is used in reference to nucleic acid molecule refers to a nucleic acid molecule in its native state or when manipulated by methods well known to those skilled in the art that can be transcribed to produce mRNA, which is then translated into a polypeptide and/or a fragment thereof. The antisense strand is the complement of such a nucleic acid molecule, and the encoding sequence can be deduced therefrom.

[00178] The term "excipient" refers to an inert substance which is commonly used as a diluent, vehicle, preservative, binder, or stabilizing agent, and includes, but not limited to, proteins (*e.g.,* serum albumin, etc.), amino acids (*e.g.,* aspartic acid,

glutamic acid, lysine, arginine, glycine, histidine, etc.), fatty acids and phospholipids (*e.g.,* alkyl sulfonates, caprylate, etc.), surfactants (*e.g.,* SDS, polysorbate, nonionic surfactant, etc.), saccharides (*e.g.,* sucrose, maltose, trehalose, etc.) and polyols (*e.g.,* mannitol, sorbitol, etc.). See, also, Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA, which is hereby incorporated by reference in its entirety.

[00179] In the context of a peptide or polypeptide, the term "fragment" as used herein refers to a peptide or polypeptide that comprises less than the full length amino acid sequence. Such a fragment may arise, for example, from a truncation at the amino terminus, a truncation at the carboxy terminus, and/or an internal deletion of a residue(s) from the amino acid sequence. Fragments may, for example, result from alternative RNA splicing or from *in vivo* protease activity. In certain embodiments, beta klotho fragments include polypeptides comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least contiguous 100 amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, at least 200 contiguous amino acid residues, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, or at least 950, contiguous amino acid residues of the amino acid sequence of a beta klotho polypeptide or an antibody that binds to a beta klotho polypeptide. In a specific embodiment, a fragment of a beta klotho polypeptide or an antibody that binds to a beta klotho antigen retains at least 1, at least 2, or at least 3 or more functions of the polypeptide or antibody.

[00180] The terms "manage," "managing," and "management" refer to the beneficial effects that a subject derives from a therapy (*e.g.,* a prophylactic or therapeutic agent), which does not result in a cure of the disease. In certain embodiments, a subject is administered one or more therapies (*e.g.,* prophylactic or

therapeutic agents, such as an antibody provided herein) to "manage" a beta klotho-mediated disease, one or more symptoms thereof, so as to prevent the progression or worsening of the disease.

[00181] The terms "about" or "approximately" mean within 20%, within 15%, within 10%, within 9%, within 8%, within 7%, within 6%, within 5%, within 4%, within 3%, within 2%, within or 1% or less of a given value or range.

[00182] "Administer" or "administration" refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body (*e.g.,* an anti-beta klotho antibody as described herein) into a patient, such as by mucosal, intradermal, intravenous, intramuscular delivery and/or any other method of physical delivery described herein or known in the art. When a disease, disorder, or condition, or a symptom thereof, is being treated, administration of the substance typically occurs after the onset of the disease, disorder, or condition, or symptoms thereof. When a disease, disorder, or condition or symptoms thereof, are being prevented, administration of the substance typically occurs before the onset of the disease, disorder, or condition, or symptoms thereof.

[00183] In the context of a polypeptide, the term "analog" as used herein refers to a polypeptide that possesses a similar or identical function as a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or an anti-beta klotho antibody but does not necessarily comprise a similar or identical amino acid sequence of a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or an anti-beta klotho antibody, or possess a similar or identical structure of a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or an anti-beta klotho antibody. A polypeptide that has a similar amino acid sequence refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide having an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of a beta klotho polypeptide (*e.g.,* SEQ ID NO:297, a fragment of a beta klotho polypeptide, or an anti-beta klotho antibody described herein; (b) a polypeptide encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or an anti-beta klotho antibody (or VH or VL region

thereof) described herein of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues (see, *e.g.,* Sambrook *et al.* (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Maniatis *et al.* (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, NY); and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the nucleotide sequence encoding a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or an anti-beta klotho antibody (or VH or VL region thereof) described herein. A polypeptide with similar structure to a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or an anti-beta klotho antibody described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a beta klotho polypeptide, a fragment of a beta klotho, or a beta klotho antibody described herein. The structure of a polypeptide can determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

[00184] The term "composition" is intended to encompass a product containing the specified ingredients (*e.g.,* an antibody provided herein) in, optionally, the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in, optionally, the specified amounts.

[00185] In the context of a polypeptide, the term "derivative" as used herein refers to a polypeptide that comprises an amino acid sequence of a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or an antibody that binds to a beta klotho polypeptide which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or an antibody that binds to a beta klotho polypeptide which has been chemically

modified, *e.g.,* by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or a beta klotho antibody may be chemically modified, *e.g.,* by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. The derivatives are modified in a manner that is different from naturally occurring or starting peptide or polypeptides, either in the type or location of the molecules attached. Derivatives further include deletion of one or more chemical groups which are naturally present on the peptide or polypeptide. A derivative of a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or a beta klotho antibody may be chemically modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or a beta klotho antibody may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a beta klotho polypeptide, a fragment of a beta klotho polypeptide, or a beta klotho antibody described herein.

COMPOSITIONS AND METHODS OF MAKING THE SAME

[00186] Binding proteins such as antibodies that bind to beta klotho (*e.g.,* human and/or cyno beta klotho) are provided. Antibodies of the present disclosure are useful, for example, for the diagnosis or treatment of diseases, disorders, or conditions associated with expression, of beta klotho. In certain embodiments, antibodies of the present disclosure are useful for the diagnosis or treatment of a diseases, disorder, or condition, such as Type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, metabolic syndrome or broadly any disease, disorder, or condition in which it is desirable to mimic or augment the *in vivo* effects of FGF19 and/or FGF21.

[00187] Provided herein are antibodies that bind to a beta klotho polypeptide, a beta klotho polypeptide fragment, beta klotho peptide, or a beta klotho epitope. In some embodiments, the anti-beta klotho antibodies bind to the extracellular domain (ECD) of beta klotho. Also provided are antibodies that competitively block an anti-beta klotho antibody provided herein from binding to a beta klotho polypeptide. The

anti-beta klotho antibodies provided herein can also be conjugated or recombinantly fused to a diagnostic agent, detectable agent or therapeutic agent. Further provided are compositions comprising an beta klotho antibody.

[00188] Also provided herein are isolated nucleic acid molecules encoding an immunoglobulin heavy chain, light chain, VH region, VL region, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of anti-beta klotho antibodies that bind to a beta klotho polypeptide, a beta klotho polypeptide fragment, a beta klotho peptide or a beta klotho epitope. Further provided are vectors and host cells comprising nucleic acid molecules encoding anti-beta klotho antibodies that bind to a beta klotho polypeptide, a beta klotho polypeptide fragment, a beta klotho peptide or a beta klotho epitope. Also provided are methods of making antibodies that bind to a beta klotho polypeptide, a beta klotho polypeptide fragment, a beta klotho peptide or a beta klotho epitope.

[00189] Methods of using the anti-beta klotho antibodies are provided. The methods include treating, preventing or alleviating a disease, disorder or condition, including treating, preventing or alleviating one or more symptoms of a disease, disorder or condition in a subject. Non limiting examples of diseases, disorders, or conditions include glucose utilization disorders and the sequelae associated therewith, including diabetes mellitus (Type I and Type-2), gestational diabetes, hyperglycemia, insulin resistance, abnormal glucose metabolism, "pre-diabetes" (Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT)), or other physiological disorders associated with, or that result from, the hyperglycemic condition, including, for example, histopathological changes such as pancreatic β-cell destruction. For example subjects with a diseases, disorders, or condition, in need of treatment may have a fasting plasma glucose (FPG) level greater than about 100 mg/dl. Other hyperglycemic-related disorders, include kidney damage (*e.g.,* tubule damage or nephropathy), liver degeneration, eye damage (*e.g.,* diabetic retinopathy or cataracts), and diabetic foot disorders. Other of diseases, disorders, or conditions include dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary artery disease, cerebrovascular disorders and the like or other of diseases, disorders, or conditions which may be associated with the metabolic syndrome, such as obesity and elevated body mass (including the co-morbid conditions thereof such as, but not limited to, nonalcoholic fatty liver disease

(NAFLD), nonalcoholic steatohepatitis (NASH), and polycystic ovarian syndrome (PCOS)), or thromboses, hypercoagulable and prothrombotic states (arterial and venous), hypertension, cardiovascular disease, stroke and heart failure. These diseases, disorders, or conditions include atherosclerosis, chronic inflammatory bowel diseases (*e.g.,* Crohn's disease and ulcerative colitis), asthma, lupus erythematosus, arthritis, or other inflammatory rheumatic disorders. Other diseases, disorders, or conditions include adipose cell tumors, lipomatous carcinomas including, for example, liposarcomas, solid tumors, and neoplasms. Other diseases, disorders, or conditions include neurodegenerative diseases and/or demyelinating disorders of the central and peripheral nervous systems and/or neurological diseases involving neuroinflammatory processes and/or other peripheral neuropathies, including Alzheimer's disease, multiple sclerosis, Parkinson's disease, progressive multifocal leukoencephalopathy and Guillian-Barre syndrome. Other diseases, disorders, or conditions include skin and dermatological disorders and/or disorders of wound healing processes, including erythemato-squamous dermatoses. Other diseases, disorders, or conditions include syndrome X, osteoarthritis, and acute respiratory distress syndrome. As used herein, the term “hyperglycemic” or “hyperglycemia,” when used in reference to a disease, disorder, or condition of a subject refers to a transient or chronic abnormally high level of glucose present in the blood of a subject. The disease, disorder, or condition may be caused by a delay in glucose metabolism or absorption such that the subject exhibits glucose intolerance or a state of elevated glucose not typically found in normal subjects (*e.g.,* in glucose-intolerant pre-diabetic subjects at risk of developing diabetes, or in diabetic subjects). For example, fasting plasma glucose (FPG) levels for normoglycemia may be less than about 100 mg/dl, for impaired glucose metabolism, between about 100 and 126 mg/dl, and for diabetics greater than about 126 mg/dl. Methods of preventing (*e.g.,* in subjects predisposed to having a particular disorder(s)), relate to delaying, slowing or inhibiting progression of, the onset of, or treating (*e.g.,* ameliorating) obesity or an undesirable body mass (*e.g.,* a greater than normal body mass index, or “BMI” relative to an appropriate matched subject of comparable age, gender, race, etc.). Methods of treating obesity or an undesirable body mass (including the co-morbid conditions of obesity, for example, obstructive sleep apnea, arthritis, cancer (*e.g.,* breast, endometrial, and colon), gallstones or hyperglycemia, include contacting or administering a binding protein such as an anti-beta klotho antibody as described

herein in an amount effective to treat obesity or an undesirable body mass. For example, a subject may have a body mass index greater than 25, for example, 25-30, 30-35, 35-40, or greater than 40. Methods of preventing (*e.g.,* in subjects predisposed to having a particular disorder(s)), relate to delaying, slowing or inhibiting the progression of, the onset of, or treating undesirable levels or abnormally elevated serum/plasma LDL, VLDL, triglycerides or cholesterol, all of which, alone or in combination, can lead to, for example, plaque formation, narrowing or blockage of blood vessels, and increased risk of hypertension, stroke and coronary artery disease. Such diseases, disorders, or conditions may be due to, for example, genetic predisposition or diet.

Anti-Beta Klotho Antibodies

[00190] In one embodiment, the present disclosure provides anti-beta klotho antibodies that may find use herein as therapeutic agents. Exemplary antibodies include polyclonal, monoclonal, humanized, human, bispecific, and heteroconjugate antibodies, as well as variants thereof having improved affinity or other properties.

[00191] In some embodiments, provided herein are antibodies that bind to beta klotho, including a beta klotho polypeptide, a beta klotho polypeptide fragment, a beta klotho peptide or a beta klotho epitope. In some embodiments the anti-beta klotho antibodies are humanized antibodies (*e.g.,* comprising human constant regions) that bind beta klotho, including beta klotho polypeptide, a beta klotho polypeptide fragment, a beta klotho peptide or a beta klotho epitope.

[00192] In certain embodiments, the anti-beta klotho antibody comprises a VH region, VL region, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of any one of the murine monoclonal antibodies described herein, such as an amino acid sequence depicted in Tables 1-10. Accordingly, in some embodiments, the isolated antibody or functional fragment thereof provided herein comprises one, two, and/or three heavy chain CDRs and/or one, two, and/or three light chain CDRs from: (a) the antibody designated 5H23; (b) the antibody designated 1C17; (c) the antibody designated 1D19; (d) the antibody designated 2L12; (e) the antibody designated 3L3; (f) the antibody designated 3N20; (g) the antibody designated 4P5; (h) the antibody designated 5C23; (i) the antibody designated 5F7; (j) the antibody designated 1G19, as shown in Tables 1-10.

[00193] The antibody designated 5H23 comprises a VH sequence that is SEQ ID NO:25 and a VL sequence that is SEQ ID NO:26.

[00194] The antibody designated 1C17 comprises a VH sequence that is SEQ ID NO:51 and a VL sequence that is SEQ ID NO:52.

[00195] The antibody designated 1D19 comprises a VH sequence that is SEQ ID NO:77 and a VL sequence that is SEQ ID NO:78.

[00196] The antibody designated 2L12 comprises a VH sequence that is SEQ ID NO:103 and a VL sequence that is SEQ ID NO:104.

[00197] The antibody designated 3L3 comprises a VH sequence that is SEQ ID NO:129 and a VL sequence that is SEQ ID NO:130.

[00198] The antibody designated 3N20 comprises a VH sequence that is SEQ ID NO:155 and a VL sequence that is SEQ ID NO:156.

[00199] The antibody designated 4P5 comprises a VH sequence that is SEQ ID NO:181 and a VL sequence that is SEQ ID NO:182.

[00200] The antibody designated 5C23 comprises a VH sequence that is SEQ ID NO:207 and a VL sequence that is SEQ ID NO:208.

[00201] The antibody designated 5F7 comprises a VH sequence that is SEQ ID NO:233 and a VL sequence that is SEQ ID NO:234.

[00202] The antibody designated IG19 comprises a VH sequence that is SEQ ID NO:259 and a VL sequence that is SEQ ID NO:260.

Table 1: Antibody 5H23 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYTFTSYDIN (SEQ ID NO:1)	GYTFTSYD (SEQ ID NO:7)	SYDIN (SEQ ID NO:12)	GYTFTSY (SEQ ID NO:13)	TSYDIN (SEQ ID NO:18)	GYTFTSYDIN (SEQ ID NO:1)
	VH CDR2	WIYPGDGSTKYNEKFKG (SEQ ID NO:2)	IYPGDGST (SEQ ID NO:8)	WIYPGDGSTKYNEKFKG (SEQ ID NO:2)	PGDG (SEQ ID NO:14)	WIGWIYPGDGSTK (SEQ ID NO:19)	WIYPGDGSTK (SEQ ID NO:24)
	VH CDR3	SDYYGSRSFAY (SEQ ID NO:3)	ARSDYYGSRSFAY (SEQ ID NO:9)	SDYYGSRSFAY (SEQ ID NO:3)	DYYGSRSFA (SEQ ID NO:15)	ARSDYYGSRSFA (SEQ ID NO:20)	SDYYGSRSFAY (SEQ ID NO:3)
VL CDR Seq.	VL CDR1	RASKSVSTSGYVYMH (SEQ ID NO:4)	KSVSTSGYVY (SEQ ID NO:10)	RASKSVSTSGYVYMH (SEQ ID NO:4)	SKSVSTSGYVY (SEQ ID NO:16)	STSGYVYMHWN (SEQ ID NO:21)	RASKSVSTSGYVYMH (SEQ ID NO:4)
	VL CDR2	LASYLES (SEQ ID NO:5)	LAS (SEQ ID NO:11)	LASYLES (SEQ ID NO:5)	LAS (SEQ ID NO:11)	LLIYLASYLE (SEQ ID NO:22)	LASYLES (SEQ ID NO:5)
	VL CDR3	QHSRDLTFP (SEQ ID NO:6)	QHSRDLTFP (SEQ ID NO:6)	QHSRDLTFP (SEQ ID NO:6)	SRDLTF (SEQ ID NO:17)	QHSRDLTF (SEQ ID NO:23)	QHSRDLTFP (SEQ ID NO:6)
VH Sequence: QVQLQQSGPELVKPGALVKISCKASGYTFTSYDINWVKQRPGQGLEWIGWIYPGDGSTKYNEKFKGKATLTADKSSRTAYMQLSSLTSENSAVYFCARSDYYGSRS FAYWGQGTLVTVSA (SEQ ID NO: 25)						
VL Sequence: DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYVYMHWNQQKPGQPPKLLIYLASYLESGVPARFSGSGSGTDFTLNIHPVEEEDAAIYYCQHSRDLTFPFGGGTKL EIK (SEQ ID NO:26)						

Table 2: Antibody 1C17 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYSITSGYYWN (SEQ ID NO:27)	GYSITSGYY (SEQ ID NO:33)	SGYYWN (SEQ ID NO:38)	GYSITSGY (SEQ ID NO:39)	TSGYYWN (SEQ ID NO:44)	GYSITSGYYWN (SEQ ID NO:27)
	VH CDR2	YINYDGNSNYTPSLKN (SEQ ID NO:28)	INYDGNS (SEQ ID NO:34)	YINYDGNSNYTPSLKN (SEQ ID NO:28)	YDG (SEQ ID NO:40)	WMGYINYDGNSN (SEQ ID NO:45)	YINYDGNSN (SEQ ID NO:50)
	VH CDR3	KGAYYSNYDSFDV (SEQ ID NO:29)	ARKGAYYSNYDSFDV (SEQ ID NO:35)	KGAYYSNYDSFDV (SEQ ID NO:29)	GAYYSNYDSFD (SEQ ID NO:41)	ARKGAYYSNYDSFD (SEQ ID NO:46)	KGAYYSNYDSFDV (SEQ ID NO:29)
VL CDR Seq.	VL CDR1	KASQDINSYLS (SEQ ID NO:30)	QDINSY (SEQ ID NO:36)	KASQDINSYLS (SEQ ID NO:30)	SQDINSY (SEQ ID NO:42)	NSYLSWV (SEQ ID NO:47)	KASQDINSYLS (SEQ ID NO:30)
	VL CDR2	RANRLVD (SEQ ID NO:31)	RAN (SEQ ID NO:37)	RANRLVD (SEQ ID NO:31)	RAN (SEQ ID NO:37)	TLIYRANRLV (SEQ ID NO:48)	RANRLVD (SEQ ID NO:31)
	VL CDR3	LQYDEFPFT (SEQ ID NO:32)	LQYDEFPFT (SEQ ID NO:32)	LQYDEFPFT (SEQ ID NO:32)	YDEFPF (SEQ ID NO:43)	LQYDEFPF (SEQ ID NO:49)	LQYDEFPFT (SEQ ID NO:32)
VH Sequence: QVQLQESGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLEWMGYINYDGNSNYTPSLKNRISITRDTSKNQFFLKLNSVTPEDTATYYCARKGAYYSNYD SFDVWGTGTTVTVSS (SEQ ID NO:51)						
VL Sequence: DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWVQQKPGKSPKTLIYRANRLVDGVPSRFSGSGSGQDYSLTISSLEYEDMGIYYCLQYDEFPFTFGSGTKLEIK (SEQ ID NO:52)							

[00203] Table 3: Antibody 1D19 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYTFTRYDIN (SEQ ID NO:53)	GYTFTRYD (SEQ ID NO:59)	RYDIN (SEQ ID NO:64)	GYTFTRY (SEQ ID NO:65)	TRYDIN (SEQ ID NO:70)	GYTFTRYDIN (SEQ ID NO:53)
	VH CDR2	WIYPGDSSTKFNENFKD (SEQ ID NO:54)	IYPGDSST (SEQ ID NO:60)	WIYPGDSSTKFNENFKD (SEQ ID NO:54)	PGDS (SEQ ID NO:66)	WIGWIYPGDSSTK (SEQ ID NO:71)	WIYPGDSSTK (SEQ ID NO:76)
	VH CDR3	SDYYGSRSFTY (SEQ ID NO:55)	ARSDYYGSRSFTY (SEQ ID NO:61)	SDYYGSRSFTY (SEQ ID NO:55)	DYYGSRSFT (SEQ ID NO:67)	ARSDYYGSRSFT (SEQ ID NO:72)	SDYYGSRSFTY (SEQ ID NO:55)
VL CDR Seq.	VL CDR1	RASKSVSTSGYSYMH (SEQ ID NO:56)	KSVSTSGYSY (SEQ ID NO:62)	RASKSVSTSGYSYMH (SEQ ID NO:56)	SKSVSTSGYSY (SEQ ID NO:68)	STSGYSYMHWY (SEQ ID NO:73)	RASKSVSTSGYSYMH (SEQ ID NO:56)
	VL CDR2	LASNLES (SEQ ID NO:57)	LAS (SEQ ID NO:63)	LASNLES (SEQ ID NO:57)	LAS (SEQ ID NO:63)	LLIYLASNLE (SEQ ID NO:74)	LASNLES (SEQ ID NO:57)
	VL CDR3	QHSRELPYT (SEQ ID NO:58)	QHSRELPYT (SEQ ID NO:58)	QHSRELPYT (SEQ ID NO:58)	SRELPY (SEQ ID NO:69)	QHSRELPY (SEQ ID NO:75)	QHSRELPYT (SEQ ID NO:58)
VH Sequence: QVQPQESGPELVKPGALVKISCKASGYTFTRYDINWMKQRPGQGLEWIGWIYPGDSSTKFNENFKDKATLTADKSSSTAYMQLSSLTSENSTVYFCARSDYYGSRS FTYWGQGTLVTVSA (SEQ ID NO:77)						
VL Sequence: DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPYTFGGGTKL EIK (SEQ ID NO:78)						

Table 4: Antibody 2L12 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYTFTRYDIN (SEQ ID NO:79)	GYTFTRYD (SEQ ID NO:85)	RYDIN (SEQ ID NO:90)	GYTFTRY (SEQ ID NO:91)	TRYDIN (SEQ ID NO:96)	GYTFTRYDIN (SEQ ID NO:79)
	VH CDR2	WIYPGDDSTKYNEKFKG (SEQ ID NO:80)	IYPGDDST (SEQ ID NO:86)	WIYPGDDSTKYNEKFKG (SEQ ID NO:80)	PGDD (SEQ ID NO:92)	WIGWIYPGDDSTK (SEQ ID NO:97)	WIYPGDDSTK (SEQ ID NO:102)
	VH CDR3	SDYYGSRSFVY (SEQ ID NO:81)	ARSDYYGSRSFVY (SEQ ID NO:87)	SDYYGSRSFVY (SEQ ID NO:81)	DYYGSRSFV (SEQ ID NO:93)	ARSDYYGSRSFV (SEQ ID NO:98)	SDYYGSRSFVY (SEQ ID NO:81)
VL CDR Seq.	VL CDR1	RASKSVSTSGYSYLH (SEQ ID NO:82)	KSVSTSGYSY (SEQ ID NO:88)	RASKSVSTSGYSYLH (SEQ ID NO:82)	SKSVSTSGYSY (SEQ ID NO:94)	STSGYSYLHWY (SEQ ID NO:99)	RASKSVSTSGYSYLH (SEQ ID NO:82)
	VL CDR2	LASNLES (SEQ ID NO:83)	LAS (SEQ ID NO:89)	LASNLES (SEQ ID NO:83)	LAS (SEQ ID NO:89)	LLIYLASNLE (SEQ ID NO:100)	LASNLES (SEQ ID NO:83)
	VL CDR3	QHSGELPYT (SEQ ID NO:84)	QHSGELPYT (SEQ ID NO:84)	QHSGELPYT (SEQ ID NO:84)	SGELPY (SEQ ID NO:95)	QHSGELPY (SEQ ID NO:101)	QHSGELPYT (SEQ ID NO:84)
VH Sequence: QVQLQQSGPELVKPGALVKISCKASGYTFTRYDINWVKKRPGQGLEWIGWIYPGDDSTKYNEKFKGKATLTADKSSSTAYMQLSSLTSENSAVYFCARSDYYGSRSFVYWGQGTLVTVSA (SEQ ID NO:103)						
VL Sequence: DIVLTQSPASLPVSLGQRATISCRASKSVSTSGYSYLHWYQQKPGQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSGELPYTFGGGTKLEIK (SEQ ID NO:104)						

Table 5: Antibody 3L3 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYTFTSYDIN (SEQ ID NO:105)	GYTFTSYD (SEQ ID NO:111)	SYDIN (SEQ ID NO:116)	GYTFTSY (SEQ ID NO:117)	TSYDIN (SEQ ID NO:122)	GYTFTSYDIN (SEQ ID NO:105)
	VH CDR2	WIYPGDGSPKYDEKFKG (SEQ ID NO:106)	IYPGDGSP (SEQ ID NO:112)	WIYPGDGSPKYDEKFKG (SEQ ID NO:106)	PGDG (SEQ ID NO:118)	WIGWIYPGDGSPK (SEQ ID NO:123)	WIYPGDGSPK (SEQ ID NO:128)
	VH CDR3	SDYYGSRSFVY (SEQ ID NO:107)	ARSDYYGSRSFVY (SEQ ID NO:113)	SDYYGSRSFVY (SEQ ID NO:107)	DYYGSRSFV (SEQ ID NO:119)	ARSDYYGSRSFV (SEQ ID NO:124)	SDYYGSRSFVY (SEQ ID NO:107)
VL CDR Seq.	VL CDR1	RASKSVSTSGYSYVH (SEQ ID NO:108)	KSVSTSGYSY (SEQ ID NO:114)	RASKSVSTSGYSYVH (SEQ ID NO:108)	SKSVSTSGYSY (SEQ ID NO:120)	STSGYSYVHWY (SEQ ID NO:125)	RASKSVSTSGYSYVH (SEQ ID NO:108)
	VL CDR2	LASNLES (SEQ ID NO:109)	LAS (SEQ ID NO:115)	LASNLES (SEQ ID NO:109)	LAS (SEQ ID NO:115)	LLIYLASNLE (SEQ ID NO:126)	LASNLES (SEQ ID NO:109)
	VL CDR3	QHSGELPYT (SEQ ID NO:110)	QHSGELPYT (SEQ ID NO:110)	QHSGELPYT (SEQ ID NO:110)	SGELPY (SEQ ID NO:121)	QHSGELPY (SEQ ID NO:127)	QHSGELPYT (SEQ ID NO:110)
VH Sequence: QVQPQESGPELVKPGTLVKISCKASGYTFTSYDINWVKQRPGQGLEWIGWIYPGDGSPKYDEKFKGKATLTADKSSSTAYMQLSSLTSENSAVYFCARSDYYGSRS FVYWGQGTLVTVSA (SEQ ID NO:129)						
VL Sequence: DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYVHWYQQKPGQPPKLLIYLASNLESGVPARFSGRGSGTDFTLNIHPVEEEDAATYYCQHSGELPYTFGGGTKL EIK (SEQ ID NO:130)						

Table 6: Antibody 3N20 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYIFTNYGIS (SEQ ID NO:131)	GYIFTNYG (SEQ ID NO:137)	NYGIS (SEQ ID NO:142)	GYIFTNY (SEQ ID NO:143)	TNYGIS (SEQ ID NO:148)	GYIFTNYGIS (SEQ ID NO:131)
	VH CDR2	EIYPRSGNTYYNEKFKG (SEQ ID NO:132)	IYPRSGNT (SEQ ID NO:138)	EIYPRSGNTYYNEKFKG (SEQ ID NO:132)	PRSG (SEQ ID NO:144)	WIGEIYPRSGNTY (SEQ ID NO:149)	EIYPRSGNTY (SEQ ID NO:154)
	VH CDR3	HWDGVLDYFDY (SEQ ID NO:133)	ARHWDGVLDYFDY (SEQ ID NO:139)	HWDGVLDYFDY (SEQ ID NO:133)	WDGVLDYFD (SEQ ID NO:145)	ARHWDGVLDYFD (SEQ ID NO:150)	HWDGVLDYFDY (SEQ ID NO:133)
VL CDR Sequences	VL CDR1	KSSQSLLNSGNQKNYLA (SEQ ID NO:134)	QSLLNSGNQKNY (SEQ ID NO:140)	KSSQSLLNSGNQKNYLA (SEQ ID NO:134)	SQSLLNSGNQKNY (SEQ ID NO:146)	LNSGNQKNYLAWY (SEQ ID NO:151)	KSSQSLLNSGNQKNYLA (SEQ ID NO:134)
	VL CDR2	GASTRES (SEQ ID NO:135)	GAS (SEQ ID NO:141)	GASTRES (SEQ ID NO:135)	GAS (SEQ ID NO:141)	LLIYGASTRE (SEQ ID NO:152)	GASTRES (SEQ ID NO:135)
	VL CDR3	LNDHSYPFT (SEQ ID NO:136)	LNDHSYPFT (SEQ ID NO:136)	LNDHSYPFT (SEQ ID NO:136)	DHSYPF (SEQ ID NO:147)	LNDHSYPF (SEQ ID NO:153)	LNDHSYPFT (SEQ ID NO:136)
VH Sequence: QVQLQESGAELARPGASVKLSCKVSGYIFTNYGISWVKQRTGQGLEWIGEIYPRSGNTYYNEKFKGKATLTADMSSSTAYMDLRSLTSEDSAVYFCARHWDGVLDYFDYWG QGTSLTVSS (SEQ ID NO:155)						
VL Sequence: DIVMTQSPSSLSVSAGEKVTMSCKSSQSLLNSGNQKNYLAWYQQKPGQPPKLLIYGASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCLNDHSYPFTFGAGTKLEL K (SEQ ID NO:156)						

Table 7: Antibody 4P5 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYTFTRYDIN (SEQ ID NO:157)	GYTFTRYD (SEQ ID NO:163)	RYDIN (SEQ ID NO:168)	GYTFTRY (SEQ ID NO:169)	TRYDIN (SEQ ID NO:174)	GYTFTRYDIN (SEQ ID NO:157)
	VH CDR2	WIYPGDDSTKYNEKFKG (SEQ ID NO:158)	IYPGDDST (SEQ ID NO:164)	WIYPGDDSTKYNEKFKG (SEQ ID NO:158)	PGDD (SEQ ID NO:170)	WIGWIYPGDDSTK (SEQ ID NO:175)	WIYPGDDSTK (SEQ ID NO:180)
	VH CDR3	SDYYGSRSFVY (SEQ ID NO:159)	ARSDYYGSRSFVY (SEQ ID NO:165)	SDYYGSRSFVY (SEQ ID NO:159)	DYYGSRSFV (SEQ ID NO:171)	ARSDYYGSRSFV (SEQ ID NO:176)	SDYYGSRSFVY (SEQ ID NO:159)
VL CDR Seq.	VL CDR1	RASKSVSTSGYSYMH (SEQ ID NO:160)	KSVSTSGYSY (SEQ ID NO:166)	RASKSVSTSGYSYMH (SEQ ID NO:160)	SKSVSTSGYSY (SEQ ID NO:172)	STSGYSYMHWY (SEQ ID NO:177)	RASKSVSTSGYSYMH (SEQ ID NO:160)
	VL CDR2	LASNLES (SEQ ID NO:161)	LAS (SEQ ID NO:167)	LASNLES (SEQ ID NO:161)	LAS (SEQ ID NO:167)	LLIYLASNLE (SEQ ID NO:178)	LASNLES (SEQ ID NO:161)
	VL CDR3	HHSGELPYT (SEQ ID NO:162)	HHSGELPYT (SEQ ID NO:162)	HHSGELPYT (SEQ ID NO:162)	SGELPY (SEQ ID NO:173)	HHSGELPY (SEQ ID NO:179)	HHSGELPYT (SEQ ID NO:162)
VH Sequence: QVQLQQSGPELVKPGALVKISCKASGYTFTRYDINWVKKRPGQGLEWIGWIYPGDDSTKYNEKFKGKATLTADKSSSTAYMQLSSLTSENSAVYFCARSDYYGSRSF VYWGQGTLVTVSA (SEQ ID NO:181)						
VL Sequence: DILLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNLESGVPARFSGRGSGTDFTLNIHPVEEEDAATYYCHHSGELPYTFGGGTKL EIK (SEQ ID NO:182)						

Table 8: Antibody 5C23 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYTFTRYDIN (SEQ ID NO:183)	GYTFTRYD (SEQ ID NO:189)	RYDIN (SEQ ID NO:194)	GYTFTRY (SEQ ID NO:195)	TRYDIN (SEQ ID NO:200)	GYTFTRYDIN (SEQ ID NO:183)
	VH CDR2	WIYPGDGSTKYNEKFEG (SEQ ID NO:184)	IYPGDGST (SEQ ID NO:190)	WIYPGDGSTKYNEKFEG (SEQ ID NO:184)	PGDG (SEQ ID NO:196)	WIGWIYPGDGSTK (SEQ ID NO:201)	WIYPGDGSTK (SEQ ID NO:206)
	VH CDR3	SDYYGSRSFVY (SEQ ID NO:185)	ARSDYYGSRSFVY (SEQ ID NO:191)	SDYYGSRSFVY (SEQ ID NO:185)	DYYGSRSFV (SEQ ID NO:197)	ARSDYYGSRSFV (SEQ ID NO:202)	SDYYGSRSFVY (SEQ ID NO:185)
VL CDR Seq.	VL CDR1	RASKSVSTSGYSYMH (SEQ ID NO:186)	KSVSTSGYSY (SEQ ID NO:192)	RASKSVSTSGYSYMH (SEQ ID NO:186)	SKSVSTSGYSY (SEQ ID NO:198)	STSGYSYMHWY (SEQ ID NO:203)	RASKSVSTSGYSYMH (SEQ ID NO:186)
	VL CDR2	LASNLES (SEQ ID NO:187)	LAS (SEQ ID NO:193)	LASNLES (SEQ ID NO:187)	LAS (SEQ ID NO:193)	LLIYLASNLE (SEQ ID NO:204)	LASNLES (SEQ ID NO:187)
	VL CDR3	QHSRELPYT (SEQ ID NO:188)	QHSRELPYT (SEQ ID NO:188)	QHSRELPYT (SEQ ID NO:188)	SRELPY (SEQ ID NO:199)	QHSRELPY (SEQ ID NO:205)	QHSRELPYT (SEQ ID NO:188)
VH Sequence: QVQPQESGPELVKPGALVKISCKASGYTFTRYDINWVKKRPGQGLEWIGWIYPGDGSTKYNEKFEGKATLTADKSSSTAYMQLSSLTSENSAVYFCARSDYYGSRSFVYWGQGTLVTVSA (SEQ ID NO:207)						
VL Sequence: DIVLTQSPDSLTVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPYTFGGGTKLEIK (SEQ ID NO:208)						

Table 9: Antibody 5F7 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYTFTRYDIN (SEQ ID NO:209)	GYTFTRYD (SEQ ID NO:215)	RYDIN (SEQ ID NO:220)	GYTFTRY (SEQ ID NO:221)	TRYDIN (SEQ ID NO:226)	GYTFTRYDIN (SEQ ID NO:209)
	VH CDR2	WIYPGDISTKYNEKFKG (SEQ ID NO:210)	IYPGDIST (SEQ ID NO:216)	WIYPGDISTKYNEKFKG (SEQ ID NO:210)	PGDI (SEQ ID NO:222)	WIGWIYPGDISTK (SEQ ID NO:227)	WIYPGDISTK (SEQ ID NO:232)
	VH CDR3	SDYYGSRSFVY (SEQ ID NO:211)	ARSDYYGSRSFVY (SEQ ID NO:217)	SDYYGSRSFVY (SEQ ID NO:211)	DYYGSRSFV (SEQ ID NO:223)	ARSDYYGSRSFV (SEQ ID NO:228)	SDYYGSRSFVY (SEQ ID NO:211)
VL CDR Seq.	VL CDR1	RASKSVSTSGYSYMH (SEQ ID NO:212)	KSVSTSGYSY (SEQ ID NO:218)	RASKSVSTSGYSYMH (SEQ ID NO:212)	SKSVSTSGYSY (SEQ ID NO:224)	STSGYSYMHWY (SEQ ID NO:229)	RASKSVSTSGYSYMH (SEQ ID NO:212)
	VL CDR2	LASNLES (SEQ ID NO:213)	LAS (SEQ ID NO:219)	LASNLES (SEQ ID NO:213)	LAS (SEQ ID NO:219)	LLIYLASNLE (SEQ ID NO:230)	LASNLES (SEQ ID NO:213)
	VL CDR3	QHSRELPYT (SEQ ID NO:214)	QHSRELPYT (SEQ ID NO:214)	QHSRELPYT (SEQ ID NO:214)	SRELPY (SEQ ID NO:225)	QHSRELPY (SEQ ID NO:231)	QHSRELPYT (SEQ ID NO:214)
VH Sequence: QVQPQESGPELVKPGALVKISCKASGYTFTRYDINWVKQRPGQGLEWIGWIYPGDISTKYNEKFKGKATLTADKSSSTAYMQLNSLTSENSAVYFCARSDYYGSRSF VYWGQGTLVTVSA (SEQ ID NO:233)						
VL Sequence: DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPYTFGGGTKV EIK (SEQ ID NO:234)						

Table 10: Antibody 1G19 CDR Sequences

		Exemplary	IMGT	Kabat	Chothia	Contact	AbM
VH CDR Seq.	VH CDR1	GYSITSGYYWN (SEQ ID NO:235)	GYSITSGYY (SEQ ID NO:241)	SGYYWN (SEQ ID NO:246)	GYSITSGY (SEQ ID NO:247)	TSGYYWN (SEQ ID NO:252)	GYSITSGYYWN (SEQ ID NO:235)
	VH CDR2	YINYGGSNNYNPSLKN (SEQ ID NO:236)	INYGGSN (SEQ ID NO:242)	YINYGGSNNYNPSLKN (SEQ ID NO:236)	YGG (SEQ ID NO:248)	WMGYINYGGSNN (SEQ ID NO:253)	YINYGGSNN (SEQ ID NO:258)
	VH CDR3	RGAYYSNYDSFDV (SEQ ID NO:237)	ARRGAYYSNYDSFDV (SEQ ID NO:243)	RGAYYSNYDSFDV (SEQ ID NO:237)	GAYYSNYDSFD (SEQ ID NO:249)	ARRGAYYSNYDSFD (SEQ ID NO:254)	RGAYYSNYDSFDV (SEQ ID NO:237)
VL CDR Seq.	VL CDR1	KASQDINSYLS (SEQ ID NO:238)	QDINSY (SEQ ID NO:244)	KASQDINSYLS (SEQ ID NO:238)	SQDINSY (SEQ ID NO:250)	NSYLSWF (SEQ ID NO:255)	KASQDINSYLS (SEQ ID NO:238)
	VL CDR2	RANRLVD (SEQ ID NO:239)	RAN (SEQ ID NO:245)	RANRLVD (SEQ ID NO:239)	RAN (SEQ ID NO:245)	TLIYRANRLV (SEQ ID NO:256)	RANRLVD (SEQ ID NO:239)
	VL CDR3	LQYDEFPYT (SEQ ID NO:240)	LQYDEFPYT (SEQ ID NO:240)	LQYDEFPYT (SEQ ID NO:240)	YDEFPY (SEQ ID NO:251)	LQYDEFPY (SEQ ID NO:257)	LQYDEFPYT (SEQ ID NO:240)
VH Sequence: QVQLQESGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLEWMGYINYGGSNNYNPSLKNRISITRDTSKNQFFLKLTSVTTEDTATYYCARRGAYYSNYD SFDVWGTGTTVTVSS (SEQ ID NO:259)						
VL Sequence: DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIYRANRLVDGVPSRFSGSGSGQDYSLTISSLEYEEMGIYYCLQYDEFPYTFGGGTKLEIK (SEQ ID NO:260)							

[00204] In some embodiments, the antibodies provided herein comprise a VH region or VH domain In other embodiments, the antibodies provided herein comprise a VL region or VL chain. In some embodiments, the antibodies provided herein have a combination of (i) a VH domain or VH region; and/or (ii) a VL domain or VL region.

[00205] In some embodiments, an antibody provided herein comprises or consists of six CDRs, for example, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in Tables 1-10. In some embodiments, an antibody provided herein can comprise less than six CDRs. In some embodiments, the antibody comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in tables 1-10. In some embodiments, the antibody comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of the murine monoclonal antibody selected from the group consisting of: (a) the antibody designated 5H23; (b) the antibody designated 1C17; (c) the antibody designated 1D19; (d) the antibody designated 2L12; (e) the antibody designated 3L3; (f) the antibody designated 3N20; (g) the antibody designated 4P5; (h) the antibody designated 5C23; (i) the antibody designated 5F7; (j) the antibody designated 1G19; described herein. Accordingly, in some embodiments, the antibody comprises or consists of one, two, three four or five CDRs of anyone of the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in Tables 1-10.

[00206] In some embodiments, the antibodies provided herein comprise one or more (*e.g.,* one, two or three) VH CDRs listed in Tables 1-10. In other embodiments, the antibodies provided herein comprise one or more (*e.g.,* one, two or three) VL CDRs listed in Tables 1-10. In yet other embodiments, the antibodies provided herein comprise one or more (*e.g.,* one, two or three) VH CDRs listed in Tables 1-10 and one or more VL CDRs listed in Tables 1-10. Accordingly, in some embodiments, the antibodies comprise a VH CDR1 having the amino acid sequence of any one of SEQ ID NOS: 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252. In some embodiments, the antibodies comprise a VH CDR2 having the amino

acid sequence of any one of SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258. In some embodiments, the antibodies comprise a VH CDR3 having the amino acid sequence of any one of SEQ ID NOS: 3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254. In some embodiments, the antibodies comprise a VH CDR1 and/or a VH CDR2 and/or a VH CDR3 independently selected from a VH CDR1, VH CDR2, VH CDR3 as depicted in any one of the amino acid sequences depicted in Table 1-10. In some embodiments, the antibodies comprise a VL CDR1 having the amino acid sequence of any one of SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255. In another embodiment, the antibodies comprise a VL CDR2 having the amino acid sequence of any one of SEQ ID NOS: 5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256. In some embodiments, the antibodies comprise a VL CDR3 having the amino acid sequence of any one of SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257. In some embodiments, the antibodies comprise a VL CDR1 and/or a VL CDR2 and/or a VL CDR3 independently selected from a VL CDR1, VL CDR2, VL CDR3 as depicted in any one of the amino acid sequences depicted in Tables 1-10.

[00207] In some embodiments, the antibodies provided herein comprise a heavy chain variable (VH) region comprising: (1) a VH CDR1 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:1, 27, 53, 79, 105, 131, 157, 183, 209, and or 235, (ii) SEQ ID NO:7, 33, 59, 85, 111, 137, 163, 189, 215 or 241, (iii) SEQ ID NO:12, 38, 64, 90, 116, 142, 168, 194, 220 or 246, (iv) SEQ ID NO:13, 39, 65, 91, 117, 143, 169, 195, 221 or 247, and (v) SEQ ID NO:18, 44, 70, 96, 122, 148, 174, 200, 226 or 252; (2) a VH CDR2 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:2, 28, 54, 80, 106, 132, 158, 184, 210, and or 236, (ii) SEQ ID NO:8, 34, 60, 86, 112, 138, 164, 190, 216 or 242, (iii) SEQ ID NO:14, 40, 66, 92, 118, 144, 170, 196, 222 or 248, (iv)

SEQ ID NO:19, 45, 71, 97, 123, 149, 175, 201, 227 or 253, and (v) SEQ ID NO:24, 50, 76, 102, 128, 154, 180, 206, 232 or 258; and (3) a VH CDR3 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO: 3, 29, 55, 81, 107, 133, 159, 185, 211, and or 237, (ii) SEQ ID NO:9, 35, 61, 87, 113, 139, 165, 191, 217 or 243, (iii) SEQ ID NO:15, 41, 67, 93, 119, 145, 171, 197, 223 or 249, and (iv) SEQ ID NO:20, 46, 72, 98, 124, 150, 176, 202, 228 or 254; and/or a light chain variable (VL) region comprising: (1) a VL CDR1 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:4, 30, 56, 82, 108, 134, 160, 186, 212, and or 238, (ii) SEQ ID NO:10, 36, 52, 88, 114, 140, 166, 192, 218 or 244, (iii) SEQ ID NO:16, 42, 68, 94, 120, 146, 172, 198, 224 or 250, and (iv) SEQ ID NO:21, 47, 73, 99, 125, 151, 177, 203, 229 or 255; (2) a VL CDR2 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:5, 31, 57, 83, 109, 135, 161, 187, 213, and or 239, (ii) SEQ ID NO:11, 37, 63, 89, 115, 141, 167, 193, 219 or 245, and (iii) SEQ ID NO:22, 48, 74, 100, 126, 152, 178, 204, 230 or 256; and (3) a VL CDR3 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:6, 32, 58, 84, 110, 136, 162, 188, 214, and or 240, (ii) SEQ ID NO:17, 43, 69, 95, 121, 147, 173, 199, 225 or 251, and (iii) SEQ ID NO:23, 49, 75, 101, 127, 153, 179, 205, 231 or 257.

[00208] In some embodiments, the antibodies provided herein comprise a heavy chain variable (VH) region comprising: (1) a VH CDR1 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:1, 27, 53, 79, 105, 131, 157, 183, 209, and or 235, (ii) SEQ ID NO:7, 33, 59, 85, 111, 137, 163, 189, 215 or 241, (iii) SEQ ID NO:12, 38, 64, 90, 116, 142, 168, 194, 220 or 246, (iv) SEQ ID NO:13, 39, 65, 91, 117, 143, 169, 195, 221 or 247, and (v) SEQ ID NO:18, 44, 70, 96, 122, 148, 174, 200, 226 or 252; (2) a VH CDR2 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:2, 28, 54, 80, 106, 132, 158, 184, 210, and or 236, (ii) SEQ ID NO:8, 34, 60, 86, 112, 138, 164, 190, 216 or 242, (iii) SEQ ID NO:14, 40, 66, 92, 118, 144, 170, 196, 222 or 248, (iv) SEQ ID NO:19, 45, 71, 97, 123, 149, 175, 201, 227 or 253, and (v) SEQ ID NO:24, 50, 76, 102, 128, 154, 180, 206, 232 or 258; and (3) a VH CDR3 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO: 3, 29, 55, 81, 107, 133, 159, 185, 211, and or 237, (ii) SEQ ID NO:9, 35, 61, 87, 113,

139, 165, 191, 217 or 243, (iii) SEQ ID NO:15, 41, 67, 93, 119, 145, 171, 197, 223 or 249, and (iv) SEQ ID NO:20, 46, 72, 98, 124, 150, 176, 202, 228 or 254.

[00209] In some embodiments, the antibodies provided herein comprise a light chain variable (VL) region comprising: (1) a VL CDR1 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:4, 30, 56, 82, 108, 134, 160, 186, 212, and or 238, (ii) SEQ ID NO:10, 36, 52, 88, 114, 140, 166, 192, 218 or 244, (iii) SEQ ID NO:16, 42, 68, 94, 120, 146, 172, 198, 224 or 250, and (iv) SEQ ID NO:21, 47, 73, 99, 125, 151, 177, 203, 229 or 255; (2) a VL CDR2 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:5, 31, 57, 83, 109, 135, 161, 187, 213, and or 239, (ii) SEQ ID NO:11, 37, 63, 89, 115, 141, 167, 193, 219 or 245, and (iii) SEQ ID NO:22, 48, 74, 100, 126, 152, 178, 204, 230 or 256; and (3) a VL CDR3 having an amino acid sequence of selectedselected from the group consisting of: (i) SEQ ID NO:6, 32, 58, 84, 110, 136, 162, 188, 214, and or 240, (ii) SEQ ID NO:17, 43, 69, 95, 121, 147, 173, 199, 225 or 251, and (iii) SEQ ID NO:23, 49, 75, 101, 127, 153, 179, 205, 231 or 257.

[00210] Also provided herein are antibodies comprising one or more VH CDRs and one or more (*e.g.,* one, two or three) VL CDRs listed in Tables 1-10. In particular, provided herein is an antibody comprising a VH CDR1 (SEQ ID NOS: 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252.) and a VL CDR1 (SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255); a VH CDR1 (SEQ ID NOS: 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252); a VL CDR2 (SEQ ID NOS: 5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256) and a VH CDR1 (SEQ ID NOS 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252) VL CDR3 (SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240,

251, and 257) and a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258); a VL CDR1 (SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258); and a VL CDR3 (SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR3 (SEQ ID NOS: 3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254) and a VL CDR1 (SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255); a VH CDR3 (SEQ ID NOS: 3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254) and a VL CDR2 (SEQ ID NOS: 5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256); a VH CDR3 (SEQ ID NOS: 3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254) and a VL CDR3 (SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS: 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258) and a VL CDR1 (SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255); a VH CDR1 (SEQ

ID NOS: 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258) and a VL CDR2 (SEQ ID NOS: 5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256); a VH CDR1 (SEQ ID NOS: : 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258) and a VL CDR3 (SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257);a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS: 3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254) and a VL CDR1 (SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255), a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS: 3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254) and a VL CDR2 (SEQ ID NOS: 5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256); a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170,

175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS: 3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254) and a VL CDR3 (SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS: 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252.), a VL CDR1 (SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR2 (SEQ ID NOS: 5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VL CDR1 (SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR3 (SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS: 1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VL CDR2 (SEQ ID NOS: 5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256) and a VL CDR3 (SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR2 (SEQ ID NOS: 2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VL CDR1 (SEQ ID NOS: 4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR2 (SEQ ID

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(SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR3 (SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256) and a VL CDR3 (SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18,

27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR3 (SEQ ID NOS: 6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256) and a VL CDR3 (SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150,

159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256); a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255); a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256) and a VL CDR3 (SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212,

218, 224, 229, 238, 244, 250, and 255) and a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255) and a VL CDR3 (SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256) and a VL CDR3 (SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210,

216, 222, 227, 232, 236, 242, 248, 253, and 258), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255), a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256), and a VL CDR3 (SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR1 (SEQ ID NOS:1, 7, 12, 13, 18, 27, 33, 38, 39, 44, 53, 59, 64, 65, 70, 79, 85, 90, 91, 96, 105, 111, 116, 117, 122, 131, 137, 142, 143, 148, 157, 163, 168, 169, 174, 183, 189, 194, 195, 200, 209, 215, 220, 221, 226, 235, 241, 246, 247, and 252), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255), a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256), and a VL CDR3 (SEQ ID NOS:6, 17, 23, 32, 43, 49, 58, 69, 75, 84, 95, 101, 110, 121, 127, 136, 147, 153, 162, 173, 179, 188, 199, 205, 214, 225, 231, 240, 251, and 257); a VH CDR2 (SEQ ID NOS:2, 8, 14, 19, 24, 28, 34, 40, 45, 50, 54, 60, 66, 71, 76, 80, 86, 92, 97, 102, 106, 112, 118, 123, 128, 132, 138, 144, 149, 154, 158, 164, 170, 175, 180, 184, 190, 196, 201, 206, 210, 216, 222, 227, 232, 236, 242, 248, 253, and 258), a VH CDR3 (SEQ ID NOS:3, 9, 15, 20, 29, 35, 41, 46, 55, 61, 67, 72, 81, 87, 93, 98, 107, 113, 119, 124, 133, 139, 145, 150, 159, 165, 171, 176, 185, 191, 197, 202, 211, 217, 223, 228, 237, 243, 249, and 254), a VL CDR1 (SEQ ID NOS:4, 10, 16, 21, 30, 36, 42, 47, 56, 62, 68, 73, 82, 88, 94, 99, 108, 114, 120, 125, 134, 140, 146, 151, 160, 166, 172, 177, 186, 192, 198, 203, 212, 218, 224, 229, 238, 244, 250, and 255), a VL CDR2 (SEQ ID NOS:5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 141, 152, 161, 167, 178, 187, 193, 204, 213, 219, 230, 239, 245, and 256) or any combination thereof of the VH CDRs and VL CDRs listed in Tables 1-10.

[00211] In yet another aspect, the CDRs disclosed herein include consensus sequences derived from groups of related antibodies (see, *e.g.,* Tables 1-10). As

described herein, a "consensus sequence" refers to amino acid sequences having conserved amino acids common among a number of sequences and variable amino acids that vary within a given amino acid sequences. The CDR consensus sequences provided include CDRs corresponding to CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and/or CDRL3. Consensus sequences of CDRs of anti-beta klotho antibodies are shown in Figure 2.

[00212] In certain embodiments, an antibody of fragment thereof described herein comprises a VH region that comprises: (1) a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 278, 279, 280 and 378; (2) a VH FR2 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 281, 282, and 283; (3) a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 284, 285, 286, 287 and 379-381; and/or (4) a VH FR4 having an amino acid of SEQ ID NO: 288. Accordingly, in some aspects, the humanized antibody comprises a VH region that includes a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 278, 279, 280 and 378. In some aspects, the humanized antibody comprises a VH region that includes a VH FR2 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 281, 282, and 283. In some aspects, the humanized antibody comprises a VH region that includes a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 284, 285, 286, 287 and 379-381. In some aspects, the humanized antibody comprises a VH region that includes a VH FR4 having an amino acid of SEQ ID NO: 288.

[00213] In certain embodiments, an antibody of fragment thereof described herein comprises a VL region that comprises: (1) a VL FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 289, 290 and 382-384; (2) a VL FR2 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 291, 292 and 385-392; (3) a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 293, 294, 295 and 393-404; and/or (4) a VL FR4 having an amino acid of SEQ ID NO: 296 and 405-407. Accordingly, in some aspects, the humanized antibody comprises a VL region that includes a VL FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 289, 290 and 382-384. In some aspects, the humanized antibody comprises a

VL region that includes a VL FR2 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 291, 292 and 385-392. In some aspects, the humanized antibody comprises a VL region that includes a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 293, 294, 295 and 393-404. In some aspects, the humanized antibody comprises a VL region that includes a VL FR4 having an amino acid of SEQ ID NO: 296 and 405-407.

[00214] In certain embodiments, an antibody of fragment thereof described herein comprises a VH region and a VL region, wherein the VH region further comprises: (1) a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 278, 279, 280 and 378; (2) a VH FR2 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 281, 282, and 283; (3) a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 284, 285, 286, 287 and 379-381; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO: 288; and wherein the VL region further comprises: (1) a VL FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 289, 290 and 382-384; (2) a VL FR2 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 291, 292 and 385-392; (3) a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS: 293, 294, 295 and 393-404; and/or (4) a VL FR4 having an amino acid of SEQ ID NO: 296 and 405-407.

[00215] Also provided herein are antibodies comprising one or more (*e.g.,* one, two, three or four) VH FRs and one or more VL FRs listed in Table 19. In particular, provided herein is an antibody comprising a VH FR1 (SEQ ID NOS:278, 279, 280 and 378) and a VL FR1 (SEQ ID NOS:289, 290 and 382-384); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR2 (SEQ ID NOS:281, 282, and 283) and a VL FR1 (SEQ ID NOS:289, 290 and 382-384); a VH FR2 (SEQ ID NOS:281, 282, and 283) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR2 (SEQ ID NOS:281, 282, and 283) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR2 (SEQ ID NOS:281, 282, and 283) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VH

FR1 (SEQ ID NOS:278, 279, 280 and 378); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283) and a VL FR1 (SEQ ID NOS:289, 290 and 382-384); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404);a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283) and a VL FR4 (SEQ ID NO:296 and 405-407);a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR1 (SEQ ID NOS:289, 290 and 382-384), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR2 (SEQ ID

NOS:281, 282, and 283), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR4 (SEQ ID NO:288), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR4 (SEQ ID NO:288), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR4 (SEQ ID NO:288), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR4 (SEQ ID NO:288), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR4 (SEQ ID NO:288), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR1 (SEQ ID NOS:289, 290 and 382-384); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR4 (SEQ ID NO:288) and a VL FR1 (SEQ ID NOS:289, 290 and 382-384); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and

283), a VH FR4 (SEQ ID NO:288) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR4 (SEQ ID NO:288) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR4 (SEQ ID NO:288) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288) and a VL FR1 (SEQ ID NOS:289, 290 and 382-384); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288) and a VL FR1 (SEQ ID NOS:289, 290 and 382-384); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR1 (SEQ ID NOS:289, 290 and 382-384) and a VL FR2 (SEQ ID NOS:291, 292 and 385-392); a VH FR1 (SEQ ID NOS:278, 279, 280 and

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NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR4 (SEQ ID NO:288), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR4 (SEQ ID NO:288), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR4 (SEQ ID NO:288), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR4 (SEQ ID NO:288), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404); a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VH FR4 (SEQ ID NO:288), a VL FR2 (SEQ ID NOS:291, 292 and 385-392) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR2 (SEQ ID NOS:281, 282, and 283), a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR1 (SEQ ID NOS:278, 279, 280 and 378), a VH FR4 (SEQ ID NO:288), a VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404) and a VL FR4 (SEQ ID NO:296 and 405-407); a VH FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286,

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[00216] In yet another aspect, antibodies are provided that compete with one of the exemplified antibodies or functional fragments for binding to (i) beta klotho or (ii) a complex comprising beta klotho and one of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Such antibodies may also bind to the same epitope as one of the herein exemplified antibodies, or an overlapping epitope. Antibodies and fragments that compete with or bind to the same epitope as the exemplified antibodies are expected to show similar functional properties. The exemplified antigen binding proteins and fragments include those with the VH and VL regions, and CDRs provided herein, including those in Tables 1-10. Thus, as a specific example, the antibodies that are provided include those that compete with an antibody comprising: (a) 1, 2, 3, 4, 5 or all 6 of the CDRs listed for an antibody listed in Tables 1-10; (b) a VH and a VL selected from the VH and a VL regions listed for an antibody listed in Tables 1-10, such as for antibody 5H23 (Table 1) or (c) two light chains and two heavy chains comprising a VH and a VL as specified for an antibody listed in Tables 1-10.

In still yet another aspect, antibodies are provided herein that bind to a region, including an epitope, of human beta klotho or cyno beta klotho. For example, in some embodiments, an antibody provided herein binds to a KLB2 domain of human beta klotho comprising amino acid residues 509 to 1044 of SEQ ID NO:297. As another example, in some embodiments, an antibody provided herein 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. As yet another example, in some embodiments, an antibody provided herein binds to a region of human beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:297. As still another example, in some embodiments, an antibody provided herein binds to a

region of cyno beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:299.

[00217] In another aspect, antibodies are provided herein that bind to a specific epitope of human beta klotho. For example, in some embodiments, an antibody provided herein binds 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). Accordingly, in some embodiments, an antibody provided herein binds to an epitope of human beta klotho, wherein the epitope of human beta klotho comprise at least amino acid residue 657 of SEQ ID NO: 297. In some embodiments, an antibody provided herein binds to an epitope of human beta klotho, wherein the epitope of human beta klotho comprise at least amino acid residue 701 of SEQ ID NO: 297. In some embodiments, an antibody provided herein binds to an epitope of human beta klotho, wherein the epitope of human beta klotho comprise at least amino acid residue 703 of SEQ ID NO: 297. In some embodiments, an antibody provided herein binds to an epitope of human beta klotho, wherein the epitope of human beta klotho comprise at least amino acid residues 657 and 701 of SEQ ID NO: 297. In some embodiments, an antibody provided herein binds to an epitope of human beta klotho, wherein the epitope of human beta klotho comprise at least amino acid residues 657 and 703 of SEQ ID NO: 297. In some embodiments, an antibody provided herein binds to an epitope of human beta klotho, wherein the epitope of human beta klotho comprise at least amino acid residues 701 and 703 of SEQ ID NO: 297. In some embodiments, an antibody provided herein binds to an epitope of human beta klotho, wherein the epitope of human beta klotho comprise 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 in a cell that expresses human beta klotho and an FGF receptor. Additionally, in some embodiments, the antibody is a humanized, human or chimeric antibody.

1. Polyclonal Antibodies

[00218] The antibodies of the present disclosure may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple

subcutaneous or intraperitoneal injections. The immunizing agent may include a beta klotho polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized or to immunize the mammal with the protein and one or more adjuvants. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Ribi, CpG, Poly 1C, Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation. The mammal can then be bled, and the serum assayed for beta klotho antibody titer. If desired, the mammal can be boosted until the antibody titer increases or plateaus. Additionally or alternatively, lymphocytes may be obtained from the immunized animal for fusion and the preparation of monoclonal antibodies from hybridoma as described below.

2. Monoclonal Antibodies

[00219] The antibodies of the present disclosure may alternatively be monoclonal antibodies. Monoclonal antibodies may be made using the hybridoma method first described by Kohler *et al.,* Nature, 256:495 (1975), or may be made by recombinant DNA methods (see, *e.g.,* U.S. Patent No. 4,816,567).

[00220] In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as described above to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. After immunization, lymphocytes are isolated and then fused with a myeloma cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)).

[00221] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium which medium preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells (also referred to as fusion partner). For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the selective

culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[00222] Preferred fusion partner myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a selective medium that selects against the unfused parental cells. Preferred myeloma cell lines are murine myeloma lines, such as SP-2 and derivatives, for example, X63-Ag8-653 cells available from the American Type Culture Collection, Manassas, Virginia, USA and those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J., *Immunol.*, 133:3001 (1984); and Brodeur *et al.*, *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

[00223] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. The binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA). The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis described in Munson *et al.*, *Anal. Biochem.*, 107:220 (1980).

[00224] Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal, for example, by i.p. injection of the cells into mice.

[00225] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such as, for example, affinity chromatography (*e.g.*, using

protein A or protein G-Sepharose) or ion-exchange chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, etc.

[00226] DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.,* by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra *et al.*, *Curr. Opinion in Immunol.*, 5:256-262 (1993) and Plückthun, *Immunol. Revs.* 130:151-188 (1992).

[00227] In some embodiments, an antibody that binds a beta klotho epitope comprises an amino acid sequence of a VH domain and/or an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes to (1) the complement of a nucleotide sequence encoding any one of the VH and/or VL domain described herein under stringent conditions (*e.g.,* hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C) under highly stringent conditions (*e.g.,* hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C), or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3).

[00228] In some embodiments, an antibody that binds a beta klotho epitope comprises an amino acid sequence of a VH CDR or an amino acid sequence of a VL CDR encoded by a nucleotide sequence that hybridizes to the complement of a nucleotide sequence encoding any one of the VH CDRs and/or VL CDRs depicted in Tables 1-10 under stringent conditions (*e.g.,* hybridization to filter-bound DNA in 6X SSC at about 45° C followed by one or more washes in 0.2X SSC/0.1% SDS at about 50-65° C), under highly stringent conditions (*e.g.,* hybridization to filter-bound

nucleic acid in 6X SSC at about 45° C followed by one or more washes in 0.1X SSC/0.2% SDS at about 68° C), or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3)

[00229] In a further embodiment, monoclonal antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in, for example, *Antibody Phage Display: Methods and Protocols*, P.M. O'Brien and R. Aitken, eds, Humana Press, Totawa N.J., 2002. In principle, synthetic antibody clones are selected by screening phage libraries containing phage that display various fragments of antibody variable region (Fv) fused to phage coat protein. Such phage libraries are screened for against the desired antigen. Clones expressing Fv fragments capable of binding to the desired antigen are adsorbed to the antigen and thus separated from the non-binding clones in the library. The binding clones are then eluted from the antigen, and can be further enriched by additional cycles of antigen adsorption/elution.

[00230] Variable domains can be displayed functionally on phage, either as single-chain Fv (scFv) fragments, in which VH and VL are covalently linked through a short, flexible peptide, or as Fab fragments, in which they are each fused to a constant domain and interact non-covalently, as described, for example, in Winter *et al.*, *Ann. Rev. Immunol.*, 12: 433-455 (1994).

[00231] Repertoires of VH and VL genes can be separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be searched for antigen-binding clones as described in Winter *et al.*, *supra*. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned to provide a single source of human antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths *et al.*, *EMBO J*, 12: 725-734 (1993). Finally, naive libraries can also be made synthetically by cloning the unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions

and to accomplish rearrangement *in vitro* as described, for example, by Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381-388 (1992).

[00232] Screening of the libraries can be accomplished by various techniques known in the art. For example, beta klotho, (*e.g.,* a beta klotho polypeptide, fragment or epitope) can be used to coat the wells of adsorption plates, expressed on host cells affixed to adsorption plates or used in cell sorting, or conjugated to biotin for capture with streptavidin-coated beads, or used in any other method for panning display libraries. The selection of antibodies with slow dissociation kinetics (*e.g.,* good binding affinities) can be promoted by use of long washes and monovalent phage display as described in Bass *et al.*, *Proteins*, 8: 309-314 (1990) and in WO 92/09690, and a low coating density of antigen as described in Marks *et al.*, *Biotechnol.*, 10: 779-783 (1992).

[00233] Anti-beta klotho antibodies can be obtained by designing a suitable antigen screening procedure to select for the phage clone of interest followed by construction of a full length anti-beta klotho antibody clone using VH and/or VL sequences (*e.g.,* the Fv sequences), or various CDR sequences from VH and VL sequences, from the phage clone of interest and suitable constant region (*e.g.,* Fc) sequences described in Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, Fifth Edition, NIH Publication 91-3242, Bethesda MD (1991), vols. 1-3.

3. Antibody Fragments

[00234] The present disclosure provides antibodies and antibody fragments that bind to beta klotho. In certain circumstances there are advantages of using antibody fragments, rather than whole antibodies. The smaller size of the fragments allows for rapid clearance, and may lead to improved access to cells, tissues or organs. For a review of certain antibody fragments, see Hudson *et al.* (2003) *Nat. Med.* 9:129-134.

[00235] Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, *e.g.,* Morimoto *et al.*, *Journal of Biochemical and Biophysical Methods* 24:107-117 (1992); and Brennan *et al.*, *Science*, 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli* or yeast cells, thus allowing the facile production of large amounts of these fragments.

Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form $F(ab')_2$ fragments (Carter *et al.*, *Bio/Technology* 10:163-167 (1992)). According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. Fab and $F(ab')_2$ fragment with increased *in vivo* half-life comprising salvage receptor binding epitope residues are described, for example, U.S. Pat. No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In certain embodiments, an antibody is a single chain Fv fragment (scFv) (see, *e.g.,* WO 93/16185; U.S. Pat. Nos. 5,571,894; and 5,587,458). Fv and scFv have intact combining sites that are devoid of constant regions; thus, they may be suitable for reduced nonspecific binding during *in vivo* use. scFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an scFv. (See, *e.g.,* Antibody Engineering, ed. Borrebaeck, *supra)*. The antibody fragment may also be a "linear antibody", for example, as described, for example, in the references cited above. Such linear antibodies may be monospecific or multi-specific, such as bispecific.

[00236] Smaller antibody-derived binding structures are the separate variable domains (V domains) also termed single variable domain antibodies (SdAbs). Certain types of organisms, the camelids and cartilaginous fish, possess high affinity single V-like domains mounted on an Fc equivalent domain structure as part of their immune system. (Woolven *et al.*, *Immunogenetics* 50: 98-101, 1999; Streltsov *et al.*, *Proc Natl Acad Sci USA*. 101:12444-12449, 2004). The V-like domains (called VhH in camelids and V-NAR in sharks) typically display long surface loops, which allow penetration of cavities of target antigens. They also stabilize isolated VH domains by masking hydrophobic surface patches.

[00237] These VhH and V-NAR domains have been used to engineer sdAbs. Human V domain variants have been designed using selection from phage libraries and other approaches that have resulted in stable, high binding VL- and VH-derived domains.

[00238] Antibodies that bind to beta klotho as provided herein include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bi-specific antibodies), human

antibodies, humanized antibodies, camelized antibodies, chimeric antibodies, intrabodies, anti-idiotypic (anti-Id) antibodies, and functional fragments, (*e.g.,* beta klotho binding fragments) of any of the above. Non-limiting examples of functional fragments (*e.g.,* fragments that bind to beta klotho) include single-chain Fvs (scFv) (*e.g.,* including monospecific, bispecific, etc.), Fab fragments, F(ab') fragments, F(ab)2 fragements, F(ab')2 fragments, disulfide-linked Fvs (sdFv), Fd fragments, Fv fragments, diabody, triabody, tetrabody and minibody.

[00239] Antibodies provided herein include, but are not limited to, immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, for example, molecules that contain an antigen binding site that bind to a beta klotho epitope. The immunoglobulin molecules provided herein can be of any type (*e.g.,* IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.,* IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

[00240] Variants and derivatives of antibodies include antibody functional fragments that retain the ability to bind to a beta klotho epitope. Exemplary functional fragments include Fab fragments (*e.g.,* an antibody fragment that contains the antigen-binding domain and comprises a light chain and part of a heavy chain bridged by a disulfide bond); Fab' (*e.g.,* an antibody fragment containing a single anti-binding domain comprising an Fab and an additional portion of the heavy chain through the hinge region); F(ab')2 (*e.g.,* two Fab' molecules joined by interchain disulfide bonds in the hinge regions of the heavy chains; the Fab' molecules may be directed toward the same or different epitopes); a bispecific Fab (*e.g.,* a Fab molecule having two antigen binding domains, each of which may be directed to a different epitope); a single chain Fab chain comprising a variable region, also known as, a sFv (*e.g.,* the variable, antigen-binding determinative region of a single light and heavy chain of an antibody linked together by a chain of 10-25 amino acids); a disulfide-linked Fv, or dsFv (*e.g.,* the variable, antigen-binding determinative region of a single light and heavy chain of an antibody linked together by a disulfide bond); a camelized VH (*e.g.,* the variable, antigen-binding determinative region of a single heavy chain of an antibody in which some amino acids at the VH interface are those found in the heavy chain of naturally occurring camel antibodies); a bispecific sFv (*e.g.,* a sFv or a dsFv molecule having two antigen-binding domains, each of which may be directed to a different epitope); a diabody (*e.g.,* a dimerized sFv formed

when the VH domain of a first sFv assembles with the VL domain of a second sFv and the VL domain of the first sFv assembles with the VH domain of the second sFv; the two antigen-binding regions of the diabody may be directed towards the same or different epitopes); and a triabody (*e.g.,* a trimerized sFv, formed in a manner similar to a diabody, but in which three antigen-binding domains are created in a single complex; the three antigen binding domains may be directed towards the same or different epitopes). Derivatives of antibodies also include one or more CDR sequences of an antibody combining site. The CDR sequences may be linked together on a scaffold when two or more CDR sequences are present. In certain embodiments, the antibody comprises a single-chain Fv ("scFv"). scFvs are antibody fragments comprising the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. The scFv polypeptide may further comprise a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding. For a review of scFvs see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994).

4. Humanized Antibodies

[00241] The present disclosure provides humanized antibodies that bind beta klotho, including human and/or cyno beta klotho. Humanized antibodies of the present disclosure may comprise one or more CDRs as shown in Tables 1-10. Various methods for humanizing non-human antibodies are known in the art. For example, a humanized antibody can have one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization may be performed, for example, following the method of Winter and co-workers (Jones *et al.* (1986) *Nature* 321:522-525; Riechmann *et al.* (1988) *Nature* 332:323-327; Verhoeyen *et al.* (1988) *Science* 239:1534-1536), by substituting hypervariable region sequences for the corresponding sequences of a human antibody.

[00242] In some cases, the humanized antibodies are constructed by CDR grafting, in which the amino acid sequences of the six complementarity determining regions (CDRs) of the parent non-human antibody (*e.g.,* rodent) are grafted onto a human antibody framework. For example, Padlan *et al.* (*FASEB J.* 9:133-139, 1995)

determined that only about one third of the residues in the CDRs actually contact the antigen, and termed these the "specificity determining residues," or SDRs. In the technique of SDR grafting, only the SDR residues are grafted onto the human antibody framework (see, *e.g.,* Kashmiri *et al.*, *Methods* 36: 25-34, 2005).

[00243] The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies can be important to reduce antigenicity. For example, according to the so-called "best-fit" method, the sequence of the variable domain of a non-human (*e.g.,* rodent) antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent may be selected as the human framework for the humanized antibody (Sims *et al.* (1993) *J. Immunol.* 151:2296; Chothia *et al.* (1987) *J. Mol. Biol.* 196:901. Another method uses a particular framework derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter *et al.* (1992) *Proc. Natl. Acad. Sci. USA*, 89:4285; Presta *et al.* (1993) *J. Immunol.*, 151:2623. In some cases, the framework is derived from the consensus sequences of the most abundant human subclasses, V_L6 subgroup I (V_L6I) and V_H subgroup III (V_HIII). In another method, human germline genes are used at the source of the framework regions.

[00244] In an alternative paradigm based on comparison of CDRs, called Superhumanization, FR homology is irrelevant. The method consists of comparison of the non-human sequence with the functional human germline gene repertoire. Those genes encoding the same or closely related canonical structures to the murine sequences are then selected. Next, within the genes sharing the canonical structures with the non-human antibody, those with highest homology within the CDRs are chosen as FR donors. Finally, the non-human CDRs are grafted onto these FRs (see, *e.g.,* Tan *et al.*, *J. Immunol.* 169: 1119-1125, 2002).

[00245] It is further generally desirable that antibodies be humanized with retention of their affinity for the antigen and other favorable biological properties. To achieve this goal, according to one method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to

those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. These include, for example, WAM (Whitelegg and Rees, *Protein Eng.* 13: 819-824, 2000), Modeller (Sali and Blundell, *J. Mol. Biol.* 234: 779-815, 1993), and Swiss PDB Viewer (Guex and Peitsch, Electrophoresis 18: 2714-2713, 1997). Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *e.g.,* the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

[00246] Another method for antibody humanization is based on a metric of antibody humanness termed Human String Content (HSC). This method compares the mouse sequence with the repertoire of human germline genes and the differences are scored as HSC. The target sequence is then humanized by maximizing its HSC rather than using a global identity measure to generate multiple diverse humanized variants. (Lazar *et al.*, *Mol. Immunol.* 44: 1986-1998, 2007).

[00247] In addition to the methods described above, empirical methods may be used to generate and select humanized antibodies. These methods include those that are based upon the generation of large libraries of humanized variants and selection of the best clones using enrichment technologies or high throughput screening techniques. Antibody variants may be isolated from phage, ribosome and yeast display libraries as well as by bacterial colony screening (see, *e.g.,* Hoogenboom, *Nat. Biotechnol.* 23: 1105-1116, 2005; Dufner *et al.*, *Trends Biotechnol.* 24: 523-529, 2006; Feldhaus *et al.*, *Nat. Biotechnol.* 21: 163-70, 2003; Schlapschy *et al.*, *Protein Eng. Des. Sel.* 17: 847-60, 2004).

[00248] In the FR library approach, a collection of residue variants are introduced at specific positions in the FR followed by selection of the library to select the FR that best supports the grafted CDR. The residues to be substituted may include some or all of the "Vernier" residues identified as potentially contributing to CDR structure (see, *e.g.,* Foote and Winter, *J. Mol. Biol.* 224: 487-499, 1992), or from the more

limited set of target residues identified by Baca *et al.* (*J. Biol. Chem.* 272: 10678-10684, 1997).

[00249] In FR shuffling, whole FRs are combined with the non-human CDRs instead of creating combinatorial libraries of selected residue variants (see, *e.g.,* Dall'Acqua *et al.*, *Methods* 36: 43-60, 2005). The libraries may be screened for binding in a two-step selection process, first humanizing VL, followed by VH. Alternatively, a one-step FR shuffling process may be used. Such a process has been shown to be more efficient than the two-step screening, as the resulting antibodies exhibited improved biochemical and physico-chemical properties including enhanced expression, increased affinity and thermal stability (see, *e.g.,* Damschroder *et al.*, *Mol. Immunol.* 44: 3049-60, 2007).

[00250] The "humaneering" method is based on experimental identification of essential minimum specificity determinants (MSDs) and is based on sequential replacement of non-human fragments into libraries of human FRs and assessment of binding. It begins with regions of the CDR3 of non-human VH and VL chains and progressively replaces other regions of the non-human antibody into the human FRs, including the CDR1 and CDR2 of both VH and VL. This methodology typically results in epitope retention and identification of antibodies from multiple sub-classes with distinct human V-segment CDRs. Humaneering allows for isolation of antibodies that are 91-96 % homologous to human germline gene antibodies. (see, *e.g.,* Alfenito, Cambridge Healthtech Institute's Third Annual PEGS, The Protein Engineering Summit, 2007).

[00251] The "human engineering" method involves altering an non-human antibody or antibody fragment, such as a mouse or chimeric antibody or antibody fragment, by making specific changes to the amino acid sequence of the antibody so as to produce a modified antibody with reduced immunogenicity in a human that nonetheless retains the desirable binding properties of the original non-human antibodies. Generally, the technique involves classifying amino acid residues of a non-human (*e.g.,* mouse) antibody as "low risk", "moderate risk", or "high risk" residues. The classification is performed using a global risk/reward calculation that evaluates the predicted benefits of making particular substitution (*e.g.,* for immunogenicity in humans) against the risk that the substitution will affect the resulting antibody's folding and/or are substituted with human residues. The

particular human amino acid residue to be substituted at a given position (*e.g.,* low or moderate risk) of a non-human (*e.g.,* mouse) antibody sequence can be selected by aligning an amino acid sequence from the non-human antibody's variable regions with the corresponding region of a specific or consensus human antibody sequence. The amino acid residues at low or moderate risk positions in the non-human sequence can be substituted for the corresponding residues in the human antibody sequence according to the alignment. Techniques for making human engineered proteins are described in greater detail in Studnicka *et al.*, Protein Engineering, 7: 805-814 (1994), U.S. Patents 5,766,886, 5,770,196, 5,821,123, and 5,869,619, and PCT Application Publication WO 93/11794.

5. Human Antibodies

[00252] Human anti-beta klotho antibodies can be constructed by combining Fv clone variable domain sequence(s) selected from human-derived phage display libraries with known human constant domain sequences(s). Alternatively, human monoclonal anti-beta klotho antibodies of the present disclosure can be made by the hybridoma method. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described, for example, by Kozbor *J. Immunol.*, 133: 3001 (1984); Brodeur *et al.*, *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner *et al.*, *J. Immunol.*, 147: 86 (1991).

[00253] It is also possible to produce transgenic animals (*e.g.,* mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. Transgenic mice that express human antibody repertoires have been used to generate high-affinity human sequence monoclonal antibodies against a wide variety of potential drug targets (see, *e.g.,* Jakobovits, A., *Curr. Opin. Biotechnol.* 1995, 6(5):561-6; Brüggemann and Taussing, *Curr. Opin. Biotechnol.* 1997, 8(4):455-8; U.S. Pat. Nos. 6,075,181 and 6,150,584; and Lonberg *et al.*, *Nature Biotechnol.* 23: 1117-1125, 2005).

[00254] Alternatively, the human antibody may be prepared via immortalization of human B lymphocytes producing an antibody directed against a target antigen (*e.g.,* such B lymphocytes may be recovered from an individual or may have been immunized *in vitro*) (see, *e.g.,* Cole *et al.*, *Monoclonal Antibodies and Cancer*

Therapy, Alan R. Liss, p. 77 (1985); Boerner *et al.*, *J. Immunol.*, 147 (1):86-95 (1991); and US Pat No. 5,750,373).

[00255] Gene shuffling can also be used to derive human antibodies from non-human, for example, rodent, antibodies, where the human antibody has similar affinities and specificities to the starting non-human antibody. According to this method, which is also called "epitope imprinting" or "guided selection", either the heavy or light chain variable region of a non-human antibody fragment obtained by phage display techniques as described herein is replaced with a repertoire of human V domain genes, creating a population of non-human chain/human chain scFv or Fab chimeras. Selection with antigen results in isolation of a non-human chain/human chain chimeric scFv or Fab wherein the human chain restores the antigen binding site destroyed upon removal of the corresponding non-human chain in the primary phage display clone, (*e.g.,* the epitope guides (imprints) the choice of the human chain partner). When the process is repeated in order to replace the remaining non-human chain, a human antibody is obtained (see, *e.g.,* PCT WO 93/06213; and Osbourn *et al.*, Methods., 36, 61-68, 2005). Unlike traditional humanization of non-human antibodies by CDR grafting, this technique provides completely human antibodies, which have no FR or CDR residues of non-human origin. Examples of guided selection to humanize mouse antibodies towards cell surface antigens include the folate-binding protein present on ovarian cancer cells (see, *e.g.,* Figini *et al.*, *Cancer Res.*, 58, 991-996, 1998) and CD147, which is highly expressed on hepatocellular carcinoma (see, *e.g.,* Bao *et al.*, *Cancer Biol. Ther.*, 4, 1374-1380, 2005).

[00256] A potential disadvantage of the guided selection approach is that shuffling of one antibody chain while keeping the other constant could result in epitope drift. In order to maintain the epitope recognized by the non-human antibody, CDR retention can be applied (see, *e.g.,* Klimka *et al.*, *Br. J. Cancer.*, 83, 252-260, 2000; VH CDR2 Beiboer *et al.*, *J. Mol. Biol.*, 296, 833-49, 2000) In this method, the non-human VH CDR3 is commonly retained, as this CDR may be at the center of the antigen-binding site and may be to be the most important region of the antibody for antigen recognition. In some instances, however, VH CDR3 and VL CDR3, as well as VH CDR3, VL CDR3 and VL CFR1, of the non-human antibody may be retained.

6. Bispecific Antibodies

[00257] Bispecific antibodies are monoclonal antibodies that have binding specificities for at least two different antigens. In certain embodiments, bispecific antibodies are human or humanized antibodies. In certain embodiments, one of the binding specificities is for beta klotho and the other is for any other antigen. In some embodiments, one of the binding specificities is for beta klotho, and the other is for another surface antigen expressed on cells expressing beta klotho and a FGF receptor (*e.g.,* FGFR1c, FGFR2c, FGFR3c, FGFR4). In certain embodiments, bispecific antibodies may bind to two different epitopes of beta klotho. Bispecific antibodies can be prepared as full length antibodies or antibody fragments (*e.g.,* $F(ab')_2$ bispecific antibodies).

[00258] Methods for making bispecific antibodies are known in the art, such as, for example, by co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (see, *e.g.,* Milstein and Cuello, *Nature*, 305: 537 (1983)). For further details of generating bispecific antibodies see, for example, *Bispecific Antibodies*, Kontermann, ed., Springer-Verlag, Hiedelberg (2011).

7. Multivalent Antibodies

[00259] A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The antibodies of the present disclosure can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (*e.g.,* tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen binding sites. In certain embodiments, the dimerization domain comprises (or consists of) an Fc region or a hinge region. In this scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc region. In certain embodiments, a multivalent antibody comprises (or consists of) three to about eight antigen binding sites. In one such embodiment, a multivalent antibody comprises (or consists of) four antigen binding sites. The multivalent antibody comprises at least one polypeptide chain (for example, two polypeptide chains), wherein the polypeptide chain(s) comprise two or more variable domains. For instance, the polypeptide chain(s) may comprise VD1-(X1)n -VD2-(X2)n -Fc, wherein VD1 is a first variable

domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1. For instance, the polypeptide chain(s) may comprise: VH-CH1-flexible linker-VH-CH1-Fc region chain; or VH-CH1-VH-CH1-Fc region chain. The multivalent antibody herein may further comprise at least two (for example, four) light chain variable domain polypeptides. The multivalent antibody herein may, for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further comprise a CL domain.

8. Fc Engineering

[00260] It may be desirable to modify an antibody to beta klotho via Fc engineering, including, with respect to effector function, for example, so as to decrease or remove antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) of the antibody. This may be achieved by introducing one or more amino acid substitutions in an Fc region of the antibody. For example, substitutions into human IgG1 using IgG2 residues as positions 233-236 and IgG4 residues at positions 327, 330 and 331 were shown to greatly reduce ADCC and CDC (see, *e.g.,* Armour *et al.*, *Eur. J. Immunol.* 29:(8):2613-24 (1999); Shields *et al.*, *J. Biol..Chem.* 276(9): 6591-604 (2001).

[00261] To increase the serum half life of the antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment), for example, as described in U.S. Patent 5,739,277. Term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (*e.g.,* IgG1, IgG2, IgG3, or IgG4) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

9. Alternative Binding Agents

[00262] The present disclosure encompasses non-immunoglobulin binding agents that specifically bind to the same epitope as an anti-beta klotho antibody disclosed herein. In some embodiments, a non-immunoglobulin binding agent is identified an agent that displaces or is displaced by an anti-beta klotho antibody of the present disclosure in a competive binding assay. These alternative binding agents may include, for example, any of the engineered protein scaffolds known in the art. Such

scaffolds may comprise one or more CDRs as shown in Tables 1-10. Such scaffolds include, for example, anticalins, which are based upon the lipocalin scaffold, a protein structure characterized by a rigid beta-barrel that supports four hypervariable loops which form the ligand binding site. Novel binding specificities may be engineered by targeted random mutagenesis in the loop regions, in combination with functional display and guided selection (see, *e.g.,* Skerra (2008) *FEBS J.* 275: 2677-2683). Other suitable scaffolds may include, for example, adnectins, or monobodies, based on the tenth extracellular domain of human fibronectin III (see, *e.g.,* Koide and Koide (2007) *Methods Mol. Biol.* 352: 95-109); affibodies, based on the Z domain of staphylococcal protein A (see, *e.g.,* Nygren *et al.* (2008) *FEBS J.* 275: 2668-2676)); DARPins, based on ankyrin repeat proteins (see, *e.g.,* Stumpp *et al.* (2008) *Drug. Discov. Today* 13: 695-701); fynomers, based on the SH3 domain of the human Fyn protein kinase Grabulovski *et al.* (2007) *J. Biol. Chem.* 282: 3196-3204); affitins, based on Sac7d from Sulfolobus acidolarius (see, *e.g.,* Krehenbrink *et al.* (2008) *J. Mol. Biol.* 383: 1058-1068); affilins, based on human y-B-crystallin (see, *e.g.,* Ebersbach *et al.* (2007) *J. Mol. Biol.* 372: 172-185); avimers, based on the A domains of membrane receptor proteins (see, *e.g.,* Silverman *et al.* (2005) *Biotechnol.* 23: 1556-1561); cysteine-rich knottin peptides (see, *e.g.,* Kolmar (2008) *FEBS J.* 275: 2684-2690); and engineered Kunitz-type inhibitors (see, *e.g.,* Nixon and Wood (2006) *Curr. Opin. Drug. Discov. Dev.* 9: 261-268) For a review, see, for example, Gebauer and Skerra (2009) *Curr. Opin. Chem. Biol.* 13: 245-255.

Antibody Variants

[00263] In some embodiments, amino acid sequence modification(s) of the antibodies that bind to beta klotho or described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody, including but not limited to specificity, thermostability, expression level, effector functions, glycosylation, reduced immunogenicity or solubility. This, in addition to the anti-beta klotho antibodies described herein, it is contemplated that anti-beta klotho antibody variants can be prepared. For example, anti-beta klotho antibody variants can be prepared by introducing appropriate nucleotide changes into the encoding DNA, and/or by synthesis of the desired antibody or polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the anti-beta klotho antibody, such

as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

[00264] In some embodiments, antibodies provided herein are chemically modified, for example, by the covalent attachment of any type of molecule to the antibody. The antibody derivatives may include antibodies that have been chemically modified, for example, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited, to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, etc. Additionally, the antibody may contain one or more non-classical amino acids.

[00265] Variations may be a substitution, deletion or insertion of one or more codons encoding the antibody or polypeptide that results in a change in the amino acid sequence as compared with the native sequence antibody or polypeptide. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, *e.g.,* conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. In certain embodiments, the substitution, deletion or insertion includes less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the original molecule. In a specific embodiment, the substitution is a conservative amino acid substitution made at one or more predicted non-essential amino acid residues. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

[00266] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the

fusion to the N- or C-terminus of the antibody to an enzyme (*e.g.,* for antibody-directed enzyme prodrug therapy) or a polypeptide which increases the serum half-life of the antibody.

[00267] Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Alternatively, conservative (*e.g.,* within an amino acid group with similar properties and/or sidechains) substitutions may be made, so as to maintain or not significantly change the properties. Amino acids may be grouped according to similarities in the properties of their side chains (see, *e.g.,* A. L. Lehninger, in *Biochemistry*, 2nd Ed., pp. 73-75, Worth Publishers, New York (1975)): (1) non-polar: Ala (A), Val (V), Leu (L), Ile (I), Pro (P), Phe (F), Trp (W), Met (M); (2) uncharged polar: Gly (G), Ser (S), Thr (T), Cys (C), Tyr (Y), Asn (N), Gln (Q); (3) acidic: Asp (D), Glu (E); and (4) basic: Lys (K), Arg (R), His(H).

[00268] Alternatively, naturally occurring residues may be divided into groups based on common side-chain properties: (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

[00269] Non-conservative substitutions entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, into the remaining (non-conserved) sites. Accordingly, in one embodiment, an antibody or fragment thereof that binds to a beta klotho epitope comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of a murine monoclonal antibody described herein. In one embodiment, an antibody or fragment thereof that binds to a beta klotho epitope comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%

identical to an amino acid sequence depicted in Tables 1-10. In yet another embodiment, an antibody or fragment thereof that binds to a beta klotho epitope comprises a VH CDR and/or a VL CDR amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to a VH CDR amino acid sequence depicted in Tables 1-10 and/or a VL CDR amino acid sequence depicted in Tables 1-10. The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis (see, *e.g.,* Carter *et al.*, *Nucl. Acids Res.*, 13:4331 (1986); Zoller *et al.*, *Nucl. Acids Res.*, 10:6487 (1987)), cassette mutagenesis (see, *e.g.,* Wells *et al.*, *Gene*, 34:315 (1985)), restriction selection mutagenesis (see, *e.g.,* Wells *et al.*, *Philos. Trans. R. Soc. London SerA*, 317:415 (1986)) or other known techniques can be performed on the cloned DNA to produce the anti-beta klotho antibody variant DNA.

[00270] Any cysteine residue not involved in maintaining the proper conformation of the anti-beta klotho antibody also may be substituted, for example, with with another amino acid such as alanine or serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the anti-beta klotho antibody to improve its stability (*e.g.,* where the antibody is an antibody fragment such as an Fv fragment).

[00271] In some embodiments, an anti-beta klotho antibody molecule of the present disclosure is a “de-immunized” antibody. A “de-immunized” anti-beta klotho antibody is an antibody derived from a humanized or chimeric anti-beta klotho antibody, that has one or more alterations in its amino acid sequence resulting in a reduction of immunogenicity of the antibody, compared to the respective original non-de-immunized antibody. One of the procedures for generating such antibody mutants involves the identification and removal of T-cell epitopes of the antibody molecule. In a first step, the immunogenicity of the antibody molecule can be determined by several methods, for example, by *in vitro* determination of T-cell epitopes or in silico prediction of such epitopes, as known in the art. Once the critical residues for T-cell epitope function have been identified, mutations can be made to remove

immunogenicity and retain antibody activity. For review, see, for example, Jones *et al.*, *Methods in Molecular Biology* 525: 405-423, 2009.

1. In vitro Affinity Maturation

[00272] In some embodiments, antibody variants having an improved property such as affinity, stability, or expression level as compared to a parent antibody may be prepared by *in vitro* affinity maturation. Like the natural prototype, *in vitro* affinity maturation is based on the principles of mutation and selection. Libraries of antibodies are displayed as Fab, scFv or V domain fragments either on the surface of an organism (*e.g.,* phage, bacteria, yeast or mammalian cell) or in association (*e.g.,* covalently or non-covalently) with their encoding mRNA or DNA. Affinity selection of the displayed antibodies allows isolation of organisms or complexes carrying the genetic information encoding the antibodies. Two or three rounds of mutation and selection using display methods such as phage display usually results in antibody fragments with affinities in the low nanomolar range. Preferred affinity matured antibodies will have nanomolar or even picomolar affinities for the target antigen.

[00273] Phage display is a widepread method for display and selection of antibodies. The antibodies are displayed on the surface of Fd or M13 bacteriophages as fusions to the bacteriophage coat protein. Selection involves exposure to antigen to allow phage-displayed antibodies to bind their targets, a process referred to as "panning." Phage bound to antigen are recovered and infected in bacteria to produce phage for further rounds of selection. For review, see, for example, Hoogenboom, *Methods. Mol. Biol.* 178: 1-37, 2002; Bradbury and Marks, *J. Immuno. Methods* 290: 29-49, 2004).

[00274] In a yeast display system (see, *e.g.,* Boder *et al.*, *Nat. Biotech.* 15: 553–57, 1997; Chao *et al.*, *Nat. Protocols* 1:755-768, 2006), the antibody may be displayed as single-chain variable fusions (scFv) in which the heavy and light chains are connected by a flexible linker. The scFv is fused to the adhesion subunit of the yeast agglutinin protein Aga2p, which attaches to the yeast cell wall through disulfide bonds to Aga1p. Display of a protein via Aga2p projects the protein away from the cell surface, minimizing potential interactions with other molecules on the yeast cell wall. Magnetic separation and flow cytometry are used to screen the library to select for antibodies with improved affinity or stability. Binding to a soluble antigen of

interest is determined by labeling of yeast with biotinylated antigen and a secondary reagent such as streptavidin conjugated to a fluorophore. Variations in surface expression of the antibody can be measured through immunofluorescence labeling of either the hemagglutinin or c-Myc epitope tag flanking the scFv. Expression has been shown to correlate with the stability of the displayed protein, and thus antibodies can be selected for improved stability as well as affinity (see, *e.g.,* Shusta *et al.*, *J. Mol. Biol.* 292: 949-956, 1999). An additional advantage of yeast display is that displayed proteins are folded in the endoplasmic reticulum of the eukaryotic yeast cells, taking advantage of endoplasmic reticulum chaperones and quality-control machinery. Once maturation is complete, antibody affinity can be conveniently 'titrated' while displayed on the surface of the yeast, eliminating the need for expression and purification of each clone. A theoretical limitation of yeast surface display is the potentially smaller functional library size than that of other display methods; however, a recent approach uses the yeast cells' mating system to create combinatorial diversity estimated to be 10^{14} in size (see, *e.g.,* US Patent Publication 2003/0186,374; Blaise *et al.*, *Gene* 342: 211–218, 2004).

[00275] In ribosome display, antibody-ribosome-mRNA (ARM) complexes are generated for selection in a cell-free system. The DNA library coding for a particular library of antibodies is genetically fused to a spacer sequence lacking a stop codon. This spacer sequence, when translated, is still attached to the peptidyl tRNA and occupies the ribosomal tunnel, and thus allows the protein of interest to protrude out of the ribosome and fold. The resulting complex of mRNA, ribosome, and protein can bind to surface-bound ligand, allowing simultaneous isolation of the antibody and its encoding mRNA through affinity capture with the ligand. The ribosome-bound mRNA is then reversed transcribed back into cDNA, which can then undergo mutagenesis and be used in the next round of selection (see, *e.g.,* Fukuda *et al.*, *Nucleic Acids Res.* 34, e127, 2006). In mRNA display, a covalent bond between antibody and mRNA is established using puromycin as an adaptor molecule (Wilson *et al.*, *Proc. Natl. Acad. Sci. USA* 98, 3750–3755, 2001).

[00276] As these methods are performed entirely *in vitro*, they provide two main advantages over other selection technologies. First, the diversity of the library is not limited by the transformation efficiency of bacterial cells, but only by the number of ribosomes and different mRNA molecules present in the test tube. Second, random

mutations can be introduced easily after each selection round, for example, by non-proofreading polymerases, as no library must be transformed after any diversification step.

[00277] Diversity may be introduced into the CDRs or the whole V genes of the antibody libraries in a targeted manner or via random introduction. The former approach includes sequentially targeting all the CDRs of an antibody via a high or low level of mutagenesis or targeting isolated hot spots of somatic hypermutations (see, *e.g.,* Ho, *et al.*, *J. Biol. Chem.* 280: 607–617, 2005) or residues suspected of affecting affinity on experimental basis or structural reasons. Random mutations can be introduced throughout the whole V gene using *E. coli* mutator strains, error-prone replication with DNA polymerases (see, *e.g.,* Hawkins *et al.*, *J. Mol. Biol.* 226: 889-896, 1992) or RNA replicases. Diversity may also be introduced by replacement of regions that are naturally diverse via DNA shuffling or similar techniques (see, *e.g.,* Lu *et al.*, *J. Biol. Chem.* 278: 43496-43507, 2003; US Pat. No. 5,565,332; US Pat. No. 6,989,250). Alternative techniques target hypervariable loops extending into framework-region residues (see, *e.g.,* Bond *et al.*, *J. Mol. Biol.* 348: 699-709, 2005) employ loop deletions and insertions in CDRs or use hybridization-based diversification (see, *e.g.,* US Patent Publication No. 2004/0005709). Additional methods of generating diversity in CDRs are disclosed, for example, in US Pat. No. 7,985,840.

[00278] Screening of the libraries can be accomplished by various techniques known in the art. For example, beta klotho can be immobilized onto solid supports, columns, pins or cellulose/poly(vinylidene fluoride) membranes/ other filters, expressed on host cells affixed to adsorption plates or used in cell sorting, or conjugated to biotin for capture with streptavidin-coated beads, or used in any other method for panning display libraries.

[00279] For review of *in vitro* affinity maturation methods, see, *e.g.,* Hoogenboom, *Nature Biotechnology* 23: 1105-1116, 2005 and Quiroz and Sinclair, Revista Ingeneria Biomedia 4: 39-51, 2010 and references therein.

2. Modifications of Anti-Beta Klotho Antibodies

[00280] Covalent modifications of anti-beta klotho antibodies are included within the scope of the present disclosure. Covalent modifications include reacting targeted

amino acid residues of an anti-beta klotho antibody with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the anti-beta klotho antibody. Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains (see, *e.g.,* T.E. Creighton, *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[00281] Other types of covalent modification of the anti-beta klotho antibody included within the scope of this present disclosure include altering the native glycosylation pattern of the antibody or polypeptide (see, *e.g.,* Beck *et al.*, *Curr. Pharm. Biotechnol.* 9: 482-501, 2008; Walsh, *Drug Discov. Today* 15: 773-780, 2010), and linking the antibody to one of a variety of nonproteinaceous polymers, *e.g.,* polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth, for example, in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

[00282] An anti-beta klotho antibody of the present disclosure may also be modified to form chimeric molecules comprising an anti-beta klotho antibody fused to another, heterologous polypeptide or amino acid sequence, for example, an epitope tag (see, *e.g.,* Terpe, *Appl. Microbiol. Biotechnol.* 60: 523-533, 2003) or the Fc region of an IgG molecule (see, *e.g.,* Aruffo, "Immunoglobulin fusion proteins" in Antibody Fusion Proteins, S.M. Chamow and A. Ashkenazi, eds., Wiley-Liss, New York, 1999, pp. 221-242).

[00283] Also provided herein are fusion proteins comprising an antibody provided herein that binds to a beta klotho antigen and a heterologous polypeptide. In some embodiments, the heterologous polypeptide to which the antibody is fused is useful for targeting the antibody to cells having cell surface-expressed beta klotho.

[00284] Also provided herein are panels of antibodies that bind to a beta klotho antigen. In specific embodiments, panels of antibodies have different association rate constants different dissociation rate constants, different affinities for beta klotho

antigen, and/or different specificities for a beta klotho antigen. In some embodiments, the panels comprise or consist of about 10, about 25, about 50, about 75, about 100, about 125, about 150, about 175, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 antibodies or more. Panels of antibodies can be used, for example, in 96 well or 384 well plates, such as for assays such as ELISAs.

Preparation of Anti-Beta Klotho Antibodies

[00285] Anti-beta klotho antibodies may be produced by culturing cells transformed or transfected with a vector containing anti-beta klotho antibody-encoding nucleic acids. Polynucleotide sequences encoding polypeptide components of the antibody of the present disclosure can be obtained using standard recombinant techniques. Desired polynucleotide sequences may be isolated and sequenced from antibody producing cells such as hybridomas cells. Alternatively, polynucleotides can be synthesized using nucleotide synthesizer or PCR techniques. Once obtained, sequences encoding the polypeptides are inserted into a recombinant vector capable of replicating and expressing heterologous polynucleotides in host cells. Many vectors that are available and known in the art can be used for the purpose of the present disclosure. Selection of an appropriate vector will depend mainly on the size of the nucleic acids to be inserted into the vector and the particular host cell to be transformed with the vector. Host cells suitable for expressing antibodies of the present disclosure include prokaryotes such as Archaebacteria and Eubacteria, including Gram-negative or Gram-positive organisms, eukaryotic microbes such as filamentous fungi or yeast, invertebrate cells such as insect or plant cells, and vertebrate cells such as mammalian host cell lines. Host cells are transformed with the above-described expression vectors and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. Antibodies produced by the host cells are purified using standard protein purification methods as known in the art.

[00286] Methods for antibody production including vector construction, expression and purification are further described, in Plückthun *et al.*, (1996) in *Antibody Engineering: Producing antibodies in Escherichia coli: From PCR to fermentation*

(McCafferty, J., Hoogenboom, H. R., and Chiswell, D. J., eds), 1 Ed., pp. 203-252, IRL Press, Oxford; Kwong, K. & Rader, C., *E. coli* expression and purification of Fab antibody fragments, Current protocols in protein science editorial board John E Coligan *et al.*, Chapter 6, Unit 6.10 (2009); Tachibana and Takekoshi, "Production of Antibody Fab Fragments in Escherischia coli," in *Antibody Expression and Production*, M. Al-Rubeai, Ed., Springer, New York, 2011; *Therapeutic Monoclonal Antibodies: From Bench to Clinic* (ed Z. An), John Wiley & Sons, Inc., Hoboken, NJ, USA.

[00287] It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare anti-beta klotho antibodies. For instance, the appropriate amino acid sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques (see, *e.g.,* Stewart *et al.*, *Solid-Phase Peptide Synthesis*, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, *J. Am. Chem. Soc.*, 85:2149-2154 (1963)). *In vitro* protein synthesis may be performed using manual techniques or by automation. Various portions of the anti-beta klotho antibody may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the desired anti-beta klotho antibody. Alternatively, antibodies may be purified from cells or bodily fluids, such as milk, of a transgenic animal engineered to express the antibody, as disclosed, for example, in US Pat. No. 5,545,807 and US Pat. No. 5,827,690.

Immunoconjugates

[00288] The present disclosure also provides conjugates comprising any one of the anti-beta klotho antibodies of the present disclosure covalently bound by a synthetic linker to one or more non-antibody agents.

[00289] A variety of radioactive isotopes are available for the production of radioconjugated antibodies. Examples include At^{211}, I4, I4, Y4, Re4, Re4, Sm4, Bi4, P4, Pb4 and radioactive isotopes of Lu. When the conjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example tc4 or I4, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, MRI), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron. The radioisotopes may be incorporated in the conjugate in known ways as described,

e.g., in Reilly, "The radiochemistry of monoclonal antibodies and peptides," in Monoclonal Antibody and Peptide-Targeted Radiotherapy of Cancer, R.M. Reilly, ed., Wiley, Hoboken N.J., 2010.

[00290] In some embodiments, antibodies provided herein are conjugated or recombinantly fused to a diagnostic, detectable or therapeutic agent or any other molecule. The conjugated or recombinantly fused antibodies can be useful, for example, for monitoring or prognosing the onset, development, progression and/or severity of a beta klotho-mediated disease as part of a clinical testing procedure, such as determining the efficacy of a particular therapy.

[00291] Such diagnosis and detection can accomplished, for example, by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; chemiluminescent material, such as but not limited to, an acridinium based compound or a HALOTAG; radioactive materials, such as, but not limited to, iodine (^{131}I, ^{125}I, ^{123}I, and ^{121}I,), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, and ^{111}In,), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Sn; and positron emitting metals using various positron emission tomographies, and non-radioactive paramagnetic metal ions.

[00292] Also provided herein are antibodies that are conjugated or recombinantly fused to a therapeutic moiety (or one or more therapeutic moieties), as well as uses thereof. The antibody may be conjugated or recombinantly fused to a therapeutic moiety, including a cytotoxin such as a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion such as alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells.

[00293] Further, an antibody provided herein may be conjugated or recombinantly fused to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, γ-interferon, α-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, *e.g.,* TNF-γ, TNF-γ, AIM I (see, *e.g.,* International Publication No. WO 97/33899), AIM II (see, *e.g.,* International Publication No. WO 97/34911), Fas Ligand (see, *e.g.,*Takahashi *et al.*, 1994, J. Immunol., 6:1567-1574), and VEGF (see, *e.g.,* International Publication No. WO 99/23105), an anti-angiogenic agent, including, for example angiostatin, endostatin or a component of the coagulation pathway (*e.g.,* tissue factor); or, a biological response modifier such as, for example, a lymphokine (*e.g.,* interferon gamma, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-5 ("IL-5"), interleukin-6 ("IL-6"), interleukin-7 ("IL-7"), interleukin 9 ("IL-9"), interleukin-10 ("IL-10"), interleukin-12 ("IL-12"), interleukin-15 ("IL-15"), interleukin-23 ("IL-23"), granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF")), or a growth factor (*e.g.,* growth hormone ("GH")), or a coagulation agent (*e.g.,* calcium, vitamin K, tissue factors, such as but not limited to, Hageman factor (factor XII), high-molecular-weight kininogen (HMWK), prekallikrein (PK), coagulation proteins-factors II (prothrombin), factor V, XIIa, VIII, XIIIa, XI, XIa, IX, IXa, X, phospholipid, and fibrin monomer).

[00294] Also provided herein are antibodies that are recombinantly fused or chemically conjugated (covalent or non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, for example, to a polypeptide of about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90 or about 100 amino acids) to generate fusion proteins, as well as uses thereof. In particular, provided herein are fusion proteins comprising an antigen-binding fragment of an antibody provided herein (*e.g.,* a Fab fragment, Fd fragment, Fv fragment, $F(ab)_2$ fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide. In one embodiment, the

heterologous protein, polypeptide, or peptide that the antibody is fused to is useful for targeting the antibody to a particular cell type, such as a cell that expresses beta klotho or an beta klotho receptor. For example, an antibody that binds to a cell surface receptor expressed by a particular cell type (*e.g.,* an immune cell) may be fused or conjugated to a modified antibody provided herein.

[00295] In addition, an antibody provided herein can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alpha-emitters such as ^{213}Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{131}In, ^{131}LU, ^{131}Y, ^{131}Ho, ^{131}Sm, to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described, for example, in Denardo *et al.*, 1998, *Clin Cancer Res.* 4(10):2483-90; Peterson *et al.*, 1999, *Bioconjug. Chem.* 10(4):553-7; and Zimmerman *et al.*, 1999, *Nucl. Med. Biol.* 26(8):943-50.

[00296] Moreover, antibodies provided herein can be fused to marker or "tag" sequences, such as a peptide to facilitate purification. In specific embodiments, the marker or tag amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (see, *e.g.,* QIAGEN, Inc.), among others, many of which are commercially available. For example, as described in Gentz *et al.*, 1989, Proc. Natl. Acad. Sci. USA 86:821-824, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, 1984, Cell 37:767), and the "FLAG" tag.

[00297] Methods for fusing or conjugating therapeutic moieties (including polypeptides) to antibodies are well known, (see, *e.g.,* Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic

Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), Thorpe *et al.*, 1982, Immunol. Rev. 62:119-58; U.S. Pat. Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, 5,723,125, 5,783,181, 5,908,626, 5,844,095, and 5,112,946; EP 307,434; EP 367,166; EP 394,827; PCT publications WO 91/06570, WO 96/04388, WO 96/22024, WO 97/34631, and WO 99/04813; Ashkenazi *et al.*, Proc. Natl. Acad. Sci. USA, 88: 10535-10539, 1991; Traunecker *et al.*, Nature, 331:84-86, 1988; Zheng *et al.*, J. Immunol., 154:5590-5600, 1995; Vil *et al.*, Proc. Natl. Acad. Sci. USA, 89:11337-11341, 1992).

[00298] Fusion proteins may be generated, for example, through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of anti-beta klotho antibodies as provided herein, including, for example, antibodies with higher affinities and lower dissociation rates (see, *e.g.,* U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten *et al.*, 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson *et al.*, 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308- 313). Antibodies, or the encoded antibodies, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody provided herein may be recombined with one or more components, motifs, sections, parts, domains, fragments, *etc.* of one or more heterologous molecules.

[00299] An antibody provided herein can also be conjugated to a second antibody to form an antibody heteroconjugate as described, for example, in U.S. Patent No. 4,676,980.

[00300] The therapeutic moiety or drug conjugated or recombinantly fused to an antibody provided herein that binds to beta klotho (*e.g.,* a beta klotho polypeptide, fragment, epitope) should be chosen to achieve the desired prophylactic or therapeutic effect(s). In certain embodiments, the antibody is a modified antibody. A clinician or other medical personnel may consider, for example, the following when deciding on which therapeutic moiety or drug to conjugate or recombinantly fuse to

an antibody provided herein: the nature of the disease, the severity of the disease, and the condition of the subject.

[00301] Antibodies that bind to beta klotho as provided herein may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[00302] The linker may be a "cleavable linker" facilitating release of the conjugated agent in the cell, but non-cleavable linkers are also contemplated herein. Linkers for use in the conjugates of the present disclosure include without limitation acid labile linkers (*e.g.,* hydrazone linkers), disulfide-containing linkers, peptidase-sensitive linkers (*e.g.,* peptide linkers comprising amino acids, for example, valine and/or citrulline such as citrulline-valine or phenylalanine-lysine), photolabile linkers, dimethyl linkers (see, *e.g.,* Chari *et al.*, *Cancer Research* 52:127-131 (1992); U.S. Patent No. 5,208,020), thioether linkers, or hydrophilic linkers designed to evade multidrug transporter-mediated resistance (see, *e.g.*Kovtun *et al.*, *Cancer Res.* 70: 2528-2537, 2010).

[00303] Conjugates of the antibody and agent may be made using a variety of bifunctional protein coupling agents such as BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate). The present disclosure further contemplates that conjugates of antibodies and agents may be prepared using any suitable methods as disclosed in the art, (see, *e.g.,* in *Bioconjugate Techniques*, 2nd Ed., G.T. Hermanson, ed., Elsevier, San Francisco, 2008).

[00304] Conventional conjugation strategies for antibodies and agents have been based on random conjugation chemistries involving the ε-amino group of Lys residues or the thiol group of Cys residues, which results in heterogenous conjugates. Recently developed techniques allow site-specific conjugation to antibodies, resulting in homogeneous loading and avoiding conjugate subpopulations with altered antigen-binding or pharmacokinetics. These include engineering of "thiomabs" comprising cysteine substitutions at positions on the heavy and light chains that provide reactive thiol groups and do not disrupt immunoglobulin

folding and assembly or alter antigen binding (see, *e.g.,* Junutula *et al.*, *J. Immunol. Meth.* 332: 41-52 (2008); Junutula *et al.*, *Nat. Biotechnol.* 26: 925-932, 2008). In another method, selenocysteine is cotranslationally inserted into an antibody sequence by recoding the stop codon UGA from termination to selenocysteine insertion, allowing site specific covalent conjugation at the nucleophilic selenol group of selenocysteine in the presence of the other natural amino acids (see, *e.g.,*Hofer *et al.*, *Proc. Natl. Acad. Sci. USA* 105: 12451-12456 (2008); Hofer *et al.*, *Biochemistry* 48(50): 12047-12057, 2009).

Pharmaceutical Formulations

[00305] Anti-beta klotho antibodies of the present disclosure may be administered by any route appropriate to the condition to be treated. The antibody will typically be administered parenterally, for example, infusion, subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural. The antibody dose will vary, including depending on the nature and/or severity of the disease as well as the condition of the subject, may include doses between 1mg and 100 mg. Doses may also include those between 1 mg/kg and 15 mg/kg. In some embodiments, the dose is between about 5 mg/kg and about 7.5 mg/kg. In some embodiments, the dose is about 5 mg/kg. In some embodiments, the dose is about 7.5 mg/kg. Flat doses selected from the group consisting of: (a) 375-400 mg every two weeks and (b) 550-600 mg every three weeks. In some embodiments, the flat dose is 375-400 mg every two weeks. In some embodiments, the flat dose is 550-600 mg every three weeks. In some embodiments the flat dose is 400 mg every two weeks. In some embodiments the flat dose is 600 mg every three weeks. In some embodiments of sequential dosing, a first dose and a second dose are each between 1 mg/kg and 15 mg/kg with the second dose following the first does by between 1 and 4 weeks. In some embodiments, the first dose and the second dose are each between 5 mg/kg and 7.5 mg/kg and the second dose follows the first dose by between 2 and 3 weeks. In some embodiments, the first dose and the second dose are each 5 mg/kg and the second dose follows the first dose by 2 weeks. In some embodiments, the first dose and the second dose are each 7.5 mg/kg and the second dose follows the first dose by 3 weeks.

[00306] For treating diseases, disorders and conditions, the antibody in some embodiments is administered via intravenous infusion. The dosage administered via

infusion is in the range of about 1 $\mu g/m^2$ to about 10,000 $\mu g/m^2$ per dose, generally one dose per week for a total of one, two, three or four doses. Alternatively, the dosage range is of about 1 $\mu g/m^2$ to about 1000 $\mu g/m^2$, about 1 $\mu g/m^2$ to about 800 $\mu g/m^2$, about 1 $\mu g/m^2$ to about 600 $\mu g/m^2$, about 1 $\mu g/m^2$ to about 400 $\mu g/m^2$; alternatively, about 10 $\mu g/m^2$ to about 500 $\mu g/m^2$, about 10 $\mu g/m^2$ to about 300 $\mu g/m^2$, about 10 $\mu g/m^2$ to about 200 $\mu g/m^2$, and about 1 $\mu g/m^2$ to about 200 $\mu g/m^2$. The dose may be administered once per day, once per week, multiple times per week, but less than once per day, multiple times per month but less than once per day, multiple times per month but less than once per week, once per month or intermittently to relieve or alleviate symptoms of the disease, disorder, or condition. Administration may continue at any of the disclosed intervals until amelioration of the disease, disorder or condition, or amelioration of symptoms of the disease, disorder or condition being treated. Administration may continue after remission or relief of symptoms is achieved where such remission or relief is prolonged by such continued administration.

[00307] In one aspect, the present disclosure further provides pharmaceutical formulations comprising at least one anti-beta klotho antibody of the present disclosure. In some embodiments, a pharmaceutical formulation comprises 1) an anti-beta klotho antibody, and 2) a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical formulation comprises 1) an anti-beta klotho antibody and/or an immunoconjugate thereof, and optionally, 2) at least one additional therapeutic agent.

[00308] Pharmaceutical formulations comprising an antibody is prepared for storage by mixing the antibody having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (see, *e.g.,* Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)) in the form of aqueous solutions or lyophilized or other dried formulations. The formulations herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, in addition to an anti-beta klotho antibody, it may be desirable to include in the one formulation, an additional antibody, *e.g.,* a second anti-beta klotho antibody which binds a different epitope on the beta klotho polypeptide, or an antibody to some other target. Alternatively, or additionally, the

composition may further comprise another agent, including, for example, a chemotherapeutic agent, cytotoxic agent, cytokine, growth inhibitory agent, anti-hormonal agent, and/or cardioprotectant. In some embodiments the formulation includes an alkylating agent (*e.g.,* chlorambucil, bendamustine hydrochloride or cyclophosphamide) a nucleoside analog (*e.g.,* fludurabine, pentostatin, cladribine or cytarabine) a corticosteroid (*e.g.,* prednisone, prednisolone or methylprednisolone), an immunomodulatory agent (*e.g.,* lenalidomide), an antibiotic (*e.g.,* doxorubicin, daunorubicin idarubicin or mitoxentrone), a synthetic flavon (*e.g.,* flavopiridol), a Bcl2 antagonist, (*e.g.,* oblimersen or ABT-263), a hypomethylating agent (*e.g.,* azacytidine or decitabine), an FLT3 inhibitor (*e.g.,* midostaurin, sorafenib and AC220). Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[00309] The antibodies of the present disclosure may be formulated in any suitable form for delivery to a target cell/tissue, *e.g.,* as microcapsules or macroemulsions (Remington's *Pharmaceutical Sciences*, 16th edition, Osol, A. Ed. (1980); Park *et al.*, *Molecules* 10: 146-161 (2005); Malik *et al.*, *Curr. Drug. Deliv.* 4: 141-151 (2007)); as sustained release formulations (Putney and Burke, *Nature Biotechnol.* 16: 153-157, (1998)) or in liposomes (Maclean *et al.*, *Int. J. Oncol.* 11: 235-332 (1997); Kontermann, *Curr. Opin. Mol. Ther.* 8: 39-45 (2006)).

[00310] An antibody provided herein can also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed, for example, in Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA.

[00311] Various delivery systems are known and can be used to administer a prophylactic or therapeutic agent (*e.g.,* an antibody that binds to beta klotho as described herein), including, but not limited to, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody, receptor-mediated endocytosis (see, *e.g.,* Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. In another embodiment, a prophylactic or therapeutic agent, or a composition

provided herein can be delivered in a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see, *e.g.,* Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:20; Buchwald *et al.*, 1980, Surgery 88:507; Saudek *et al.*, 1989, N. Engl. J. Med. 321:574). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of a prophylactic or therapeutic agent (*e.g.,* an antibody that binds to beta klotho as described herein) or a composition of the invention (see, *e.g.,* Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, J., Macromol. Sci. Rev. Macromol. Chem. 23:61; see also *Levy et al.*, 1985, Science 228:190; During et al., 1989, Ann. Neurol. 25:351; Howard et al., 1989, J. Neurosurg. 7 1:105); U.S. Patent No. 5,679,377; U.S. Patent No. 5,916,597; U.S. Patent No. 5,912,015; U.S. Patent No. 5,989,463; U.S. Patent No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253). Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In one embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable.

[00312] In yet another embodiment, a controlled or sustained release system can be placed in proximity of the therapeutic target, for example, the nasal passages or lungs, thus requiring only a fraction of the systemic dose (see, *e.g.,* Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)). Controlled release systems are discussed, for example, by Langer (1990, Science 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more antibodies that bind to beta klotho as described herein. (See, *e.g.,* U.S. Patent No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning et al., 1996, "Intratumoral Radioimmunotherapy of a Human Colon Cancer Xenograft Using a

Sustained-Release Gel," Radiotherapy & Oncology 39:179- 189, Song et al., 1995, "Antibody Mediated Lung Targeting of Long-Circulating Emulsions," PDA Journal of Pharmaceutical Science & Technology 50:372-397, Cleek et al., 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, and Lam et al., 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760).

Therapeutic methods

[00313] An antibody of the present disclosure may be used in, for example, *in vitro*, *ex vivo*, and *in vivo* therapeutic methods. In one aspect, the present disclosure provides methods for treating or preventing a disease, disorder, or condition, either *in vivo* or *in vitro*, the method comprising exposing a cell to an anti-beta klotho antibody.

[00314] In one aspect, an antibody of the present disclosure is used to treat or prevent a disease, disorder, or condition, including, for example, Type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, metabolic syndrome or broadly any disease, disorder, or condition in which it is desirable to mimic or augment the *in vivo* effects of FGF19 and/or FGF21.

[00315] In one aspect, methods are provided for treating a disease, disorder or condition comprising administering to an individual an effective amount of an anti-beta klotho antibody or fragment thereof. In certain embodiments, a method for treating a disease, disorder, or condition comprises administering to an individual an effective amount of a pharmaceutical formulation comprising an anti-beta klotho antibody and, optionally, at least one additional therapeutic agent, such as those described herein.

[00316] An anti-beta klotho antibody or fragment thereof can be administered to a human for therapeutic purposes. Moreover, an anti-beta klotho antibody or fragment thereof can be administered to a non-human mammal expressing beta klotho with which the antibody cross-reacts (*e.g.,* a primate, pig, rat, or mouse) for veterinary purposes or as an animal model of human disease. Regarding the latter, such animal models may be useful for evaluating the therapeutic efficacy of antibodies of the present disclosure (*e.g.,* testing of dosages and time courses of administration).

[00317] Antibodies of the present disclosure can be used either alone or in combination with other compositions in a therapy. For example, an anti-beta klotho antibody of the present disclosure may be co-administered with at least one additional therapeutic agent and/or adjuvant. In some embodiments, the additional compound is a therapeutic antibody other than an anti-beta klotho antibody.

[00318] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of an anti-beta klotho antibody or fragment thereof of the present disclosure can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent and/or adjuvant. Antibodies of the present disclosure can also be used in combination with additional therapeutic regimens including, without limitation, those described herein.

[00319] An antibody of the present disclosure (and any additional therapeutic agent or adjuvant) can be administered by any suitable means, including parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In addition, the antibody or conjugate is suitably administered by pulse infusion, particularly with declining doses of the antibody or fragment thereof. Dosing can be by any suitable route, for example, by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic.

[00320] Antibodies of the present disclosure would be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The anti-beta klotho antibody need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of antibody or immunoconjugate present in the formulation, the type of disorder or treatment, and

other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[00321] For the prevention or treatment of a disease, disorder, or condition, the appropriate dosage of an anti-beta klotho antibody of the present disclosure (when used alone or in combination with one or more other additional therapeutic agents, such as agents described herein) will depend on the type of disease, disorder, or condition, to be treated, the type of antibody, the severity and course of the disease, disorder, or condition, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The anti-beta klotho antibody is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 µg/kg to 100 mg/kg (*e.g.,* 0.1mg/kg-20mg/kg, 1mg/kg-15mg/kg, etc.) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. Exemplary dosages of the antibody may be in the range from about 0.05 mg/kg to about 10.0 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 3.0 mg/kg, 4.0 mg/kg, 5.0 mg/kg, 6.0 mg/kg, 7.0 mg/kg, 8.0 mg/kg, 9.0 mg/kg, or 10.0 mg/kg (or any combination thereof) of antibody may be administered to the patient. Such doses may be administered intermittently, *e.g.,* every week or every three weeks (*e.g.,* such that the patient receives from about two to about twenty, or *e.g.,* about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses may be administered. An exemplary dosing regimen comprises administering an initial loading dose, followed by a maintenance dose (*e.g.,* weekly) of the antibody. The initial loading dose may be greater than the maintenance dose. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

Diagnostic methods and methods of detection

[00322] In one aspect, anti-beta klotho antibodies and fragments thereof of the present disclosure are useful for detecting the presence of beta klotho in a biological sample. Such anti-beta klotho antibodies may include those that bind to human and/or cyno beta klotho, but do not induce FGF19-like signaling and/or FGF21-like signaling activity. The term "detecting" as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises a cell or tissue.

[00323] In one aspect, the present disclosure provides a method of detecting the presence of beta klotho in a biological sample. In certain embodiments, the method comprises contacting the biological sample with an anti-beta klotho antibody under conditions permissive for binding of the anti-beta klotho antibody to beta klotho, and detecting whether a complex is formed between the anti-beta klotho antibody and beta klotho.

[00324] In one aspect, the present disclosure provides a method of diagnosing a disorder associated with expression of beta klotho. In certain embodiments, the method comprises contacting a test cell with an anti-beta klotho antibody; determining the level of expression (either quantitatively or qualitatively) of beta klotho by the test cell by detecting binding of the anti-beta klotho antibody to beta klotho; and comparing the level of expression of beta klotho by the test cell with the level of expression of beta klotho by a control cell (*e.g.,* a normal cell of the same tissue origin as the test cell or a cell that expresses beta klotho at levels comparable to such a normal cell), wherein a higher level of expression of beta klotho by the test cell as compared to the control cell indicates the presence of a disorder associated with increased expression of beta klotho. In certain embodiments, the test cell is obtained from an individual suspected of having a disease, disorder or condition associated with expression of beta klotho and/or a disease, disorder or condition in which it is desirable to mimic or augment the *in vivo* effects of FGF19 and/or FGF21. In certain embodiments, the disease, disorder or condition is, for example, Type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease or metabolic syndrome. Such exemplary diseases, disorders or conditions may be diagnosed using an anti-beta klotho antibody of the present disclosure.

[00325] In certain embodiments, a method of diagnosis or detection, such as those described above, comprises detecting binding of an anti-beta klotho antibody to beta klotho expressed on the surface of a cell or in a membrane preparation obtained from a cell expressing beta klotho on its surface. In certain embodiments, the method comprises contacting a cell with an anti-beta klotho antibody under conditions permissive for binding of the anti-beta klotho antibody to beta klotho, and detecting whether a complex is formed between the anti-beta klotho antibody and beta klotho on the cell surface. An exemplary assay for detecting binding of an anti-beta klotho antibody to beta klotho expressed beta klotho on the surface of a cell is a "FACS" assay.

[00326] Certain other methods can be used to detect binding of anti-beta klotho antibodies to beta klotho. Such methods include, but are not limited to, antigen-binding assays that are well known in the art, such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, fluorescent immunoassays, protein A immunoassays, and immunohistochemistry (IHC).

[00327] In certain embodiments, anti-beta klotho antibodies are labeled. Labels include, but are not limited to, labels or moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, for example, through an enzymatic reaction or molecular interaction. Exemplary labels include, but are not limited to, the radioisotopes ^{32}P, ^{14}C, ^{125}I, ^{3}H, and ^{131}I, fluorophores such as rare earth chelates or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, luceriferases, for example, firefly luciferase and bacterial luciferase (see, *e.g.,* U.S. Pat. No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, horseradish peroxidase (HRP), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases, *e.g.,* glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, heterocyclic oxidases such as uricase and xanthine oxidase, coupled with an enzyme that employs hydrogen peroxide to oxidize a dye precursor such as HRP, lactoperoxidase, or microperoxidase, biotin/avidin, spin labels, bacteriophage labels, stable free radicals, and the like.

[00328] In certain embodiments, anti-beta klotho antibodies are immobilized on an insoluble matrix. Immobilization entails separating the anti-beta klotho antibody from any beta klotho that remains free in solution. This conventionally is accomplished by either insolubilizing the anti-beta klotho antibody before the assay procedure, as by adsorption to a water-insoluble matrix or surface (see, *e.g.,* Bennich *et al.*, U.S. 3,720,760), or by covalent coupling (for example, using glutaraldehyde cross-linking), or by insolubilizing the anti-beta klotho antibody after formation of a complex between the anti-beta klotho antibody and beta klotho, for example, by immunoprecipitation.

[00329] Any of the above embodiments of diagnosis or detection may be carried out using an immunoconjugate of the present disclosure in place of or in addition to an anti-beta klotho antibody.

Assays

[00330] Anti-beta klotho antibodies of the present disclosure may be characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

1. Activity assays

[00331] In one aspect, assays are provided for identifying anti-beta klotho antibodies thereof having biological activity. Biological activity may include, for example, assays which measure effects on glucose and/or lipid metabolism. For example, a blood glucose assay may be used. Blood glucose (*e.g.,* in mouse tail snip or in a human blood sample) may be measured using ACCU-CHEK Active test strips read by ACCU-CHEK Active meter (Roche Diagnostics, Indianapolis, IN) following manufacturer's instruction. In addition, for example, a lipid profile assay may be used. Whole blood (*e.g.,* from mouse tail snips or from a human blood sample) may be collected into plain capillary tubes (BD Clay Adams SurePrep, Becton Dickenson and Co. Sparks, MD). Serum and blood cells can be separated by spinning the tubes in an Autocrit Ultra 3 (Becton Dickinson and Co. Sparks, MD). Serum samples can be assayed for lipid profile (triglyceride, total cholesterol, HDL, and non-HDL) using Integra 400 Clinical Analyzer (Roche Diagnostics, Indianapolis, IN) following the manufacturer's instructions.

2. Binding assays and other assays

[00332] In one aspect, an anti-beta klotho antibody is tested for its antigen binding activity. For example, in certain embodiments, an anti-beta klotho antibody is tested for its ability to bind to exogenous or endogenous beta klotho expressed on the surface of a cell. A FACS assay may be used for such testing.

[00333] A panel of monoclonal antibodies raised against beta klotho may be grouped based upon the epitiopes they recognize, a process known as epitope binning. Epitope binning is typically carried out using competition assays, which evaluate an antibody's ability to bind to an antigen in the presence of another antibody. In an exemplary competition assay, immobilized beta klotho is incubated in a solution comprising a first labeled antibody that binds to beta klotho and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to beta klotho. The second antibody may be present in a hybridoma supernatant. As a control, immobilized beta klotho is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to beta klotho, excess unbound antibody is removed, and the amount of label associated with immobilized beta klotho is measured. If the amount of label associated with immobilized beta klotho is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to beta klotho. In certain embodiments, immobilized beta klotho is present on the surface of a cell or in a membrane preparation obtained from a cell expressing beta klotho on its surface.

[00334] High-throughput methods of epitope binning are also known in the art (see, *e.g.,* Jia *et al.*, *J. Immunol. Methods* 2004, 288(1-2):91-98, describing a method of multiplexed competitive antibody binning for the characterization of monoclonal antibodies; and Miller *et al.*, *J. Immunol. Methods* 2011, 365(1-2):118-25, describing epitope binning of murine monoclonal antibodies by a multiplexed pairing assay).

3. Epitope mapping

[00335] Epitope mapping is the process of identifying the binding sites, or epitopes, of an antibody on its target protein antigen. Antibody epitopes may be linear epitopes or conformational epitopes. Linear epitopes are formed by a continuous sequence of amino acids in a protein. Conformational epitopes are formed of amino

acids that are discontinuous in the protein sequence, but which are brought together upon folding of the protein into its three-dimensional structure.

[00336] A variety of methods are known in the art for mapping antibody epitopes on target protein antigens. These include mutagenesis methods, peptide scanning methods, display methods, methods involving and mass spectroscopy, and structural determination.

[00337] The site directed mutagenesis method involves targeted site-directed mutagenesis where critical amino acids are identified by systematically introducing substitutions along the protein sequence and then determining the effects of each substitution on antibody binding. This may be done by "alanine scanning mutagenesis," as described, for example, by Cunningham and Wells (1989) *Science* 244: 1081-1085, or some other form of point mutagenesis of amino acid residues in human beta klotho. Mutagenesis studies, however, may also reveal amino acid residues that are crucial to the overall three-dimensional structure of beta klotho but that are not directly involved in antibody-antigen contacts, and thus other methods may be necessary to confirm a functional epitope determined using this method.

[00338] Shotgun mutagenesis mapping utilizes a comprehensive plasmid-mutation library for the target gene, with each clone in the library bearing a unique amino acid mutation and the entire library covering every amino acid in the target protein. The clones that constitute the mutation library are individually arranged in microplates, expressed within living mammalian cells, and tested for immunoreactivity with antibodies of interest. Amino acids critical for antibody epitopes are identified by a loss of reactivity and are then mapped onto a protein structure to visualize epitopes. By automating the analysis, new epitope maps can be derived within days to weeks. Because it uses the native structure of proteins within mammalian cells, the technique allows both linear and conformational epitope structures to be mapped on complex proteins. (See, *e.g.,* Paes *et al.*, *J. Am. Chem. Soc.* 131(20): 6952-6954 (2009); Banik and Doranz, *Genetic Engineering and Biotechnology News* 3(2): 25-28 (2010)).

[00339] The epitope bound by an anti-beta klotho antibody may also be determined using peptide scanning methods. In peptide scanning, libraries of short peptide sequences from overlapping segments of the target protein, beta klotho, are tested

for their ability to bind antibodies of interest. The peptides are synthesized and screened for binding, *e.g.,* using ELISA or BIACORE, or on a chip, by any of the multiple methods for solid-phase screening (see, *e.g.,* Reineke *et al.*, *Curr. Opin. Biotechnol.* 12: 59-64, 2001) as in the "pepscan" methodology (see, *e.g.,* WO 84/03564; WO 93/09872). Such peptide screening methods may not be capable of detecting some discontinuous functional epitopes, i.e. functional epitopes that involve amino acid residues that are not contiguous along the primary sequence of the beta klotho polypeptide chain.

[00340] A recently developed technology termed CLIPS (chemical linkage of peptides onto scaffolds) may be used to map conformational epitopes. The loose ends of the peptides are affixed onto synthetic scaffolds, so that the scaffolded peptide may be able to adopt the same spatial structure as the corresponding sequence in the intact protein. CLIPS technology is used to fix linear peptides into cyclic structures ('single-loop' format), and to bring together different parts of a protein binding site ('double-loop', 'triple-loop', etc. format), so as to create conformational epitopes that may be assayed for antibody binding (see, *e.g.,* US Pat. No. 7,972,993).

[00341] The epitopes bound by antibodies of the present disclosure may also be mapped using display techniques, including, for example, phage display, microbial display, and ribosome/mRNA display as described above. In these methods, libraries of peptide fragments are displayed on the surface of the phage or cell. Epitopes are then mapped by screening mAbs against these fragments using selective binding assays. A number of computational tools have been developed which allow the prediction of conformational epitopes based upon linear affinity-selected peptides obtained using phage display (see, *e.g.,*Mayrose *et al.*, *Bioinformatics* 23: 3244-3246 , 2007). Methods are also available for the detection of conformational epitopes by phage display. Microbial display systems may also be used to express properly folded antigenic fragments on the cell surface for identification of conformational epitopes (see, *e.g.,* Cochran *et al.*, *J. Immunol. Meth.* 287: 147-158, 2004; Rockberg *et al.*, *Nature Methods* 5: 1039-1045, 2008).

[00342] Methods involving proteolysis and mass spectroscopy may also be used to determine antibody epitopes (see, *e.g.,* Baerga-Ortiz *et al.*, *Protein Sci.* 2002 June; 11(6): 1300–1308). In limited proteolysis, the antigen is cleaved by different

proteases, in the presence and in the absence of the antibody, and the fragments are identified by mass spectrometry. The epitope is the region of the antigen that becomes protected from proteolysis upon binding of the antibody (see, *e.g.,* Suckau *et al.*, *Proc. Natl. Acad. Sci. USA* 87:9848-9852, 1990). Additional proteolysis based methods include, for example, selective chemical modification (see, *e.g.,* Fiedler *et al.*, *Bioconjugate Chemistry* 1998, 9(2): 236-234, 1998), epitope excision (see, *e.g.,* Van de Water *et al.*, *Clin. Immunol. Immunopathol.* 1997, 85(3): 229-235, 1997), and the recently developed method of hydrogen-deuterium (H/D) exchange (see, *e.g.,* Flanagan, N., *Genetic Engineering and Biotechnology News* 3(2): 25-28, 2010).

[00343] The epitope bound by antibodies of the present disclosure may also be determined by structural methods, such as X-ray crystal structure determination (see, *e.g.,* WO 2005/044853), molecular modeling and nuclear magnetic resonance (NMR) spectroscopy, including NMR determination of the H-D exchange rates of labile amide hydrogens when free and when bound in a complex with an antibody of interest (see, *e.g.,* Zinn-Justin *et al.* (1992) *Biochemistry* 31:11335-11347; Zinn-Justin *et al.* (1993) *Biochemistry* 32:6884-6891).

[00344] Additional antibodies binding to the same epitope as an antibody of the present disclosure may be obtained, for example, by screening of antibodies raised against beta klotho for binding to the epitope, by immunization of an animal with a peptide comprising a fragment of human beta klotho comprising the epitope sequence, or by selection of antibodies using phage display for binding to the epitope sequence. Antibodies that bind to the same functional epitope might be expected to exhibit similar biological activities, such as blocking a biological activity of beta klotho, and such activities can be confirmed by functional assays of the antibodies.

Additional Activity Assays

[00345] In one embodiment, an anti-beta klotho antibody of the present disclosure is an antagonist antibody that inhibits a biological activity of beta klotho. The anti-beta klotho antibodies of the present disclosure may be assayed to determine if they inhibit a biological activity of beta klotho.

[00346] In one aspect, purified anti-beta klotho antibodies can be further characterized by a series of assays including, but not limited to, N-terminal

sequencing, amino acid analysis, non-denaturing size exclusion high pressure liquid chromatography (HPLC), mass spectrometry, ion exchange chromatography and papain digestion.

[00347] In one embodiment, the present disclosure contemplates an altered antibody that possesses some but not all effector functions, which make it a desirable candidate for many applications in which the half life of the antibody *in vivo* is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. In certain embodiments, the Fc activities of the antibody are measured to ensure that only the desired properties are maintained. *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. An *in vitro* assay to assess ADCC activity of a molecule of interest is described, for example, in U.S. Patent No. 5,500,362 or 5,821,337. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, for example, in a animal model such as that disclosed in Clynes *et al.* PNAS (USA) 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. To assess complement activation, a CDC assay, for example, as described in Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996), may be performed. FcRn binding and *in vivo* clearance/half life determinations can also be performed using methods known in the art.

[00348] Although the foregoing present disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the present disclosure. The disclosures of all patent and scientific literatures cited herein are expressly incorporated in their entirety by reference.

EXAMPLES

[00349] The following are examples of methods and compositions of the present disclosure.

EXAMPLE 1: GENERATION OF ANTIBODIES TO BETA KLOTHO

[00350] Antibodies to beta klotho were generated, for example, by immunizations of mice (i) with cells expressing human beta klotho (HuKLB) and FGF receptor 1c (FGFRIc or RIc) and (ii) with HuKLB and cynomologous beta klotho (cyno KLB) protein.

[00351] For example, beta klotho expressing cells were prepared as follows. 293EXPI (Invitrogen) cells were transiently co-transfected with nucleic acid sequences encoding a variant of FGFR1c with a mutation at amino acid position 623 (see, *e.g.,* SEQ ID NO:308 but with a mutation D623N) and HuKLB (SEQ ID NO:297). Cells were analyzed for expression of R1c and HuKLB by the respective specific antibodies by FACS. Cells were washed 2 times in PBS, pelleted by centrifugation and frozen in individual vials at 6×10^7 cells for immunization. 129/B6 animals were immunized with 1×10^7 cells with adjuvants (Ribi, CpG, and PolyIC). Animals were boosted every 2 weeks for the duration necessary to induce a suitable titer. Animals were boosted with HuKLB and CyKLB protein after 4 boosts with R1c and HuKLB overexpressing-293EXPI cells. Titers were determined by ELISA and FACS. Single cell suspensions of lymphocytes were obtained from spleen and draining lymph nodes of animals with suitable titers. Cells were fused with SP2/0 myeloma cells at a ratio of 1:2 by electrofusion. Fused cells were plated at 2.5×10^6 cells per plate in 70 µL into twenty-four x 384-well plates in the presence of HAT selection. After 7 days, 50 µL of supernatant were removed and replaced with fresh HAT containing media. After 10-14 days of culture, supernatants were collected and subjected to screening by FACS using R1c and HuKLB overexpressing-293EXPI cells or by Biacore using HuKLB protein to confirm binding. Positive clones were further selected and subjected to subcloning.

[00352] In a first campaign of immunizations and fusions, at least 25-30 384 well plates were screened for binding to HuKLB (*e.g.,* HuKLB protein and/or cells expressing HuKLB). In a second campaign for immunizations and fusions, a similar number of plates were screened as described for the first campaign. Thousands of clones were screened and hundreds of clones were selected for additional study, including in assays for binding, affinity and epitope specificity as described in Examples 2 and 3. Hundreds of hybridoma supernatants were also tested in functional assays as described, in Examples 4 and 5, including for agonist activity

similar to FGF receptor ligands FGF19 and/or FGF21 (*e.g.,* FGF19-like and/or FGF21-like signaling activity).

EXAMPLE 2: SCREENING AND SELECTION OF ANTIBODIES TO BETA KLOTHO

[00353] Antibodies to beta klotho were generated from hybridomas, for example, such as described in Example 1. Hybridoma supernatants were screened for binding to beta klotho (*e.g.,* human and/or cyno beta klotho) in FACS-based and/or Biacore-based assays.

[00354] For example, after 2 weeks of culture, hybridoma supernatants were screened for monoclonal antibodies binding to human beta klotho by a FACS based binding screen. Briefly, hybridoma supernatants were co-incubated with human beta klotho over-expressing cells for 30 minutes at 4°C. After washing with PBS/1% BSA/0.1% azide, human beta klotho over-expressing cells were co-incubated with labeled anti-mouse Fc (Jackson Immunoresearch) for 30 minutes at 4°C. After washing with PBS/1% BSA/0.1% azide, cells were acquired on flow cytometer (FACS Calibur) and analyzed by cytometric analytical software (FlowJo). A binding antibody is one that shows a shift from cells incubated with labeled anti-mouse Fc only.

[00355] For example, after 2 weeks of culture, hybridoma supernatants were screened for monoclonal antibodies binding to human beta klotho by a Biacore based binding screen. Briefly, anti-mouse Fc antibody (Sigma-Aldrich, St. Louis, MO) was immobilized on all four flow cells of a CM5 chip using amine coupling reagents (GE Healthcare LifeSciences, Piscataway, NJ). Hybridoma supernatants were diluted three fold with PBS-P buffer (PBS containing 0.005% P20) and injected for 30 seconds on flow cells 2,3 and 4 to capture the antibody (flow cell 1 was used as a reference). This was followed by a short injection of human beta klotho (25 nM, R&D Systems, Minneapolis, MN) for 60 seconds at a flow rate of 30 µL/min to test for binding to captured antibody on each flow cell.

[00356] From two immunization and fusion campaigns as described in Example 1, fifty-sixty 384 well plates of hybridoma supernatants were assayed for binding by FACS and /or Biacore. From these assays, approximately of 250 antibodies were identified as binders to human beta klotho. These antibodies were purified and

subsequently tested for their binding affinity to human beta klotho and cyno beta klotho by Biacore and for their functional activity by reporter assays as described in Example 3.

[00357] In additional Biacore-based binding/screening assays, the binding affinity of antibodies to human and cyno beta klotho were measured. For example, antibodies were rank ordered based on their binding affinity to human beta klotho and cyno beta klotho by low resolution K_D measurement by Biacore. Briefly, anti-mouse Fc antibody (Sigma-Aldrich, St. Louis, MO) was immobilized on all four flow cells of a CM5 chip using amine coupling reagents (GE Healthcare LifeSciences, Piscataway, NJ). Purified antibodies were captured (~100 RUs) on flow cells 2, 3 and 4 using flow cell 1 as a reference. This was followed by injection of human or cyno beta klotho (25 nM in PBS-P buffer) at a flow rate of 70 µL/min and monitoring the binding kinetics at 25°C.

[00358] Binding affinity measurements were also made in additional Biacore based assays. For example, equilibrium dissociation constant (K_D) measurements were carried out with purified antibodies to evaluate their binding to human beta klotho and cyno beta klotho. As mentioned above, anti-mouse Fc antibody (Sigma-Aldrich, St. Louis, MO) was immobilized on all four flow cells of a CM5 chip using amine coupling reagents (GE Healthcare LifeSciences, Piscataway, NJ). Purified antibodies were captured (~100 RUs) on flow cells 2, 3 and 4 using flow cell 1 as a reference. This was followed by injection of different concentrations of human or cyno beta klotho (1.56 nM to 25 nM, two-fold dilutions in PBS-P buffer) at a flow rate of 70 µL/min and the binding kinetics were evaluated at 25°C.

[00359] Representative results are reported as K_D (nM) values as shown in Table 11 below.

Table 11

Affinity KD (nM)		
	HuKLB	Cyno KLB
5H23	~pM	0.72
1C17	0.89	3.1
1D19	1.25	2.9
2L12	0.22	1.42
3L3	1.14	2.2
3N20	3.3	3.52
4P5	0.26	0.44
5F7	1.7	2.5

1G19	N/A	N/A
5C23	1.2	2.4

EXAMPLE 3: SCREENING AND SELECTION OF ANTIBODIES TO BETA KLOTHO

[00360] Antibodies that were selected for binding to beta klotho, for example, such as described in Example 2, were evaluated in competition binding assays and epitope binning experiments.

[00361] For example, for competition binding assays by FACS analysis, antibody standards were prepared that were conjugated to a fluorochrome using either A488 or A647 antibody labeling kit (Invitrogen) following manufacturer's instructions. A dose titration of the conjugated antibody standard was evaluated using HuKLB overexpressing cells. The plateau of the maximal signal of antibody binding is EC=100 and the background signal is EC=0. Competition by FACS against the fluorochrome labeled antibody was performed by pre-incubating HuKLB overexpressing cells with hybridoma supernatants for 15 minutes at room temperature. Without washing, an EC=10 concentration of A488 or A647 labelled antibody standard was added. EC=10 for an individual antibody was determined by 10% of signal using the maximum signal as (100%) and background signal as (0%). After 30 minutes at 4°C, cells are washed and analyzed by FACS. In these assays, a competing antibody is one that shows signal comparable to the competition by 5H23. A non-competing antibody is one that shows signal equal to labelled antibody alone. A partial competing antibody is one sample that show signal between labelled antibody alone and background. Antibodies that show complete competition against the same standard antibody are considered to be in the same bin.

[00362] In exemplary competition binding experiments by FACS, antibody 5H23 or 3I13 was used as an antibody standard for a positive control (competing antibody) or a negative control (non-competing antibody), respectively. Representative results are shown in Table 12 below reported as mean fluorescence intensity (MFI). For these experiments, signal comparable to labeled antibody alone is a non-competing antibody, while signal comparable to the competition by 5H23 is a competing antibody.

Table 12

Antibody	Mean Florescence Intensity (MFI)	
	5H23 – Alexa647	3I13 – Alexa488
5H23	2.3	29.8
1C17	2.4	26.7
1D19	2.5	30.6
2L12	3.1	30.9
3L3	4.2	28.7
3N20	2.4	30.5
4P5	2.4	30.1
5C23	2.4	29.3
5F7	2.3	28.5
1G19	2.2	29.0
3I13	9.4	7.4
Labeled antibody alone	10.8	32.4

[00363] To further evaluate the binding sites of the antibodies on human beta klotho, competition experiments were also set up on the Biacore. For example, two antibodies were immobilized on two flow cells of a CM5 chip. Human beta klotho-antibody complexes were prepared with different antibodies (antibody concentration was titrated from 0.1-50 nM while keeping beta klotho concentration constant at 5 nM) in a 96-well micro plate and injected on the antibody surfaces. The measured signal (Response Unit, RU) was plotted against the solution antibody concentration [nM]. If the antibody in solution recognized the same epitope as the antibody immobilized on the chip surface, then a decrease in RU was observed with increase in concentration of antibody in solution (demonstrating competition for the binding site on beta klotho). However, if the antibody in solution recognized a distinct epitope relative to the immobilized antibody, an increase in RU was observed. In the latter scenario, the antibody-klotho complex could bind to the immobilized antibody surface leading to the observed increase in signal.

[00364] In exemplary competition binding experiments by Biacore, antibody 5H23 competed with itself for binding to HuKLB and additional antibodies 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 and 1G19 competed with 5H23. These antibodies were designated as members of the 5H23 epitope bin. The sequences for these

epitope-related antibodies are aligned and shown in Figures 1 and 2. Figure 2 also shows conserved amino acid sequences for the CDRs of these related antibodies.

EXAMPLE 4: FUNCTIONAL ASSAYS

[00365] Antibodies to beta klotho generated, for example, such as described in Example 1, were tested for their functional activity in cell-based reporter assays.

[00366] For example, ELK1-luciferase reporter assays, which measure FGFRIc/beta klotho signaling, were performed using transiently transfected HEK293, HEK293T, or L6 cells (ATCC). The transfecting plasmids consisted of two reporter plasmids Gal4-Elk1 and 5×UAS-Luc (Agilent Technologies PathDetect Elk1 trans-reporting system Cat# 219005), and plasmids encoding human beta klotho (GeneCopoeia Cat# EX-E1104-MO2) or cynomolgus monkey beta klotho (cyno beta klotho) and human FGFR1c (GeneCopoeia Cat# EX-A0260-MO2). In these assays, activation of recombinantly expressed FGFR1c/beta klotho receptor complex in the cells induces intracellular signaling transduction, which leads to ERK and then Elk1 phosphorylation. Once Gal4-Elk1 is phosphorylated, Gal4-Elk1 binds to the 5×UAS promoter region and turns on luciferase reporter gene transcription. The activity of luciferase is then measured in luciferase enzymatic assays.

[00367] For these experiments, the above mentioned four plasmids (*e.g.,* 2 reporter plasmids, beta klotho, R1c) were transfected into newly harvested cells in suspension using FuGene6 or Fugene HD transfection reagent (Promega). Cell density and transfection reagent amount were optimized for each cell type and each Fugene batch. Beta klotho and FGFR1c DNA ratio in transfection was optimized for each cell line and varied between 6:1 to 27:1. Transfected cells were seeded into 96-well (30,000 cells/100 µL/well), or 384-well plate (7500 cells/25 µL/well) in normal growth medium. After overnight incubation at 37°C, a variety of antibodies to beta klotho were added. After 6 hrs of 37°C incubation with the antibodies, an equal volume of Bright-Glo reagent (Promega) was added and luminescence signal was read using Enspire reader (Perkin Elmer).

[00368] Representative results using human beta klotho and cyno beta klotho, transfected into HEK 293 cells, are reported as EC50 values as shown in Table 13 and Table 14, respectively, below.

Table 13

	Experiment – A	Experiment – B
mAb	HEK293 huKLB/R1c reporter assay EC50 (pM)	HEK293 huKLB/R1c reporter assay EC50 (pM)
control*	45.3	27.9
5H23	102	34.2
1D19	620	
2L12	373	
3L3	773	
3N20	527	
4P5	600	78.3
1G19	231	127

*Control mAB comprises SEQ ID NO: 358 and SEQ ID NO: 360

Table 14

	Experiment – A	Experiment – B
mAb	HEK293 cynoKLB/R1c reporter assay EC50 (pM)	HEK293 cynoKLB/R1c reporter assay EC50 (pM)
control*	108 178	227
5H23	165	218
1D19		954
2L12	260	410
3L3	3576	1672
3N20	2464	>10000
4P5	347	465
1G19	2354	2447

*Control mAB comprises SEQ ID NO: 358 and SEQ ID NO: 360

[00369] Representative results using human beta klotho, transfected into L6 cells, are reported as EC50 values as shown in Table 15 below.

Table 15

mAb	L6 huKLB/R1c reporter assay EC50 (nM)	L6 huKLB/R2c reporter assay EC50 (nM)	L6 huKLB/R3c reporter assay EC50 (nM)	L6 huKLB/R4 reporter assay EC50 (nM)
control	FGF19: 2.66	FGF19: 0.16	FGF19: 2.1	FGF19: 0.05
5H23	0.28	>67	>67	>67
2L12	4.65	>67	>67	>67
4P5	0.39	>67	>67	>67

[00370] L6 cells lack endogenous receptors and are often used to investigate antibody specificity to various tranfected FGF receptor subtypes. Activation of the receptor via FGFR1c/beta klotho signaling in the absence of ligand (*e.g.,* FGF19 (*e.g.*, SEQ ID NO: 304) or FGF21(*e.g.*, SEQ ID NO: 429)) by the exemplary anti-beta klotho antibodies of the present disclosure was observed with L6 cells transfected with FGFR1c (R1c), but not with L6 cells transfected with FGFR2c (R2c), FGFR3c (R3c), or FGFR4 (R4), whereas activation by the FGF19 control was observed with L6 cells transfected with R1c, R2c, R3c and R4.

EXAMPLE 5: ADDITIONAL FUNCTIONAL ASSAYS

[00371] Antibodies to beta klotho generated, for example, as described in Example 1, were tested for their functional activity in a cell-based assay, such as an adipocyte assay, which measures endogenous FGFR1c/beta klotho signaling. FGF19 or FGF21 stimulate ERK phosphorylation, increase glucose uptake and lipolyses in cultured adipocytes. Adipocytes are considered physiologically relevant for demonstrating the functional activity of receptor ligands or agonist antibodies which mimic the function of ligands (*e.g.,* signaling of the receptor by the ligands).

[00372] For example, frozen human preadipocytes (Lonza Cat# PT-5005) were thawed on day 1, differentiated on day 3 and maintained in differentiation medium for about two weeks before the experiment (*e.g.*, then starved on day 17, and assayed on day 18). The seeding medium was 1:1 DMEM/F12K + 10% FBS. Seeding cell density was 25,000 cells/100 µL/well in 96-well plate. On day 3, medium was replaced with human adipocytes differentiation medium (Cell Applications Inc). From then on, fresh differentiation medium was added onto cells every 2-3 days. On day 17 (the day before the assay), the cells were rinsed two times and left with DMEM /0.1% BSA (Sigma cat# A3803 essential fatty acids free BSA) overnight. The next day, fresh DMEM /0.1% BSA medium was added for 1 hour before the cells were treated with test anti-beta klotho antibodies for 15 minutes at 37°C. Cis-bio Cellul'erk assay kit (Cat# 64ERKPEH) was used to assay for ERK phosphorylation level following the manufacturer's protocol.

[00373] Representative results using human adipocytes are reported as EC50 values as shown in Table 16 below:

Table 16

	Experiment - A	Experiment - B
mAb	hAdip pERK assay	hAdip pERK assay EC50 (nM)
Control	+++	FGF19 5.49
5H23	+++	1.66
1C17	++	>>67
1D19	+++	>67
2L12	+++	1.23
3L3	+++	~30
3N20	+++	>67
4P5	+++	0.89
5F7	++	>67
5C23	++	>>67
1G19	+++	1.3

EXAMPLE 6: LIGAND COMPETITION

[00374] Ligand (FGF19 or FGF21) competition assays were conducted to evaluate whether antibody-human beta klotho interaction influences the binding of beta klotho to its natural ligand, FGF19 or FGF21.

[00375] For example, Biacore-based competition assays were set up in which FGF19 (*e.g.*, SEQ ID NO: 304) or FGF21(*e.g.*, SEQ ID NO: 429) was immobilized on a flow cell (Fc2) of a CM5 chip (using Fc1 as a reference surface). Human beta klotho-antibody complexes were prepared with exemplary antibodies of the present disclosure, such as 5H23 (*e.g.,* VH SEQ ID NO: 25 and VL SEQ ID NO: 26) or a humanized 5H23 (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276)). For example, concentrations of 5H23 and a control antibody were titrated from 0.1-67 nM while keeping beta klotho concentration constant at 5 nM in a 96-well micro plate and injected on the FGF19 surface. For another example, concentrations of a humanized 5H23 (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276) were titrated from 0.001-67 nM while keeping beta klotho concentration constant at 2.5 nM in a 96-well micro plate and injected on the FGF 21 surface. The measured signal (Response Unit, RU) was plotted against the solution antibody concentration [nM]. If the antibody in solution recognized the same epitope as FGF19 ligand or FGF21 ligand immobilized on the chip surface, then a decrease in RU was observed with increase in concentration of antibody in solution, demonstrating competition with FGF19 ligand or FGF21 ligand for the binding site on beta klotho. However, if the antibody in solution recognized a distinct epitope relative to the immobilized FGF19

ligand or FGF21 ligand, an increase in RU was observed. In the latter scenario, the antibody-klotho complex could bind to the immobilized FGF19 ligand surface or immobilized FGF21 ligand surface leading to the observed increase in signal. In the exemplary data shown below in Table 17A, a control antibody partially competed with the FGF19 ligand resulting in a significant reduction of RU signal, where 5H23 did not compete with the FGF19 ligand for binding to beta klotho. In the exemplary data shown below in Table 17B, a control antibody competed with the FGF21 ligand resulting in a significant reduction in RU signal, where a humanized 5H23 did not compete with the FGF21 ligand for binding to beta klotho.

Table 17A

Experiment 1	**RU**	**% Change**	**Remark**
RU signal for 5nM β-Klotho (no complex)	127	100%	Control antibody*
RU signal for klotho-Control antibody complex	60	47% reduction	Partial competition between Control antibody* and FGF19 for binding to β-klotho
Experiment 1	**RU**	**% Change**	**Remark**
RU signal for 5nM β-Klotho (no complex)	109	100%	Control antibody*
RU signal for klotho-5H23 complex	125	114% increase	5H23-klotho complex binds to FGF19, hence no competition

*Control antibody comprises SEQ ID NO:358 and SEQ ID NO:360

Table 17B

Experiment 1	**Normalized RU**	**% Change**	**Remark**
RU signal for 2.5nM β-Klotho (no complex)	1	100%	Control antibody*
RU signal for klotho-FGF21 complex	0.03	97% reduction	FGF21 competes with itself for binding to β-klotho
Experiment 1	**Normalized RU**	**% Change**	**Remark**
RU signal for 2.5nM β-Klotho (no complex)	1	100%	Control antibody*
RU signal for klotho-humanized 5H23 complex	1.1	110% increase	Humanized 5H23-klotho complex binds to FGF21, hence no competition

*Control antibody comprises SEQ ID NO:358 and SEQ ID NO:360

[00376] Because 5H23 and a humanized 5H23 antibody bind to a different epitope of beta klotho as compared to endogenous ligands, such as FGF19 and FGF21, experiments were conducted to test if there were synergistic effects between FGF21

and 5H23 or a humanized 5H23 antibody. In a HEK293 reporter assay (see, *e.g.,* Example 4), combinations of FGF21 and a humanized 5H23 antibody (*e.g.*, VH SEQ ID NO: 271 and VL SEQ ID NO: 276) were tested in a 1:1 molar ratio or fixing one and titrating the concentration of the other. No evidence of synergistic effects was observed; the maximum effect of FGF21 was not enhanced by the humanized 5H23 antibody, and vice versa.

EXAMPLE 7: HUMANIZATION

[00377] Humanized anti-beta klotho antibodies were generated, including from antibodies selected as described in Examples 1-6.

[00378] A number of anti-beta klotho antibodies were selected for sequencing and their VH and VL regions, including their CDRs, are shown in Tables 1-10 and in Figures 1 and 2. An exemplary anti-beta klotho antibody, 5H23, was selected for humanization. Several methods of humanization were utilized. For some of the humanized antibodies, the method for humanization was empirical and based in part on structural information related to immunoglobulin variable regions including molecular models and requirements of antibody structural stability (see, *e.g.,* Ewert et al., 2004, Methods 34:184-199; Honegger, 2008, Handb. Exp. Pharmacol. 181:47-68; Kügler et al., 2009, Protein Eng. Des. Sel. 22: 135-147). The method was also based in part on considerations of antigen contact residues and/or framework stability residues. For example, consideration of typical antigen contact residues depends on the size of the antigen particularly residues outside CDRs which can contact the antigen, upper core, central core and lower core divisions, VH:VL interface residues, conserved Pro/Gly (positive phi angles) and VH subtype correlated residues match (see, *e.g.,* Ewert et al., *supra*; Honegger, *supra*; Kügler et al., *supra*).

[00379] For example, human VH sequences homologous to the 5H23 VH framework sequences were searched for and the VH sequence encoded by the human germline IGHV1-3*01 (see, *e.g.,* Ehrenmann et al., 2011, Cold Spring Harbor Protoc. G:737-749) was chosen as an acceptor for humanization. For some of the humanized antibodies, the CDR sequences of 5H23 VH were first transferred to the corresponding positions of IGHV1-3*01. Next, a number of amino acid residues of

5H23 VH were substituted for the corresponding human residues individually or in combinations.

[00380] Also, for example, human VL sequences homologous to the 5H23 VL framework sequences, were searched for and the human Vκ region encoded by the IGKV4-1*01 (see, *e.g.,* Ehrennmann et al., *supra*) was chosen as an acceptor for humanization. For some of the humanized antibodies, the CDR sequences of 5H23 VL were first transferred to the corresponding positions of IGKV4-1*01. Next, a number of amino acid residues of 5H23 VL were substituted for the corresponding human residues individually or in combinations.

[00381] For some of the humanized antibodies, the method of humanization used an algorithm to construct a three-dimensional map of the mouse variable regions. This method also identified framework amino acids and residues important for the formation of CDR structure or necessary for binding to beta klotho. In addition, human VH and VL amino acid sequences with high homology to the mouse sequences were selected for possible framework sequences for humanization. As described above, the CDR sequences of 5H23 antibody may be transferred to such additional human framework sequences. A variety of human framework sequences, including germline sequences (*e.g.,* IGHV1-3, IGHV1-46, IGHV1-69, IGKV4-1, IGKV1-39 or IGKV3-20) and mature individual sequences, may be suitable for the method of humanization. Next, a number of amino acid residues of 5H23 VH and/or 5H23 VL may be substituted for the corresponding human residues individually or in combination.

[00382] For some of the humanized light chains, IG BLAST searches were used to identify human germline sequences that were close matches in sequence with 5H23 VL and/or that were commonly used sequences, including, for example, IGKV1-39 and IGKV3-20. For some of the humanized light chains, the CDR sequences of 5H23 VL were first transferred to the corresponding positions of IGKV1-39 or IGKV3-20 and then certain amino acids were selected empirically for substation.

[00383] The amino acid sequences of the resulting humanized VH (vH1-vH9) and VL (vL1 to vL5, v1-39a to v1-39p and v3-20a to v3-20j) sequences are shown with 5H23 VH and VL sequences in Figure 3A-3D. For example, using the various humanization methods described in this Example, a number of amino acid residues

of 5H23 VH and VL were substituted for the corresponding human residue to obtain humanized sequences as shown in Figure 3A-3D.

[00384] Humanized beta klotho antibodies may be prepared using any of the CDR sequences in Table 18 in combination with any of the framework sequences in Table 19.

Table 18
CDR Sequences for Humanized Anti-Beta Klotho Antibodies

VH CDR1
SEQ ID NO:1 GYTFTSYDIN
SEQ ID NO:27 GYSITSGYYWN
SEQ ID NO:53 GYTFTRYDIN
SEQ ID NO:79 GYTFTRYDIN
SEQ ID NO:105 GYTFTSYDIN
SEQ ID NO:131 GYIFTNYGIS
SEQ ID NO:157 GYTFTRYDIN
SEQ ID NO:183 GYTFTRYDIN
SEQ ID NO:209 GYTFTRYDIN
SEQ ID NO:235 GYSITSGYYWN
VH CDR2
SEQ ID NO:2 WIYPGDGSTKYNEKFKG
SEQ ID NO:28 YINYDGNSNYTPSLKN
SEQ ID NO:54 WIYPGDSSTKFNENFKD
SEQ ID NO:80 WIYPGDDSTKYNEKFKG
SEQ ID NO:106 WIYPGDGSPKYDEKFKG
SEQ ID NO:132 EIYPRSGNTYYNEKFKG
SEQ ID NO:158 WIYPGDDSTKYNEKFKG
SEQ ID NO:184 WIYPGDGSTKYNEKFEG
SEQ ID NO:210 WIYPGDISTKYNEKFKG
SEQ ID NO:236 YINYGGSNNYNPSLKN
VH CDR3
SEQ ID NO:3 SDYYGSRSFAY
SEQ ID NO:29 KGAYYSNYDSFDV
SEQ ID NO:55 SDYYGSRSFTY
SEQ ID NO:81 SDYYGSRSFVY
SEQ ID NO:107 SDYYGSRSFVY
SEQ ID NO:133 HWDGVLDYFDY
SEQ ID NO:159 SDYYGSRSFVY
SEQ ID NO:185 SDYYGSRSFVY
SEQ ID NO:211 SDYYGSRSFVY
SEQ ID NO:237 RGAYYSNYDSFDV
VL CDR1
SEQ ID NO:4 RASKSVSTSGYVYMH
SEQ ID NO:30 KASQDINSYLS
SEQ ID NO:56 RASKSVSTSGYSYMH

SEQ ID NO:82 RASKSVSTSGYSYLH
SEQ ID NO:108 RASKSVSTSGYSYVH
SEQ ID NO:134 KSSQSLLNSGNQKNYLA
SEQ ID NO:160 RASKSVSTSGYSYMH
SEQ ID NO:186 RASKSVSTSGYSYMH
SEQ ID NO:212 RASKSVSTSGYSYMH
SEQ ID NO:238 KASQDINSYLS
VL CDR2
SEQ ID NO:5 LASYLES
SEQ ID NO:31 RANRLVD
SEQ ID NO:57 LASNLES
SEQ ID NO:83 LASNLES
SEQ ID NO:109 LASNLES
SEQ ID NO:135 GASTRES
SEQ ID NO:161 LASNLES
SEQ ID NO:187 LASNLES
SEQ ID NO:213 LASNLES
SEQ ID NO:239 RANRLVD
VL CDR3
SEQ ID NO:6 QHSRDLTFP
SEQ ID NO:32 LQYDEFPFT
SEQ ID NO:58 QHSRELPYT
SEQ ID NO:84 QHSGELPYT
SEQ ID NO:110 QHSGELPYT
SEQ ID NO:136 LNDHSYPFT
SEQ ID NO:162 HHSGELPYT
SEQ ID NO:188 QHSRELPYT
SEQ ID NO:214 QHSRELPYT
SEQ ID NO:240 LQYDEFPYT

Table 19
Framework Sequences for Humanized Anti-Beta Klotho Antibodies

VH
Framework 1 (FR1)
SEQ ID NO:278 QVQLVQSGAEVKKPGASVKVSCKAS
SEQ ID NO:279 QVQLQQSGAEVKKPGASVKVSCKAS
SEQ ID NO:280 QVQLVQSGPEVKKPGASVKVSCKAS
SEQ ID NO:378 QVQLVQSGAEVKKPGSSVKVSCKAS
Framework 2 (FR2)
SEQ ID NO:281 WVRQAPGQGLEWMG
SEQ ID NO:282 WVRQAPGQGLEWIG
SEQ ID NO:283 WVKQAPGQGLEWIG
Framework 3 (FR3)
SEQ ID NO:284 RVTITRDTSASTAYMELSSLRSEDTAVYYCAR
SEQ ID NO:285 KATITRDTSASTAYMELSSLRSEDTAVYFCAR
SEQ ID NO:286 KATLTADTSASTAYMELSSLRSENTAVYFCAR
SEQ ID NO:287 KATLTADKSARTAYMELSSLRSENTAVYFCAR
SEQ ID NO:379 RATLTADKSTSTAYMELSSLRSEDTAVYYCAR
SEQ ID NO:380 RATLTADKSTRTAYMELSSLRSEDTAVYYCAR
SEQ ID NO:381 RATITADKSTSTAYMELSSLRSEDTAVYYCAR

Framework 4 (FR4)
SEQ ID NO:288 WGQGTLVTVSS
VL
Framework 1 (FR1)
SEQ ID NO:289 DIVLTQSPDSLAVSLGERATINC
SEQ ID NO:290 DIVMTQSPDSLAVSLGERATINC
SEQ ID NO:382 DIQMTQSPSSLSASVGDRVTITC
SEQ ID NO:383 DIQLTQSPSSLSASVGDRVTITC
SEQ ID NO:384 EIVLTQSPATLSLSPGERATLSC
Framework 2 (FR2)
SEQ ID NO:291 WNQQKPGQPPKLLIY
SEQ ID NO:292 WYQQKPGQPPKLLIY
SEQ ID NO:385 WYQQKPGKAPKLLIY
SEQ ID NO:386 WNQQKPGKAPKLLIY
SEQ ID NO:387 WYQQKPGKPPKLLIY
SEQ ID NO:388 WNQQKPGKPPKLLIY
SEQ ID NO:389 WYQQKPGQAPRLLIY
SEQ ID NO:390 WNQQKPGQAPRLLIY
SEQ ID NO:391 WYQQKPGQPPRLLIY
SEQ ID NO:392 WNQQKPGQPPRLLIY
Framework 3 (FR3)
SEQ ID NO:293 GVPDRFSGSGSGTDFTLTISSVQAEDAAIYYC
SEQ ID NO:294 GVPDRFSGSGSGTDFTLTISSVQAEDVAVYYC
SEQ ID NO:295 GVPDRFSGSGSGTDFTLTISSVQAEDVAIYYC
SEQ ID NO:393 GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC
SEQ ID NO:394 GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
SEQ ID NO:395 GVPSRFSGSGSGTDFTLTISSVQPEDFATYYC
SEQ ID NO:396 GVPSRFSGSGSGTDFTLTISSLQEEDFATYYC
SEQ ID NO:397 GVPSRFSGSGSGTDFTLTISSVQEEDFATYYC
SEQ ID NO:398 GVPSRFSGSGSGTDFTLTISSVQEEDAATYYC
SEQ ID NO:399 GIPARFSGSGSGTDFTLTISRLEPEDFAVYYC
SEQ ID NO:400 GIPARFSGSGSGTDFTLTISRVEPEDFAVYYC
SEQ ID NO:401 GIPARFSGSGSGTDFTLTISRLEPEDAAVYYC
SEQ ID NO:402 GIPARFSGSGSGTDFTLTISRLEEEDFAVYYC
SEQ ID NO:403 GIPARFSGSGSGTDFTLTISRVEEEDFAVYYC
SEQ ID NO:404 GIPARFSGSGSGTDFTLTISRVEEEDAAVYYC
Framework 4 (FR4)
SEQ ID NO:296 FGGGTKLEIK
SEQ ID NO:405 FGGGTKVEIK
SEQ ID NO:406 FGQGTKLEIK
SEQ ID NO:407 FGGQTKLEIK

[00385] For example, a humanized anti-beta klotho antibody may comprise a heavy chain variable region (VH) comprising: FR1 (*e.g.,* SEQ ID NO:278, 279, 280, or 378); CDR1 (*e.g.,* SEQ ID NO:1, 27, 53, 79, 105, 131, 157, 183, 209, 235); FR2 (*e.g.,* SEQ ID NO:281, 282, or 283); CDR2 (*e.g.,* SEQ ID NO:2, 28, 54, 80, 106, 132, 158, 184, 210, or 236); FR3 (*e.g.,* SEQ ID NO:284, 285, 286, 287, 379, 380, or 381); CDR3 (*e.g.,* SEQ ID NO:3, 29, 55, 81, 107, 133, 159, 185, 211, or 237); and/or FR4

(*e.g.,* SEQ ID NO:288); and/or a light chain variable region (VL) comprising: FR1 (*e.g.,* SEQ ID NO:289, 290, 382, 383, or 384); CDR1 (*e.g.,* SEQ ID NO:4, 30, 56, 82, 108, 134, 160, 186, 212, or 238); FR2 (*e.g.,* SEQ ID NO:291, 292, or 385-392); CDR2 (*e.g.,* SEQ ID NO:5, 31, 57, 83, 109, 135, 161, 187, 213, or 239); FR3 (*e.g.,* SEQ ID NO:293, 294, 295, or 393-404); CDR3 (*e.g.,* SEQ ID NO:6, 32, 58, 84, 110, 136, 162, 188, 214, 240); and/or FR4 (*e.g.,* SEQ ID NO:296, 405, 406, or 407).

[00386] As described in this Example, humanized anti-beta klotho antibodies were empirically designed and expressed as beta klotho binding proteins, including nine humanized variants of the VH region of antibody 5H23 and thirty-one humanized variants of the VL region of antibody 5H23 that were created. The sequences of these exemplary humanized 5H23 VH and VL regions are shown in Figure 3A-3D.

[00387] Humanized antibodies were prepared with humanized VH and humanized VL regions with sequences as shown in Figure 3A-3D. For example, eighteen (6 X 3) combinations of vH 1-6 and vL1-3 were constructed using an IgG1 (ala-ala) constant region (SEQ ID NO:316) and a kappa constant region (SEQ ID NO:318): vH1-VL1, vH1-vL2, vH1-vL3, vH2-vL1, vH2-vL2, vH2-vL3, vH3-vL1, vH3-vL2, vH3-vL3, vH4-vL1, vH4-vL2, vH4-vL3, vH5-vL1, vH5-vL2, vH5-vL3, vH6-vL1, vH6-vL2, vH6-vL3, with sequences as shown in Figure 3A-3D. Additionally, humanized antibodies were constructed with an exemplary humanized VH region (*e.g.*, vH3) and twenty-six humanized VL regions (v1-39a to v1-39p and v3-20a to v3-20j) with sequences as shown in Figure 3A-3D.

[00388] The humanized antibodies were tested from their activity in a variety of assays, including, for example, as described in Examples 2-6. Expression of the humanized antibodies with light chains comprising vL3 or v1-39c was low and those antibodies were not further tested. Exemplary results with a variety of humanized anti-beta klotho antibodies are shown in Table 20A and 20B below.

Table 20A

Antibody	Expression (mg/L)	KD-huKLB (nM)	KD-cyKLB (nM)	EC50 reporter assay (nM)	EC50-adipocyte (nM)
Control mAb		0.08	0.7	0.2,0.54	3.4
5H23		0.05	0.7	0.27,0.51	3.4
vL1					
vH1	80	1.5	≥ 50	2.7	ND

vH2	80	1.7	≥ 50	3.2	ND
vH3	50	0.43	≥ 50	1.1	ND
vH4	80	2.26	≥ 50	3.0	ND
vH5	20	0.81	≥ 50	8.2	ND
vH6				NA	
vL2					
vH1	200	0.21	0.95	NA	8.4
vH2	66	0.41	0.75	1.3	13.3
vH3	50-60	0.23	0.59	0.68	5.5
vH4	66	0.33	0.61	3.5	16.4
vH5	30	0.19	0.61	1.1	8.1
vH6	20	0.4	0.83	1.7	15.3

Table 20B

Antibody	Estimated Titer (mg/L)	KD-huKLB (nM)	EC50 reporter assay (nM)	EC50 adipocyte (nM)
h5H23 (Prep 1)	--	0.64	--	--
h5H23 (Prep 2)	--	0.58	0.6	11.2
vH3				
VL v1-39a	50	0.90	--	--
VL v1-39b	50	0.53	1.03	--
VL v1-39c	10	--	--	--
VL v1-39d	50	0.73	1.49	--
VL v1-39e	>100	1.00	--	--
VL v1-39f	>100	0.28	0.80	21.4
VL v1-39g	>100	1.10	--	--
VL v1-39h	10	2.10	--	--
VL v1-39i	50	0.63	1.12	--
VL v1-39j	100	0.70	--	--
VL v1-39k	100	1.50	--	--
VL v1-39l	100	--	--	--
VL v1-39m	50	<0.1	--	--
VL v1-39n	>100	<0.1	--	--
VL v1-39o	25	0.36	--	--
VL v1-39p	10	0.36	--	--
VL v3-20a	25	0.64	--	--
VL v3-20b	50	1.90	--	--
VL v3-20c	0	1.60	--	--
VL v3-20d	50	--	--	--
VL v3-20e	50	1.60	--	--
VL v3-20f	10	1.80	--	--
VL v3-20g	--	--	--	--
VL v3-20h	25	1.50	--	--
VL v3-20i	10	--	--	--
VL v3-20j	10	--	--	--

Prep 1 = humanized 5H23 antibody (*e.g.*, VH SEQ ID NO: 271 and VL SEQ ID NO: 276) preparation expressed at the same time as LC variants; Prep 2 = humanized 5H23 antibody (*e.g.*, VH SEQ ID NO: 271 and VL SEQ ID NO: 276) purified

preparation. Control antibody = VH SEQ ID NO: 358 and VL SEQ ID NO: 360.

[00389] In additional assays, for example, reporter assays with HEK293T cells as described in Example 4, wherein the cells were transfected with plasmids encoding mouse beta klotho (*e.g.,* SEQ ID NO: 301), rat beta klotho (*e.g.,* SEQ ID NO: 356), hamster beta klotho (*e.g.,* SEQ ID NO: 408), rabbit beta klotho (*e.g.,* SEQ ID NO: 410), or dog beta klotho (*e.g.,* SEQ ID NO: 412) and were also transfected with plasmids encoding chimeric mouse FGFR1-βIIIc receptor (*e.g.,* SEQ ID NO: 416), chimeric rat FGFR1-βIIIc receptor (*e.g.,* SEQ ID NO: 419), chimeric hamster FGFR1-βIIIc receptor (*e.g.,* SEQ ID NO: 417), chimeric rabbit FGFR1-βIIIc receptor (*e.g.,* SEQ ID NO: 420), or dog FGFR1-βIIIc receptor (*e.g.,* SEQ ID NO: 418), respectively, when treated with an anti-beta klotho antibody such as a humanized 5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276), did not activate the chimeric mouse, rat, hamster, rabbit or dog beta klotho-FGFR1c receptor complex, respectively. The anti-beta klotho antibodies as described herein, including 5H23 and humanized 5H23 antibodies, as well as antibodies that compete with 5H23 (*e.g.*, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 and 1G19 as described in Example 3) with CDR sequences as shown in Tables 1-10, activate a human and cyno beta klotho/FGF receptor complex, but not mouse, rat, hamster, rabbit, or dog beta klotho/FGF receptor complexes as demonstrated by reporter assays described above. When a monovalent Fab of anti-beta klotho antibody prepared from a papain digestion of an anti-beta klotho antibody, such as a humanized 5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276), was tested in a HEK293 reporter assay for its ability to activate human FGFR1c/KLB receptor complex, the Fab showed no antibody activity up to 67 nM, whereas the humanized 5H23 antibody showed activity with low nanomolar concentrations similar to that shown in Table 20B.

EXAMPLE 8: ANIMAL STUDIES

[00390] Effects of anti-beta klotho antibodies are evaluated in animal studies, including with cynomolgus monkeys.

In obese cynomolgus monkey studies, an exemplary anti-beta klotho antibody that binds to human beta klotho and cyno beta klotho (*e.g.,* antibody 5H23 or

humanized variant thereof), as well as an antibody comprising one or more of the CDRs of 5H23 as shown in Table 1 or alternatively, an antibody comprising one or more of the CDRs of an antibody or humanized variant thereof shown in Tables 2-10 that compete for the binding of 5H23 to human beta klotho as described in Example 3, is administered. Effects on a variety of metabolic parameters may be measured. Exemplary parameters include food intake, body weight, body mass index (BMI), abdominal circumference (AC), skin fold thickness (SFT), oral glucose tolerance test (OGTT), fasting and/or fed (*e.g.*, postprandial) blood (*e.g.*, serum) glucose levels, insulin levels, and/or triglyceride levels.

[00391] In an actual study, twenty spontaneous obese cynomolgus monkeys with body mass index equal to or above 40 are selected and randomized into vehicle (n = 10) and antibody treatment (n =10) groups. Animals receive subcutaneous injection of either vehicle or anti-beta klotho antibody on days 1 and 14. Food intake for each meal is recorded and body weight is measured once a week. Blood samples are taken once a week for 7 weeks for the measurements of plasma (alternatively, serum) glucose, insulin, lipids and parameters of interest. On days 14, 28 and 49, an oral glucose tolerance test is conducted.

[00392] Exemplary treatment effects may include reduced food intake, decreased body weight, decreased BMI, AC and/or SFT, improved glucose tolerance, decreased insulin levels, decreased fasting and/or fed (*e.g.*, postprandial) plasma (alternatively, serum) glucose levels, insulin levels, and/or reduced triglyceride levels. These effects indicate improved metabolic parameters with treatment with anti-beta klotho antibodies.

[00393] For example, twenty male cynomolgus monkeys were selected for treatment with a humanized 5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276) or a vehicle control based on their BMI (> 40) and were trained for chair restraint, subcutaneous injection, blood draw, and oral gavage. A routine feeding schedule was established.

[00394] Baseline values of various parameters of interest were measured prior to the treatments. For example, on day -7, baseline body weight, BMI, abdominal circumference, and skin fold thickness were measured, and a dual energy X-ray absorptiometry ("DEXA") scan was conducted to the cynomolgus monkeys under

ketamine anesthesia to measure bone mineral density. Blood samples were taken on day -3, following an overnight fast. Baseline levels of serum glucose, insulin, total cholesterol, LDL, HDL, triglyceride, and a panel of hematology and clinical chemistry parameters were measured and analyzed. Immediately after the baseline samples, animals were subjected to oral glucose tolerance test (OGTT) by receiving a gavage of 4 g/kg glucose and were sampled at 5, 15, 30, 60, 120 and 180 minutes after the glucose challenge, and serum glucose and insulin were measured. Based on the baseline data, the animals were assigned into two groups with 10 animals in each group (*e.g.,* one group for antibody treatment and the other group as a vehicle control group) to achieve similar baseline levels of the various parameters, *e.g.,* body weight, BMI, and levels of serum glucose, insulin, and triglyceride.

[00395] Starting from day 0, one group of animals (n=10) received a dose of subcutaneous injection of 10 mg/kg of an anti-beta klotho antibody, such as a humanized 5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276) biweekly (*e.g.,* on days 0, 14, 28, and 42) for 4 doses. The vehicle control group received matched vehicles on the same days. The treatments were carried out in the morning 30 minutes before the morning meal, and the dosing volume was 0.1 to 0.2 mL/kg.

[00396] Parameters of interest, *e.g.,* food intake, body weight, clinical chemistry, and OGTT, were monitored throughout the study. For example, food intake was measured daily. Body weight, BMI, abdominal circumference, and skin fold thickness were measured weekly, *e.g.,* on days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, and 98. Blood samples were collected weekly, *e.g.,* on days 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70, following an overnight fast, to measure glucose, insulin, and lipids, such as triglyceride. An additional blood sample was taken on day 98, following an overnight fast. OGTTs were conducted after the initiation of the study, *e.g.*, on days 14, 28, and 56, in which animals received a gavage of 4 g/kg glucose and were sampled at 5, 15, 30, 60, 120 and 180 minutes after the glucose challenge, and serum glucose and insulin were measured. A DEXA scan was conducted on days 30 and 72. In addition, a hematology and clinical chemistry panel was analyzed on days 28 and 70. Two animals from vehicle group and two animals from the anti-beta klotho antibody group were euthanized and necropsy was

performed on day 50 for safety assessment. During the study, all animals were closely monitored for their health.

[00397] Exemplary results from this study are shown in Tables 21 to 25 below. As shown in Table 21, the body weight of animals treated with vehicle remained constant (with slight increase over the course); while the body weight of animals treated with the anti-beta klotho antibody progressively decreased, and the body weight did not return to baseline level during weeks 8-14 (*e.g.,* recovery phase). Similarly, as shown in Table 22, animals treated with vehicle showed relatively stable BMI throughout the study, while animals treated with the anti-beta klotho antibody showed decreased level of BMI over the course of the study. BMI level also did not come back to baseline values (*e.g.,* during the recovery phase). These results suggest that the anti-beta klotho antibody treatment resulted in reduction of fat mass.

[00398] As shown in Table 23, the serum insulin levels in animals treated with vehicle increased over the course of the study; while the serum insulin levels in animals treated with the anti-beta klotho antibody significantly decreased. The serum glucose levels were also reduced in animals treated the anti-beta klotho antibody, as shown in Table 24. Similarly, as shown in Table 25, the triglyceride levels in animals treated with vehicle increased over the course of the study; while the triglyceride levels in animals treated with the anti-beta klotho antibody were significantly reduced.

[00399] Results of OGTTs demonstrated that before treatments, baseline levels of insulin were not significantly different between the vehicle and the anti-beta klotho antibody groups. In contrast, after treatment, there was a trend towards glucose reduction and insulin levels were reduced in animals treated with the anti-beta klotho antibody compared with animals treated with vehicle.

Table 21A: Body Weight (kg)																
	Week	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Vehicle	**Mean**	10.84	10.75	10.66	10.63	10.61	10.75	10.67	10.66	10.75	10.98	10.96	11.08	11.09	11.12	11.23	11.18
	sem	0.49	0.50	0.50	0.48	0.48	0.47	0.48	0.46	0.47	0.59	0.59	0.61	0.60	0.59	0.58	0.59
h5H23	**Mean**	10.87	10.84	10.60	10.45	10.27	10.21	10.00	9.86	9.76	9.58	9.52	9.46	9.43	9.43	9.39	9.27
	sem	0.33	0.36	0.36	0.38	0.37	0.40	0.41	0.41	0.42	0.50	0.51	0.51	0.53	0.56	0.53	0.56

Table 21B: Body Weight Change (kg)															
	Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Vehicle	**Mean**	0.00	-0.09	-0.12	-0.14	0.00	-0.08	-0.09	0.00	0.14	0.13	0.24	0.26	0.28	0.39	0.34
	sem	0.00	0.05	0.07	0.09	0.09	0.09	0.10	0.10	0.12	0.13	0.13	0.14	0.17	0.18	0.17
h5H23	**Mean**	0.00	-0.24	-0.39	-0.57	-0.63	-0.84	-0.98	-1.08	-1.07	-1.13	-1.19	-1.22	-1.22	-1.25	-1.38
	sem	0.00	0.05	0.08	0.10	0.13	0.15	0.17	0.19	0.26	0.27	0.28	0.31	0.34	0.31	0.34

Table 22: BMI																
	Week	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Vehicle	**Mean**	57.59	57.06	56.59	56.44	56.33	57.08	56.63	56.59	57.06	58.27	58.17	58.76	58.86	59.00	59.60	59.33
	sem	2.41	2.45	2.45	2.33	2.31	2.28	2.30	2.23	2.25	2.55	2.52	2.60	2.60	2.53	2.46	2.51

h5H23	**Mean**	57.52	57.32	56.03	55.24	54.28	53.95	52.82	52.07	51.54	48.85	48.56	48.24	48.09	48.07	47.94	47.28
	sem	2.53	2.61	2.50	2.51	2.44	2.50	2.52	2.54	2.48	2.29	2.30	2.32	2.44	2.54	2.46	2.60

Table 23: Insulin (uU/mL)

	Week	**-1 to 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Vehicle	**Mean**	114.85	100.09	91.06	124.79	187.36	159.20	226.53	145.78	186.75	204.96	181.32
	sem	32.75	19.94	26.33	37.48	62.09	51.60	130.94	34.74	39.85	52.63	52.28
h5H23	**Mean**	89.18	34.73	36.19	38.11	46.75	48.28	35.42	37.95	57.29	63.23	55.30
	sem	9.51	4.91	4.14	7.24	6.54	6.80	4.98	5.03	12.99	12.43	13.62

Table 24: Glucose (mg/dL)

	Week	**-1 to 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Vehicle	**Mean**	90.81	93.69	95.41	90.21	94.51	98.31	97.70	95.78	94.73	93.53	90.06
	sem	10.00	9.07	9.73	7.93	9.17	10.46	13.12	10.21	11.62	12.09	12.49
h5H23	**Mean**	90.85	87.37	83.19	84.92	85.62	80.52	80.97	79.60	81.90	78.20	76.60
	sem	11.67	6.61	6.92	8.02	6.75	5.67	6.32	4.30	4.97	7.07	5.49

Table 25: Triglyceride (mmol/L)												
	Week	**-1 to 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Vehicle	**Mean**	0.93	0.76	0.92	0.70	1.36	0.90	1.15	1.20	1.54	1.35	1.26
	sem	0.25	0.08	0.16	0.10	0.27	0.14	0.38	0.22	0.35	0.38	0.37
h5H23	**Mean**	1.05	0.65	0.65	0.59	0.70	0.59	0.56	0.70	0.90	0.73	0.71
	sem	0.17	0.09	0.12	0.08	0.10	0.05	0.07	0.12	0.13	0.08	0.10

[00400] In another exemplary study, forty spontaneous obese male cynomolgus were selected, trained and fed as described above.

[00401] Baseline values of various parameters were measured prior to the treatments as discussed above. For example, baseline body weight, BMI, abdominal circumference and skin fold thickness were measured on day -4, and baseline blood samples were taken for measurements of serum glucose, insulin, total cholesterol, LDL, HDL and triglyceride on day -3, following an overnight fast. Based on these baseline data, animals were assigned into 5 groups (8 animals in each group) with 4 groups to receive various doses of an anti-beta klotho antibody such as a humanized 5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276) and one group to receive a vehicle control.

[00402] On day 0, the first group of animals (n=8) received a single dose of subcutaneous injection of 0.1 mg/kg of the anti-beta klotho antibody; the second group of animals (n=8) received a single dose of subcutaneous injection of 1 mg/kg the anti-beta klotho antibody, and the third group of animals (n=8) received a single dose of subcutaneous injection of 10 mg/kg the anti-beta klotho antibody. Starting from day 0, the fourth group of animals (n=8) received a dose of subcutaneous injection of 0.1 mg/kg of the anti-beta klotho antibody once every 4 weeks for a duration of 12 weeks. As a control, the fifth group of animals (n=8) received a dose of vehicle once every 4 weeks for 12 weeks. The treatments were carried out in the morning 30 minutes before the morning meal, and the dosing volume was 0.2 mL/kg.

[00403] Parameters of interest were monitored throughout the study. For example, food intake was measured for each meal. Body weight, BMI, abdominal circumference, and skin fold thickness were measured weekly. Blood examples were taken at, *e.g.*, 3, 6, 12 and 24 hours and 3, 4, 7, 10, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, and 112 days after the dose(s), and parameters of interest, *e.g.,* serum glucose, insulin, total cholesterol, LDL, HDL and triglyceride, were measured. During the study, all animals were closely monitored for their health as described above.

[00404] Exemplary results of this dose-response study are shown in Tables 26-29. Table 26 shows the relative body weight changes in animals treated with the anti-

beta klotho antibody compared with the body weight changes in animals treated with vehicle. As shown, a single dose of subcutaneous injection of 0.1 mg/kg, 1mg/kg, or 10mg/kg the anti-beta klotho antibody, or four doses of subcutaneous injection of 1mg/kg the anti-beta klotho antibody significantly reduced body weight. In addition, the reduced body weight was maintained on day 112 for animals receiving a single dose of 10 mg/kg the anti-beta klotho antibody, or for animals receiving four doses of 1mg/kg the anti-beta klotho antibody compared with vehicle.

[00405] As shown in Table 27, a single dose of subcutaneous injection of 0.1 mg/kg, 1mg/kg, or 10mg/kg the anti-beta klotho antibody, or four doses of subcutaneous injection of 1mg/kg the anti-beta klotho antibody reduced serum insulin level compared with the vehicle control group. In addition, four doses of subcutaneous injection of 1mg/kg the anti-beta klotho antibody significantly reduced serum glucose level, as shown in Table 28. Furthermore, serum triglyceride levels in animals treated with a single dose of subcutaneous injection of 1mg/kg, or 10mg/kg the anti-beta klotho antibody, or four doses of subcutaneous injection of 1mg/kg the anti-beta klotho antibody, were reduced compared the animals treated with vehicle, as shown in Table 29.

Table 26A Body Weight

	Days	-4	4	10	14	21	28	35	42	49	56	63	70	77	84	112
Vehicle	Mean	10.17	10.07	9.89	9.87	9.91	9.83	9.82	9.73	9.71	9.63	9.61	9.57	9.53	9.45	9.24
	sem	0.78	0.80	0.77	0.79	0.81	0.81	0.82	0.82	0.83	0.83	0.83	0.83	0.83	0.83	0.81
5H23 (0.1 mg/kg SD)	Mean	10.00	9.92	9.70	9.62	9.52	9.47	9.37	9.28	9.27	9.36	9.34	9.27	9.34	9.34	9.21
	sem	0.67	0.71	0.69	0.71	0.73	0.76	0.76	0.79	0.79	0.81	0.83	0.85	0.86	0.87	0.85
5H23 (1 mg/kg SD)	Mean	9.84	9.69	9.49	9.36	9.28	9.19	9.05	8.92	8.90	8.85	8.85	8.83	8.89	8.93	9.24
	sem	0.54	0.55	0.54	0.53	0.54	0.55	0.55	0.55	0.55	0.54	0.55	0.55	0.55	0.55	0.56
5H23 (10 mg/kg SD)	Mean	10.07	9.95	9.73	9.61	9.49	9.33	9.20	9.07	8.98	8.88	8.80	8.73	8.74	8.67	8.51
	sem	0.58	0.56	0.57	0.57	0.59	0.59	0.58	0.58	0.56	0.56	0.58	0.55	0.55	0.54	0.50
5H23 (1 mg/kg q4w)	Mean	10.05	9.86	9.66	9.51	9.40	9.31	9.14	8.92	8.84	8.74	8.63	8.53	8.45	8.41	8.29
	sem	0.42	0.45	0.43	0.42	0.44	0.44	0.43	0.43	0.42	0.41	0.42	0.40	0.40	0.39	0.38

Table 26B Body Weight Change (kg)

	Days	-4	4	10	14	21	28	35	42	49	56	63	70	77	84	112
Vehicle	Mean	0.00	-0.09	-0.28	-0.30	-0.26	-0.34	-0.35	-0.44	-0.45	-0.53	-0.56	-0.60	-0.64	-0.71	-0.93
	sem	0.00	0.05	0.05	0.04	0.06	0.08	0.10	0.13	0.14	0.16	0.18	0.19	0.22	0.23	0.27
5H23 (0.1 mg/kg SD)	Mean	0.00	-0.08	-0.30	-0.38	-0.49	-0.54	-0.64	-0.72	-0.74	-0.65	-0.66	-0.74	-0.66	-0.66	-0.80
	sem	0.00	0.08	0.06	0.09	0.11	0.15	0.17	0.20	0.22	0.24	0.26	0.28	0.30	0.31	0.28
5H23 (1 mg/kg SD)	Mean	0.00	-0.16	-0.35	-0.48	-0.56	-0.65	-0.79	-0.93	-0.95	-0.99	-1.00	-1.01	-0.95	-0.91	-0.60
	sem	0.00	0.03	0.04	0.04	0.05	0.07	0.08	0.09	0.11	0.13	0.15	0.19	0.21	0.22	0.20
5H23 (10 mg/kg SD)	Mean	0.00	-0.12	-0.34	-0.47	-0.59	-0.74	-0.88	-1.00	-1.10	-1.20	-1.27	-1.35	-1.34	-1.40	-1.56
	sem	0.00	0.05	0.07	0.08	0.10	0.12	0.12	0.11	0.15	0.15	0.16	0.17	0.15	0.16	0.23
5H23 (1 mg/kg q4w)	Mean	0.00	-0.18	-0.38	-0.54	-0.65	-0.74	-0.90	-1.13	-1.20	-1.30	-1.41	-1.52	-1.60	-1.64	-1.75
	sem	0.00	0.08	0.06	0.05	0.05	0.06	0.08	0.10	0.11	0.13	0.15	0.15	0.16	0.17	0.26

Table 27 Insulin

	Days	-3 d	7 d	14 d	21 d	28 d	35 d	42 d	49 d	56 d	70 d	84 d	112 d
Vehicle	Mean	78.96	75.44	85.96	98.23	90.35	80.65	71.70	76.54	80.11	80.61	70.61	51.41
	sem	17.16	16.65	15.18	23.76	21.01	15.17	13.01	12.82	16.32	20.81	17.91	11.05
5H23 (0.1 mg/kg SD)	Mean	118.28	64.70	65.09	65.83	61.15	62.26	84.34	68.17	85.20	82.99	95.31	57.32
	sem	62.16	20.06	22.84	20.26	22.41	19.93	37.61	24.82	41.19	45.77	46.91	20.74
5H23 (1 mg/kg SD)	Mean	74.75	54.52	51.50	54.88	42.31	46.42	46.28	38.83	56.57	40.89	51.84	64.91
	sem	14.42	15.27	10.80	15.55	13.92	11.97	10.53	7.93	16.04	7.15	14.73	21.66
5H23 (10 mg/kg SD)	Mean	84.03	51.57	46.50	54.45	53.42	38.67	37.25	34.70	32.83	25.49	33.33	22.38
	sem	18.06	10.75	7.19	14.43	15.43	7.95	5.16	5.04	6.61	3.18	7.10	2.46
5H23 (1 mg/kg q4w)	Mean	133.82	52.88	61.67	109.20	49.94	38.83	37.60	47.85	40.18	32.42	30.58	22.14
	sem	57.35	18.45	14.30	40.07	13.96	9.93	12.32	13.85	11.96	8.21	10.73	4.17

Table 28 Glucose

	Days	-3 d	7 d	14 d	21 d	28 d	35 d	42 d	49 d	56 d	70 d	84 d	112 d
Vehicle	Mean	90.95	76.41	69.57	68.60	63.90	59.94	68.27	70.79	58.12	70.16	73.60	71.46
	sem	8.29	9.37	5.55	7.89	6.31	3.46	6.14	7.93	4.42	7.37	7.52	11.33
5H23 (0.1 mg/kg SD)	Mean	92.54	72.59	67.10	63.23	54.14	58.19	62.37	62.53	62.46	64.24	79.27	73.80
	sem	15.41	5.49	4.54	4.52	4.82	3.37	3.69	3.39	5.17	3.60	10.90	6.91
5H23 (1 mg/kg SD)	Mean	97.67	73.82	64.51	57.74	54.72	67.07	62.39	62.96	65.25	65.88	68.56	70.02
	sem	11.08	4.64	2.69	3.29	4.38	4.98	3.91	2.36	2.59	8.34	5.21	6.84
5H23 (10 mg/kg SD)	Mean	89.71	73.24	68.74	61.13	58.93	60.55	66.49	61.11	63.14	59.11	69.59	66.49
	sem	11.76	5.56	3.10	5.11	1.92	2.68	2.14	3.56	2.21	2.52	3.98	3.11
5H23 (1 mg/kg q4w)	Mean	130.01	87.28	81.11	77.56	71.89	67.82	67.79	66.98	65.34	63.23	72.56	69.50
	sem	21.21	15.15	10.15	13.41	6.83	7.05	7.56	4.99	6.98	3.75	6.66	4.98

Table 29 Triglycerides

	Days	-3 d	7 d	14 d	21 d	28 d	35 d	42 d	49 d	56 d	70 d	84 d	112 d
Vehicle	Mean	0.90	0.61	1.00	1.45	1.04	1.51	1.03	1.30	0.99	1.10	1.12	0.79
	sem	0.18	0.12	0.19	0.33	0.23	0.32	0.17	0.23	0.19	0.25	0.30	0.13
5H23 (0.1 mg/kg SD)	Mean	0.69	0.54	0.57	0.67	0.59	0.70	0.78	0.85	1.09	0.89	1.18	0.98
	sem	0.13	0.10	0.11	0.17	0.15	0.14	0.22	0.20	0.40	0.25	0.39	0.27
5H23 (1 mg/kg SD)	Mean	1.27	0.58	0.76	0.91	0.73	0.59	0.59	0.72	0.83	0.95	1.33	1.61
	sem	0.37	0.06	0.20	0.22	0.21	0.06	0.14	0.17	0.27	0.30	0.36	0.24
5H23 (10 mg/kg SD)	Mean	1.12	0.61	0.64	0.68	0.54	0.97	0.55	0.64	0.65	0.59	0.65	0.71
	sem	0.18	0.09	0.12	0.15	0.09	0.38	0.09	0.13	0.12	0.12	0.11	0.12
5H23 (1 mg/kg q4w)	Mean	1.24	0.65	0.68	0.77	0.65	0.57	0.56	0.55	0.57	0.49	0.53	0.53
	sem	0.36	0.18	0.19	0.28	0.11	0.11	0.09	0.13	0.14	0.10	0.08	0.07

[00406] The results from these animal studies demonstrate improved metabolic parameters with treatment with anti-beta klotho antibodies provided herein, for example, such as decreases in body weight, body mass index, abdominal circumference, skinfold thickness, glucose (*e.g.*, serum glucose), insulin (*e.g.*, serum insulin) and/or triglycerides (*e.g.*, serum triglycerides).

EXAMPLE 9: EPITOPE AND DOMAIN MAPPING

[00407] Studies were performed in order to localize the binding site on human KLB of anti-beta klotho antibodies in the 5H23 epitope bin, including 5H23 as described in Example 3, with sequences shown in Tables 1-10 and Figures 1-3, and human anti-beta klotho antibodies in the 5H23 epitope bin, such as humanized 5H23 antibodies (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276). For example, FACS-based binding assays for domain mapping were performed on Expi293 cells (Life Technologies, A14635) that were transiently transfected with plasmids encoding variants of KLB: human, mouse, cynomolgus, a chimeric version in which the KL1 domain sequence of mouse KLB (M1-F506) replaces the KL1 domain of human KLB (M1-F508) to create mouse-human KLB (SEQ ID NO: 376), and a second chimera in which the human KL1 sequence (M1-F508) replaces the KL1 domain of mouse KLB (M1-F506) to create human-mouse KLB (SEQ ID NO: 374). Additionally, the expression vector pYD7 harboring no KLB sequence was transfected as a negative control.

[00408] In some studies, binding of a purified sample of a humanized 5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276) to KLB variants was determined by FACS analysis. Two day post-transfection cells were co-incubated with purified antibodies: humanized 5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276), a control antibody (*e.g.*, VH SEQ ID NO: 358 and VL SEQ ID NO: 360), and a negative control antibody (*e.g.*, anti-keyhole limpet hemocyanin (KLH) antibody expressed from a construct comprising SEQ ID NO: 424 and 425) diluted to 1 µg/ml in PBS/1%BSA/0.1% azide for 30 minutes at 4°C. After washing with PBS/1% BSA/0.1% azide, transfected cells were then co-incubated with labeled anti-human Fc (Jackson Immunoresearch) for 30 minutes at 4°C. After washing with PBS/1% BSA/0.1% azide, cells were acquired on flow cytometer (FACS Calibur) and analyzed by cytometric software (FlowJo). To display the resulting data, graphs

plotting the number of cells as a function of fluorescence intensity were generated, and the median fluorescence intensity (MFI) was determined for each sample as shown in Table 30.

Table 30

Antibody	Mouse KLB	Mouse-Human chimeric KLB	Human-Mouse chimeric KLB	Human KLB	Cynomolgus KLB	Empty Vector (-control)
h5H23	14.2	26.1	9.29	865	1909	8.29
Control	10.6	5.6	71.9	620	1757	6.82
Neg. Control	9.59	5.44	6.01	6.2	9.26	5.41

* Mean Fluorescence intensity calculated from FACS data using FlowJo analysis software; Neg. Control is anti-KLH antibody.

[00409] An exemplary humanized 5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276) bound to human KLB and cynomolgus KLB, as indicated by a large proportion of cells having high-fluorescence intensity compared to cells treated with the anti-KLH negative control antibody, but the exemplary humanized 5H23 antibody did not bind to mouse KLB. The exemplary humanized 5H23 antibody also bound to the mouse-human KLB chimeric protein, but not the human-mouse KLB chimeric protein indicating that anti-beta klotho antibodies in the 5H23 epitope bin, including 5H23 as described in Example 3, with sequences shown in Tables 1-10 and Figures 1-3, and human anti-beta klotho antibodies in the 5H23 epitope bin, such as humanized 5H23 antibodies (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276) bind to the KL2 domain of human KLB. In contrast, the control antibody bound to the KL1 domain of human KLB as demonstrated by its binding to cells transfected with the human-mouse KLB chimeric protein, but not the mouse-human KLB chimeric protein.

[00410] In order to further identify specific binding residues within human beta klotho KL2 domain, shotgun mutagenesis was used to separately mutate individual residues of the KL2 domain of human beta klotho to an alanine (*e.g.,* residues F508A-L1008A). The resulting beta klotho mutant proteins were expressed within HEK-293T cells and assayed by fluorescence-activated cell sorting (FACS) for binding to anti-beta klotho antibodies in the 5H23 epitope bin, including 5H23 as described in Example 3, with sequences shown in Tables 1-10 and Figures 1-3, and human anti-beta klotho antibodies in the 5H23 epitope bin, such as a humanized

5H23 antibody (*e.g.,* VH SEQ ID NO: 271 and VL SEQ ID NO: 276), or a monovalent Fab fragment of the humanized 5H23 antibody. For example, screening of the beta klotho mutant proteins was conducted at a concentration of 0.5 µg/ml for the humanized 5H23 antibody, 1.0 µg/ml for the Fab fragment, and 2.0 µg/ml for a positive control polyclonal anti-beta klotho antibodies.

[00411] The resulting mapping identified three specific binding residues, H657, Y701 and R703, which were negative for binding by the humanized 5H23 antibody, but were positive for the control polyclonal anti-beta klotho antibodies. These residues represented amino acids whose side changes made the highest energetic contributions to the antibody-epitope interation as shown in Table 31. The locations of the three identified residues were modeled by showing them (dark spheres) at the equivalent positions on human cytosolic beta-glucosidase (PDB ID# 2JFE; Tribolo et al., J. Mol. Biol. *370*, 964-975 (2007)), identified by BLAST alignment of the two proteins as shown in Figure 6. The structure shows the equivalent of beta klotho residues 521-963. Lower reactivity of the Y701A and R703A mutations with the humanized 5H23 antibody indicates that Y701 and R703 are major energetic contributors to binding.

Table 31

Binding Reactivity (%WT)		
Protein Mutation	**Humanized 5H23 Antibody**	**Control Polyclonal Antibody**
H657A	16.88 (±11.93)	120.35 (±55.21)
Y701A	0.64 (±0.09)	43.37 (±5.78)
R703A	1.64 (±1.69)	131.59 (±19.98)

[00412] Thus, the anti-beta klotho antibodies provided herein, including 5H23 and antibodies in the 5H23 epitope bin recognize an epitope in the KLB2 domain that comprises residues H657, Y701 and/or R703. Such antibodies, as described in Example 3 and respresed by and comprising CDR sequences in Tables 1-10 and Figures 1-3, are useful as agonist antibodies to induce FGF19-mediate and/or FGF21-mediated signaling, including, for example, to reduce body weight, food intake, BMI, insulin, glucose and/or triglycerides.

[00413] Additionally, the anti-beta klotho antibodies provided herein share the common feature of competing with each other for the bindng of beta klotho (see, *e.g.*, Example 3 describing antibodies in the 5H23 epitope bin). This competitive

inhibition indicates that each antibody binds to the same region of beta klotho (*e.g.*, the same epitope), thereby asserting similar effects. As further exemplified herein, the anti-beta klotho antibodies include humanized anti-beta klotho antibodies, including humanized anti-beta klotho antibodies derived from or based on 5H23, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 and/or 1G19 having CDR sequence as described in Tables 1-10 or Figures 1-3, such as anti-beta klotho antibodies, including humanized anti-beta klotho antibodies, bind to a specific domain of human beta klotho (*e.g.*, KL2 (residues S509-S1044) as described above). Moreover, such binding can be largely attributed to particular amino acid residues within the KL2 region (*e.g.*, H657, Y701 and R703 as described above), which comprise the epitope recognized by the anti-beta klotho antibodies described herein. Taken together, these results demonstrate that the effects observed for an anti-beta klotho antibody that is derived from or based on 5H23 or an antibody in the 5H23 eptitope bin, including an antibody having one or more CDRs described in Tables 1-10 or Figures 1-3, can be extrapolated to other anti-beta klotho antibodies described herein having the same or similar eptitope specificity (*e.g.*, the same or similar CDRs). For example, the *in vitro* activities of antibodies as shown in Examples 4-7 and above, as well as the *in vivo* effects demonstrated in Example 8 for an exemplary humanized anti-beta klotho antibody, are representative of the activites and effects of the the anti-beta klotho antibodies described herein.

[00414] The embodiments of the present disclosure described above are intended to be merely exemplary, and those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. All such equivalents are considered to be within the scope of the present disclosure and are covered by the following claims. Furthermore, as used in this specification and claims, the singular forms “a,” “an” and “the” include plural forms unless the content clearly dictates otherwise. Thus, for example, reference to “an antibody” may include a mixture of two or more such antibodies, and the like. Additionally, ordinarily skilled artisans will recognize that operational sequences must be set forth in some specific order for the purpose of explanation and claiming, but the present disclosure contemplates various changes beyond such specific order.

[00415] The contents of all references described herein are hereby incorporated by reference.

[00416] Other embodiments are within the following claims.

WHAT IS CLAIMED:

1. An antibody or fragment thereof that (i) binds 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) 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. An antibody or fragment thereof that binds to beta klotho, wherein the antibody or binding fragment thereof comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:1, 27, 53, 79, 105, 131, 157, 183, 209, or 235,

(ii) SEQ ID NO:7, 33, 59, 85, 111, 137, 163, 189, 215 or 241,

(iii) SEQ ID NO:12, 38, 64, 90, 116, 142, 168, 194, 220 or 246,

(iv) SEQ ID NO:13, 39, 65, 91, 117, 143, 169, 195, 221 or 247, and

(v) SEQ ID NO:18, 44, 70, 96, 122, 148, 174, 200, 226 or 252;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:2, 28, 54, 80, 106, 132, 158, 184, 210, or 236,

(ii) SEQ ID NO:8, 34, 60, 86, 112, 138, 164, 190, 216 or 242,

(iii) SEQ ID NO:14, 40, 66, 92, 118, 144, 170, 196, 222 or 248,

(iv) SEQ ID NO:19, 45, 71, 97, 123, 149, 175, 201, 227 or 253, and

(v) SEQ ID NO:24, 50, 76, 102, 128, 154, 180, 206, 232 or 258; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO: 3, 29, 55, 81, 107, 133, 159, 185, 211, or 237,

(ii) SEQ ID NO:9, 35, 61, 87, 113, 139, 165, 191, 217 or 243,

(iii) SEQ ID NO:15, 41, 67, 93, 119, 145, 171, 197, 223 or 249, and

(iv) SEQ ID NO:20, 46, 72, 98, 124, 150, 176, 202, 228 or 254;

and/or

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:4, 30, 56, 82, 108, 134, 160, 186, 212, or 238,

(ii) SEQ ID NO:10, 36, 52, 88, 114, 140, 166, 192, 218 or 244,

(iii) SEQ ID NO:16, 42, 68, 94, 120, 146, 172, 198, 224 or 250, and

(iv) SEQ ID NO:21, 47, 73, 99, 125, 151, 177, 203, 229 or 255;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:5, 31, 57, 83, 109, 135, 161, 187, 213, or 239,

(ii) SEQ ID NO:11, 37, 63, 89, 115, 141, 167, 193, 219 or 245, and

(iii) SEQ ID NO:22, 48, 74, 100, 126, 152, 178, 204, 230 or 256; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:6, 32, 58, 84, 110, 136, 162, 188, 214, or 240,

(ii) SEQ ID NO:17, 43, 69, 95, 121, 147, 173, 199, 225 or 251, and

(iii) SEQ ID NO:23, 49, 75, 101, 127, 153, 179, 205, 231 or 257.

3. An antibody or fragment thereof that binds to beta klotho, wherein the antibody or binding fragment thereof comprises a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:1, 27, 53, 79, 105, 131, 157, 183, 209, or 235,

(ii) SEQ ID NO:7, 33, 59, 85, 111, 137, 163, 189, 215 or 241,

(iii) SEQ ID NO:12, 38, 64, 90, 116, 142, 168, 194, 220 or 246,

(iv) SEQ ID NO:13, 39, 65, 91, 117, 143, 169, 195, 221 or 247, and

(v) SEQ ID NO:18, 44, 70, 96, 122, 148, 174, 200, 226 or 252;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:2, 28, 54, 80, 106, 132, 158, 184, 210, or 236,

(ii) SEQ ID NO:8, 34, 60, 86, 112, 138, 164, 190, 216 or 242,

(iii) SEQ ID NO:14, 40, 66, 92, 118, 144, 170, 196, 222 or 248,

(iv) SEQ ID NO:19, 45, 71, 97, 123, 149, 175, 201, 227 or 253, and

(v) SEQ ID NO:24, 50, 76, 102, 128, 154, 180, 206, 232 or 258; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO: 3, 29, 55, 81, 107, 133, 159, 185, 211, or 237,

(ii) SEQ ID NO:9, 35, 61, 87, 113, 139, 165, 191, 217 or 243,

(iii) SEQ ID NO:15, 41, 67, 93, 119, 145, 171, 197, 223 or 249, and

(iv) SEQ ID NO:20, 46, 72, 98, 124, 150, 176, 202, 228 or 254.

4. An antibody or fragment thereof that binds to beta klotho, wherein the antibody or binding fragment thereof comprises a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:4, 30, 56, 82, 108, 134, 160, 186, 212, or 238,

(ii) SEQ ID NO:10, 36, 52, 88, 114, 140, 166, 192, 218 or 244,

(iii) SEQ ID NO:16, 42, 68, 94, 120, 146, 172, 198, 224 or 250, and

(iv) SEQ ID NO:21, 47, 73, 99, 125, 151, 177, 203, 229 or 255;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:5, 31, 57, 83, 109, 135, 161, 187, 213, or 239,

(ii) SEQ ID NO:11, 37, 63, 89, 115, 141, 167, 193, 219 or 245, and

(iii) SEQ ID NO:22, 48, 74, 100, 126, 152, 178, 204, 230 or 256; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of:

(i) SEQ ID NO:6, 32, 58, 84, 110, 136, 162, 188, 214, or 240,

(ii) SEQ ID NO:17, 43, 69, 95, 121, 147, 173, 199, 225 or 251, and

(iii) SEQ ID NO:23, 49, 75, 101, 127, 153, 179, 205, 231 or 257.

5. The antibody or fragment thereof of any one of claims 2-4, wherein the antibody or binding fragment thereof comprises:

(a) a heavy chain variable (V_H) region further comprising:

(1) a FR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:278, 279, 280 and 378;

(2) a FR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:281, 282, and 283;

(3) a FR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:284, 285, 286, 287 and 379-381; and

(4) a FR4 having an amino acid sequence of SEQ ID NO:288;

and/or

(b) a light chain variable (V_L) region further comprising:

(1) a FR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:289, 290 and 382-384;

(2) a FR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:291, 292 and 385-392;

(3) a FR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:293, 294, 295 and 393-404; and

(4) a FR4 having an amino acid sequence selected from the group consisting of SEQ ID NO:296 and 405-407.

6. The antibody or fragment thereof of claim 1, wherein the antibody or binding fragment thereof comprises a V_H sequence that is SEQ ID NO:269, 270, 271,

272, 273, 274, 320, 321 or 322 and/or a V_L sequence that is SEQ ID NO:275, 276, 277, or 325-352.

7. An antibody or fragment thereof that binds to beta klotho comprising all three heavy chain complementarity determining regions (CDRs) and/or all three light chain CDRs from:

the antibody designated 5H23 that comprises a VH sequence that is SEQ ID NO:25 and a VL sequence that is SEQ ID NO:26;

the antibody designated 1C17 that comprises a VH sequence that is SEQ ID NO:51 and a VL sequence that is SEQ ID NO:52;

the antibody designated 1D19 that comprises a VH sequence that is SEQ ID NO:77 and a VL sequence that is SEQ ID NO:78;

the antibody designated 2L12 that comprises a VH sequence that is SEQ ID NO:103 and a VL sequence that is SEQ ID NO:104;

the antibody designated 3L3 that comprises a VH sequence that is SEQ ID NO:129 and a VL sequence that is SEQ ID NO:130;

the antibody designated 3N20 that comprises a VH sequence that is SEQ ID NO:155 and a VL sequence that is SEQ ID NO:156;

the antibody designated 4P5 that comprises a VH sequence that is SEQ ID NO:181 and a VL sequence that is SEQ ID NO:182;

the antibody designated 5C23 that comprises a VH sequence that is SEQ ID NO:207 and a VL sequence that is SEQ ID NO:208;

the antibody designated 5F7 that comprises a VH sequence that is SEQ ID NO:233 and a VL sequence that is SEQ ID NO:234; or

the antibody designated IG19 that comprises a VH sequence that is SEQ ID NO:259 and a VL sequence that is SEQ ID NO:260.

8. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 5H23.

9. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 1C17.

10. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 1D19.

11. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 2L12.

12. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 3L3.

13. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 3N20.

14. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 4P5.

15. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 5C23.

16. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated 5F7.

17. The antibody of claim 7, wherein the antibody or fragment thereof comprises all three heavy chain CDRs and/or all three light chain CDRs from the antibody designated IG19.

18. An antibody or fragment thereof that binds to beta klotho, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of:

(i) GYTFTX$_1$YDIN (SEQ ID NO:261) wherein X_1 is a naturally occurring amino acid,

(ii) GYSITSGYYWN (SEQ ID NO:27), and

(iii) GYIFTNYGIS (SEQ ID NO:131);

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of:

(i) WIYPGDX$_1$STKYNEKFKG (SEQ ID NO:262) wherein X_1 is a naturally occurring amino acid,

(ii) YINYX$_1$GX$_2$X$_3$NYX$_4$PSLKN (SEQ ID NO:264) wherein X_1, X_2, X_3, and X_4 are naturally occurring amino acids, and

(iii) EIYPRSGNTYYNEKFKG (SEQ ID NO:132);

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of:

(i) SDYYGSRSFX$_1$Y (SEQ ID NO:263) wherein X_1 is a naturally occurring amino acid,

(ii) X$_1$GAYYSNYDSFDV (SEQ ID NO:265) wherein X_1 is a naturally occurring amino acid, and

(iii) HWDGVLDYFDY (SEQ ID NO:133);

and/or

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of:

(i) RASKSVSTSGYSYX$_1$H (SEQ ID NO:266) wherein X_1 is a naturally occurring amino acid,

(ii) KASQDINSYLS (SEQ ID NO:30), and

(iii) KSSQSLLNSGNQKNYLA (SEQ ID NO:134);

(2) a V_L CDR2 having an amino acid sequence of:

(i) LASNLES (SEQ ID NO:57),

(ii) RANRLVD (SEQ ID NO:31), and

(iii) GASTRES (SEQ ID NO:135);

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of:

(i) X_1HSX_2ELPYT (SEQ ID NO:267) wherein X_1 and X_2 are naturally occurring amino acids,

(ii) $LQYDEFPX_1T$ (SEQ ID NO:268) wherein X_1 is a naturally occurring amino acid, and

(iii) LNDHSYPFT (SEQ ID NO:136).

19. The antibody or fragment thereof of claim 18, wherein the antibody fragment thereof comprises a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of:

(i) $GYTFTX_1YDIN$ (SEQ ID NO:261) wherein X_1 is a naturally occurring amino acid,

(ii) GYSITSGYYWN (SEQ ID NO:27), and

(iii) GYIFTNYGIS (SEQ ID NO:131);

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of:

(i) $WIYPGDX_1STKYNEKFKG$ (SEQ ID NO:262) wherein X_1 is a naturally occurring amino acid,

(ii) $YINYX_1GX_2X_3NYX_4PSLKN$ (SEQ ID NO:264) wherein X_1, X_2, X_3, and X_4 are naturally occurring amino acids, and

(iii) EIYPRSGNTYYNEKFKG (SEQ ID NO:132);

and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of:

(i) $SDYYGSRSFX_1Y$ (SEQ ID NO:263) wherein X_1 is a naturally occurring amino acid,

(ii) $X_1GAYYSNYDSFDV$ (SEQ ID NO:265) wherein X_1 is a naturally occurring amino acid, and

(iii) HWDGVLDYFDY (SEQ ID NO:133).

20. The antibody or fragment thereof of claim 18, wherein the antibody or fragment thereof comprises a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of:

(i) RASKSVSTSGYSYX$_1$H (SEQ ID NO:266) wherein X_1 is a naturally occurring amino acid,

(ii) KASQDINSYLS (SEQ ID NO:30), and

(iii) KSSQSLLNSGNQKNYLA (SEQ ID NO:134);

(2) a V_L CDR2 having an amino acid sequence of:

(i) LASNLES (SEQ ID NO:57),

(ii) RANRLVD (SEQ ID NO:31), and

(iii) GASTRES (SEQ ID NO:135);

and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of:

(i) X$_1$HSX$_2$ELPYT (SEQ ID NO:267) wherein X_1 and X_2 are naturally occurring amino acids,

(ii) LQYDEFPX$_1$T (SEQ ID NO:268) wherein X_1 is a naturally occurring amino acid, and

(iii) LNDHSYPFT (SEQ ID NO:136).

21. The antibody or fragment thereof of claim 18, wherein the antibody or fragment thereof comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence of GYTFTX$_1$YDIN (SEQ ID NO:261) wherein X_1 is a naturally occurring amino acid;

(2) a V_H CDR2 having an amino acid sequence of WIYPGDX$_1$STKYNEKFKG (SEQ ID NO:262) wherein X_1 is an naturally occurring amino acid; and

(3) a V_H CDR3 having an amino acid sequence of SDYYGSRSFX$_1$Y (SEQ ID NO:263) wherein X_1 is a naturally occurring amino acid.

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence of RASKSVSTSGYSYX$_1$H (SEQ ID NO:266) wherein X_1 is a naturally occurring amino acid;

(2) a V_L CDR2 having an amino acid sequence of LASNLES (SEQ ID NO:57); and

(3) a V_L CDR3 having an amino acid sequence of X_1HSX$_2$ELPYT (SEQ ID NO:267) wherein X_1 and X_2 are naturally occurring amino acids.

22. The antibody or fragment thereof of claim 21, wherein the antibody or fragment thereof comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence of GYTFTX$_1$YDIN (SEQ ID NO:261) wherein X_1 is R or S;

(2) a V_H CDR2 having an amino acid sequence of WIYPGDX$_1$STKYNEKFKG (SEQ ID NO:262) wherein X_1 is G, D, S, or I; and

(3) a V_H CDR3 having an amino acid sequence of SDYYGSRSFX$_1$Y (SEQ ID NO:263) wherein X_1 is V, T, or A. and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence of RASKSVSTSGYSYX$_1$H (SEQ ID NO:266) wherein X_1 is M, L, or V;

(2) a V_L CDR2 having an amino acid sequence of LASNLES (SEQ ID NO:57); and

(3) a V_L CDR3 having an amino acid sequence of X$_1$HSX$_2$ELPYT (SEQ ID NO:267) wherein X_1 is Q or H, and X_2 is R or G.

23. The antibody or fragment thereof of claim 22, wherein the antibody or fragment thereof comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:1, and SEQ ID NO:53,

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:80, SEQ ID NO:54, and SEQ ID NO:210,

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:81, SEQ ID NO:55, SEQ ID NO:3;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:82, SEQ ID NO:108,

(2) a V_L CDR2 having an amino acid sequence of LASNLES (SEQ ID NO:57); and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:84.

24. The antibody of claim 18, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence of GYSITSGYYWN (SEQ ID NO:27),

(2) a V_H CDR2 having an amino acid sequence of $YINYX_1GX_2X_3NYX_4PSLKN$ (SEQ ID NO:264) wherein X_1, X_2, X_3, and X_4 are naturally occurring amino acids, and

(3) a V_H CDR3 having an amino acid sequence of $X_1GAYYSNYDSFDV$ (SEQ ID NO:265) wherein X1 is a naturally occurring amino acid.

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence of KASQDINSYLS (SEQ ID NO:30),

(2) a V_L CDR2 having an amino acid sequence of RANRLVD (SEQ ID NO:31), and

(3) a V_L CDR3 having an amino acid sequence of LQYDEFPX$_1$T (SEQ ID NO:268) wherein X_1 is an naturally occurring amino acid.

25. The antibody of claim 24, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence of GYSITSGYYWN (SEQ ID NO:27),

(2) a V_H CDR2 having an amino acid sequence of YINYX$_1$GX$_2$X$_3$NYX$_4$PSLKN (SEQ ID NO:264) wherein X_1 is D or G, wherein X_2 is N or S, wherein X_3 is S or N, and wherein X_4 is T or N,

(3) a V_H CDR3 having an amino acid sequence of X$_1$GAYYSNYDSFDV (SEQ ID NO:265) wherein X_1 is K or R; and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence of KASQDINSYLS (SEQ ID NO:30),

(2) a V_L CDR2 having an amino acid sequence of RANRLVD (SEQ ID NO:31), and

(3) a V_L CDR3 having an amino acid sequence of LQYDEFPX$_1$T (SEQ ID NO:268) wherein X_1 is F or Y.

26. The antibody of claim 25, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence of GYSITSGYYWN (SEQ ID NO:27),

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:28, SEQ ID NO:263,

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:29, SEQ ID NO:237; and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence of KASQDINSYLS (SEQ ID NO:30),

(2) a V_L CDR2 having an amino acid sequence of RANRLVD (SEQ ID NO:31), and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:32, SEQ ID NO:240.

27. The antibody of claim 18, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence of GYIFTNYGIS (SEQ ID NO:131);

(2) a V_H CDR2 having an amino acid sequence of EIYPRSGNTYYNEKFKG (SEQ ID NO:132); and

(3) a V_H CDR3 having an amino acid sequence of HWDGVLDYFDY (SEQ ID NO:133).

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence of KSSQSLLNSGNQKNYLA (SEQ ID NO:134;

(2) a V_L CDR2 having an amino acid sequence of GASTRES (SEQ ID NO:135); and

(3) a V_L CDR3 having an amino acid sequence of LNDHSYPFT (SEQ ID NO:136).

28. An antibody or fragment thereof that binds to beta klotho , wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising a V_H CDR1, a V_H CDR2, and a V_H CDR3 amino acid sequence depicted in Tables 1-10; and/or

(b) a light chain variable (V_L) region comprising a V_L CDR1, a V_L CDR2, and a V_L CDR3 amino acid sequence depicted in Tables 1-10.

29. The antibody of claim 28, wherein the antibody comprises a heavy chain variable (V_H) region comprising a V_H CDR1, a V_H CDR2, and a V_H CDR3 amino acid sequence depicted in Tables 1-10.

30. The antibody of claim 28, wherein the antibody comprises a light chain variable (V_L) region comprising a V_L CDR1, a V_L CDR2, and a V_L CDR3 amino acid sequence depicted in Tables 1-10.

31. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:1, 7, 12, 13, and 18;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:2, 8, 14, 19 and 24;

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:3, 9, 15 and 20;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:4, 10, 16 and 21;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:5, 11, and 22; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:6, 17, and 23.

32. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO: 1;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO: 2; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO: 3;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:4;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:5; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:6.

33. The antibody of claim 31, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:7;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:8; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:9;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:10;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:11; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:6.

34. The antibody of claim 31, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:12;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:2; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:3;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:4;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:5; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:6.

35. The antibody of claim 31, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:13;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:14; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:15;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:16;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:11; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:17.

36. The antibody of claim 31, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:18;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:19; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:20;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:21;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:22; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:23.

37. The antibody of claim 31, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:1;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:24; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:3;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:4;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:5; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:6.

38. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:27, 33, 38, 39 and 44;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:28, 34, 40, 45 and 50; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:29, 35, 41 and 46;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:30, 36, 42, and 47;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:31, 37 and 48 and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:32, 43 and 49.

39. The antibody of claim 38, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:27;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:28; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:29;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:30;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:31; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:32.

40. The antibody of claim 38, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:33;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:34; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:35;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:36;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:37; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:32.

41. The antibody of claim 38, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:38;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:28; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:29;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:30;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:31; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:32.

42. The antibody of claim 38, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:39;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:40; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:41;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:42;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:37; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:43.

43. The antibody of claim 38, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:44;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:45; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:46;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:47;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:48; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:49.

44. The antibody of claim 38, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:27;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:50; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:29;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:30;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:31; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:32.

45. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:53, 59, 64, 65, and 70;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:54, 60, 66, 71, and 76; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:55, 61, 67, and 72;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:56, 62, 68, and 73;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:57, 63 and 74; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:58, 59, and 75.

46. The antibody of claim 45, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:53;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:54; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:55;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:56;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:57; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:58.

47. The antibody of claim 45, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:59;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:60; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:61;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:62;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:63; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:58.

48. The antibody of claim 45, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:64;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:54; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:55;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:56;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:57; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:58.

49. The antibody of claim 45, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:65;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:66; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:67;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:68;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:63; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:69.

50. The antibody of claim 45, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:70;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:71; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:72;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:73;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:74; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:75.

51. The antibody of claim 45, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:53;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:76; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:55;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:56;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:57; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:58.

52. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:79, 85, 90, 91 and 96;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:80, 86, 92, 97 and 102; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:81, 87, 93 and 98;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:82, 88, 94 and 99;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:83, 89 and 100; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:84, 95 and 101.

53. The antibody of claim 52, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:79;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:80; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO: 81;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:82;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:83; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:84.

54. The antibody of claim 52, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:85;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:86; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:87;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:88;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:89; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:84.

55. The antibody of claim 52, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:90;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:80; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:81;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:82;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:83; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:84.

56. The antibody of claim 52, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:91;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:92; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:93;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:94;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:89; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:95.

57. The antibody of claim 52, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:96;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:97; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:98;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:99;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:100; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:101.

58. The antibody of claim 52, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:79

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:102 and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:81;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:82;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:83; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:84.

59. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:105, 111, 116, 117 and 122;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:106, 112, 118, 123 and 128; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:107, 113, 119, and 124;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:108, 114, 120 and 125;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:109, 115, and 126; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:110, 121, and 127.

60. The antibody of claim 59, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:105;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:106; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:107; and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:108;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:109; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:110.

61. The antibody of claim 59, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:111;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:112; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:113; and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:114;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:115; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:110.

62. The antibody of claim 59, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:116;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:106; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:107; and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:108;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:109; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:110.

63. The antibody of claim 59, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:117;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:118; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:119; and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:120;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:115; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:121.

64. The antibody of claim 59, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:122;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:123; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:124;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:125;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:126; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:127.

65. The antibody of claim 59, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:105;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:128; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:107;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:108;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:109; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:110.

66. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:131, 137, 142, 143 and 148;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:132, 138, 144, 149 and 154; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:133, 139, 145, and 150; and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:134,140, 146, and 151;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:135, 141 and 152; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:136, 147 and 153.

67. The antibody of claim 66, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:131;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:132; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:133;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:134;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:135; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:136.

68. The antibody of claim 66, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:137;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:138; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:139;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:140;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:141; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:136.

69. The antibody of claim 66, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:142;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:132; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:133;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:134;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:135; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:136.

70. The antibody of claim 66, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:143;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:144; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:145;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:146;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:141; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:147.

71. The antibody of claim 66, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:148;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:149; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:150;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:151;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:152; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:153.

72. The antibody of claim 66, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:131;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:154; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:133;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:134;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:135; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:136.

73. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:157, 163, 168, 169 and 174;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:158, 164, 170, 175 and 180; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:159, 165, 171 and 176;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:160, 166, 172 and 177;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:161, 167, and 178; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:162, 173, and 179.

74. The antibody of claim 73, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:157;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:158; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:159;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:160;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:161; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:162.

75. The antibody of claim 73, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:163;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:164; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:165;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:166;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:167; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:162.

76. The antibody of claim 73, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:168;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:158; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:159;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:160;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:161; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:162.

77. The antibody of claim 73, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:169;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:170; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:171;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:172;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:167; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:173.

78. The antibody of claim 73, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:174;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:175; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:176;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:177;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:178; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:179.

79. The antibody of claim 73, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:157;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:180; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:159;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:160;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:161; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:162.

80. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:183, 189, 194, 195, and 200;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:184, 190, 196, 201 and 206; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:185, 191, 197 and 202;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:186, 192, 198 and 203;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:187, 193 and 204; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:188, 199, and 205.

81. The antibody of claim 80, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:183;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:184; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:185;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:186;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:187; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:188.

82. The antibody of claim 80, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:189;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:190; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:191;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:192;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:193; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:188.

83. The antibody of claim 80, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:194;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:184; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:185;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:186;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:187; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:188.

84. The antibody of claim 80, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:195;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:196; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:197;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:198;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:193; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:199.

85. The antibody of claim 80, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:200;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:201; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:202;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:203;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:204; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:205.

86. The antibody of claim 80, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:183;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:206; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:185;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:186;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:187; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:188.

87. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:209, 215, 220, 221 and 226;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:210, 216, 222, 227 and 232;

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:211, 217, 223 and 228;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:212, 218, 224 and 229;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:213, 219, and 230; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:214, 225, and 231.

88. The antibody of claim 87, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:209;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:210; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:211;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:212;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:213; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:214.

89. The antibody of claim 87, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:215;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:216; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:217;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:218;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:219; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:214.

90. The antibody of claim 87, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:220;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:210; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:211;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:212;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:213; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:214.

91. The antibody of claim 87, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:221;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:222; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:223;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:224;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:219; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:225.

92. The antibody of claim 87, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:226;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:227; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:228;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:229;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:230; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:231.

93. The antibody of claim 87, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:209;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:232; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:211;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:212;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:213; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:214.

94. The antibody of claim 28, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:235, 241, 246, 247, and 252;

(2) a V_H CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:236, 242, 248, 253, and 258; and

(3) a V_H CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:237, 243, 249, and 254;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:238, 244, 250, and 255;

(2) a V_L CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:239, 245, and 256; and

(3) a V_L CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:240, 251, and 257.

95. The antibody of claim 94, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:235;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:236; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:237;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:238;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:239; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:240.

96. The antibody of claim 94, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:241;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:242; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:243;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:244;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:245; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:240.

97. The antibody of claim 94, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:246;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:236; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:237;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:238;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:239; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:240.

98. The antibody of claim 94, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:247;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:248; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:249;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:250;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:245; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:251.

99. The antibody of claim 94, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:252;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:253; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:254;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:255;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:256; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:257.

100. The antibody of claim 94, wherein the antibody comprises:

(a) a heavy chain variable (V_H) region comprising:

(1) a V_H CDR1 having the amino acid sequence of SEQ ID NO:235;

(2) a V_H CDR2 having the amino acid sequence of SEQ ID NO:258; and

(3) a V_H CDR3 having the amino acid sequence of SEQ ID NO:237;

and

(b) a light chain variable (V_L) region comprising:

(1) a V_L CDR1 having the amino acid sequence of SEQ ID NO:238;

(2) a V_L CDR2 having the amino acid sequence of SEQ ID NO:239; and

(3) a V_L CDR3 having the amino acid sequence of SEQ ID NO:240.

101. The antibody of any one of claims 28-100, wherein the V_H region and/or V_L region further comprises human framework sequences.

102. The antibody of any one of claims 28-100, wherein the V_H region and/or V_L region further comprises a framework 1 (FR1). a framework 2 (FR2), a framework 3 (FR3) and/or a framework 4 (FR4) sequence.

103. The antibody of any one of claims 28-100, wherein the antibody or binding fragment thereof comprises:

(a) a heavy chain variable (V_H) region further comprising:

(1) a FR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:278, 279, 280 and 378;

(2) a FR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:281, 282, and 283;

(3) a FR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:284, 285, 286, 287 and 379-381; and

(4) a FR4 having an amino acid sequence of SEQ ID NO:288;

and/or

(b) a light chain variable (V_L) region further comprising:

(1) a FR1 having an amino acid sequence selected from the group consisting of SEQ ID NO:289, 290 and 382-384;

(2) a FR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:291, 292 and 385-392;

(3) a FR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:293, 294, 295 and 393-404; and

(4) a FR4 having an amino acid sequence selected from the group consisting of SEQ ID NO:296 and 405-407.

104. The antibody or fragment of any one of claims 1-103, wherein the antibody is a monoclonal antibody.

105. The antibody or fragment of claim 104, wherein the monoclonal antibody is a humanized, human or chimeric antibody.

106. The antibody or fragment thereof of any one of claims 1-105, wherein the fragment is an Fab, Fab', $F(ab')_2$, Fv, scFv, $(scFv)_2$, single chain antibody molecule, dual variable region antibody, single variable region antibody, linear antibody, V region, or a multspecific antibody formed from antibody fragments.

107. The antibody or fragment of any one of claims 1-106, wherein the antibody or fragment is conjugated to a detectable marker.

108. The antibody or fragment of claim 107, wherein the detectable marker is selected from a radioisotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound and a chemiluminescent compound.

109. A binding agent that binds to essentially the same epitope as an antibody of any one of claims 1-108.

110. The binding agent of claim 109, wherein the binding agent induces FGF19- and/or FGF21- mediated signaling in cells expressing beta klotho and an FGF receptor.

111. The binding agent of claim 109, which is an antibody or fragment thereof.

112. The binding agent of claim 109, which is an anticalin, an adnectin, an affibody, a DARPin, a fynomer, an affitin, an affilin, an avimer, a cysteine-rich knottin peptide, or an engineered Kunitz-type inhibitor.

113. A binding agent capable of binding to beta klotho, wherein the antibody of any one of claims 1-108 displaces the binding agent in a competitive binding assay.

114. A binding agent capable of binding to beta klotho, wherein the binding agent displaces the antibody of any one of claims 1-108 in a competitive binding assay.

115. The binding agent of claim 114, wherein the binding agent is an antibody, or fragment thereof.

116. The binding agent of claim 114, wherein the binding agent is an antibody, or fragment thereof.

117. A transgenic animal that produces the monoclonal antibody of any one of claims 1-108.

118. A hybridoma that produces the monoclonal antibody of any one of claims 1-108.

119. A vector comprising a polynucleotide encoding the antibody or fragment thereof of any one of claims 1-108.

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

121. A 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. A 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 method of claim 121 or 122, wherein the cells express human beta klotho and a human FGF receptor IC.

124. 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 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 of claim 124, wherein the subject is 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 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 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 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. 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. 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. 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. 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. 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. 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. The antibody or fragment thereof of claim 139, wherein the epitope of human beta klotho comprise at least amino acid residue 657 of SEQ ID NO: 297.

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

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

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

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

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

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

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

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

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

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

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

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

153. 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. 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. The method of claim 154, 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. The method of any one of claims 153-155, wherein the subject is 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. The method of any one of claims 153-155, 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. The method of any one of claims 153-155, 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.