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(54) **ANTIBODIES BINDING BETA KLOTHO DOMAIN 2 AND METHODS OF USE THEREOF**
BETA-KLOTHO 2 BINDENDE ANTIKÖRPER UND VERFAHREN ZUR VERWENDUNG DAVON
ANTICORPS LIANT BETA-KLOTHO 2 ET LEURS PROCÉDÉS D'UTILISATION

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Description**FIELD**

- 5 **[0001]** 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

- 10 **[0002]** 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).
15 Beta klotho forms a complex with fibroblast growth factor (FGF) receptors and functions as a co-receptor for FGFs, including FGF19 and FGF21.

- [0003]** 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
20 in turn leads to the phosphorylation and activation of downstream signaling molecules.

- [0004]** 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
25 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).

- [0005]** 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
30 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).

- 35 **[0006]** 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 on 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.

- [0007]** US 2011/135657 and US 2012/328616 disclose antibodies binding to beta-klotho and/or a complex comprising beta-klotho and one of FGFR1c, FGFR2c, FGFR3c and FGFR4 to induce FGF21-like signaling. www.rndsystems.com/pdf/MAB3738.pdf (retrieved from the Internet on 2011-02-21; "Monoclonal Anti-human/mouse Klotho beta
40 Antibody", February 6, 2007) discloses an antibody that binds human/mouse beta-klotho.

SUMMARY

- 45 **[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
50 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]** The present invention provides an antibody that binds within beta klotho domain 2 (KLB2) comprising amino acid residues 657 to 703 of human beta klotho (SEQ ID NO:297), wherein the antibody comprises:

- 55 (a) a heavy chain variable region comprising:

a CDR1 comprising SEQ ID NO:1, SEQ ID NO:12, or SEQ ID NO:13;
a CDR2 comprising SEQ ID NO:2 or SEQ ID NO:14; and

a CDR3 comprising SEQ ID NO:3 or SEQ ID NO:15;

and

(b) a light chain variable region comprising:

a CDR1 comprising SEQ ID NO:4 or SEQ ID NO:16;
a CDR2 comprising SEQ ID NO:5 or SEQ ID NO:11; and
a CDR3 comprising SEQ ID NO:6 or SEQ ID NO:17.

[0011] In some embodiments the antibody comprises:

(a) a heavy chain variable region comprising a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3; and

(b) a light chain variable region comprising a CDR1 comprising SEQ ID NO:4, a CDR2 comprising SEQ ID NO:5, and a CDR3 comprising SEQ ID NO:6.

[0012] In some embodiments the antibody comprises:

(a) a heavy chain variable region comprising a CDR1 comprising SEQ ID NO:12, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3; and

(b) a light chain variable region comprising a CDR1 comprising SEQ ID NO:4, a CDR2 comprising SEQ ID NO:5, and a CDR3 comprising SEQ ID NO:6.

[0013] In some embodiments the antibody comprises:

(a) a heavy chain variable region comprising a CDR1 comprising SEQ ID NO:13, a CDR2 comprising SEQ ID NO:14, and a CDR3 comprising SEQ ID NO:15; and

(b) a light chain variable region comprising a CDR1 comprising SEQ ID NO:16, a CDR2 comprising SEQ ID NO:11, and a CDR3 comprising SEQ ID NO:17.

[0014] In some embodiments the antibody comprises a heavy chain variable region that has at least 90% sequence identity to SEQ ID NO:25 and a light chain variable region that has at least 90% sequence identity to SEQ ID NO:26.

[0015] In some embodiments the antibody comprises a heavy chain variable region that comprises SEQ ID NO:25 and a light chain variable region that comprises SEQ ID NO:26.

[0016] In some embodiments the antibody comprises a heavy chain variable region that comprises SEQ ID NO:271 and a light chain variable region that comprises SEQ ID NO:276.

[0017] In some embodiments the antibody binds an epitope comprising at least one of amino acid residues 657, 701 and/or 703 of the human beta klotho (SEQ ID NO: 297).

[0018] In some embodiments the antibody is a monoclonal antibody, a humanized antibody, a human antibody, or a chimeric antibody.

[0019] In some embodiments the antibody is a 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 multispecific antibody formed from antibody fragments.

[0020] The present invention also provides an isolated polynucleotide encoding the antibody of the invention.

[0021] The present invention also provides a vector comprising the polynucleotide encoding the antibody of the invention.

[0022] The present invention also provides a host cell comprising the polynucleotide encoding the antibody of the invention or the vector comprising the polynucleotide encoding the antibody of the invention.

[0023] The present invention also provides a pharmaceutical composition comprising the antibody of the present invention, and a pharmaceutically acceptable carrier.

[0024] The present invention also provides an antibody as defined in the claims for use in a method for improving glucose metabolism in a subject.

[0025] In some embodiments of the use of the antibody of the inventions in a method for improving glucose metabolism in a subject, the method for improving glucose metabolism results in:

(a) reduced glucose levels;
(b) reduced insulin levels;
(c) increased insulin sensitivity;

- (d) reduced insulin resistance;
- (e) improved glucose tolerance; and/or
- (f) improved pancreatic function.

[0026] The present invention also provides the antibody as defined in the claims for use in a method for treating Type 1 diabetes, Type 2 diabetes, dyslipidemia, nonalcoholic steatohepatitis (NASH), cardiovascular disease, metabolic syndrome, obesity, or non-alcoholic fatty liver disease (NAFLD).

[0027] In some embodiments of the inventive use of antibody the method further comprises administration of one or more therapeutic agents in combination with the antibody.

[0028] In some embodiments of the inventive use of the antibody, the one or more therapeutic agents is selected from the group consisting of biguanides, sulphonylureas, thiazolidinediones, GLP-1 analogues, PPAR gamma agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, bromocriptine, bile acid sequestrants, insulin, alpha glucosidase inhibitors, metformin, SGLT-2 inhibitors, appetite suppression agents, and weight loss drugs.

[0029] 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. The 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, 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.

[0030] Described herein is a binding protein (e.g., an anti-beta klotho antibody) comprising six CDRs or less than six CDRs. A binding protein described herein (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. The anti-beta klotho antibody of the invention comprises 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, as described herein, or a humanized variant thereof.

In some embodiments, the 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.

[0031] 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.

[0032] 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. 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. 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.

[0033] The present disclosure also provides binding proteins, including antibodies or fragments thereof, that (i) bind to an epitope of human beta klotho and cynomolgous 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. Binding proteins, including antibodies or fragments thereof, are described herein that bind to a region, including an epitope, of human beta klotho or cyno beta klotho. Antibodies of the present invention bind to a region of human beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:297 or a region of cyno beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:299.

[0034] Antibodies of the present invention bind to a specific epitope of human beta klotho, including: (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 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 or chimeric antibody.

[0035] Anti-beta klotho antibodies provided herein may be 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., colestevlam), and insulin (e.g., bolus and basal analogs), alpha glucosidase inhibitors (e.g., acarbose, roglitose), 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® / orlistat). In some aspects, the detectable agent is a radioisotope, an enzyme, a fluorescent compound, a bioluminescent compound or a chemiluminescent compound.

[0036] In certain embodiments, compositions are provided comprising an anti-beta klotho antibody of the invention. Also provided herein are pharmaceutical compositions comprising an anti-beta klotho antibody of the invention.

[0037] 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 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 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.

[0038] The present disclosure also provides an antibody as defined in the claims for use in methods of treating, preventing or alleviating a disease, disorder or condition (e.g., one or more symptoms) comprising administering a therapeutically effective amount of the anti-beta klotho antibody 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).

[0039] 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 1 diabetes, Type 2 diabetes, gestational diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, metabolic syndrome, or obesity).

[0040] The use in methods of treating, preventing or ameliorating include methods of improving glucose metabolism and/or methods of improving lipid metabolism. The use in 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.

[0041] 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.

[0042] 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 a 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.

[0043] 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 embodiments, 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.

[0044] The present disclosure also provides an antibody as defined in the claims for use in 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).

[0045] The present disclosure also provides methods for detecting beta klotho in a sample comprising contacting the sample with an anti-beta klotho antibody of the invention, that comprises a detectable agent. In certain embodiments, the sample comprises a cell expressing beta klotho on its surface.

[0046] 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

[0047]

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.

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.

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.

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.

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.

Figure 3C-1 and 3C-2 shows a sequence alignment 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.

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.

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.

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

Figure 6 shows a three-dimensional 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

[0048] 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.

[0049] 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 binding 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 epitope 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 epitope 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 activities and effects of the anti-beta klotho antibodies described herein.

[0050] In some aspects 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

[0051] 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

[0052] 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.

[0053] 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:

```

1 MKPGCAAGSP GNEWIFFSTD EITTRYRNTM SNGGLQRSVI LSALILLRAV
51 TGFSGDGRAI WSKNPNFTPV NESQLFLYDT FPKNFFWGIG TGALQVEGSW

101 KKDGGKPSIW DHFIHThLKN VSSTNGSSDS YIFLEKDLA LDFIGVSYFQ
151 FSISWPRLFP DGIVTVANAK GLQYYSTLLD ALVLRNIEPI VTLYHWDLPL
201 ALQEKYGGWK NDTIIDIFND YATYCFQMGF DRVKYWITIH NPYLVAWHGY
251 GTGMHAPGEK GNLAAYTVG 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)

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

EP 3 097 122 B9

atgaagccaggctgtgcggcaggatctccagggaatgaatggatTTTTCTTCAGCACTGATGA
aataaccacacgctataggaataacaatgtccaacgggggattgcaaagatctgtcatcctgt
5 cagcacttattctgctacgagctgttactggattctctggagatggaagagctatatgggtct
aaaaatcctaatttttactccggtaaataaaagtcagctgtttctctatgacactttccctaa
aaactttttctggggatttgggactggagcattgcaagtgggaaggagttggaagaaggatg
10 gaaaaggaccttctatatatgggatcatttcatccacacacaccttaaaaatgtcagcagcacg
aatggttccagtgacagttatatTTTTCTGGAAAAAGACTTATCAGCCCTGGATTTTATAGG
agtttctttttatcaattttcaatttcttggccaaggcttttccccgatggaatagtaacag
15 ttgccaacgcaaaaggctctgcagtactacagtactcttctggacgctctagtgccttagaaac
attgaacctatagttactttataccactgggatttgcctttggcactacaagaaaaatatgg
ggggtggaaaaatgataccataatagatatcttcaatgactatgccacatactgtttccaga
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tgtttggggaccgtgtcaaatattggattacaattcacaacccatatctagtggccttggcat
 gggatatgggacaggtatgcatgcccctggagagaagggaaatttagcagctgtctacactgt
 5 gggacacaacttgatcaaggctcactcgaagtttggcataactacaacacacatttccgcc
 cacatcagaaggggttggttatcgatcacgttgggatctcattggatcgagccaaaccggctcg
 gaaaacacgatggatatattcaaatgtcaacaatccatggtttctgtgcttggatggtttgc
 10 caaccctatccatggggatggcgactatccagaggggatgagaaagaagttgttctccgttc
 taccatttttctctgaagcagagaagcatgagatgagaggcacagctgatttctttgccttt
 tcttttggaccaacaacttcaagcccctaaacacccatggctaaaatgggacaaaatgtttc
 15 acttaattttaagagaagcgctgaactggattaaactggaatacaacaaccctcgaatcttga
 ttgctgagaatggctgggtcacagacagtcgtgtgaaaacagaagacaccacggccatctac
 atgatgaagaatttccctcagccaggtgcttcaagcaataagggttagatgaaatacagagtgtt
 20 tgggtatactgcctggctctctcctggatggctttgaatggcaggatgcttacaccatccgcc
 gaggattattttatgtggattttaacagtaaacagaaaagagcggaaacctaatcttcagca
 cactactacaaacagatcatacgagaaaatggtttttctttaaaagagtccacgccagatgt
 25 gcagggccagtttccctgtgacttctcctgggggtgtcactgaatctgttcttaagcccaggt
 ctgtggcttcgtccccacagttcagcgatcctcatctgtacgtgtggaacgccactggcaac
 agactgttgccagagtgggaaggggtgaggctgaaaacacgacccgctcaatgcacagattt
 30 tgtaaacatcaaaaaacaacttgagatgttggcaagaatgaaagtcacccactaccggtttg
 ctctggattgggcctcggctccttcccactggcaacctgtccgcggtgaaccgacaggccctg
 aggtactacaggtgcgtgggtcagtgaggggctgaagcttggcatctccgcgatgggtcacct
 35 gtattatccgacccacgcccacctaggcctccccgagcctctgttgcatgccgacgggtggc
 tgaacccatcgacggccgaggccttccaggcctacgctgggctgtgcttccaggagctgggg
 gacctgggtgaagctctggatcaccatcaacgagcctaaccggctaagtacatctacaaccg
 40 ctctggcaacgacacctacggggcgggcgcaaacctgctgggtggcccacgccctggcctggc
 gcctctacgaccggcagttcaggccctcacagcgcgggggcgtgtcgtgtcgtgtcacgcg
 gactggggcggaacccgccaacccctatgctgactcgcactggagggcgggccgagcgcttcc
 45 gcagttcgagatcgcttgggttcgccgagccgctcttcaagaccggggactaccccgcgggcca
 tgagggaatacattgcctccaagcaccgacgggggctttccagctcggccctgccgcgctc
 accgaggccgaaaggaggctgctcaagggcacggctcgacttctgcgcgctcaaccacttcac
 50 cactaggttcgtgatgcacgagcagctggccggcagccgctacgactcggacagggacatcc
 agtttctgcaggacatcacccgctgagctccccacgcgctggctgtgattccctggggg
 gtgcgcaagctgctgcggtgggtccggaggaactacggcgacatggacatttacatcacgc
 55 cagtggcatcgacgaccaggtcttgaggatgaccggctccggaagtactacctaggggaagt
 accttcaggaggtgctgaaagcatacctgattgataaagtcagaatcaaaggctattatgca

ttcaaactggctgaagagaaatctaaaccagatttggattcttcacatctgatttttaaagc
 taaatcctcaatacaattttacaacaaagtgatcagcagcaggggcttcccttttgagaaca
 5 gtagttctagatgcagtcagaccaagaaaatacagagtgcactgtctgcttattccttgtg
 cagaagaaaccactgatattcctgggttggttcttcttccaccctgggttctactcttatac
 aattgccatttttcaaaggcagaagagaagaaagttttggaaagcaaaaaacttacaacaca
 10 taccattaaagaaaggcaagagagttgtagc

(SEQ ID NO: 298)

[0055] 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
 20 101 KKDGGKPSIW DHFVHThLKN VSSTNGSSDS YIFLEKDLA LDFIGVSFYQ
 151 FSISWPRLFP DGIVTVANAK GLQYYNTLLD SLVLRNIEPI VTLYHWDLPL
 201 ALQEKYGGWK NDTIIDIFND YATYCFQTFG DRVKYWITIH NPYLVAWHGY
 25 251 GTGMHAPGEK GNLAAYVTVG HNLIKAHASKV WHNYNTHFRP HQKGWLSITL
 301 GSHWIEPNRS ENTMDILKCQ QSMVSVLGWF ANPIHGDGDY PEGMKKKLLS
 351 ILPLFSEAEK NEVRGTADFF AFSFGPNFVK PLNTMAKMGQ NVSLNLREAL
 401 NWIKLEYNNP RILIAENGWF TDSHVKTEDT TAIYMMKNFL SQVLQAIRLD
 451 EIRVFGYTAW SLLDGFWEQD AYTIIRGLFY VDFNSKQKER KPKSSAHYYK
 501 QIIRENGFSL KEATPDVQGG FPCDFSWGVT ESVLKPESVA SSPQFSDPYL
 551 YVWNATGNRL LHRVEGVRLK TRPAQCTDFV NIKKQLEMLA RMKVTHYRFA
 601 LDWASVLPTG NLSAVNRQAL RYRCVVSSEG LKLGISAMVT LYYPTHALHG
 651 LPEPLLHAGG WLNPSVEAF QAYAGLCFQE LGDLVKLWIT INEPNRLSDI
 701 YNRSGNDTYG AAHNLLVAHA LAWRLYDRQF RPSQRGAVSL SLHADWAEPA
 751 NPYADSHWRA AERFLQFEIA WFAEPLFKTG DYPAAAMREYI ASKHRRGLSS
 801 SALPRLTEAE RRLLKGTVD F CALNHFTTRF VMHEQLAGSR YDSDRDIQFL
 851 QDITRLSSPT RLAVIPWGV KLLRWVRRNY GDMDIYITAS GIDDQALEDD
 901 RLRKYYLEKY LQEVLKAYLI DKVRIKGYA FKLAEKSKP RFGFFTSDFK
 951 AKSSIQFYNK MISSSGFPSE NSSRCSQTQ KNTCTVCLF LVQKKPLIFL
 1001 GCCFFSTLVL LLSITIFHRQ KRRKFWKAKN LQHIPLKKGK RVLS

(SEQ ID NO: 299)

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

atgaagcctggatgtgcccgcggaagccccggcaacgagtggaatcttcttcagcaccgacga
 gatcaccatccggtacagaaacaccatgagcaacggcggcctgcagcggagcgtgatcctgt
 5 ctgctctgaccctgctgagagccgtgaccggcttcagcggagatggcagagccgtgtggtcc
 aagaacccccaaacttcacccccgtgaacgagagccagctgttcctgtacgataccttcccaa
 gaacttcttctggggcgtgggcacaggcgccctgcaggtggaaggatcctggaagaaggacg
 10 gcaagggccccagcatctgggaccactttgtgcacaccacctgaagaacgtgtccagcacc
 aacggcgagcagcgacagctacatctttctggaaaaggacctgagcgccttggaacttcacg
 cgtgtccttctaccagttcagcatcagctggcccagactgttccccgacggcatcgtgacag
 15 tggccaatgccaagggcctgcagtactacaacaccctgctggacagcctgggtgctgcggaac
 atcgagcccatcgtgaccctgtaccactgggacctgccactggctctgcaggagaaatacgg
 cggctggaagaacgacaccatcatcgacatcttcaacgactacgccacctaactgcttccaga
 20 ccttcggcgacagagtgaagtactggatcacaatccacaaccctacctgggtggcctggcac
 ggctatggcacccggaatgcatgcccctggcgagaagggaatctggccgcccgtgtacaccgt
 gggccacaacctgatcaaggcccacagcaaagtgtggcacaactacaataccacttccggc
 25 cccaccagaagggtggtgtctatcacactgggcagccactggatcgagcctaaccgcagc
 gagaacaccatggacatcctgaagtgccagcagagcatgggtgtccgtgctgggatgggttcgc
 caacccccattcacggcgacggcgattaccccgagggcatgaagaagaagctgctgagcatcc
 30 tggccctgttcagcagggccgagaagaacgaagtgcggggcaccgcccgatcttcttcgccttt
 agcttcggccccaacaacttcaagcccctgaataccatggccaagatgggcccagaatgtgtc
 cctgaacctgagagagggcctgaactggatcaagctggagtacaacaacccccggatcctga
 35 tcgcccgagaacggctgggtcaccgacagccacgtgaaaaccgaggacaccaccgccatctat
 atgatgaagaacttccctgagccaggtgctgcaggctatccggctggatgagatccgggtgtt
 cggctacaccgcctgggtcactgctggacggcttcgaatggcaggacgcctacaccatcagac
 40 ggggcctgttctacgtggacttcaacagcaagcagaaagagcgggaagcccaagagcagcgcc
 cactactacaagcagatcatcagagagaatggcttcagcctgaaagaggccacccccgacgt
 45 gcagggccagttcccttgtgatttctcttggggcgtgaccgagagcgtgctgaagcctgaaa
 gcgtggccagcagccccagttcagcgacccttacctgtacgtgtggaacgccaccggcaac
 cggctgctgcatagagtggaaggcgtgaggctgaaaaccagacccgcccagtgacccgactt
 50 cgtgaacatcaagaacagctggaaatgctggcccggatgaaagtgaccactacagattcg
 ccctggactgggcccagcgtgctgcctaccggaaatctgagcgccgtgaacagacaggccctg
 cggactacagatgcgtggtgtccgagggcctgaagctgggcatcagcgccatgggtcacct
 55 gtactaccctaccacgcccacctgggactgcctgaacctctgctgcatgctggcggtggc
 tgaaccctagcaccgtggaagcctttcaggcctacgcgggctgtgcttccaggaactgggc

gacctcgtgaagctgtggatcaccatcaacgagcccaacagactgagcgacatctacaacag
 aagcggcaacgacacctacggcgctgccacaatctgctgggtggctcatgccctggcttggc
 5 ggctgtacgacagacagtccggccttctcagcggggagccgtgtctctgtctctgcatgcc
 gattggggccgagcccgccaacccttacgccgactctcattggagagccgccgagcggttcct
 gcagttcgagatcgcttggtttgccgagccctgttcaagaccggcgattaccctgccgcca
 10 tgagagagtatatcgccagcaagcacagacggggcctgagcagctctgccctgcctagactg
 accgaggccgagcggagactgctgaagggaaccgtggatttctgcgccctgaaccacttcac
 caccagattcgtgatgcacgagcagctggccggcagcagatacgacagcgaccgggacatcc
 15 agtttctgcaggacatcaccggctgagcagccctacaagactggccgtgatcccttgggga
 gtgcggaagctgctgagatgggtgctgcagaaactacggcgacatggatatctacatcaccgc
 cagcggcatcgacgaccaggccctggaagatgaccggctgcggaagtactacctggaaaagt
 20 acctgcaggaagtgctgaaggcctacctgatcgacaaagtgcggatcaagggtactacgcc
 ttcaagctggccgaggaaaagagcaagcccagattcggcttcttcaccagcgacttcaaggc
 caagagcagcatccagttctacaacaagatgatcagcagcagcggcttccccagcgagaaca
 25 gcagctccagatgcagccagaccagaaaaacaccgagtgtaccgtgtgcctgttcctgggtg
 cagaagaagccctgatcttcctgggctgctgcttcttttagcaccctgggtgctgctgctg
 30 catcaccatcttccaccggcagaagcggagaaagtcttgggaaggccaaaaacctgcagcaca
 tccccctgaagaaaggcaagcgggtgctgagctga

(SEQ ID NO: 300)

35
[0057] The amino acid sequence of beta klotho homolog from mouse, scientific name *Mus musculus*, is provided below:

1 MKTGCAAGSP GNEWIFFSSD ERNTRSRKTM SNRALQRSV LSAFVLLRAV
 40 51 TGFSGDGKAI WDKKQYVSPV NPSQLFLYDT FPKNFSWGVG TGAFQVEGSW
 101 KTDGRGPSIW DRYVYSHLRG VNGTDRSTD YIFLEKDLLA LDFLGVSFYQ
 151 FSISWPRLFP NGTVAAVNAQ GLRYRALLD SLVLRNIEPI VTLYHWDLPL
 45 201 TLQEEYGGWK NATMIDLFND YATYCFQTFG DRVKYWITIH NPYLVAWHGF
 251 GTGMHAPGEK GNLTAVYTVG HNLIKAHSKV WHNYDKNFRP HQKGWLSITL
 301 GSHWIEPNRT DNMEDVINCQ HSMSSVLGWF ANPIHGDGDY PEFMKTGAMI
 50 351 PEFSEAEKEE VRGTADFFAF SFGPNNFRPS NTVVKMGQNV SLNLRQVLNW
 401 IKLEYDDPQI LIENGWFTD SYIKTEDTTA IYMMKNFLNQ VLQAIKFDEI
 451 RVFGYTAWTL LDGFEWQDAY TTRRGLFYVD FNSEQKERKP KSSAHYYKQI
 55 501 IQDNGFPLKE STPDMKGRFP CDFSWGVTES VLKPEFTVSS PQFTDPHLYV

551 WNV TGNRLLY RVEGVRLKTR PSQCTDYVSI KKRVEMLAKM KVTHYQFALD
 601 WTSILPTGNL SKVNRQVRLRY YRCVVSEGLK LGVFPMVTLY HPTHSHLGLP
 5 651 LPLLSSGGWL NMNTAKAFQD YAE LCFREL G DLVKLWITIN EPNRLSDMYN
 701 RTSNDTYRAA HNL MIAHAQV WHLYDRQYRP VQHGAVSLSL HCDWAE PANP
 751 FVD SHWKAAE RFLQFEIAWF ADPLFKTGDY PSVMKEYIAS KNQRGLSSSV
 10 801 LPRFTAKESR LVKGTVD FYA LNHFTTRFVI HKQLNTNRSV ADRDVQFLQD
 851 ITRLSSPSRL AVTPWGVRLK LAWIRRN YRD RDIYITANGI DDLALED DQI
 901 RKYYLEKYVQ EALKAYLIDK VKIKGY YAFK LTEEKSKPRF GFFTSDFRAK
 15 951 SSVQFY SKLI SSSGLPAENR SPACGQPAED TDCTICSFLV EKKPLIFFGC
 1001 CFISTLAVLL SITVFHHQKR RKFQKARNLQ NIPLKKGHSR VFS

(SEQ ID NO: 301)

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

atgaagacaggctgtgcagcagggctctccggggaatgaatggattttcttcagctctgatga
 25 aagaaacacacgctctaggaaaacaatgtccaacagggcactgcaaagatctgccgtgctgt
 ctgcgtttgttctgctgcgagctgttaccggcttctccggagacgggaaagcaatatgggat
 aaaaaacagtacgtgagtc ccggtaaacccaagtcagctgttcctctatgacactttccctaa
 30 aaacttttcctggggcggttgggaccggagcatttcaagtggaagggagttggaagacagatg
 gaagaggaccctcgatctgggatcgggtacgtctactcacacctgagaggtgtcaacggcaca
 gacagatccactgacagttacatctttctggaaaaagacttggttggtctctggatttttttagg
 35 agtttctttttatcagttctcaatctcctggccacgggttggttcccaatggaacagtagcag
 cagtgaatgcgcaaggtctccggtactaccgtgcacttctggactcgctggtagtaggaat
 atcgagcccattgttaccttgtaccattgggatttgcctctgacgctccaggaagaatatgg
 40 gggctggaaaaatgcaactatgatagatctcttcaacgactatgccacatactgcttccaga
 cctttggagaccgtgtcaaataattggattacaattcacaacccttaccttggtgcttggcat
 gggtttggcacaggtatgcatgcaccaggagagaagggaatttaacagctgtctacactgt
 45 gggacacaacctgatcaaggcacattcgaaagtgtggcataactacgacaaaaacttccgcc
 ctcatcagaaggggttggtctccatcaccttgggggtcccattggatagagccaaacagaaca
 gacaacatggaggacgtgatcaactgccagcactccatgtcctctgtgcttggatggttcgc
 50 caaccccatccacggggacggcgactaccctgagttcatgaagacgggcgcatgatccccg
 agttctctgaggcagagaaggaggaggtgaggggcacggctgatttctttgccttttccttc
 55 gggcccaacaacttcaggccctcaaacaccgtggtgaaaatgggacaaaatgtatcactcaa

cttaaggcaggtgctgaactggattaaactggaatac gatgaccctcaa atcttgatttcgg
agaacggctgggttcacagatagctatataaagacagaggacaccacggccatctacatgatg
5 aagaatttcctaaaccaggttcttcaagcaataaaaatttgatgaaatccgcgtgttttggtta
tacggcctggactctcctggatggctttgagtggcaggatgcctatac gaccgcagagggc
tgttttatgtggacttttaacagtgagcagaaagagaggaaacccaagtcctcggctcattac
10 tacaagcagatcatacaagacaacggcttccctttgaaagagtccacgccagacatgaaggg
tcggttccctctgtgatttctcttggggagtcactgagtcgttcttaagcccaggtttacgg
tctcctccccgcagttttaccgatcctcacctgtatgtgtggaatgtcactggcaacagattg
15 ctctaccgagtggaaggggtaaggctgaaaacaagaccatcccagtgcacagattatgtgag
catcaaaaaacgagttgaaatgttggaacaaaatgaaagtcacccactaccagtttgctctgg
actggacctctatccttcccactggcaatctgtccaaagttaacagacaagtgttaagggtac
20 tatagggtgtgtggtgagcgaaggactgaagctgggcgtcttccccatggtgacgttgtacca
cccaaccactcccatctcggcctccccctgccacttctgagcagtggggggtggctaaaca
tgaacacagccaaggccttccaggactacgctgagctgtgcttccgggagttgggggacttg
25 gtgaagctctggatcaccatcaatgagcctaacaggctgagtgacatgtacaaccgcacgag
taatgacacctaccgtgcagcccacaacctgatgatcgcccatgccaggtctggcacctct
atgataggcagtataggccggtccagcatggggctgtgtcgtgtccttacattgcgactgg
30 gcagaacctgccaaaccctttgtggattcacactggaaggcagccgagcgcttccctccagtt
tgagatcgcttggtttgcagatccgctcttcaagactggcgactatccatcggttatgaagg
aatacatcgctccaagaaccagcgagggctgtctagctcagtcctgccgcgcttcaccgcg
35 aaggagagcaggctggtgaagggtagcgtcgacttctacgcactgaaccacttcactacgag
gttcgtgatacacaaagcagctgaacaccaaccgctcagttgcagacagggacgtccagttcc
tgcaggacatcacccgcctaagctcgccagccgctggtgtaacaccctggggagtgcg
40 aagctccttgcggtgatccggaggaaactacagagacagggatatctacatcacagccaatgg
catcgatgacctggctctagaggatgatcagatccgaaagtactacttggagaagtatgtcc
aggaggctctgaaagcatatctcattgacaaggtcaaaatcaaaggctactatgcattcaaa
45 ctgactgaagagaaatctaagcctagatttggatttttcacctctgacttcagagctaagtc
ctctgtccagttttacagcaagctgatcagcagcagtggcctccccgctgagaacagaagtc
ctgctgtggtcagcctgcggaagacacagactgcaccatttgctcatttctcgtggagaag
50 aaaccactcatcttcttcggttgctgcttcatctccactctggctgtactgctatccatcac
cgtttttcatcatcaaaagagaagaaaattccagaaagcaaggaaacttcaaaaatataccat
55 tgaagaaaggccacagcagagttttcagc

(SEQ ID NO: 302)

[0059] The amino acid sequence of beta klotho from rat, scientific name *Rattus norvegicus*, is provided below:

5 MKTGCAAGSPGNEWVFFSSDERSTRSRKTMSNGALQRSASVLSALVLLRAVTGFSG
 DGKAIWDKKQYVSPVNPQGQLFLYDTFPKNFSWGVGTGAFQVEGSWKADGRGPSI
 WDRYVDSHLRGVNSTDRSTDYVFLEKDLLALDFLGVSFYQFSISWPRLFPNGTVA
 10 AVNAKGLQYYRALLDSLVLRNIEPIVTLYHWDLPRTLQEEYGGWKNATMIDLFNDYA
 TYCFQTFGDRVKYWITIHNPYLVAWHGFGTGMHAPGEKGNLTAVYTVGHNLKAHS
 KVWHNYDKNFRPHQKGWLSITLGSHWIEPNRTENMEDVINCQHSMSSVLGWFAN
 15 PIHGDGDYPEFMKTSSVIPEFSEAEKEEVRGTAFFAFSFGPNNFRPSNTVVKMGQ
 NVSLNLRQVLNWKLEYDNPRILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAIK
 FDEIQVFGYTAWTLLDGFQWQDAYTTRRGLFYVDFNSEQKERKPKSSAHYYKQIIQ
 20 DNGFPLQESTPDMKGQFPCDFSWGVTESVLKPEFTVSSPQFTDPHLYVWNVTGN
 RLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFALDWTSLPTGNLSKI
 NRQVLRYRRCVVSEGLKLGISPMVTLYHPTHSHLGLPMPDLLSSGGWLNTNTAKAFQ
 25 DYAGLCFKELGDLVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHAQVWHLYD
 RQYRPVQHGAVSLSLHSDWAEPANPYVESHWKAERFLQFEIAWFADPLFKTGDY
 PLAMKEYIASKKQRGLSSSVLPRFTLKESSLVKGTIDFYALNHFTTRFVIHKQLNTNC
 30 SVADRDVQFLQDITRLSSPSRLAVTPWGMRKLLGWIRRNRYRDMDIYVTANGIDDLA
 LEDDQIRKYYLEKYVQEALKAYLIDKVKIKGYAFKLTEEKSKPRFGFFTSDFKAKSS
 VQFYSKLISSSGFSSSENRSACGQPPEDTECAICSFLTQKKPLIFFGCCFISTLAALL
 35 SITIFHHRKRRKFQKARNLQNIPLKKGHSRVFS (SEQ ID NO:356)

[0060] An encoding nucleic acid sequence of rat beta klotho is provided below:

40 ATGAAGACAGGCTGTGCAGCAGGGTCTCCAGGGAATGAATGGGTTTTCTTCAG
 CTCTGATGAAAGAAGCACACGCTCTAGGAAAACAATGTCCAACGGAGCACTGC
 AAAGATCTGCCGTGCTGTCTGCATTGGTTCTGCTGCGAGCTGTTACCGGCTTCT
 45 CTGGAGACGGAAAAGCAATATGGGATAAAAAACAATACGTGAGTCCGGTAAACC
 CAGGTCAGCTGTTCTCTATGACACTTTCCCTAAAACTTTTCTGGGGCGTTG
 GGACCGGAGCATTTCAAGTGGAAGGGAGTTGGAAGGCAGATGGAAGAGGACC
 50 CTCGATCTGGGACCGTTATGTGCGACTCACACCTGAGAGGTGTCAACAGCACAG
 ACAGATCCACTGACAGTTATGTCTTTCTGGAAAAGGACTTGCTGGCTCTGGATT
 55 TTTTAGGAGTTTCTTTTATCAGTTCTCAATCTCCTGGCCGCGGTTGTTCCCCAA
 CGGAACAGTAGCAGCTGTGAATGCAAAGGTCTCCAGTACTACAGAGCACTTCT

GGA CT CGCTGGTACTTAGGAATATCGAACCCATTGTTACCTTATACCATTTGGGA
 TTTGCCTTTGACGCTACAGGAAGAATATGGGGGCTGGAAAAATGCAACTATGAT
 5 AGATCTCTTCAATGACTATGCCACATACTGCTTCCAGACCTTTGGAGACCGTGT
 CAAATATTGGATTACAATTCACAACCCTTACCTCGTTGCTTGGCATGGGTTTGGC
 ACAGGTATGCATGCGCCAGGAGAGAAGGGAAATTTAACAGCTGTCTACACTGT
 10 GGGACACAACCTGATCAAGGCGCATTGCAAAGTGTGGCATAACTACGACAAAA
 ACTTCCGCCCTCATCAGAAGGGTTGGCTCTCCATCACCTTGGGGTCCCATTGG
 ATAGAACCAAACAGAACAGAAAACATGGAGGACGTGATCAACTGCCAGCACTC
 15 CATGTCTTCTGTGCTCGGATGGTTTGCCAACCCCATCCACGGAGACGGCGACT
 ACCCCGAGTTCATGAAGACGAGCTCCGTAATCCCTGAGTTCTCTGAGGCAGAG
 AAGGAGGAGGTGCGGGGGCACTGCTGACTTCTTTGCCTTTTCCTTCGGGGCCCAA
 20 CAATTTCAAGGCCCTCGAACACCGTGGTAAAAATGGGACAAAATGTATCACTCAA
 CTTAAGACAGGTGCTGAACTGGATTAACTAGAATATGACAACCCTCGAATCTT
 GATTTCCGAGAACGGCTGGTTCACAGATAGTTATATAAAGACGGAAGATACCAC
 25 GGCCATCTACATGATGAAGAATTTCTCAACCAGGTTCTTCAAGCAATAAAGTTT
 GATGAAATACAAGTGTTTGGTTATACGGCTTGGACTCTCCTGGATGGCTTTGAG
 TGGCAGGATGCCTACACGACCCGACGAGGGGCTGTTTTATGTGGACTTTAATAGT
 30 GAGCAGAAAGAGAGGAAACCCAAGTCCTCCGCTCATTACTACAAACAGATTATA
 CAAGACAACGGTTTCCCTTTGCAAGAATCCACACCAGACATGAAGGGTCAGTTT
 CCCTGTGACTTCTCCTGGGGAGTCACTGAGTCTGTTCTTAAGCCGGAGTTTACG
 35 GTGTCCTCCCCACAGTTTACTGATCCTCACCTGTATGTGTGGAATGTCACTGGC
 AACAGATTGCTATACCGAGTGGAAGGAGTCAGGCTAAAAACAAGACCGTCCCA
 ATGCACAGATTATGTGAGCATCAAAAAACGAGTTGAAATGTTGGCCAAAATGAA
 40 AGTCACCCACTACCAAGTTTGCTCTGGACTGGACCTCTATCCTCCCTACCGGAAA
 TCTGTCTAAAATTAATAGACAAGTGTTGAGGTACTATAGGTGTGTGGTGAGCGA
 AGGACTGAAGCTGGGCATCTCCCCTATGGTGACGTTGTACCACCCGACCCACT
 45 CCCATCTAGGCCTCCCCATGCCACTTCTGAGCAGTGGGGGATGGCTAAACACC
 AACACAGCCAAGGCCTTCCAGGACTACGCAGGCCTGTGCTTCAAGGAGCTGGG
 GGA CT TGGTAAAGCTCTGGATCACCATCAATGAACCCAATAGGCTGAGTGACAT
 50 GTACAACCGCACGAGTAACGACACCTACCGTGCGGGCCCAACCTGATGATCG
 CCCATGCCCAGGTCTGGCACCTCTATGATAGGCAGTATAGGCCGGTCCAGCAC
 GGGGCTGTGTGCTGTCCTTACATTCCGACTGGGCAGAACCTGCCAACCCTA
 55 TGTGGAGTCTCACTGGAAGGCAGCCGAGCGCTTCCTCCAGTTTGAGATCGCCT
 GGTTTGCGGATCCACTCTTCAAGACTGGTGACTACCCGCTGGCCATGAAGGAA

TACATCGCCTCCAAGAAGCAGCGAGGGCTGTCTAGCTCAGTCCTGCCGCGCTT
 TACCTTGAAGGAGAGCAGGCTGGTGAAGGGGACCATCGACTTTTACGCACTGA
 5 ACCACTTCACTACTAGATTCGTGATACACAAGCAGTTGAATACCAACTGCTCAGT
 GGCAGACAGGGACGTCCAGTTCCTGCAGGACATCACCCGCCTGAGCTCGCCC
 AGTCGCCTAGCCGTAACGCCCTGGGGAATGCGCAAGCTCCTTGGGTGGATCC
 10 GGAGGAACTACAGAGACATGGATATCTACGTCACAGCCAATGGCATTGATGATC
 TTGCTCTAGAGGACGATCAGATTAGAAAGTACTACTTGGAGAAGTACGTCCAGG
 AGGCTCTGAAAGCATATCTGATTGACAAGGTCAAAATCAAAGGCTACTATGCAT
 15 TCAAAGTACTGAAGAGAAATCTAAGCCTAGATTTGGATTTTTTACATCTGACTT
 CAAAGCTAAATCTTCTGTACAGTTTTATAGCAAGCTGATCAGCAGCAGCGGCTT
 CTCCTCTGAGAACAGAAGTCCTGCCTGTGGTCAGCCTCCAGAAGACACAGAAT
 20 GCGCCATTTGCTCCTTCCTTACACAGAAGAAACCACTCATCTTCTTTGGTTGTTG
 CTTTCATCTCCACTCTGGCTGCACTGCTATCAATCACTATTTTTTCATCATCGGAAG
 25 AGAAGAAAATTCCAGAAAGCAAGGAAGTTACAAAATATACCATTGAAGAAAGGG
 CACAGCAGAGTTTTTAGCTAA (SEQ ID NO:357)

[0061] The amino acid sequence of beta klotho from Hamster, scientific name *Cricetulus griseus*, is provided below:

MKAGCAAGSPGNEWIFLSSYERNTRSKKTMSNRALQRSVVLISAFVLLRAVTGLSG
 DGKAIWDKKQYVSPVNASQLFLYDTFPKNFFWGVGTGAFQVEGNWQADGRGPSI
 35 WDRFIYTHLRDVSITEKSADSYIFLEKDLLALDFLGVSFYQFSISWPRLFPNGTVASV
 NAKGLQYYNKLDSLILRNIEPVVTLYHWDLPALQEDYGGWKATMIDLFNDYATY
 CFQTFGDRVKYWITIHPYLVAWHGFATGMHAPGETGNLTAVYIVGHNLIAHASKV
 40 WHNYDKNFRPHQKGLLSITLGSHWIEPNKTENMADTISCQHSMAFVLGWFANPIHA
 DGDYPEFMKTLSTMPVFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVS
 45 LNLQRVLNWIKLEYDNPRILISENGWFTDSDIKTEDTTAIYMMKHFLNQVLQAIQFDEI
 RVFGYTAWSLLDGFEWQYAYTSRRGLFYVDFNSEQKERKPKTSAHYKQIIQENG
 FPLKESTPDMQGQFPCDFS WGVTESVLKPEFMVSSPQFTDPHLYVWNATGNRLL
 50 QRVEGVRLKTKPSHCTDYVSIKKRVEMLAKMKVTHYQFALDWATILPTGNLSEVNR
 QVLRYYRCVVSEGLKLGVSMPVTLYHPHSHLGLPEPLLNSSGWLNTYTAKAFQD
 YAGLCFQELGDLVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHAQVWRLYDR
 55 QYRPVQHGAVSLSLHSDWVEPANPYVDSHWKAAERFLLFEIAWFADPLFKTGDYP
 LAMKEYIASKNQQLSRSVLPRFTPEESRLVKGITIDFYALNHFTTRFVIHKQLNSSR

SMADRDVQFLQDITRLSSPSRLAVMPWGARKLLGWIQRNYGDMDIYITANGIDDLA
 LENDGIRKYYLEKYIQEALKAYLIDKVKIKGYAFKLTEEKSKPRFGFFTSDFKAKSS
 5 VEFYSKLISRSGFPSETSNPACGQPPEDTDCTICSFFTQKKSLIFFGCCFISTLAVLLS
 ITIFHHRKRRFHKSKNLENIPLKEGHSRVLS (SEQ ID NO: 408)

[0062] An encoding nucleic acid sequence of Hamster beta klotho is provided below:

10 atgtccaacagggcactgcaaagatctgtcgtgctgtcagcgttgttctgctgagctgttaccggattgtctggagac
 gggaaagcgatatgggataaaaaacagtacgtgagtcgggtgaatgcaagtcagctgttctctatgacactttcccta
 15 aaaacttttctggggtgttgaactggagcatttcaagtgaagggaattggcaggcagacggaagaggacctcg
 atttgggatcgtttcatctacacacacctgagagatgtcagcatcacagagaaatccgccgacagttacattttctgga
 aaaagatttgttggtctggtatttttaggagtttcttttatcagttctcaatctcctggccacggtgttcccaatggaaca
 20 gtagcatccgtgaatgcaaaaggctccaatactacaacaaacttctggactcgctgatacttaggaatattgagcccg
 ttgttaccttataccattgggatttgccttggcgctacaggaagactatgggggttgaaaaatgcaactatgatagatc
 tcttcaatgactatgccacatactgcttccagaccttggagaccgtgtcaagtattggattacaattcacaaccttacct
 25 ggttgcttggcatgggtttgccacaggtatgcatgcgccaggagagacgggaaatttaacagctgtctacattgtggga
 cacaacctgatcaaggctcattcgaaagtgtggcataactacgacaaaaacttccgcccccatcagaagggttct
 gtccattaccttgggtcccactggatagaaccaaacaaaacagaaaacatggccgatacaatcagctgccagca
 30 ctctatggcttttgtgcttgggtggtttgccaacccccatccatgcagacggcgactacctgagttcatgaaaacattgtc
 caccatgccagtggttctctgaggcagagaaggaggagggtgaggggcacagctgacttcttgccttttcttgggccc
 aacaatttcaggccctcgaacactgtagtgaatatgggacaaaatgtatcactcaacttaagacagggtgctgaactg
 35 gattaaattagaatatgacaacctcgaatcttgatttcggagaatggctgggtcacagatagtgacataaagacaga
 ggacaccacagccatctacatgatgaagcatttctcaaccagggttctcaagcaatacagtttgatgaaatacagagt
 40 tttgggttacacggcctggtctctcctggatggcttgaatggcagtatgcctacacgtctcgccgaggactgtttatgtgga
 cttaatagtgaacagaaagaaaggaaaccaagacctcggcacattactacaaacagatcatacaagaaaatgg
 tttcccttgaaagagtccacgccagacatgcagggtcagttccctgtgacttctcctggggggtcaccgagctgttctt
 45 aagccggagtttatggttctccccacagtttaccgacctcacctgtatgtgtggaatgccactggcaacagattgct
 acagcgagtagaaggagtaaggctaaaaacaaaacatcccactgcacagactatgttagcatcaaaaaacgag
 ttgagatgttgccaaaatgaaagtcacccactaccagtttctctggactgggccaccatccttcccactggcaatctg
 50 tctgaagttaatagacaagtactaagggtactataggtgtgtggtgagcgaaggactgaagctgggcgtctctcccatg
 gtgacgtgttaccacccccacccactcccacttaggcctccctgagccgcttctaacagtgggggatggctaaacactt
 acaccgccaaggccttccaggactacgcaggactgtgcttccaggaactaggggacttggtgaagctctggatcac
 55 catcaatgagcctaataaggctgagtgacatgtacaaccgcacgagtaatgacacctaccgtgcagcccataacctg

atgattgcccattgcccaggctctggcgtctctacgacaggcagtataggccagtcagcatggagctgtgtcgctgtccc
 tacattctgactgggtggaacctgccaacccctatgtggactcacactggaaggcagcggagcgcttctctctgttga
 5 gatcgctgggtcgctgatccgctcttcaagactggcgactatccactggccatgaaggagtacatcgccccaagaa
 ccagcaagggctgtcccgtcagtcctgccgcgttcaccccagaggagagcaggctgggaagggcaccatcga
 cttctacgcactgaaccacttactactaggttcgtgatacacaacagctcaacagcagccgctctatggcagacag
 10 ggacgtccagttcctgcaggacatcacccgcctgagctcgcccagccgcctggctgttatgccctggggagcacgca
 agctgcttgggtggatccagaggaactatggggacatggacatctacatcacagccaatggcatcgatgatctggct
 ctggagaatgatgggatccgaaagtactacttggagaagtacatccaggaggctctgaaagcatacctcattgacaa
 15 agtcaaaatcaaaggctattatgcattcaaactgactgaagagaaatctaagcctagatttggattttcacatctgactt
 caaagctaagtcactcttagagttttatagcaagttgatcagcagaagtggcttcccctctgagactagcaatcccgcat
 gtggtcagcctccagaagacacagactgcaccatctgctcattttcactcagaagaaatctctgatcttcttggttgtg
 20 cttcatctccactctggctgtactgtgtcaatcaccattttcatcatcgaaagagaagatttcataaatcaaagaactta
 gaaaatataccattgaaggaaggccacagtagagttcttagctaa (SEQ ID NO: 409)

[0063] The amino acid sequence of beta klotho from rabbit, scientific name *Oryctolagus cuniculus*, is provided below:

MKPGCAAGSPGNEWVSFCTDERNRRCRETMSSGRLRRSVMLSAFILLRAVTGFP
 GDGRAVWSQNPNLSPVNESQLFLYDTFPKNFFWGVGTGAFQVEGSWKKDGKGL
 30 SVWDHFIATHLVSSRDGSSDSYIFLEKDLSALDFLGVSFYQFSISWPRLFPDGTVA
 VANAQGLQYYNRLDLSLLRNIEPVVTLYHWDLPWALQEKYGGWKNETLIDLFNDY
 35 ATYCFQTFGDRVKYWITIHPYLVAWHGYGTGLHAPGEKGNVAAVYTVGHNLLKA
 HSKVWHNYNRNFRPHQKGWLSITLGSHWIEPNRAESIVDILKCQQSMVSVLWFA
 NPIHGDGDYPEVMTKKLLSVLPFSEAEKNEVRGTADFFAFSFGPNNFKPLNTMAK
 40 MGQNVSLNLRQVLNWIKLEYGNPRILIAENGWFTDSYVQTEDTTAIYMMKNFLNQV
 LQAIRLDGVRVFGYTAWSLLDGFEWQDAYNTRRGLFYVDFNSEQRERRPKSSAHY
 YKQVIGENGFTLREATPDLQGGFPCDFSWGVTESVLKPESVASSPQFSDPHLYVW
 45 NATGNRMLHRVEGVRLKTRPAQCTDFITIKKQLEMLARMKVTHFRFALDWASVLPT
 GNLSEVNRQALRYRRCVVTEGLKLNISPMVTLYPHTAHLGLPAPLLHSGGWLDPS
 TAKAFRDYAGLCFRELGDVLKWLITINEPNRLSDVYNRTSNDTYQAAHNLLIAHALV
 50 WHLYDRQYRPSQRGALSLSLHSDWAEPANPYVASHWQAAERFLQFEIAWFAEPLF
 KTGDPVAMREYIASKTRRGLSSSVLPRFSDAERRLVKGAADFYALNHFTTRFVMH
 EQQNGSRYDSRDVQFLQDITRLASPSRLAVMPWGEGKLLRWMRNNGDLDVYI
 55 TANGIDDQALQNDQLRQYYLEKYVQEALKAYLIDKIKIKGYAFKLTEEKSKPRFGFF

TSDFKAKSSIQFYNNKLITSNGFPSENGGPRCNQTQGNPECTVCLLLLQKKPLIFFSC
CFFCTLVLLSSITIFHRRKRRKFWKAKDLQHIPLKKGHKRVLS (SEQ ID NO: 410)

[0064] An encoding nucleic acid sequence of rabbit beta klotho is provided below:

tgaagccgtgataagacgggtcccgagttcgtggcaaataagccaggctgtgcggcaggatctccagggaaatga
atgggtttccttctgcaccgatgaaagaaacagacgctgtagggaaacgatgtccagcggacgcctgcggagatct
gtcatgctgtcagccttcatcctgctgcgagccgtgactgggttccccggagacggaagagctgtatggtcgcaaaat
cctaatttgagtccggtaaacgaaagtcagctgttttctatgacactttccaaaaaacttttctgggggtggtgggactg
gagccttccaagtgaaggagggtggaagaaggatgggaaaggactctctgtatgggatcattcatcgctacacac
ctgaacgtcagcagccgcgatggctccagtacagctacattttttggagaaagacttatcggcgctggatttttagg
agtctcttttatcagtttcaatttctggccaagactgttcccgatggcacagtagcagtcgccaatgcaaaaggctctc
cagtactataatcggtcctggactctctgctacttagaaacattgaacctgtagtcactttataccattgggatctgccttg
ggcgctacaagaaaaatacgggggggtggaaaaacgagacgttgattgatttattcaatgactatgccacctactgtttc
cagacgtttggggaccgtgtcaaatactggatcaccattcacaatccctatctggtggcttgcatggctacgggacag
gtctgcatgtccgggagagaaggggaatgtggcagctgtctacactgtgggacacaacctgcttaaggctcattca
aaagtctggcacaactacaacaggaatttccgcccgcacagaaaggctggctgtcgatcacgctgggatcccact
ggattgagccaaacagagcggaaagcatcgtggacatactcaagtgccagcagtcctatggtctcggtgctgggctg
gtttgccaacccgatccacggggacggggactaccagaggatgacaaaagaagctgctctccgtcctgcccgtt
tctcagaagcagagaagaacgaggtaacgagggcaccgcagacttctttgccttttctgtttggaccaacaactcaagc
ccttaaacaccatggctaaaatggggcagaatgtgtcactcaatctaagacagggtgctgaactggattaaactggaat
atggcaaccctcgaatcctgatcgctgagaacggctggttcacagacagttacgtgcaaacagaagacaccacag
ccatctacatgatgaagaatttctcaaccagggttctcaagcaataagggtggatggagtccgagtgtttggctacact
gcctggtctctcctggatggcttcaatggcaggacgcttacaacacccgcggtggactgtttatgtggacttcaacag
cgaacagagagaaagaaggcccaagtcctcggcgcattactataaacagggtcataggagaaaacgggttcacgc
tcagagaggccaccccgatctgcaggggcagtttccctgtgacttctcctggggcgacccgagtctgttcttaagcc
cgagtccgtggcttctcgcacagttcagcgacctcacctctacgtgtggaacgccactggcaaccgaatgcttca
ccgggtggaaggggtgaggctgaaaacacggcccgctcagtgacagattcatcaccatcaagaacaactcga
gatgttggaagaatgaaagtcacccacttccggttctctggactgggctcgttctccacgggcaacctgtcc
gaggatgaaccgacaagccctgagggtactacagggtgtgtggtcaccgaggggctgaagctcaacatctcgccatgg
tcacctgtactacccgacccatgccacctgggctgcccgcgcccgtgctgcacagcgggggggtggctggaccc
atccacggccaaggccttccgagactacgcagggctgtgcttccgggagctgggggacctggatgaagctctggatc
accatcaacgagcccaaccggctgagcgacgtctacaaccgcaccagcaacgacacctaccaggccgcccaca
acctgctgatcgcgacgcgctcgtgtggcacctgtacgaccgacagtagccggcgtcgacgcgggggcgctgtc

gctgtccctgcactcggactgggcccagccccccaacccctacgtggcctgcactggcaggcgccgagcgcttc
 ctgcagttcgagattgcgtggttcgcccagcccctgttcaagaccggggactaccgggtggccatgagggagtacat
 5 cgccccaagacccggcgccggctctccagctccgtgctgccccgcttcagcgacgccgagcgggcggtgtgcaa
 gggcgccgcccacttctacgcccctcaaccacttcaccaccaggttcgtgatgcacgagcagcagaacggcagccg
 ctacgactcggacagggacgtgcagttcctgcaggacatcaccgcctggcctcaccagccgcctggccgtgatg
 10 ccttggggcgagggcaagctgctgcggtggatgcggaacaactacggagacctggacgtctacatcacggccaat
 ggcacgcagcaccaggcccctgcagaacgaccagcttcgccagtactacctggagaagtacgtccaggaggctctg
 aaagcatatctgatagataaaaataaaaatcaaaggctattatgcattcaaactgactgaagaaaaatctaaaccag
 15 gtttgattcttcacctctgatttcaaagccaagtcttcaatacagttttacaacaaactaattaccagcaacggcttccc
 tctgagaacggcggtcctagatgcaatcagactcaaggaaatcccagagtgcaccgtctgcttactcctcctgcagaa
 gaagccgctgatattctttagctgctgcttctgcaccctgggttctactctcatcaattaccatcttccacagacggaaga
 20 gaagaaaatttggaaagcaaaggacttacaacacataccattaaagaaaggccacaagagagtccttagctaaa
 gtgaactatttctctgaagagtttagaaaattcactccagttccatatgctggtaacacaaaagacatacccgattgta
 cacagagtatttgagatactgtgctaaccaaggcgtgacaatcaaaacctctgcatgtggttgatgcattttccctt
 25 aagcgggtgacaatcagcgaactcagttcttgggttctaaaggaggcttcgcactgccactaggctatgagtattacctga
 cgcattgcttgtcaagttgatgagctgttcgcatcattctctagcttctttagataccaatagctactatggtaaaagttgt
 ttttaaagtcaaactctgtaaggcttcacagcagattttaaactattctttacactggatctgtgatttgcactcgtagca
 30 aggtgcttcccccttttggctcctagtggctctcaaatagaaagcaaacacatcttagggtaattctacttatctatagccaat
 cacagcactgaccacaactacacaaatccgttagctcttctccataaaacacctaatttgtgatctttaaagtaattctg
 aaatgtaaaagtagactccgtaacccatctcatggaaagatcgactaaggagagccataccagctgtgaggac
 35 aatttagtactaatctcaccgtactgcaacttctcctttagagcaggcattccttaccatttttgaagatgacatgattta
 gcatctagaacccctatctgcagtttcttctatggcttacctacatttcaagaatattgaacggaaaattcagaaagattt
 ccaagttttaaattgtgtactagcattagtgcatgatgaaatctcatttcttctgctccatcctgcacaggatgtgaaacatc
 40 cctctgtccagcaagtccaagctacctatattactcacttgatagtcaccatgggtatccagctgttattacttgctcatacc
 caggtaacccctttttattttaaataatagctccaaagtataagactagtgatgaaaaggaggtaagtcatacaaatatggaa
 ggacagattaactctggcactaagtgggaatgctgcagggttttacaggaaaacaaaattcagtcagtggtttaaagca
 45 tcctctgaggtacctggggcacaatctccacagataaggggaaagagcactgacaaagactaaacatcctaaaaa
 gacgcaatgttctacttactggccatcagaataatggcaaaggaccctatactgcttgcctctctagccaagtttcgctg
 cacatagggtgtagaatgcagcgactgaccctggatgcgattcagaatgctgatctgagtgaactagtttttatacagca
 50 ctttttaaagcctagaattcttccatctgaactgggagtttgactttttgaaattaattgtgcttaagattattcagtgattct
 aaacactggaggtagaaaactgtataccattatgcctattaattttcttgattagccaacatttaaataaccacaaagt
 ggccagtcggtgtcttcccttcaggaatttaagtcaaaggatgctgctgcctgcgatgctggcacttcataggggtgac
 55 agtttgtgtccctgcggttccacttccatccagctccctgctaattggcttgggagagccctgcacccacatgggagacc
 caaagcagatcctgctgcttccagcctgctgcggccacttggagatgaaccagtggtggaagatcaatgtctctcc

caacaattctttgaataaatttttcaaaagtcaaaataaaattctccagctcaaaaagcttagtagaaaacgatcctac
 attaaggcggttgtagtgatcccaagtgcatctacgttacaaaccaaattgagtagcaattcagtagctactagact
 5 ataaggagaaaacagccaattcaaaacaaaataccaaagtcacgtgcagttaatttgcttctggttgccaaatgttttt
 ttctcttctgcccaccactgtttacatgtactttagaagaaatttgacttttgcttcttgagaaatcactattatcaaaggc
 aattcataattacaagtggtccattgtcttaagagctcaagattatagcccttcaaacttgccaaactcctcaaatagtaga
 10 agctcctaacgaagggtttacaacatcctgttccttaggggttatattttaagtgactgtaatttacctaacaaatttaatct
 ggctatctattggaatacatgtaataattcagggttatcataaaccacttaaaaactaaagggttaagtggaagttgctgct
 ttcaaagtaacaggcttctcaggggaaaatatcaccttagcgtccacctggtactacatctcgtgtattcactgtaaccc
 15 atctttccgaacatgtctgatataatggaaacaacactagtgcttagcctctggaaatgaggccaggattttgtgattaa
 atgtctaattattccaaataaactgatttacgccaata (SEQ ID NO: 411)

[0065] The amino acid sequence of beta klotho from dog, scientific name *Canis lupus familiaris*, is provided below:

MKPGCAAGSPGNEWIFLSTDESNTHYRKTCMNHGLQRSVILSAFILLGAVPGFSGD
 GRAIWSKNPHFSPVNESQLFLYDTFPKNFFWGVGTGAFQVEGNWKTDGKGPSIW
 25 DHFIHHLKKNVNSMNSSSDSYIFLEKDLSALDFIGVSFYQFSISWPRLFPDGIAAVAN
 AKGLQYYNSLLDALVLRNIEPIVTLYHWDLPALQEKYGGWKNETITDIFNDYATYCF
 QTFGDRVKYWITIHNPYLVAVWHGYGTGMHAPGEKGNLAAVYTVGHNLIAHASKVW
 30 HNYNTNFRPYQKGLLSITLGSHWIEPNRSENMMDILKCQQSMVSVLGWFANPIHGN
 GDYPEVMKKKLLSTLPLFSEAEKNEVRGTADFFAFSFGPNNFKPQNTMAKMGQNV
 35 SLNLREVLNWKLEYGNPRILIAENGWFTDSHVKTEDTTAIYMMKNFLNQVLQAIRFD
 EIQVFGYTAWSLLDGFEWQDAYSTRRGLFYVDFNSKQKERKPKSSAYYYKQIIQEN
 GFTFKESTPDVQQGFPCDFS WGVTESVLKPKVVASSPQFSDPHLYVWNVTGNRLL
 40 HRVEGVRLKTRPAQCTDFVSIKRQLEMLARMNVTHYRFALDWPSILPTGNLSTVNR
 QALRYRCVVSESLKLSISPMVTLYYPTHAGHLGLPSPLLHSGGWLNASTARAFQDY
 AGLCFQELGDLVKLWITINEPNRLSDVYSHTSSDTYRAAHNLLIAHALVWHLYDRRY
 45 RPAQRGAVSLSLHSDWAEPANPYADSHWKAERFLQFEIAWFAEPLFKTGDYPPA
 MREYIASKNRQGLSRSTLPRFTDEERRLVKGAADFYALNHFTTRFVMHARQNGSR
 YDADRDVQFLQDITCLSSPSRLAVLPWGERKVLRWIQKNYGDVDVYITASGIDDQS
 50 LENDELKYYLEKYIQEALKAHLIDKVVKGYAFKLTEEKSKPRFGFFTSEFKAKSS
 VQLYNKLISNSGFPSENRSPRCSETQRNTECMVCLFLVQKKPLIFFSCFFSTLVLL
 55 SSITILHKRKRRIWKAKNLQHIPLKSKNSLQS (SEQ ID NO: 412)

[0066] An encoding nucleic acid sequence of dog beta klotho is provided below:

acaatcacaagctttactgaagcgttgataagacaggcgagcagttagtggaatgaagccaggctgtgcggctg
 gatctccagggaatgaatggatttctcagcaccgatgaaagcaacacacactataggaaaacaatgtgcaacca
 5 cgggctacagagatctgtcatcctgtcagcatttattctcctaggagctgttctctggattctctggagacggaagagctat
 atggctaaaaatcctcatttagtccggtaaatgaaagtcagctgttctctatgacacttttctaaaaacttttttggggc
 gttgggactggagcattcaagtgaagggaattggaagacagatggaaaaggaccctctatatgggatcatttcac
 10 cacacacaccttaaaaatgtcaacagcatgaatagttccagtgacagttacattttctggaaaaagacctatcagccc
 tggattttatcggagtttcttttatcaattttcaatttctggccaaggcttttcccgatggaatagcagcagttgccaacgc
 aaaaggctccagctactacaattctctctcgtatgctctagtaggaacattgaacctatagttactttataccattggg
 15 atttgcctttggcactacaagaaaaatgggggggtgaaaaatgaaaccataacggatatctcaatgactatgcc
 cctactgtttccagacgttcggggatcgtgtcaatactggattacaattcacaatccatatctagttgcttggcatgggta
 tgggacaggtatgcacgcgcctggagagaagggaacttagcagctgtctacactgtgggacacaacctaatcaa
 20 ggctcattcgaaagtttggcataactacaacacaaatttccgcccatatcagaagggtttgtatcaatcacgttgggat
 cccattggattgaaccaaacagatcagaaaacatgatggatatactcaaatgtcaacaatccatggttcagtgtctg
 ggtggtttgccaaccccatccatgggaatggagactatccagaagtgtgaaaaagaagttgtctccactctacccc
 25 tttctctgaagcagagaagaatgaagtgaggggcacagctgacttcttgccttttcttggacccaacaattcaagc
 cccagaacaccatggctaaaatgggacaaaatgtgtcactcaatttaagagaagtgtgaattggattaaactggaa
 tatggcaacccccgaatcttgattgtgagaatggctgggtcacagacagtcagtgtgaaaacagaagataccacagc
 30 catttacatgatgaagaatttctcaaccagggttctcaagcaataagggttgacgaaatacaagtgttggctacactgc
 ttggtctctcctggatggctttgaatggcaggatgcttactccactcgccgaggatttttatgtggatttaatagtaaaca
 aaaagaaagaaagcccaagtcttcggcatattactataaacagatcatacaagaaaatggtttactttcaagagtc
 35 caccccagatgtgcagggtcagtttccctgtgacttctcatgggggtgcaccgaatctgtccttaagcccaaagtctgg
 ctctctcccacagttcagcgaccctcacctgtacgtgtggaatgtgacaggcaacagactgttgacccgagtgaag
 gggtagggctgaagacacggccggctcaatgcacagattttgtcagcatcaaaagacaactgagatgttggcgag
 40 gatgaacgtcactcactacaggttctgtgactggccctccatccttcccacgggcaacctgtccaaggtaaccga
 caagccctgaggtactacaggtgtgtggtcagcgagtcgtgaagtcagcatctcccgatggtcacgctgtactac
 ccgacccacgcccacctgggctcccctcgccgtgtgtgcacagcgggggtggctgaacgcgtccaccgcccgc
 45 gccttccaggactatgccgggtgtgttccaggagctgggggacctggtgaagctctggatcaccatcaatgagcc
 caaccggctgagtgacgtctacagccacaccagcagcgacacctaccgggcagcgcacaacctgtgatcgccc
 acgcccgtgtgtggcacctgtacgaccggcggtaccggccggcgagcgcggggcccgtgtcgtgtccctgcactc
 50 ggactgggcgagcccggcaacccctacgccgactcgcactggaaggcgccgagcgcttctctcagttcgaaat
 cgctgtgttcggcagccgctctcaagaccggggactaccgcccggcatgaggagtagatcgctccaagaa
 caggcaggggctctcgctccaccctgccccgcttaccgacgaggagaggaggctggtcaagggcgccgccc
 55 acttctacgcgtgaaccacttaccaccagggttctgtatgcacgcgcgcagaaacggcagccgtacgacgcgg
 accgcgacgtccagttctgcaggacatcacctgcctgagctccccagccgcctggccgtctctgcccgggggga

gcgcaaggtgctcaggtggatccagaagaactacggagacgtggacgtgtacatcacggccagtggtcatcgatga
 ccagtctctggaaaatgatgagctcagaaaatactacttggagaaatacatccaggaggctctgaaagcacaccta
 5 attgataaagtcaaagtcaaaggctattatgcattcaaactgactgaagaaaaatctaaaccagatttggattcttcac
 gtctgaattcaaagctaaatcctcagttcagctttacaacaaactgatcagcaacagtggttcccttctgagaacagg
 agtcttagatgcagtgagactcaaagaaacacagagtgcatggctgtcttatttctgtgcaaaagaaaccactgatat
 10 tctttagttgttgccttctctctaccctggttctactttcatcgattaccattcttcataagcgaaagagaagaaaaatttgaa
 agcaaagaacttacaatataccattaaagtgaggccacagaaagttcttagtgaactgatcctatttctgtctgcat
 gatagaaagtctaaaaattcactccagtcctcaataactggtaacatagaagacaatttgaaacactagtagtaacca
 15 aggtgatgacaatcaaggtctctgtgtgtgtgtccaaatgaattttccattagggtgttgacatcactgaatacagtttttag
 atctgaagactaagatctagagagtaagctaggattatctgatacaatgcttcattaagttaataagctgttatccatcat
 tcttctctggcttccctctagaaataccaatagctaattatagcaacttagaaaaaagtgaacttttgctagactccatag
 20 cagaaatctaaaactcttaacactggatattcagtgattattctatcacttctaacaagggtgcttttccctttagaagatat
 acaatagggtaaatagtgctcctttatcatccattccagcactttttttccagcatagactcttaaacacattgatcctagtt
 ttttcaatagaaataaaaaatcatttagaaaacatggaattttgtgaggtctctccttgcattagatctgagtttttttaaaa
 25 aaaagacttaacttcataacccatctcatgggaagatcacaggactaagattaaggagagtttagacccatcaactg
 cctgaggagacagcactcaacctcacagtacagcaaatccttgggacaaactgacagcaatctccgcacttggat
 30 tgttgaggcagcacacaagatcttaacatacttaggaaagttaaatttctaaaaagatgtaaagttttattttattatcaa
 gtcttcaaaggaccatattattccataagacttgctctctcctgagttccactcttctgacactatgtgtatatggggacact
 caaactgcaccttgacattgcaactttggatacaattcagaatgtaaagtgttgaggactaaaactttctccactgcac
 35 cttttgaagctgggattaagtaaatacgaactgggagtttgactttttgaactctgtgcttgattattcactgtattctaaattt
 taaggaaaacctgaatgtaaaccattcataccctttcttgggttagtaaacatttaaccacccatttca (SEQ ID
 NO: 413).

40 **[0067]** The amino acid sequence of human/mouse beta klotho chimeric protein (human KLB (M1-F508)-mouse KLB
 (P507-S1043)) is provided below:

45 MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAVTGFSGDG
 RAIWSKNPNFTPVNESQLFLYDTFKNFFWIGTGALQVEGSWKKGKGPSIWDH
 FIHTHLKNVSSTNGSSDSYIFLEKDLSDFIGVSYQFSISWPRLFPDGIVTVANAK
 50 GLQYYSTLLDALVLRNIEPIVTLYHWDLPLALQEKYGGWKNDTIIDIFNDYATYCFQM
 FGDRVKYWITIHNPLYVAWHGYGTGMHAPGEKGNLAAVYTVGHNLIAHASKVWHN
 YNTHFRPHQKGWLSITLGSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDG
 55 DYPEGMRKKLFSVLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVN
 LNLREALNWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLDE

IRVFGYTAWSLLDGFEWQDAYTIRRGLFYVDFNSKQKERKPKSSAHYYKQIIRENG
 FPLKESTPDMKGRFPCDFSWGVTESVLKPEFTVSSPQFTDPHLYVWNVGTGNRLLY
 5 RVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFALDWTSLIPTGNLSKVNRRQ
 VLRYRYRCVVSEGLKLGVFPMVTLYHPTHSHLGLPLPLLSSGGWLNMTAKAFQDY
 AELCFRELGDLVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHAQVWHLYDRQ
 10 YRPVQHGAVSLSLHCDWAEPANPFVDSHWKAAERFLQFEIAWFADPLFKTGDYPS
 VMKEYIASKNQRLSSSVLPRFTAKESRLVKGTVDYFALNHFTTRFVIHKQLNTNRS
 VADRDVQFLQDITRLSSPSRLAVTPWGVVRKLLAWIRRNRYRDRDIYITANGIDDLALE
 15 DDQIRKYYLEKYVQEALKAYLIDKVKIKGYAFKLTEEKS KPRFGFFTSDFRAKSSV
 QFYSKLISSSGLPAENRSPACGQPAEDTDCTICSFLVEKKPLIFFGCCFISTLAVLLSI
 TVFHHQKRRKFQKARNLQNIPLKKGHSRVFS (SEQ ID NO:374).
 20

[0068] An encoding nucleic acid sequence of human/mouse beta klotho chimeric protein is provided below:

ATGAAGCCAGGCTGTGCGGCAGGATCTCCAGGGAATGAATGGATTTTCTTCAG
 25 CACTGATGAAATAACACACGCTATAGGAATACAATGTCCAACGGGGGATTGCA
 AAGATCTGTCATCCTGTCAGCACTTATTCTGCTACGAGCTGTTACTGGATTCTCT
 30 GGAGATGGAAGAGCTATATGGTCTAAAAATCCTAATTTTACTCCGGTAAATGAAA
 GTCAGCTGTTTCTCTATGACACTTTCCCTAAAAACTTTTTCTGGGGTATTGGGAC
 TGGAGCATTGCAAGTGGAAGGGAGTTGGAAGAAGGATGGAAAAGGACCTTCTA
 35 TATGGGATCATTTTCATCCACACACACCTTAAAAATGTCAGCAGCACGAATGGTT
 CCAGTGACAGTTATATTTTTCTGGAAAAAGACTTATCAGCCCTGGATTTTATAGG
 AGTTTCTTTTTATCAATTTTCAATTTCTGGCCAAGGCTTTTCCCCGATGGAATA
 40 GTAACAGTTGCCAACGCAAAAGGTCTGCAGTACTACAGTACTCTTCTGGACGCT
 CTAGTGCTTAGAAACATTGAACCTATAGTTACTTTATACCACTGGGATTTGCCTT
 TGGCACTACAAGAAAAATATGGGGGGTGGAAAAATGATACCATAATAGATATCT
 45 TCAATGACTATGCCACATACTGTTTCCAGATGTTTGGGGACCGTGTCAAATATTG
 GATTACAATTCACAACCCATATCTAGTGGCTTGGCATGGGTATGGGACAGGTAT
 GCATGCCCCCTGGAGAGAAGGGAAATTTAGCAGCTGTCTACACTGTGGGACACA
 50 ACTTGATCAAGGCTCACTCGAAAGTTTGGCATAACTACAACACACATTTCCGCC
 CACATCAGAAGGGTTGGTTATCGATCACGTTGGGATCTCATTGGATCGAGCCAA
 ACCGGTCGGAAAAACACGATGGATATATTCAAATGTCAACAATCCATGGTTTCTG
 55 TGCTTGGATGGTTTGGCAACCCTATCCATGGGGATGGCGACTATCCAGAGGGG

ATGAGAAAGAAGTTGTTCTCCGTTCTACCCATTTTCTCTGAAGCAGAGAAGCAT
 GAGATGAGAGGCACAGCTGATTTCTTTGCCTTTTCTTTTGGACCCAACAACCTTCA
 5 AGCCCCTAAACACCATGGCTAAAATGGGACAAAATGTTTCACTTAATTTAAGAGA
 AGCGCTGAACTGGATTAACTGGAATACAACAACCCTCGAATCTTGATTGCTGA
 GAATGGCTGGTTCACAGACAGTCGTGTGAAAACAGAAGACACCACGGCCATCT
 10 ACATGATGAAGAATTTCTCAGCCAGGTGCTTCAAGCAATAAGGTTAGATGAAA
 TACGAGTGTTTGGTTATACTGCCTGGTCTCTCCTGGATGGCTTTGAATGGCAGG
 ATGCTTACACCATCCGCCGAGGATTATTTTATGTGGATTTTAACAGTAAACAGAA
 15 AGAGCGGAAACCTAAGTCTTCAGCACACTACTACAAACAGATCATACGAGAAAA
 TGGTTTTCTTTGAAAGAGTCCACGCCAGACATGAAGGGTCGGTTCCCCTGTGA
 TTTCTCTTGGGGAGTCACTGAGTCTGTTCTTAAGCCCGAGTTTACGGTCTCCTC
 20 CCCGCAGTTTACCGATCCTCACCTGTATGTGTGGAATGTCACTGGCAACAGATT
 GCTCTACCGAGTGGAAGGGGTAAAGGCTGAAAACAAGACCATCCCAGTGCACAG
 ATTATGTGAGCATCAAAAAACGAGTTGAAATGTTGGCAAAAATGAAAGTCACCC
 25 ACTACCAGTTTGCTCTGGACTGGACCTCTATCCTTCCCCTGGCAATCTGTCCA
 AAGTTAACAGACAAGTGTTAAGGTACTATAGGTGTGTGGTGAGCGAAGGACTGA
 AGCTGGGCGTCTTCCCCATGGTGACGTTGTACCACCCAACCCACTCCCATCTC
 30 GGCCTCCCCCTGCCACTTCTGAGCAGTGGGGGGTGGCTAAACATGAACACAGC
 CAAGGCCTTCCAGGACTACGCTGAGCTGTGCTTCCGGGAGTTGGGGGACTTGG
 TGAAGCTCTGGATCACCATCAATGAGCCTAACAGGCTGAGTGACATGTACAACC
 35 GCACGAGTAATGACACCTACCGTGCAGCCCACAACCTGATGATCGCCCATGCC
 CAGGTCTGGCACCTCTATGATAGGCAGTATAGGCCGGTCCAGCATGGGGCTGT
 GTCGCTGTCTTACATTGCGACTGGGCAGAACCTGCCAACCCCTTTGTGGATTG
 40 AACTGGAAGGCAGCCGAGCGCTTCCTCCAGTTTGAGATCGCCTGGTTTGCAG
 ATCCGCTCTTCAAGACTGGCGACTATCCATCGGTTATGAAGGAATACATCGCCT
 CCAAGAACCAGCGAGGGCTGTCTAGCTCAGTCCTGCCGCGCTTACCGCGAAG
 45 GAGAGCAGGCTGGTGAAGGGTACCGTCGACTTCTACGCACTGAACCACTTCAC
 TACGAGGTTTCGTGATACACAAGCAGCTGAACACCAACCGCTCAGTTGCAGACA
 GGGACGTCCAGTTCTGCAGGACATCACCCGCCTAAGCTCGCCCAGCCGCCT
 50 GGCTGTAACACCCTGGGGAGTGCGCAAGCTCCTTGCGTGGATCCGGAGGAAC
 TACAGAGACAGGGATATCTACATCACAGCCAATGGCATCGATGACCTGGCTCTA
 GAGGATGATCAGATCCGAAAGTACTACTTGGAGAAGTATGTCCAGGAGGCTCT
 55 GAAAGCATATCTCATTGACAAGGTCAAATCAAAGGCTACTATGCATTCAAACCTG
 ACTGAAGAGAAATCTAAGCCTAGATTTGGATTTTTCACCTCTGACTTCAGAGCTA

AGTCCTCTGTCCAGTTTTACAGCAAGCTGATCAGCAGCAGTGGCCTCCCCGCT
 GAGAACAGAAGTCCTGCGTGTGGTCAGCCTGCGGAAGACACAGACTGCACCAT
 5 TTGCTCATTCTCGTGGAGAAGAAACCACTCATCTTCTTCGGTTGCTGCTTCATC
 TCCACTCTGGCTGTACTGCTATCCATCACCGTTTTTCATCATCAAAAGAGAAGAA
 AATTCCAGAAAGCAAGGAACTTACAAAATATACCATTGAAGAAAGGCCACAGCA
 10 GAGTTTTTCAGCTGA (SEQ ID NO:375)

[0069] The amino acid sequence of mouse/human beta klotho chimeric protein (mouse KLB (M1-F506) - human KLB(S509-S1044)) is provided below:

MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSVLSAFVLLRAVTGFSG
 DGKAIWDKKQYVSPVNPSQLFLYDTFPKNFSWGVGTGAFQVEGSWKTDGRGPSI
 20 WDRYVYSHLRGVNGTDRSTDYIFLEKDLLALDFLGVSFYQFSISWPRLFPNGTVA
 AVNAQGLRYYRALLDSLVLRNIEPIVTLYHWDLP LTLQEEYGGWKNATMIDLFNDYA
 TYCFQTFGDRVKYWITIHNPYLVAWHGFGTGMHAPGEKGNLTAVYTVGHNLKAHS
 25 KVWHNYDKNFRPHQKGWLSITLGSHWIEPNRTDNMEDVINCQHSMSSVLGWFAN
 PIHGDGDYPEFMKTGAMIPEFSEAEKEEVRGTADFFAFSFGPNNFRPSNTVVKMG
 QNVSLNLRQVLNWKLEYDDPQILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAI
 30 KFDEIRVFGYTAWTLLDGFQWQDAYTTRRGLFYVDFNSEQKERKPKSSAHYYKQII
 QDNGFSLKESTPDVQGGQFPCDFSWGVTESVLKPESVASSPQFSDPHLYVWNATG
 NRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFALDWASVLPTGNLS
 35 AVNRQALRYRCVVSEGLKLGISAMVTLYYPHTAHLGLPEPLLHADGWLNPSTAEA
 FQAYAGLCFQELGDLVKLWITINEPNRLSDIYNRSGNDTYGAAHLLVAHALAWRLY
 DRQFRPSQRGAVSLSLHADWAEPANPYADSHWRAAERFLQFEIAWFAEPLFKTGD
 40 YPAAMREYIASKHRRGLSSSALPRLTEAERRLLKGTVDFCALNHFTTRFVMHEQLA
 GSRYSDDRDIQFLQDITRLSSPTRLAVIPWGVVRKLLRWVRRNYGDMDIYITASGIDD
 45 QALEDRLRKYYLGKYLQEV LKAYLIDKVRIGYYAFKLAEEKSKPRFGFFTSDFKA
 KSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGCCFFSTLV
 LLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS (SEQ ID NO:376)

[0070] An encoding nucleic acid sequence of mouse/human beta klotho chimeric protein is provided below:

ATGAAGACAGGCTGTGCAGCAGGGTCTCCGGGGAATGAATGGATTTTCTTCAG
 55 CTCTGATGAAAGAAACACACGCTCTAGGAAAACAATGTCCAACAGGGCACTGCA

AAGATCTGCCGTGCTGTCTGCGTTTGTCTGCTGCGAGCTGTTACCGGCTTCTC
 CGGAGACGGGAAAGCAATATGGGATAAAAAACAGTACGTGAGTCCGGTAAACC
 5 CAAGTCAGCTGTTCCCTCTATGACACTTTCCTAAAAACTTTTCCTGGGGCGTTG
 GGACCGGAGCATTTCAGTGGAAGGGAGTTGGAAGACAGATGGAAGAGGACC
 CTCGATCTGGGATCGGTACGTCTACTCACACCTGAGAGGTGTCAACGGCACAG
 10 ACAGATCCACTGACAGTTACATCTTCTGGAAAAAGACTTGTTGGCTCTGGATTT
 TTTAGGAGTTTCTTTTTATCAGTTCTCAATCTCCTGGCCACGGTTGTTTCCCAAT
 GGAACAGTAGCAGCAGTGAATGCGCAAGGTCTCCGGTACTACCGTGCACTTCT
 15 GGACTIONGCTGGTACTTAGGAATATCGAGCCCATTGTTACCTTGTAACATTGGGA
 TTTGCCTCTGACGCTCCAGGAAGAATATGGGGGCTGGAAAAATGCAACTATGAT
 AGATCTCTTCAACGACTATGCCACATACTGCTTCCAGACCTTTGGAGACCGTGT
 20 CAAATATTGGATTACAATTCACAACCCTTACCTTGTTGCTTGGCATGGGTTTGGC
 ACAGGTATGCATGCACCAGGAGAGAAGGGAAATTTAACAGCTGTCTACACTGTG
 GGACACAACCTGATCAAGGCACATTCGAAAGTGTGGCATAACTACGACAAAAAC
 25 TTCCGCCCTCATCAGAAGGGTTGGCTCTCCATCACCTTGGGGTCCCATTGGATA
 GAGCCAAACAGAACAGACAACATGGAGGACGTGATCAACTGCCAGCACTCCAT
 GTCCTCTGTGCTTGGATGGTTCGCCAACCCCATCCACGGGGACGGCGACTACC
 30 CTGAGTTCATGAAGACGGGCGCCATGATCCCCGAGTTCTCTGAGGCAGAGAAG
 GAGGAGGTGAGGGGCACGGCTGATTTCTTTGCCTTTTCCTTCGGGCCCAACAA
 CTTCAGGCCCTCAAACACCGTGGTGAAAATGGGACAAAATGTATCACTCAACTT
 35 AAGGCAGGTGCTGAACTGGATTAACTGGAATACGATGACCCTCAAATCTTGAT
 TTCGGAGAACGGCTGGTTCACAGATAGCTATATAAAGACAGAGGACACCACGG
 CCATCTACATGATGAAGAATTTCTAAACCAGGTCTTCAAGCAATAAAATTTGA
 40 TGAAATCCGCGTGTTTGGTTATACGGCCTGGACTCTCCTGGATGGCTTTGAGTG
 GCAGGATGCCTATACGACCCGACGAGGGCTGTTTTATGTGGACTTTAACAGTGA
 GCAGAAAGAGAGGAAACCCAAGTCCTCGGCTCATTACTACAAGCAGATCATACA
 45 AGACAACGGCTTCTCTTTAAAAGAGTCCACGCCAGATGTGCAGGGCCAGTTTCC
 CTGTGACTTCTCCTGGGGTGTCACTGAATCTGTTCTTAAGCCCGAGTCTGTGGC
 TTCGTCCCCACAGTTCAGCGATCCTCATCTGTACGTGTGGAACGCCACTGGCAA
 50 CAGACTGTTGCACCGAGTGGAAGGGGTGAGGCTGAAAACACGACCCGCTCAAT
 GCACAGATTTTGTAAACATCAAAAAACAACCTTGAGATGTTGGCAAGAATGAAAGT
 CACCCACTACCGGTTTGCTCTGGATTGGGCCTCGGTCCTTCCCACTGGCAACC
 55 TGTCCGCGGTGAACCGACAGGCCCTGAGGTACTACAGGTGCGTGGTCAGTGA
 GGGGCTGAAGCTTGGCATCTCCGCGATGGTCACCCTGTATTATCCGACCCACG

CCCACCTAGGCCTCCCCGAGCCTCTGTTGCATGCCGACGGGTGGCTGAACCCA
 TCGACGGCCGAGGCCTTCCAGGCCTACGCTGGGCTGTGCTTCCAGGAGCTGG
 5 GGGACCTGGTGAAGCTCTGGATCACCATCAACGAGCCTAACCGGCTAAGTGAC
 ATCTACAACCGCTCTGGCAACGACACCTACGGGGCGGCGCACAACTGCTGGT
 GGCCACGCCCCTGGCCTGGCGCCTCTACGACCGGCAGTTCAGGCCCTCACAG
 10 CGCGGGGGCCGTGTGCTGTGCTGCACGCGGACTGGGCGGAACCCGCCAAC
 CCCTATGCTGACTCGCACTGGAGGGCGGCCGAGCGCTTCCTGCAGTTCGAGAT
 CGCCTGGTTCGCCGAGCCGCTCTTCAAGACCGGGGACTACCCCGCGGCCATG
 15 AGGGAATACATTGCCTCCAAGCACCGACGGGGGCTTTCCAGCTCGGCCCTGCC
 GCGCCTCACCGAGGCCGAAAGGAGGCTGCTCAAGGGCACGGTCGACTTCTGC
 GCGCTCAACCACTTCACCACTAGGTTCGTGATGCACGAGCAGCTGGCCGGCAG
 20 CCGCTACGACTCGGACAGGGACATCCAGTTTCTGCAGGACATCACCCGCCTGA
 GCTCCCCCACGCGCCTGGCTGTGATTCCCTGGGGGGTGCGCAAGCTGCTGCG
 GTGGGTCCGGAGGAACTACGGCGACATGGACATTTACATCACCGCCAGTGGCA
 25 TCGACGACCAGGCTCTGGAGGATGACCGGCTCCGGAAGTACTACCTAGGGAA
 GTACCTTCAGGAGGTGCTGAAAGCATACCTGATTGATAAAGTCAGAATCAAAGG
 CTATTATGCATTCAAACCTGGCTGAAGAGAAATCTAAACCCAGATTTGGATTCTTC
 ACATCTGATTTTAAAGCTAAATCCTCAATACAATTTTACAACAAAGTGATCAGCA
 GCAGGGGCTTCCCTTTTGAGAACAGTAGTTCTAGATGCAGTCAGACCCAAGAAA
 35 ATACAGAGTGCAGTGTCTGCTTATTCCTTGTGCAGAAGAAACCACTGATATTCCT
 GGGTTGTTGCTTCTTCTCCACCCTGGTTCTACTCTTATCAATTGCCATTTTCAA
 AGGCAGAAGAGAAGAAAGTTTTGGAAAGCAAAAACTTACAACACATACCATTA
 40 AAGAAAGGCAAGAGAGTTGTTAGCTAG (SEQ ID NO:377)

[0071] 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.

[0072] 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.

[0073] The terms "FGF19-like signaling" and "induces FGF19-like signaling," when applied to a binding protein such as 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).

[0074] 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.

[0075] The terms "FGF21-like signaling" and "induces FGF21-like signaling," when applied to a binding protein such as 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).

[0076] 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.

[0077] 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. 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 aspects, the binding proteins (e.g., antibodies) may bind with a K_D of $1-2 \times 10^{-9}$ M.

[0078] The term "antibody" and "immunoglobulin" or "Ig" are used interchangeably herein, and is used in the broadest

sense and specifically covers, for example, individual anti-beta klotho monoclonal antibodies (including agonist, antagonist, neutralizing antibodies, full length or intact monoclonal antibodies), anti-beta klotho antibody compositions with polypeptopic 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 variable 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). The specific molecular antigen that 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 *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., antigens-binding fragments such as beta *klotho* binding fragments) of any of the above, which refers a portion of an antibody heavy or light chain polypeptide that retains 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-binding 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 *antigen* (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.

[0079] 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. 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.
[0080] Binding proteins, such as anti-beta klotho antibodies, 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.

atgcggagcgggtgtgtggtgggtccacgtatggatcctggccggcctctggctggccgtggc
cgggcgccccctcgcttctcggaacgcggggcccccacgtgcactacggctggggcgaccca
 tccgctgcggcacctgtacacctccggccccccacgggctctccagctgcttctgcgcatc
 cgtgccgacggcgctcgtggactgcgcgcggggccagagcgcgcacagtttgctggagatcaa
 ggcagtcgctctgcggaaccgtggccatcaagggcgctgcacagcgtgcggtacctctgcatgg
 gcgcccgaacggcaagatgcaggggctgcttcagtactcggaggaagactgtgctttcgaggag
 gagatccgcccagatggctacaatgtgtaccgatccgagaagcaccgcctcccgggtctccct
 gagcagtgccaaacagcggcagctgtacaagaacagaggctttcttccactctctcatttcc
 tgcccatgctgccccatgggtcccagaggagcctgaggacctcagggggccacttggaatctgac
 atgttctcttcgccccctggagaccgacagcatggacccatttgggcttgtcaccggactgga
 ggccgtgaggagtcccagctttgagaagtaa

(SEQ ID NO:303)

[0081] The amino acid sequence of full length FGF19 is provided; the amino acids that make up the signal sequence are underlined:

mrsgcvvvhvhwilaglwlavagRPLAFSDAGPHVHYGWGDPRLRLHLYTSGPHGLSSCFLRI
 RADGVVDCARGQSAHSLLEIKAVALLRTVAIKGVH SVRYLCMGADGKMQGLLQYSEEDCAFEE
 EIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLRGHLESD
 MFSSPLETDSMDPFGLVTGLEAVRSPSFEK

(SEQ ID NO:304)

[0082] 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
 5 atc cct gac tcc agt cct ctc ctg caa ttc ggg ggc caa gtc cgg
 cag cgg tac ctc tac aca gat gat gcc cag cag aca gaa gcc cac
 ctg gag atc agg gag gat ggg acg gtg ggg ggc gct gct gac cag
 10 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
 15 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
 20 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
 25 (SEQ ID NO:305).

[0083] An amino acid sequence of a full length FGF21 is provided below; the amino acids that make up the signal sequence are underlined:

30 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
 35 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
 40 A P R G P A R F L P L P G L P P A P 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).

[0084] A nucleic acid sequence also encoding a full length FGF21 is provided; the nucleotides encoding the signal sequence are underlined:

50

55

atggactcggacgagaccgggttcgagcactcaggactgtgggtttctgtgctggctgggtcttctgctgggagcc
tgccaggcaCACCCCATCCCTGACTCCAGTCCTCTCCTGCAATTCGGGGGCCAAGTCCGGCAGCGGTACCTCTAC
 ACAGATGATGCCCAGCAGACAGAAGCCCACCTGGAGATCAGGGAGGATGGGACGGTGGGGGGCGCTGCTGACCAG
 AGCCCCGAAAGTCTCCTGCAGCTGAAAGCCTTGAAGCCGGGAGTTATTCAAATCTTGGGAGTCAAGACATCCAGG
 TTCTGTGCCCAGCGGCCAGATGGGGCCCTGTATGGATCGCTCCACTTTGACCCTGAGGCCTGCAGCTTCCGGGAG
 CTGCTTCTTGAGGACGGATACAATGTTTACCAGTCCGAAGCCCACGGCCTCCCGCTGCACCTGCCAGGGAACAAG
 TCCCCACACCGGGACCCTGCACCCCGAGGACCAGCTCGCTTCCTGCCACTACCAGGCCTGCCCCCGCACTCCCG
 GAGCCACCCGGAATCCTGGCCCCCAGCCCCCGATGTGGGCTCCTCGGACCCTCTGAGCATGGTGGGACCTTCC
 CAGGGCCGAAGCCCCAGCTACGCTTCCTGA

(SEQ ID NO:428).

[0085] An amino acid sequence also encoding a full length FGF21 is provided; the amino acids encoding the signal sequence are underlined:

mdsdetgfehsglwsvlagllgacqaHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIR
 EDGTVGGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEA
 CSFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPE
 PPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS

(SEQ ID NO:429)

[0086] 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 FGFR α IIIc) is provided below:

atgtggagctggaagtgcctcctcttctgggctgtgctggtcacagcc
 acactctgcaccgctagggcgtccccgaccttgctgaacaagcccag
 5 ccttggggagccccctgtggaagtggagtccttcctgggtccaccccgg
 gacctgctgcagcttcgctgtcggctgcgggacgatgtgcagagcatc
 aactggctgcgggacggggtgcagctggcggaaagcaaccgcacccg
 10 catcacaggggaggaggtggaggtgcaggactccgtgcccgcagact
 ccggcctctatgcttgcgtaaccagcagccccctcgggcagtgacacca
 cctacttctccgtcaatgtttcagatgctctcccctcctcggaggatga
 15 tgatgatgatgatgactcctcttcagaggagaaagaaacagataaca
 ccaaaccaaaccgtatgcccgtagctccatattggacatcaccagaaa
 agatggaaaagaaattgcatgcagtgccggctgccaagacagtgaag
 20 ttcaaatgcccttccagtgggacaccaaaccacaactgcgctggttg
 aaaaatggcaaagaattcaaacctgaccacagaattggaggctacaa
 ggtccgttatgccacctggagcatcataatggactctgtggtgccctc
 25 tgacaagggcaactacacctgcattgtggagaatgagtacggcagca
 tcaaccacacataaccagctggatgtcgtggagcgggtcccctcaccggc
 ccattcctgcaagcaggggttgcccgccaacaaaacagtggccctgggt
 30 agcaacgtggagttcatgtgtaagggtgtacagtgacccgcagccgcac
 atccagtggctaaagcacatcgaggtgaatgggagcaagattggccc
 agacaacctgccttatgtccagatcttgaagactgctggagttaatac
 35 caccgacaaagagatggaggtgcttcacttaagaaatgtctcctttga
 ggacgcaggggaggtatacgtgcttgggcgggtaactctatcggactctc
 ccattactctgcatgggtgaccgttctggaagccctggaagagagggc
 40 ggcagtgatgacctcgcacctgtacctggagatcatcatctattgcac
 aggggccttcctcatctcctgcatgggtggggtcggatcatcgtctacaa
 gatgaagagtgggtaccaagaagagtgacttccacagccagatggctg
 45 tgcacaagctggccaagagcatccctctgcgcagacaggtaaacagtg
 tctgctgactccagtgcatccatgaactctgggggttcttctgggttcggc
 50 catcacggctctcctccagtgggactcccatgctagcaggggtctctg
 agtatgagcttcccgaagaccctcgtcgggagctgcctcgggacagac
 tgggtcttaggcaaaccctgggagagggctgctttgggcaggtggtgt
 55 tggcagaggctatcgggctggacaaggacaaaccacaaccgtgtgacc

aaagtggctgtgaagatggtgaagtcggacgcaacagagaaagactt
 gtcagacctgatctcagaaatggagatgatgaagatgatcgggaagc
 5 ataagaatatcatcaacctgctgggggcctgcacgcaggatggtccct
 tgtatgtcatcgtggagtatgcctccaagggcaacctgcgggagtacc
 tgcaggccccggaggccccccagggtggaatactgctacaaccccagc
 10 cacaaccagaggagcagctctcctccaaggacctggtgtcctgcgcc
 taccaggtggcccgaggcatggagtatctggcctccaagaagtgcata
 caccgagacctggcagccaggaatgtcctggtgacagaggacaatgt
 15 gatgaagatagcagactttggcctcgcacgggacattcaccacatcga
 ctactataaaaagacaaccaacggccgactgcctgtgaagtggatgg
 cacccgaggcattatttgaccggatctacaccaccagagtgatgtgt
 20 ggtcttttcggggtgctcctgtgggagatcttcactctgggcggctcccc
 ataccccggtgtgcctgtggaggaacttttcaagctgctgaaggaggg
 tcaccgcatggacaagcccagtaactgcaccaacgagctgtacatgat
 25 gatgcgggactgctggcatgcagtgccctcacagagaccaccttcaa
 gcagctggtggaagacctggaccgcatcgtggccttgacctccaacca
 30 ggagtacctggacctgtccatgcccctggaccagtactccccagctt
 tcccgacaccggagctctacgtgctcctcaggggaggattccgtctt
 ctctcatgagccgctgcccgaggagccctgcctgccccgacaccagc
 35 ccagcttgccaatggcggactcaaacgccgctga.

(SEQ ID NO:307)

40 **[0087]** The amino acid sequence of human FGFR1c (GenBank Accession Number NP 075598) (also designated
 FGFR α IIIc) is provided below:

MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPG
 DLLQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGL
 45 YACVTSSPSGSDTTYFSVNVSDALPSSSEDDDDDDSSSEEKETDNTKPNR
 MPVAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEF
 KPDHRIGGYKVRYATWSIIMDSVVP SDKGN YTCIVENEYGSINHTYQLDV
 50 VERSPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNG
 SKIGPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSI
 GLSHHSAWLTVLEALEERPAVMTSPLYLEIIIIYCTGAFLISCMVGSVIVY
 55 KMKSGTKKSDFHSQMAVHKLAKSIPLRRQVTVSADSSASMNSGVLLVRPS
 RLSSSGTPMLAGVSEYELPEDPRWELPRDRLVLGKPLGEGCFGQVVLAEA

IGLDKDKPNRVTKVAVKMLKSDATEKDLSDLISEMEMMKMIGKHKNIIN
 LLGACTQDGPLYVIVEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQLS
 5 SKDLVSCAYQVARGMEYLASKKCIHRDLAARNVLVLTEDNVMKIADFGL
 ARDIHHIDYYKKTNGRLPVKWMapeALFDRIYTHQSDVWSFGVLLWEI
 FTLGGSPYPGVPVEELFKLLKEGHRMDKPSNCTNELYMMMRDCWHAVP
 10 SQRPTFKQLVEDLDRIVALTSNQEYLDLSMPLDQYSPSPDTRSSTCSSG
 EDSVFSHEPLPEEPCLPRHPAQLANGGLKRR .

(SEQ ID NO:308)

[0088] 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
 20 LQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGLYA
 CVTSSPSGSDTTYFSVNVSDALPSSSEDDDDDDSSSEEKETDNTKPNRMP
 VAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEFKPD
 25 HRIGGYKVRYATWSIIMDSVVPSPDKGNYTCIVENEYGSINHTYQLDVVER
 SPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKI
 GPDNLPHYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLS
 30 HHSAWLTVLEALEERPAMTSPLY . (SEQ ID NO:309)

[0089] An example of an extracellular region of FGFR1c (α IIIc) is:

RPSPTLPEQAQPWGAPVEVESFLVHPGDLQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADS
 GLYACVTSSPSGSDTTYFSVNVSDALPSSSEDDDDDDSSSEEKETDNTKPNRMPVAPYWTSPEKMEKKLHAVPAA
 KTVKFKCPSSGTPNPTLRWLKNGKEFKPDHRIGGYKVRYATWSIIMDSVVPSPDKGNYTCIVENEYGSINHTYQLD
 40 VVERSPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKIGPDNLPHYVQILKTAGVNTTDK
 EMEVLHLRNVSFEDAGEYTCLAGNSIGLSHHSAWLTVLEALEERPAMTSPLYE .

(SEQ ID NO:427)

[0090] An example of an extracellular region of FGFR1c (β IIIc) is:

RPSPTLPEQDALPSSSEDDDDDDSSSEEKETDNTKPNPVAPYWTSPEKMEKKLHAVPAAKTV
 50 KFKCPSSGTPNPTLRWLKNGKEFKPDHRIGGYKVRYATWSIIMDSVVPSPDKGNYTCIVENEY
 GSINHTYQLDVVERSPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGS

KIGPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLSHHSAWLTVLE
ALEERPAVMTSPLYLE.

5

(SEQ ID NO: 426)

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[0091] 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.

[0092] 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.

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[0093] 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:

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atggtcagctggggctcgtttcatctgcctggctcgtggtcacccatggcaaccttgctccctggc
ccggccctccttcagtttagttgaggataccacattagagccagaagagccaccaaccaa
accaaattctctcaaccagaagtgtacgtggctgcgccaggggagtcgctagaggtgcgctgc
ctggtgaaagatgccgccgtgatcagttggactaaggatgggggtgcacttggggcccaacaa
taggacagtgccttattggggagttacttgcagataaagggcgccacgcctagagactccggcc
tctatgcttgtactgccagtaggactgtagacagtgaacttgggtacttcatgggtgaatgtc
acagatgccatctcatccggagatgatgaggatgacaccgatgggtgcggaagattttgtcag
tgagaacagtaacaacaagagagcaccatactggaccaacacagaaaagatggaaaagcggc
tccatgctgtgcctgcggccaacactgtcaagtttcgctgcccagccggggggaacccaatg
ccaaccatgcggtggctgaaaaacgggaaggagtttaagcaggagcatcgcatggaggcta
caaggtacgaaaccagcactggagccctcattatggaaagtgtggtcccatctgacaagggaa
attatacctgtgtagtgaggagaatgaatacgggtccatcaatcacacgtaccacctggatgtt
gtggagcgatcgccctaccggccccatcctccaagccggactgccggcaaatgcctccacagt
ggtcggaggagacgtagagtttgtctgcaaggtttacagtgatgccagccccacatccagt
ggatcaagcacgtggaaaagaacggcagtaatacgggccccgacgggctgcctacctcaag
gttctcaaggccgcccgtgttaacaccacggacaaaagagattgaggttctctatatattcggaa
tgtaacttttgaggacgctggggaatatacgtgcttggcgggtaattctattgggatatcct
ttcactctgcatggttgacagttctgccagcgccctggaagagaaaaggagattacagcttcc
ccagactacctggagatagccatttactgcataggggtcttcttaatcgccctgtatgggtggt

50

55

aacagtcacccctgtgccgaatgaagaacacgaccaagaagccagacttcagcagccagccgg
 ctgtgcacaagctgaccaaacgtatccccctgaggagacaggttaacagtttcggctgagtcc
 5 agctcctccatgaactccaacacccccgctgggtgaggataacaacacgcctctcttcaacggc
 agacaccccccatgctggcaggggtctccgagtatgaacttccagaggacccaaaatgggagt
 ttccaagagataagctgacactgggcaagccccctgggagaaggttgctttgggcaagtggtc
 10 atggcggaagcagtgagggaattgacaaagacaagcccaaggaggcggtcaccgtggccgtgaa
 gatgttgaaagatgatgccacagagaaaagacctttctgatctgggtgtcagagatggagatga
 tgaagatgattgggaaacacaagaatatcataaatcttcttggagcctgcacacaggatggg
 15 cctctctatgtcatagttgagtatgcctctaaaggcaacctccgagaatacctccgagccccg
 gaggccacccgggatggagtactcctatgacattaaccgtgttcctgaggagcagatgacct
 tcaaggacttgggtgtcatgcacctaccagctggccagaggcatggagtacttggcttcccaa
 20 aatgtattcatcgagatttagcagccagaaatgttttggtaacagaaaacaatgtgatgaa
 aatagcagactttggactcgccagagatatcaacaatatagactattacaaaaagaccacca
 atgggcgggcttccagtcgaagtggatggctccagaagccctgtttgatagagtatacactcat
 25 cagagtgatgtctggtccttcgggggtgttaatgtgggagatcttcactttagggggctcgcc
 ctaccagggattcccgtggaggaactttttaagctgctgaaggaaggacacagaatggata
 agccagccaactgcaccaacgaactgtacatgatgatgagggactgttggcatgcagtggcc
 30 tcccagagaccaacgttcaagcagttggtagaagacttggatcgaattctcactctcacaac
 caatgaggaataacttggacctcagccaacctctcgaacagtattcacctagttaccctgaca
 caagaagttcttgttcttcaggagatgattctgttttttctccagacccccatgccttacgaa
 35 ccatgccttcctcagtatccacacataaacggcagtgtaaacaatga

(SEQ ID NO:310)

40 **[0094]** The amino acid sequence of human FGFR2c is provided below; the amino acids that make up the signal
 sequence are underlined:

mvswwgrficlvvvvmtatlslaRPSFSLVEDTTLEPEEPPTKYQISQPEVYVAAPGESLEVRC
 45 LLKDAAVISWTKDGVHLGPNNRTVLIGEYLQIKGATPRDSGLYACTASRTVDSETWYFMVNV
 TDAISSGDEDDTDGAEDFVSENSNNKRAPYWTNTEKMEKRLHAVPAANTVKFRCPAGGNPM
 PTMRWLKNGKEFKQEHRIGGYKVRNQHWSLIMESVVP SDKGNYTCVVENEYGSINHTYHLDV
 50 VERSPHRPILQAGLPANASTVVGGDVEFVCKVYSDAQPHIQWIKHVEKNGSKYGPDGLPYLK
 VLKAAGVNTTDKEIEVLYIRNVTFEDAGEYTCLAGNSIGISFHSAWLTVLPAPGREKEITAS
 PDYLEIAIYCIGVFLIACMVVTVILCRMKNNTTKPDFSSQPAVHKLTKRIPLRQVTVSAES
 55 SSSMNSNTPLVRITTRLSSSTADTPMLAGVSEYELPEDPKWEFPRDKLTLGKPLGEGCFGQVV
 MAEAVGIDKDKPKEAVTVAVKMLKDDATEKDLSDLVSEMEMMKMIGKHKNI INLLGACTQDG

PLYVIVEYASKGNLREYLRARRPPGMEYSYDINRVPEEQMTFKDLVSCTYQLARGMEYLASQ
 KCIHRDLAARNVLVTENNVMKIADFGGLARDINNIDYYKKTNGRLPVKWMAPEALFDRVYTH
 5 QSDVWSFGVLMWEIFTLGGSPYPGIPVEELFKLLKEGHRMDKPANCTNELYMMMRDCWHAVP
 SQRPTFKQLVEDLDRILTLTTNEEYLDLSQPLEQYSPSYPDTRSSCSSGDDSVFSPDMPYE
 PCLPQYPHINGSVKT
 10 (SEQ ID NO:311)

[0095] 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:

atgggcgccccctgctgcgccctcgcgctctgctggtggccgtggccatcgtggccggcgccctc
 ctcgagtccttggggacggagcagcgctcgtggggcgagcggcagaagtcccgggcccag
 20 agccccggccagcaggagcagttggtcttcggcagcggggatgctgtggagctgagctgtccc
 ccgccccgggggtggtcccatggggcccactgtctgggtcaaggatggcacagggtggtgcc
 ctcgagcgtgtcctgggtggggccccagcggctgcaggtgctgaatgcctcccacgaggact
 25 ccggggcctacagctgccggcagcggctcacgcagcgcgtactgtgccacttcagtgtgcgg
 gtgacagacgctccatcctcgggagatgacgaagacggggaggacgaggctgaggacacagg
 tgtggacacagggggccccttactggacacggccccgagcggatggacaagaagctgctggccg
 30 tgccggcccgccaacaccgtccgcttcgctgcccagccgctggcaacccccactccctccatc
 tcctggctgaagaacggcagggagttccgcggcgagcacccgattggaggcatcaagctgcg
 gcatcagcagtgaggacctggtcatggaaagcgtggtgccctcggaccgcggcaactacacct
 35 gcgtcgtggagaacaagtttggcagcatccggcagacgtacacgctggacgtgctggagcgc
 tccccgcaccggcccatcctgcaggcggggctgccggccaaccagacggcggtgctgggcag
 cgacgtggagttccactgcaaggtgtacagtgcgcacagccccacatccagtgggtcaagc
 40 acgtggaggtgaatggcagcaaggtgggccccggacggcacaccctacgttacgtgctcaag
 acggcggggcgctaacaccaccgacaaggagctagaggttctctccttgccacaacgtcacctt
 45 tgaggacgccccgggagtacacctgcctggcgggcaattctattgggttttctcatcactctg
 cgtggctggtggtgctgccagccgaggaggagctggtggaggctgacgaggcgggcagtggtg
 tatgcaggcatcctcagctacgggggtgggcttcttccctgttcacatcctgggtggtggcggtgt
 50 gacgctctgccgcctgcgcagcccccccaagaaaggcctggggtccccccaccgtgcacaaga
 tctcccgttcccgtcgaagcgacaggtgtccctggaggtccaacgcgtccatgagctccaac
 acaccactggtgcgcacgcgaaggtgtcctcaggggagggccccacgctggccaatgtctc
 55 cgagctcgagctgcctgccgacccccaaatgggagctgtctcgggccccggctgaccctgggca

agccccttggggagggctgcttcggccaggtggcatggcggaggccatcggcattgacaag
 gaccgggcccgaagcctgtcaccgtagccgtgaagatgctgaaagacgatgccactgacaa
 5 ggacctgtcggacctggtgtctgagatggagatgatgaagatgatcgggaaacacaaaaaca
 tcatcaacctgctgggcgctgcacgcagggcgggccctgtacgtgctgggtggagtacgcg
 gccaagggtaacctgcgggagtttctgcgggcgcgggcgcccccgggcctggactactcctt
 10 cgacacctgcaagccgccccgaggagcagctcaccttcaaggacctggtgtcctgtgcctacc
 aggtggccccggggcatggagtacttggcctcccagaagtgcacccacagggacctggctgcc
 cgcaatgtgctgggtgaccgaggacaacgtgatgaagatcgagacttcgggctggccccggga
 15 cgtgcacaacctcgactactacaagaagacaaccaacggccggctgcccgatgaagtggatgg
 cgctgaggccttgtttgaccgagctctacactcaccagagtgcgtctggtcctttggggtc
 ctgctctgggagatcttcacgtggggggctccccgtaccccgcatccctgtggaggagct
 20 cttcaagctgctgaaggagggccaccgcatggacaagcccgcgaactgcacacacgacctgt
 acatgatcatgcgggagtgctggcatgccgcgccctcccagaggcccaccttcaagcagctg
 gtggaggacctggaccgtgtccttaccgtgacgtccaccgacgagtacctggacctgtcggc
 25 gcctttcgagcagtagtactccccgggtggccaggacacccccagctccagctcctcaggggacg
 actccgtgtttgcccacgacctgctgcccccgggccccaccagcagtgggggctcgcgagc
 30 tga

(SEQ ID NO:312)

35 **[0096]** The amino acid sequences of human FGFR3c is provided below; the amino acids that make-up the signal
 sequence are underlined:

mgapacalalcvavaivagassESLGTEQRVVGRAAEVPGPPEPGQQEQLVFGSGDAVELSCP
 40 PPGGGPMGPTVWVKDGTGLVPSERVLVGPQRLQVLNASHEDSGAYSCRQRLTQRVLCHFQSVR
 VTDAPSSGDDDEGEDEAEDTGVDTGAPYWTRPERMDKKLLAVPAANTVRFRCPAAGNPTPSI
 SWLKNGREFRGEHRIGGIKLRHQWQSLVMESVVPVSDRGNYTCVVENKFGSIRQTYTLDVLER
 45 SPHRPILQAGLPANQTAVLGSDVEFHCKVYSDAQPHIQWLKHVEVNGSKVGPDPGTPYVTVLK
 TAGANTTDKELEVLSLHNVTFEDAGEYTCLAGNSIGFSHSAWLVLPAEEELVEADEAGSV
 YAGILSYGVGFFLFILVVAAVTLCRLRSPKKGLGSPTVHKISRFPPLKRQVSLESNASMSSN
 50 TPLVRIARLSSGEGPTLANVSELELPADPKWELSRARLTGKPLGEGCFGQVVMMAEAIGIDK
 DRAAKPVTAVKMLKDDATDKDLSDLVSEMEMMKMIGKHKNIINLLGACTQGGPLYVLVEYA
 AKGNLREFLRARRPPGLDYSFDTCKPPEEQLTFKDLVSCAYQVARGMEYLASQKCIHRDLAA
 55 RNVLVTEDNVMKIADFGGLARDVHNLDDYKKTNGRLPVKWMPEALFDRVYTHQSDVWSFGV
 LLWEIFTLGGSPYPGIPVEELFKLLKEGHRMDKPANCTHDLYMIMRECWHHAAPSQRPTFKQL

VEDLDRVLTVTSTDEYLDLSAPFEQYSPGGQDTPSSSSSGDDSVFAHDL LPPAPPSSGGSR T
(SEQ ID NO:313)

5

[0097] 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 nucleic acid sequence of human FGFR4 is provided below:

10 atgcggctgctgctggccctggtgggggtcctgctgagtgtgcctgggcctccagtcttgct
cctggaggcctctgaggaagtggagcttgagccctgcctggctcccagcctggagcagcaag
agcaggagctgacagtagcccttgggcagcctgtgcgtctgtgctgtgggcgggctgagcgt
15 ggtggccactggtacaaggagggcagtcgcctggcacctgctggccgtgtacggggctggag
gggcccctagagattgccagcttctctacctgaggatgctggccgctacctctgcctggcac
gaggctccatgatcgtcctgcagaatctcaccttgattacaggtgactccttgacctccagc
20 aacgatgatgaggaccccaagtcccatagggacccctcgaataggcacagttacccccagca
agcacccctactggacacacccccagcgcctgggagaagaaactgcatgcagtacctgcgggga
acaccgtcaagttccgctgtccagctgcaggcaacccccacgcccaccatccgctggcttaag
25 gatggacaggcctttcatggggagaaccgcattggaggcattcggctgcgccatcagcactg
gagtctcgtgatggagagcgtggtgccctcggaccgcggcacatacacctgcctggtagaga
acgctgtgggcagcatccgctataactacctgctagatgtgctggagcgggtccccgcaccgg
30 cccatcctgcaggccgggctcccggccaacaccacagccgtggtgggcagcgacgtggagct
gctgtgcaaggtgtacagcgatgccagccccacatccagtggctgaagcacatcgtcatca
acggcagcagcttcggagccgacgggtttcccctatgtgcaagtcctaaagactgcagacatc
35 aatagctcagagggtggaggtcctgtacctgcggaacgtgtcagccgaggacgcaggcgagta
cacctgcctcgcaggcaattccatcggcctctcctaccagtctgcctggctcacgggtgctgc
cagaggaggacccccacatggaccgcagcagcgcccaggccaggtatacggacatcatcctg
40 tacgcgtcgggctccctggccttggtgtgctcctgctgctggccgggctgtatcaggggca
ggcgctccacggccggcacccccgcccggccgcccactgtgcagaagctctcccgttccctc
tggcccgacagttctccctggagtcaggctcttccggcaagtcaagctcatccctggtacga
45 ggcgtgcgtctctcctccagcggccccgccttgctcgccggcctcgtgagtctagatctacc
tctcgacccactatgggagttcccccgggacaggctggtgcttgggaagcccctaggcgagg
50 gctgctttggccaggtagtagctgcagaggcctttggcatggacctgcccggcctgaccaa
gccagcactgtggccgtcaagatgctcaaagacaacgcctctgacaaggacctggccgacct
ggtctcggagatggaggtgatgaagctgatcgccgcacacaagaacatcatcaacctgcttg
55 gtgtctgcacccaggaaggggccctgtacgtgatcgtggagtgcgccgccaagggaacctg
cgggagttcctgcggggcccgggccccccaggccccgacctcagccccgacggctcctcggag

cagtgaggggcccgtctctccttcccagtcctggtctcctgcgcctaccaggtggcccgaggca
 tgcagtatctggagtcgccggaagtgtatccaccgggacctggctgcccgcaatgtgctggtg
 5 actgaggacaatgtgatgaagattgctgactttgggctggcccgcggtccaccacattga
 ctactataagaaaaccagcaacggccgcctgcctgtgaagtggatggcgcccgaggccttgt
 ttgaccgggtgtacacacaccagagtgacgtgtggtcttttgggatcctgctatgggagatc
 10 ttcaccctcgggggctccccgtatcctggcatcccggtggaggagctgttctcgctgctgcg
 ggagggacatcggatggaccgacccccacactgccccccagagctgtacgggctgatgcgtg
 agtgctggcacgcagcgccctcccagaggcctaccttcaagcagctggtggaggcgctggac
 15 aaggtcctgctggccgtctctgaggagtacctcgacctccgcctgaccttcggaccctattc
 cccctctggtggggacgccagcagcacctgctcctccagcgattctgtcttcagccacgacc
 ccctgccattgggatccagctccttcccccttcgggtctgggggtgcagacatga

(SEQ ID NO:314)

[0098] 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
 GGHWYKEGSRLAPAGRVRGWRGRLEIASFLPEDAGRYLCLARGSMIVLQNLTLITGDSLTS
 30 NDDEDPKSHRDPSNRHSYPQQAPYWTHPQRMEKKLHAVPAGNTVKFRCPAAGNPTPTIRWLK
 DGQAFHGENRIGGIRLRHQHWSLVMSVVPDRGTYTCLVENAVGSIRYNYLLDVLERSPHR
 PILQAGLPANTTAVVGSDELCKVYSDAQPHIQWLKHIVINGSSFGADGFPYVQVLKTADI
 35 NSSEVEVLYLRNVSAEDAGEYTCLAGNSIGLSYQSAWLTVLPEEDPTWTAAPEARYTDIIL
 YASGSLALAVLLLLLAGLYRGQALHGRHPRPPATVQKLSRFPLARQFSLES GSSGKSSSSLVR
 GVRLSSSGPALLAGLVSLDLPLDPLWEFPRDRLVLGKPLGEGCFGQVVRAEAFGMDPARPDQ
 40 ASTVAVKMLKDNASDKDLADLVSEMEVMKLI GRHKNIINLLGVCTQEGPLYVIVECAAKGNL
 REFLRARRPPGPDLS PDGPRSSEGPLSFPVLVSCAYQVARGMQYLESRKCIHRDLAARNVLV
 TEDNVMKIADFGLARGVHHIDYYKKT SNGRLPVKWM APEALFDRVYTHQSDVWSFGILLWEI
 45 FTLGGSPYPGIPVEELFSLREGHRMDRPPHCPPELYGLMRECWHAAPSQRPTFKQLVEALD
 KVLLAVSEEYLDLRLTFGPYSPSGGDASSTCSSSDSVFSDPLPLGSSSFPPFGSGVQT

(SEQ ID NO:315)

[0099] 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.

[0100] 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)).

[0101] 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 (k_1) to dissociation (k_{-1}) of an antibody to a monovalent antigen (k_1/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 k_1 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.

[0102] 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 K_d 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. 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 (K_d) 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).

[0103] 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., Stahl 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.

[0104] 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. An antibody that binds to beta klotho, as defined in the claims has a dissociation constant (K_d) 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 0.1 nM. 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).

[0105] 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.

[0106] 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] "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.

[0111] 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).

[0112] 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. The fusion protein comprises a beta klotho antibody VH region, VL region, VH CDR (three VH CDRs), and/or VL CDR (three VL CDRs), as defined in the claims wherein

the fusion protein binds to a beta klotho epitope, a beta klotho fragment and/or a beta klotho polypeptide.

[0113] 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.

[0114] 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) or 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.

[0115] The term "host" as used herein refers to an animal, such as a mammal (e.g., a human).

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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)).

[0120] "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. Acad. 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).

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

	<u>Exemplary</u>	<u>IMGT</u>	<u>Kabat</u>	<u>AbM</u>	<u>Chothia</u>	<u>Contact</u>
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

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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 Biomedica* 4 : 39-51 (2010).

[0129] 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.

[0130] 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.

[0131] 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. An antibody of the invention 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. The antibodies of the invention are agonistic anti-beta klotho antibodies, including antibodies that induce FGF19-like signaling and/or FGF21-like signaling.

[0132] "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 BIAcore™-2000 or a BIAcore™-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 BIAcore™-2000 or a BIAcore™-3000 (BIAcore, Inc., Piscataway, NJ), or the OctetQK384 sytem (ForteBio, Menlo Park, CA).

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] 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**AL**AGGPSVF
 5 LFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
 SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
 TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
 10 MHEALHNHYTQKSLSLSPGK

(SEQ ID NO:316)

Such a variant sequence may be used in humanized heavy chain constructs such as shown below for a humanized
 15 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:

mdmrvpaqllgllllwlrgarc**QVQLQQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQA**
 20 **PGQGLEWIGWIYPGDGSTKYNEKFKGKATITRDTSA**TAYMELSSLRSEDTAVYFCARSDYY
GSRSFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
 ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
 25 HTCPPCPAPALAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH
 NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
 VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
 30 LTVDKSRWQQGNVFSCSV**MHEALHNHYTQKSLSLSPGK**

(SEQ ID NO:317)

35 **[0140]** A "light chain constant region" includes kappa and lambda constant regions. An exemplary kappa constant
 region is provided below:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK
 40 DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 318)

45 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:

mdmrvpaqllgllllwlrgarc**DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYVYMHWF**
 50 **QQKPGQP**PKLLIY**LASYLESGVPDRFSGSGGTDF**TLTISSV**QAEDVAVYYCQHSRDLTFP**
GGGTKLE**IK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
 55 ESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

(SEQ ID NO: 319)

[0141] 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. As described herein, the beta klotho variant or anti-beta klotho antibody variant at least retains beta klotho or anti-beta klotho antibody functional activity, respectively. As described herein, an anti-beta klotho antibody variant binds beta klotho and/or is antagonistic to beta klotho activity. As described herein, an anti-beta klotho antibody variant binds beta klotho and/or is agonistic to beta klotho activity. As described herein, 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.

[0142] 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.

[0143] "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.

[0144] "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)).

[0145] "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.

[0146] 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.

[0147] 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.

[0148] Exemplary 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.

[0149] 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.

[0150] "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 (DNAS-TAR) 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.

[0151] 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.

[0152] 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. A beta klotho epitope may be a three-dimensional surface feature of a beta klotho polypeptide. Alternatively, a beta klotho epitope may be linear feature of a beta klotho polypeptide. Generally an antigen has several or many different epitopes and may react with many different antibodies.

[0153] 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.

[0154] "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 FGF receptor such as FGFR1c, FGFR2c, FGFR3c, or FGFR4c).

[0155] "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.

[0156] 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.

[0157] 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. 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.

[0158] 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.

[0159] 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.

[0160] "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.

[0161] 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, 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.

[0162] 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, piroprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxipinac, 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 tenoxicam), 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-1 β , 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, p75TNFR1gG (ENBRELE[®]) or p55TNFR1gG (LENERCEPT[®]), soluble IL-13 receptor (sIL-13), and also TNF α 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- β 1a (AVONEX); interferon- β 1b (BETASERON[®]); copaxone; hyperbaric oxygen; intravenous immunoglobulin; clabiribine; and antibodies to or antagonists of other human cytokines

or growth factors (e.g., antibodies to CD40 ligand and CD80).

[0163] "Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are non-toxic 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.

[0164] 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.

[0165] 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.

[0166] A "sterile" formulation is aseptic or free from all living microorganisms and their spores.

[0167] "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).

[0168] 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.

[0169] "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.

[0170] 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."

[0171] 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.

[0172] 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).

[0173] 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.

[0174] 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.

[0175] 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.

[0176] 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). As described herein, 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*.

[0177] 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.

[0178] 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, dyspnea, 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).

[0179] 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.

[0180] "Substantially all" 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%.

[0181] 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. A therapeutic agent refers to an anti-beta klotho antibody of the invention. A therapeutic agent may also refer to an agent other than an antibody provided herein. A therapeutic agent may be 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.

[0182] 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.

[0183] 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.

[0184] 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.

[0185] 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. A diagnostic agent is a substance that is conjugated to an anti-beta klotho antibody of the invention, that when administered to a subject or contacted to a sample from a subject aids in the diagnosis a beta klotho-mediated disease.

[0186] 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).

[0187] 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.

[0188] 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.

[0189] 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. As described herein 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. As described herein, 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.

[0190] 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. 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.

[0191] 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.

[0192] "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.

[0193] 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 acid 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 be 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.

[0194] 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.

[0195] 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

[0196] Binding proteins such as antibodies that bind to beta klotho (e.g., human and/or cyno beta klotho) are described. 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 invention 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.

[0197] Described herein are antibodies that bind to a beta klotho polypeptide, a beta klotho polypeptide fragment, beta klotho peptide, or a beta klotho epitope. The anti-beta klotho antibodies bind to the extracellular domain (ECD) of beta klotho. Also described antibodies that competitively block an anti-beta klotho antibody provided herein from binding to a beta klotho polypeptide. The anti-beta klotho antibodies described 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 of the invention.

[0198] 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 as defined in the claims. 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 as defined in the claims. Also described 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.

[0199] Methods of using the anti-beta klotho antibodies of the invention 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 erythematous-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

[0200] 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.

[0201] Provided herein are antibodies as defined in the claims 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.

[0202] 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 as defined in the claims. Accordingly, the isolated antibody or functional fragment thereof provided herein comprises three heavy chain CDRs and three light chain CDRs from the antibody designated 5H23 as shown in Tables 1.

[0203] The antibody designated 5H23 comprises a VH sequence that is SEQ ID NO:25 and a VL sequence that is SEQ ID NO:26.

[0204] The antibody designated 1C17 comprises a VH sequence that is SEQ ID NO:51 and a VL sequence that is SEQ ID NO:52.

[0205] The antibody designated 1D19 comprises a VH sequence that is SEQ ID NO:77 and a VL sequence that is SEQ ID NO:78.

[0206] The antibody designated 2L12 comprises a VH sequence that is SEQ ID NO:103 and a VL sequence that is SEQ ID NO:104.

[0207] The antibody designated 3L3 comprises a VH sequence that is SEQ ID NO:129 and a VL sequence that is SEQ ID NO:130.

[0208] The antibody designated 3N20 comprises a VH sequence that is SEQ ID NO:155 and a VL sequence that is SEQ ID NO:156.

[0209] The antibody designated 4P5 comprises a VH sequence that is SEQ ID NO:181 and a VL sequence that is SEQ ID NO:182.

[0210] The antibody designated 5C23 comprises a VH sequence that is SEQ ID NO:207 and a VL sequence that is SEQ ID NO:208.

[0211] The antibody designated 5F7 comprises a VH sequence that is SEQ ID NO:233 and a VL sequence that is SEQ ID NO:234.

[0212] 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	GYTFTSY-DIN (SEQ ID NO:1)	SYDIN (SEQ ID NO:12)	GYTFTSY (SEQ ID NO:13)	TSYDIN (SEQ ID NO:18)	GYTFTSYDIN (SEQ ID NO:1)
	VH CDR2	WIYPGDG-STKYNEK-FKG (SEQ ID NO:2)	WIYPGDG-STKYNEK-FKG (SEQ ID NO:2)	PGDG (SEQ ID NO:14)	WIGWIYPGDG (SEQ ID NO:19)	WIYPGDG (SEQ ID NO:24)
	VH CDR3	SDYYGSRSFAY (SEQ ID NO:3)	SDYYGSRSFAY (SEQ ID NO:9)	DYYGSRSFAY (SEQ ID NO:15)	ARSDYYGSRSFAY (SEQ ID NO:20)	SDYYGSRSFAY (SEQ ID NO:3)
VL CDR Seq.	VL CDR1	RASKSVSTSGYVMH (SEQ ID NO:4)	RASKSVSTSGYVMH (SEQ ID NO:4)	SKSVSTSGYVMH (SEQ ID NO:16)	STSGYVMHWN (SEQ ID NO:21)	RASKSVSTSGYVMH (SEQ ID NO:4)
	VL CDR2	LASYLES (SEQ ID NO:5)	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)	SRDLTF (SEQ ID NO:17)	QHSRDLTF (SEQ ID NO:23)	QHSRDLTFP (SEQ ID NO:6)
VH Sequence:						
QVQLQQSGPELVKPGALVKISKASGYTFTSYDINWVKQRPQGGLWIGWIYPGDGSKTYNEKFKGKATLTADKSSRTAYMQLSSLTSENSAVYFCARSDYYGSRSFAYWGQGLTVTSA (SEQ ID NO: 25)						
VL Sequence:						
DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYVMHWNQKPGQPPKLLIYLASYLESGLVPARFSGSGGTDFTLNHPVEEEDAAIYYCQHSRDLTFPFGGGTKLEIK (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	YINYDGNSTYPSLKN (SEQ ID NO:28)	INYDGN (SEQ ID NO:34)	YINYDGNSTYPSLKN (SEQ ID NO:28)	YDG (SEQ ID NO:40)	WMGYINYDGN (SEQ ID NO:45)	YINYDGN (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: QVQLQESGPGLVKPSQSLTCSVTGYSTGYWNWIRQFPGNKLEWMGYINYDGNSTYPSLKNRISITRDTSKNQFLKLSVTPEDTATYYCARKGAYYSNYD SFDWVGTTVTSS (SEQ ID NO:51)							
VL Sequence: DIKMTQSPSSMYASLGERVTITCKASQDINSYLSWVQKPKGSPKTLIYRANRLVDGVPFRFSGSGGQDYSLTISSEYEDMGIYYCLQYDEFPFTGSGTKLEIK (SEQ ID NO:52)							

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	WI- YPGDSSTKF- NENFKD (SEQ ID NO: 54)	IYPGDSST (SEQ ID NO: 60)	WI- YPGDSSTKF- NENFKD (SEQ ID NO: 54)	PGDS (SEQ ID NO: 66)	WIGWIYPGDSSTK (SEQ ID NO:71)	WIYPGDSSTK (SEQ ID NO: 76)
	VH CDR3	SDYYGSR- FTY (SEQ ID NO:55)	ARSDYYGSRSTY (SEQ ID NO:61)	SDYYGSR- FTY (SEQ ID NO:55)	DYYGSRST (SEQ ID NO:67)	ARSDYYGSRST (SEQ ID NO:72)	SDYYGSRSTY (SEQ ID NO:55)
VL CDR Seq.	VL CDR1	RASKSVST- GYSYMH (SEQ ID NO: 56)	KSVSTSGYSY (SEQ ID NO:62)	RASKSVST- GYSYMH (SEQ ID NO: 56)	SKSVSTSGYSY (SEQ ID NO:68)	STSGYSYMHY (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	QHSRELPTY (SEQ ID NO: 58)	QHSRELPTY (SEQ ID NO:58)	QHSRELPTY (SEQ ID NO: 58)	SRELPTY (SEQ ID NO:69)	QHSRELPTY (SEQ ID NO:75)	QHSRELPTY (SEQ ID NO: 58)
VH Sequence: QVQPESGPVLKPGALVKISKASGYTFTRYDINWMKQRFQGQLEWIGWIYPGDSSTKFNENFKDKATLTADKSSSTAYMQLSSLTSENSTVYFCARSDYYGSR FTYWGQGLTVTSA (SEQ ID NO:77)							
VL Sequence: DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHYQQKPGQPPKLLIYLASNLESGLVPARFSGSGGTDFTLNHPVVEEDAATYYCQHSRELPTYTFGGGTKL 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	WI- YPGDDSTKY NEKFKG (SEQ ID NO: 80)	IYPGDDST (SEQ ID NO: 86)	WI- YPGDDSTKY NEKFKG (SEQ ID NO: 80)	PGDD (SEQ ID NO: 92)	WIGWIYPGDDSTK (SEQ ID NO:97)	WIYPGDDSTK (SEQ ID NO: 102)
	VH CDR3	SDYYGSR- FVY (SEQ ID NO:81)	ARSDYYGSRFVY (SEQ ID NO:87)	SDYYGSR- FVY (SEQ ID NO:81)	DYYGSRFV (SEQ ID NO:93)	ARSDYYGSRFV (SEQ ID NO:98)	SDYYGSRFVY (SEQ ID NO:81)
VL CDR Seq.	VL CDR1	RASKSVST- GYSYLH (SEQ ID NO:82)	KSVSTSGYSY (SEQ ID NO:88)	RASKSVST- GYSYLH (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: QVQLQSGPELVKPGALVKISCKASGYTFTRYDINWVKRPGQGLEWIGWIYPGDDSTKYNEKFKGKATLTADKSSSTAYMQLSSTSENSAVYFCARSDYYGSRFVYWGQGTLTVSA (SEQ ID NO: 103)							
VL Sequence: DIVLTQSPASLPVSLGQRATISCRASKSVSTSGYSYLHWYQQKPGQPPKLLIYLASNLESQVPARFSGSGSGTDFTLNHPHVEEDAATYYCQHSGELPYTFGGGTKLEIK (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	WIYPGDGSPKYDEK-FKG (SEQ ID NO:106)	IYPGDGSP (SEQ ID NO:112)	WIYPGDGSPKYDEK-FKG (SEQ ID NO:106)	PGDG (SEQ ID NO:118)	WIGWIYPGDGSPK (SEQ ID NO:123)	WIYPGDGSPK (SEQ ID NO:128)
	VH CDR3	SDYYGSRFSFY (SEQ ID NO:107)	ARSDYYGSRFSFY (SEQ ID NO:113)	SDYYGSRFSFY (SEQ ID NO:107)	DYYGSRFSV (SEQ ID NO:119)	ARSDYYGSRFSV (SEQ ID NO:124)	SDYYGSRFSFY (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)
	VLCDR3	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:							
QVQRPQESGPQLV/KPGTLVKISKASGYTFTSYDINWWKQRPQGQGLEWIGWIYPGDGSPKYDEKFGKATLTADKSSSTAYMQLSSLTSENSAVYFCARSDYYGSRFSFYWGQGLTVTUSA (SEQ ID NO:129)							
VL Sequence:							
DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYVHWYQQKPGQPKLLIYLASNLESVGPAPRFGSGRGTDFTLNIHPVEEDAATYYCQHSGELPYTFGGGTKLEIK (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	EIYPRSGNTYYNEK-FKG (SEQ ID NO:132)	IYPRSGNT (SEQ ID NO:138)	EIYPRSGNTYYNEK-FKG (SEQ ID NO:132)	PRSG (SEQ ID NO:144)	WIGEYPRSGNTY (SEQ ID NO:149)	EIYPRSGNTY (SEQ ID NO:154)
	VH CDR3	HWDGVLDYFDY (SEQ ID NO:133)	ARHWDGVLDY-FDY (SEQ ID NO:139)	HWDGVLDYFDY (SEQ ID NO:133)	WDGVLDYFDY (SEQ ID NO:145)	ARHWDGVLDYFDY (SEQ ID NO:150)	HWDGVLDYFDY (SEQ ID NO:133)
VL CDR Sequences	VL CDR1	KSSQSLLNSGNQKNY-LA (SEQ ID NO:134)	QSLNSGNQKNY (SEQ ID NO:140)	KSSQSLLNSGNQKNY-LA (SEQ ID NO:134)	SQSLLNSGN-QKNY (SEQ ID NO:146)	LNSGNQKNY-LAWY (SEQ ID NO:151)	KSSQSLLNSGNQKNY-LA (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	LNDHSPFT (SEQ ID NO:136)	LNDHSPFT (SEQ ID NO:136)	LNDHSPFT (SEQ ID NO:136)	DHSPFT (SEQ ID NO:147)	LNDHSPFT (SEQ ID NO:153)	LNDHSPFT (SEQ ID NO:136)
VH Sequence: QVQLQESGAELARPGASVKLSCKVSGYIFTNYGISWVKQRTGQGLEWIGEYPRSGNTYYNEKFGKATLTADMSSSTAYMDLRSLTSEDSAVYFCARHWDGVLDYFDYWGQGTSLTVSS (SEQ ID NO:155)							
VL Sequence: DIVMTQSPSSLSVSGAEKVTMSCKSSQSLLNSGNQKNYLAWYQQKPGQPPKLLIYGASTRESGVPRFTGSGSGTDFTLTISSVQAEDLAVYYCLNDHSPFTFGAGTKLELK (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	WIYPGDDSTKYNEK-FKG (SEQ ID NO:158)	IYPGDDST (SEQ ID NO:164)	WIYPGDDSTKYNEK-FKG (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)	STSGYSYMHY (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)
	VLCDR3	HHSGLPYT (SEQ ID NO:162)	HHSGLPYT (SEQ ID NO:162)	HHSGLPYT (SEQ ID NO:162)	SGELPY (SEQ ID NO:173)	HHSGLPY (SEQ ID NO:179)	HHSGLPYT (SEQ ID NO:162)
VH Sequence:							
QVQLQQSGPELVKPGALVKISKASGYTFTRYDINWVKRPQGQGLEWIGWIYPGDDSTKYNEKFGKATLTADKSSSTAYMQLSSLTSENSAVYFCARSDYYGSRSFVYWGQGLTVVSA (SEQ ID NO:181)							
VL Sequence:							
DILLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHYQQKPGQPPKLLIYLASNLESGLVPARFSGRSGTDFTLNIHPVEEEDAATYYCHHSGLPYTFGGGTKLEIK (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	WIYPGDGSKYNEK-FEG (SEQ ID NO: 184)	IYPGDGST (SEQ ID NO:190)	WIYPGDGSKYNEK-FEG (SEQ ID NO:184)	PGDG (SEQ ID NO:196)	WIGWIYPGDGSK (SEQ ID NO:201)	WIYPGDGSK (SEQ ID NO:206)
	VH CDR3	SDYYGSRFSVY (SEQ ID NO:185)	ARSDYYGSRFSVY (SEQ ID NO:191)	SDYYGSRFSVY (SEQ ID NO:185)	DYYGSRFSV (SEQ ID NO:197)	ARSDYYGSRFSV (SEQ ID NO:202)	SDYYGSRFSVY (SEQ ID NO:185)
VL CDR Seq.	VLCDR1	RASKSVSTSGYSYM (SEQ ID NO:186)	KSVSTSGYSY (SEQ ID NO:192)	RASKSVSTSGYSYM (SEQ ID NO:186)	SKSVSTSGYSY (SEQ ID NO:198)	STSGYSYMHY (SEQ ID NO:203)	RASKSVSTSGYSYM (SEQ ID NO:186)
	VLCDR2	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)
	VLCDR3	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:							
QVQPGESGPGLVKPGALVKISKASGYTFTRYDINWKKRPGQGLEWIGWIYPGDGSKYNEKFEKGATLTADKSSSTAYMQLSSLTSENSAVYFCARSDYYGSRSF							
VYWGQGGTLTVSA (SEQ ID NO:207)							
VL Sequence:							
DIVLTQSPDLSLTSLGQRATISCRASKSVSTSGYSYMHYQQKPGQPPKLLIYLASNLESQVPAFSGSGGTDFTLNIHPVEEEDAATYYCOHSRELPYTFGGGKTL							
EIK (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	WIYPGDI STKYNEKFKG (SEQ ID NO:210)	IYPGDI ST (SEQ ID NO:216)	WIYPGDI STKYNEKFKG (SEQ ID NO:210)	PGDI (SEQ ID NO:222)	WIGWIYPGDI STK (SEQ ID NO:227)	WIYPGDI STK (SEQ ID NO:232)
	VH CDR3	SDYYGSR SFVY (SEQ ID NO:211)	ARSDYYGSR SFVY (SEQ ID NO:217)	SDYYGSR SFVY (SEQ ID NO:211)	DYYGSR SFV (SEQ ID NO:223)	ARSDYYGSR SFV (SEQ ID NO:228)	SDYYGSR SFVY (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)	STSGYSYMHY (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	QHSRELPTY (SEQ ID NO:214)	QHSRELPTY (SEQ ID NO:214)	QHSRELPTY (SEQ ID NO:214)	SRELPTY (SEQ ID NO:225)	QHSRELPTY (SEQ ID NO:231)	QHSRELPTY (SEQ ID NO:214)
VH Sequence: QVQPGESGP ELVKPGALVKISCKASGYTFTRYDINWKQRPQGGLWIGWIYPGDI STKYNEKFKGKATLTADKSSSTAYMQLNSLTSENSAVYFCARSDYYGSRSF VYWGQGTLVTVSA (SEQ ID NO:233)							
VL Sequence: DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHYQQKPGQPPKLLIYLASNLESVGPAREFSGSGGTDFTLNIHPVEEEDAATYYCQHSRELPTYFGGGTKV 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	YINYGGSNYNPSLKN (SEQ ID NO:236)	INYGGSN (SEQ ID NO:242)	YINYGGSNYNPSLKN (SEQ ID NO:236)	YGG (SEQ ID NO:248)	WMGYINYGGSN (SEQ ID NO:253)	YINYGGSN (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: QVQLQESGPGLVKPSQSLSLTCSVTGYSTGYWNWIRQFPGNKLEWMGYINYGGSNYNPSLKNRISITRDTSKNQFFLKLTSTTDTATYYCARRGAYYSNYD SFDVWGTGTTVTSS (SEQ ID NO:259)							
VL Sequence: DIKMTQSPSPMYASLGERVTITCKASQDINSYLSWFGQKPGKSPKTLIYRANRLVDGVPSRFGSGSGGDYSLTISSEYEEMGIYCLQYDEFPYTFGGGKLEIK (SEQ ID NO:260)							

[0213] Antibodies described herein may comprise a VH region or VH domain. Antibodies described herein may also comprise a VL region or VL chain. Antibodies described herein may have a combination of (i) a VH domain or VH region; and/or (ii) a VL domain or VL region.

[0214] An antibody described herein comprises or consists of six CDRs, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in Tables 2-10. An antibody described herein can comprise less than six CDRs. As described herein the antibody may comprise or consist 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. As described herein, the antibody may comprise or consist 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, the antibody described herein may comprise 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.

[0215] Antibodies described herein comprise one or more (e.g., one, two or three) VH CDRs listed in Tables 1-10. Antibodies described herein may also comprise one or more (e.g., one, two or three) VL CDRs listed in Tables 1-10. Antibodies described herein may 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, the antibodies described herein may 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. The antibodies described herein may 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. The antibodies described herein may 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. The antibodies described herein may 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. The antibodies described herein may 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. The antibodies described herein may 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. The antibodies described herein may 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. The antibodies described herein may 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.

[0216] Antibodies described herein may comprise a heavy chain variable (VH) region comprising: (1) a VH CDR1 having an amino acid sequence of selected 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 selected 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 selected 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 selected 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 selected 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 selected 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.

[0217] Antibodies described herein may comprise a heavy chain variable (VH) region comprising: (1) a VH CDR1 having an amino acid sequence of selected 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 selected 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 selected 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.

[0218] Antibodies described herein may comprise a light chain variable (VL) region comprising: (1) a VL CDR1 having an amino acid sequence of selected 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 selected 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 selected 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.

[0219] Also described 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, described 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,

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), 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 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 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) 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), 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 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) and a VL CDR2 (SEQ ID NOS: 5, 11, 22, 31, 37, 48, 57, 63, 74, 83, 89, 100, 109, 115, 126, 135, 14

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 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) 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,

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.

[0220] 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.

[0221] In certain embodiments, an antibody of the present invention 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.

[0222] In certain embodiments, an antibody of the present invention 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.

[0223] In certain embodiments, an antibody of the present invention 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.

[0224] 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

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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 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), VL FR1 (SEQ ID NOS:289, 290 and 382-384), 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), a VH FR4 (SEQ ID NO:288), VL FR2 (SEQ ID NOS:291, 292 and 385-392), 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 FR2 (SEQ ID NOS:281, 282, and 283), a VH FR3 (SEQ ID NOS:284, 285, 286, 287 and 379-381), a VL FR1 (SEQ ID NOS:289, 290 and 382-384), VL FR2 (SEQ ID NOS:291, 292 and 385-392), 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 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), a VL FR1 (SEQ ID NOS:289, 290 and 382-384), VL FR2 (SEQ ID NOS:291, 292 and 385-392), VL FR3 (SEQ ID NOS:293, 294, 295 and 393-404) and a VL FR4 (SEQ ID NO:296 and 405-407); or any combination thereof of the VH FRs (SEQ ID NOS: 278, 279, 280, 378, 281, 282, 283, 284, 285, 286, 287, 379-381 and 288) and VL FRs (SEQ ID NOS: 289, 290, 382-384, 291, 292, 385-392, 293, 294, 295, 393-404, 296, 405-407) listed in Table 19.

[0225] In yet another aspect, antibodies are described 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 described herein, including those in Tables 1-10. Thus, as a specific example, the antibodies that are described 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.

[0226] In still yet another aspect, antibodies are described herein that bind to a region, including an epitope, of human beta klotho or cyno beta klotho. For example, 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, 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. The antibody of the present invention binds to a region of human beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:297. As still another example, an antibody provided herein binds to a region of cyno beta klotho comprising amino acid residues 657 to 703 of SEQ ID NO:299.

[0227] In another aspect, antibodies are described herein that bind to a specific epitope of human beta klotho. For example, 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, 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. 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. 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. 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. 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. 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. 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, 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

[0228] 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

[0229] 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).

[0230] 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)).

[0231] 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.

[0232] 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)).

[0233] 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).

[0234] 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.

[0235] 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.

[0236] 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).

[0237] As described herein, 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).

[0238] As described herein, 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)

[0239] 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.

[0240] 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).

[0241] 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).

[0242] 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).

[0243] 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

[0244] 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.

[0245] 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.

[0246] 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.

[0247] 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.

[0248] 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 fragments, F(ab')₂ fragments, disulfide-linked Fvs (sdFv), Fd fragments, Fv fragments, diabody, triabody, tetrabody and minibody.

[0249] 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.

[0250] 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, Rosenberg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994).

4. Humanized Antibodies

[0251] 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.

[0252] 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).

[0253] 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.

[0254] 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).

[0255] 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.

[0256] 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).

[0257] 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).

[0258] 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).

[0259] 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).

[0260] 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).

[0261] The "human engineering" method involves altering a 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

[0262] 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).

[0263] 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).

[0264] 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).

[0265] 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).

[0266] 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 CDR1, of the non-human antibody may be retained.

6. Bispecific Antibodies

[0267] Bispecific antibodies are monoclonal antibodies that have binding specificities for at least two different antigens. As described herein, bispecific antibodies may be human or humanized antibodies. One of the binding specificities may be for beta klotho and the other may be for any other antigen. One of the binding specificities may be for beta klotho, and the other may be for another surface antigen expressed on cells expressing beta klotho and a FGF receptor (e.g., FGFR1c, FGFR2c, FGFR3c, FGFR4). 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).

[0268] 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 Cuellar, *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

[0269] 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. The dimerization domain may comprise (or consist 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. A multivalent antibody may comprise (or consist of) three to about eight antigen binding sites. A multivalent antibody may comprise (or consist 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

[0270] 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)).

[0271] 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

[0272] The present disclosure encompasses non-immunoglobulin binding agents that specifically bind to the same epitope as an anti-beta klotho antibody disclosed herein. As described herein, a non-immunoglobulin binding agent is identified as an agent that displaces or is displaced by an anti-beta klotho antibody of the present disclosure in a competitive 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 γ -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

[0273] As described herein, 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.

[0274] Antibodies of the present invention may be 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.

[0275] 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. The substitution, deletion or insertion may include 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. The substitution may be 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.

[0276] 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.

[0277] 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).

[0278] 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.

[0279] 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, as described herein, 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. As described herein, 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. As described herein, 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.

[0280] 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).

[0281] An anti-beta klotho antibody molecule of the present disclosure may be 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

[0282] As described herein, 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.

[0283] Phage display is a widespread 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).

[0284] 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).

[0285] 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).

[0286] 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.

[0287] 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.

[0288] 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.

[0289] For review of *in vitro* affinity maturation methods, see, e.g., Hoogenboom, *Nature Biotechnology* 23: 1105-1116, 2005 and Quiroz and Sinclair, *Revista Ingenieria Biomedica* 4: 39-51, 2010 and references therein.

2. Modifications of Anti-Beta Klotho Antibodies

[0290] Covalent modifications of anti-beta klotho antibodies 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.

[0291] Other types of covalent modification of the anti-beta klotho antibody 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.

[0292] 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).

[0293] Also described herein are fusion proteins comprising an antibody provided herein that binds to a beta klotho antigen and a heterologous polypeptide. The heterologous polypeptide to which the antibody is fused is useful for targeting the antibody to cells having cell surface-expressed beta klotho.

[0294] Also described herein are panels of antibodies that bind to a beta klotho antigen. 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. The panels may 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

[0295] 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 Archaeobacteria 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.

[0296] 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 Escherichia 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.

[0297] 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

[0298] The present disclosure also provides conjugates comprising an anti-beta klotho antibodies of the present invention covalently bound by a synthetic linker to one or more non-antibody agents.

[0299] A variety of radioactive isotopes are available for the production of radioconjugated antibodies. Examples include At²¹¹, ¹⁴Am, ¹⁴C, ¹⁴Y, ¹⁴Re, ¹⁴Sm, ¹⁴Bi, ¹⁴P, ¹⁴Pb and radioactive isotopes of Lu. When the conjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example ¹⁴C or ¹⁴Am, 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.

[0300] Antibodies of the present invention may be 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.

[0301] Such diagnosis and detection can be 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 isothiocyanate, 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 (¹³¹I, ¹²⁵I, ¹²³I, and ¹²¹I), carbon (¹⁴C), sulfur (³⁵S), tritium (³H), indium (¹¹⁵In, ¹¹³In, ¹¹²In, and ¹¹¹In), technetium (⁹⁹Tc), thallium (²⁰¹Tl), gallium (⁶⁸Ga, ⁶⁷Ga), palladium (¹⁰³Pd), molybdenum (⁹⁹Mo), xenon (¹³³Xe), fluorine (¹⁸F), ¹⁵³Sm, ¹⁷⁷Lu, ¹⁵⁹Gd, ¹⁴⁹Pm, ¹⁴⁰La, ¹⁷⁵Yb, ¹⁶⁶Ho, ⁹⁰Y, ⁴⁷Sc, ¹⁸⁶Re, ¹⁸⁸Re, ¹⁴²Pr, ¹⁰⁵Rh, ⁹⁷Ru, ⁶⁸Ge, ⁵⁷Co, ⁶⁵Zn, ⁸⁵Sr, ³²P, ¹⁵³Gd, ¹⁶⁹Yb, ⁵¹Cr, ⁵⁴Mn, ⁷⁵Se, ¹¹³Sn, and ¹¹⁷Sn; and positron emitting metals using various positron emission tomographies, and non-radioactive paramagnetic metal ions.

[0302] Also provided herein are antibodies of the present invention 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 cytotoxic 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.

[0303] Further, an antibody of the present invention 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).

[0304] Also provided herein are antibodies of the present invention 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 of the present invention (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. The heterologous protein, polypeptide, or peptide that the antibody is fused to may be 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 described herein.

[0305] In addition, an antibody of the present invention can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alpha-emitters such as ²¹³Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ¹³¹In, ¹³¹Lu, ¹³¹Y, ¹³¹Ho, ¹³¹Sm, to polypeptides. The macrocyclic chelator may be 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.

[0306] Moreover, antibodies of the present invention can be fused to marker or "tag" sequences, such as a peptide to facilitate purification. The marker or tag amino acid sequence may be 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.

[0307] 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).

[0308] 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 described 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. Opin. 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.

[0309] An antibody provided of the present invention 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.

[0310] The therapeutic moiety or drug conjugated or recombinantly fused to an antibody of the present invention 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). The antibody may be 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.

[0311] 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.

[0312] 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).

[0313] 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).

[0314] 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 heterogeneous 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

[0315] 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. The dose may be between about 5 mg/kg and about 7.5 mg/kg. The dose may be about 5 mg/kg. The dose may be 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. The flat dose may be 375-400 mg every two weeks. The flat dose may be 550-600 mg every three weeks. The flat dose may be 400 mg every two weeks. The flat dose may be 600 mg every three weeks. In course of sequential dosing, a first dose and a second dose may be each between 1 mg/kg and 15 mg/kg with the second dose following the first does by between 1 and 4 weeks. The first dose and the second dose may be each between 5 mg/kg and 7.5 mg/kg and the second dose follows the first dose by between 2 and 3 weeks. The first dose and the second dose may be each 5 mg/kg and the second dose follows the first dose by 2 weeks. The first dose and the second dose may be each 7.5 mg/kg and the second dose follows the first dose by 3 weeks.

[0316] For treating diseases, disorders and conditions, the antibody may be administered via intravenous infusion. The dosage administered via infusion is in the range of about 1 $\mu\text{g}/\text{m}^2$ to about 10,000 $\mu\text{g}/\text{m}^2$ 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 $\mu\text{g}/\text{m}^2$ to about 1000 $\mu\text{g}/\text{m}^2$, about 1 $\mu\text{g}/\text{m}^2$ to about 800 $\mu\text{g}/\text{m}^2$, about 1 $\mu\text{g}/\text{m}^2$ to about 600 $\mu\text{g}/\text{m}^2$, about 1 $\mu\text{g}/\text{m}^2$ to about 400 $\mu\text{g}/\text{m}^2$; alternatively, about 10 $\mu\text{g}/\text{m}^2$ to about 500 $\mu\text{g}/\text{m}^2$, about 10 $\mu\text{g}/\text{m}^2$ to about 300 $\mu\text{g}/\text{m}^2$, about 10 $\mu\text{g}/\text{m}^2$ to about 200 $\mu\text{g}/\text{m}^2$, and about 1 $\mu\text{g}/\text{m}^2$ to about 200 $\mu\text{g}/\text{m}^2$. 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.

[0317] In one aspect, the present disclosure further provides pharmaceutical formulations comprising at least one anti-beta klotho antibody of the present invention. In some embodiments, a pharmaceutical formulation comprises 1) an anti-beta klotho antibody of the present invention, and 2) a pharmaceutically acceptable carrier. A pharmaceutical formulation may also comprise 1) an anti-beta klotho antibody of the present invention and/or an immunoconjugate thereof, and optionally, 2) at least one additional therapeutic agent.

[0318] Pharmaceutical formulations comprising an antibody are 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. The formulation may include 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 mitoxentron), 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.

[0319] 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)).

[0320] 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-(methylmethacrylate) 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.

[0321] 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. A prophylactic or therapeutic agent, or a composition described herein can be delivered in a controlled release or sustained release system. 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). 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. 71:105); 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. The polymer used in a sustained release formulation may be inert, free of leachable impurities, stable on storage, sterile, and biodegradable.

[0322] 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

[0323] 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 antibodies for use in 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.

[0324] 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.

[0325] In one aspect, antibodies for use in 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. The use of an antibody in 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 of the present invention and, optionally, at least one additional therapeutic agent, such as those described herein.

[0326] 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).

[0327] Antibodies of the present invention can be used either alone or in combination with other compositions in a therapy. For example, an anti-beta klotho antibody of the present invention 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.

[0328] 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.

[0329] 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.

[0330] 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.

[0331] 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 μ g/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 μ g/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

[0332] 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. A biological sample may comprise a cell or tissue.

[0333] In one aspect, the present disclosure provides a method of detecting the presence of beta klotho in a biological sample. The method may comprise 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.

[0334] In one aspect, the present disclosure provides a method of diagnosing a disorder associated with expression of beta klotho. The method may comprise 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. The test cell may be 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. The disease, disorder or condition may be, 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.

[0335] A method of diagnosis or detection, such as those described above, may comprise 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. The method may comprise 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.

[0336] 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).

[0337] Anti-beta klotho antibodies 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 ³²P, ¹⁴C, ¹²⁵I, ³H, and ¹³¹I, fluorophores such as rare earth chelates or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, luciferases, 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.

[0338] Anti-beta klotho antibodies 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 crosslinking), 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.

[0339] Any of the above described methods 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

5 **[0340]** 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

10 **[0341]** In one aspect, assays are described 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.,
15 from mouse tail snips or from a human blood sample) may be collected into plain capillary tubes (BD Clay Adams SurePrep, Becton Dickinson 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

25 **[0342]** In one aspect, an anti-beta klotho antibody is tested for its antigen binding activity. For example, an anti-beta klotho antibody may be 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.

[0343] A panel of monoclonal antibodies raised against beta klotho may be grouped based upon the epitopes 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. 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.

35 **[0344]** 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

45 **[0345]** 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.

50 **[0346]** 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 mass spectroscopy, and structural determination.

[0347] 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.

[0348] 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)).

[0349] 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.

[0350] 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).

[0351] 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).

[0352] 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).

[0353] 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).

[0354] 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

[0355] An anti-beta klotho antibody of the present disclosure may be 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.

[0356] 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.

[0357] 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. The Fc activities of the antibody may be 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 Fc γ R 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.

EXAMPLES

[0358] The following are examples of methods and compositions of the present disclosure.

EXAMPLE 1: GENERATION OF ANTIBODIES TO BETA KLOTHO

[0359] Antibodies to beta klotho were generated, for example, by immunizations of mice (i) with cells expressing human beta klotho (HuKLB) and FGF receptor 1c (FGFR1c or R1c) and (ii) with HuKLB and cynomolgous beta klotho (cyno KLB) protein.

[0360] 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 μ L into twenty-four x 384-well plates in the presence of HAT selection. After 7 days, 50 μ L 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.

[0361] 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

[0362] 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.

[0363] 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.

[0364] 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 μ L/min to test for binding to captured antibody on each flow cell.

[0365] 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.

[0366] 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 μ L/min and monitoring the binding kinetics at 25°C.

[0367] 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 μ L/min and the binding kinetics were evaluated at 25°C.

[0368] Representative results are reported as K_D (nM) values as shown in Table 11 below.

Table 11

Affinity K_D (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

[0369] 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.

[0370] 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 $4^{\circ}C$, 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.

[0371] In exemplary competition binding experiments by FACS, antibody 5H23 or 3113 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	3113 - 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
3113	9.4	7.4
Labeled antibody alone	10.8	32.4

[0372] 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.

[0373] 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

[0374] Antibodies to beta klotho generated, for example, such as described in Example 1, were tested for their functional activity in cell-based reporter assays.

[0375] For example, ELK1-luciferase reporter assays, which measure FGFR1c/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 FGFR1 c/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.

[0376] 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).

[0377] 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		

[0378] 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

[0379] L6 cells lack endogenous receptors and are often used to investigate antibody specificity to various transfected 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 FGFR1 c (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

[0380] 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 FGFR1 c/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).

[0381] 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 μ L/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.

[0382] 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

(continued)

	Experiment - A	Experiment - B
mAb	hAdip pERK assay	hAdip pERK assay EC50 (nM)
1G19	+++	1.3

EXAMPLE 6: LIGAND COMPETITION

[0383] 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.

[0384] 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

(continued)

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			

[0385] 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

[0386] Humanized anti-beta klotho antibodies were generated, including from antibodies selected as described in Examples 1-6.

[0387] 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*).

[0388] 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.

[0389] Also, for example, human VL sequences homologous to the 5H23 VL framework sequences, were searched for and the human V κ region encoded by the IGKV4-1*01 (see, e.g., Ehrenmann 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.

[0390] 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.

[0391] 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 substitution.

[0392] 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.

[0393] 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 WIYPGDSSTKFNFNFKD	
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 SDYYGSRSFY	
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	

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(continued)

5

10

15

20

25

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35

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55

VH CDR3
SEQ ID NO:237 RGAYYSNYDSFDV
VL CDR1
SEQ ID NO:4 RASKSVSTSGYVYM
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 HHSGLPYT
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	
5	VH
	Framework 1 (FR1)
	SEQ ID NO:278 QVQLVQSGAEVKKPGASVKVSCKAS
	SEQ ID NO:279 QVQLQQSGAEVKKPGASVKVSCKAS
10	SEQ ID NO:280 QVQLVQSGPEVKKPGASVKVSCKAS
	SEQ ID NO:378 QVQLVQSGAEVKKPGSSVKVSCKAS
	Framework 2 (FR2)
15	SEQ ID NO:281 WVRQAPGQGLEWMG
	SEQ ID NO:282 WVRQAPGQGLEWIG
	SEQ ID NO:283 WVKQAPGQGLEWIG
	Framework 3 (FR3)
20	SEQ ID NO:284 RVTITRDTSASTAYMELSSLRSEDTAVYYCAR
	SEQ ID NO:285 KATITRDTSASTAYMELSSLRSEDTAVYFCAR
	SEQ ID NO:286 KATLTADTSASTAYMELSSLRSENTAVYFCAR
25	SEQ ID NO:287 KATLTADKSARTAYMELSSLRSENTAVYFCAR
	SEQ ID NO:379 RATLTADKSTSTAYMELSSLRSEDTAVYYCAR
	SEQ ID NO:380 RATLTADKSTRTAYMELSSLRSEDTAVYYCAR
	SEQ ID NO:381 RATITADKSTSTAYMELSSLRSEDTAVYYCAR
30	Framework 4 (FR4)
	SEQ ID NO:288 WGQGTLVTVSS
	VL
35	Framework 1 (FR1)
	SEQ ID NO:289 DIVLTQSPDSLAVSLGERATINC
	SEQ ID NO:290 DIVMTQSPDSLAVSLGERATINC
	SEQ ID NO:382 DIQMTQSPSSLSASVGDRVITIC
40	SEQ ID NO:383 DIQLTQSPSSLSASVGDRVITIC
	SEQ ID NO:384 EIVLTQSPATLSLSPGERATLSC
	Framework 2 (FR2)
45	SEQ ID NO:291 WNQQKPGQPPKLLIY
	SEQ ID NO:292 WYQQKPGQPPKLLIY
	SEQ ID NO:385 WYQQKPGKAPKLLIY
50	SEQ ID NO:386 WNQQKPGKAPKLLIY
	SEQ ID NO:387 WYQQKPGKPPKLLIY
	SEQ ID NO:388 WNQQKPGKPPKLLIY
	SEQ ID NO:389 WYQQKPGQAPRLLIY
55	SEQ ID NO:390 WNQQKPGQAPRLLIY
	SEQ ID NO:391 WYQQKPGQPPRLLIY

(continued)

	Framework 2 (FR2)
5	SEQ ID NO:392 WNQQKPGQPRLIY
	Framework 3 (FR3)
	SEQ ID NO:293 GVPDRFSGSGSGTDFTLTISVQAEDAAIYYC
	SEQ ID NO:294 GVPDRFSGSGSGTDFTLTISVQAEDVAVYYC
10	SEQ ID NO:295 GVPDRFSGSGSGTDFTLTISVQAEDVAIYYC
	SEQ ID NO:393 GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC
	SEQ ID NO:394 GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
15	SEQ ID NO:395 GVPSRFSGSGSGTDFTLTISVQPEDFATYYC
	SEQ ID NO:396 GVPSRFSGSGSGTDFTLTISSLQEEDFATYYC
	SEQ ID NO:397 GVPSRFSGSGSGTDFTLTISVQEEDFATYYC
	SEQ ID NO:398 GVPSRFSGSGSGTDFTLTISVQEEDAATYYC
20	SEQ ID NO:399 GIPARFSGSGSGTDFTLTISRLEPEDFAVYYC
	SEQ ID NO:400 GIPARFSGSGSGTDFTLTISRVEPEDFAVYYC
	SEQ ID NO:401 GIPARFSGSGSGTDFTLTISRLEPEDAAVYYC
25	SEQ ID NO:402 GIPARFSGSGSGTDFTLTISRLEEEDFAVYYC
	SEQ ID NO:403 GIPARFSGSGSGTDFTLTISRVEEEDFAVYYC
	SEQ ID NO:404 GIPARFSGSGSGTDFTLTISRVEEEDAATYYC
	Framework 4 (FR4)
30	SEQ ID NO:296 FGGGTKLEIK
	SEQ ID NO:405 FGGGTKVEIK
	SEQ ID NO:406 FGQGTKLEIK
35	SEQ ID NO:407 FGGQTKLEIK

[0394] 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).

[0395] 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.

[0396] 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 vL 1-3 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.

[0397] 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

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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	--	--

(continued)

vH3				
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.				

[0398] 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- β IIIc receptor (e.g., SEQ ID NO: 416), chimeric rat FGFR1- β IIIc receptor (e.g., SEQ ID NO: 419), chimeric hamster FGFR1- β IIIc receptor (e.g., SEQ ID NO: 417), chimeric rabbit FGFR1- β IIIc receptor (e.g., SEQ ID NO: 420), or dog FGFR1- β IIIc 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 FGFR1 c/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

[0399] Effects of anti-beta klotho antibodies are evaluated in animal studies, including with cynomolgus monkeys.

[0400] 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.

[0401] 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.

[0402] 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.

[0403] 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.

[0404] 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.

[0405] 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.

[0406] 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.

[0407] 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.

[0408] 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.

[0409] 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.

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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
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
	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
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
	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

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
	Mean	89.18	34.73	36.19	38.11	46.75	48.28	35.42	37.95	57.29	63.23	55.30
h5H23	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

[0410] In another exemplary study, forty spontaneous obese male cynomolgus were selected, trained and fed as described above.

[0411] 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.

[0412] 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.

[0413] 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.

[0414] 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.

[0415] 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

[0416] 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: EPIOTOPE AND DOMAIN MAPPING

[0417] 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.

[0418] 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 μ g/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

(continued)

Antibody	Mouse KLB	Mouse-Human chimeric KLB	Human-Mouse chimeric KLB	Human KLB	Cynomolgus KLB	Empty Vector (-control)
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.						

[0419] 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.

[0420] 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 μ g/ml for the humanized 5H23 antibody, 1.0 μ g/ml for the Fab fragment, and 2.0 μ g/ml for a positive control polyclonal anti-beta klotho antibodies.

[0421] 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 interaction 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 ($\pm$ 11.93)	120.35 ($\pm$ 55.21)
Y701A	0.64 ($\pm$ 0.09)	43.37 ($\pm$ 5.78)
R703A	1.64 ($\pm$ 1.69)	131.59 ($\pm$ 19.98)

[0422] Thus, the anti-beta klotho antibodies described 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 respressed 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.

[0423] Additionally, the anti-beta klotho antibodies described herein share the common feature of competing with each other for the binding 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 anti-

bodies, 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 epitope 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 epitope 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 activities and effects of the anti-beta klotho antibodies described herein.

[0424] 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.

[0425] Other embodiments are within the following claims.

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40 Ile Asn Tyr Asp Gly Asn Ser
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Tyr Asp Gly
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15 Gly Ala Tyr Tyr Ser Asn Tyr Asp Ser Phe Asp
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40 Tyr Asp Glu Phe Pro Phe
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				20					25					30		
	Tyr	Tyr	Trp	Asn	Trp	Ile	Arg	Gln	Phe	Pro	Gly	Asn	Lys	Leu	Glu	Trp
			35					40					45			
	Met	Gly	Tyr	Ile	Asn	Tyr	Asp	Gly	Asn	Ser	Asn	Tyr	Thr	Pro	Ser	Leu
		50					55					60				
35	Lys	Asn	Arg	Ile	Ser	Ile	Thr	Arg	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Phe
		65				70					75				80	
	Leu	Lys	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys
				85						90					95	
	Ala	Arg	Lys	Gly	Ala	Tyr	Tyr	Ser	Asn	Tyr	Asp	Ser	Phe	Asp	Val	Trp
				100					105					110		
40	Gly	Thr	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser						
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	Glu	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp	Ile	Asn	Ser	Tyr
			20						25					30		
5	Leu	Ser	Trp	Val	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Lys	Thr	Leu	Ile
			35					40					45			
	Tyr	Arg	Ala	Asn	Arg	Leu	Val	Asp	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50						55					60				
	Ser	Gly	Ser	Gly	Gln	Asp	Tyr	Ser	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Tyr
10	65					70					75					80
	Glu	Asp	Met	Gly	Ile	Tyr	Tyr	Cys	Leu	Gln	Tyr	Asp	Glu	Phe	Pro	Phe
				85						90					95	
	Thr	Phe	Gly	Ser	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
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<211> 7

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Ile Tyr Pro Gly Asp Ser Ser Thr
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Arg Tyr Asp Ile Asn
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Gly Tyr Thr Phe Thr Arg Tyr
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Pro Gly Asp Ser
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Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr
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1 5 10

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 Gln His Ser Arg Glu Leu Pro Tyr
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	Gln	Val	Gln	Pro	Gln	Glu	Ser	Gly	Pro	Glu	Leu	Val	Lys	Pro	Gly	Ala
	1				5					10					15	
	Leu	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Arg	Tyr
				20					25					30		
5	Asp	Ile	Asn	Trp	Met	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
			35					40					45			
	Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Ser	Ser	Thr	Lys	Phe	Asn	Glu	Asn	Phe
		50					55					60				
	Lys	Asp	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr
10						70					75					80
	Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asn	Ser	Thr	Val	Tyr	Phe	Cys
					85					90					95	
	Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Thr	Tyr	Trp	Gly	Gln
				100					105					110		
15	Gly	Thr	Leu	Val	Thr	Val	Ser	Ala								
			115					120								

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	Gln	Arg	Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
30	Gly	Tyr	Ser	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Asn	Leu	Glu	Ser	Gly	Val	Pro	Ala
		50					55					60				
35	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Asn	Ile	His
		65				70				75						80
	Pro	Val	Glu	Glu	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85				90					95		
	Glu	Leu	Pro	Tyr	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
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Trp	Ile	Tyr	Pro	Gly	Asp	Asp	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe	Lys
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Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Val	Tyr
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Ile Tyr Pro Gly Asp Asp Ser Thr
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Asp Tyr Tyr Gly Ser Arg Ser Phe Val
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Ser Gly Glu Leu Pro Tyr
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Thr Arg Tyr Asp Ile Asn
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20 25 30
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35 40 45
Gly Trp Ile Tyr Pro Gly Asp Asp Ser Thr Lys Tyr Asn Glu Lys Phe
25 50 55 60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asn Ser Ala Val Tyr Phe Cys

30 85 90 95
Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Val Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ala
115 120

35

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20 25 30
Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45
Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80
Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Gly
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Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

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 Gly Tyr Thr Phe Thr Ser Tyr Asp Ile Asn
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 1 5 10 15
 Gly
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 Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Val Tyr
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 Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Val His
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Leu Ala Ser Asn Leu Glu Ser
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Gln His Ser Gly Glu Leu Pro Tyr Thr
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Asp	Ile	Asn 35	Trp	Val	Lys	Gln	Arg 40	Pro	Gly	Gln	Gly	Leu 45	Glu	Trp	Ile
Gly	Trp 50	Ile	Tyr	Pro	Gly	Asp 55	Gly	Ser	Pro	Lys	Tyr 60	Asp	Glu	Lys	Phe
Lys 65	Gly	Lys	Ala	Thr	Leu 70	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr 80
Met	Gln	Leu	Ser	Ser 85	Leu	Thr	Ser	Glu	Asn 90	Ser	Ala	Val	Tyr	Phe 95	Cys
Ala	Arg	Ser	Asp 100	Tyr	Tyr	Gly	Ser	Arg 105	Ser	Phe	Val	Tyr	Trp 110	Gly	Gln
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      Gly Tyr Ser Tyr Val His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
      35           40           45
      Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
      50           55           60
10     Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
      65           70           75           80
      Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Gly
      85           90           95
15     Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
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40     Glu Ile Tyr Pro Arg Ser Gly Asn Thr Tyr Tyr Asn Glu Lys Phe Lys
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 20 25 30
 Gly Ile Ser Trp Val Lys Gln Arg Thr Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Tyr Pro Arg Ser Gly Asn Thr Tyr Tyr Asn Glu Lys Phe
 50 55 60
 10 Lys Gly Lys Ala Thr Leu Thr Ala Asp Met Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Asp Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
 85 90 95
 Ala Arg His Trp Asp Gly Val Leu Asp Tyr Phe Asp Tyr Trp Gly Gln
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 20 25 30
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 35 40 45
 Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu Ser Gly Val
 35
 50 55 60
 Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Leu Asn
 85 90 95
 40 Asp His Ser Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
 100 105 110
 Lys

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His His Ser Gly Glu Leu Pro Tyr Thr
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			20					25					30		
Asp	Ile	Asn	Trp	Val	Lys	Lys	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Asp	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
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Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr
	65				70					75				80	
Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asn	Ser	Ala	Val	Tyr	Phe	Cys
				85					90					95	
Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Val	Tyr	Trp	Gly	Gln
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Gly	Thr	Leu	Val	Thr	Val	Ser	Ala								
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 20 25 30
 5 Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
 35 40 45
 Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
 50 55 60
 Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65 70 75 80
 10 Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys His His Ser Gly
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 Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
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Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His
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Ser Arg Glu Leu Pro Tyr
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Thr Arg Tyr Asp Ile Asn
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Trp Ile Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Lys
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Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Val
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Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Tyr
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10 Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
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20 <400> 205

Gln His Ser Arg Glu Leu Pro Tyr
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30 <220>
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<400> 206

35 Trp Ile Tyr Pro Gly Asp Gly Ser Thr Lys
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40 <210> 207
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	1				5					10					15	
	Leu	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Arg	Tyr
				20					25					30		
5	Asp	Ile	Asn	Trp	Val	Lys	Lys	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
			35					40					45			
	Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
		50					55					60				
	Glu	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr
10	65					70					75				80	
	Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asn	Ser	Ala	Val	Tyr	Phe	Cys
					85					90					95	
	Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Val	Tyr	Trp	Gly	Gln
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			115					120								

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	Gln	Arg	Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
30	Gly	Tyr	Ser	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Asn	Leu	Glu	Ser	Gly	Val	Pro	Ala
		50					55					60				
35	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Asn	Ile	His
	65					70					75				80	
	Pro	Val	Glu	Glu	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90				95		
	Glu	Leu	Pro	Tyr	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
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Gly	Tyr	Thr	Phe	Thr	Arg	Tyr	Asp	Ile	Asn
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Gly															

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Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Val	Tyr
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<223> 5F7 VL CDR1- Exemplary

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Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser	Gly	Tyr	Ser	Tyr	Met	His
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Gln His Ser Arg Glu Leu Pro Tyr Thr
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15 Gly Tyr Thr Phe Thr Arg Tyr Asp
1 5

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Ile Tyr Pro Gly Asp Ile Ser Thr
1 5

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<400> 217

40 Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Val Tyr
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Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr
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 Leu Ala Ser
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 Arg Tyr Asp Ile Asn
 1 5

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 Gly Tyr Thr Phe Thr Arg Tyr
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 1 5

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 Pro Gly Asp Ile
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Asp Tyr Tyr Gly Ser Arg Ser Phe Val
1 5

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<400> 224

15 Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr
1 5 10

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Ser Arg Glu Leu Pro Tyr
1 5

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<400> 226

40 Thr Arg Tyr Asp Ile Asn
1 5

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55 Trp Ile Gly Trp Ile Tyr Pro Gly Asp Ile Ser Thr Lys
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Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Val

1 5 10

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Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Tyr

1 5 10

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<400> 230

Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu

1 5 10

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<211> 8

<212> PRT

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<220>

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<400> 231

Gln His Ser Arg Glu Leu Pro Tyr

1 5

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<210> 232

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<212> PRT

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<223> 5F7 VH CDR2 - AbM

<400> 232

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Trp Ile Tyr Pro Gly Asp Ile Ser Thr Lys
1 5 10

<210> 233
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<400> 233

Gln Val Gln Pro Gln Glu Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
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Leu Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30
Asp Ile Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile

35 40 45
Gly Trp Ile Tyr Pro Gly Asp Ile Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asn Ser Ala Val Tyr Phe Cys
85 90 95
Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Val Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ala
115 120

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<400> 234

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30
Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45
Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80
Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
85 90 95
Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

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<223> 1G19 VH CDR1- Exemplary

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Gly	Tyr	Ser	Ile	Thr	Ser	Gly	Tyr	Tyr	Trp	Asn
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Tyr	Ile	Asn	Tyr	Gly	Gly	Ser	Asn	Asn	Tyr	Asn	Pro	Ser	Leu	Lys	Asn
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<223> 1G19 VH CDR3- Exemplary

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Arg	Gly	Ala	Tyr	Tyr	Ser	Asn	Tyr	Asp	Ser	Phe	Asp	Val
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Lys	Ala	Ser	Gln	Asp	Ile	Asn	Ser	Tyr	Leu	Ser
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<400> 239

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Arg Ala Asn Arg Leu Val Asp
1 5

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15 Leu Gln Tyr Asp Glu Phe Pro Tyr Thr
1 5

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Gly Tyr Ser Ile Thr Ser Gly Tyr Tyr

30 1 5

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Ile Asn Tyr Gly Gly Ser Asn
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55 <400> 243

Ala Arg Arg Gly Ala Tyr Tyr Ser Asn Tyr Asp Ser Phe Asp Val
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 Gln Asp Ile Asn Ser Tyr
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 Arg Ala Asn
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 Gly Tyr Ser Ile Thr Ser Gly Tyr
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<400> 248

5 Tyr Gly Gly
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1 5 10

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30 Ser Gln Asp Ile Asn Ser Tyr
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45 Tyr Asp Glu Phe Pro Tyr
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Thr Ser Gly Tyr Tyr Trp Asn
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 Ala Arg Arg Gly Ala Tyr Tyr Ser Asn Tyr Asp Ser Phe Asp
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 Thr Leu Ile Tyr Arg Ala Asn Arg Leu Val
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<223> 1G19 VL CDR3 - Contact

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5 Leu Gln Tyr Asp Glu Phe Pro Tyr
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15 <223> 1G19 VH CDR2 - AbM

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20 Tyr Ile Asn Tyr Gly Gly Ser Asn Asn
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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15
Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Gly
20 25 30
35 Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45
Met Gly Tyr Ile Asn Tyr Gly Gly Ser Asn Asn Tyr Asn Pro Ser Leu
50 55 60
Lys Asn Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80
40 Leu Lys Leu Thr Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Ala Tyr Tyr Ser Asn Tyr Asp Ser Phe Asp Val Trp
100 105 110
45 Gly Thr Gly Thr Thr Val Thr Val Ser Ser
115 120

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50 <213> Artificial Sequence

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	Glu	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp	Ile	Asn	Ser	Tyr
				20					25					30		
5	Leu	Ser	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Lys	Thr	Leu	Ile
			35				40						45			
	Tyr	Arg	Ala	Asn	Arg	Leu	Val	Asp	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60					
	Ser	Gly	Ser	Gly	Gln	Asp	Tyr	Ser	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Tyr
10	65				70					75					80	
	Glu	Glu	Met	Gly	Ile	Tyr	Tyr	Cys	Leu	Gln	Tyr	Asp	Glu	Phe	Pro	Tyr
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	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
				100					105							

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45 <400> 262

50					Trp	Ile	Tyr	Pro	Gly	Asp	Xaa	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe	Lys
					1				5					10					15	
					Gly															

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 <400> 263

	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Xaa	Tyr
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 <223> Xaa = Ser or Asn

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 <223> Xaa = Thr or Asn

 <400> 264
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	Tyr	Ile	Asn	Tyr	Xaa	Gly	Xaa	Xaa	Asn	Tyr	Xaa	Pro	Ser	Leu	Lys	Asn
	1				5					10					15	

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Xaa Gly Ala Tyr Tyr Ser Asn Tyr Asp Ser Phe Asp Val
1 5 10

5 <210> 266
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<400> 266

20 Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Xaa His
1 5 10 15

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Xaa His Ser Xaa Glu Leu Pro Tyr Thr
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Leu Gln Tyr Asp Glu Phe Pro Xaa Thr
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5 <210> 269
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<223> vH1

<400> 269

15 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
20 Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
25 Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

30 <210> 270
<211> 120
<212> PRT
<213> Artificial Sequence

35 <220>
<223> vH2

<400> 270

40 Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Asp Ile Asn Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
45 Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Ala Arg Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
50 Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Ala Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

55 <210> 271 <211> 120
<212> PRT
<213> Artificial Sequence

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<220>

<223> vH3

<400> 271

5

10

15

20

Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Asp	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
	50					55					60				
Lys	Gly	Lys	Ala	Thr	Ile	Thr	Arg	Asp	Thr	Ser	Ala	Ser	Thr	Ala	Tyr
65					70				75					80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Phe	Cys
				85					90					95	
Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Ala	Tyr	Trp	Gly	Gln
			100					105					110		
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
		115					120								

<210> 272

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> vH4

<400> 272

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35

40

45

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Asp	Ile	Asn	Trp	Val	Arg	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
	50					55					60				
Lys	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Ala	Arg	Thr	Ala	Tyr
65					70				75					80	
Met	Glu	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Ala	Tyr	Trp	Gly	Gln
			100					105					110		
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
		115					120								

<210> 273

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> vH5

<400> 27

55

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

	1		5		10		15									
5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25						30		
	Asp	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
			35					40					45			
10	Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
		50					55					60				
	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Ala	Ser	Thr	Ala	Tyr
	65					70				75					80	
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asn	Thr	Ala	Val	Tyr	Phe	Cys
				85					90					95		
15	Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Ala	Tyr	Trp	Gly	Gln
			100					105						110		
	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
			115					120								

<210> 274

20 <211> 120

<212> PRT

<213> Artificial Sequence

<220>

25 <223> vH6

<400> 274

	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
30	1				5					10					15	
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
				20					25					30		
	Asp	Ile	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
			35					40					45			
35	Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
		50					55					60				
	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Ala	Arg	Thr	Ala	Tyr
	65					70				75					80	
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asn	Thr	Ala	Val	Tyr	Phe	Cys
				85					90					95		
40	Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Ala	Tyr	Trp	Gly	Gln
			100					105						110		
	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
			115					120								

45 <210> 275

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

50 <223> vL1

<400> 275

55

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	Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Ile	Asn	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
		35						40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Asp
	50					55						60				
10	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70					75					80
	Ser	Val	Gln	Ala	Glu	Asp	Ala	Ala	Ile	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
15	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

<210> 276

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> vL2

<400> 276

	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Ile	Asn	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
		35						40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Asp
	50					55						60				
35	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70					75					80
	Ser	Val	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

<210> 277

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> vL3

<400> 277

EP 3 097 122 B9

	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Ile	Asn	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Asp
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65					70					75					80
	Ser	Val	Gln	Ala	Glu	Asp	Val	Ala	Ile	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

15 <210> 278
 <211> 25
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> Humanized Anti-Beta Klotho VH FR1

<400> 278

25	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
	1				5					10					15	
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser							
				20					25							

30 <210> 279
 <211> 25
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Humanized Anti-Beta Klotho VH FR1

<400> 279

40	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
	1				5					10					15	
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser							
				20					25							

45 <210> 280
 <211> 25
 <212> PRT
 <213> Artificial Sequence

50 <220>
 <223> Humanized Anti-Beta Klotho VH FR1

<400> 280

55	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Val	Lys	Lys	Pro	Gly	Ala
	1				5					10					15	
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser							
				20					25							

<210> 281
 <211> 14
 <212> PRT
 <213> Artificial Sequence

5

<220>
 <223> Humanized Anti-Beta Klotho VH FR2

10

<400> 281

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
 1 5 10

15

<210> 282
 <211> 14
 <212> PRT
 <213> Artificial Sequence

20

<220>
 <223> Humanized Anti-Beta Klotho VH FR2

<400> 282

25

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
 1 5 10

30

<210> 283
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Humanized Anti-Beta Klotho VH FR2

35

<400> 283

Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
 1 5 10

40

<210> 284
 <211> 32
 <212> PRT
 <213> Artificial Sequence

45

<220>
 <223> Humanized Anti-Beta Klotho VH FR3

<400> 284

50

Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr Met Glu
 1 5 10 15
 Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 20 25 30

55

<210> 285
 <211> 32
 <212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VH FR3

5

<400> 285

10 Lys Ala Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr Met Glu
 1 5 10 15
 Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg
 20 25 30

<210> 286

<211> 32

15

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VH FR3

20

<400> 286

25 Lys Ala Thr Leu Thr Ala Asp Thr Ser Ala Ser Thr Ala Tyr Met Glu
 1 5 10 15
 Leu Ser Ser Leu Arg Ser Glu Asn Thr Ala Val Tyr Phe Cys Ala Arg
 20 25 30

<210> 287

<211> 32

30

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VH FR3

35

<400> 287

40 Lys Ala Thr Leu Thr Ala Asp Lys Ser Ala Arg Thr Ala Tyr Met Glu
 1 5 10 15
 Leu Ser Ser Leu Arg Ser Glu Asn Thr Ala Val Tyr Phe Cys Ala Arg
 20 25 30

<210> 288

<211> 11

45

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VH FR4

50

<400> 288

55 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 1 5 10

<210> 289 <211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR1

<400> 289

5

Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Ile	Asn	Cys									
			20												

10

<210> 290

<211> 23

<212> PRT

<213> Artificial Sequence

15

<220>

<223> Humanized Anti-Beta Klotho VL FR1

<400> 290

20

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Ile	Asn	Cys									
			20												

25

<210> 291

<211> 15

<212> PRT

<213> Artificial Sequence

30

<220>

<223> Humanized Anti-Beta Klotho VL FR2

<400> 291

35

Trp	Asn	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Ile	Tyr
1				5					10					15

40

<210> 292

<211> 15

<212> PRT

<213> Artificial Sequence

45

<220>

<223> Humanized Anti-Beta Klotho VL FR2

<400> 292

50

Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Ile	Tyr
1				5					10					15

55

<210> 293

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR3

<400> 293

	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
	1				5					10				15		
5	Leu	Thr	Ile	Ser	Ser	Val	Gln	Ala	Glu	Asp	Ala	Ala	Ile	Tyr	Tyr	Cys
				20					25					30		

<210> 294

<211> 32

10 <212> PRT

<213> Artificial Sequence

<220>

15 <223> Humanized Anti-Beta Klotho VL FR3

<400> 294

	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
	1				5					10				15		
20	Leu	Thr	Ile	Ser	Ser	Val	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys
				20					25					30		

<210> 295

<211> 32

25 <212> PRT

<213> Artificial Sequence

<220>

30 <223> Humanized Anti-Beta Klotho VL FR3

<400> 295

	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
	1				5					10				15		
35	Leu	Thr	Ile	Ser	Ser	Val	Gln	Ala	Glu	Asp	Val	Ala	Ile	Tyr	Tyr	Cys
				20					25					30		

<210> 296

<211> 10

40 <212> PRT

<213> Artificial Sequence

<220>

45 <223> Humanized Anti-Beta Klotho VL FR4

<400> 296

					Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys
					1				5					10
50														

<210> 297

<211> 1044

<212> PRT

55 <213> Homo sapiens

<220>

<223> human beta klotho

<400> 297

	Met	Lys	Pro	Gly	Cys	Ala	Ala	Gly	Ser	Pro	Gly	Asn	Glu	Trp	Ile	Phe
	1				5				10						15	
5	Phe	Ser	Thr	Asp	Glu	Ile	Thr	Thr	Arg	Tyr	Arg	Asn	Thr	Met	Ser	Asn
				20					25					30		
	Gly	Gly	Leu	Gln	Arg	Ser	Val	Ile	Leu	Ser	Ala	Leu	Ile	Leu	Leu	Arg
			35					40					45			
10	Ala	Val	Thr	Gly	Phe	Ser	Gly	Asp	Gly	Arg	Ala	Ile	Trp	Ser	Lys	Asn
		50					55					60				
	Pro	Asn	Phe	Thr	Pro	Val	Asn	Glu	Ser	Gln	Leu	Phe	Leu	Tyr	Asp	Thr
	65					70					75					80
	Phe	Pro	Lys	Asn	Phe	Phe	Trp	Gly	Ile	Gly	Thr	Gly	Ala	Leu	Gln	Val
				85						90					95	
15	Glu	Gly	Ser	Trp	Lys	Lys	Asp	Gly	Lys	Gly	Pro	Ser	Ile	Trp	Asp	His
				100					105					110		
	Phe	Ile	His	Thr	His	Leu	Lys	Asn	Val	Ser	Ser	Thr	Asn	Gly	Ser	Ser
			115					120					125			
	Asp	Ser	Tyr	Ile	Phe	Leu	Glu	Lys	Asp	Leu	Ser	Ala	Leu	Asp	Phe	Ile
		130					135					140				
20	Gly	Val	Ser	Phe	Tyr	Gln	Phe	Ser	Ile	Ser	Trp	Pro	Arg	Leu	Phe	Pro
						150					155					160
	Asp	Gly	Ile	Val	Thr	Val	Ala	Asn	Ala	Lys	Gly	Leu	Gln	Tyr	Tyr	Ser
					165				170						175	
	Thr	Leu	Leu	Asp	Ala	Leu	Val	Leu	Arg	Asn	Ile	Glu	Pro	Ile	Val	Thr
				180					185						190	
25	Leu	Tyr	His	Trp	Asp	Leu	Pro	Leu	Ala	Leu	Gln	Glu	Lys	Tyr	Gly	Gly
			195					200					205			
	Trp	Lys	Asn	Asp	Thr	Ile	Ile	Asp	Ile	Phe	Asn	Asp	Tyr	Ala	Thr	Tyr
		210				215						220				
30	Cys	Phe	Gln	Met	Phe	Gly	Asp	Arg	Val	Lys	Tyr	Trp	Ile	Thr	Ile	His
		225				230					235					240
	Asn	Pro	Tyr	Leu	Val	Ala	Trp	His	Gly	Tyr	Gly	Thr	Gly	Met	His	Ala
				245						250					255	
	Pro	Gly	Glu	Lys	Gly	Asn	Leu	Ala	Ala	Val	Tyr	Thr	Val	Gly	His	Asn
				260				265						270		
35	Leu	Ile	Lys	Ala	His	Ser	Lys	Val	Trp	His	Asn	Tyr	Asn	Thr	His	Phe
			275					280					285			
	Arg	Pro	His	Gln	Lys	Gly	Trp	Leu	Ser	Ile	Thr	Leu	Gly	Ser	His	Trp
		290					295					300				
	Ile	Glu	Pro	Asn	Arg	Ser	Glu	Asn	Thr	Met	Asp	Ile	Phe	Lys	Cys	Gln
		305				310					315					320
40	Gln	Ser	Met	Val	Ser	Val	Leu	Gly	Trp	Phe	Ala	Asn	Pro	Ile	His	Gly
					325					330					335	

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	Asp	Gly	Asp	Tyr	Pro	Glu	Gly	Met	Arg	Lys	Lys	Leu	Phe	Ser	Val	Leu
			340						345					350		
	Pro	Ile	Phe	Ser	Glu	Ala	Glu	Lys	His	Glu	Met	Arg	Gly	Thr	Ala	Asp
			355					360					365			
5	Phe	Phe	Ala	Phe	Ser	Phe	Gly	Pro	Asn	Asn	Phe	Lys	Pro	Leu	Asn	Thr
		370					375					380				
	Met	Ala	Lys	Met	Gly	Gln	Asn	Val	Ser	Leu	Asn	Leu	Arg	Glu	Ala	Leu
	385					390					395					400
	Asn	Trp	Ile	Lys	Leu	Glu	Tyr	Asn	Asn	Pro	Arg	Ile	Leu	Ile	Ala	Glu
				405						410					415	
10	Asn	Gly	Trp	Phe	Thr	Asp	Ser	Arg	Val	Lys	Thr	Glu	Asp	Thr	Thr	Ala
			420					425						430		
	Ile	Tyr	Met	Met	Lys	Asn	Phe	Leu	Ser	Gln	Val	Leu	Gln	Ala	Ile	Arg
			435					440					445			
	Leu	Asp	Glu	Ile	Arg	Val	Phe	Gly	Tyr	Thr	Ala	Trp	Ser	Leu	Leu	Asp
15		450					455					460				
	Gly	Phe	Glu	Trp	Gln	Asp	Ala	Tyr	Thr	Ile	Arg	Arg	Gly	Leu	Phe	Tyr
	465					470					475					480
	Val	Asp	Phe	Asn	Ser	Lys	Gln	Lys	Glu	Arg	Lys	Pro	Lys	Ser	Ser	Ala
				485					490						495	
20	His	Tyr	Tyr	Lys	Gln	Ile	Ile	Arg	Glu	Asn	Gly	Phe	Ser	Leu	Lys	Glu
			500						505					510		
	Ser	Thr	Pro	Asp	Val	Gln	Gly	Gln	Phe	Pro	Cys	Asp	Phe	Ser	Trp	Gly
			515					520					525			
	Val	Thr	Glu	Ser	Val	Leu	Lys	Pro	Glu	Ser	Val	Ala	Ser	Ser	Pro	Gln
		530					535					540				
25	Phe	Ser	Asp	Pro	His	Leu	Tyr	Val	Trp	Asn	Ala	Thr	Gly	Asn	Arg	Leu
	545					550					555					560
	Leu	His	Arg	Val	Glu	Gly	Val	Arg	Leu	Lys	Thr	Arg	Pro	Ala	Gln	Cys
				565						570					575	
	Thr	Asp	Phe	Val	Asn	Ile	Lys	Lys	Gln	Leu	Glu	Met	Leu	Ala	Arg	Met
			580						585					590		
30	Lys	Val	Thr	His	Tyr	Arg	Phe	Ala	Leu	Asp	Trp	Ala	Ser	Val	Leu	Pro
			595					600					605			
	Thr	Gly	Asn	Leu	Ser	Ala	Val	Asn	Arg	Gln	Ala	Leu	Arg	Tyr	Tyr	Arg
		610					615					620				
	Cys	Val	Val	Ser	Glu	Gly	Leu	Lys	Leu	Gly	Ile	Ser	Ala	Met	Val	Thr
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[illegible]

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<212> DNA
<213> Homo sapiens

<220>
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<211> 1043

55 <212> PRT

<213> Mus musculus

<220>

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<223> Mouse beta klotho

<400> 301

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<211> 3129

<212> DNA

<213> Mus musculus

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<223> Mouse beta klotho

<400> 302

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<210> 303
 <211> 651
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> full length FGF19 (NM_005117.2)

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<400> 303

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<210> 304
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<400> 304

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<213> Artificial Sequence

<220>

<223> A full length FGF21

<400> 305

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<210> 306

<211> 209

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<212> PRT

<213> Artificial Sequence

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<223> A full length FGF21

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<400> 306

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Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val Arg Gln Arg Tyr
      35      40      45
Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His Leu Glu Ile Arg
      50      55      60
Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser Pro Glu Ser Leu

65      70      75      80
Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln Ile Leu Gly Val
      85      90      95
Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly Ala Leu Tyr Gly
      100      105      110
Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg Glu Leu Leu Leu
      115      120      125
Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His Gly Leu Pro Leu
      130      135      140
His Leu Pro Gly Asn Lys Ser Pro His Arg Asp Pro Ala Pro Arg Gly
      145      150      155      160
Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro Ala Pro Pro Glu
      165      170      175
Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val Gly Ser Ser Asp
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Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg Ser Pro Ser Tyr Ala
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Ser

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<210> 307

<211> 2469

<212> DNA

<213> Homo sapiens

<220>

<223> human FGFR1c NM_023110.2 (also designated FGFR alpha-IIIc)

5

<400> 307

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50

<210> 308

<211> 822

<212> PRT

<213> Homo sapiens

55

<220>

<223> human FGFR1c NP_075598.2 (also designated FGFR alpha-IIIc)

<400> 308

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	Thr	Leu	Cys	Thr	Ala	Arg	Pro	Ser	Pro	Thr	Leu	Pro	Glu	Gln	Ala	Gln
				20					25					30		
5	Pro	Trp	Gly	Ala	Pro	Val	Glu	Val	Glu	Ser	Phe	Leu	Val	His	Pro	Gly
			35					40					45			
	Asp	Leu	Leu	Gln	Leu	Arg	Cys	Arg	Leu	Arg	Asp	Asp	Val	Gln	Ser	Ile
	50						55					60				
	Asn	Trp	Leu	Arg	Asp	Gly	Val	Gln	Leu	Ala	Glu	Ser	Asn	Arg	Thr	Arg
10	65					70					75					80
	Ile	Thr	Gly	Glu	Glu	Val	Glu	Val	Gln	Asp	Ser	Val	Pro	Ala	Asp	Ser
				85						90					95	
	Gly	Leu	Tyr	Ala	Cys	Val	Thr	Ser	Ser	Pro	Ser	Gly	Ser	Asp	Thr	Thr
				100					105					110		
	Tyr	Phe	Ser	Val	Asn	Val	Ser	Asp	Ala	Leu	Pro	Ser	Ser	Glu	Asp	Asp
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	Asp	Asp	Asp	Asp	Asp	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Thr	Asp	Asn	Thr
		130					135					140				
	Lys	Pro	Asn	Arg	Met	Pro	Val	Ala	Pro	Tyr	Trp	Thr	Ser	Pro	Glu	Lys
	145					150					155					160
20	Met	Glu	Lys	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe
					165					170					175	
	Lys	Cys	Pro	Ser	Ser	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg	Trp	Leu	Lys
				180					185					190		
	Asn	Gly	Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val
			195					200					205			
25	Arg	Tyr	Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp
		210					215					220				
	Lys	Gly	Asn	Tyr	Thr	Cys	Ile	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn
	225					230					235					240
	His	Thr	Tyr	Gln	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile
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	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu	Gly	Ser	Asn
				260					265					270		
	Val	Glu	Phe	Met	Cys	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro	His	Ile	Gln
			275					280					285			
	Trp	Leu	Lys	His	Ile	Glu	Val	Asn	Gly	Ser	Lys	Ile	Gly	Pro	Asp	Asn
35		290				295						300				
	Leu	Pro	Tyr	Val	Gln	Ile	Leu	Lys	Thr	Ala	Gly	Val	Asn	Thr	Thr	Asp
	305					310					315					320
	Lys	Glu	Met	Glu	Val	Leu	His	Leu	Arg	Asn	Val	Ser	Phe	Glu	Asp	Ala
				325						330					335	
40	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Leu	Ser	His	His
				340					345					350		

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	Ser	Ala	Trp	Leu	Thr	Val	Leu	Glu	Ala	Leu	Glu	Glu	Arg	Pro	Ala	Val
			355					360					365			
	Met	Thr	Ser	Pro	Leu	Tyr	Leu	Glu	Ile	Ile	Ile	Tyr	Cys	Thr	Gly	Ala
		370					375					380				
5	Phe	Leu	Ile	Ser	Cys	Met	Val	Gly	Ser	Val	Ile	Val	Tyr	Lys	Met	Lys
	385					390					395					400
	Ser	Gly	Thr	Lys	Lys	Ser	Asp	Phe	His	Ser	Gln	Met	Ala	Val	His	Lys
				405						410					415	
	Leu	Ala	Lys	Ser	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala	Asp
				420					425					430		
10	Ser	Ser	Ala	Ser	Met	Asn	Ser	Gly	Val	Leu	Leu	Val	Arg	Pro	Ser	Arg
			435					440					445			
	Leu	Ser	Ser	Ser	Gly	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	Glu	Tyr	Glu
		450					455					460				
	Leu	Pro	Glu	Asp	Pro	Arg	Trp	Glu	Leu	Pro	Arg	Asp	Arg	Leu	Val	Leu
15		465				470					475					480
	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val	Leu	Ala	Glu
				485						490					495	
	Ala	Ile	Gly	Leu	Asp	Lys	Asp	Lys	Pro	Asn	Arg	Val	Thr	Lys	Val	Ala
				500					505					510		
20	Val	Lys	Met	Leu	Lys	Ser	Asp	Ala	Thr	Glu	Lys	Asp	Leu	Ser	Asp	Leu
			515					520					525			
	Ile	Ser	Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile
		530					535					540				
	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	Tyr	Val	Ile
		545				550					555					560
25	Val	Glu	Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu	Gln	Ala	Arg
				565						570					575	
	Arg	Pro	Pro	Gly	Leu	Glu	Tyr	Cys	Tyr	Asn	Pro	Ser	His	Asn	Pro	Glu
				580					585					590		
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				595				600					605			
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	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asp	Asn	Val	Met	Lys	Ile	Ala
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	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	His	His	Ile	Asp	Tyr	Tyr	Lys	Lys
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				660					665					670		
	Phe	Asp	Arg	Ile	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val
		675						680					685			
40	Leu	Leu	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr	Pro	Gly	Val
		690					695						700			
	Pro	Val	Glu	Glu	Leu	Phe	Lys	Leu	Leu	Lys	Glu	Gly	His	Arg	Met	Asp
		705				710					715					720
	Lys	Pro	Ser	Asn	Cys	Thr	Asn	Glu	Leu	Tyr	Met	Met	Met	Arg	Asp	Cys
				725						730				735		
45	Trp	His	Ala	Val	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln	Leu	Val	Glu
				740					745					750		
	Asp	Leu	Asp	Arg	Ile	Val	Ala	Leu	Thr	Ser	Asn	Gln	Glu	Tyr	Leu	Asp
			755					760					765			
	Leu	Ser	Met	Pro	Leu	Asp	Gln	Tyr	Ser	Pro	Ser	Phe	Pro	Asp	Thr	Arg
		770					775					780				
50	Ser	Ser	Thr	Cys	Ser	Ser	Gly	Glu	Asp	Ser	Val	Phe	Ser	His	Glu	Pro
		785				790					795					800
	Leu	Pro	Glu	Glu	Pro	Cys	Leu	Pro	Arg	His	Pro	Ala	Gln	Leu	Ala	Asn
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<210> 309

<211> 374

<212> PRT

<213> Artificial Sequence

<220>

5 <223> example of extracellular region of FGFR1c

<400> 309

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      20      25      30
      Pro Trp Gly Ala Pro Val Glu Val Glu Ser Phe Leu Val His Pro Gly
      35      40      45
15      Asp Leu Leu Gln Leu Arg Cys Arg Leu Arg Asp Asp Val Gln Ser Ile
      50      55      60
      Asn Trp Leu Arg Asp Gly Val Gln Leu Ala Glu Ser Asn Arg Thr Arg
      65      70      75      80
      Ile Thr Gly Glu Glu Val Glu Val Gln Asp Ser Val Pro Ala Asp Ser
      85      90      95
20      Gly Leu Tyr Ala Cys Val Thr Ser Ser Pro Ser Gly Ser Asp Thr Thr
      100      105      110
      Tyr Phe Ser Val Asn Val Ser Asp Ala Leu Pro Ser Ser Glu Asp Asp
      115      120      125
      Asp Asp Asp Asp Asp Ser Ser Ser Glu Glu Lys Glu Thr Asp Asn Thr
      130      135      140
25      Lys Pro Asn Arg Met Pro Val Ala Pro Tyr Trp Thr Ser Pro Glu Lys
      145      150      155      160
      Met Glu Lys Lys Leu His Ala Val Pro Ala Ala Lys Thr Val Lys Phe
      165      170      175
      Lys Cys Pro Ser Gly Thr Pro Asn Pro Thr Leu Arg Trp Leu Lys
      180      185      190
30      Asn Gly Lys Glu Phe Lys Pro Asp His Arg Ile Gly Gly Tyr Lys Val
      195      200      205
      Arg Tyr Ala Thr Trp Ser Ile Ile Met Asp Ser Val Val Pro Ser Asp
      210      215      220
35      Lys Gly Asn Tyr Thr Cys Ile Val Glu Asn Glu Tyr Gly Ser Ile Asn
      225      230      235      240
      His Thr Tyr Gln Leu Asp Val Val Glu Arg Ser Pro His Arg Pro Ile
      245      250      255
      Leu Gln Ala Gly Leu Pro Ala Asn Lys Thr Val Ala Leu Gly Ser Asn
      260      265      270
40      Val Glu Phe Met Cys Lys Val Tyr Ser Asp Pro Gln Pro His Ile Gln
      275      280      285
      Trp Leu Lys His Ile Glu Val Asn Gly Ser Lys Ile Gly Pro Asp Asn
      290      295      300
45      Leu Pro Tyr Val Gln Ile Leu Lys Thr Ala Gly Val Asn Thr Thr Asp
      305      310      315      320
      Lys Glu Met Glu Val Leu His Leu Arg Asn Val Ser Phe Glu Asp Ala
      325      330      335
      Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu Ser His His
      340      345      350
50      Ser Ala Trp Leu Thr Val Leu Glu Ala Leu Glu Glu Arg Pro Ala Val
      355      360      365
      Met Thr Ser Pro Leu Tyr
      370

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<210> 310

55 <211> 2466

<212> DNA

<213> Homo sapiens

<220>

<223> Coding sequence of human FGFR2c (NM_000141.4)

<400> 310

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      gaagattttg tcagtgaaga cagtaacaac aagagagcac catactggac caacacagaa 480
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      gagcatcgca ttggaggcta caaggtacga aaccagcact ggagcctcat tatggaaagt 660
      gtggtcccat ctgacaaggg aaattatacc tgtgtagtgg agaatgaata cgggtccatc 720
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20     tacggggccg acgggctgcc ctacctcaag gttctcaagg ccgccggtgt taacaccacg 960
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      aaaatagcag actttggact cgccagagat atcaacaata tagactatta caaaaagacc 1980
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      cctagttacc ctgacacaag aagttcttgt tcttcaggag atgattctgt tttttctcca 2400
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<210> 311

<211> 821

<212> PRT

<213> Homo sapiens

<220>

<223> human FGFR2c (NP_000132.3)

<400> 311

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Met	Val	Ser	Trp	Gly	Arg	Phe	Ile	Cys	Leu	Val	Val	Val	Thr	Met	Ala
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5	Thr	Leu	Ser	Leu	Ala	Arg	Pro	Ser	Phe	Ser	Leu	Val	Glu	Asp	Thr	Thr
				20					25					30		

10

15

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25

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55

EP 3 097 122 B9

	Leu	Glu	Pro	Glu	Glu	Pro	Pro	Thr	Lys	Tyr	Gln	Ile	Ser	Gln	Pro	Glu	
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5	Val	Tyr	Val	Ala	Ala	Pro	Gly	Glu	Ser	Leu	Glu	Val	Arg	Cys	Leu	Leu	
		50					55					60					
10	Lys	Asp	Ala	Ala	Val	Ile	Ser	Trp	Thr	Lys	Asp	Gly	Val	His	Leu	Gly	
	65					70					75					80	
15	Pro	Asn	Asn	Arg	Thr	Val	Leu	Ile	Gly	Glu	Tyr	Leu	Gln	Ile	Lys	Gly	
					85					90					95		
20	Ala	Thr	Pro	Arg	Asp	Ser	Gly	Leu	Tyr	Ala	Cys	Thr	Ala	Ser	Arg	Thr	
				100					105					110			
25	Val	Asp	Ser	Glu	Thr	Trp	Tyr	Phe	Met	Val	Asn	Val	Thr	Asp	Ala	Ile	
			115					120					125				
30	Ser	Ser	Gly	Asp	Asp	Glu	Asp	Asp	Thr	Asp	Gly	Ala	Glu	Asp	Phe	Val	
		130					135					140					
35	Ser	Glu	Asn	Ser	Asn	Asn	Lys	Arg	Ala	Pro	Tyr	Trp	Thr	Asn	Thr	Glu	
	145					150					155					160	
40	Lys	Met	Glu	Lys	Arg	Leu	His	Ala	Val	Pro	Ala	Ala	Asn	Thr	Val	Lys	
					165					170					175		
45	Phe	Arg	Cys	Pro	Ala	Gly	Gly	Asn	Pro	Met	Pro	Thr	Met	Arg	Trp	Leu	
				180					185					190			
50	Lys	Asn	Gly	Lys	Glu	Phe	Lys	Gln	Glu	His	Arg	Ile	Gly	Gly	Tyr	Lys	
			195					200					205				
55	Val	Arg	Asn	Gln	His	Trp	Ser	Leu	Ile	Met	Glu	Ser	Val	Val	Pro	Ser	
		210					215					220					
60	Asp	Lys	Gly	Asn	Tyr	Thr	Cys	Val	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	
	225					230					235					240	
65	Asn	His	Thr	Tyr	His	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	
					245					250					255		
70	Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Ala	Ser	Thr	Val	Val	Gly	Gly	
				260					265					270			
75	Asp	Val	Glu	Phe	Val	Cys	Lys	Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	
			275					280					285				

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	Gln	Trp	Ile	Lys	His	Val	Glu	Lys	Asn	Gly	Ser	Lys	Tyr	Gly	Pro	Asp	
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5	Gly	Leu	Pro	Tyr	Leu	Lys	Val	Leu	Lys	Ala	Ala	Gly	Val	Asn	Thr	Thr	
	305					310					315					320	
10	Asp	Lys	Glu	Ile	Glu	Val	Leu	Tyr	Ile	Arg	Asn	Val	Thr	Phe	Glu	Asp	
					325					330					335		
15	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Ile	Ser	Phe	
				340					345					350			
20	His	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro	Ala	Pro	Gly	Arg	Glu	Lys	Glu	
			355					360					365				
25	Ile	Thr	Ala	Ser	Pro	Asp	Tyr	Leu	Glu	Ile	Ala	Ile	Tyr	Cys	Ile	Gly	
	370						375					380					
30	Val	Phe	Leu	Ile	Ala	Cys	Met	Val	Val	Thr	Val	Ile	Leu	Cys	Arg	Met	
	385					390					395					400	
35	Lys	Asn	Thr	Thr	Lys	Lys	Pro	Asp	Phe	Ser	Ser	Gln	Pro	Ala	Val	His	
					405					410					415		
40	Lys	Leu	Thr	Lys	Arg	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala	
				420					425					430			
45	Glu	Ser	Ser	Ser	Ser	Met	Asn	Ser	Asn	Thr	Pro	Leu	Val	Arg	Ile	Thr	
			435					440					445				
50	Thr	Arg	Leu	Ser	Ser	Thr	Ala	Asp	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	
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55	Glu	Tyr	Glu	Leu	Pro	Glu	Asp	Pro	Lys	Trp	Glu	Phe	Pro	Arg	Asp	Lys	
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				500					505					510			
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			515					520					525				
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	530		535		540	
5	Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu	545	550	555	560	
10	Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu	565	570	575		
15	Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Ile Asn Arg	580	585	590		
20	Val Pro Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser Cys Thr Tyr	595	600	605		
25	Gln Leu Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile His	610	615	620		
30	Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn Asn Val Met	625	630	635	640	
35	Lys Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn Ile Asp Tyr	645	650	655		
40	Tyr Lys Lys Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro	660	665	670		
45	Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val Trp Ser	675	680	685		
50	Phe Gly Val Leu Met Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr	690	695	700		
55	Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His	705	710	715	720	
	Arg Met Asp Lys Pro Ala Asn Cys Thr Asn Glu Leu Tyr Met Met Met	725	730	735		
	Arg Asp Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln	740	745	750		
	Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr Asn Glu Glu	755	760	765		
	Tyr Leu Asp Leu Ser Gln Pro Leu Glu Gln Tyr Ser Pro Ser Tyr Pro	770	775	780		

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Asp Thr Arg Ser Ser Cys Ser Ser Gly Asp Asp Ser Val Phe Ser Pro
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5 Asp Pro Met Pro Tyr Glu Pro Cys Leu Pro Gln Tyr Pro His Ile Asn
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10 Gly Ser Val Lys Thr
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<400> 313

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5	Val	Ala	Gly	Ala	Ser	Ser	Glu	Ser	Leu	Gly	Thr	Glu	Gln	Arg	Val	Val	
				20					25					30			
10	Gly	Arg	Ala	Ala	Glu	Val	Pro	Gly	Pro	Glu	Pro	Gly	Gln	Gln	Glu	Gln	
			35					40					45				
15	Leu	Val	Phe	Gly	Ser	Gly	Asp	Ala	Val	Glu	Leu	Ser	Cys	Pro	Pro	Pro	
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20	Gly	Gly	Gly	Pro	Met	Gly	Pro	Thr	Val	Trp	Val	Lys	Asp	Gly	Thr	Gly	
	65					70				75						80	
25	Leu	Val	Pro	Ser	Glu	Arg	Val	Leu	Val	Gly	Pro	Gln	Arg	Leu	Gln	Val	
					85					90					95		
30	Leu	Asn	Ala	Ser	His	Glu	Asp	Ser	Gly	Ala	Tyr	Ser	Cys	Arg	Gln	Arg	
				100					105					110			
35	Leu	Thr	Gln	Arg	Val	Leu	Cys	His	Phe	Ser	Val	Arg	Val	Thr	Asp	Ala	
			115					120					125				
40	Pro	Ser	Ser	Gly	Asp	Asp	Glu	Asp	Gly	Glu	Asp	Glu	Ala	Glu	Asp	Thr	
		130					135					140					
45	Gly	Val	Asp	Thr	Gly	Ala	Pro	Tyr	Trp	Thr	Arg	Pro	Glu	Arg	Met	Asp	
	145					150					155					160	
50	Lys	Lys	Leu	Leu	Ala	Val	Pro	Ala	Ala	Asn	Thr	Val	Arg	Phe	Arg	Cys	
					165					170					175		
55	Pro	Ala	Ala	Gly	Asn	Pro	Thr	Pro	Ser	Ile	Ser	Trp	Leu	Lys	Asn	Gly	
				180					185					190			
60	Arg	Glu	Phe	Arg	Gly	Glu	His	Arg	Ile	Gly	Gly	Ile	Lys	Leu	Arg	His	
			195					200					205				
65	Gln	Gln	Trp	Ser	Leu	Val	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	
		210					215					220					

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	Asn	Tyr	Thr	Cys	Val	Val	Glu	Asn	Lys	Phe	Gly	Ser	Ile	Arg	Gln	Thr	225	230	235	240
5	Tyr	Thr	Leu	Asp	Val	Leu	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln		245	250	255
10	Ala	Gly	Leu	Pro	Ala	Asn	Gln	Thr	Ala	Val	Leu	Gly	Ser	Asp	Val	Glu		260	265	270
15	Phe	His	Cys	Lys	Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu		275	280	285
20	Lys	His	Val	Glu	Val	Asn	Gly	Ser	Lys	Val	Gly	Pro	Asp	Gly	Thr	Pro		290	295	300
25	Tyr	Val	Thr	Val	Leu	Lys	Thr	Ala	Gly	Ala	Asn	Thr	Thr	Asp	Lys	Glu		305	310	315
	Leu	Glu	Val	Leu	Ser	Leu	His	Asn	Val	Thr	Phe	Glu	Asp	Ala	Gly	Glu		325	330	335
30	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Phe	Ser	His	His	Ser	Ala		340	345	350
35	Trp	Leu	Val	Val	Leu	Pro	Ala	Glu	Glu	Glu	Leu	Val	Glu	Ala	Asp	Glu		355	360	365
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40	Leu	Phe	Ile	Leu	Val	Val	Ala	Ala	Val	Thr	Leu	Cys	Arg	Leu	Arg	Ser		385	390	395
45	Pro	Pro	Lys	Lys	Gly	Leu	Gly	Ser	Pro	Thr	Val	His	Lys	Ile	Ser	Arg		405	410	415
50	Phe	Pro	Leu	Lys	Arg	Gln	Val	Ser	Leu	Glu	Ser	Asn	Ala	Ser	Met	Ser		420	425	430
	Ser	Asn	Thr	Pro	Leu	Val	Arg	Ile	Ala	Arg	Leu	Ser	Ser	Gly	Glu	Gly		435	440	445
55	Pro	Thr	Leu	Ala	Asn	Val	Ser	Glu	Leu	Glu	Leu	Pro	Ala	Asp	Pro	Lys		450	455	460
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10	Asp	Arg	Ala	Ala	Lys	Pro	Val	Thr	Val	Ala	Val	Lys	Met	Leu	Lys	Asp
				500					505					510		
15	Asp	Ala	Thr	Asp	Lys	Asp	Leu	Ser	Asp	Leu	Val	Ser	Glu	Met	Glu	Met
			515					520					525			
20	Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile	Ile	Asn	Leu	Leu	Gly	Ala
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25	Cys	Thr	Gln	Gly	Gly	Pro	Leu	Tyr	Val	Leu	Val	Glu	Tyr	Ala	Ala	Lys
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					565					570					575	
35	Tyr	Ser	Phe	Asp	Thr	Cys	Lys	Pro	Pro	Glu	Glu	Gln	Leu	Thr	Phe	Lys
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40	Asp	Leu	Val	Ser	Cys	Ala	Tyr	Gln	Val	Ala	Arg	Gly	Met	Glu	Tyr	Leu
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45	Ala	Ser	Gln	Lys	Cys	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu
	610						615					620				
50	Val	Thr	Glu	Asp	Asn	Val	Met	Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ala	Arg
	625					630				635						640
55	Asp	Val	His	Asn	Leu	Asp	Tyr	Tyr	Lys	Lys	Thr	Thr	Asn	Gly	Arg	Leu
				645					650						655	
60	Pro	Val	Lys	Trp	Met	Ala	Pro	Glu	Ala	Leu	Phe	Asp	Arg	Val	Tyr	Thr
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65	His	Gln	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile	Phe
			675					680					685			
70	Thr	Leu	Gly	Gly	Ser	Pro	Tyr	Pro	Gly	Ile	Pro	Val	Glu	Glu	Leu	Phe
	690						695					700				
75	Lys	Leu	Leu	Lys	Glu	Gly	His	Arg	Met	Asp	Lys	Pro	Ala	Asn	Cys	Thr
	705					710					715					720

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His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
725 730 735

5 Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
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10 Thr Val Thr Ser Thr Asp Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu
755 760 765

Gln Tyr Ser Pro Gly Gly Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly
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25 <212> DNA

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<400> 315

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5	Pro	Pro	Val	Leu	Ser	Leu	Glu	Ala	Ser	Glu	Glu	Val	Glu	Leu	Glu	Pro
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10	Cys	Leu	Ala	Pro	Ser	Leu	Glu	Gln	Gln	Glu	Gln	Glu	Leu	Thr	Val	Ala
			35					40					45			
15	Leu	Gly	Gln	Pro	Val	Arg	Leu	Cys	Cys	Gly	Arg	Ala	Glu	Arg	Gly	Gly
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20	His	Trp	Tyr	Lys	Glu	Gly	Ser	Arg	Leu	Ala	Pro	Ala	Gly	Arg	Val	Arg
	65					70					75					80
25	Gly	Trp	Arg	Gly	Arg	Leu	Glu	Ile	Ala	Ser	Phe	Leu	Pro	Glu	Asp	Ala
					85					90					95	
30	Gly	Arg	Tyr	Leu	Cys	Leu	Ala	Arg	Gly	Ser	Met	Ile	Val	Leu	Gln	Asn
				100					105					110		
35	Leu	Thr	Leu	Ile	Thr	Gly	Asp	Ser	Leu	Thr	Ser	Ser	Asn	Asp	Asp	Glu
			115					120					125			
40	Asp	Pro	Lys	Ser	His	Arg	Asp	Pro	Ser	Asn	Arg	His	Ser	Tyr	Pro	Gln
		130					135					140				
45	Gln	Ala	Pro	Tyr	Trp	Thr	His	Pro	Gln	Arg	Met	Glu	Lys	Lys	Leu	His
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50	Ala	Val	Pro	Ala	Gly	Asn	Thr	Val	Lys	Phe	Arg	Cys	Pro	Ala	Ala	Gly
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	Asn	Pro	Thr	Pro	Thr	Ile	Arg	Trp	Leu	Lys	Asp	Gly	Gln	Ala	Phe	His	
				180					185					190			
5	Gly	Glu	Asn	Arg	Ile	Gly	Gly	Ile	Arg	Leu	Arg	His	Gln	His	Trp	Ser	
			195					200					205				
10	Leu	Val	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys	
		210					215					220					
15	Leu	Val	Glu	Asn	Ala	Val	Gly	Ser	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp	
	225					230					235					240	
20	Val	Leu	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro	
					245					250					255		
25	Ala	Asn	Thr	Thr	Ala	Val	Val	Gly	Ser	Asp	Val	Glu	Leu	Leu	Cys	Lys	
				260					265					270			
30	Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val	
			275					280					285				
35	Ile	Asn	Gly	Ser	Ser	Phe	Gly	Ala	Asp	Gly	Phe	Pro	Tyr	Val	Gln	Val	
	290						295					300					
40	Leu	Lys	Thr	Ala	Asp	Ile	Asn	Ser	Ser	Glu	Val	Glu	Val	Leu	Tyr	Leu	
	305					310					315					320	
45	Arg	Asn	Val	Ser	Ala	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	
				325						330					335		
50	Asn	Ser	Ile	Gly	Leu	Ser	Tyr	Gln	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro	
				340					345					350			
55	Glu	Glu	Asp	Pro	Thr	Trp	Thr	Ala	Ala	Ala	Pro	Glu	Ala	Arg	Tyr	Thr	
			355					360					365				
60	Asp	Ile	Ile	Leu	Tyr	Ala	Ser	Gly	Ser	Leu	Ala	Leu	Ala	Val	Leu	Leu	
							375					380					
65	Leu	Leu	Ala	Gly	Leu	Tyr	Arg	Gly	Gln	Ala	Leu	His	Gly	Arg	His	Pro	
	385					390					395					400	
70	Arg	Pro	Pro	Ala	Thr	Val	Gln	Lys	Leu	Ser	Arg	Phe	Pro	Leu	Ala	Arg	
				405						410					415		
75	Gln	Phe	Ser	Leu	Glu	Ser	Gly	Ser	Ser	Gly	Lys	Ser	Ser	Ser	Ser	Leu	

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	420		425		430											
5	Val	Arg	Gly	Val	Arg	Leu	Ser	Ser	Ser	Gly	Pro	Ala	Leu	Leu	Ala	Gly
			435					440					445			
	Leu	Val	Ser	Leu	Asp	Leu	Pro	Leu	Asp	Pro	Leu	Trp	Glu	Phe	Pro	Arg
10			450				455					460				
	Asp	Arg	Leu	Val	Leu	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln
	465					470					475					480
15	Val	Val	Arg	Ala	Glu	Ala	Phe	Gly	Met	Asp	Pro	Ala	Arg	Pro	Asp	Gln
					485					490					495	
	Ala	Ser	Thr	Val	Ala	Val	Lys	Met	Leu	Lys	Asp	Asn	Ala	Ser	Asp	Lys
20				500					505					510		
	Asp	Leu	Ala	Asp	Leu	Val	Ser	Glu	Met	Glu	Val	Met	Lys	Leu	Ile	Gly
			515					520					525			
25	Arg	His	Lys	Asn	Ile	Ile	Asn	Leu	Leu	Gly	Val	Cys	Thr	Gln	Glu	Gly
	530						535					540				
30	Pro	Leu	Tyr	Val	Ile	Val	Glu	Cys	Ala	Ala	Lys	Gly	Asn	Leu	Arg	Glu
	545					550					555					560
	Phe	Leu	Arg	Ala	Arg	Arg	Pro	Pro	Gly	Pro	Asp	Leu	Ser	Pro	Asp	Gly
35					565					570					575	
	Pro	Arg	Ser	Ser	Glu	Gly	Pro	Leu	Ser	Phe	Pro	Val	Leu	Val	Ser	Cys
				580					585					590		
40	Ala	Tyr	Gln	Val	Ala	Arg	Gly	Met	Gln	Tyr	Leu	Glu	Ser	Arg	Lys	Cys
			595					600					605			
45	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asp	Asn
	610						615					620				
	Val	Met	Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Gly	Val	His	His	Ile
50	625					630					635					640
	Asp	Tyr	Tyr	Lys	Lys	Thr	Ser	Asn	Gly	Arg	Leu	Pro	Val	Lys	Trp	Met
					645					650					655	
55	Ala	Pro	Glu	Ala	Leu	Phe	Asp	Arg	Val	Tyr	Thr	His	Gln	Ser	Asp	Val
				660					665					670		

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	Trp	Ser	Phe	Gly	Ile	Leu	Leu	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser
			675					680					685			
5	Pro	Tyr	Pro	Gly	Ile	Pro	Val	Glu	Glu	Leu	Phe	Ser	Leu	Leu	Arg	Glu
		690					695					700				
10	Gly	His	Arg	Met	Asp	Arg	Pro	Pro	His	Cys	Pro	Pro	Glu	Leu	Tyr	Gly
	705					710					715					720
	Leu	Met	Arg	Glu	Cys	Trp	His	Ala	Ala	Pro	Ser	Gln	Arg	Pro	Thr	Phe
					725					730					735	
15	Lys	Gln	Leu	Val	Glu	Ala	Leu	Asp	Lys	Val	Leu	Leu	Ala	Val	Ser	Glu
				740					745					750		
20	Glu	Tyr	Leu	Asp	Leu	Arg	Leu	Thr	Phe	Gly	Pro	Tyr	Ser	Pro	Ser	Gly
			755					760					765			
25	Gly	Asp	Ala	Ser	Ser	Thr	Cys	Ser	Ser	Ser	Asp	Ser	Val	Phe	Ser	His
		770					775					780				
	Asp	Pro	Leu	Pro	Leu	Gly	Ser	Ser	Ser	Phe	Pro	Phe	Gly	Ser	Gly	Val
	785					790					795					800
30	Gln	Thr														
	<210> 316															
	<211> 330															
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	<223> human IgG1 Fc with two amino acid changes to alanine															
40	<400> 316															
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	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys
	1				5					10					15	
	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
				20					25					30		
5	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
			35					40					45			
	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
		50					55					60				
	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr
10	65					70					75					80
	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
				85						90					95	
	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys
				100					105					110		
	Pro	Ala	Pro	Ala	Leu	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro
15			115					120					125			
	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
		130					135					140				
20	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp
	145					150					155					160
	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
				165						170					175	
	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu
				180					185					190		
25	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
			195					200					205			
	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
		210					215					220				
	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu
						230					235					240
30	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
				245						250					255	
	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
				260					265					270		
	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
35			275					280					285			
	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
		290					295					300				
	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
						310					315					320
40	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						
					325					330						

<210> 317

<211> 472

<212> PRT

45 <213> Artificial Sequence

<220>

<223> Humanized 5H23-vH3-human IgG1 (E233A) (L235A)

50 <400> 317

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	Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp
	1				5					10					15	
5	Leu	Arg	Gly	Ala	Arg	Cys	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu
				20					25					30		
	Val	Lys	Lys	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly
10			35					40					45			
	Tyr	Thr	Phe	Thr	Ser	Tyr	Asp	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly
		50					55					60				
15																
	Gln	Gly	Leu	Glu	Trp	Ile	Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr
	65					70					75					80
20	Lys	Tyr	Asn	Glu	Lys	Phe	Lys	Gly	Lys	Ala	Thr	Ile	Thr	Arg	Asp	Thr
					85					90					95	
	Ser	Ala	Ser	Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp
25				100					105					110		
30																
35																
40																
45																
50																
55																

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	Thr	Ala	Val	Tyr	Phe	Cys	Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	
			115					120					125				
5	Phe	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	
		130					135					140					
10	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	
	145					150					155					160	
	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	
					165					170					175		
15	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	
				180					185					190			
20	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	
			195					200					205				
	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	
25		210					215					220					
	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	
	225					230					235					240	
30	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	
					245					250					255		
	Pro	Ala	Leu	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	
35				260					265					270			
	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	
			275					280					285				
40	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	
		290					295					300					
45	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	
	305					310					315					320	
	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	
50				325						330					335		
	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	
				340					345					350			
55	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	
			355					360					365				

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	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	
	370						375					380					
5	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	
	385					390					395					400	
10	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	
					405					410					415		
15	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	
				420					425					430			
20	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	
			435					440					445				
25	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	
		450					455					460					
30	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys									
	465					470											
	<210> 318																
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	<212> PRT																
	<213> Homo sapiens																
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	<223> Human kappa constant region of light chain																
	<400> 318																
35	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	
	1				5					10					15		
40	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	
				20					25					30			
45	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	
		35					40						45				
50	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	
	50						55					60					
55	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	
	65					70					75					80	
60	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	
				85						90					95		
65	Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys						
				100					105								
70	<210> 319																
	<211> 240																
	<212> PRT																
	<213> Artificial Sequence																
75	<220>																
	<223> humanized 5H23-vL2-human kappa constant region of light chain																
80	<400> 319																

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	Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp
	1				5					10					15	
5	Leu	Arg	Gly	Ala	Arg	Cys	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser
				20					25					30		
10	Leu	Ala	Val	Ser	Leu	Gly	Glu	Arg	Ala	Thr	Ile	Asn	Cys	Arg	Ala	Ser
			35					40					45			
15	Lys	Ser	Val	Ser	Thr	Ser	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln
	50						55					60				
20	Lys	Pro	Gly	Gln	Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu
	65					70					75					80
25	Glu	Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp
					85					90					95	
30	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Val	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr
				100					105					110		
35	Tyr	Cys	Gln	His	Ser	Arg	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr
			115					120					125			
40	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe
	130						135					140				
45	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys
	145					150					155					160
50	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val
					165					170					175	
55	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln
				180				185						190		
60	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser
			195					200					205			
65	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His
	210						215					220				
70	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys
	225					230					235					240
75	<210> 320															
	<211> 120															
	<212> PRT															
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<220>

<223> vH7

<400> 320

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10

15

20

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1          5          10          15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
          20          25          30
Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
          35          40          45
Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Lys Tyr Asn Glu Lys Phe
 50          55          60
Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
 65          70          75          80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
          85          90          95
Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Ala Tyr Trp Gly Gln
          100          105          110
Gly Thr Leu Val Thr Val Ser Ser
          115          120

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<210> 321

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> vH8

<400> 321

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
          20          25          30
Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
          35          40          45
Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Lys Tyr Asn Glu Lys Phe
 50          55          60
Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Arg Thr Ala Tyr
 65          70          75          80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
          85          90          95
Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Ala Tyr Trp Gly Gln
          100          105          110
Gly Thr Leu Val Thr Val Ser Ser
          115          120

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<210> 322

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> vH9

<400> 322

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	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
	1				5					10					15	
5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
				20				25						30		
	Asp	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
			35					40					45			
	Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
		50					55					60				
10	Lys	Gly	Arg	Ala	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
	65					70					75					80
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Ala	Tyr	Trp	Gly	Gln
				100					105					110		
15	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
			115					120								

<210> 323

<211> 120

20 <212> PRT

<213> Artificial Sequence

<220>

<223> 5H23v1-3

25

<400> 323

	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
	1				5					10					15	
30	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
				20				25						30		
	Asp	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Arg	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
		50					55					60				
35	Lys	Gly	Arg	Val	Thr	Ile	Thr	Arg	Asp	Thr	Ser	Ala	Ser	Thr	Ala	Tyr
	65					70					75					80
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Ala	Tyr	Trp	Gly	Gln
				100					105					110		
40	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
			115					120								

<210> 324

45 <211> 120

<212> PRT

<213> Artificial Sequence

<220>

50 <223> 5H23v1-46

<400> 324

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5 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Tyr Pro Gly Asp Gly Ser Thr Lys Tyr Asn Glu Lys Phe
 50 55 60
 10 Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

15 85 90 95
 Ala Arg Ser Asp Tyr Tyr Gly Ser Arg Ser Phe Ala Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120

20 <210> 325
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25 <220>
 <223> vL4
 <400> 325

30 Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
 20 25 30
 Gly Tyr Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro
 35 40 45
 35 Lys Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Asp
 50 55 60
 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
 65 70 75 80
 Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His Ser Arg
 85 90 95
 40 Asp Leu Thr Phe Pro Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

45 <210> 326
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50 <220>
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 <400> 326

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EP 3 097 122 B9

	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Ile	Asn	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Asp
	50						55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65					70					75					80
	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	
				100					105						110	

15 <210> 327
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20 <220>
 <223> v1-39a

<400> 327

25	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
	50						55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70					75					80
35	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105						110	

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45 <220>
 <223> v1-39b

<400> 328

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EP 3 097 122 B9

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	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70					75				80	
10	Ser	Val	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
				85						90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

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- <210> 329
- <211> 111
- <212> PRT
- <213> Artificial Sequence

20 <220>
 <223> vl-39c

<400> 329

25	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
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	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20						25					30		
	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro
30			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70					75					80
35																
	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

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<212> PRT
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<220>
<223> v1-39d

<400> 330

EP 3 097 122 B9

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65					70				75						80
	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105						110	

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 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> v1-39e

<400> 331

25	Asp	Ile	Gln	Leu	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75						80
35	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105						110	

40 <210> 332
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 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> v1-39f

<400> 332

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EP 3 097 122 B9

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30			
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35				40					45				
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55				60					
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75					80	
10	Ser	Val	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
				85					90					95		
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

15 <210> 333
 <211> 111
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> v1-39g

<400> 333

25	Asp	Ile	Gln	Leu	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30			
	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35				40					45				
30	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55				60					
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75					80	
	Ser	Val	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
35				85					90					95		
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

40 <210> 334
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 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> v1-39h

<400> 334

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EP 3 097 122 B9

5 Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
 20 25 30
 Gly Tyr Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Lys Pro Pro
 35 40 45
 Lys Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ser
 50 55 60
 10 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
 65 70 75 80
 Ser Val Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ser Arg

15 85 90 95
 Asp Leu Thr Phe Pro Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 335

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> v1-39i

<400> 335

30 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
 20 25 30
 Gly Tyr Val Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
 35 40 45
 Lys Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ser
 50 55 60
 35 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
 65 70 75 80
 Ser Leu Gln Glu Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ser Arg
 85 90 95
 Asp Leu Thr Phe Pro Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 336

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> v1-39j

<400> 336

EP 3 097 122 B9

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	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30			
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro
			35				40						45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75					80	
10	Ser	Val	Gln	Glu	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
				85						90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105						110	

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 <213> Artificial Sequence

20 <220>
 <223> v1-39k

<400> 337

25	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30			
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35				40						45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75					80	
35	Ser	Val	Gln	Glu	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
				85						90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105						110	

40 <210> 338
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 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> v1-391

<400> 338

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EP 3 097 122 B9

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	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20						25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65					70					75				80	
	Ser	Val	Gln	Glu	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

15 <210> 339
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 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> v1-39m

<400> 339

25	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20						25					30		
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70					75				80	
35	Ser	Val	Gln	Glu	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	

40 Asp Leu Thr Phe Pro Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 340
 <211> 111
 <212> PRT
 45 <213> Artificial Sequence

<220>
 <223> v1-39n

50 <400> 340

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EP 3 097 122 B9

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30			
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35				40					45				
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50				55					60					
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65					70				75					80	
	Ser	Val	Gln	Glu	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
				85					90					95		
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

15 <210> 341
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 <212> PRT
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20 <220>
 <223> v1-39o

<400> 341

25	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30			
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35				40					45				
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
		50				55					60					
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75					80	
35	Ser	Val	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
				85					90					95		
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gln	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

40 <210> 342
 <211> 111
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> v1-39p

<400> 342

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EP 3 097 122 B9

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30			
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro
			35				40					45				
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ser
	50					55					60					
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65				70					75					80	
	Ser	Val	Gln	Glu	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Arg
				85					90					95		
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gln	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

15 <210> 343
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 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> v3-20a

<400> 343

25	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
			20					25					30			
	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
30			35				40					45				
	Arg	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Ile	Pro	Ala
	50					55					60					
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65				70					75					80	
	Arg	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
35				85					90					95		
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

40 <210> 344
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 <223> v3-20b

<400> 344

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EP 3 097 122 B9

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Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30
Gly Tyr Val Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45
Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Ile Pro Ala
50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80
Arg Val Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
85 90 95
Asp Leu Thr Phe Pro Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

<210> 345
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<212> PRT
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<400> 345

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105
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Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30
Gly Tyr Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45
Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Ile Pro Ala
50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80
Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
85 90 95
Asp Leu Thr Phe Pro Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 346
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> v3-20d

<400> 346

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	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
			35					40					45			
	Arg	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Ile	Pro	Ala
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75						80
10	Arg	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105						110	

15 <210> 347
 <211> 111
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> v3-20e

<400> 347

25	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
			35					40					45			
	Arg	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Ile	Pro	Ala
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
35	65					70				75						80
	Arg	Leu	Glu	Pro	Glu	Asp	Ala	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105						110	

40 <210> 348
 <211> 111
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> v3-20f

<400> 348

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	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
			35					40					45			
	Arg	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Ile	Pro	Ala
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65					70				75						80
	Arg	Val	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

15 <210> 349
 <211> 111
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> v3-20g

<400> 349

25	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
			35					40					45			
	Arg	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Ile	Pro	Ala
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75						80
35	Arg	Val	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

40 <210> 350
 <211> 111
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> v3-20h

<400> 350

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	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
			35					40					45			
	Arg	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Ile	Pro	Ala
	50						55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65					70				75						80
	Arg	Leu	Glu	Glu	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

15 <210> 351
 <211> 111
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> v3-20i

<400> 351

25	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
30	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
			35					40					45			
	Arg	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Ile	Pro	Ala
	50						55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75						80
35	Arg	Val	Glu	Glu	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

40 <210> 352
 <211> 111
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> v3-20j

<400> 352

50	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	

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5 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
 20 25 30
Gly Tyr Val Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro
 35 40 45
10 Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Ile Pro Ala
 50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80
Arg Val Glu Glu Glu Asp Ala Ala Val Tyr Tyr Cys Gln His Ser Arg
10 85 90 95
Asp Leu Thr Phe Pro Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 353

15 <211> 111

<212> PRT

<213> Artificial Sequence

<220>

20 <223> hz5H23v1-39

<400> 353

25 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
 20 25 30
Gly Tyr Val Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
 35 40 45
30 Lys Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ser
 50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ser Arg
 85 90 95
35 Asp Leu Thr Phe Pro Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 354

40 <211> 111

<212> PRT

<213> Artificial Sequence

<220>

45 <223> hz5H23v3-20

<400> 354

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	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro
			35					40					45			
	Arg	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Ile	Pro	Ala
	50						55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
10	65					70				75						80
	Arg	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

15 <210> 355
 <211> 111
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> hz5H23v4-1

<400> 355

25	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Ile	Asn	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
	Gly	Tyr	Val	Tyr	Met	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
30			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Asp
	50						55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
	65					70				75						80
	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Gln	His	Ser	Arg
35					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
				100					105					110		

40 <210> 356
 <211> 1043
 <212> PRT
 <213> Rattus

45 <220>
 <223> Rat beta klotho

<400> 356

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	Met	Lys	Thr	Gly	Cys	Ala	Ala	Gly	Ser	Pro	Gly	Asn	Glu	Trp	Val	Phe
	1				5					10					15	
	Phe	Ser	Ser	Asp	Glu	Arg	Ser	Thr	Arg	Ser	Arg	Lys	Thr	Met	Ser	Asn
				20					25					30		
5	Gly	Ala	Leu	Gln	Arg	Ser	Ala	Val	Leu	Ser	Ala	Leu	Val	Leu	Leu	Arg
			35					40					45			
	Ala	Val	Thr	Gly	Phe	Ser	Gly	Asp	Gly	Lys	Ala	Ile	Trp	Asp	Lys	Lys
		50					55					60				
	Gln	Tyr	Val	Ser	Pro	Val	Asn	Pro	Gly	Gln	Leu	Phe	Leu	Tyr	Asp	Thr
10	65					70					75				80	
	Phe	Pro	Lys	Asn	Phe	Ser	Trp	Gly	Val	Gly	Thr	Gly	Ala	Phe	Gln	Val
				85						90					95	
	Glu	Gly	Ser	Trp	Lys	Ala	Asp	Gly	Arg	Gly	Pro	Ser	Ile	Trp	Asp	Arg
			100					105						110		
	Tyr	Val	Asp	Ser	His	Leu	Arg	Gly	Val	Asn	Ser	Thr	Asp	Arg	Ser	Thr
15			115					120					125			
	Asp	Ser	Tyr	Val	Phe	Leu	Glu	Lys	Asp	Leu	Leu	Ala	Leu	Asp	Phe	Leu
		130					135					140				
	Gly	Val	Ser	Phe	Tyr	Gln	Phe	Ser	Ile	Ser	Trp	Pro	Arg	Leu	Phe	Pro
	145					150					155				160	
20	Asn	Gly	Thr	Val	Ala	Ala	Val	Asn	Ala	Lys	Gly	Leu	Gln	Tyr	Tyr	Arg
				165						170					175	
	Ala	Leu	Leu	Asp	Ser	Leu	Val	Leu	Arg	Asn	Ile	Glu	Pro	Ile	Val	Thr
			180					185						190		
	Leu	Tyr	His	Trp	Asp	Leu	Pro	Leu	Thr	Leu	Gln	Glu	Glu	Tyr	Gly	Gly
			195					200					205			
25	Trp	Lys	Asn	Ala	Thr	Met	Ile	Asp	Leu	Phe	Asn	Asp	Tyr	Ala	Thr	Tyr
		210					215					220				

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	Cys	Phe	Gln	Thr	Phe	Gly	Asp	Arg	Val	Lys	Tyr	Trp	Ile	Thr	Ile	His
	225					230					235					240
	Asn	Pro	Tyr	Leu	Val	Ala	Trp	His	Gly	Phe	Gly	Thr	Gly	Met	His	Ala
					245					250						255
5	Pro	Gly	Glu	Lys	Gly	Asn	Leu	Thr	Ala	Val	Tyr	Thr	Val	Gly	His	Asn
				260					265					270		
	Leu	Ile	Lys	Ala	His	Ser	Lys	Val	Trp	His	Asn	Tyr	Asp	Lys	Asn	Phe
			275					280					285			
	Arg	Pro	His	Gln	Lys	Gly	Trp	Leu	Ser	Ile	Thr	Leu	Gly	Ser	His	Trp
		290					295					300				
10	Ile	Glu	Pro	Asn	Arg	Thr	Glu	Asn	Met	Glu	Asp	Val	Ile	Asn	Cys	Gln
	305					310					315					320
	His	Ser	Met	Ser	Ser	Val	Leu	Gly	Trp	Phe	Ala	Asn	Pro	Ile	His	Gly
					325					330					335	
	Asp	Gly	Asp	Tyr	Pro	Glu	Phe	Met	Lys	Thr	Ser	Ser	Val	Ile	Pro	Glu
				340					345					350		
15	Phe	Ser	Glu	Ala	Glu	Lys	Glu	Glu	Val	Arg	Gly	Thr	Ala	Asp	Phe	Phe
			355					360					365			
	Ala	Phe	Ser	Phe	Gly	Pro	Asn	Asn	Phe	Arg	Pro	Ser	Asn	Thr	Val	Val
							375						380			
20	Lys	Met	Gly	Gln	Asn	Val	Ser	Leu	Asn	Leu	Arg	Gln	Val	Leu	Asn	Trp
	385					390					395					400
	Ile	Lys	Leu	Glu	Tyr	Asp	Asn	Pro	Arg	Ile	Leu	Ile	Ser	Glu	Asn	Gly
					405					410					415	
	Trp	Phe	Thr	Asp	Ser	Tyr	Ile	Lys	Thr	Glu	Asp	Thr	Thr	Ala	Ile	Tyr
				420					425					430		
25	Met	Met	Lys	Asn	Phe	Leu	Asn	Gln	Val	Leu	Gln	Ala	Ile	Lys	Phe	Asp
			435					440					445			
	Glu	Ile	Gln	Val	Phe	Gly	Tyr	Thr	Ala	Trp	Thr	Leu	Leu	Asp	Gly	Phe
							455					460				
	Glu	Trp	Gln	Asp	Ala	Tyr	Thr	Thr	Arg	Arg	Gly	Leu	Phe	Tyr	Val	Asp
	465					470					475					480
30	Phe	Asn	Ser	Glu	Gln	Lys	Glu	Arg	Lys	Pro	Lys	Ser	Ser	Ala	His	Tyr
					485					490					495	
	Tyr	Lys	Gln	Ile	Gln	Asp	Asn	Gly	Phe	Pro	Leu	Gln	Glu	Glu	Ser	Thr
				500				505					510			
	Pro	Asp	Met	Lys	Gly	Gln	Phe	Pro	Cys	Asp	Phe	Ser	Trp	Gly	Val	Thr
				515				520					525			
35	Glu	Ser	Val	Leu	Lys	Pro	Glu	Phe	Thr	Val	Ser	Ser	Pro	Gln	Phe	Thr
							535					540				
	Asp	Pro	His	Leu	Tyr	Val	Trp	Asn	Val	Thr	Gly	Asn	Arg	Leu	Leu	Tyr
	545					550					555					560
	Arg	Val	Glu	Gly	Val	Arg	Leu	Lys	Thr	Arg	Pro	Ser	Gln	Cys	Thr	Asp
					565					570					575	
40	Tyr	Val	Ser	Ile	Lys	Lys	Arg	Val	Glu	Met	Leu	Ala	Lys	Met	Lys	Val
				580					585					590		
	Thr	His	Tyr	Gln	Phe	Ala	Leu	Asp	Trp	Thr	Ser	Ile	Leu	Pro	Thr	Gly
								600					605			
	Asn	Leu	Ser	Lys	Ile	Asn	Arg	Gln	Val	Leu	Arg	Tyr	Tyr	Arg	Cys	Val
							615					620				
45	Val	Ser	Glu	Gly	Leu	Lys	Leu	Gly	Ile	Ser	Pro	Met	Val	Thr	Leu	Tyr
	625					630					635					640
	His	Pro	Thr	His	Ser	His	Leu	Gly	Leu	Pro	Met	Pro	Leu	Leu	Ser	Ser
					645					650					655	
50	Gly	Gly	Trp	Leu	Asn	Thr	Asn	Thr	Ala	Lys	Ala	Phe	Gln	Asp	Tyr	Ala
					660				665					670		
	Gly	Leu	Cys	Phe	Lys	Glu	Leu	Gly	Asp	Leu	Val	Lys	Leu	Trp	Ile	Thr
								680					685			
	Ile	Asn	Glu	Pro	Asn	Arg	Leu	Ser	Asp	Met	Tyr	Asn	Arg	Thr	Ser	Asn
							695					700				
55	Asp	Thr	Tyr	Arg	Ala	Ala	His	Asn	Leu	Met	Ile	Ala	His	Ala	Gln	Val
	705					710					715					720
	Trp	His	Leu	Tyr	Asp	Arg	Gln	Tyr	Arg	Pro	Val	Gln	His	Gly	Ala	Val

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				725					730				735			
	Ser	Leu	Ser	Leu	His	Ser	Asp	Trp	Ala	Glu	Pro	Ala	Asn	Pro	Tyr	Val
				740					745				750			
5	Glu	Ser	His	Trp	Lys	Ala	Ala	Glu	Arg	Phe	Leu	Gln	Phe	Glu	Ile	Ala
			755					760					765			
	Trp	Phe	Ala	Asp	Pro	Leu	Phe	Lys	Thr	Gly	Asp	Tyr	Pro	Leu	Ala	Met
		770					775					780				
	Lys	Glu	Tyr	Ile	Ala	Ser	Lys	Lys	Gln	Arg	Gly	Leu	Ser	Ser	Ser	Val
	785					790					795					800
10	Leu	Pro	Arg	Phe	Thr	Leu	Lys	Glu	Ser	Arg	Leu	Val	Lys	Gly	Thr	Ile
				805						810						
	Asp	Phe	Tyr	Ala	Leu	Asn	His	Phe	Thr	Thr	Arg	Phe	Val	Ile	His	Lys
				820					825					830		
	Gln	Leu	Asn	Thr	Asn	Cys	Ser	Val	Ala	Asp	Arg	Asp	Val	Gln	Phe	Leu
			835					840					845			
15	Gln	Asp	Ile	Thr	Arg	Leu	Ser	Ser	Pro	Ser	Arg	Leu	Ala	Val	Thr	Pro
		850					855					860				
	Trp	Gly	Met	Arg	Lys	Leu	Gly	Trp	Ile	Arg	Arg	Asn	Tyr	Arg	Asp	
	865					870				875						880
	Met	Asp	Ile	Tyr	Val	Thr	Ala	Asn	Gly	Ile	Asp	Asp	Leu	Ala	Leu	Glu
				885					890							895
20	Asp	Asp	Gln	Ile	Arg	Lys	Tyr	Tyr	Leu	Glu	Lys	Tyr	Val	Gln	Glu	Ala
				900					905					910		
	Leu	Lys	Ala	Tyr	Leu	Ile	Asp	Lys	Val	Lys	Ile	Lys	Gly	Tyr	Tyr	Ala
			915					920					925			
	Phe	Lys	Leu	Thr	Glu	Glu	Lys	Ser	Lys	Pro	Arg	Phe	Gly	Phe	Phe	Thr
		930					935					940				
25	Ser	Asp	Phe	Lys	Ala	Lys	Ser	Ser	Val	Gln	Phe	Tyr	Ser	Lys	Leu	Ile
		945				950					955					960
	Ser	Ser	Ser	Gly	Phe	Ser	Ser	Glu	Asn	Arg	Ser	Pro	Ala	Cys	Gly	Gln
				965					970						975	
30	Pro	Pro	Glu	Asp	Thr	Glu	Cys	Ala	Ile	Cys	Ser	Phe	Leu	Thr	Gln	Lys
				980					985						990	
	Lys	Pro	Leu	Ile	Phe	Phe	Gly	Cys	Cys	Phe	Ile	Ser	Thr	Leu	Ala	Ala
			995					1000					1005			
	Leu	Leu	Ser	Ile	Thr	Ile	Phe	His	His	Arg	Lys	Arg	Arg	Lys	Phe	Gln
		1010					1015					1020				
35	Lys	Ala	Arg	Asn	Leu	Gln	Asn	Ile	Pro	Leu	Lys	Lys	Gly	His	Ser	Arg
		1025				1030					1035					1040
	Val	Phe	Ser													

<210> 357
 <211> 3132
 <212> DNA
 <213> Rattus

<220>
 <223> Rat beta klotho

<400> 357

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 5 ttccttaaaa acttttcctg gggcggtggg accggagcat ttcaagtggg agggagttgg 300
 aaggcagatg gaagaggacc ctcgatctgg gaccgttatg tcgactcaca cctgagaggt 360
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 aacggaacag tagcagctgt gaatgcaaaa ggtctccagt actacagagc acttctggac 540
 10 tcgctggtac tttaggaatat cgaacccatt gttaccttat accattggga tttgcctttg 600
 acgctacagg aagaatatgg gggctggaaa aatgcaacta tgatagatct cttcaatgac 660

tatgccacat actgcttcca gacctttgga gaccgtgtca aatattggat tacaattcac 720
 15 aacccttacc tcgttgcttg gcatgggttt ggcacaggta tgcattgcgc aggagagaag 780
 ggaaatttaa cagctgtcta cactgtggga cacaacctga tcaaggcgca ttcgaaagtg 840
 tggcataact acgacaaaaa cttccgacct catcagaagg gttggctctc caactgacctg 900
 ggggtccatt ggatagaacc aaacagaaca gaaaacatgg aggacgtgat caactgccag 960
 cactccatgt cttctgtgct cggatgggtt gccaacccca tccacggaga cggcgactac 1020
 20 cccgagttca tgaagacgag ctccgtaatc cctgagttct ctgaggcaga gaaggaggag 1080
 gtgcggggca ctgctgactt ctttgccttt tccttcgggc ccaacaattt caggccctcg 1140
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 25 gttcttcaag caataaagtt tgatgaaata caagtgtttg gttatacggc ttggactctc 1380
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 30 cgagtggag gagtcaggct aaaaacaaga ccgtcccaat gcacagatta tgtgagcatc 1740
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 caccgcaccc actcccatct aggcctcccc atgccacttc tgagcagtgg gggatggcta 1980
 35 aacaccaaca cagccaaggc cttccaggac tacgcaggcc tgtgcttcaa ggagctgggg 2040
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 40 ccgctggcca tgaaggaata catcgccctc aagaagcagc gagggctgtc tagctcagtc 2400
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 45 atggatatct acgtcacagc caatggcatt gatgatcttg ctctagagga cgatcagatt 2700
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 50 tgcttcatct ccactctggc tgcactgcta tcaatcacta tttttcatca tcggaagaga 3060
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 gtttttagct aa 3132

<210> 358

<211> 472

<212> PRT

<213> Artificial Sequence

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<220>

<223> Heavy Chain SEQ ID NO: 32 in U.S. Publication US20110135657

<400> 358

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Leu	Arg	Gly	Ala	Arg	Cys	Gln	Val	Thr	Leu	Lys	Glu	Ser	Gly	Pro	Val
			20					25					30		
Leu	Val	Lys	Pro	Thr	Glu	Thr	Leu	Thr	Leu	Thr	Cys	Thr	Val	Ser	Gly
		35					40					45			
Phe	Ser	Leu	Asn	Asn	Ala	Arg	Met	Gly	Val	Ser	Trp	Ile	Arg	Gln	Pro
	50					55					60				
Pro	Gly	Lys	Ala	Leu	Glu	Trp	Leu	Ala	His	Ile	Phe	Ser	Asn	Asp	Glu
65					70					75				80	
Lys	Ser	Tyr	Ser	Thr	Ser	Leu	Lys	Ser	Arg	Leu	Thr	Ile	Ser	Lys	Asp

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					85					90				95		
	Thr	Ser	Lys	Ser	Gln	Val	Val	Leu	Ile	Met	Thr	Asn	Met	Asp	Pro	Val
				100					105					110		
5	Asp	Thr	Ala	Thr	Tyr	Tyr	Cys	Ala	Arg	Ser	Val	Val	Thr	Gly	Gly	Tyr
			115					120					125			
	Tyr	Tyr	Asp	Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val
		130					135					140				
	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys
	145					150					155					160
10	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys
					165				170					175		
	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu
			180					185					190			
	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu
			195					200					205			
15	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr
		210					215					220				
	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val
	225					230					235					240
	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro
					245					250					255	
20	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro
				260					265					270		
	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
		275						280					285			
	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val
25		290					295				300					
	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln
	305					310					315					320
	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln
					325					330					335	
30	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly
			340						345					350		
	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro
		355						360					365			
	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr
		370					375					380				
35	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
		385				390					395					400
	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr
					405				410					415		
	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
			420					425					430			
40	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe
		435						440					445			
	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys
		450				455					460					
45	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys								
	465					470										

<210> 359

<211> 1419

<212> DNA

50 <213> Artificial Sequence

<220>

<223> Coding sequence of Heavy Chain SEQ ID NO: 32 in U.S. Publication US20110135657

55 <400> 359

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agatgtcagg tgacgctgaa agagtccgga ccgggtcctgg tgaaaccaac tgaaacccta 120

5 actctcacgt gcactgtcag cggcttctct ctcaacaacg caagaatggg tgtgtcttgg 180
atcagacagc caccaggtaa agcgcttgag tggctggcac acatcttctc caacgatgag 240
aagagctact ctaccagcct caagtctcgt ctgaccatca gtaaagatac gtccaagtcc 300
caagtagtcc tcatcatgac taacatggac cccgtggata ccgcgacctc ctactgtgcg 360
aggagcgtcg tgaccggtgg ctactactac gacggcatgg atgtgtgggg tcagggtagc 420
10 acggtgaccg tcagcagcgc gagcaccaag ggtccgtccg tgtttccgct cgcctcttgt 480
agccggagca cctcagagtc tactgccgca ctaggctgcc tggatgaagg ctacttccct 540
gaaccctga cagttagctg gaactccgga gcactgacta gcggcgtgca cacttcccc 600
gctgtcttgc agtctagcgg cctgtattcg ctctccagcg tggtcactgt accgtccagc 660
aatttcggaa cccagacctc cacatgtaac gtcgatcata aaccgtccaa cactaaggta 720
15 gacaaaaccg tggaaaggaa atgctgcgtg gactgtcccc cctgcccgag tccgccagtg 780
gcaggcccca gcgtgttctt gttcccccca aagccaaaag acaccctgat gatctcgaga 840
acccccgagg tgacttgctg cgtcgtcgat gtctcccatg aggatccaga agtacagttc 900
aactggtacg tggacggcgt ggaagtgcac aatgcaaaaa cgaagccccg agaagagcag 960
ttcaactcca cattccgggt ggtatcagtc ctgactgtgg tccaccagga ttggctgaac 1020
20 ggggaaggaat acaaagttaa agtgagcaat aagggtctgc ccgcaccgat cgagaaaact 1080
atctcaaaaa ctaagggtca gcctcgcgag cctcaagtgt atacgctgcc gccaaagtagg 1140
gaggagatga ccaaaaacca ggtgtcactg acatgtctgg tgaaaggctt ctaccccgag 1200
gacatcgccg tggagtggga gtcaaatggc cagccggaga acaactacaa gaccacaccg 1260
ccgatgctgg actcagacgg gtcctttttc ctctattcca agctcaccgt cgacaaaagc 1320
cgttggcagc agggaaacgt attctcatgc tctgtgatgc acgaggccct tcacaaccat 1380
25 tacactcaga aatcgttgtc cctttctccc ggaaaatga 1419

<210> 360

<211> 236

<212> PRT

30 <213> Artificial Sequence

<220>

<223> Light Chain SEQ ID No: 14 in U.S. Publication US20110135657

35 <400> 360

40

45

50

55

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	Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp
	1				5					10				15		
	Leu	Arg	Gly	Ala	Arg	Cys	Ser	Tyr	Val	Leu	Thr	Gln	Pro	Pro	Ser	Val
			20					25					30			
5	Ser	Val	Ala	Pro	Gly	Gln	Thr	Ala	Arg	Ile	Thr	Cys	Gly	Gly	Asn	Asn
		35					40					45				
	Ile	Gly	Ser	Glu	Ser	Val	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala
	50					55					60					
	Pro	Val	Leu	Val	Val	Tyr	Asp	Asp	Ser	Asp	Arg	Pro	Ser	Gly	Ile	Pro
10	65				70					75						80
	Glu	Arg	Phe	Ser	Gly	Ser	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile
				85				90						95		
	Ser	Arg	Val	Glu	Ala	Gly	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Val	Trp
			100					105					110			
	Asp	Gly	Asn	Ser	Asp	His	Val	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr
15		115					120					125				
	Val	Leu	Gly	Gln	Pro	Lys	Ala	Asn	Pro	Thr	Val	Thr	Leu	Phe	Pro	Pro
	130					135					140					
	Ser	Ser	Glu	Glu	Leu	Gln	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile
	145				150				155							160
20	Ser	Asp	Phe	Tyr	Pro	Gly	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Gly
			165					170					175			
	Ser	Pro	Val	Lys	Ala	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser
			180					185					190			
	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln
		195					200					205				
25	Trp	Lys	Ser	His	Arg	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser
	210					215					220					
	Thr	Val	Glu	Lys	Thr	Val	Ala	Pro	Thr	Glu	Cys	Ser				
	225				230					235						

30 <210> 361
 <211> 711
 <212> DNA
 <213> Artificial Sequence

35 <220>
 <223> Coding sequence for Light Chain SEQ ID No: 14 in U.S. Publication US20110135657

<400> 361

40	atggacatga	gggtccccgc	tcagctcctg	gggctcctgc	tactctggct	ccgaggtgcc	60
	agatgttcat	acgtgctgac	tcagccccca	tccgtgtctg	tggcaccggg	acaaactgcc	120
	aggatcactt	gcggagggaa	taacatcggg	agcgagagcg	tccactggta	ccagcaaaaa	180
	ccaggccagg	caccggtcct	cgtggtatac	gacgattctg	accgaccgtc	cggcattcca	240
	gaaagattct	cgggtagcaa	ctctggcaac	acggctaccc	tgaccatcag	ccgtgtcgag	300
45	gccggtgacg	aggcggatta	ctactgccag	gtgtgggacg	ggaactccga	tcatgtggtg	360
	ttcggcggag	gcactaagct	gaccgtattg	ggtcagccca	aagcaaatcc	caccgtgacg	420
	ctctttcccc	ctagctccga	ggagctgcag	gcgaacaagg	caactcttgt	ctgtctcatc	480
	tcggacttct	atccggggagc	ggtgaccgtc	gcatggaaag	cagatgggtc	tccggtcaaa	540
	gcaggcgtgg	aaacgaccaa	gccttccaaa	cagagtaaca	acaagtatgc	tgccagctcc	600
50	tacctaagcc	tgacaccgga	gcagtggaa	agccaccggg	catacagctg	ccaggtaact	660
	catgaaggct	caacagtggg	gaaaaccgtg	gcgcacaacc	agtgttcctg	a	711

<210> 362
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>

<223> IGHV1-3

<400> 362

5
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 10 Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
 65 70 75 80
 15 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg

<210> 363

20 <211> 98

<212> PRT

<213> Artificial Sequence

<220>

25 <223> IGHV1-18

<400> 363

30
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35
 35 40 45
 Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
 50 55 60
 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 40 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg

<210> 364

45 <211> 98

<212> PRT

<213> Artificial Sequence

<220>

50 <223> IGHV1-46

<400> 364

55

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	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
	1				5					10					15	
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
				20				25						30		
5	Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Ile	Ile	Asn	Pro	Ser	Gly	Gly	Ser	Thr	Ser	Tyr	Ala	Gln	Lys	Phe
		50					55					60				
	Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
10		65				70					75					80
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg														

15 <210> 365
 <211> 98
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> IGHV1-69

<400> 365

	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
	1				5					10					15	
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Ser	Ser	Tyr
				20				25						30		
	Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
30			35					40					45			
	Gly	Gly	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe
		50					55					60				
	Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr
		65				70					75					80
35	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg														

40 <210> 366
 <211> 121
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> U00583

<400> 366

50

55

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	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
	1				5					10				15		
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Ser	Ser	Tyr
			20					25						30		
5	Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35				40						45			
	Gly	Gly	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe
		50				55					60					
	Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
10	65					70					75					80
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95		
	Ala	Arg	Gly	Asp	Ile	Leu	Thr	Gly	Leu	Asn	Trp	Phe	Asp	Pro	Trp	Gly
			100					105						110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
15			115					120								

<210> 367

<211> 101

<212> PRT

20 <213> Artificial Sequence

<220>

<223> IGKV4-1

25 <400> 367

	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Ile	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Val	Leu	Tyr	Ser
30			20					25						30		
	Ser	Asn	Asn	Lys	Asn	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln
			35				40						45			
	Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Val
		50				55					60					
35	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr
	65				70					75						80
	Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Gln	Gln
				85				90						95		
	Tyr	Tyr	Ser	Thr	Pro											
40				100												

<210> 368

<211> 95

<212> PRT

45 <213> Artificial Sequence

<220>

<223> IGKV1-39

50 <400> 368

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr
55			20					25						30		

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5 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro
 85 90 95

10 <210> 369
 <211> 90
 <212> PRT
 <213> Artificial Sequence

15 <220>
 <223> IGKV3-20

<400> 369

20 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 25 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
 50 55 60
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 65 70 75 80
 30 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln
 85 90

35 <210> 370
 <211> 450
 <212> PRT
 <213> Artificial Sequence

40 <220>
 <223> hlgK-5H23(VH)-hlgG1(E233A)(L235A) (5H23 chimera)

<400> 370

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	Leu	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
				20				25					30			
5	Asp	Ile	Asn	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45				
	Gly	Trp	Ile	Tyr	Pro	Gly	Asp	Gly	Ser	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
	50					55					60					
10	Lys	Gly	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Arg	Thr	Ala	Tyr	
	65				70					75					80	
	Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asn	Ser	Ala	Val	Tyr	Phe	Cys
				85					90					95		
	Ala	Arg	Ser	Asp	Tyr	Tyr	Gly	Ser	Arg	Ser	Phe	Ala	Tyr	Trp	Gly	Gln
			100					105				110				
15	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
		115					120					125				
	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
	130					135						140				
	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
	145				150					155					160	
20	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
				165						170					175	
	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro
			180					185						190		
25	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
			195				200					205				
	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp
	210				215						220					
30	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Ala	Leu	Ala	Gly	Gly
	225				230					235					240	
	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
				245					250					255		
	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
			260					265						270		
35	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
		275					280					285				
	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg
	290					295					300					
	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
	305				310					315					320	
40	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
				325						330					335	
	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
			340					345						350		
	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
		355					360						365			
45	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
	370					375						380				
	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
	385				390					395					400	
	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
				405					410					415		
50	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His
			420					425						430		
	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro
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55	Gly	Lys														
		450														

<210> 371

<211> 1419

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<212> DNA

<213> Artificial Sequence

<220>

5 <223> Coding sequence of hIgK-5H23(VH)-hIgG1(E233A)(L235A) (5H23 chimera)

<400> 371

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      agatgtcaag tgcaacttca acagtcaggc ccagaactcg tcaaaccggg agcactcgtg 120
      aagatctcgt gcaaggcgctc gggttacact ttacagtcct acgacatcaa ttgggtgaag 180
      cagaggcctg gacagggcct ggagtggatt ggatggatct acccggggga tgggtctacc 240
      aagtacaacg aaaagttcaa aggcaaagcc actctgaccg cagacaagag cagcagaacc 300
      gcgtacatgc agttgtcatc cctgaccagc gagaactcgg ccgtctactt ttgtgctcgc 360
15      tccgattact atggatcccg gagcttcgcc tactggggac agggaactct ggtgactgtg 420
      tcatcggtca gcaccaaggg cccatcggtc ttccccctgg caccctcctc caagagcacc 480
      tctgggggca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540
      gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca ccttcccggc tgtcctacag 600
      tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacc 660
20      cagacctaca tctgcaacgt gaatcacaag ccagcaaca ccaaggtgga caagaaagtt 720
      gagcccaaat cttgtgacaa aactcacaca tgcccaccgt gccagcacc tgcactcgcg 780
      gggggaccgt cagtcttcct cttcccccca aaaccaagg acaccctcat gatctcccg 840
      acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 900

25      aactggtacg tggacggcgt ggaggtgcat aatgccaaaga caaagccgcg ggaggagcag 960
      tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctgggtgaat 1020
      ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagcccccat cgagaaaacc 1080
      atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1140
      gaggatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 1200
      gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1260
30      ccggtgctgg actccgacgg ctcttcttct ctctacagca agctcaccgt ggacaagagc 1320
      aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1380
      tacacgcaga agagcctctc cctgtctccg ggtaaatga 1419

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<210> 372

35 <211> 218

<212> PRT

<213> Artificial Sequence

<220>

40 <223> hIgK-5H23(VL)-hIgK (5H23 chimera)

<400> 372

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	Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Ser	Leu	Ala	Val	Ser	Leu	Gly
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	Gln	Arg	Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Lys	Ser	Val	Ser	Thr	Ser
				20					25					30		
5	Gly	Tyr	Val	Tyr	Met	His	Trp	Asn	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
			35					40					45			
	Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Tyr	Leu	Glu	Ser	Gly	Val	Pro	Ala
		50					55					60				
	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Asn	Ile	His
10	65					70					75					80
	Pro	Val	Glu	Glu	Glu	Asp	Ala	Ala	Ile	Tyr	Tyr	Cys	Gln	His	Ser	Arg
					85					90					95	
	Asp	Leu	Thr	Phe	Pro	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg
				100					105						110	
	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln
15			115					120					125			
	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr
		130					135					140				
	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser
					150						155					160
20	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr
				165						170					175	
	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys
				180					185					190		
	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro
			195					200					205			
25	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys						
		210					215									

<210> 373

<211> 723

30 <212> DNA

<213> Artificial Sequence

<220>

35 <223> Coding sequence of hlgK-5H23(VL)-hlgK (5H23 chimera)

<400> 373

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40	gctaccattt	cctgccgcgc	atcgaagtct	gtgagcactt	ccggctacgt	ctacatgcac	180
	tggaaccagc	agaagccagg	acaaccgccg	aagctgctga	tctatctcgc	gtcatacctg	240
	gaatcgggag	tgccggcgag	gttttcggga	tcgggctccg	gaaccgactt	caccctgaat	300
45	atccatccag	tggaagagga	ggatgcogcc	atctactact	gtcagcacag	ccgggatctc	360
	actttccctt	tcggcggagg	gacgaaattg	gaaatcaaac	gtacgggtggc	tgaccatctt	420
	gtcttcatct	tcccgccatc	tgatgagcag	ttgaaatctg	gaactgcctc	tggtgtgtgc	480
	ctgctgaata	acttctatcc	cagagaggcc	aaagtacagt	ggaaggtgga	taacgccctc	540
	caatcgggta	actcccagga	gagtgtcaca	gagcaggaca	gcaaggacag	cacctacagc	600
	ctcagcagca	ccctgacgct	gagcaaagca	gactacgaga	aacacaaagt	ctacgcctgc	660
50	gaagtcaccc	atcagggcct	gagctcgccc	gtcacaaaga	gcttcaacag	gggagagtgt	720
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<210> 374

<211> 1045

55 <212> PRT

<213> Artificial Sequence

<220>

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<223> human KLB (M1-F508)- mouse KLB (P507-S1043)

<400> 374

5	Met	Lys	Pro	Gly	Cys	Ala	Ala	Gly	Ser	Pro	Gly	Asn	Glu	Trp	Ile	Phe
	1				5					10					15	
	Phe	Ser	Thr	Asp	Glu	Ile	Thr	Thr	Arg	Tyr	Arg	Asn	Thr	Met	Ser	Asn
				20					25					30		
10	Gly	Gly	Leu	Gln	Arg	Ser	Val	Ile	Leu	Ser	Ala	Leu	Ile	Leu	Leu	Arg
			35					40					45			
	Ala	Val	Thr	Gly	Phe	Ser	Gly	Asp	Gly	Arg	Ala	Ile	Trp	Ser	Lys	Asn
	50						55					60				
	Pro	Asn	Phe	Thr	Pro	Val	Asn	Glu	Ser	Gln	Leu	Phe	Leu	Tyr	Asp	Thr
	65				70						75				80	
15	Phe	Pro	Lys	Asn	Phe	Phe	Trp	Gly	Ile	Gly	Thr	Gly	Ala	Leu	Gln	Val
				85						90					95	
	Glu	Gly	Ser	Trp	Lys	Lys	Asp	Gly	Lys	Gly	Pro	Ser	Ile	Trp	Asp	His
				100					105					110		
	Phe	Ile	His	Thr	His	Leu	Lys	Asn	Val	Ser	Ser	Thr	Asn	Gly	Ser	Ser
			115					120					125			
20	Asp	Ser	Tyr	Ile	Phe	Leu	Glu	Lys	Asp	Leu	Ser	Ala	Leu	Asp	Phe	Ile
	130						135					140				
	Gly	Val	Ser	Phe	Tyr	Gln	Phe	Ser	Ile	Ser	Trp	Pro	Arg	Leu	Phe	Pro
	145				150						155				160	
25	Asp	Gly	Ile	Val	Thr	Val	Ala	Asn	Ala	Lys	Gly	Leu	Gln	Tyr	Tyr	Ser
				165					170					175		
	Thr	Leu	Leu	Asp	Ala	Leu	Val	Leu	Arg	Asn	Ile	Glu	Pro	Ile	Val	Thr
				180					185					190		
	Leu	Tyr	His	Trp	Asp	Leu	Pro	Leu	Ala	Leu	Gln	Glu	Lys	Tyr	Gly	Gly
			195				200						205			
30	Trp	Lys	Asn	Asp	Thr	Ile	Ile	Asp	Ile	Phe	Asn	Asp	Tyr	Ala	Thr	Tyr
	210					215						220				
	Cys	Phe	Gln	Met	Phe	Gly	Asp	Arg	Val	Lys	Tyr	Trp	Ile	Thr	Ile	His
	225				230					235					240	
	Asn	Pro	Tyr	Leu	Val	Ala	Trp	His	Gly	Tyr	Gly	Thr	Gly	Met	His	Ala
				245					250					255		
35	Pro	Gly	Glu	Lys	Gly	Asn	Leu	Ala	Ala	Val	Tyr	Thr	Val	Gly	His	Asn
				260				265						270		
	Leu	Ile	Lys	Ala	His	Ser	Lys	Val	Trp	His	Asn	Tyr	Asn	Thr	His	Phe
			275				280						285			
	Arg	Pro	His	Gln	Lys	Gly	Trp	Leu	Ser	Ile	Thr	Leu	Gly	Ser	His	Trp
	290					295						300				
40	Ile	Glu	Pro	Asn	Arg	Ser	Glu	Asn	Thr	Met	Asp	Ile	Phe	Lys	Cys	Gln
	305				310					315					320	
	Gln	Ser	Met	Val	Ser	Val	Leu	Gly	Trp	Phe	Ala	Asn	Pro	Ile	His	Gly
				325					330					335		
45	Asp	Gly	Asp	Tyr	Pro	Glu	Gly	Met	Arg	Lys	Lys	Leu	Phe	Ser	Val	Leu
				340				345				350				
	Pro	Ile	Phe	Ser	Glu	Ala	Glu	Lys	His	Glu	Met	Arg	Gly	Thr	Ala	Asp

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				355				360					365				
		Phe	Phe	Ala	Phe	Ser	Phe	Gly	Pro	Asn	Asn	Phe	Lys	Pro	Leu	Asn	Thr
			370					375					380				
5		Met	Ala	Lys	Met	Gly	Gln	Asn	Val	Ser	Leu	Asn	Leu	Arg	Glu	Ala	Leu
		385					390					395					400
		Asn	Trp	Ile	Lys	Leu	Glu	Tyr	Asn	Asn	Pro	Arg	Ile	Leu	Ile	Ala	Glu
						405					410					415	
		Asn	Gly	Trp	Phe	Thr	Asp	Ser	Arg	Val	Lys	Thr	Glu	Asp	Thr	Thr	Ala
					420					425					430		
10		Ile	Tyr	Met	Met	Lys	Asn	Phe	Leu	Ser	Gln	Val	Leu	Gln	Ala	Ile	Arg
				435					440					445			
		Leu	Asp	Glu	Ile	Arg	Val	Phe	Gly	Tyr	Thr	Ala	Trp	Ser	Leu	Leu	Asp
			450					455					460				
		Gly	Phe	Glu	Trp	Gln	Asp	Ala	Tyr	Thr	Ile	Arg	Arg	Gly	Leu	Phe	Tyr
		465					470					475					480
15		Val	Asp	Phe	Asn	Ser	Lys	Gln	Lys	Glu	Arg	Lys	Pro	Lys	Ser	Ser	Ala
					485						490					495	
		His	Tyr	Tyr	Lys	Gln	Ile	Ile	Arg	Glu	Asn	Gly	Phe	Pro	Leu	Lys	Glu
					500				505						510		
		Ser	Thr	Pro	Asp	Met	Lys	Gly	Arg	Phe	Pro	Cys	Asp	Phe	Ser	Trp	Gly
			515						520					525			
20		Val	Thr	Glu	Ser	Val	Leu	Lys	Pro	Glu	Phe	Thr	Val	Ser	Ser	Pro	Gln
			530					535					540				
		Phe	Thr	Asp	Pro	His	Leu	Tyr	Val	Trp	Asn	Val	Thr	Gly	Asn	Arg	Leu
		545					550					555					560
		Leu	Tyr	Arg	Val	Glu	Gly	Val	Arg	Leu	Lys	Thr	Arg	Pro	Ser	Gln	Cys
					565						570					575	
25		Thr	Asp	Tyr	Val	Ser	Ile	Lys	Lys	Arg	Val	Glu	Met	Leu	Ala	Lys	Met
				580						585					590		
		Lys	Val	Thr	His	Tyr	Gln	Phe	Ala	Leu	Asp	Trp	Thr	Ser	Ile	Leu	Pro
			595					600						605			
		Thr	Gly	Asn	Leu	Ser	Lys	Val	Asn	Arg	Gln	Val	Leu	Arg	Tyr	Tyr	Arg
			610					615					620				
30		Cys	Val	Val	Ser	Glu	Gly	Leu	Lys	Leu	Gly	Val	Phe	Pro	Met	Val	Thr
		625					630					635					640
		Leu	Tyr	His	Pro	Thr	His	Ser	His	Leu	Gly	Leu	Pro	Leu	Pro	Leu	Leu
					645						650					655	
35		Ser	Ser	Gly	Gly	Trp	Leu	Asn	Met	Asn	Thr	Ala	Lys	Ala	Phe	Gln	Asp
				660					665						670		
		Tyr	Ala	Glu	Leu	Cys	Phe	Arg	Glu	Leu	Gly	Asp	Leu	Val	Lys	Leu	Trp
				675					680					685			
		Ile	Thr	Ile	Asn	Glu	Pro	Asn	Arg	Leu	Ser	Asp	Met	Tyr	Asn	Arg	Thr
			690					695					700				
40		Ser	Asn	Asp	Thr	Tyr	Arg	Ala	Ala	His	Asn	Leu	Met	Ile	Ala	His	Ala
		705					710					715					720
		Gln	Val	Trp	His	Leu	Tyr	Asp	Arg	Gln	Tyr	Arg	Pro	Val	Gln	His	Gly
					725						730					735	
		Ala	Val	Ser	Leu	Ser	Leu	His	Cys	Asp	Trp	Ala	Glu	Pro	Ala	Asn	Pro
				740						745					750		
45		Phe	Val	Asp	Ser	His	Trp	Lys	Ala	Ala	Glu	Arg	Phe	Leu	Gln	Phe	Glu
				755					760					765			
		Ile	Ala	Trp	Phe	Ala	Asp	Pro	Leu	Phe	Lys	Thr	Gly	Asp	Tyr	Pro	Ser
			770					775					780				
		Val	Met	Lys	Glu	Tyr	Ile	Ala	Ser	Lys	Asn	Gln	Arg	Gly	Leu	Ser	Ser
		785					790					795					800
50		Ser	Val	Leu	Pro	Arg	Phe	Thr	Ala	Lys	Glu	Ser	Arg	Leu	Val	Lys	Gly
					805						810					815	
		Thr	Val	Asp	Phe	Tyr	Ala	Leu	Asn	His	Phe	Thr	Thr	Arg	Phe	Val	Ile
				820						825					830		
		His	Lys	Gln	Leu	Asn	Thr	Asn	Arg	Ser	Val	Ala	Asp	Arg	Asp	Val	Gln
				835					840					845			
55		Phe	Leu	Gln	Asp	Ile	Thr	Arg	Leu	Ser	Ser	Pro	Ser	Arg	Leu	Ala	Val
			850					855					860				

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	Thr	Pro	Trp	Gly	Val	Arg	Lys	Leu	Leu	Ala	Trp	Ile	Arg	Arg	Asn	Tyr	
	865					870					875					880	
	Arg	Asp	Arg	Asp	Ile	Tyr	Ile	Thr	Ala	Asn	Gly	Ile	Asp	Asp	Leu	Ala	
					885					890						895	
5	Leu	Glu	Asp	Asp	Gln	Ile	Arg	Lys	Tyr	Tyr	Leu	Glu	Lys	Tyr	Val	Gln	
					900					905						910	
	Glu	Ala	Leu	Lys	Ala	Tyr	Leu	Ile	Asp	Lys	Val	Lys	Ile	Lys	Gly	Tyr	
					915				920							925	
	Tyr	Ala	Phe	Lys	Leu	Thr	Glu	Glu	Lys	Ser	Lys	Pro	Arg	Phe	Gly	Phe	
							930		935							940	
10	Phe	Thr	Ser	Asp	Phe	Arg	Ala	Lys	Ser	Ser	Val	Gln	Phe	Tyr	Ser	Lys	
						950										960	
	Leu	Ile	Ser	Ser	Ser	Gly	Leu	Pro	Ala	Glu	Asn	Arg	Ser	Pro	Ala	Cys	
					965						970					975	
	Gly	Gln	Pro	Ala	Glu	Asp	Thr	Asp	Cys	Thr	Ile	Cys	Ser	Phe	Leu	Val	
15					980				985							990	
	Glu	Lys	Lys	Pro	Leu	Ile	Phe	Phe	Gly	Cys	Cys	Phe	Ile	Ser	Thr	Leu	
					995				1000							1005	
	Ala	Val	Leu	Leu	Ser	Ile	Thr	Val	Phe	His	His	Gln	Lys	Arg	Arg	Lys	
					1010				1015							1020	
20	Phe	Gln	Lys	Ala	Arg	Asn	Leu	Gln	Asn	Ile	Pro	Leu	Lys	Lys	Gly	His	
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	Ser	Arg	Val	Phe	Ser												
					1045												

<210> 375

25 <211> 3138

<212> DNA

<213> Artificial Sequence

<220>

30 <223> Coding sequence of human KLB (M1-F508)- mouse KLB (P507-S1043)

<400> 375

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	gaaataacca	cacgctatag	gaataacaatg	tccaacgggg	gattgcaaag	atctgtcatc	120
	ctgtcagcac	ttattctgct	acgagctgtt	actggattct	ctggagatgg	aagagctata	180
5	tggtctaaaa	atcctaattt	tactccggta	aatgaaagtc	agctgtttct	ctatgacact	240
	ttccctaaaa	actttttctg	gggtattggg	actggagcat	tgcaagtggg	agggagttgg	300
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<210> 376

<211> 1042

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Mouse KLB (M1-F506) - human KLB(S509-S1044)

<400> 376

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	Ala	Leu	Leu	Asp	Ser	Leu	Val	Leu	Arg	Asn	Ile	Glu	Pro	Ile	Val	Thr
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25	Leu	Tyr	His	Trp	Asp	Leu	Pro	Leu	Thr	Leu	Gln	Glu	Glu	Tyr	Gly	Gly
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	His	Ser	Met	Ser	Ser	Val	Leu	Gly	Trp	Phe	Ala	Asn	Pro	Ile	His	Gly
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<210> 377

40 <211> 3129

<212> DNA

<213> Artificial Sequence

<220>

45 <223> Coding sequence of Mouse KLB (M1-F506) - human KLB(S509-S1044)

<400> 377

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<210> 378

<211> 25

55 <212> PRT

<213> Artificial Sequence

<220>

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<223> Humanized Anti-Beta Klotho VH FR1

<400> 378

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15 <220>
 <223> Humanized Anti-Beta Klotho VH FR3

<400> 379

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25 <210> 380
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30 <220>
 <223> Humanized Anti-Beta Klotho VH FR3

<400> 380

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35      Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Arg Thr Ala Tyr Met Glu
      1          5          10          15
      Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
          20          25          30

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40 <210> 381
 <211> 32
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Humanized Anti-Beta Klotho VH FR3

<400> 381

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50      Arg Ala Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu
      1          5          10          15
      Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
          20          25          30

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55 <210> 382
 <211> 23
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR1

<400> 382

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Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys									
			20												

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<210> 383

<211> 23

<212> PRT

<213> Artificial Sequence

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<220>

<223> Humanized Anti-Beta Klotho VL FR1

<400> 383

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Asp	Ile	Gln	Leu	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys									
			20												

25

<210> 384

<211> 23

<212> PRT

<213> Artificial Sequence

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<220>

<223> Humanized Anti-Beta Klotho VL FR1

<400> 384

35

Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Leu	Ser	Cys									
			20												

40

<210> 385

<211> 15

<212> PRT

<213> Artificial Sequence

45

<220>

<223> Humanized Anti-Beta Klotho VL FR2

<400> 385

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Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr
1				5					10					15

55

<210> 386

<211> 15

<212> PRT

<213> Artificial Sequence

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<220>

<223> Humanized Anti-Beta Klotho VL FR2

<400> 386

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Trp	Asn	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr
1				5					10					15

<210> 387

10

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

15

<223> Humanized Anti-Beta Klotho VL FR2

<400> 387

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Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro	Lys	Leu	Leu	Ile	Tyr
1				5					10					15

<210> 388

<211> 15

<212> PRT

25

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR2

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<400> 388

Trp	Asn	Gln	Gln	Lys	Pro	Gly	Lys	Pro	Pro	Lys	Leu	Leu	Ile	Tyr
1				5					10					15

35

<210> 389

<211> 15

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Humanized Anti-Beta Klotho VL FR2

<400> 389

45

Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile	Tyr
1				5					10					15

<210> 390

<211> 15

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<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR2

55

<400> 390

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Trp Asn Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
1 5 10 15

<210> 391

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR2

<400> 391

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr
1 5 10 15

<210> 392

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR2

<400> 392

Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr
1 5 10 15

<210> 393

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR3

<400> 393

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15
Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
20 25 30

<210> 394

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR3

<400> 394

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15
Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> 395
 <211> 32
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Humanized Anti-Beta Klotho VL FR3

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Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
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Leu	Thr	Ile	Ser	Ser	Val	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys
			20					25					30		

15

<210> 396
 <211> 32
 <212> PRT
 <213> Artificial Sequence

20

<220>
 <223> Humanized Anti-Beta Klotho VL FR3

25

Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5					10					15	
Leu	Thr	Ile	Ser	Ser	Leu	Gln	Glu	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys
			20					25					30		

30

<210> 397
 <211> 32
 <212> PRT
 <213> Artificial Sequence

35

<220>
 <223> Humanized Anti-Beta Klotho VL FR3

40

Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5					10					15	
Leu	Thr	Ile	Ser	Ser	Val	Gln	Glu	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys
			20					25					30		

45

<210> 398
 <211> 32
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Humanized Anti-Beta Klotho VL FR3

55

<400> 398

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Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5					10					15	
Leu	Thr	Ile	Ser	Ser	Val	Gln	Glu	Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys
			20					25					30		

5

<210> 399
 <211> 32
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Humanized Anti-Beta Klotho VL FR3

15

Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5					10					15	
Leu	Thr	Ile	Ser	Arg	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys
			20					25					30		

20

<210> 400
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 <212> PRT
 <213> Artificial Sequence

25

<220>
 <223> Humanized Anti-Beta Klotho VL FR3

30

Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5					10					15	
Leu	Thr	Ile	Ser	Arg	Val	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys
			20					25					30		

35

<210> 401
 <211> 32
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Humanized Anti-Beta Klotho VL FR3

45

Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5					10					15	
Leu	Thr	Ile	Ser	Arg	Leu	Glu	Pro	Glu	Asp	Ala	Ala	Val	Tyr	Tyr	Cys
			20					25					30		

50

<210> 402
 <211> 32
 <212> PRT
 <213> Artificial Sequence

55

<220>
 <223> Humanized Anti-Beta Klotho VL FR3

<400> 402

5 Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 1 5 10 15
 Leu Thr Ile Ser Arg Leu Glu Glu Glu Asp Phe Ala Val Tyr Tyr Cys
 20 25 30

<210> 403

<211> 32

10 <212> PRT

<213> Artificial Sequence

<220>

15 <223> Humanized Anti-Beta Klotho VL FR3

<400> 403

20 Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 1 5 10 15
 Leu Thr Ile Ser Arg Val Glu Glu Glu Asp Phe Ala Val Tyr Tyr Cys
 20 25 30

<210> 404

<211> 32

25 <212> PRT

<213> Artificial Sequence

<220>

30 <223> Humanized Anti-Beta Klotho VL FR3

<400> 404

35 Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 1 5 10 15
 Leu Thr Ile Ser Arg Val Glu Glu Glu Asp Ala Ala Val Tyr Tyr Cys
 20 25 30

<210> 405

<211> 10

40 <212> PRT

<213> Artificial Sequence

<220>

45 <223> Humanized Anti-Beta Klotho VL FR4

<400> 405

50 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 1 5 10

<210> 406

<211> 10

55 <212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR4

<400> 406

Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
1				5					10

<210> 407

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized Anti-Beta Klotho VL FR4

<400> 407

Phe	Gly	Gly	Gln	Thr	Lys	Leu	Glu	Ile	Lys
1				5					10

<210> 408

<211> 1042

<212> PRT

<213> Cricetulus griseus

<220>

<223> hamster beta klotho

<400> 408

Met	Lys	Ala	Gly	Cys	Ala	Ala	Gly	Ser	Pro	Gly	Asn	Glu	Trp	Ile	Phe
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Leu	Ser	Ser	Tyr	Glu	Arg	Asn	Thr	Arg	Ser	Lys	Lys	Thr	Met	Ser	Asn
			20					25					30		
Arg	Ala	Leu	Gln	Arg	Ser	Val	Val	Leu	Ser	Ala	Phe	Val	Leu	Leu	Arg
		35					40					45			
Ala	Val	Thr	Gly	Leu	Ser	Gly	Asp	Gly	Lys	Ala	Ile	Trp	Asp	Lys	Lys
	50					55					60				
Gln	Tyr	Val	Ser	Pro	Val	Asn	Ala	Ser	Gln	Leu	Phe	Leu	Tyr	Asp	Thr
65					70					75					80
Phe	Pro	Lys	Asn	Phe	Phe	Trp	Gly	Val	Gly	Thr	Gly	Ala	Phe	Gln	Val
			85						90					95	
Glu	Gly	Asn	Trp	Gln	Ala	Asp	Gly	Arg	Gly	Pro	Ser	Ile	Trp	Asp	Arg
			100					105					110		
Phe	Ile	Tyr	Thr	His	Leu	Arg	Asp	Val	Ser	Ile	Thr	Glu	Lys	Ser	Ala
		115					120					125			
Asp	Ser	Tyr	Ile	Phe	Leu	Glu	Lys	Asp	Leu	Leu	Ala	Leu	Asp	Phe	Leu
	130					135					140				
Gly	Val	Ser	Phe	Tyr	Gln	Phe	Ser	Ile	Ser	Trp	Pro	Arg	Leu	Phe	Pro
145					150					155					160
Asn	Gly	Thr	Val	Ala	Ser	Val	Asn	Ala	Lys	Gly	Leu	Gln	Tyr	Tyr	Asn
			165					170					175		
Lys	Leu	Leu	Asp	Ser	Leu	Ile	Leu	Arg	Asn	Ile	Glu	Pro	Val	Val	Thr
			180					185					190		

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	Leu	Tyr	His	Trp	Asp	Leu	Pro	Leu	Ala	Leu	Gln	Glu	Asp	Tyr	Gly	Gly
			195					200					205			
	Trp	Lys	Asn	Ala	Thr	Met	Ile	Asp	Leu	Phe	Asn	Asp	Tyr	Ala	Thr	Tyr
		210					215					220				
5	Cys	Phe	Gln	Thr	Phe	Gly	Asp	Arg	Val	Lys	Tyr	Trp	Ile	Thr	Ile	His
	225					230					235					240
	Asn	Pro	Tyr	Leu	Val	Ala	Trp	His	Gly	Phe	Ala	Thr	Gly	Met	His	Ala
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	Pro	Gly	Glu	Thr	Gly	Asn	Leu	Thr	Ala	Val	Tyr	Ile	Val	Gly	His	Asn
				260					265					270		
10	Leu	Ile	Lys	Ala	His	Ser	Lys	Val	Trp	His	Asn	Tyr	Asp	Lys	Asn	Phe
			275					280					285			
	Arg	Pro	His	Gln	Lys	Gly	Leu	Ser	Ile	Thr	Leu	Gly	Ser	His	Trp	
		290					295					300				
	Ile	Glu	Pro	Asn	Lys	Thr	Glu	Asn	Met	Ala	Asp	Thr	Ile	Ser	Cys	Gln
15	305					310					315					320
	His	Ser	Met	Ala	Phe	Val	Leu	Gly	Trp	Phe	Ala	Asn	Pro	Ile	His	Ala
					325					330					335	
	Asp	Gly	Asp	Tyr	Pro	Glu	Phe	Met	Lys	Thr	Leu	Ser	Thr	Met	Pro	Val
				340					345					350		
	Phe	Ser	Glu	Ala	Glu	Lys	Glu	Glu	Val	Arg	Gly	Thr	Ala	Asp	Phe	Phe
20			355					360					365			
	Ala	Phe	Ser	Phe	Gly	Pro	Asn	Asn	Phe	Arg	Pro	Ser	Asn	Thr	Val	Val
							375					380				
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	Ile	Lys	Leu	Glu	Tyr	Asp	Asn	Pro	Arg	Ile	Leu	Ile	Ser	Glu	Asn	Gly
25					405					410					415	
	Trp	Phe	Thr	Asp	Ser	Asp	Ile	Lys	Thr	Glu	Asp	Thr	Thr	Ala	Ile	Tyr
				420					425					430		
	Met	Met	Lys	His	Phe	Leu	Asn	Gln	Val	Leu	Gln	Ala	Ile	Gln	Phe	Asp
				435				440					445			
30	Glu	Ile	Arg	Val	Phe	Gly	Tyr	Thr	Ala	Trp	Ser	Leu	Leu	Asp	Gly	Phe
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	Glu	Trp	Gln	Tyr	Ala	Tyr	Thr	Ser	Arg	Arg	Gly	Leu	Phe	Tyr	Val	Asp
	465					470					475					480
	Phe	Asn	Ser	Glu	Gln	Lys	Glu	Arg	Lys	Pro	Lys	Thr	Ser	Ala	His	Tyr
					485					490					495	
35	Tyr	Lys	Gln	Ile	Ile	Gln	Glu	Asn	Gly	Phe	Pro	Leu	Lys	Glu	Ser	Thr
				500					505					510		
	Pro	Asp	Met	Gln	Gly	Gln	Phe	Pro	Cys	Asp	Phe	Ser	Trp	Gly	Val	Thr
			515					520					525			
	Glu	Ser	Val	Leu	Lys	Pro	Glu	Phe	Met	Val	Ser	Ser	Pro	Gln	Phe	Thr
40							535					540				
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					565					570					575	
	Tyr	Val	Ser	Ile	Lys	Lys	Arg	Val	Glu	Met	Leu	Ala	Lys	Met	Lys	Val
45				580					585					590		
	Thr	His	Tyr	Gln	Phe	Ala	Leu	Asp	Trp	Ala	Thr	Ile	Leu	Pro	Thr	Gly
				595				600					605			
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						615						620				
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	His	Pro	Thr	His	Ser	His	Leu	Gly	Leu	Pro	Glu	Pro	Leu	Leu	Asn	Ser
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	Gly	Gly	Trp	Leu	Asn	Thr	Tyr	Thr	Ala	Lys	Ala	Phe	Gln	Asp	Tyr	Ala
				660					665					670		
55	Gly	Leu	Cys	Phe	Gln	Glu	Leu	Gly	Asp	Leu	Val	Lys	Leu	Trp	Ile	Thr
			675					680					685			
	Ile	Asn	Glu	Pro	Asn	Arg	Leu	Ser	Asp	Met	Tyr	Asn	Arg	Thr	Ser	Asn

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	690		695		700	
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5	Trp Arg Leu Tyr Asp Arg Gln Tyr Arg Pro Val Gln His Gly Ala Val					
		725		730		735
	Ser Leu Ser Leu His Ser Asp Trp Val Glu Pro Ala Asn Pro Tyr Val					
		740		745		750
	Asp Ser His Trp Lys Ala Ala Glu Arg Phe Leu Leu Phe Glu Ile Ala					
		755		760		765
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	Gln Leu Asn Ser Ser Arg Ser Met Ala Asp Arg Asp Val Gln Phe Leu					
		835		840		845
	Gln Asp Ile Thr Arg Leu Ser Ser Pro Ser Arg Leu Ala Val Met Pro					
		850		855		860
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		865		870		875
	Met Asp Ile Tyr Ile Thr Ala Asn Gly Ile Asp Asp Leu Ala Leu Glu					
			885		890	895
25	Asn Asp Gly Ile Arg Lys Tyr Tyr Leu Glu Lys Tyr Ile Gln Glu Ala					
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	Leu Lys Ala Tyr Leu Ile Asp Lys Val Lys Ile Lys Gly Tyr Tyr Ala					
		915		920		925
	Phe Lys Leu Thr Glu Glu Lys Ser Lys Pro Arg Phe Gly Phe Phe Thr					
		930		935		940
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	Ser Arg Ser Gly Phe Pro Ser Glu Thr Ser Asn Pro Ala Cys Gly Gln					
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	Pro Pro Glu Asp Thr Asp Cys Thr Ile Cys Ser Phe Phe Thr Gln Lys					
		980		985		990
35	Lys Ser Leu Ile Phe Phe Gly Cys Cys Phe Ile Ser Thr Leu Ala Val					
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	Leu Leu Ser Ile Thr Ile Phe His His Arg Lys Arg Arg Phe His Lys					
		1010		1015		1020
	Ser Lys Asn Leu Glu Asn Ile Pro Leu Lys Glu Gly His Ser Arg Val					
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<210> 409

<211> 3042

45 <212> DNA

<213> Cricetulus griseus

<220>

<223> Coding sequence of hamster beta klotho

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<400> 409

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[illegible]

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	Ala	Ile	Gly	Leu	Asp	Lys	Asp	Lys	Pro	Asn	Arg	Val	Thr	Lys	Val	Ala
15	385					390					395					400
	Val	Lys	Met	Leu	Lys	Ser	Asp	Ala	Thr	Glu	Lys	Asp	Leu	Ser	Asp	Leu
					405					410					415	
	Ile	Ser	Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile
				420					425					430		
	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	Tyr	Val	Ile
20			435					440					445			
	Val	Glu	Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu	Gln	Ala	Arg
	450						455				460					
	Arg	Pro	Pro	Gly	Leu	Glu	Tyr	Cys	Tyr	Asn	Pro	Ser	His	Asn	Pro	Glu
	465					470				475						480
25	Glu	Gln	Leu	Ser	Ser	Lys	Asp	Leu	Val	Ser	Cys	Ala	Tyr	Gln	Val	Ala
					485					490					495	
	Arg	Gly	Met	Glu	Tyr	Leu	Ala	Ser	Lys	Lys	Cys	Ile	His	Arg	Asp	Leu
				500					505					510		
	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asp	Asn	Val	Met	Lys	Ile	Ala
			515					520					525			
30	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	His	His	Ile	Asp	Tyr	Tyr	Lys	Lys
	530						535					540				
	Thr	Thr	Asn	Gly	Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro	Glu	Ala	Leu
	545					550				555						560
	Phe	Asp	Arg	Ile	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val
					565					570					575	
35	Leu	Leu	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr	Pro	Gly	Val
				580					585					590		
	Pro	Val	Glu	Glu	Leu	Phe	Lys	Leu	Leu	Lys	Glu	Gly	His	Arg	Met	Asp
			595					600					605			
	Lys	Pro	Ser	Asn	Cys	Thr	Asn	Glu	Leu	Tyr	Met	Met	Met	Arg	Asp	Cys
40							615					620				
	Trp	His	Ala	Val	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln	Leu	Val	Glu
	625					630				635						640
	Asp	Leu	Asp	Arg	Ile	Val	Ala	Leu	Thr	Ser	Asn	Gln	Glu	Tyr	Leu	Asp
					645					650					655	
45	Leu	Ser	Met	Pro	Leu	Asp	Gln	Tyr	Ser	Pro	Ser	Phe	Pro	Asp	Thr	Arg
				660				665					670			
	Ser	Ser	Thr	Cys	Ser	Ser	Gly	Glu	Asp	Ser	Val	Phe	Ser	His	Glu	Pro
			675					680					685			
	Leu	Pro	Glu	Glu	Pro	Cys	Leu	Pro	Arg	His	Pro	Ala	Gln	Leu	Ala	Asn
		690					695					700				
50	Gly	Gly	Leu	Lys	Arg	Arg										
	705					710										

<210> 417

<211> 710

55 <212> PRT

<213> Artificial Sequence

<220>

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<223> hamster-FGFR1 (R54-E319) (Beta-IIIc) XP_007610900.1 fused to human FGFR1 (I286-R731, NP_075594)

<400> 417

5	Arg	Pro	Ala	Pro	Thr	Leu	Pro	Glu	Gln	Asp	Ala	Leu	Pro	Ser	Ser	Glu
	1				5					10					15	
	Asp	Asp	Asp	Asp	Asp	Asp	Asp	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Thr	Asp
				20					25					30		
	Asn	Thr	Lys	Pro	Asn	Pro	Val	Ala	Pro	Tyr	Trp	Thr	Ser	Pro	Glu	Lys
10			35					40					45			
	Met	Glu	Lys	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe
		50					55					60				
	Lys	Cys	Pro	Ser	Ser	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg	Trp	Leu	Lys
	65					70					75					80
	Asn	Gly	Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val
15					85					90					95	
	Arg	Tyr	Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp
				100					105						110	
	Lys	Gly	Asn	Tyr	Thr	Cys	Ile	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn
			115					120					125			
20	His	Thr	Tyr	Gln	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile
		130					135					140				
	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu	Gly	Ser	Asn
	145					150					155					160
	Val	Glu	Phe	Met	Cys	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro	His	Ile	Gln
				165						170					175	
25	Trp	Leu	Lys	His	Ile	Glu	Val	Asn	Gly	Ser	Lys	Ile	Gly	Pro	Asp	Asn
			180					185						190		
	Leu	Pro	Tyr	Val	Gln	Ile	Leu	Lys	Thr	Ala	Gly	Val	Asn	Thr	Thr	Asp
		195					200						205			
	Lys	Glu	Met	Glu	Val	Leu	His	Leu	Arg	Asn	Val	Ser	Phe	Glu	Asp	Ala
30		210				215						220				
	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Leu	Ser	His	His
					230						235					240
	Ser	Ala	Trp	Leu	Thr	Val	Leu	Glu	Ala	Leu	Glu	Glu	Arg	Pro	Ala	Val
				245					250						255	
35	Met	Thr	Ser	Pro	Leu	Tyr	Leu	Glu	Ile	Ile	Ile	Tyr	Cys	Thr	Gly	Ala
			260					265						270		
	Phe	Leu	Ile	Ser	Cys	Met	Val	Gly	Ser	Val	Ile	Val	Tyr	Lys	Met	Lys
			275					280					285			
	Ser	Gly	Thr	Lys	Lys	Ser	Asp	Phe	His	Ser	Gln	Met	Ala	Val	His	Lys
		290				295						300				
40	Leu	Ala	Lys	Ser	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala	Asp
		305				310					315					320
	Ser	Ser	Ala	Ser	Met	Asn	Ser	Gly	Val	Leu	Val	Arg	Pro	Ser	Ser	Arg
				325					330						335	
	Leu	Ser	Ser	Ser	Gly	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	Glu	Tyr	Glu
				340				345						350		
45	Leu	Pro	Glu	Asp	Pro	Arg	Trp	Glu	Leu	Pro	Arg	Asp	Arg	Leu	Val	Leu
			355					360					365			
	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val	Leu	Ala	Glu
		370					375					380				
	Ala	Ile	Gly	Leu	Asp	Lys	Asp	Lys	Pro	Asn	Arg	Val	Thr	Lys	Val	Ala
50		385				390					395					400
	Val	Lys	Met	Leu	Lys	Ser	Asp	Ala	Thr	Glu	Lys	Asp	Leu	Ser	Asp	Leu
				405						410					415	
	Ile	Ser	Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile
				420				425						430		
55	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	Tyr	Val	Ile
			435				440						445			
	Val	Glu	Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu	Gln	Ala	Arg
		450				455					460					
	Arg	Pro	Pro	Gly	Leu	Glu	Tyr	Cys	Tyr	Asn	Pro	Ser	His	Asn	Pro	Glu

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	465				470				475				480
	Glu	Gln	Leu	Ser	Ser	Lys	Asp	Leu	Val	Ser	Cys	Ala	Tyr
					485					490			495
5	Arg	Gly	Met	Glu	Tyr	Leu	Ala	Ser	Lys	Lys	Cys	Ile	His
				500					505				510
	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asp	Asn	Val	Met
			515					520				525	
	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	His	His	Ile	Asp	Tyr
		530				535					540		
10	Thr	Thr	Asn	Gly	Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro
	545					550				555			
	Phe	Asp	Arg	Ile	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser
				565				570					575
	Leu	Leu	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr
			580					585				590	
15	Pro	Val	Glu	Glu	Leu	Phe	Lys	Leu	Lys	Glu	Gly	His	Arg
		595					600					605	
	Lys	Pro	Ser	Asn	Cys	Thr	Asn	Glu	Leu	Tyr	Met	Met	Met
		610				615				620			
	Trp	His	Ala	Val	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln
20	625				630				635				640
	Asp	Leu	Asp	Arg	Ile	Val	Ala	Leu	Thr	Ser	Asn	Gln	Glu
				645				650					655
	Leu	Ser	Met	Pro	Leu	Asp	Gln	Tyr	Ser	Pro	Ser	Phe	Pro
			660					665				670	
25	Ser	Ser	Thr	Cys	Ser	Ser	Gly	Glu	Asp	Ser	Val	Phe	Ser
		675					680					685	
	Leu	Pro	Glu	Glu	Pro	Cys	Leu	Pro	Arg	His	Pro	Ala	Gln
		690				695					700		
	Gly	Gly	Leu	Lys	Arg	Arg							
30	705				710								

<210> 418

<211> 710

<212> PRT

<213> Artificial Sequence

<220>

<223> dog-FGFR1 (R22-E287) (Beta-IIIc), XP_005629909.1 fused to human FGFR1 (I286-R731, NP_075594)

<400> 418

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	Arg	Pro	Ala	Pro	Thr	Leu	Pro	Glu	Gln	Asp	Ala	Leu	Pro	Ser	Ser	Glu
	1				5					10					15	
	Asp	Asp	Asp	Asp	Asp	Asp	Asp	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Thr	Asp
				20					25					30		
5	Asn	Thr	Lys	Pro	Asn	Pro	Val	Ala	Pro	Tyr	Trp	Thr	Ser	Pro	Glu	Lys
			35					40					45			
	Met	Glu	Lys	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe
		50					55					60				
	Lys	Cys	Pro	Ser	Ser	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg	Trp	Leu	Lys
10	65					70					75					80
	Asn	Gly	Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val
					85					90					95	
	Arg	Tyr	Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp
				100					105					110		
	Lys	Gly	Asn	Tyr	Thr	Cys	Ile	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn
15			115					120					125			
	His	Thr	Tyr	Gln	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile
		130					135					140				
	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu	Gly	Ser	Asn
20	145					150					155					160

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	Val	Glu	Phe	Met	Cys	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro	His	Ile	Gln
				165						170					175	
	Trp	Leu	Lys	His	Ile	Glu	Val	Asn	Gly	Ser	Lys	Ile	Gly	Pro	Asp	Asn
5				180					185					190		
	Leu	Pro	Tyr	Val	Gln	Ile	Leu	Lys	Thr	Ala	Gly	Val	Asn	Thr	Thr	Asp
			195					200					205			
	Lys	Glu	Met	Glu	Val	Leu	His	Leu	Arg	Asn	Val	Ser	Phe	Glu	Asp	Ala
		210					215					220				
	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Leu	Ser	His	His
10		225				230					235					240
	Ser	Ala	Trp	Leu	Thr	Val	Leu	Glu	Ala	Leu	Glu	Glu	Arg	Pro	Ala	Ala
				245					250						255	
	Met	Thr	Ser	Pro	Leu	Tyr	Leu	Glu	Ile	Ile	Ile	Tyr	Cys	Thr	Gly	Ala
			260						265					270		
	Phe	Leu	Ile	Ser	Cys	Met	Val	Gly	Ser	Val	Ile	Val	Tyr	Lys	Met	Lys
15			275					280					285			
	Ser	Gly	Thr	Lys	Lys	Ser	Asp	Phe	His	Ser	Gln	Met	Ala	Val	His	Lys
		290					295					300				
	Leu	Ala	Lys	Ser	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala	Asp
		305				310					315					320
20	Ser	Ser	Ala	Ser	Met	Asn	Ser	Gly	Val	Leu	Leu	Val	Arg	Pro	Ser	Arg
				325						330					335	
	Leu	Ser	Ser	Ser	Gly	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	Glu	Tyr	Glu
			340						345					350		
	Leu	Pro	Glu	Asp	Pro	Arg	Trp	Glu	Leu	Pro	Arg	Asp	Arg	Leu	Val	Leu
			355					360					365			
25	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val	Leu	Ala	Glu
		370					375					380				
	Ala	Ile	Gly	Leu	Asp	Lys	Asp	Lys	Pro	Asn	Arg	Val	Thr	Lys	Val	Ala
		385				390					395					400
	Val	Lys	Met	Leu	Lys	Ser	Asp	Ala	Thr	Glu	Lys	Asp	Leu	Ser	Asp	Leu
				405						410					415	
30	Ile	Ser	Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile
			420						425					430		
	Ile	Asn	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	Tyr	Val	Ile	
			435					440					445			
	Val	Glu	Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu	Gln	Ala	Arg
		450					455					460				
35	Arg	Pro	Pro	Gly	Leu	Glu	Tyr	Cys	Tyr	Asn	Pro	Ser	His	Asn	Pro	Glu
		465				470					475					480
	Glu	Gln	Leu	Ser	Ser	Lys	Asp	Leu	Val	Ser	Cys	Ala	Tyr	Gln	Val	Ala
				485						490					495	
	Arg	Gly	Met	Glu	Tyr	Leu	Ala	Ser	Lys	Lys	Cys	Ile	His	Arg	Asp	Leu
40			500						505					510		
	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asp	Asn	Val	Met	Lys	Ile	Ala
			515					520					525			
	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	His	His	Ile	Asp	Tyr	Tyr	Lys	Lys
		530					535					540				
45	Thr	Thr	Asn	Gly	Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro	Glu	Ala	Leu
		545				550					555					560
	Phe	Asp	Arg	Ile	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val
				565						570					575	
	Leu	Leu	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr	Pro	Gly	Val
			580						585					590		
50	Pro	Val	Glu	Glu	Leu	Phe	Lys	Leu	Leu	Lys	Glu	Gly	His	Arg	Met	Asp
			595					600					605			
	Lys	Pro	Ser	Asn	Cys	Thr	Asn	Glu	Leu	Tyr	Met	Met	Met	Arg	Asp	Cys
		610					615					620				
	Trp	His	Ala	Val	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln	Leu	Val	Glu
		625				630					635					640
55	Asp	Leu	Asp	Arg	Ile	Val	Ala	Leu	Thr	Ser	Asn	Gln	Glu	Tyr	Leu	Asp
				645						650					655	
	Leu	Ser	Met	Pro	Leu	Asp	Gln	Tyr	Ser	Pro	Ser	Phe	Pro	Asp	Thr	Arg

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				660					665				670			
	Ser	Ser	Thr	Cys	Ser	Ser	Gly	Glu	Asp	Ser	Val	Phe	Ser	His	Glu	Pro
			675					680					685			
5	Leu	Pro	Glu	Glu	Pro	Cys	Leu	Pro	Arg	His	Pro	Ala	Gln	Leu	Ala	Asn
		690					695					700				
	Gly	Gly	Leu	Lys	Arg	Arg										
	705					710										

<210> 419

<211> 710

<212> PRT

<213> Artificial Sequence

<220>

<223> rat-FGFR1 (R22-E287) (Beta-IIIc), XP_006253387.1 fused to human FGFR1 (I286-R731, NP_075594)

<400> 419

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	Arg	Pro	Ala	Pro	Thr	Leu	Pro	Glu	Gln	Asp	Ala	Leu	Pro	Ser	Ser	Glu
	1				5					10					15	
	Asp	Asp	Asp	Asp	Asp	Asp	Asp	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Thr	Asp
				20				25						30		
5	Asn	Thr	Lys	Pro	Asn	Pro	Val	Ala	Pro	Tyr	Trp	Thr	Ser	Pro	Glu	Lys
			35					40					45			
	Met	Glu	Lys	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe
		50					55					60				
	Lys	Cys	Pro	Ser	Ser	Gly	Thr	Pro	Ser	Pro	Thr	Leu	Arg	Trp	Leu	Lys
10	65					70					75					80
	Asn	Gly	Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val
					85					90					95	
	Arg	Tyr	Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp
				100					105					110		
	Lys	Gly	Asn	Tyr	Thr	Cys	Ile	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn
15			115					120					125			
	His	Thr	Tyr	Gln	Leu	Asp	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	
		130					135					140				
	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu	Gly	Ser	Asn
					150						155					160
20	Val	Glu	Phe	Met	Cys	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro	His	Ile	Gln
					165					170					175	
	Trp	Leu	Lys	His	Ile	Glu	Val	Asn	Gly	Ser	Lys	Ile	Gly	Pro	Asp	Asn
				180					185					190		
	Leu	Pro	Tyr	Val	Gln	Ile	Leu	Lys	Thr	Ala	Gly	Val	Asn	Thr	Thr	Asp
			195					200					205			
25	Lys	Glu	Met	Glu	Val	Leu	His	Leu	Arg	Asn	Val	Ser	Phe	Glu	Asp	Ala
		210					215					220				
	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Leu	Ser	His	His
					230						235					240
	Ser	Ala	Trp	Leu	Thr	Val	Leu	Glu	Ala	Leu	Glu	Glu	Arg	Pro	Ala	Val
30					245					250					255	
	Met	Thr	Ser	Pro	Leu	Tyr	Leu	Glu	Ile	Ile	Ile	Tyr	Cys	Thr	Gly	Ala
				260					265					270		
	Phe	Leu	Ile	Ser	Cys	Met	Val	Gly	Ser	Val	Ile	Val	Tyr	Lys	Met	Lys
			275					280					285			
	Ser	Gly	Thr	Lys	Lys	Ser	Asp	Phe	His	Ser	Gln	Met	Ala	Val	His	Lys
35		290					295					300				
	Leu	Ala	Lys	Ser	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala	Asp
					310						315					320
	Ser	Ser	Ala	Ser	Met	Asn	Ser	Gly	Val	Leu	Leu	Val	Arg	Pro	Ser	Arg
					325					330					335	
40	Leu	Ser	Ser	Ser	Gly	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	Glu	Tyr	Glu
				340					345					350		

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5 Leu Pro Glu Asp Pro Arg Trp Glu Leu Pro Arg Asp Arg Leu Val Leu
 355 360 365
 Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val Leu Ala Glu
 370 375 380
 10 Ala Ile Gly Leu Asp Lys Asp Lys Pro Asn Arg Val Thr Lys Val Ala
 385 390 395 400
 Val Lys Met Leu Lys Ser Asp Ala Thr Glu Lys Asp Leu Ser Asp Leu
 405 410 415
 Ile Ser Glu Met Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile
 420 425 430
 15 Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu Tyr Val Ile
 435 440 445
 Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Gln Ala Arg
 450 455 460
 Arg Pro Pro Gly Leu Glu Tyr Cys Tyr Asn Pro Ser His Asn Pro Glu
 465 470 475 480
 Glu Gln Leu Ser Ser Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala
 485 490 495
 Arg Gly Met Glu Tyr Leu Ala Ser Lys Lys Cys Ile His Arg Asp Leu
 500 505 510
 20 Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala
 515 520 525
 Asp Phe Gly Leu Ala Arg Asp Ile His His Ile Asp Tyr Tyr Lys Lys
 530 535 540
 Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu
 545 550 555 560
 25 Phe Asp Arg Ile Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val
 565 570 575
 Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser Pro Tyr Pro Gly Val
 580 585 590
 Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His Arg Met Asp
 595 600 605
 30 Lys Pro Ser Asn Cys Thr Asn Glu Leu Tyr Met Met Met Arg Asp Cys
 610 615 620
 Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu
 625 630 635 640
 35 Asp Leu Asp Arg Ile Val Ala Leu Thr Ser Asn Gln Glu Tyr Leu Asp
 645 650 655
 Leu Ser Met Pro Leu Asp Gln Tyr Ser Pro Ser Phe Pro Asp Thr Arg
 660 665 670
 Ser Ser Thr Cys Ser Ser Gly Glu Asp Ser Val Phe Ser His Glu Pro
 675 680 685
 40 Leu Pro Glu Glu Pro Cys Leu Pro Arg His Pro Ala Gln Leu Ala Asn
 690 695 700
 Gly Gly Leu Lys Arg Arg
 705 710

<210> 420

<211> 713

<212> PRT

<213> Artificial Sequence

<220>

<223> rabbit-FGFR1 (R22-E288) (Beta-IIIc), XP_008272198.1 fused to human FGFR1 (I286-R731, NP_075594)

<400> 420

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 1 5 10 15
 Glu Asp Asp Asp Asp Asp Asp Ser Ser Ser Glu Glu Lys Glu Thr
 20 25 30
 Asp Asn Thr Lys Pro Asn Arg Met Pro Val Ala Pro Tyr Trp Thr Ser

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			35				40				45					
	Pro	Glu	Lys	Met	Glu	Lys	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr
	50						55				60					
5	Val	Lys	Phe	Lys	Cys	Pro	Ser	Ser	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg
	65					70					75					80
	Trp	Leu	Lys	Asn	Gly	Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly
					85					90					95	
	Tyr	Lys	Val	Arg	Tyr	Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val
				100					105					110		
10	Pro	Ser	Asp	Lys	Gly	Asn	Tyr	Thr	Cys	Ile	Val	Glu	Asn	Glu	Tyr	Gly
			115					120					125			
	Ser	Ile	Asn	His	Thr	Tyr	Gln	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His
			130				135					140				
	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu
	145				150						155					160
15	Gly	Ser	Asn	Val	Glu	Phe	Met	Cys	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro
				165						170					175	
	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Glu	Val	Asn	Gly	Ser	Lys	Ile	Gly
			180					185						190		
	Pro	Asp	Asn	Leu	Pro	Tyr	Val	Gln	Ile	Leu	Lys	Thr	Ala	Gly	Val	Asn
			195				200						205			
20	Thr	Thr	Asp	Lys	Glu	Met	Glu	Val	Leu	His	Leu	Arg	Asn	Val	Ser	Phe
		210				215						220				
	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Leu
	225				230						235					240
	Ser	His	His	Ser	Ala	Trp	Leu	Thr	Val	Leu	Glu	Ala	Leu	Glu	Glu	Arg
				245						250					255	
25	Pro	Ala	Val	Met	Thr	Ser	Pro	Leu	Tyr	Leu	Glu	Ile	Ile	Ile	Tyr	Cys
			260					265						270		
	Thr	Gly	Ala	Phe	Leu	Ile	Ser	Cys	Met	Val	Gly	Ser	Val	Ile	Val	Tyr
		275					280						285			
	Lys	Met	Lys	Ser	Gly	Thr	Lys	Lys	Ser	Asp	Phe	His	Ser	Gln	Met	Ala
		290				295					300					
30	Val	His	Lys	Leu	Ala	Lys	Ser	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val
		305				310					315					320
	Ser	Ala	Asp	Ser	Ser	Ala	Ser	Met	Asn	Ser	Gly	Val	Leu	Leu	Val	Arg
				325						330					335	
	Pro	Ser	Arg	Leu	Ser	Ser	Ser	Gly	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser
			340					345						350		
35	Glu	Tyr	Glu	Leu	Pro	Glu	Asp	Pro	Arg	Trp	Glu	Leu	Pro	Arg	Asp	Arg
		355					360						365			
	Leu	Val	Leu	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val
		370				375						380				
40	Leu	Ala	Glu	Ala	Ile	Gly	Leu	Asp	Lys	Asp	Lys	Pro	Asn	Arg	Val	Thr
		385			390						395					400
	Lys	Val	Ala	Val	Lys	Met	Leu	Lys	Ser	Asp	Ala	Thr	Glu	Lys	Asp	Leu
				405					410						415	
	Ser	Asp	Leu	Ile	Ser	Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His
			420				425						430			
45	Lys	Asn	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	
		435					440						445			
	Tyr	Val	Ile	Val	Glu	Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu
		450				455						460				
	Gln	Ala	Arg	Arg	Pro	Pro	Gly	Leu	Glu	Tyr	Cys	Tyr	Asn	Pro	Ser	His
		465			470					475						480
50	Asn	Pro	Glu	Glu	Gln	Leu	Ser	Ser	Lys	Asp	Leu	Val	Ser	Cys	Ala	Tyr
				485						490					495	
	Gln	Val	Ala	Arg	Gly	Met	Glu	Tyr	Leu	Ala	Ser	Lys	Lys	Cys	Ile	His
			500					505						510		
	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asp	Asn	Val	Met
		515					520					525				
55	Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	His	His	Ile	Asp	Tyr
		530				535						540				

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	Tyr	Lys	Lys	Thr	Thr	Asn	Gly	Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro
	545					550					555					560
	Glu	Ala	Leu	Phe	Asp	Arg	Ile	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser
					565					570					575	
5	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr
				580					585					590		
	Pro	Gly	Val	Pro	Val	Glu	Glu	Leu	Phe	Lys	Leu	Leu	Lys	Glu	Gly	His
			595					600					605			
	Arg	Met	Asp	Lys	Pro	Ser	Asn	Cys	Thr	Asn	Glu	Leu	Tyr	Met	Met	Met
10		610					615					620				
	Arg	Asp	Cys	Trp	His	Ala	Val	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln
	625					630					635					640
	Leu	Val	Glu	Asp	Leu	Asp	Arg	Ile	Val	Ala	Leu	Thr	Ser	Asn	Gln	Glu
				645						650					655	
15	Tyr	Leu	Asp	Leu	Ser	Met	Pro	Leu	Asp	Gln	Tyr	Ser	Pro	Ser	Phe	Pro
			660						665					670		
	Asp	Thr	Arg	Ser	Ser	Thr	Cys	Ser	Ser	Gly	Glu	Asp	Ser	Val	Phe	Ser
			675					680					685			
	His	Glu	Pro	Leu	Pro	Glu	Glu	Pro	Cys	Leu	Pro	Arg	His	Pro	Ala	Gln
		690					695					700				
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<210> 421

<211> 465

25 <212> PRT

<213> Artificial Sequence

<220>

<223> hlgK alpha-KLH VH mlgG1

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<400> 421

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	Leu	Arg	Gly	Ala	Arg	Cys	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu
				20				25					30			
5	Val	Lys	Lys	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly
			35				40					45				
	Tyr	Thr	Phe	Thr	Gly	Tyr	His	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly
		50					55					60				
	Gln	Gly	Leu	Glu	Trp	Met	Gly	Trp	Ile	Asn	Pro	Asn	Ser	Gly	Gly	Thr
10	65					70				75						80
	Asn	Tyr	Ala	Gln	Lys	Phe	Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr
				85					90						95	
	Ser	Ile	Ser	Thr	Ala	Tyr	Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp
				100					105					110		
	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Gly	Ser	Tyr	Tyr	Trp	Phe
15			115				120						125			
	Asp	Pro	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Lys	Thr
		130					135					140				
	Thr	Pro	Pro	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala	Ala	Gln	Thr
	145					150					155					160
20	Asn	Ser	Met	Val	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro	Glu
				165						170					175	
	Pro	Val	Thr	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val	His
			180						185					190		
	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Asp	Leu	Tyr	Thr	Leu	Ser	Ser	Ser
			195				200						205			
25	Val	Thr	Val	Pro	Ser	Ser	Thr	Trp	Pro	Ser	Glu	Thr	Val	Thr	Cys	Asn
		210					215					220				
	Val	Ala	His	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Val	Pro
	225					230					235					240
30																
	Arg	Asp	Cys	Gly	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Val	Pro	Glu	Val	Ser
					245					250					255	
	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile	Thr
			260					265						270		
35	Leu	Thr	Pro	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp	Asp
			275				280						285			
	Pro	Glu	Val	Gln	Phe	Ser	Trp	Phe	Val	Asp	Asp	Val	Glu	Val	His	Thr
		290					295					300				
	Ala	Gln	Thr	Gln	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Ser
	305					310					315					320
40	Val	Ser	Glu	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
				325						330					335	
	Phe	Lys	Cys	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	Lys
			340						345					350		
	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	Thr
			355				360						365			
45	Ile	Pro	Pro	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr
		370					375					380				
	Cys	Met	Ile	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln
	385					390					395					400
	Trp	Asn	Gly	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	Met
				405						410					415	
50	Asp	Thr	Asp	Gly	Ser	Tyr	Phe	Val	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys
			420						425					430		
	Ser	Asn	Trp	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu
			435					440					445			
	Gly	Leu	His	Asn	His	His	Thr	Glu	Lys	Ser	Leu	Ser	His	Ser	Pro	Gly
55		450					455					460				
	Lys															
	465															

<210> 422
 <211> 471
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> hlgK alpha-KLH VH mlgG2-alpha

<400> 422

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Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu
      20      25      30
Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
      35      40      45
Tyr Thr Phe Thr Gly Tyr His Met His Trp Val Arg Gln Ala Pro Gly
      50      55      60
Gln Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr
      65      70      75      80
Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr
      85      90      95
Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp
      100      105      110
Thr Ala Val Tyr Tyr Cys Ala Arg Asp Arg Gly Ser Tyr Tyr Trp Phe
      115      120      125
Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Lys Thr
      130      135      140
Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Thr
      145      150      155      160
Gly Ser Ser Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
      165      170      175

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	Pro	Val	Thr	Leu	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val	His
				180					185					190		
5	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Asp	Leu	Tyr	Thr	Leu	Ser	Ser	Ser
			195					200					205			
	Val	Thr	Val	Thr	Ser	Ser	Thr	Trp	Pro	Ser	Gln	Ser	Ile	Thr	Cys	Asn
		210					215					220				
	Val	Ala	His	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Glu	Pro
	225					230					235					240
10	Arg	Gly	Pro	Thr	Ile	Lys	Pro	Cys	Pro	Pro	Cys	Lys	Cys	Pro	Ala	Pro
				245						250					255	
	Asn	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys	Ile	Lys
			260						265					270		
	Asp	Val	Leu	Met	Ile	Ser	Leu	Ser	Pro	Ile	Val	Thr	Cys	Val	Val	Val
			275					280					285			
15	Asp	Val	Ser	Glu	Asp	Asp	Pro	Asp	Val	Gln	Ile	Ser	Trp	Phe	Val	Asn
		290					295					300				
	Asn	Val	Glu	Val	His	Thr	Ala	Gln	Thr	Gln	Thr	His	Arg	Glu	Asp	Tyr
	305					310					315					320
	Asn	Ser	Thr	Leu	Arg	Val	Val	Ser	Ala	Leu	Pro	Ile	Gln	His	Gln	Asp
					325						330				335	
20	Trp	Met	Ser	Gly	Lys	Glu	Phe	Lys	Cys	Lys	Val	Asn	Asn	Lys	Asp	Leu
			340						345					350		
	Pro	Ala	Pro	Ile	Glu	Arg	Thr	Ile	Ser	Lys	Pro	Lys	Gly	Ser	Val	Arg
			355					360					365			
	Ala	Pro	Gln	Val	Tyr	Val	Leu	Pro	Pro	Pro	Glu	Glu	Glu	Met	Thr	Lys
25			370				375					380				
	Lys	Gln	Val	Thr	Leu	Thr	Cys	Met	Val	Thr	Asp	Phe	Met	Pro	Glu	Asp
	385					390					395					400
	Ile	Tyr	Val	Glu	Trp	Thr	Asn	Asn	Gly	Lys	Thr	Glu	Leu	Asn	Tyr	Lys
				405						410					415	
30	Asn	Thr	Glu	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Tyr	Phe	Met	Tyr	Ser
			420						425					430		
	Lys	Leu	Arg	Val	Glu	Lys	Lys	Asn	Trp	Val	Glu	Arg	Asn	Ser	Tyr	Ser
			435					440					445			
	Cys	Ser	Val	Val	His	Glu	Gly	Leu	His	Asn	His	His	Thr	Thr	Lys	Ser
		450					455					460				
35	Phe	Ser	Arg	Thr	Pro	Gly	Lys									
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<210> 423

<211> 236

40 <212> PRT

<213> Artificial Sequence

<220>

<223> hlgK alpha-KLH VL mKappa

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<400> 423

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	Leu	Arg	Gly	Ala	Arg	Cys	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser
			20					25					30			
5	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser
			35				40						45			
	Gln	Gly	Ile	Arg	Asn	Asp	Leu	Gly	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys
		50					55					60				
	Ala	Pro	Lys	Arg	Leu	Ile	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val
10		65				70					75					80
	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr
				85						90					95	
	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln
				100				105						110		
15																
	His	Asn	Ser	Tyr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile
			115					120					125			
	Lys	Arg	Ala	Asp	Ala	Ala	Pro	Thr	Val	Ser	Ile	Phe	Pro	Pro	Ser	Ser
		130					135					140				
20	Glu	Gln	Leu	Thr	Ser	Gly	Gly	Ala	Ser	Val	Val	Cys	Phe	Leu	Asn	Asn
		145				150					155				160	
	Phe	Tyr	Pro	Lys	Asp	Ile	Asn	Val	Lys	Trp	Lys	Ile	Asp	Gly	Ser	Glu
				165					170					175		
	Arg	Gln	Asn	Gly	Val	Leu	Asn	Ser	Trp	Thr	Asp	Gln	Asp	Ser	Lys	Asp
				180					185					190		
25	Ser	Thr	Tyr	Ser	Met	Ser	Ser	Thr	Leu	Thr	Leu	Thr	Lys	Asp	Glu	Tyr
			195					200					205			
	Glu	Arg	His	Asn	Ser	Tyr	Thr	Cys	Glu	Ala	Thr	His	Lys	Thr	Ser	Thr
		210					215					220				
	Ser	Pro	Ile	Val	Lys	Ser	Phe	Asn	Arg	Asn	Glu	Cys				
30		225				230					235					

<210> 424

<211> 471

<212> PRT

<213> Artificial Sequence

<220>

<223> hlgK-KLH-(VH)-hlgG1(E233A)(L235A)

<400> 424

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	Leu	Arg	Gly	Ala	Arg	Cys	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu
			20				25						30			
5	Val	Lys	Lys	Pro	Gly	Ala	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly
		35					40					45				
	Tyr	Thr	Phe	Thr	Gly	Tyr	His	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly
	50					55						60				
	Gln	Gly	Leu	Glu	Trp	Met	Gly	Trp	Ile	Asn	Pro	Asn	Ser	Gly	Gly	Thr
10	65				70					75						80
	Asn	Tyr	Ala	Gln	Lys	Phe	Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr
				85					90					95		
	Ser	Ile	Ser	Thr	Ala	Tyr	Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp
			100					105					110			
	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Gly	Ser	Tyr	Tyr	Trp	Phe
15			115					120					125			
	Asp	Pro	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr
	130					135						140				
	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser
	145				150					155						160
20	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu
				165					170					175		
	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His
			180					185						190		
	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser
		195					200					205				
25	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys
	210				215							220				
	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu
	225				230						235					240
	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro
				245						250					255	
30	Ala	Leu	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
			260					265						270		
	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val
		275						280					285			
35	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp
	290					295						300				
	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr
	305				310						315					320
40	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp
				325						330					335	
	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu
			340						345					350		
	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
		355					360						365			
45	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys
	370					375						380				
	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp
	385				390						395					400
	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
				405						410					415	
50	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
			420						425					430		
	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser
		435						440					445			
	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
	450					455						460				
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	465					470										

<210> 425

<211> 236
 <212> PRT
 <213> Artificial Sequence

5 <220>
 <223> hlgK-KLH-(VL)-hlgK

<400> 425

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 Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
 15 35 40 45
 Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
 50 55 60
 Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
 65 70 75 80
 Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
 20 85 90 95
 Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
 100 105 110
 His Asn Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
 115 120 125
 Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 25 130 135 140
 Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 145 150 155 160
 Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 30 165 170 175
 Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 180 185 190
 Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
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 225 230 235

40 <210> 426

<211> 264
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Example of extracellular region of FGFR1c (beta-IIIc, NP_075594)

<400> 426

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55

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 20 25 30
 10 Asn Thr Lys Pro Asn Pro Val Ala Pro Tyr Trp Thr Ser Pro Glu Lys
 35 40 45
 Met Glu Lys Lys Leu His Ala Val Pro Ala Ala Lys Thr Val Lys Phe
 50 55 60
 Lys Cys Pro Ser Ser Gly Thr Pro Asn Pro Thr Leu Arg Trp Leu Lys
 65 70 75 80
 Asn Gly Lys Glu Phe Lys Pro Asp His Arg Ile Gly Gly Tyr Lys Val
 85 90 95
 Arg Tyr Ala Thr Trp Ser Ile Ile Met Asp Ser Val Val Pro Ser Asp
 100 105 110
 15 Lys Gly Asn Tyr Thr Cys Ile Val Glu Asn Glu Tyr Gly Ser Ile Asn
 115 120 125
 His Thr Tyr Gln Leu Asp Val Val Glu Arg Ser Pro His Arg Pro Ile
 130 135 140
 Leu Gln Ala Gly Leu Pro Ala Asn Lys Thr Val Ala Leu Gly Ser Asn
 145 150 155 160
 20 Val Glu Phe Met Cys Lys Val Tyr Ser Asp Pro Gln Pro His Ile Gln
 165 170 175
 Trp Leu Lys His Ile Glu Val Asn Gly Ser Lys Ile Gly Pro Asp Asn
 180 185 190
 Leu Pro Tyr Val Gln Ile Leu Lys Thr Ala Gly Val Asn Thr Thr Asp
 195 200 205
 25 Lys Glu Met Glu Val Leu His Leu Arg Asn Val Ser Phe Glu Asp Ala
 210 215 220
 Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu Ser His His
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<210> 427

<211> 354

<212> PRT

<213> Artificial Sequence

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<223> Example of extracellular region of FGFR1c (Alpha-IIIc, NP_056934)

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				20				25				30				
	Arg	Cys	Arg	Leu	Arg	Asp	Asp	Val	Gln	Ser	Ile	Asn	Trp	Leu	Arg	Asp
			35					40				45				
5	Gly	Val	Gln	Leu	Ala	Glu	Ser	Asn	Arg	Thr	Arg	Ile	Thr	Gly	Glu	Glu
		50					55					60				
	Val	Glu	Val	Gln	Asp	Ser	Val	Pro	Ala	Asp	Ser	Gly	Leu	Tyr	Ala	Cys
	65					70					75				80	
	Val	Thr	Ser	Ser	Pro	Ser	Gly	Ser	Asp	Thr	Thr	Tyr	Phe	Ser	Val	Asn
				85						90					95	
10	Val	Ser	Asp	Ala	Leu	Pro	Ser	Ser	Glu	Asp	Asp	Asp	Asp	Asp	Asp	Asp
				100					105				110			
	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Thr	Asp	Asn	Thr	Lys	Pro	Asn	Arg	Met
			115					120					125			
	Pro	Val	Ala	Pro	Tyr	Trp	Thr	Ser	Pro	Glu	Lys	Met	Glu	Lys	Lys	Leu
		130					135					140				
15	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe	Lys	Cys	Pro	Ser	Ser
	145					150					155					160
	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg	Trp	Leu	Lys	Asn	Gly	Lys	Glu	Phe
				165					170						175	
	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val	Arg	Tyr	Ala	Thr	Trp
				180				185						190		
20	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp	Lys	Gly	Asn	Tyr	Thr
			195					200					205			
	Cys	Ile	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn	His	Thr	Tyr	Gln	Leu
		210					215					220				
25	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu
		225				230					235					240
	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu	Gly	Ser	Asn	Val	Glu	Phe	Met	Cys
				245					250						255	
	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile
			260					265						270		
30	Glu	Val	Asn	Gly	Ser	Lys	Ile	Gly	Pro	Asp	Asn	Leu	Pro	Tyr	Val	Gln
			275					280					285			
	Ile	Leu	Lys	Thr	Ala	Gly	Val	Asn	Thr	Thr	Asp	Lys	Glu	Met	Glu	Val
		290				295						300				
	Leu	His	Leu	Arg	Asn	Val	Ser	Phe	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys
		305				310				315						320
35	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Leu	Ser	His	His	Ser	Ala	Trp	Leu	Thr
				325					330						335	
	Val	Leu	Glu	Ala	Leu	Glu	Glu	Arg	Pro	Ala	Val	Met	Thr	Ser	Pro	Leu
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	Tyr	Glu														

<210> 428

<211> 630

<212> DNA

<213> Artificial Sequence

<220>

<223> A full length FGF21, NM_019113.2

<400> 428

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tgcagcttcc gggagctgct tcttgaggac ggatacaatg tttaccagtc cgaagcccac 420
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<210> 429
 <211> 209
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 <223> A full length FGF21, NP_061986.1

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			20					25					30		
Asp	Ser	Ser	Pro	Leu	Leu	Gln	Phe	Gly	Gly	Gln	Val	Arg	Gln	Arg	Tyr
		35					40					45			
Leu	Tyr	Thr	Asp	Asp	Ala	Gln	Gln	Thr	Glu	Ala	His	Leu	Glu	Ile	Arg
	50					55					60				
Glu	Asp	Gly	Thr	Val	Gly	Gly	Ala	Ala	Asp	Gln	Ser	Pro	Glu	Ser	Leu
65					70					75					80
Leu	Gln	Leu	Lys	Ala	Leu	Lys	Pro	Gly	Val	Ile	Gln	Ile	Leu	Gly	Val
			85						90					95	
Lys	Thr	Ser	Arg	Phe	Leu	Cys	Gln	Arg	Pro	Asp	Gly	Ala	Leu	Tyr	Gly
			100					105					110		
Ser	Leu	His	Phe	Asp	Pro	Glu	Ala	Cys	Ser	Phe	Arg	Glu	Leu	Leu	Leu
		115					120					125			
Glu	Asp	Gly	Tyr	Asn	Val	Tyr	Gln	Ser	Glu	Ala	His	Gly	Leu	Pro	Leu
	130					135					140				
His	Leu	Pro	Gly	Asn	Lys	Ser	Pro	His	Arg	Asp	Pro	Ala	Pro	Arg	Gly
145					150					155					160
Pro	Ala	Arg	Phe	Leu	Pro	Leu	Pro	Gly	Leu	Pro	Pro	Ala	Leu	Pro	Glu
			165						170					175	
Pro	Pro	Gly	Ile	Leu	Ala	Pro	Gln	Pro	Pro	Asp	Val	Gly	Ser	Ser	Asp
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 <212> PRT
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 35 40 45
 10 Trp Leu Ala His Ile Phe Ser Asn Asp Glu Lys Ser Tyr Ser Thr Ser
 50 55 60
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Ser Gln Val
 65 70 75 80
 Val Leu Ile Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
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<210> 431

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> VH SEQ ID NO: 50 in U.S. Patent Publication 20110135657

<400> 431

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 20 25 30
 35 His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
 35 40 45
 Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
 65 70 75 80
 40 Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Gly Asn Ser Asp His
 85 90 95
 Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

Claims

1. An antibody that binds within beta klotho domain 2 (KLB2) comprising amino acid residues 657 to 703 of human beta klotho (SEQ ID NO:297), wherein the antibody comprises:

(a) a heavy chain variable region comprising:

a CDR1 comprising SEQ ID NO:1, SEQ ID NO:12, or SEQ ID NO:13;

a CDR2 comprising SEQ ID NO:2 or SEQ ID NO:14; and

a CDR3 comprising SEQ ID NO:3 or SEQ ID NO:15;

and

(b) a light chain variable region comprising:

a CDR1 comprising SEQ ID NO:4 or SEQ ID NO:16;
a CDR2 comprising SEQ ID NO:5 or SEQ ID NO:11; and
a CDR3 comprising SEQ ID NO:6 or SEQ ID NO:17.

2. The antibody of claim 1, wherein the antibody comprises:

(a) a heavy chain variable region comprising a CDR1 comprising SEQ ID NO:1, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3; and
(b) a light chain variable region comprising a CDR1 comprising SEQ ID NO:4, a CDR2 comprising SEQ ID NO:5, and a CDR3 comprising SEQ ID NO:6.

3. The antibody of claim 1, wherein the antibody comprises:

(a) a heavy chain variable region comprising a CDR1 comprising SEQ ID NO:12, a CDR2 comprising SEQ ID NO:2, and a CDR3 comprising SEQ ID NO:3; and
(b) a light chain variable region comprising a CDR1 comprising SEQ ID NO:4, a CDR2 comprising SEQ ID NO:5, and a CDR3 comprising SEQ ID NO:6.

4. The antibody of claim 1, wherein the antibody comprises:

(a) a heavy chain variable region comprising a CDR1 comprising SEQ ID NO:13, a CDR2 comprising SEQ ID NO:14, and a CDR3 comprising SEQ ID NO:15; and
(b) a light chain variable region comprising a CDR1 comprising SEQ ID NO:16, a CDR2 comprising SEQ ID NO:11, and a CDR3 comprising SEQ ID NO:17.

5. The antibody of any one of claims 1 to 4, wherein the heavy chain variable region has at least 90% sequence identity to SEQ ID NO:25 and the light chain variable region has at least 90% sequence identity to SEQ ID NO:26.

6. The antibody of any one of claim 1 to 4, wherein the heavy chain variable region comprises SEQ ID NO:25 and the light chain variable region comprises SEQ ID NO:26.

7. The antibody of any one of claims 1 to 4, wherein the heavy chain variable region comprises SEQ ID NO:271 and the light chain variable region comprises SEQ ID NO:276.

8. The antibody of any one of claims 1 to 7, wherein the antibody binds an epitope comprising at least one of amino acid residues 657, 701 and/or 703 of the human beta klotho (SEQ ID NO: 297).

9. The antibody of any one of claims 1 to 8, wherein the antibody is a monoclonal antibody, a humanized antibody, or a chimeric antibody.

10. The antibody of any one of claims 1 to 8, wherein the antibody is a Fab, Fab', F(ab')₂, Fv, scFv, (scFv)₂, single chain antibody molecule, dual variable region antibody, linear antibody, or a multispecific antibody formed from antibody fragments.

11. An isolated polynucleotide encoding the antibody of any one of claims 1 to 10.

12. A vector comprising the polynucleotide of claim 11.

13. A host cell comprising the polynucleotide of claim 11 or the vector of claim 12.

14. A pharmaceutical composition comprising the antibody of any one of claims 1 to 10, and a pharmaceutically acceptable carrier.

15. An antibody as defined in any one of claims 1 to 10 for use in a method for improving glucose metabolism in a subject.

16. The antibody for the use of claim 15, wherein the method for improving glucose metabolism results in:

(a) reduced glucose levels;

- (b) reduced insulin levels;
- (c) increased insulin sensitivity;
- (d) reduced insulin resistance;
- (e) improved glucose tolerance; and/or
- (f) improved pancreatic function.

17. An antibody as defined in any one of claims 1 to 10 for use in a method for treating Type 1 diabetes, Type 2 diabetes, dyslipidemia, nonalcoholic steatohepatitis (NASH), cardiovascular disease, metabolic syndrome, obesity, or non-alcoholic fatty liver disease (NAFLD).

18. The antibody for use of any one of claims 15 to 17, wherein the method further comprises administration of one or more therapeutic agents in combination with the antibody.

19. The antibody for use of claim 18, wherein the one or more therapeutic agents is selected from the group consisting of biguanides, sulphonylureas, thiazolidinediones, GLP-1 analogues, PPAR gamma agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, bromocriptine, bile acid sequestrants, insulin, alpha glucosidase inhibitors, metformin, SGLT-2 inhibitors, appetite suppression agents, and weight loss drugs.

Patentansprüche

1. Antikörper, der innerhalb der Beta-Klotho-Domäne 2 (KLB2) bindet, umfassend die Aminosäurereste 657 bis 703 des menschlichen Beta-Klotho (SEQ ID NO:297), wobei der Antikörper Folgendes umfasst:

(a) eine variable Region der schweren Kette, umfassend:

- eine CDR1, die SEQ ID NO:1, SEQ ID NO:12 oder SEQ ID NO: 13 umfasst;
- eine CDR2, die SEQ ID NO:2 oder SEQ ID NO:14 umfasst; und
- eine CDR3, die SEQ ID NO:3 oder SEQ ID NO:15 umfasst;

und

(b) eine variable Region der leichten Kette, umfassend:

- eine CDR1, die SEQ ID NO:4 oder SEQ ID NO:16 umfasst;
- eine CDR2, die SEQ ID NO:5 oder SEQ ID NO:11 umfasst; und
- eine CDR3, die SEQ ID NO:6 oder SEQ ID NO:17 umfasst.

2. Antikörper nach Anspruch 1, wobei der Antikörper Folgendes umfasst:

- (a) eine variable Region der schweren Kette, die eine CDR1, die SEQ ID NO:1 umfasst, eine CDR2, die SEQ ID NO:2 umfasst, und eine CDR3 umfasst, die SEQ ID NO:3 umfasst; und
- (b) eine variable Region der leichten Kette, die eine CDR1, die SEQ ID NO:4 umfasst, eine CDR2, die SEQ ID NO:5 umfasst, und eine CDR3 umfasst, die SEQ ID NO:6 umfasst.

3. Antikörper nach Anspruch 1, wobei der Antikörper Folgendes umfasst:

- (a) eine variable Region der schweren Kette, die eine CDR1, die SEQ ID NO:12 umfasst, eine CDR2, die SEQ ID NO:2 umfasst, und eine CDR3 umfasst, die SEQ ID NO:3 umfasst;
- und
- (b) eine variable Region der leichten Kette, die eine CDR1, die SEQ ID NO:4 umfasst, eine CDR2, die SEQ ID NO:5 umfasst, und eine CDR3 umfasst, die SEQ ID NO:6 umfasst.

4. Antikörper nach Anspruch 1, wobei der Antikörper Folgendes umfasst:

- (a) eine variable Region der schweren Kette, die eine CDR1, die SEQ ID NO:13 umfasst, eine CDR2, die SEQ ID NO:14 umfasst, und eine CDR3 umfasst, die SEQ ID NO:15 umfasst;
- und
- (b) eine variable Region der leichten Kette, die eine CDR1, die SEQ ID NO:16 umfasst, eine CDR2, die SEQ

ID NO:11 umfasst, und eine CDR3 umfasst, die SEQ ID NO:17 umfasst.

- 5 5. Antikörper nach einem der Ansprüche 1 bis 4, wobei die variable Region der schweren Kette eine Sequenzidentität von mindestens 90 % mit SEQ ID NO:25 aufweist und die variable Region der leichten Kette eine Sequenzidentität von mindestens 90 % mit SEQ ID NO:26 aufweist.
6. Antikörper nach einem der Ansprüche 1 bis 4, wobei die variable Region der schweren Kette SEQ ID NO:25 umfasst und die variable Region der leichten Kette SEQ ID NO:26 umfasst.
- 10 7. Antikörper nach einem der Ansprüche 1 bis 4, wobei die variable Region der schweren Kette SEQ ID NO:271 umfasst und die variable Region der leichten Kette SEQ ID NO:276 umfasst.
8. Antikörper nach einem der Ansprüche 1 bis 7, wobei der Antikörper ein Epitop bindet, das mindestens einen der Aminosäurereste 657, 701 und/oder 703 des menschlichen Beta-Klotho (SEQ ID NO: 297) umfasst.
- 15 9. Antikörper nach einem der Ansprüche 1 bis 8, wobei der Antikörper ein monoklonaler Antikörper, ein humanisierter Antikörper oder ein chimärer Antikörper ist.
- 20 10. Antikörper nach einem der Ansprüche 1 bis 8, wobei der Antikörper ein Fab, Fab', F(ab')₂, Fv, scFv, (scFv)₂, ein einkettiges Antikörpermolekül, ein Antikörper mit zweifacher variabler Region, ein linearer Antikörper oder ein multispezifischer Antikörper ist, der aus Antikörperfragmenten gebildet ist.
11. Isoliertes Polynukleotid, kodierend den Antikörper nach einem der Ansprüche 1 bis 10.
- 25 12. Vektor, umfassend das Polynukleotid nach Anspruch 11.
13. Wirtszelle, umfassend das Polynukleotid nach Anspruch 11 oder den Vektor nach Anspruch 12.
- 30 14. Pharmazeutische Zusammensetzung, umfassend den Antikörper nach einem der Ansprüche 1 bis 10 oder einen pharmazeutisch akzeptablen Träger.
15. Antikörper nach einem der Ansprüche 1 bis 10 zur Verwendung bei einem Verfahren zum Verbessern des Glucosestoffwechsels bei einem Individuum.
- 35 16. Antikörper zur Verwendung nach Anspruch 15, wobei das Verfahren zum Verbessern des Glucosestoffwechsels zu Folgendem führt:
 - (a) verringerte Glucosespiegel;
 - (b) verringerte Insulinspiegel;
 - 40 (c) erhöhte Insulinempfindlichkeit;
 - (d) verringerte Insulinresistenz;
 - (e) verbesserte Glucosetoleranz; und/oder
 - (f) verbesserte Pankreasfunktion.
- 45 17. Antikörper nach einem der Ansprüche 1 bis 10 zur Verwendung bei einem Verfahren zum Behandeln von Diabetes Typ 1, Diabetes Typ 2, Dyslipidämie, nicht-alkoholischer Fettleber (non-alcoholic steatohepatitis - NASH), der kardiovaskulären Krankheit, des metabolischen Syndroms, der Adipositas oder der nicht-alkoholischen Fettlebererkrankung (non-alcoholic fatty liver disease - NAFLD).
- 50 18. Antikörper zur Verwendung nach einem der Ansprüche 15 bis 17, wobei das Verfahren ferner das Verabreichen eines oder mehrerer Therapeutika in Kombination mit dem Antikörper umfasst.
- 55 19. Antikörper zur Verwendung nach Anspruch 18, wobei das eine oder die mehrere Therapeutika aus der Gruppe ausgewählt ist/sind, die aus Biguaniden, Sulphonylharnstoffen, Thiazolidindionen, GLP-1-Analoga, PPAR-gamma-Agonisten, Dipeptidylpeptidase-4(DPP4)-Hemmern, Bromocriptin, Gallensäure-Komplexbildnern, Insulin, Alpha-Glucosidasehemmern, Metformin, SGLT-2-Hemmern, Appetitzüglern und Medikamenten zur Gewichtsabnahme besteht.

Revendications

1. Anticorps qui se lie à l'intérieur du domaine bêta klotho 2 (KLB2) comprenant les résidus d'acides aminés 657 à 703 de bêta klotho humain (SEQ ID NO : 297), dans lequel l'anticorps comprend :

(a) une région variable de chaîne lourde comprenant :

une CDR1 comprenant SEQ ID NO : 1, SEQ ID NO : 12, ou SEQ ID NO : 13 ;

une CDR2 comprenant SEQ ID NO : 2 ou SEQ ID NO : 14 ; et une CDR3 comprenant SEQ ID NO : 3 ou SEQ ID NO : 15 ;

et

(b) une région variable de chaîne légère comprenant :

une CDR1 comprenant SEQ ID NO : 4 ou SEQ ID NO : 16 ;

une CDR2 comprenant SEQ ID NO : 5 ou SEQ ID NO : 11 ; et une CDR3 comprenant SEQ ID NO : 6 ou SEQ ID NO : 17.

2. Anticorps selon la revendication 1, dans lequel l'anticorps comprend :

(a) une région variable de chaîne lourde comprenant une CDR1 comprenant SEQ ID NO : 1, une CDR2 comprenant SEQ ID NO : 2, et une CDR3 comprenant SEQ ID NO : 3 ; et

(b) une région variable de chaîne légère comprenant une CDR1 comprenant SEQ ID NO : 4, une CDR2 comprenant SEQ ID NO : 5, et une CDR3 comprenant SEQ ID NO : 6.

3. Anticorps selon la revendication 1, dans lequel l'anticorps comprend :

(a) une région variable de chaîne lourde comprenant une CDR1 comprenant SEQ ID NO : 12, une CDR2 comprenant SEQ ID NO : 2, et une CDR3 comprenant SEQ ID NO : 3 ; et

(b) une région variable de chaîne légère comprenant une CDR1 comprenant SEQ ID NO : 4, une CDR2 comprenant SEQ ID NO : 5, et une CDR3 comprenant SEQ ID NO : 6.

4. Anticorps selon la revendication 1, dans lequel l'anticorps comprend :

(a) une région variable de chaîne lourde comprenant une CDR1 comprenant SEQ ID NO : 13, une CDR2 comprenant SEQ ID NO : 14, et une CDR3 comprenant SEQ ID NO : 15 ; et

(b) une région variable de chaîne légère comprenant une CDR1 comprenant SEQ ID NO : 16, une CDR2 comprenant SEQ ID NO : 11, et une CDR3 comprenant SEQ ID NO : 17.

5. Anticorps selon l'une quelconque des revendications 1 à 4, dans lequel la région variable de chaîne lourde présente une identité de séquence d'au moins 90 % avec SEQ ID NO : 25 et dans lequel la région variable de chaîne légère présente une identité de séquence d'au moins 90 % avec SEQ ID NO : 26.

6. Anticorps selon l'une quelconque des revendications 1 à 4, dans lequel la région variable de chaîne lourde comprend SEQ ID NO : 25 et la région variable de chaîne légère comprend SEQ ID NO : 26.

7. Anticorps selon l'une quelconque des revendications 1 à 4, dans lequel la région variable de chaîne lourde comprend SEQ ID NO : 271 et la région variable de chaîne légère comprend SEQ ID NO : 276.

8. Anticorps selon l'une quelconque des revendications 1 à 7, dans lequel l'anticorps se lie à un épitope comprenant au moins l'un des résidus d'acides aminés 657, 701 et/ou 703 du bêta klotho humain (SEQ ID NO : 297).

9. Anticorps selon l'une quelconque des revendications 1 à 8, dans lequel l'anticorps est un anticorps monoclonal, un anticorps humanisé, ou un anticorps chimérique.

10. Anticorps selon l'une quelconque des revendications 1 à 8, dans lequel l'anticorps est un Fab, Fab', F(ab')₂, Fv, scFv, (scFv)₂, une molécule d'anticorps à chaîne unique, un anticorps à région variable double, un anticorps linéaire, ou un anticorps multispécifique formé à partir de fragments d'anticorps.

11. Polynucléotide isolé codant pour l'anticorps selon l'une quelconque des revendications 1 à 10.

12. Vecteur comprenant le polynucléotide selon la revendication 11.

5 13. Cellule hôte comprenant le polynucléotide selon la revendication 11 ou le vecteur selon la revendication 12.

14. Composition pharmaceutique comprenant l'anticorps selon l'une quelconque des revendications 1 à 10, et un vecteur pharmaceutiquement acceptable.

10 15. Anticorps selon l'une quelconque des revendications 1 à 10 pour son utilisation dans un procédé d'amélioration du métabolisme du glucose chez un sujet.

16. Anticorps pour son utilisation selon la revendication 15, dans lequel le procédé d'amélioration du métabolisme du glucose résulte en :

15

(a) des niveaux de glucose réduits ;

(b) des niveaux d'insuline réduits ;

(c) une sensibilité à l'insuline accrue ;

(d) une résistance à l'insuline réduite ;

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(e) une meilleure tolérance au glucose ; et/ou

(f) une meilleure fonction pancréatique.

17. Anticorps selon l'une quelconque des revendications 1 à 10 pour son utilisation dans un procédé de traitement du diabète de type 1, du diabète de type 2, de la dyslipidémie, de la stéatohépatite non alcoolique (NASH), d'une maladie cardiovasculaire, du syndrome métabolique, de l'obésité, ou de la stéatose hépatique non alcoolique (NAFLD).

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18. Anticorps pour son utilisation selon l'une quelconque des revendications 15 à 17, dans lequel le procédé comprend en outre l'administration d'un ou plusieurs agents thérapeutiques en combinaison avec l'anticorps.

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19. Anticorps pour son utilisation selon la revendication 18, dans lequel les un ou plusieurs agents thérapeutiques sont sélectionnés dans le groupe consistant en les biguanides, les sulfonilurées, les thiazolidinediones, les analogues du GLP-1, les agonistes du PPAR γ , les inhibiteurs de la dipeptidyl peptidase-4 (DPP-4), la bromocriptine, les séquestrants de l'acide biliaire, l'insuline, les inhibiteurs de l'alpha glucosidase, la metformine, les inhibiteurs de SGLT-2, les coupe-faim, et les médicaments pour la perte de poids.

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Kabat	1	10	22	31	35	40	50	abc	60	65
AbM	1	10	22	26	35	40	50	abc	58	65
Choithia	1	10	22	26	32	40		abc	55	65
Contact	1	10	22	30	35	40	47	abc	58	65
IMGT	1	23	27	27	38	41		56	65	74
AHon	1	23	27		42					76
5H23	QVQLQQSGPELVKPGALVKISKAS	GYTFTS-YDIN	WVKQRPQGQLEWIG	WIYP--GDG	STKYNEKFKG					
1C17	QVQLQESGPGLVKPSQSLTCSVT	GYSITSGYYWN	WIRQFPGNKLEWNG	YIN---YDG	NSNYTPSLKN					
1D19	QVQPQESGPELVKPGALVKISKAS	GYTFTR-YDIN	WMKQRPQGQLEWIG	WIYP--GDS	STKFNFENFKD					
2L12	QVQLQQSGPELVKPGALVKISKAS	GYTFTR-YDIN	WVKRRPGQGLEWIG	WIYP--GDD	STKYNEKFKG					
3L3	QVQPQESGPELVKPGTTLVKISKAS	GYTFTS-YDIN	WVKQRPQGQLEWIG	WIYP--GDG	SPKYDEKFKG					
3N20	QVQLQESGAELARPGASVKLSCKVS	GYIFTN-YGIS	WVKQRTGQGLEWIG	EIYP--RSG	NTYYNEKFKG					
4P5	QVQLQQSGPELVKPGALVKISKAS	GYTFTR-YDIN	WVKRRPGQGLEWIG	WIYP--GDD	STKYNEKFKG					
5C23	QVQPQESGPELVKPGALVKISKAS	GYTFTR-YDIN	WVKRRPGQGLEWIG	WIYP--GDG	STKYNEKFKG					
5F7	QVQPQESGPELVKPGALVKISKAS	GYTFTR-YDIN	WVKQRPQGQLEWIG	WIYP--GDI	STKYNEKFKG					
1G19	QVQLQESGPGLVKPSQSLTCSVT	GYSITSGYYWN	WIRQFPGNKLEWNG	YIN---YGS	NNYNPSLKN					

Kabat	70	80	abc	90	95	100	102			110
AbM	70	80	abc	90	95	100	102			110
Choithia	70	80	abc	90	96	100	101			110
Contact	70	80	abc	90	93	100	101			110
IMGT	75	89		105	100	117				
AHon		106	109			138				
5H23	KATLTADKSSRTAYMQLSLTSSENSAVYFCAR	SDYYGSRSF--AY	WGQGLVTVSA	(SEQ	ID NO:25)					
1C17	RISITRDTSKNQFFLKLSVTPEDTATYYCAR	KGAYYSNYDSFDV	WGTGTTVTVSS	(SEQ	ID NO:51)					
1D19	KATLTADKSSSTAYMQLSLTSSENSVYFCAR	SDYYGSRSF--TY	WGQGLVTVSA	(SEQ	ID NO:77)					
2L12	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYYGSRSF--VY	WGQGLVTVSA	(SEQ	ID NO:103)					
3L3	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYYGSRSF--VY	WGQGLVTVSA	(SEQ	ID NO:129)					
3N20	KATLTADMSSSTAYMDLRSLTSEDSAVYFCAR	HWDGVLDYF--DY	WGQGLSLTVSS	(SEQ	ID NO:155)					
4P5	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYYGSRSF--VY	WGQGLVTVSA	(SEQ	ID NO:181)					
5C23	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYYGSRSF--VY	WGQGLVTVSA	(SEQ	ID NO:207)					
5F7	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYYGSRSF--VY	WGQGLVTVSA	(SEQ	ID NO:233)					
1G19	RISITRDTSKNQFFLKLSVTPEDTATYYCAR	RGAYYSNYDSFDV	WGTGTTVTVSS	(SEQ	ID NO:259)					

FIGURE 1A

Kabat	1	10	20	24-27abcd-----34	40	50-----56
AbM	1	10	20	24-----30abcd-----34	40	50-----56
Chothia	1	10	20	26---30abcd--32	40	50--
Contact	1	10	20	30abcd-----36	40	46-----55
IMGT	1	23	27	27-----38	41	56-65 69
AHon	1	23	42		58	72
5H23	DIVLTQSPASLAVSLGQRATIS	PASKSVST--SGVVMH	WNQKPGQPPKLLIY	LASYLES		
1C17	DIKMTQSPSSMYASLGERVTITC	KASQDINS-----YLS	WVQKPGKSPKTLIY	RANRLVD		
1D19	DIVLTQSPASLAVSLGQRATIS	PASKSVST--SGYSYH	WYQKPGQPPKLLIY	LASNLES		
2L12	DIVLTQSPASLPVSLGQRATIS	RASKSVST--SGYSYH	WYQKPGQPPKLLIY	LASNLES		
3L3	DIVLTQSPASLAVSLGQRATIS	PASKSVST--SGYSYH	WYQKPGQPPKLLIY	LASNLES		
3N20	DIVMTQSPSSLSVSAGEKVTMSC	KSSQSLNSGNQKNYLA	WYQKPGQPPKLLIY	GASTRES		
4P5	DILLTQSPASLAVSLGQRATIS	PASKSVST--SGYSYH	WYQKPGQPPKLLIY	LASNLES		
5C23	DIVLTQSPDSTVSLGQRATIS	PASKSVST--SGYSYH	WYQKPGQPPKLLIY	LASNLES		
5F7	DIVLTQSPASLAVSLGQRATIS	PASKSVST--SGYSYH	WYQKPGQPPKLLIY	LASNLES		
1G19	DIKMTQSPSSMYASLGERVTITC	KASQDINS-----YLS	WFQKPGKSPKTLIY	RANRLVD		

Kabat	60	70	80	89-----97	
AbM	60	70	80	89-----97	
Chothia	60	70	80	91---96	
Contact	60	70	80	89-----96	
IMGT	70	89		105-----117	
AHon	73	91	107	107	138
5H23	GVPAFSGSGSGTDFTLNIHPVEEEDAAIYYC	QHSRDLTFP	FGGGTKLEIK	(SEQ ID NO:26)	
1C17	GVPSRFSGSGGQDYSLTISSLEYEDMGIYYC	LQYDEEFT	FGSGTKLEIK	(SEQ ID NO:52)	
1D19	GVPAFSGSGSGTDFTLNIHPVEEEDAAIYYC	QHSRELPT	FGGGTKLEIK	(SEQ ID NO:78)	
2L12	GVPAFSGSGSGTDFTLNIHPVEEEDAAIYYC	QHSRELPT	FGGGTKLEIK	(SEQ ID NO:104)	
3L3	GVPAFSGRSGTDFTLNIHPVEEEDAAIYYC	QHSRELPT	FGGGTKLEIK	(SEQ ID NO:130)	
3N20	GVPDFTGSGSGTDFTLTISSVQAEEDLAVYYC	LNDSYPFT	FGAGTKLEIK	(SEQ ID NO:156)	
4P5	GVPAFSGRSGTDFTLNIHPVEEEDAAIYYC	HHSRELPT	FGGGTKLEIK	(SEQ ID NO:182)	
5C23	GVPAFSGSGSGTDFTLNIHPVEEEDAAIYYC	QHSRELPT	FGGGTKLEIK	(SEQ ID NO:208)	
5F7	GVPAFSGSGSGTDFTLNIHPVEEEDAAIYYC	QHSRELPT	FGGGTKVEIK	(SEQ ID NO:234)	
1G19	GVPSRFSGSGGQDYSLTISSLEYEEMGIYYC	LQYDEEFT	FGGGTKLEIK	(SEQ ID NO:260)	

FIGURE 1B

VH Domain (continued)

Kabat	70	80	abc	90	95--100-----102	110
AbM	70	80	abc	90	95--100-----102	110
Chothia	70	80	abc	90	96-100-----101	110
Contact	70	80	abc	90	93-----100-----101	110
IMGT	75	89		105-----117		
AHon				106 109	138	
5H23	KATLTADKSSRTAYMQLSLTSSENSAVYFCAR	SDYIGSRSF--AY	WGQGTILTVSA	(SEQ ID NO:25)		
1D19	KATLTADKSSSTAYMQLSLTSSENSVYFCAR	SDYIGSRSF--TY	WGQGTILTVSA	(SEQ ID NO:77)		
2L12	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYIGSRSF--VY	WGQGTILTVSA	(SEQ ID NO:103)		
3L3	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYIGSRSF--VY	WGQGTILTVSA	(SEQ ID NO:129)		
4P5	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYIGSRSF--VY	WGQGTILTVSA	(SEQ ID NO:181)		
5C23	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYIGSRSF--VY	WGQGTILTVSA	(SEQ ID NO:207)		
5F7	KATLTADKSSSTAYMQLSLTSSENSAVYFCAR	SDYIGSRSF--VY	WGQGTILTVSA	(SEQ ID NO:233)		
consensus		SDYIGSRSF--VY				
or		(SEQ ID NO:81)				
consensus		SDYIGSRSF--X₁Y	where X₁ = V,T,A			
		(SEQ ID NO:263)				
1C17	RISITRDTSKNQFFLKLSVTPEDTATYYCAR	KGAYYSNYDSFDV	WGTTGTTVSS	(SEQ ID NO:51)		
1G19	RISITRDTSKNQFFLKLSVTTEDTATYYCAR	RGAYYSNYDSFDV	WGTTGTTVSS	(SEQ ID NO:259)		
consensus		X₁CAYYSNYDSFDV	where X₁ = K,R			
		(SEQ ID NO:265)				
3N20	KATLTADMSSSTAYMDLRLTSEDSAVYFCAR	HWDGVLDYF--DY	WGQGTSLTVSS	(SEQ ID NO:155)		

FIGURE 2A-2

VL Domain

Kabat	1	10	20	24-27abcd-----34	40	50-----56
AbM	1	10	20	24-----30abcd-----34	40	50-----56
Chothia	1	10	20	26--30abcd--32	40	50--
Contact	1	10	20	30abcd-----36	40	46-----55
IMGT	1		23	27-----38	41	56-65 69
AHon	1		23		42	58 72
5H23				DIVLTQSPASIAVSLGQRATISC		WNQKPGQPPKLLIY LASYLE
1D19				DIVLTQSPASIAVSLGQRATISC		RASKSVST--SGYSYMH WYQKPGQPPKLLIY LASNLE
2L12				DIVLTQSPASIPVSLGQRATISC		RASKSVST--SGYSYLH WYQKPGQPPKLLIY LASNLE
3L3				DIVLTQSPASIAVSLGQRATISC		RASKSVST--SGYSYVH WYQKPGQPPKLLIY LASNLE
4P5				DIVLTQSPASIAVSLGQRATISC		RASKSVST--SGYSYMH WYQKPGQPPKLLIY LASNLE
5C23				DIVLTQSPDSLTVSLGQRATISC		RASKSVST--SGYSYMH WYQKPGQPPKLLIY LASNLE
5F7				DIVLTQSPASIAVSLGQRATISC		RASKSVST--SGYSYMH WYQKPGQPPKLLIY LASNLE
consensus				RASKSVST--SGYSYMH		LASNLE
or				(SEQ ID NO:56)		(SEQ ID NO: 57)
consensus				RASKSVST--SGYSYX₁H		LASNLE
				where X ₁ = M,L,V		
				(SEQ ID NO:266)		(SEQ ID NO: 57)
1C17				DIKMTQSPSSMYASLGERTITC		WVQKPGKSPKTLIY RANRLVD
1G19				DIKMTQSPSSMYASLGERTITC		WQKPGKSPKTLIY RANRLVD
consensus				KASQDINS-----YLS		RANRLVD
or				(SEQ ID NO:30)		(SEQ ID NO: 31)
3N20				DIVMTQSPSSLSVSAGEKVTMSC		KSSQSLINSGNQNYLA WYQKPGQPPKLLIY GASTRE

FIGURE 2B-1

VL Domain (continued)

Kabat	60	70	80	89-----97			
AbM	60	70	80	89-----97			
Chothia	60	70	80	91----96			
Contact	60	70	80	89-----96			
IMGT	70		89	105-----117			
AHon	73		91	107	138		
5H23	GVPARFSGSGGTDFTLNHPVEEEDAATYYC			QHSRDLTFF		FGGGTKLEIK	(SEQ ID NO:26)
1D19	GVPARFSGSGGTDFTLNHPVEEEDAATYYC			QHSRELPYT		FGGGTKLEIK	(SEQ ID NO:78)
2L12	GVPARFSGSGGTDFTLNHPVEEEDAATYYC			QHSGELPYT		FGGGTKLEIK	(SEQ ID NO:104)
3L3	GVPARFSGSGGTDFTLNHPVEEEDAATYYC			QHSGELPYT		FGGGTKLEIK	(SEQ ID NO:130)
4P5	GVPARFSGSGGTDFTLNHPVEEEDAATYYC			HHSGELPYT		FGGGTKLEIK	(SEQ ID NO:182)
5C23	GVPARFSGSGGTDFTLNHPVEEEDAATYYC			QHSRELPYT		FGGGTKLEIK	(SEQ ID NO:208)
5F7	GVPARFSGSGGTDFTLNHPVEEEDAATYYC			QHSRELPYT		FGGGTKVEIK	(SEQ ID NO:234)
consensus				X₁HSX₂ELPYT where X₁ = Q,H; where X₂ = R,G			
				(SEQ ID NO:267)			
1C17	GVPARFSGSGGQDYSLTISSLEYEDMGIYYC			LQYDEFFPT		FGGGTKLEIK	(SEQ ID NO:52)
1G19	GVPARFSGSGGQDYSLTISSLEYEMGIYYC			LQYDEFFPT		FGGGTKLEIK	(SEQ ID NO:260)
consensus				LQYDEFFX₁T where X₁ = F,Y			
				(SEQ ID NO:268)			
3N20	GVPDRFTGSGGTDFTLTITSSVQAEDLAVYYC			LNDHSYFFT		FGAGTKLEIK	(SEQ ID NO:156)

FIGURE 2B-2

Kabat	1	10	22	31--35	40	50--a-----60---65
AbM	1	10	22	26-----35	40	50--a-----58
Cho	1	10	22	26-----32	40	a-55
Cho	1	10	22	30-----35	40	47-----a-----58
IMGT	1	23	27	27-----38	41	56-----65
Aho	1	23	27	42		57
5H23	QVQLQQSGPELVKPGALVKISKAS	GYTFTTSYDIN	WVKQRPQGQGLEWIG	WIYPGDGSTKYNEKFKG		76
5H23v1-3	QVQLVQSGAEVKKPGASVKVSKAS	GYTFTTSYDIN	WVRQAPGQRLWVG	WIYPGDGSTKYNEKFKG		
vH1	QVQLVQSGAEVKKPGASVKVSKAS	GYTFTTSYDIN	WVRQAPGQGLEWVG	WIYPGDGSTKYNEKFKG		
vH2	QVQLVQSGPEVKKPGASVKVSKAS	GYTFTTSYDIN	WVRQRPQGQGLEWVG	WIYPGDGSTKYNEKFKG		
vH3	QVQLVQSGAEVKKPGASVKVSKAS	GYTFTTSYDIN	WVRQAPGQGLEWIG	WIYPGDGSTKYNEKFKG		
vH4	QVQLVQSGPEVKKPGASVKVSKAS	GYTFTTSYDIN	WVRQRPQGQGLEWIG	WIYPGDGSTKYNEKFKG		
vH5	QVQLVQSGAEVKKPGASVKVSKAS	GYTFTTSYDIN	WVRQAPGQGLEWIG	WIYPGDGSTKYNEKFKG		
vH6	QVQLVQSGAEVKKPGASVKVSKAS	GYTFTTSYDIN	WVKQAPGQGLEWIG	WIYPGDGSTKYNEKFKG		
5H23v1-69	QVQLVQSGAEVKKPGSSVKVSKAS	GYTFTTSYDIN	WVRQAPGQGLEWVG	WIYPGDGSTKYNEKFKG		
vH7	QVQLVQSGAEVKKPGSSVKVSKAS	GYTFTTSYDIN	WVRQAPGQGLEWIG	WIYPGDGSTKYNEKFKG		
vH8	QVQLVQSGAEVKKPGSSVKVSKAS	GYTFTTSYDIN	WVRQAPGQGLEWIG	WIYPGDGSTKYNEKFKG		
vH9	QVQLVQSGAEVKKPGSSVKVSKAS	GYTFTTSYDIN	WVRQAPGQGLEWIG	WIYPGDGSTKYNEKFKG		

FIGURE 3A-1

VH Domain (continued)

Kabat	70	80	abc	90	95--100--102	110
AbM	70	80	abc	90	95--100--102	110
Chothia	70	80	abc	90	96-100-101	110
Contact	70	80	abc	90	93-----100-101	110
IMGT	75	89		105-----117		
AHon				106 109	138	
5H23	KATLTADKSSRTAYMQLSSLTSEN	SAVF	FCAR	SDY	GSR	SFAY
5H23v1-3	RVTITRDTASASTAYMELSSLRSED	TAVY	YCAR	SDY	GSR	SFAY
VH1	RVTITRDTASASTAYMELSSLRSED	TAVY	YCAR	SDY	GSR	SFAY
VH2	RVTITADKSA ~~RT~~ AYMELSSLTSED	TAVY	YCAR	SDY	GSR	SFAY
VH3	KATITRDTASASTAYMELSSLRSED	TAVY	FCAR	SDY	GSR	SFAY
VH4	RVTITADKSA ~~RT~~ AYMELSSLTSED	TAVY	YCAR	SDY	GSR	SFAY
VH5	KATLTADTSASTAYMELSSLRSEN	TAVY	FCAR	SDY	GSR	SFAY
VH6	KATLTADKSA ~~RT~~ AYMELSSLRSEN	TAVY	FCAR	SDY	GSR	SFAY
5H23v1-69	RVTITADESTSTAYMELSSLRSED	TAVY	YCAR	SDY	GSR	SFAY
VH7	RATLTADKSTSTAYMELSSLRSED	TAVY	YCAR	SDY	GSR	SFAY
VH8	RATLTADKST ~~RT~~ AYMELSSLRSED	TAVY	YCAR	SDY	GSR	SFAY
VH9	RATITADKSTSTAYMELSSLRSED	TAVY	YCAR	SDY	GSR	SFAY

FIGURE 3A-2

VL Domain

Kabat	1	10	20	24-27abcd-----34	40	50-----56
AbM	1	10	20	24-----30ab-----34	40	50-----56
Chothia	1	10	20	26--30ab--32	40	50--
Contact	1	10	20	30ab-----36	40	46-----55
IMGT	1		23	27-----38	41	56-65 69
AHon	1		23			
5H23				42		58 72
5H23v4-1	DIVLTQSPASLAVSLGQRATISC	RASKSVSTSGYVYMH	WNQOKPGQPPKLLIY	LASYLES		
vL1	DIVMTQSPDLSAVSLGERATINC	RASKSVSTSGYVYMH	WYQOKPGQPPKLLIY	LASYLES		
vL2	DIVLTQSPDLSAVSLGERATINC	RASKSVSTSGYVYMH	WNQOKPGQPPKLLIY	LASYLES		
vL3	DIVMTQSPDLSAVSLGERATINC	RASKSVSTSGYVYMH	WNQOKPGQPPKLLIY	LASYLES		
vL4	DIVLTQSPDLSAVSLGERATINC	RASKSVSTSGYVYMH	WNQOKPGQPPKLLIY	LASYLES		
vL5	DIVMTQSPDLSAVSLGERATINC	RASKSVSTSGYVYMH	WNQOKPGQPPKLLIY	LASYLES		
Kabat	60	70	80	89-----97		
AbM	60	70	80	89-----97		
Chothia	60	70	80	91---96		
Contact	60	70	80	89-----96		
IMGT	70		89	105-----117		
AHon	73		91	107	138	
5H23	GVPARFSGSGGTDFTLNIHPVEEEDAAIYIC	QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:26)		
5H23v4-1	GVPDRFSGSGGTDFTLTISSLQAEDVAVYIC	QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:355)		
vL1	GVPDRFSGSGGTDFTLTISSVQAEDAAIYIC	QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:275)		
vL2	GVPDRFSGSGGTDFTLTISSVQAEDVAVYIC	QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:276)		
vL3	GVPDRFSGSGGTDFTLTISSVQAEDVAVYIC	QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:277)		
vL4	GVPDRFSGSGGTDFTLTISSLQAEDVAVYIC	QHSRDLTFF	FGGGTKVEIK	(SEQ ID NO:325)		
vL5	GVPDRFSGSGGTDFTLTISSLQAEDVAVYIC	QHSRDLTFF	FGGGTKVEIK	(SEQ ID NO:326)		

FIGURE 3B

VL Domain						
Kabat	1	10	20	24-27abcd-----34	40	50-----56
AbM	1	10	20	24-----30ab-----34	40	50-----56
Chothia	1	10	20	26--30ab--32	40	50--
Contact	1	10	20	30ab-----36	40	46-----55
IMGT	1	23	27	27-----38	41	56-65 69
AHon	1	23	42			58 72
5H23	DIVLTQSPASLA	SVGLQ	RATISC	RASKSVSTSGYVYMH	WNQOKPGQPPKLLIY	LASYLES
5H23v1-39	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKAPKLLIY	LASYLES
v1-39a	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKAPKLLIY	LASYLES
v1-39b	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKAPKLLIY	LASYLES
v1-39c	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WNQOKPGKAPKLLIY	LASYLES
v1-39d	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKPPKLLIY	LASYLES
v1-39e	DIQLTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKAPKLLIY	LASYLES
v1-39f	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKPPKLLIY	LASYLES
v1-39g	DIQLTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKPPKLLIY	LASYLES
v1-39h	DIQLTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WNQOKPGKPPKLLIY	LASYLES
v1-39i	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKAPKLLIY	LASYLES
v1-39j	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKAPKLLIY	LASYLES
v1-39k	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WNQOKPGKPPKLLIY	LASYLES
v1-39l	DIQLTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WNQOKPGKPPKLLIY	LASYLES
v1-39m	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKPPKLLIY	LASYLES
v1-39n	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKPPKLLIY	LASYLES
v1-39o	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKPPKLLIY	LASYLES
v1-39p	DIQMTQSPSSLS	ASVGD	RVITTC	RASKSVSTSGYVYMH	WYQOKPGKPPKLLIY	LASYLES

FIGURE 3C-1

VL Domain (continued)

Kabat	60	70	80	89-----97	
AbM	60	70	80	89-----97	
Chothia	60	70	80	91---96	
Contact	60	70	80	89-----96	
IMGT	70		89	105-----117	
AHon	73	91		107	138
5H23	GVPARFSGSGGTDFTLNHPVEEEDAAIYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:26)
5H23v1-39	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:353)
v1-39a	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:327)
v1-39b	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:328)
v1-39c	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:329)
v1-39d	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:330)
v1-39e	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:331)
v1-39f	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:332)
v1-39g	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:333)
v1-39h	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:334)
v1-39i	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:335)
v1-39j	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:336)
v1-39k	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:337)
v1-39l	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:338)
v1-39m	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:339)
v1-39n	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:340)
v1-39o	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:341)
v1-39p	GVPSRFSGSGGTDFTLTISLQPEDFATYYC			QHSRDLTFP	FGGGTKLEIK (SEQ ID NO:342)

FIGURE 3C-2

LEGURER-301

VL Domain (continued)

Kabat	60	70	80	89-----97			
AbM	60	70	80	89-----97			
Chothia	60	70	80	91---96			
Contact	60	70	80	89-----96			
IMGT	70		89	105-----117			
AHon	73	91	107	138			
5H23	GVPARFSGSGSGTDFTLNIHPVEEEDAAIYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:26)	
5H23v3-20	GIPARFSGSGSGTDFTLTISRLEPEDFAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:354)	
v3-20a	GIPARFSGSGSGTDFTLTISRLEPEDFAVYYC			QHSRDLTFF	FGQGTKLEIK	(SEQ ID NO:343)	
v3-20b	GIPARFSGSGSGTDFTLTISRVEPEDFAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:344)	
v3-20c	GIPARFSGSGSGTDFTLTISRLEPEDFAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:345)	
v3-20d	GIPARFSGSGSGTDFTLTISRLEPEDFAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:346)	
v3-20e	GIPARFSGSGSGTDFTLTISRLEPEDAAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:347)	
v3-20f	GIPARFSGSGSGTDFTLTISRVEPEDFAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:348)	
v3-20g	GIPARFSGSGSGTDFTLTISRVEPEDFAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:349)	
v3-20h	GIPARFSGSGSGTDFTLTISRLEEEDFAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:350)	
v3-20i	GIPARFSGSGSGTDFTLTISRVEEEDFAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:351)	
v3-20j	GIPARFSGSGSGTDFTLTISRVEEEDAAVYYC			QHSRDLTFF	FGGGTKLEIK	(SEQ ID NO:352)	

FIGURE 3D-2

FIGURE 4A

human	MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAVTGFSGDGRAIWSKNPNFTPVNESQLFLYDT	40	80
chMoHu	MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSVILSAFVLLRAVTGFSGDGKAIWDKKQYVSPVNPSQLFLYDT		
chHuMo	MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAVTGFSGDGRAIWSKNPNFTPVNESQLFLYDT		
mouse	MKTGCAAGSPGNEWIFFSSDERNTRSRKTMSNRALQRSVILSAFVLLRAVTGFSGDGKAIWDKKQYVSPVNPSQLFLYDT		
human	FPKNFFWIGIGTGALQVEGSWKKGKGPSIWDHFIHTHLKNVSSSTNGSSDSYIFLEKDLSDLDFIGVSYQFSISWPRLFP	120	160
chMoHu	FPKNFSWGVGTGAFQVEGSWKTDGRGPSINDRYVYVYSHLRGVNGTDRSTDYIFLEKDLLALDFLGVSYQFSISWPRLFP		
chHuMo	FPKNFFWIGIGTGALQVEGSWKKGKGPSIWDHFIHTHLKNVSSSTNGSSDSYIFLEKDLSDLDFIGVSYQFSISWPRLFP		
mouse	FPKNFSWGVGTGAFQVEGSWKTDGRGPSINDRYVYVYSHLRGVNGTDRSTDYIFLEKDLLALDFLGVSYQFSISWPRLFP		
human	DGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPALQEKYGGWKNDTIIDIFNDYATYCFQMGFGRVKYWIITH	200	240
chMoHu	NGTVAAVNAQGLRYRALLDLSVLRNIEPIVTLYHWDLPALTQEEYGGWKNAITMIDLFNDYATYCFQTFGDRVKYWIITH		
chHuMo	DGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPALQEKYGGWKNDTIIDIFNDYATYCFQMGFGRVKYWIITH		
mouse	NGTVAAVNAQGLRYRALLDLSVLRNIEPIVTLYHWDLPALTQEEYGGWKNAITMIDLFNDYATYCFQTFGDRVKYWIITH		
human	NPYLVAWHGYGTGMHAPGEKGNLAAVYTVGHNLIKAHSAKVWHNHNTHFRPHQKGWLSITLGSWHIEPNRSENTMDIFKQCQ	280	320
chMoHu	NPYLVAWHGFGTGMHAPGEKGNLTAVYTVGHNLIKAHSAKVWHNNDKNFRPHQKGWLSITLGSWHIEPNRTDNMEDVINQCQ		
chHuMo	NPYLVAWHGYGTGMHAPGEKGNLAAVYTVGHNLIKAHSAKVWHNHNTHFRPHQKGWLSITLGSWHIEPNRSENTMDIFKQCQ		
mouse	NPYLVAWHGFGTGMHAPGEKGNLTAVYTVGHNLIKAHSAKVWHNNDKNFRPHQKGWLSITLGSWHIEPNRTDNMEDVINQCQ		
human	QSMVSVLGFANPIHGDGDYPEGMRKKLFSVLPISFAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLRREAL	360	400
chMoHu	HSMSSVLGFANPIHGDGDYPEFMKTG--AMIPEFSEAEEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVSLNLRQVL		
chHuMo	QSMVSVLGFANPIHGDGDYPEGMRKKLFSVLPISFAEKHEMRGTADFFAFSFGPNNFKPLNTMAKMGQNVSLNLRREAL		
mouse	HSMSSVLGFANPIHGDGDYPEFMKTG--AMIPEFSEAEEKEEVRGTADFFAFSFGPNNFRPSNTVVKMGQNVSLNLRQVL		
human	NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLDEIRVFGYTAWSLLDGFEWQDAYTIRRGFLFY	440	480
chMoHu	NWIKLEYDDPQILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAIKFDEIRVFGYTAWTLLDGFWEWQDAYTIRRGFLFY		
chHuMo	NWIKLEYNNPRILIAENGWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLDEIRVFGYTAWSLLDGFEWQDAYTIRRGFLFY		
mouse	NWIKLEYDDPQILISENGWFTDSYIKTEDTTAIYMMKNFLNQVLQAIKFDEIRVFGYTAWTLLDGFWEWQDAYTIRRGFLFY		

FIGURE 4B

human	520	560
chMoHu	VDENSKQKERKPKSSAHYYKQII	RENGFSLKESTPDVQGGQPCDFSGWGV
chHuMo	VDENSEQKERKPKSSAHYYKQII	QDNNGFSLKESTPDVQGGQPCDFSGWGV
mouse	VDENSKQKERKPKSSAHYYKQII	RENGFPLKESTPDMKGRFP
		CDFSWGV
		TESVLKPEFTVSSPQFTDPHLYVWVNTGNRL
		VDENSEQKERKPKSSAHYYKQII
		QDNNGFPLKESTPDMKGRFP
		CDFSWGV
		TESVLKPEFTVSSPQFTDPHLYVWVNTGNRL
human	600	640
chMoHu	LHRVEGVRLKTRPAQCTDFVNI	KKQLEMLARMKVTHYRFALDWASVLP
chHuMo	LHRVEGVRLKTRPAQCTDFVNI	KKQLEMLARMKVTHYRFALDWASVLP
mouse	LYRVEGVRLKTRPSQCTDYVSI	KKRVEMLAKMKVTHYQFALDWT
		SILPTGNLSKVNROVLRYRCV
		VSEGLKLGVPFPMVT
		LYRVEGVRLKTRPSQCTDYVSI
		KKRVEMLAKMKVTHYQFALDWT
		SILPTGNLSKVNROVLRYRCV
		VSEGLKLGVPFPMVT
human	680	720
chMoHu	LYYPTHAHLGLPEPLLHADGWL	NPSTAEAFQAYAGLCFQELGDLVKL
chHuMo	LYYPTHAHLGLPEPLLHADGWL	NPSTAEAFQAYAGLCFQELGDLVKL
mouse	LYHPTHSHLGLPLPLSSGGLN	MNTAKAFQDYAELCFRELGD
		LVKLWITINEPNRLSDIYNRSGND
		TYGAAHNLLVAHA
		LYHPTHSHLGLPLPLSSGGLN
		MNTAKAFQDYAELCFRELGD
		LVKLWITINEPNRLSDIYNRSGND
		TYGAAHNLLVAHA
human	760	800
chMoHu	LAWRLYDRQFRPSQRGAVSL	SLHADWAEPANPYADSHWRAAER
chHuMo	LAWRLYDRQFRPSQRGAVSL	SLHADWAEPANPYADSHWRAAER
mouse	QVWHLYDRQYRPVQHGA	VSLSLHCDWAEPANPFVDSHWKAAER
		FLQFEIAWFADPLFKTGDYPSVMKEYI
		ASKNQRLSS
		QVWHLYDRQYRPVQHGA
		VSLSLHCDWAEPANPFVDSHWKAAER
		FLQFEIAWFADPLFKTGDYPSVMKEYI
		ASKNQRLSS
human	840	880
chMoHu	SALPRLTEAERRLLKGTVD	FCALNHFTTRFVVMHEQLAGSRVDS
chHuMo	SALPRLTEAERRLLKGTVD	FCALNHFTTRFVVMHEQLAGSRVDS
mouse	SVLPFRFTAKESRLVKGT	VDFFYALNHFTTRFVIHKQLNTNRS
		VAADRVDQLQDITRLSSPSRLAVTP
		WGVKRLLAWIRRN
		SVLPFRFTAKESRLVKGT
		VDFFYALNHFTTRFVIHKQLNTNRS
		VAADRVDQLQDITRLSSPSRLAVTP
		WGVKRLLAWIRRN
human	920	960
chMoHu	GDMDIYITASGIDDQALE	DDRRLRKYYLGKYLQEV
chHuMo	GDMDIYITASGIDDQALE	DDRRLRKYYLGKYLQEV
mouse	RDRDIYITANGIDDQALE	DDQIRKYYLEKYVQ
		EALKAYLIDKVKIKGYAFKLTEEKSKPR
		FRFGFFTSDFRAKSSVQFYSK
		RDRDIYITANGIDDQALE
		DDQIRKYYLEKYVQ
		EALKAYLIDKVKIKGYAFKLTEEKSKPR
		FRFGFFTSDFRAKSSVQFYSK

FIGURE 4C

		1000		1040
human	VISSRGFFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGCCFFSTLVLLLSIAIFQQRKRKFWKAKNLQHIPLKKGK			
chMoHu	VISSRGFFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGCCFFSTLVLLLSIAIFQQRKRKFWKAKNLQHIPLKKGK			
chHuMo	LISSSGLPAENRSPACGQPAEDTCTICSFLVEKKPLIFFGCCFISTLAVLLSITVFHHQKRKFFQKARNLQNIPLKKGH			
mouse	LISSSGLPAENRSPACGQPAEDTCTICSFLVEKKPLIFFGCCFISTLAVLLSITVFHHQKRKFFQKARNLQNIPLKKGH			
human	-RVVS (SEQUENCE ID 297)			
chMoHu	--RVVS (SEQUENCE ID 376)			
chHuMo	SRVFS (SEQUENCE ID 374)			
mouse	SRVFS (SEQUENCE ID 301)			

FIGURE 5A

	30	60
human	MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAVTFGSGDGRAI	
cyno	MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALTLLRAVTFGSGDGRAV	
mouse	MKTGCAAGSPGNEWIFFSSDERNTRSRKTMNRALQRSVLSAFVLLRAVTFGSGDGKAI	
rabbit	MKPGCAAGSPGNEWVSFCTDERNRRCRETMSGRLLRSVMLS AFILLRAVTFGFGDGRAV	
hamster	MKAGCAAGSPGNEWIFLSSYERNTRSKKTMNRALQRSVLSAFVLLRAVTCLSGDGKAI	
rat	MKTGCAAGSPGNEWVFFSSDERSTRSRKTMNGALQRSVLSALVLLRAVTFGSGDGKAI	
dog	MKPGCAAGSPGNEWIFLSTDESNTHYRKTMCNHGLQRSVILS AFILLGAVPGFSGDGRAI	
	** * * * * *	** * * * *
	90	120
human	WSKNPNFTPVNESQLFLYDTFFPKNFFWIGITGALQVEGSWKKGKGPSIWDHFIHTHLKN	
cyno	WSKNPNFTPVNESQLFLYDTFFPKNFFWGVGTGALQVEGSWKKGKGPSIWDHFEVHTHLKN	
mouse	WDKKQYVSPVNPSQLFLYDTFFPKNFSWGVGTGAFQVEGSWKTDGRGPSIWDRIYVYSHLRG	
rabbit	WSQNPMLSPVNESQLFLYDTFFPKNFFWGVGTGAFQVEGSWKKGKGLSVWDHFIATHLN--	
hamster	WDKKQYVSPVNASQLFLYDTFFPKNFFWGVGTGAFQVEGNWQADGRGPSIWDRIYTHLRD	
rat	WDKKQYVSPVNPQGQLFLYDTFFPKNFSWGVGTGAFQVEGSWKADGRGPSIWDRIYVDSHLRG	
dog	WSKNPHFSPVNESQLFLYDTFFPKNFFWGVGTGAFQVEGNWKTGKGPSIWDHFIHTHLKN	
	* * * * *	* * * * *
	150	180
human	VSSITNGSSDSYIFLEKDLALDFIGVSFYQFSISWPRLFPDGIPTVANAKGLQYYSTLLD	
cyno	VSSITNGSSDSYIFLEKDLALDFIGVSFYQFSISWPRLFPDGIPTVANAKGLQYYNTLLD	
mouse	VNGTDRSTDSYIFLEKDLALDFLGVSFYQFSISWPRLFPNGTVAAVNAQGLRYRALLD	
rabbit	VSSRDGSSDSYIFLEKDLALDFLGVSFYQFSISWPRLFPDGTVAVANAKGLQYYNRLLD	
hamster	VSITEKSADSYIFLEKDLALDFLGVSFYQFSISWPRLFPNGTVAASVNAKGLQYYNKLLD	
rat	VNSTDRSTDSYVFEKDLALDFLGVSFYQFSISWPRLFPNGTVAAVNAKGLQYYRALLD	
dog	VNSMNSSSDSYIFLEKDLALDFIGVSFYQFSISWPRLFPDGIAAVANAKGLQYYNSLLD	
	* * * * *	* * * * *

FIGURE 5B

	210		240
human	ALVLRNIEPIVTLYHHWDLPLALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITI		
cyno	SLVLRNIEPIVTLYHHWDLPLALQEKYGGWKNDTIIDIFNDYATYCFQTFGDRVKYWITI		
mouse	SLVLRNIEPIVTLYHHWDLPLTLQEEYGGWKATMIDLFNDYATYCFQTFGDRVKYWITI		
rabbit	SLLRNIEPVVTLYHHWDLPLALQEKYGGWKNETLIDLFNDYATYCFQTFGDRVKYWITI		
hamster	SLILRNIEPVVTLYHHWDLPLALQEDYGGWKATMIDLFNDYATYCFQTFGDRVKYWITI		
rat	SLVLRNIEPIVTLYHHWDLPLTLQEEYGGWKATMIDLFNDYATYCFQTFGDRVKYWITI		
dog	ALVLRNIEPIVTLYHHWDLPLALQEKYGGWKNETITDIFNDYATYCFQTFGDRVKYWITI		
	* * * * *	* * * * *	* * * * *
	270		300
human	NPYLVAWHGYGTGMHAPGEKGNLAAYTVGHNLIKAHskVWNNYNTHFRPHQKGWLSITL		
cyno	NPYLVAWHGYGTGMHAPGEKGNLAAYTVGHNLIKAHskVWNNYNTHFRPHQKGWLSITL		
mouse	NPYLVAWHGFGTGMHAPGEKGNLTAVYTVGHNLIKAHskVWNNYDKNFRPHQKGWLSITL		
rabbit	NPYLVAWHGYGTGLHAPGEKGNVAAYTVGHNLLKAHskVWNNYNNRNRPHQKGWLSITL		
hamster	NPYLVAWHGFATGMHAPGETGNLTAVYIVGHNLIKAHskVWNNYDKNFRPHQKGLLSITL		
rat	NPYLVAWHGFGTGMHAPGEKGNLTAVYTVGHNLIKAHskVWNNYDKNFRPHQKGWLSITL		
dog	NPYLVAWHGYGTGMHAPGEKGNLAAYTVGHNLIKAHskVWNNYNNTNFRPYQKGLLSITL		
	* * * * *	* * * * *	* * * * *
	330		360
human	GSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFSVLPFSEAEK		
cyno	GSHWIEPNRSENTMDILKCQQSMVSVLGWFANPIHGDGDYPEGMKKKLLSILPLFSEAEK		
mouse	GSHWIEPNRTDNMEDVINCQHSMSVSVLGWFANPIHGDGDYPEFMKT--GAMIEPFSEAEK		
rabbit	GSHWIEPNRAESIVDILKCQQSMVSVLGWFANPIHGDGDYPEVMTKKLLSVLPAPFSEAEK		
hamster	GSHWIEPNKTENMADTISCQHSMAFVLGWFANPIHADGDYPEFMKT--LSTMPVFSEAEK		
rat	GSHWIEPNRTENMEDVINCQHSMSVSVLGWFANPIHGDGDYPEFMKT--SSVIEPFSEAEK		
dog	GSHWIEPNRSENMMDILKCQQSMVSVLGWFANPIHGNNGDYPEVMKKLLSTLPLFSEAEK		
	* * * * *	* * * * *	* * * * *

FIGURE 5C

	390	420
human	HEMRGTADFFAFSFGPNNFKPLNTMAKMGQVSNLREALNWIKLEYNNPRILIAENGWF	
cyno	NEVRGTADFFAFSFGPNNFKPLNTMAKMGQVSNLREALNWIKLEYNNPRILIAENGWF	
mouse	EEVRGTADFFAFSFGPNNFRPSNTVVKMGQVSNLRQVLNWIKLEYDDPQILISENGWF	
rabbit	NEVRGTADFFAFSFGPNNFKPLNTMAKMGQVSNLRQVLNWIKLEYGNPRILIAENGWF	
hamster	EEVRGTADFFAFSFGPNNFRPSNTVVKMGQVSNLRQVLNWIKLEYDNPRILISENGWF	
rat	EEVRGTADFFAFSFGPNNFRPSNTVVKMGQVSNLRQVLNWIKLEYDNPRILISENGWF	
dog	NEVRGTADFFAFSFGPNNFKPQNTMAKMGQVSNLREVLNWIKLEYGNPRILIAENGWF	
	* * * * *	* * * * *
	450	480
human	TDSRVKTEDTTAIYMMKNFLSQVLQAIRLDEIRVFGYTAWSLLDGFEWQDAYTIRRGLEY	
cyno	TDSHVKTEDTTAIYMMKNFLSQVLQAIRLDEIRVFGYTAWSLLDGFEWQDAYTIRRGLEY	
mouse	TDSYIKTEDTTAIYMMKNFLNQVLQAIKFDEIRVFGYTAWTLLDGFEWQDAYTIRRGLEY	
rabbit	TDSYVQTEDTTAIYMMKNFLNQVLQAIRLDGVRVFGYTAWSLLDGFEWQDAYNTRRGLEY	
hamster	TDSDIKTEDTTAIYMMKHFLNQVLQAIQFDEIRVFGYTAWSLLDGFEWQYAYTSRRGLEY	
rat	TDSYIKTEDTTAIYMMKNFLNQVLQAIKFDEIQVFGYTAWTLLDGFEWQDAYTIRRGLEY	
dog	TDSHVKTEDTTAIYMMKNFLNQVLQAIRFDEIQVFGYTAWSLLDGFEWQDAYSTRRGLEY	
	*** * * * * * * * * * *	*** * * * * * * * * * *
	510	540
human	VDENSKQKERKPKSSAHYYKQIIRENGFSLKESTPDVQQGQFPDFFSWGVTEVLKPESVA	
cyno	VDENSKQKERKPKSSAHYYKQIIRENGFSLKEATPDVQQGQFPDFFSWGVTEVLKPESVA	
mouse	VDENSEQKERKPKSSAHYYKQIIQDNGFPLKESTPDMKGRFPDFFSWGVTEVLKPEFTV	
rabbit	VDENSEQRRRRPKSSAHYYKQVIGENGFTLREATPDLQQGQFPDFFSWGVTEVLKPESVA	
hamster	VDENSEQKERKPKTSAHYYKQIIQENGFFLKESTPDMQQGQFPDFFSWGVTEVLKPEFMV	
rat	VDENSEQKERKPKSSAHYYKQIIQDNGFPLQESTPDMKQFQFPDFFSWGVTEVLKPEFTV	
dog	VDENSKQKERKPKSSAHYYKQIIQENGFTFKESTPDVQQGQFPDFFSWGVTEVLKPKVVA	
	***** * * * *	***** * * * *

FIGURE 5D

	570		600
human	SSPQFSDPHLYVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA		
cyno	SSPQFSDPYLYVWNATGNRLLHRVEGVRLKTRPAQCTDFVNIKKQLEMLARMKVTHYRFA		
mouse	SSPQFTDPHLYVWNVTGNRLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFA		
rabbit	SSPQFSDPHLYVWNATGNRMLHRVEGVRLKTRPAQCTDFITIKKQLEMLARMKVTHFRFA		
hamster	SSPQFTDPHLYVWNATGNRLLQRVEGVRLKTKPSHCTDYVSIKKRVEMLAKMKVTHYQFA		
rat	SSPQFTDPHLYVWNVTGNRLLYRVEGVRLKTRPSQCTDYVSIKKRVEMLAKMKVTHYQFA		
dog	SSPQFSDPHLYVWNVTGNRLLHRVEGVRLKTRPAQCTDFVSIKKRQLEMLARMNVTHYRFA		
	*****	*****	*****
	***	***	***
	630		660
human	LDWASVLP TGNLSAVNRQALRYRCV VSEGLKLGISAMVTLYYPTHAHLGLPEPL LHADG		
cyno	LDWASVLP TGNLSAVNRQALRYRCV VSEGLKLGISAMVTLYYPTHAHLGLPEPL LHAGG		
mouse	LDWTSILP TGNLSKVN RQVLR YRCV VSEGLKLG VFFPMVTLYHP THSHLGLPLP LSSGG		
rabbit	LDWASVLP TGNLSEVNRQALRYRCV VTEGLKLNISPMTLYYPTHAHLGLPAP LLSGG		
hamster	LDWATILP TGNLSEVNRQVLR YRCV VSEGLKLG VSPMTLYHP THSHLGLPEPL LNSGG		
rat	LDWTSILP TGNLSKIN RQVLR YRCV VSEGLKLGISPMTLYYHP THSHLGLPMP LLSGG		
dog	LDWPSILP TGNLSTVNRQALRYRCV VSESLKLSISPMTLYYPTHAHLGLPSP LLSGG		
	*****	*****	*****
	***	***	***
	690		720
human	WLNPSAEAFQAYAGLCFQELGDLVKLWITINEPNRLSDIYNRSGNDTYGAAHNLLVAHA		
cyno	WLNPSVEAFQAYAGLCFQELGDLVKLWITINEPNRLSDIYNRSGNDTYGAAHNLLVAHA		
mouse	WLNMN TAKAFQDYAELCFRELGD LVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHA		
rabbit	WLDPS TAKAFRDYAGLCFRELGD LVKLWITINEPNRLSDVYNRTSNDTYQAAHNLLIAHA		
hamster	WLNTYTAKAFQDYAGLCFQELGD LVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHA		
rat	WLNTNTAKAFQDYAGLCFRELGD LVKLWITINEPNRLSDMYNRTSNDTYRAAHNLMIAHA		
dog	WLNASTARAFQDYAGLCFQELGD LVKLWITINEPNRLSDVYSHTSNDTYRAAHNLLIAHA		
	*****	*****	*****
	***	***	***

750 780

	750	780
human	LAWRLYDRQYFRPSQRGAVSLSLHADWAE	PANPYADSHWRAAERFLQFEIAWFAEPLFKTG
cyno	LAWRLYDRQYFRPSQRGAVSLSLHADWAE	PANPYADSHWRAAERFLQFEIAWFAEPLFKTG
mouse	QVWHLYDRQYRPVQHGA	VSLSLHCDWAE
rabbit	PANPYVASHWQA	ERFLQFEIAWFAEPLFKTG
hamster	PANPYVDSHWKAA	ERFLQFEIAWFAEPLFKTG
rat	PANPYVESHWKAA	ERFLQFEIAWFAEPLFKTG
dog	PANPYADSHWKAA	ERFLQFEIAWFAEPLFKTG
	* * * * *	* * * * *
human	DYPAA	REYIASKHRRGLSSSALPRL
cyno	TEAERRLLKGT	DFCALNHFTTREFVMHEQLAGSR
mouse	DYPVMKEYIASKNQ	RGLSSSVLPREF
rabbit	TAKE	SRVLVKGTVDFYALNHFTTREFVIHKQLNTNR
hamster	DYPVAMREYIASKTRRGLSSSVLPREF	SDAERLLVKGADFYALNHFTTREFVMHEQQNGSR
rat	DYPLAMKEYIASKNQ	GLSRVLPREF
dog	TPPEESRLVKG	TIDFYALNHFTTREFVIHKQLNSSR
	DYPLAMKEYIASKKQ	RGLSSSVLPREF
	TLKESRLVKG	TIDFYALNHFTTREFVIHKQLNTNC
	DYPPAMREYIASKNR	QGLSRSTLPRFTDEERRLVKGADFYALNHFTTREFVMHARQNGSR
	*** * * * * *	*** * * * * *
	810	840
human	DYPAA	REYIASKHRRGLSSSALPRL
cyno	TEAERRLLKGT	DFCALNHFTTREFVMHEQLAGSR
mouse	DYPVMKEYIASKNQ	RGLSSSVLPREF
rabbit	TAKE	SRVLVKGTVDFYALNHFTTREFVIHKQLNTNR
hamster	DYPVAMREYIASKTRRGLSSSVLPREF	SDAERLLVKGADFYALNHFTTREFVMHEQQNGSR
rat	DYPLAMKEYIASKNQ	GLSRVLPREF
dog	TPPEESRLVKG	TIDFYALNHFTTREFVIHKQLNSSR
	DYPLAMKEYIASKKQ	RGLSSSVLPREF
	TLKESRLVKG	TIDFYALNHFTTREFVIHKQLNTNC
	DYPPAMREYIASKNR	QGLSRSTLPRFTDEERRLVKGADFYALNHFTTREFVMHARQNGSR
	*** * * * * *	*** * * * * *
	870	900
human	YDS	DRDIQFLQDITRLSSPTRLAVIPWGVRKLLRWVRN
cyno	YDS	DRDIQFLQDITRLSSPTRLAVIPWGVRKLLRWVRN
mouse	SVADR	VDVQFLQDITRLSSPSRLAVTPWGVRKLLAWIRRN
rabbit	YDS	DRDVQFLQDITRLASPSRLAVMPWGEKLLRWMRN
hamster	SMADR	VDVQFLQDITRLSSPSRLAVMPWGEKLLGWIQRN
rat	SVADR	VDVQFLQDITRLSSPSRLAVTPWGMKLLGWIQRN
dog	YDADR	VDVQFLQDITCLSSPSRLAVLPWGERKVLRWIQKNY
	*** * * * * *	*** * * * * *

FIGURE 5F

	930	960
human	RLRKYVLGKYLQEVLKAYLIDKVRIGKYAFAKLAEKSKPRFGFFTSDFKAKSSIQFYNK	
cyno	RLRKYVLEKYLQEVLKAYLIDKVRIGKYAFAKLAEKSKPRFGFFTSDFKAKSSIQFYNK	
mouse	QIRKYVLEKYVQEALKAYLIDKVKIKIGYAFKLTEEKSKPRFGFFTSDFRAKSSVQFYSK	
rabbit	QLRQYVLEKYVQEALKAYLIDKIKIKIGYAFKLTEEKSKPRFGFFTSDFKAKSSIQFYNK	
hamster	GIRKYVLEKYIQEALKAYLIDKVKIKIGYAFKLTEEKSKPRFGFFTSDFKAKSSVEFFYSK	
rat	QIRKYVLEKYVQEALKAYLIDKVKIKIGYAFKLTEEKSKPRFGFFTSDFKAKSSVQFYSK	
dog	ELRKYVLEKYIQEALKAHLLIDKVKVKGYYAFKLTEEKSKPRFGFFTSEFKAKSSVQLYNK	
	* * * * *	* * * * *
	990	1020
human	VISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGCCFFSTLVLLLSIAIFQRQ	
cyno	MISSSGFPSENSSSRCSQTQKNTECTVCLFLVQKKPLIFLGCCFFSTLVLLLSITIFHRQ	
mouse	LISSSGLPAENRSPACGQPAEDTDCTICSFIVEKKPLIFFGCCFISTLAVLLSITVFHHQ	
rabbit	LITSNGFPSENGGPRCNQTQGNPECTVCLLLQKKPLIFFSCCFFCTLVLLSSITIFHRR	
hamster	LISRSGFSETSNPACGQPPEDTDCTICSEFTQKKSLIFFGCCFISTLAVLLSITIFHHR	
rat	LISSSGFSENRSRSPACGQPPEDTECAICSFILTQKKPLIFFGCCFISTLAALLSITIFHHR	
dog	LISNSGFSENRSRSPRCSETQRNTECMVCLFLVQKKPLIFFSCCFFSTLVLLSSITILHRR	
	* * * * *	* * * * *
	1045	
human	KRRKFWKAKNLQHIPLKKGKRVVS-	(SEQ ID NO:297)
cyno	KRRKFWKAKNLQHIPLKKGKRVLS-	(SEQ ID NO:299)
mouse	KRRKFQKARNLQNIPLKKGHSRVFS	(SEQ ID NO:301)
rabbit	KRRKFWKAKDLQHIPLKKGHKRVLS	(SEQ ID NO:410)
hamster	KRR-FHKSKNLENIPLKEGHSRVLS	(SEQ ID NO:408)
rat	KRRKFQKARNLQNIPLKKGHSRVFS	(SEQ ID NO:356)
dog	KRRKIWKAKNLQHIPLKKSKNLSQS	(SEQ ID NO:412)
	***	***

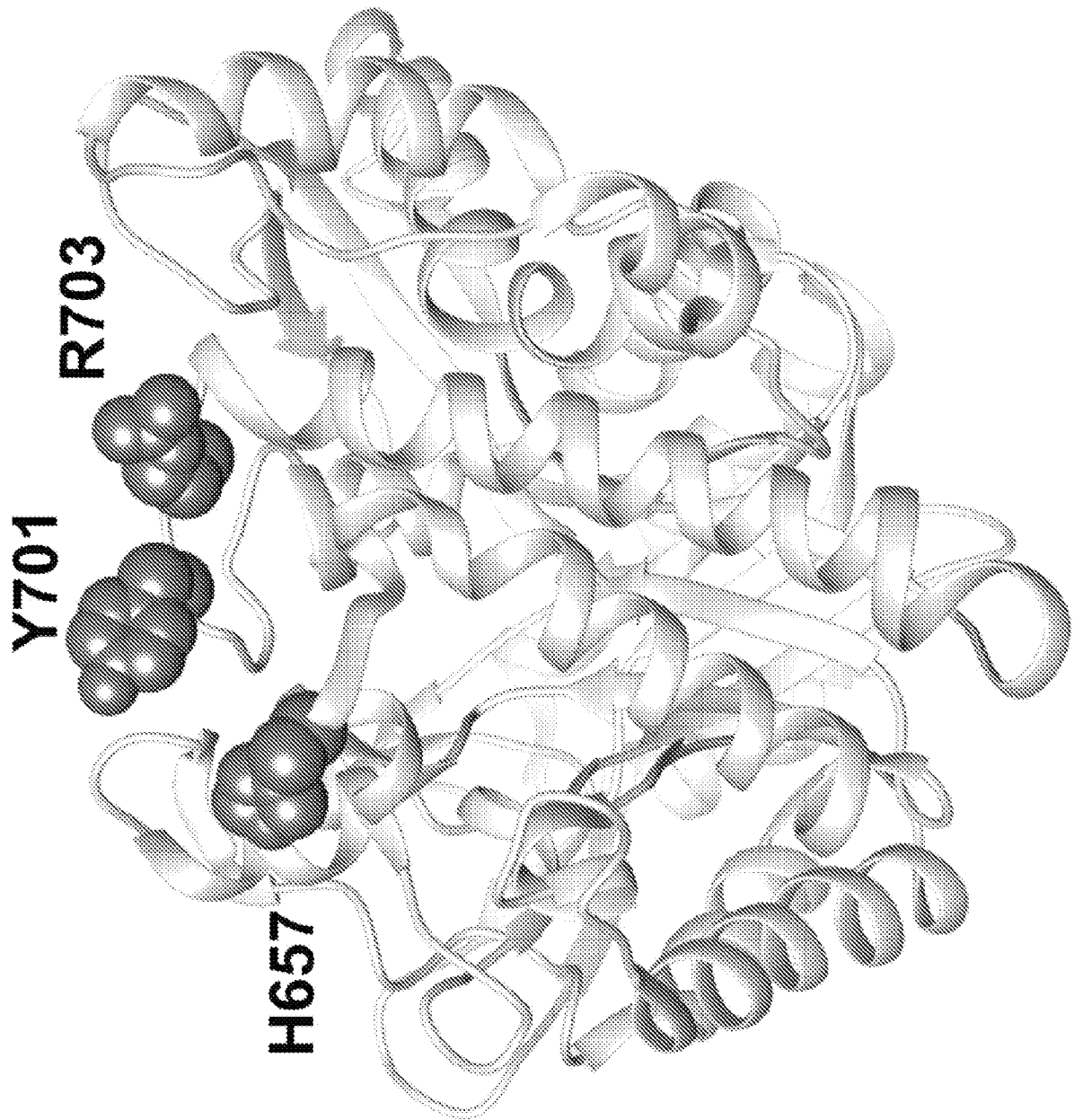


FIGURE 6

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