



(86) Date de dépôt PCT/PCT Filing Date: 2011/04/13
(87) Date publication PCT/PCT Publication Date: 2011/10/20
(85) Entrée phase nationale/National Entry: 2012/10/10
(86) N° demande PCT/PCT Application No.: US 2011/032333
(87) N° publication PCT/PCT Publication No.: 2011/130417
(30) Priorités/Priorities: 2010/04/15 (US61/324,691);
2010/10/13 (US61/392,859)

(51) Cl.Int./Int.Cl. *C07K 16/28* (2006.01),
A61K 39/395 (2006.01), *A61P 3/10* (2006.01)

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(54) Titre : PROTEINES DE LIAISON AU RECEPTEUR DE FGF HUMAIN ET A β -KLOTHO

(54) Title: HUMAN FGF RECEPTOR AND β -KLOTHO BINDING PROTEINS

(57) **Abrégé/Abstract:**

The present invention provides compositions and methods relating to or derived from antigen binding proteins and antigen binding protein-FGF21 fusions that specifically bind to β -Klotho, or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In some embodiments the antigen binding proteins and antigen binding protein-FGF21 fusions induce FGF21-like signaling. In some embodiments, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding component is a fully human, humanized, or chimeric antibody, binding fragments and derivatives of such antibodies, and polypeptides that specifically bind to β -Klotho, or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Other embodiments provide nucleic acids encoding such antigen binding proteins and antigen binding protein-FGF21 fusions, and fragments and derivatives thereof, and polypeptides, cells comprising such polynucleotides, methods of making such antigen binding proteins and antigen binding protein-FGF21 fusions, and fragments and derivatives thereof, and polypeptides, and methods of using such antigen binding proteins and antigen binding protein-FGF21 fusions, fragments and derivatives thereof, and polypeptides, including methods of treating or diagnosing subjects suffering from type 2 diabetes, obesity, NASH, metabolic syndrome and related disorders or conditions.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 October 2011 (20.10.2011)

PCT



(10) International Publication Number
WO 2011/130417 A3

(51) International Patent Classification:

C07K 16/28 (2006.01) *A61K 39/395* (2006.01)
A61P 3/10 (2006.01)

(21) International Application Number:

PCT/US2011/032333

(22) International Filing Date:

13 April 2011 (13.04.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/324,691 15 April 2010 (15.04.2010) US
61/392,859 13 October 2010 (13.10.2010) US

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(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
— with sequence listing part of description (Rule 5.2(a))

(88) **Date of publication of the international search report:**

8 March 2012

(54) **Title:** HUMAN FGF RECEPTOR AND β -KLOTHO BINDING PROTEINS

(57) **Abstract:** The present invention provides compositions and methods relating to or derived from antigen binding proteins and antigen binding protein-FGF21 fusions that specifically bind to β -Klotho, or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In some embodiments the antigen binding proteins and antigen binding protein-FGF21 fusions induce FGF21-like signaling. In some embodiments, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding component is a fully human, humanized, or chimeric antibody, binding fragments and derivatives of such antibodies, and polypeptides that specifically bind to β -Klotho, or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Other embodiments provide nucleic acids encoding such antigen binding proteins and antigen binding protein-FGF21 fusions, and fragments and derivatives thereof, and polypeptides, cells comprising such polynucleotides, methods of making such antigen binding proteins and antigen binding protein-FGF21 fusions, and fragments and derivatives thereof, and polypeptides, and methods of using such antigen binding proteins and antigen binding protein-FGF21 fusions, fragments and derivatives thereof, and polypeptides, including methods of treating or diagnosing subjects suffering from type 2 diabetes, obesity, NASH, metabolic syndrome and related disorders or conditions.



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HUMAN FGF RECEPTOR AND β -KLOTHO BINDING PROTEINS

This application claims the benefit of U.S. Provisional Application No. 61/324,691 filed April 15, 2010 and U.S. Provisional Application No. 61/392,859 filed October 13, 2010, both of which are incorporated by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 12, 2010, is named A-1554-WO-PCT.txt and is 421,443 bytes in size.

FIELD OF THE INVENTION

The present disclosure relates to nucleic acid molecules encoding antigen binding proteins that bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. The present disclosure also provides antigen binding proteins that bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4 that induce FGF21-like signaling, as well as pharmaceutical compositions comprising antigen binding proteins that bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, including antigen binding proteins that induce FGF21-like signaling, and methods for treating metabolic disorders using such nucleic acids, polypeptides, or pharmaceutical compositions. Diagnostic methods using the antigen binding proteins are also provided.

BACKGROUND

Fibroblast Growth Factor 21 (FGF21) is a secreted polypeptide that belongs to a subfamily of Fibroblast Growth Factors (FGFs) that includes FGF19, FGF21, and FGF23 (Itoh *et al.*, (2004) *Trend Genet.* 20:563-69). FGF21 is an atypical FGF in that it is heparin independent and functions as a hormone in the regulation of glucose, lipid, and energy metabolism.

It is highly expressed in liver and pancreas and is the only member of the FGF family to be primarily expressed in liver. Transgenic mice overexpressing FGF21 exhibit metabolic phenotypes of slow growth rate, low plasma glucose and triglyceride levels, and an absence of age-associated type 2 diabetes, islet hyperplasia, and obesity. Pharmacological

administration of recombinant FGF21 protein in rodent and primate models results in normalized levels of plasma glucose, reduced triglyceride and cholesterol levels, and improved glucose tolerance and insulin sensitivity. In addition, FGF21 reduces body weight and body fat by increasing energy expenditure, physical activity, and metabolic rate. Experimental research provides support for the pharmacological administration of FGF21 for the treatment of type 2 diabetes, obesity, dyslipidemia, and other metabolic conditions or disorders in humans.

FGF21 is a liver derived endocrine hormone that stimulates glucose uptake in adipocytes and lipid homeostasis through the activation of its receptor. Interestingly, in addition to the canonical FGF receptor, the FGF21 receptor also comprises the membrane associated β -Klotho as an essential cofactor. Activation of the FGF21 receptor leads to multiple effects on a variety of metabolic parameters.

In mammals, FGFs mediate their action via a set of four FGF receptors, FGFR1 – 4, that in turn are expressed in multiple spliced variants, *e.g.*, FGFR1c, FGFR2c, FGFR3c and FGFR4. Each FGF receptor contains an intracellular tyrosine kinase domain that is activated upon ligand binding, leading to downstream signaling pathways involving MAPKs (Erk1/2), RAF1, AKT1 and STATs. (Kharitononkov et al., (2008) *BioDrugs* 22:37-44). Several reports suggested that the “c”-reporter splice variants of FGFR1-3 exhibit specific affinity to β -Klotho and could act as endogenous receptor for FGF21 (Kurosu et al., (2007) *J. Biol. Chem.* 282:26687-26695); Ogawa et al., (2007) *Proc. Natl. Acad. Sci. USA* 104:7432-7437); Kharitononkov et al., (2008) *J. Cell Physiol.* 215:1-7). In the liver, which abundantly expresses both β -Klotho and FGFR4, FGF21 does not induce phosphorylation of MAPK albeit the strong binding of FGF21 to the β -Klotho-FGFR4 complex. In 3T3-L1 cells and white adipose tissue, FGFR1 is by far the most abundant receptor, and it is therefore most likely that FGF21's main functional receptors in this tissue are the β -Klotho-FGFR1c complexes.

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

SUMMARY

An isolated antigen binding protein is provided. In one embodiment the antigen binding protein comprises an amino acid sequence selected from the group consisting of: (a) a light chain CDR3 comprising a sequence selected from the group consisting of: (i) a light chain CDR3 sequence that differs by no more than two amino acid additions, substitutions, deletions, and combinations thereof, from a CDR3 sequence of L1-L11, SEQ ID NOs:17-27; (ii) MQAX₁EFPWT (SEQ ID NO: 174); (iii) GTWDSSLX₂VX₃ (SEQ ID NO: 175); (iv) QQYDNLFT (SEQ ID NO: 122); (v) QQYGSAFLT (SEQ ID NO: 123); (vi) VLYMGSGIWV (SEQ ID NO: 124); (vii) ETWDSSLAGV (SEQ ID NO: 127); wherein X₁ is L or I; X₂ is V or A; and X₃ is V or A; (b) a heavy chain CDR3 sequence comprising a sequence selected from the group consisting of: (i) a heavy chain CDR3 sequence that differs by no more than one amino acid additions, substitutions, deletions, and combinations thereof, from a CDR3 sequence of H1-H11, SEQ ID NOs:28-38; (ii) GWFDX₆ (SEQ ID NO: 178); (iii) GTSFDY (SEQ ID NO: 99); (iv) YGGSFDY (SEQ ID NO: 100); (v) MVYVLDY (SEQ ID NO: 101); (vi) VAGPFDF (SEQ ID NO: 102); wherein X₆ is Y, I or F; and (c) the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b) and the Fc sequence of (c) and wherein the antigen binding protein specifically binds β -Klotho.

In a further embodiment the antigen binding protein comprises (a) a light chain CDR1 sequence selected from the group consisting of: (i) a light chain CDR1 sequence that differs by no more than two amino acid additions, substitutions, deletions, and combinations thereof, from a CDR1 sequence of L1-L11, SEQ ID NOs:17-27; (ii) RSSQSLVX₂₂YX₂₃DGNTYLS (SEQ ID NO: 177); (iii) SGSSNIGNNYVS (SEQ ID NO: 107); (iv) QASQDINNYLN (SEQ ID NO: 108); (v) RASQSVSGNYLA (SEQ ID NO: 109); (vi) GVSSGSVSTRYYPS (SEQ ID NO: 110); wherein X₂₂ is H or absent; and X₂₃ is S or absent; (b) a light chain CDR2 sequence selected from the group consisting of: (i) a light chain CDR2 sequence that differs by no more than two amino acid additions, substitutions, deletions, and combinations thereof, from a CDR2 sequence of L1-L11, SEQ ID NOs:17-27; (ii) KISNRFS (SEQ ID NO: 112); (iii) DNNX₄RPX₅ (SEQ ID NO: 176); (iv) DTSNLET (SEQ ID NO: 114); (v) GASSRAT (SEQ ID NO: 115); (vi) STNTRSS (SEQ ID NO: 116); wherein X₄ is K, N or R; and X₅ is S or absent; and (c) a heavy chain CDR1 sequence selected from the group consisting of: (i) a heavy chain CDR1 sequence that differs by no more than three amino acid additions, substitutions, deletions, and combinations thereof, from a CDR1 sequence of H1-H11, SEQ ID NOs:28-38; (ii) X₁₉YX₂₀MX₂₁ wherein X₁₉ is A, G, R, S, T, or I; X₂₀ is Y, G or

A; and X_{21} is H or S; (d) a heavy chain CDR2 selected from the group consisting of: (i) a heavy chain CDR2 sequence that differs by no more than five amino acid additions, substitutions, and /or deletions from a CDR2 sequence of H1-H11, SEQ ID NOs:28-38; (ii) WINPX₇SGGTNSAQKFQG (SEQ ID NO: 179); (iii) VIX₈X₉DGX₁₀X₁₁X₁₂YYADSVKG (SEQ ID NO: 180); (iv) X₁₃ISGX₁₄GX₁₅X₁₆TTYADSVKG (SEQ ID NO: 181); (v) VIX₁₇YDGRNKYX₁₈ADSVKG (SEQ ID NO: 182); wherein X₇ is N or Y; X₈ is W or G; X₉ is F or Y; X₁₀ is R or S; X₁₁ is N or Y; X₁₂ is Q or K; X₁₃ is A or D; X₁₄ is S or R; X₁₅ is V or G; X₁₆ is S or Y; X₁₇ is W or S; and X₁₈ is Y or H; (e) the light chain CDR1 of (a) and the light chain CDR2 of (b); (f) the light chain CDR1 of (a) and the heavy chain CDR1 of (c); (g) the light chain CDR1 of (a) and the heavy chain CDR2 of (d); (h) the light chain CDR1 (b) and the heavy chain CDR1 of (c); (i) the heavy chain CDR1 of (c) and the heavy chain CDR2 of (d); (j) the light chain CDR2 of (b) and the heavy chain CDR2 of (d); (k) the light chain CDR1 of (a), the light chain CDR2 of (b), and the heavy chain CDR1 of (c); (l) the light chain CDR2 of (b), the heavy CDR1 of (c), and the heavy chain CDR2 of (d); (m) the light chain CDR1 of (a), the heavy chain CDR1 of (c), and the heavy chain CDR2 of (d); or (n) the light chain CDR1 of (a), the light chain CDR2 of (b), the heavy chain CDR2 of (c), and the heavy chain CDR2 of (d), wherein said antigen binding protein specifically binds β -Klotho.

In an additional embodiment, the antigen binding protein comprises (a) a light chain variable domain comprising: (i) a light chain CDR1 sequence selected from SEQ ID NOs:106-111; (ii) a light chain CDR2 sequence selected from SEQ ID NOs:112-119; (iii) a light chain CDR3 sequence selected from SEQ ID NOs:120-127; and (b) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence selected from SEQ ID NOs:83-88; (ii) a heavy chain CDR2 sequence selected from SEQ ID NOs:89-97; and (iii) a heavy chain CDR3 sequence selected from SEQ ID NOs:98-105; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b), wherein the antigen binding protein specifically binds β -Klotho.

In still a further embodiment, the antigen binding protein comprises: (a) a light chain variable domain sequence selected from the group consisting of: (i) amino acids having a sequence at least 80% identical to a light chain variable domain sequence selected from L1-L11, SEQ ID NOs:17-27; (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the light chain variable domain sequence of L1-L11, SEQ ID NOs:17-27; (b) a heavy chain variable domain

sequence selected from the group consisting of: (i) a sequence of amino acids that is at least 80% identical to a heavy chain variable domain sequence of H1-H11 of SEQ ID NOs:28-38; (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the heavy chain variable domain sequence of H1-H11, SEQ ID NOs:28-38; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein the antigen binding protein specifically binds β -Klotho.

In another embodiment the isolated antigen binding protein of claim 5, comprising either: (a) a light chain variable domain sequence selected from the group consisting of: L1-L11 of SEQ ID NOs:17-27; (b) a heavy chain variable domain sequence selected from the group consisting of: H1-H11 of SEQ ID NOs: 28-38; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b), wherein the antigen binding protein specifically binds to β -Klotho.

The light chain variable domain and a heavy chain variable domain can be selected from the group of combinations consisting of: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10 and L11H11, wherein the antigen binding protein specifically binds to β -Klotho.

In some embodiments the antigen binding protein further comprises: (a) the light chain constant sequence of SEQ ID NO: 13; (b) the light chain constant sequence of SEQ ID NO:15; (c) the heavy chain constant sequence of SEQ ID NO: 9; or (d) the light chain constant sequence of SEQ ID NO: 13 or SEQ ID NO: 15 and the heavy chain constant sequence of SEQ ID NO: 9 .

The antigen binding protein of can be selected from the group consisting of a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an F(fa')_x fragment, a domain antibody, an IgD antibody, an IgE antibody, and IgM antibody, and IgG1 antibody, and IgG2 antibody, and IgG3 antibody, and IgG4 antibody, and IgG4 antibody having at least one mutation in the hinge region.

Also provided is an antigen binding protein that, when bound to β -Klotho: (a) binds to β -Klotho with substantially the same K_d as a reference antibody; (b) induces FGF21-like signaling of 10 % or greater than the signaling induced by a wild-type FGF21 standard comprising the mature form of SEQ ID NO:2 as measured in an ELK-luciferase reporter

assay; (c) exhibits an EC50 of 10nM or less of FGF21-like signaling in an assay selected from the group consisting of: (i) a FGFR1c/ β Klotho-mediated *in vitro* recombinant cell-based assay; (d) exhibits an EC50 of less than 10nM of agonistic activity on FGFR1c in the presence of β Klotho in an *in vitro* recombinant FGFR1c receptor mediated reporter assay; and (e) an EC50 of greater than 1 μ M of agonistic activity on FGFR1c in the absence of β Klotho in an *in vitro* recombinant FGFR1c receptor mediated reporter assay; (f) competes for binding with a reference antibody to β -Klotho,

wherein the reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10 and L11H11.

Also provided is a polypeptide comprising a sequence selected from the group consisting of: TRLWKYWV (SEQ ID NO: 184); RRLYIFWE (SEQ ID NO: 185); YKAWGYV (SEQ ID NO: 186); YQAWGYV (SEQ ID NO: 187); YQAWGYLV (SEQ ID NO: 188); YQAWGYFV (SEQ ID NO: 189); FTWVFWNV (SEQ ID NO: 190); YQVWGYFV (SEQ ID NO: 191); YKWLKWNL (SEQ ID NO: 192); RRLYIFEW (SEQ ID NO: 193); WAERGG (SEQ ID NO: 194); GGWAVGRI (SEQ ID NO: 195); YKYLFWV (SEQ ID NO: 196); YKYLFWV (SEQ ID NO: 197); YKTAWYWK (SEQ ID NO: 198); YVFHKWWV (SEQ ID NO: 199); YVFYLWWK (SEQ ID NO: 200); YRWLHWHV (SEQ ID NO: 201); YKFLFWHA (SEQ ID NO: 202); RRQWGFV (SEQ ID NO: 203); YSAWSFV (SEQ ID NO: 204); LARWGFV (SEQ ID NO: 205); YDAWGYV (SEQ ID NO: 206); WRKYHFWVS (SEQ ID NO: 207); KRLYGLFWYD (SEQ ID NO: 208); KKHWSLFFE (SEQ ID NO: 209); KAWPYSWEAV (SEQ ID NO: 210); EWYCGVLFNCQQ (SEQ ID NO: 211); HFGCGVIFNCVSD (SEQ ID NO: 212); WELCASGYGWCYLH (SEQ ID NO: 213); APSCKSYIGFGLYHCWDG (SEQ ID NO: 214); and HFKCGMGLFECADP (SEQ ID NO: 215).

Also provided is an antigen binding protein heavy chain comprising a peptide that specifically binds to one or more of FGFR1c, FGFR2c, FGFR3c, FGFR4. In one embodiment the antigen binding protein heavy chain comprises a peptide sequence selected from the group consisting of: TRLWKYWV (SEQ ID NO: 184); RRLYIFWE (SEQ ID NO: 185); YKAWGYV (SEQ ID NO: 186); YQAWGYV (SEQ ID NO: 187); YQAWGYLV (SEQ ID NO: 188); YQAWGYFV (SEQ ID NO: 189); FTWVFWNV (SEQ ID NO: 190); YQVWGYFV (SEQ ID NO: 191); YKWLKWNL (SEQ ID NO: 192); RRLYIFEW (SEQ ID NO: 193); WAERGG (SEQ ID NO: 194); GGWAVGRI (SEQ ID NO: 195); YKYLFWV

(SEQ ID NO: 196); YKYLSYWV (SEQ ID NO: 197); YKTAWYWK (SEQ ID NO: 198); YVFHKWWV (SEQ ID NO: 199); YVFYLWWK (SEQ ID NO: 200); YRWLHWHV (SEQ ID NO: 201); YKFLFWHA (SEQ ID NO: 202); RRQWGFVV (SEQ ID NO: 203); YSAWSFWV (SEQ ID NO: 204); LARWGFVV (SEQ ID NO: 205); YDAWGYWV (SEQ ID NO: 206); WRKYYHFWVS (SEQ ID NO: 207); KRLYGLFWYD (SEQ ID NO: 208); KKHWSLFFE (SEQ ID NO: 209); KAWPYSWEAV (SEQ ID NO: 210); EWYCGVLFNCQQ (SEQ ID NO: 211); HFGCGVIFNCVSD (SEQ ID NO: 212); WELCASGYGWCYLH (SEQ ID NO: 213); APSCKSYIGFGLYHCWDG (SEQ ID NO: 214); and HFKCGMGLFECADP (SEQ ID NO: 215). The antigen binding protein heavy chain can comprise a CH2 loop, a CH3 loop or both a CH2 and a CH3 loop. In various embodiments the heavy chain comprises a CH3 loop, and the CH3 loop can comprise the peptide. In other embodiments the heavy chain comprises a CH2 loop and the CH2 loop can comprise the peptide.

In still another embodiment an antigen binding protein can comprise the heavy chain comprising the peptide and in a further embodiment the antigen binding protein's heavy chain comprises a heavy chain CDR3 sequence comprising a sequence selected from the group consisting of: (i) a heavy chain CDR3 sequence that differs by no more than one amino acid additions, substitutions, deletions, and combinations thereof, from a CDR3 sequence of H1-H11, SEQ ID NOs:28-38; (ii) GWFDX₆ (SEQ ID NO: 178); (iii) GTSFDY (SEQ ID NO: 99); (iv) YGGSFDY (SEQ ID NO: 100); (v) MVYVLDY (SEQ ID NO: 101); (vi) VAGPFDF (SEQ ID NO: 102); wherein X₆ is Y, I or F; and wherein the antigen binding protein specifically binds to β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, FGFR4.

In an additional embodiment the antigen binding protein further comprises: (a) a heavy chain CDR1 sequence selected from the group consisting of: (i) a heavy chain CDR1 sequence that differs by no more than three amino acid additions, substitutions, deletions, and combinations thereof, from a CDR1 sequence of H1-H11, SEQ ID NOs:28-38; (ii) X₁₉YX₂₀MX₂₁ wherein X₁₉ is A, G, R, S, T, or I; X₂₀ is Y, G or A; and X₂₁ is H or S; (b) a heavy chain CDR2 selected from the group consisting of: (i) a heavy chain CDR2 sequence that differs by no more than five amino acid additions, substitutions, and /or deletions from a CDR2 sequence of H1-H11, SEQ ID NOs:28-38; (ii) WINPX₇SGGTNSAQKFQG (SEQ ID NO: 179); (iii) VIX₈X₉DGX₁₀X₁₁X₁₂YYADSVKG (SEQ ID NO: 180); (iv) X₁₃ISGX₁₄GX₁₅X₁₆TYADSVKG (SEQ ID NO: 181); (v)

VIX₁₇YDGRNKYX₁₈ADSVKG (SEQ ID NO: 182) wherein X₇ is N or Y; X₈ is W or G; X₉ is F or Y; X₁₀ is R or S; X₁₁ is N or Y; X₁₂ is Q or K; X₁₃ is A or D; X₁₄ is S or R; X₁₅ is V or G; X₁₆ is S or Y; X₁₇ is W or S; and X₁₈ is Y or H; and wherein the antigen binding protein specifically binds to β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, FGFR4. In another embodiment the antigen binding protein comprises (a) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence selected from SEQ ID NOs:83-88; (ii) a heavy chain CDR2 sequence selected from SEQ ID NOs:89-97; and (iii) a heavy chain CDR3 sequence selected from SEQ ID NOs:98-105; or wherein the antigen binding protein specifically binds to β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, FGFR4. In still another embodiment the antigen binding protein comprises (a) a heavy chain variable domain sequence selected from the group consisting of: (i) a sequence of amino acids that is at least 80% identical to a heavy chain variable domain sequence of H1-H11 of SEQ ID NOs:28-38; (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the heavy chain variable domain sequence of H1-H11, SEQ ID NOs: 28-38; wherein the antigen binding protein specifically binds to β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, FGFR4. The isolated antigen binding protein can comprise: (a) a heavy chain variable domain sequence selected from the group consisting of: H1-H11, SEQ ID NOs:28-38; wherein the antigen binding protein specifically binds to β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, FGFR4.

Also provided is an isolated antigen binding protein that specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In one embodiment the heavy chain of the antigen binding protein comprises a sequence selected from the group consisting of: TRLWKYWV (SEQ ID NO: 184); RRLYIFWE (SEQ ID NO: 185); YKAWGYV (SEQ ID NO: 186); YQAWGYV (SEQ ID NO: 187); YQAWGYLV (SEQ ID NO: 188); YQAWGYFV (SEQ ID NO: 189); FTWVFWNV (SEQ ID NO: 190); YQVWGYFV (SEQ ID NO: 191); YKWLKWNL (SEQ ID NO: 192); RRLYIFEW (SEQ ID NO: 193); WAERGG (SEQ ID NO: 194); GGWAVGRI (SEQ ID NO: 195); YKYLFWV (SEQ ID NO: 196); YKYLSYV (SEQ ID NO: 197); YKTAWYWK (SEQ ID NO: 198); YVFHKWWV (SEQ ID NO: 199); YVFYLWWK (SEQ ID NO: 200); YRWLHWHV (SEQ ID NO: 201); YKFLFWHA (SEQ ID NO: 202); RRQWGFV (SEQ ID NO: 203); YSAWSFV (SEQ ID NO: 204); LARWGFV (SEQ ID NO: 205); YDAWGYV (SEQ ID NO: 206); WRKYHFWVS (SEQ ID NO: 207); KRLYGLFWYD (SEQ ID NO: 208);

KKHWSSLFFE (SEQ ID NO: 209); KAWPYSWEAV (SEQ ID NO: 210); EWYCGVLFNCQQ (SEQ ID NO: 211); HFGCGVIFNCVSD (SEQ ID NO: 212); WELCASGYGWCYLH (SEQ ID NO: 213); APSCKSYIGFGLYHCWDG (SEQ ID NO: 214); and HFKCGMGLFECADP (SEQ ID NO: 215).

In a further embodiment the antigen binding protein comprises an amino acid sequence selected from the group consisting of: (a) a light chain CDR3 comprising a sequence selected from the group consisting of: (i) a light chain CDR3 sequence that differs by no more than two amino acid additions, substitutions, deletions, and combinations thereof, from a CDR3 sequence of L1-L11, SEQ ID NOs:17-27; (ii) MQAX₁EFPWT (SEQ ID NO: 174); (iii) GTWDSSLX₂VX₃ (SEQ ID NO: 175); (iv) QQYDNLFT (SEQ ID NO: 122); (v) QQYGSAPLT (SEQ ID NO: 123); (vi) VLYMGSGIWV (SEQ ID NO: 124); (vii) ETWDSSLSAGV (SEQ ID NO: 127); wherein X₁ is L or I; X₂ is V or A; and X₃ is V or A; (b) a heavy chain CDR3 sequence comprising a sequence selected from the group consisting of: (i) a heavy chain CDR3 sequence that differs by no more than one amino acid additions, substitutions, deletions, and combinations thereof, from a CDR3 sequence of H1-H11, SEQ ID NOs:28-38; (ii) GWFDX₆ (SEQ ID NO: 178); (iii) GTSFYD (SEQ ID NO: 99); (iv) YGGSFYD (SEQ ID NO: 100); (v) MVYVLDY (SEQ ID NO: 101); (vi) VAGPFDF (SEQ ID NO: 102); wherein X₆ is Y, I or F; (c) the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b) and the Fc sequence of (c) and wherein the antigen binding protein specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In another embodiment the antigen binding protein comprises either: (a) a light chain CDR1 sequence selected from the group consisting of: (i) a light chain CDR1 sequence that differs by no more than two amino acid additions, substitutions, deletions, and combinations thereof, from a CDR1 sequence of L1-L11, SEQ ID NOs:27-37; (ii) RSSQSLVX₂₂YX₂₃DGNTYLS (SEQ ID NO: 177) (iii) SGSSSNIGNNYVS (SEQ ID NO: 107); (iv) QASQDINNYLN (SEQ ID NO: 108); (v) RASQSVSGNYLA (SEQ ID NO: 109); (vi) GVSSGSVSTRYYPS (SEQ ID NO: 110); wherein X₂₂ is H or absent; and X₂₃ is S or absent; (b) a light chain CDR2 sequence selected from the group consisting of: (i) a light chain CDR2 sequence that differs by no more than two amino acid additions, substitutions, deletions, and combinations thereof, from a CDR2 sequence of L1-L11, SEQ ID NOs:17-27; (ii) KISNRFS (SEQ ID NO: 112); (iii) DNNX₄RPX₅ (SEQ ID NO: 176); (iv) DTSNLET (SEQ ID NO: 114); (v) GASSRAT (SEQ ID NO: 115); (vi) STNTRSS (SEQ ID NO: 116);

wherein X_4 is K, N or R; and X_5 is S or absent; (c) a heavy chain CDR1 sequence selected from the group consisting of: (i) a heavy chain CDR1 sequence that differs by no more than three amino acid additions, substitutions, deletions, and combinations thereof, from a CDR1 sequence of H1-H11, SEQ ID NOs:28-38; (ii) $X_{19}YX_{20}MX_{21}$ wherein X_{19} is A, G, R, S, T, or I; X_{20} is Y, G or A; and X_{21} is H or S; (d) a heavy chain CDR2 selected from the group consisting of: (i) a heavy chain CDR2 sequence that differs by no more than five amino acid additions, substitutions, and /or deletions from a CDR2 sequence of H1-H11, SEQ ID NOs:28-38; (ii) WINPX₇SGGTNSAQKFQG (SEQ ID NO: 179) (iii) VIX₈X₉DGX₁₀X₁₁X₁₂YYADSVKG; (SEQ ID NO: 180); (iv) X₁₃ISGX₁₄GX₁₅X₁₆TTYADSVKG (SEQ ID NO: 181); (v) VIX₁₇YDGRNKYX₁₈ADSVKG (SEQ ID NO: 182); wherein X_7 is N or Y; X_8 is W or G; X_9 is F or Y; X_{10} is R or S; X_{11} is N or Y; X_{12} is Q or K; X_{13} is A or D; X_{14} is S or R; X_{15} is V or G; X_{16} is S or Y; X_{17} is W or S; and X_{18} is Y or H; (e) the light chain CDR1 of (a) and the light chain CDR2 of (b); (f) the light chain CDR1 of (a) and the heavy chain CDR1 of (c); (g) the light chain CDR1 of (a) and the heavy chain CDR2 of (d); (h) the light chain CDR1 (b) and the heavy chain CDR1 of (c); (i) the heavy chain CDR1 of (c) and the heavy chain CDR2 of (d); (j) the light chain CDR2 of (b) and the heavy chain CDR2 of (d); (k) the light chain CDR1 of (a), the light chain CDR2 of (b), and the heavy chain CDR1 of (c); (l) the light chain CDR2 of (b), the heavy CDR1 of (c), and the heavy chain CDR2 of (d); (m) the light chain CDR1 of (a), the heavy chain CDR1 of (c), and the heavy chain CDR2 of (d); or (n) the light chain CDR1 of (a), the light chain CDR2 of (b), the heavy chain CDR2 of (c), and the heavy chain CDR2 of (d), wherein said antigen binding protein specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In a further embodiment the antigen binding protein comprises (a) a light chain variable domain comprising: (i) a light chain CDR1 sequence selected from SEQ ID NOs:106-111; (ii) a light chain CDR2 sequence selected from SEQ ID NOs:112-119; (iii) a light chain CDR3 sequence selected from SEQ ID NOs:120-127; and (b) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence selected from SEQ ID NOs:83-88; (ii) a heavy chain CDR2 sequence selected from SEQ ID NOs:89-97; and (iii) a heavy chain CDR3 sequence selected from SEQ ID NOs:98-105; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b), wherein the antigen binding protein specifically binds β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In yet another embodiment the antigen binding protein comprises (a) a light chain variable domain sequence selected from the group consisting of: (i) amino acids having a sequence at least 80% identical to a light chain variable domain sequence selected from L1-L11, SEQ ID NOs:17-27; (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the light chain variable domain sequence of L1-L11, SEQ ID NOs:17-27; (b) a heavy chain variable domain sequence selected from the group consisting of: (i) a sequence of amino acids that is at least 80% identical to a heavy chain variable domain sequence of H1-H11 of SEQ ID NOs:28-38; (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding the heavy chain variable domain sequence of H1-H11, SEQ ID NOs: 28-38; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein the antigen binding protein specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In a further embodiment the antigen binding protein comprises (a) a light chain variable domain sequence selected from the group consisting of: L1-L11 of SEQ ID NOs:17-27; (b) a heavy chain variable domain sequence selected from the group consisting of: H1-H11 of SEQ ID NOs:28-38; or (c) the light chain variable domain of (a) and the heavy chain variable domain of (b), wherein the antigen binding protein specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In still another embodiment the the light chain variable domain and a heavy chain variable domain of the antigen binding protein are selected from the group of combinations consisting of: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10 and L11H11 wherein the antigen binding protein specifically binds to β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In a further embodiment the antigen binding protein comprises (a) the light chain constant sequence of SEQ ID NO: 13; (b) the light chain constant sequence of SEQ ID NO:15; (c) the heavy chain constant sequence of SEQ ID NO: 9; or (d) the light chain constant sequence of SEQ ID NO: 13 or SEQ ID NO: 15 and the heavy chain constant sequence of SEQ ID NO: 9.

In embodiments the antigen binding protein of can be selected from the group consisting of a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an

F(fa')x fragment, a domain antibody, an IgD antibody, an IgE antibody, and IgM antibody, and IgG1 antibody, and IgG2 antibody, and IgG3 antibody, and IgG4 antibody, and IgG4 antibody having at least one mutation in the hinge region.

Also provided is an antigen binding protein that, when bound to β -Klotho: (a) binds to β -Klotho with substantially the same K_d as a reference antibody; (b) induces FGF21-like signaling of 10 % or greater than the signaling induced by a wild-type FGF21 standard comprising the mature form of SEQ ID NO:2 as measured in an ELK-luciferase reporter assay; (c) exhibits an EC_{50} of 10nM or less of FGF21-like signaling in an assay selected from the group consisting of: (i) a FGFR1c/ β Klotho-mediated *in vitro* recombinant cell-based assay; (d) exhibits an EC_{50} of less than 10nM of agonistic activity on FGFR1c in the presence of β Klotho in an *in vitro* recombinant FGFR1c receptor mediated reporter assay; and (e) an EC_{50} of greater than 1 μ M of agonistic activity on FGFR1c in the absence of β Klotho in an *in vitro* recombinant FGFR1c receptor mediated reporter assay; (f) competes for binding with a reference antibody to β -Klotho, wherein the reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10 and L11H11. The disclosed antigen binding proteins can be of therapeutic use and in embodiments, the antigen binding proteins, when bound to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 (a) lower blood glucose in an animal model; (b) lower serum lipid levels in an animal model; or (c) (a) and (b).

Pharmaceutical compositions comprising the disclosed antigen binding protein in admixture with a pharmaceutically acceptable carrier thereof are also provided. In one embodiment, the pharmaceutical composition can comprise an additional active agent that is selected from the group consisting of a radioisotope, radionuclide, a toxin, or a therapeutic and a chemotherapeutic group.

A method of producing an antigen binding protein that specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 is provided. In one embodiment the method comprises incubating the disclosed host cell under conditions that allow it to express the antigen binding protein.

A method of preventing or treating a condition in a subject in need of such treatment is also provided. In one embodiment, the method comprises administering a therapeutically effective amount of a disclosed pharmaceutical composition to the subject, wherein the condition is treatable by lowering blood glucose. The condition can be selected from, *e.g.*,

type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

Generally, a method of preventing or treating a condition in a subject in need of such treatment, wherein the condition is treatable by lowering blood glucose. In one embodiment the method comprises administering a therapeutically effective amount of a pharmaceutical composition disclosed herein to the subject. The condition can be selected from, *e.g.*, type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

One embodiment includes expression systems, including cell lines, for the production of antigen binding proteins that bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, and methods for diagnosing and treating diseases related to human FGF21.

In yet another aspect, the isolated antigen-binding protein can compete for binding to one or more of the human or non-human forms of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, *e.g.*, the extracellular portion(s) of β -Klotho, FGFR1c, FGFR2c, FGFR3c, or FGFR4, with one of the disclosed antigen binding proteins.

In one embodiment, the isolated antigen binding protein is effective to lower plasma glucose levels, lower circulating triglycerides, cholesterol levels, improve lipoprotein abnormality and substantially improve cardiovascular risk factor profile, when administered to a patient with type 2 diabetes or other metabolic diseases.

In another aspect the isolated antigen binding protein specifically or selectively binds to β -Klotho, *e.g.*, human β -Klotho, and in another aspect the isolated antigen binding protein binds to β -Klotho, *e.g.*, β -Klotho, and induces FGF21-like signaling.

In another aspect the isolated antigen binding protein specifically or selectively binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and induces FGF21-like signaling.

In another aspect, the isolated antigen-binding protein specifically or selectively binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, and does not specifically or selectively bind to α -Klotho, FGFR2c, FGFR3c, or FGFR4.

In another aspect the isolated antigen binding protein specifically or selectively binds to a complex comprising β -Klotho, *e.g.*, human β -Klotho, and FGFR1c, *e.g.*, human FGFR1c, and in another aspect the isolated antigen binding protein binds to such a complex and induces FGF21-like signaling.

In a further aspect, also provided are isolated nucleic acid molecules that encode the antigen binding proteins disclosed herein. In some instances, the isolated nucleic acid molecules are operably-linked to a control sequence.

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

In another aspect, also provided are methods of preparing antigen binding proteins that specifically or selectively bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, FGFR4 and includes the step of preparing the antigen binding protein from a host cell that secretes the antigen binding protein.

Other embodiments further provide a method for treating or preventing a condition associated with FGF21 in a patient, comprising administering to a patient an effective amount of at least one isolated antigen-binding protein. In one embodiment, the condition is diabetes, in another embodiment the condition is obesity and in another embodiment the condition is dyslipidemia.

Also provided is an antigen binding protein-FGF21 fusion. In one embodiment the antigen binding protein-FGF21 fusion comprises (a) an antigen binding component; and (b) an FGF21 component. The antigen binding protein-FGF21 fusion can comprise any of the antigen binding component provided herein. In some embodiments the FGF21 component of the antigen binding protein-FGF21 fusion comprises at least 25 consecutive residues of SEQ ID NO:341. In other embodiments the FGF21 component of the antigen binding protein-FGF21 fusion comprises one of (a) SEQ ID NO:342 and (b) SEQ ID NO:343. The antigen binding protein-FGF21 fusion can further comprise a linker. In yet another embodiment the antigen binding protein-FGF21 fusion (a) the antigen binding component comprises 2G10; and (b) an FGF21 component selected from the group consisting of (i) SEQ ID NO: 342; and (ii) SEQ ID NO: 343. In one embodiment of the antigen binding protein-FGF21 fusion the antigen binding component is joined to the FGF21 component by a linker selected from the group consisting of $(G_4S)_3$, (SEQ ID NO: 336) $(G_4S)_6$ (SEQ ID NO: 337), $(G_4S)_9$ (SEQ ID NO: 338), $(G_4S)_{12}$ (SEQ ID NO: 339) and $(G_4S)_{15}$ (SEQ ID NO: 340). In still another embodiment the FGF21 component is joined to the heavy chain of the 2G10 antigen binding component. In particular embodiments the heavy chain of the antigen binding protein-FGF21 fusion comprises an amino acid sequence selected from the group consisting of SEQ ID

NOs:316, 320, 322, 324, 326, 318, 328, 330, 332 and 334. Alternatively the FGF21 component can be joined to the light chain of the 2G10 antigen binding component.

The provided antigen binding protein-FGF21 fusions can have various biological activities. In some embodiments, an antigen binding protein-FGF21 fusion can, when bound to β -Klotho, or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4: (a) lower blood glucose in an animal model; (b) lower serum lipid levels in an animal model; or (c) both (a) and (b).

Also provided is an isolated nucleic acid encoding the light chain, the heavy chain or both of the antigen binding component of an antigen binding protein-FGF21 fusion, wherein the sequence is selected from L1-L11, SEQ ID NOs:17-27; H1-H11, SEQ ID NOs: 28-38, and SEQ ID NOs: 316, 320, 322, 324, 326, 318, 328, 330, 332 and 334. Expression vectors comprising the disclosed nucleic acids, as well as isolated cells comprising the disclosed nucleic acids and expression vectors comprising the nucleic acids are also provided.

Also provided is a pharmaceutical composition comprising an antigen binding protein-FGF21 fusion disclosed herein, further comprising a pharmaceutically acceptable carrier. A method of preventing or treating a condition in a subject in need of such treatment is provided, and in one embodiment comprises administering a therapeutically effective amount of a pharmaceutical composition comprising an antigen binding protein-FGF21 fusion to the subject, wherein the condition is treatable by lowering blood glucose. In various embodiments the condition is selected from type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1a-1b is an alignment showing the sequence homology between human FGFR1c (GenBank Accession No P11362; SEQ ID NO: 305) and murine FGFR1c (GenBank Accession No NP_034336; SEQ ID NO: 306); various features are highlighted,

including the signal peptide, transmembrane sequence, heparin binding region and a protein kinase domain, and a consensus sequence (SEQ ID NO: 307) is provided.

Figure 2a-2c is an alignment showing the sequence homology between human β -Klotho (GenBank Accession No NP_783864; SEQ ID NO: 308) and murine β -Klotho (GenBank Accession No NP_112457; SEQ ID NO: 309); various features are highlighted, including the transmembrane sequence and two glycosyl hydrolase domains, and a consensus sequence (SEQ ID NO: 310) is provided.

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

Figure 4 is a sequence (SEQ ID NO: 311) showing an immunogen used to generate antigen binding proteins comprising the extracellular domain (ECD) of human FGFR1c fused to an IgG1 Fc via a Gly₅ linker (SEQ ID NO: 304); the FGFR1c component is in capitals, the linker is italic and underlined and the Fc is in lower case letters.

Figure 5 is a sequence (SEQ ID NO: 312) showing an immunogen used to generate antigen binding proteins comprising the extracellular domain (ECD) of human β -Klotho fused to an IgG1 Fc via a Gly₅ linker (SEQ ID NO: 304); the β -Klotho component is in capitals, the linker is italic and underlined and the Fc is in lower case letters.

Figure 6 is a SDS PAGE gel showing the level of purity achieved from preparations of a soluble FGF21 receptor complex comprising FGFR1c ECD-Fc and β -Klotho ECD-Fc, which was employed as an immunogen to generate antigen binding proteins.

Figure 7 is a table showing the calculated pI for β -Klotho binding proteins 10H3, 1A2, 1B5, 3B4, 9D10, 3F4, 1C10, 2G10 and 8F9.

Figure 8 is an alignment showing some of the structural features identified in the heavy and light chains of some of the disclosed β -Klotho binding proteins. Light chain sequences disclosed as residues 1-112 of SEQ ID NO: 23, residues 1-112 of SEQ ID NO: 24, residues 1-112 of SEQ ID NO: 22, residues 1-112 of SEQ ID NO: 17, residues 1-110 of SEQ ID NO: 26, residues 1-110 of SEQ ID NO: 27, SEQ ID NO: 313, residues 1-110 of SEQ ID NO: 25 and residues 1-110 of SEQ ID NO: 18. Heavy chain sequences disclosed as residues 1-118 of SEQ ID NO: 34, residues 1-118 of SEQ ID NO: 35, residues 1-118 of SEQ ID NO: 33, residues 1-118 of SEQ ID NO: 28, SEQ ID NO: 314, residues 1-120 of SEQ ID NO: 38, residues 1-120 of SEQ ID NO: 37, residues 1-120 of SEQ ID NO: 36 and residues 1-120 of SEQ ID NO: 29.

Figures 9A and 9B depict the results of binding studies performed on the antigen binding proteins 1A2, 1B5, 2G10, 3B4, 3E10, 3F4, 8F9, 9D10 and 10H3; Figure 9A is a series of traces from binding assays demonstrating the binding of the β -Klotho binding proteins to β -Klotho; Figure 9B is a table showing the binding constants generated in the binding assays.

Figure 10 is a series of traces from competitive binding assays performed using some of the disclosed β -Klotho binding proteins.

Figure 11 is a table summarizing the binding properties of the β -Klotho-binding antigen binding proteins 3B4, 1A2, 1B5, 10H3, 9D10, 2G10, 3F4 and 8F9.

Figure 12 is a table summarizing the sequences and properties of FGFR1c-binding peptides Rm26 (SEQ ID NO: 211), Rm27 (SEQ ID NO: 212), Rm33 (SEQ ID NO: 213), Rm37 (SEQ ID NO: 214), Rm40 (SEQ ID NO: 215) and SR4 (SEQ ID NO: 187).

Figure 13 is a series of plots depicting the results of a series of binding assays that demonstrate that the bispecific antigen binding proteins 1A2-Rm26, 1A2-SR4, 2G10-Rm26, 2G10-Rm40, 2G10-SR4 bind to both human and murine β -Klotho and FGFR1c, that the antigen binding proteins 1A2-Rm40 and 2G10-Rm40 bind to both human and murine β -Klotho and that the peptides Rm26, Rm40 and SR4 bind to human and murine FGFR1c.

Figure 14 is a series of plots depicting the results of a series of luciferase assays performed on antigen binding proteins 1A2-Rm26, 1A2-Rm40, 1A2-SR4, 2G10-Rm26, 2G10Rm40, 2G10SR4, the antigen binding proteins 1A2 and 2G10, and the peptides Rm26, Rm40, SR4 and KRm2, demonstrating that bispecific antigen binding protein 2G10-SR4 showed agonistic activities in β -Klotho/FGFR1c cell line, but not in a FGFR1c cell line; the left panel shows the results of a luciferase assay using AMID reporter cells expressing β -Klotho and FGFR1c shows agonist activity of 2G10-SR4, and the right panel shows the results of a luciferase assay using AMID reporter cells expressing FGFR1c.

Figure 15 is a series of plots depicting the results of a series of luciferase assays that demonstrate that bispecific antigen binding protein 2G10-SR4 showed agonistic (left panel) and antagonistic activity (right panel) in a β -Klotho/FGFR1c cell line; the left panel shows the results of a luciferase assay using AMID reporter cells expressing β -Klotho and FGFR1c and demonstrating the agonist activity of 2G10-SR4, and the right panel shows that when incubated along with 3nM FGF21, 2G10-SR4 and SR4 demonstrated antagonistic activity.

Figure 16 is a plot depicting the results of a series of binding assays demonstrating that antigen binding protein fusions comprising the anti- β -Klotho antibody 2G10, joined via a

linker, to a truncated form FGF21 comprising either residues 1-169 (SEQ ID NO: 342), when the configuration of the fusion is FGF21-linker-2G10 (from N- to C-terminus) residues or residues 1-170 (SEQ ID NO: 343) when the configuration of the fusion is 2G10-linker-FGF21 (from N-to C-terminus), bind to murine β -Klotho.

Figure 17 is a plot depicting the results of a series of binding assays demonstrating that antigen binding protein fusions comprising the anti- β -Klotho antibody 2G10, joined via a linker, to a truncated form of FGF21 comprising either residues 1-169 (SEQ ID NO: 342), when the configuration of the fusion is FGF21-linker-2G10 (from N- to C-terminus) residues or residues 1-170 (SEQ ID NO: 343) when the configuration of the fusion is 2G10-linker-FGF21 (from N-to C-terminus), bind to human β -Klotho.

Figure 18 is a plot depicting the results of luciferase assays demonstrating that the activity of antigen binding protein fusions comprising the anti- β -Klotho antibody 2G10, joined via a linker, to a truncated form of FGF21 comprising either residues 1-169 (SEQ ID NO: 342), when the configuration of the fusion is FGF21-linker-2G10 (from N- to C-terminus) residues or residues 1-170 (SEQ ID NO: 343) when the configuration of the fusion is 2G10-linker-FGF21 (from N-to C-terminus), is dependent on the orientation for the FGF21 component and is independent of linker length in a luciferase assay using AMID reporter cells expressing β -Klotho and FGFR1c in the absence of FGF21.

Figure 19 is a plot depicting the results of a series of luciferase assays that demonstrate that antigen binding protein fusions comprising the anti- β -Klotho antibody 2G10, joined via a linker, to a truncated form of FGF21 comprising either residues 1-169 (SEQ ID NO: 342), when the configuration of the fusion is FGF21-linker-2G10 (from N- to C-terminus) residues or residues 1-170 (SEQ ID NO: 343) when the configuration of the fusion is 2G10-linker-FGF21 (from N-to C-terminus), show no detectable antagonistic activity in a luciferase assay using AMID reporter cells expressing β -Klotho and FGFR1c when incubated with 3nM FGF21.

Figure 20 is a plot depicting the results of a series of luciferase assays that demonstrate that antigen binding protein fusions comprising the anti- β -Klotho antibody 2G10, joined via a linker, to a truncated form of FGF21 comprising either residues 1-169 (SEQ ID NO: 342), when the configuration of the fusion is FGF21-linker-2G10 (from N- to C-terminus) residues or residues 1-170 (SEQ ID NO: 343) when the configuration of the fusion is 2G10-linker-FGF21 (from N-to C-terminus), show no detectable activity in a

luciferase assay using AMID reporter cells expressing β -Klotho and FGFR1c when incubated with 3nM α -Klotho in the absence of FGF21.

Figure 21 is a plot depicting the results of a series of luciferase assays that demonstrate that antigen binding protein fusions comprising the anti- β -Klotho antibody 2G10, joined via a linker, to a truncated form of FGF21 comprising either residues 1-169 (SEQ ID NO: 342), when the configuration of the fusion is FGF21-linker-2G10 (from N- to C-terminus) residues or residues 1-170 (SEQ ID NO: 343) when the configuration of the fusion is 2G10-linker-FGF21 (from N-to C-terminus), show no detectable activity in a luciferase assay using AMID reporter cells expressing FGFR1c but not β -Klotho in the absence of FGF21.

DETAILED DESCRIPTION

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Unless otherwise defined herein, scientific and technical terms used in connection with the present application shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present application are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. *See, e.g.,* Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001), Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical

chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

It should be understood that the instant disclosure is not limited to the particular methodology, protocols, and reagents, etc., described herein and as such can vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present disclosure.

Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term “about.” The term “about” when used in connection with percentages can mean $\pm 5\%$, *e.g.*, 1%, 2%, 3%, 4% or 5%.

DEFINITIONS

As used herein, the terms “a” and “an” mean “one or more” unless specifically stated otherwise.

An “antigen binding protein” is a protein comprising a portion that specifically binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include 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 antigen 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 antigen 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.

An antigen binding protein can have, for example, the structure of a naturally occurring immunoglobulin. An “immunoglobulin” is a tetrameric molecule. In a naturally

occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one “light” (about 25 kDa) and one “heavy” chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody’s isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a “J” region of about 12 or more amino acids, with the heavy chain also including a “D” region of about 10 more amino acids. See generally, *Fundamental Immunology*, Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

Naturally occurring immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat et al. in *Sequences of Proteins of Immunological Interest*, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. As desired, the CDRs can also be redefined according an alternative nomenclature scheme, such as that of Chothia (see Chothia & Lesk, 1987, *J. Mol. Biol.* 196:901-917; or Chothia *et al.*, 1989, *Nature* 342:878-883).

An antigen binding protein or antigen binding protein-FGF21 fusion is said to “specifically bind” its target antigen when the dissociation constant (K_D) is $\leq 10^{-8}$ M. The antigen binding protein or antigen binding protein-FGF21 fusion specifically binds antigen with “high affinity” when the K_D is $\leq 5 \times 10^{-9}$ M, and with “very high affinity” when the K_D is $\leq 5 \times 10^{-10}$ M. In one embodiment, an antigen binding protein or antigen binding protein-FGF21 fusion will bind to β -Klotho (for example human β -Klotho) or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c or FGFR4, (for example, human β -Klotho, human FGFR1c, human FGFR2c, human FGFR3c, or human FGFR4), with a K_D of between about 10^{-7} M and 10^{-12} M, and in yet another embodiment the antigen binding proteins or antigen binding protein-FGF21 fusions will bind with a $K_D \leq 5 \times 10^{-9}$ M.

As used herein the term “antigen binding protein-FGF21 fusion” means a polypeptide comprising (a) an antigen binding protein component comprising an “antigen binding protein,” as defined herein, that specifically binds to β -Klotho or to a β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c or FGFR4; and (b) an FGF21 component comprising FGF21 or a fragment thereof. The β -Klotho polypeptide can be derived from any species, for example human, mouse or rat. Similarly, the FGF21 polypeptide can be derived from any species, for example human, mouse or rat. The antigen binding protein can comprise any antigen binding protein that specifically binds to β -Klotho, including the antigen binding proteins described herein in Tables 1-3 and 6.

The FGF21 polypeptide component can comprise a truncated form of the full length (SEQ ID NO:2) or mature (SEQ ID NO: 341) FGF21 polypeptide sequence. The FGF21 polypeptide sequence can be truncated at the C-terminus, the N-terminus or both the C-terminus and can range in length from 180 or fewer amino acids to 25 or more amino acids, for example 180, 179, 178, 177, 176, 175, 174, 173, 172, 171, 170, 169, 168, 167, 166, 165, 160, 155, 150, 145, 140, 135, 130, 125, 120, 115, 110, 105, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30 or 25 amino acids.

A linker can be employed to join the antigen binding protein component to the FGF21 component. Any convenient linker can be employed, for example a linker of the form (Gly_xSer)_y (SEQ ID NO: 335), wherein x and y are independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more. Specific examples of linkers include (G₄S)₃ (SEQ ID NO: 336), (G₄S)₆ (SEQ ID NO: 337), (G₄S)₉ (SEQ ID NO: 338), (G₄S)₁₂ (SEQ ID NO: 339), and (G₄S)₁₅ (SEQ ID NO: 340).

Specific examples of antigen binding protein-FGF21 fusions include human FGF21 (1-169)-(G₄S)₃-2G10 (SEQ ID NO:316), human FGF21 (1-169)-(G₄S)₆-2G10 (SEQ ID NO:320), human FGF21 (1-169)-(G₄S)₉-2G10 (SEQ ID NO:322), human FGF21 (1-169)-(G₄S)₁₂-2G10 (SEQ ID NO:324), human FGF21 (1-169)-(G₄S)₁₅-2G10 (SEQ ID NO:326), 2G10-(G₄S)₃- human FGF21 (1-170) (SEQ ID NO:318), 2G10-(G₄S)₆-human FGF21 (1-170) (SEQ ID NO:328), 2G10-(G₄S)₉-human FGF21 (1-170) (SEQ ID NO:330), 2G10-(G₄S)₁₂-human FGF21 (1-170) (SEQ ID NO:332), and 2G10-(G₄S)₁₅- human FGF21 (1-170) (SEQ ID NO:334).

The FGF21 component of a fusion can be joined to the antigen binding component of the fusion at either the N-terminus of the heavy or light chain of the antigen binding component or at the C-terminus of the heavy chain of the antigen binding component. The

two components can be joined via a linker sequence or they can be directly fused together. A fusion can optionally comprise an N-terminal methionine, which may be introduced as a consequence of expression in a non-mammalian expression system.

An “antibody” refers to an intact immunoglobulin or to an antigen binding portion thereof that competes with the intact antibody for specific binding, unless otherwise specified. Antigen binding portions can be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen binding portions include, inter alia, Fab, Fab', F(ab')₂, Fv, domain antibodies (dAbs), fragments including complementarity determining regions (CDRs), single-chain antibodies (scFv), chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

A Fab fragment is a monovalent fragment having the V_L, V_H, C_L and C_H1 domains; a F(ab')₂ fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the V_H and C_H1 domains; an Fv fragment has the V_L and V_H domains of a single arm of an antibody; and a dAb fragment has a V_H domain, a V_L domain, or an antigen-binding fragment of a V_H or V_L domain (US Pat. No. 6,846,634, 6,696,245, US App. Pub. No. 05/0202512, 04/0202995, 04/0038291, 04/0009507, 03/0039958, Ward et al., *Nature* 341:544-546 (1989)).

A single-chain antibody (scFv) is an antibody in which a V_L and a V_H region are joined via a linker (e.g., a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (*see, e.g., Bird et al., Science* 242:423-26 (1988) and Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-83 (1988)). Diabodies are bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises V_H and V_L domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (*see, e.g., Holliger et al., 1993, Proc. Natl. Acad. Sci. USA* 90:6444-48 (1993), and Poljak et al., *Structure* 2:1121-23 (1994)). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody can be identified using the system described by Kabat et al. in Sequences of Proteins of Immunological Interest, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. One or more CDRs can be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein. An antigen binding protein can incorporate the CDR(s) as part of a larger polypeptide chain, can covalently link the CDR(s) to another polypeptide chain, or can incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.

An antigen binding protein can have one or more binding sites. If there is more than one binding site, the binding sites can be identical to one another or can be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a “bispecific” or “bifunctional” antibody has two different binding sites.

The term “human antibody” includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains are derived from human immunoglobulin sequences (a fully human antibody). These antibodies can be prepared in a variety of ways, examples of which are described below, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes.

A humanized antibody has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not

significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies can be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293.

The term “chimeric antibody” refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies, such as the CDR or the CH₂, CH₃, or Fc regions. In one embodiment, one or more of the CDRs are derived from a human antibody that binds human or mouse β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4. In another embodiment, all of the CDRs are derived from a human antibody that binds human or mouse β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4. In another embodiment, the CDRs from more than one human antibody that binds human or mouse β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4 are mixed and matched in a chimeric antibody. For instance, a chimeric antibody can comprise a CDR1 from the light chain of a first human antibody that binds human or mouse β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4, a CDR2 and a CDR3 from the light chain of a second human antibody that binds human or mouse β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4, or the CDRs from the heavy chain from a third human antibody that binds human or mouse β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4, which can be joined to an CH₂, CH₃ or Fc region from yet another antibody or another source. Further, the framework regions can be derived from one of the same antibodies that bind human or mouse β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4, from one or more different antibodies, such as a human antibody, or from a humanized antibody. In one example of a chimeric antibody, a portion of the heavy and/or light chain is identical with, homologous to, or derived from an antibody from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with, homologous to, or derived from an antibody or antibodies from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies that exhibit the desired biological activity (*e.g.*, the ability to specifically bind β -Klotho).

The term “light chain” includes a full-length light chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length light chain includes a variable region domain, V_L, and a constant region domain, C_L. The variable region

domain of the light chain is at the amino-terminus of the polypeptide. Light chains include kappa chains and lambda chains.

The term “heavy chain” includes a full-length heavy chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length heavy chain includes a variable region domain, V_H , and three constant region domains, C_{H1} , C_{H2} , and C_{H3} . The V_H domain is at the amino-terminus of the polypeptide, and the C_H domains are at the carboxyl-terminus, with the C_{H3} being closest to the carboxy-terminus of the polypeptide. Heavy chains can be of any isotype, including IgG (including IgG1, IgG2, IgG3 and IgG4 subtypes), IgA (including IgA1 and IgA2 subtypes), IgM and IgE.

The term “immunologically functional fragment” (or simply “fragment”) of an antigen binding protein, *e.g.*, an antibody or immunoglobulin chain (heavy or light chain), as used herein, is an antigen binding protein comprising a portion (regardless of how that portion is obtained or synthesized) of an antibody that lacks at least some of the amino acids present in a full-length chain but which is capable of specifically binding to an antigen. Such fragments are biologically active in that they bind specifically to the target antigen and can compete with other antigen binding proteins, including intact antibodies, for specific binding to a given epitope. In one aspect, such a fragment will retain at least one CDR present in the full-length light or heavy chain, and in some embodiments will comprise a single heavy chain and/or light chain or portion thereof. These biologically active fragments can be produced by recombinant DNA techniques, or can be produced by enzymatic or chemical cleavage of antigen binding proteins, including intact antibodies. Immunologically functional immunoglobulin fragments include, but are not limited to, Fab, Fab', F(ab')₂, Fv, domain antibodies and single-chain antibodies, and can be derived from any mammalian source, including but not limited to human, mouse, rat, camelid or rabbit. It is contemplated further that a functional portion of the antigen binding proteins disclosed herein, for example, one or more CDRs, could be covalently bound to a second protein or to a small molecule to create a therapeutic agent directed to a particular target in the body, possessing bifunctional therapeutic properties, or having a prolonged serum half-life.

An “Fc” or “Fc region” comprises one or two heavy chain fragments, and can comprise the C_{H2} and/or C_{H3} domains of an antibody. When two heavy chain fragments are present, the two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_{H3} domains. An Fc region can be naturally occurring (*e.g.*, a Fc region derived from an IgG1, IgG2, IgG3, IgG4, IgE, IgA, etc) or can be an engineered sequence comprising one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,

15, 16, 17, 18, 19, 20, etc) mutations, deletions or insertions introduced into a naturally occurring heavy chain fragment or fragments that make up an Fc sequence.

An “Fab’ fragment” contains one light chain and a portion of one heavy chain that contains the V_H domain and the C_H1 domain and also the region between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab’ fragments to form an F(ab’)₂ molecule.

An “F(ab’)₂ fragment” contains two light chains and two heavy chains containing a portion of the constant region between the C_H1 and C_H2 domains, such that an interchain disulfide bond is formed between the two heavy chains. A F(ab’)₂ fragment thus is composed of two Fab’ fragments that are held together by a disulfide bond between the two heavy chains.

The “Fv region” comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

A “domain antibody” is an immunologically functional immunoglobulin fragment containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody can target the same or different antigens.

A “bivalent antigen binding protein” or “bivalent antibody” comprises two antigen binding sites. In some instances, the two binding sites have the same antigen specificities. Bivalent antigen binding proteins and bivalent antibodies can be bispecific, *see, e.g., infra*.

A “multispecific antigen binding protein” or “multispecific antibody” is one that targets more than one antigen or epitope.

A “bispecific,” “dual-specific” or “bifunctional” antigen binding protein or antibody is a hybrid antigen binding protein or antibody, respectively, having two different antigen binding sites. Bispecific antigen binding proteins and antibodies are a species of multispecific antigen binding protein or multispecific antibody and can be produced by a variety of methods including, but not limited to, fusion of hybridomas, linking an Fc to a Fab’ fragment or linking of Fab’ fragments. *See, e.g.,* Songsivilai and Lachmann, 1990, *Clin. Exp. Immunol.* 79:315-321; Kostelny *et al.*, 1992, *J. Immunol.* 148:1547-1553. The two binding sites of a bispecific antigen binding protein or antibody will bind to two different epitopes, which can reside on the same or different protein targets.

The terms “FGF21-like signaling” and “induces FGF21-like signaling,” when applied to an antigen binding protein of the present disclosure (including bispecific antigen binding

proteins), means that the antigen binding protein mimics, or modulates, the *in vivo* biological effect induced by the binding of FGF21 to an FGF receptor (*e.g.*, FGFR1c, FGFR2c, FGFR3c or FGFR4) and β -Klotho, and induces a biological response that otherwise would result from FGF21 binding to an FGF receptor (*e.g.*, FGFR1c, FGFR2c, FGFR3c or FGFR4) and β -Klotho *in vivo*. In assessing the binding and specificity and induction of a biological response of an antigen binding protein, *e.g.*, an antibody or immunologically functional fragment thereof, an antibody or fragment 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:2 (*i.e.*, 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 100nM, *e.g.*, 90 nM, 80 nM, 70nM, 60nM, 50nM, 40nM, 30nM, 20nM or 10 nM in (1) the recombinant FGF21 receptor mediated luciferase-reporter cell assay of Examples 5 and 11 and (2) ERK-phosphorylation in the recombinant FGF21 receptor mediated cell assay of Examples 5 and 11. The “potency” of an antigen binding protein is defined as exhibiting an EC50 of equal to or less than 100nM, *e.g.*, 90nM, 80nM, 70nM, 60nM, 50nM, 40nM, 30nM, 20nM, 10 nM and preferably less than 10nM of the antigen binding protein in the following assays: (1) the recombinant FGF21 receptor mediated luciferase-reporter cell assay of Examples 5 and 11 (2) the ERK-phosphorylation in the recombinant FGF21 receptor mediated cell assay of Examples 5 and 11.

It is noted that some of the antigen binding proteins and antigen binding protein-FGF21 fusions of the present disclosure may not induce FGF21-mediated signaling at therapeutically-applicable levels, nor is this property necessarily desirable in all circumstances. Nevertheless, antigen binding proteins and antigen binding protein-FGF21 fusions that do not induce FGF21-mediated signaling form aspects of the present disclosure and may be useful as diagnostic reagents or in other applications.

The term “polynucleotide” or “nucleic acid” includes both single-stranded and double-stranded nucleotide polymers. The nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine and inosine derivatives, ribose modifications such as 2', 3'-dideoxyribose, and internucleotide linkage modifications

such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate and phosphoroamidate.

The term “oligonucleotide” means a polynucleotide comprising 200 or fewer nucleotides. In some embodiments, oligonucleotides are 10 to 60 bases in length. In other embodiments, oligonucleotides are 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 nucleotides in length. Oligonucleotides can be single stranded or double stranded, *e.g.*, for use in the construction of a mutant gene. Oligonucleotides can be sense or antisense oligonucleotides. An oligonucleotide can include a label, including a radiolabel, a fluorescent label, a hapten or an antigenic label, for detection assays. Oligonucleotides can be used, for example, as PCR primers, cloning primers or hybridization probes.

An “isolated nucleic acid molecule” means a DNA or RNA of genomic, mRNA, cDNA, or synthetic origin or some combination thereof which is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, or is linked to a polynucleotide to which it is not linked in nature. For purposes of this disclosure, it should be understood that “a nucleic acid molecule comprising” a particular nucleotide sequence does not encompass intact chromosomes. Isolated nucleic acid molecules “comprising” specified nucleic acid sequences can include, in addition to the specified sequences, coding sequences for up to ten or even up to twenty other proteins or portions thereof, or can include operably linked regulatory sequences that control expression of the coding region of the recited nucleic acid sequences, and/or can include vector sequences.

Unless specified otherwise, the left-hand end of any single-stranded polynucleotide sequence discussed 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.”

The term “control sequence” refers to a polynucleotide sequence that can affect the expression and processing of coding sequences to which it is ligated. The nature of such control sequences can depend upon the host organism. In particular embodiments, control sequences for prokaryotes can include a promoter, a ribosomal binding site, and a transcription termination sequence. For example, control sequences for eukaryotes can include promoters comprising one or a plurality of recognition sites for transcription factors,

transcription enhancer sequences, and transcription termination sequence. "Control sequences" can include leader sequences and/or fusion partner sequences.

The term "vector" means any molecule or entity (*e.g.*, nucleic acid, plasmid, bacteriophage or virus) used to transfer protein coding information into a host cell.

The term "expression vector" or "expression construct" refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control (in conjunction with the host cell) expression of one or more heterologous coding regions operatively linked thereto. An expression construct can include, but is not limited to, sequences that affect or control transcription, translation, and, if introns are present, affect RNA splicing of a coding region operably linked thereto.

As used herein, "operably linked" means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions under suitable conditions. For example, a control sequence in a vector that is "operably linked" to a protein coding sequence is ligated thereto so that expression of the protein coding sequence is achieved under conditions compatible with the transcriptional activity of the control sequences.

The term "host cell" means a cell that has been transformed, or is capable of being transformed, with a nucleic acid sequence and thereby expresses a gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent cell, so long as the gene of interest is present.

The term "transduction" means the transfer of genes from one bacterium to another, usually by bacteriophage. "Transduction" also refers to the acquisition and transfer of eukaryotic cellular sequences by replication-defective retroviruses.

The term "transfection" means the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art and are disclosed herein. *See, e.g.*, Graham *et al.*, (1973) *Virology* 52:456; Sambrook *et al.*, (2001) *Molecular Cloning: A Laboratory Manual*, *supra*; Davis *et al.*, (1986) *Basic Methods in Molecular Biology*, Elsevier; Chu *et al.*, (1981) *Gene* 13:197. Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

The term "transformation" refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain new DNA or RNA. For example, a cell is transformed where it is genetically modified from its native state by introducing new genetic material *via* transfection, transduction, or other techniques.

Following transfection or transduction, the transforming DNA can recombine with that of the cell by physically integrating into a chromosome of the cell, or can be maintained transiently as an episomal element without being replicated, or can replicate independently as a plasmid. A cell is considered to have been “stably transformed” when the transforming DNA is replicated with the division of the cell.

The terms “polypeptide” or “protein” are used interchangeably herein to refer to a polymer of amino acid residues. The terms also apply to amino acid polymers in which one or more amino acid residues is an analog or mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers. The terms can also encompass amino acid polymers that have been modified, *e.g.*, by the addition of carbohydrate residues to form glycoproteins, or phosphorylated. The disclosed polypeptides and proteins can be produced by a naturally-occurring and non-recombinant cell; or they can be produced by a genetically-engineered or recombinant cell, and comprise molecules having the amino acid sequence of the native protein, or molecules having deletions from, additions to, and/or substitutions of one or more amino acids of the native sequence. The terms “polypeptide” and “protein” encompass antigen binding proteins and antigen binding protein-FGF21 fusions that specifically or selectively bind β -Klotho and antigen binding proteins and antigen binding protein-FGF21 fusions that bind (i) one or more of FGFR1c, FGFR2c, FGFR3c or FGFR4 and (ii) β -Klotho, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acids of an antigen binding protein or antigen binding protein-FGF21 fusion that specifically or selectively binds to β -Klotho or both FGFR1c and β -Klotho. The term “polypeptide fragment” refers to a polypeptide that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion as compared with the full-length protein. Such fragments can also contain modified amino acids as compared with the full-length protein. In certain embodiments, fragments are about five to 500 amino acids long. For example, fragments can be at least 5, 6, 8, 10, 14, 20, 50, 70, 100, 110, 150, 200, 250, 300, 350, 400, or 450 amino acids long. Useful polypeptide fragments include immunologically functional fragments of antibodies, including binding domains. In the case of an antigen binding protein or antigen binding protein-FGF21 fusion that specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4, useful fragments include but are not limited to a CDR region, a variable domain of a heavy or light chain, a portion of an antibody chain or just its variable region including two CDRs, and the like.

The term “isolated protein” means that a subject protein (1) is free of at least some other proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, *e.g.*, from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature. Typically, an “isolated protein” constitutes at least about 5%, at least about 10%, at least about 25%, or at least about 50% of a given sample. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof can encode such an isolated protein. Preferably, the isolated protein is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

A “variant” of a polypeptide (*e.g.*, an antigen binding protein, antigen binding protein-FGF21 fusion or an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants include fusion proteins.

A “derivative” of a polypeptide is a polypeptide (*e.g.*, an antigen binding protein, antigen binding protein-FGF21 fusion or an antibody) that has been chemically modified in some manner distinct from insertion, deletion, or substitution variants, *e.g.*, *via* conjugation to another chemical moiety.

The term “naturally occurring” as used throughout the specification in connection with biological materials such as polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature.

“Antigen binding region” means a protein, or a portion of a protein, that specifically binds a specified antigen, *e.g.*, β -Klotho or both β -Klotho and one of FGFR1c, FGFR2c, FGFR3c and FGFR4. For example, that portion of an antigen binding protein or antigen binding protein-FGF21 fusion that contains the amino acid residues that interact with an antigen and confer on the antigen binding protein or antigen binding protein-FGF21 fusion its specificity and affinity for the antigen is referred to as “antigen binding region.” An antigen binding region typically includes one or more “complementary binding regions” (“CDRs”). Certain antigen binding regions also include one or more “framework” regions. A “CDR” is an amino acid sequence that contributes to antigen binding specificity and affinity.

“Framework” regions can aid in maintaining the proper conformation of the CDRs to promote binding between the antigen binding region and an antigen.

In certain aspects, recombinant antigen binding proteins and antigen binding protein-FGF21 fusions that bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4 are provided. In this context, a “recombinant protein” is a protein made using recombinant techniques, *i.e.*, through the expression of a recombinant nucleic acid as described herein. Methods and techniques for the production of recombinant proteins are well known in the art.

The term “compete” when used in the context of antigen binding proteins and antigen binding protein-FGF21 fusions (*e.g.*, neutralizing antigen binding proteins, neutralizing antibodies, agonistic antigen binding protein or agonistic antibodies) that compete for the same epitope means competition between antigen binding proteins or antigen binding protein-FGF21 fusions is determined by an assay in which the antigen binding protein or antigen binding protein-FGF21 fusion (*e.g.*, antibody or immunologically functional fragment thereof) under test prevents or inhibits specific binding of a reference antigen binding protein or antigen binding protein-FGF21 fusion (*e.g.*, a ligand, or a reference antibody) to a common antigen (*e.g.*, FGFR1c, FGFR2c, FGFR3c, FGFR4, β -Klotho or a fragment thereof). Numerous types of competitive binding assays can be used, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (*see, e.g.*, Stahli *et al.*, (1983) *Methods in Enzymology* 9:242-253); solid phase direct biotin-avidin EIA (*see, e.g.*, Kirkland *et al.*, (1986) *J. Immunol.* 137:3614-3619) solid phase direct labeled assay, solid phase direct labeled sandwich assay (*see, e.g.*, Harlow and Lane, (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using I-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 purified antigen bound to a solid surface or cells bearing either of these, an unlabelled test antigen binding protein or antigen binding protein-FGF21 fusion and a labeled reference antigen binding protein or antigen binding protein-FGF21 fusion. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antigen binding protein or antigen binding protein-FGF21 fusion. Usually the test antigen binding protein or antigen binding protein-FGF21 fusion is present in excess. Antigen binding

proteins or antigen binding protein-FGF21 fusions identified by competition assay (competing antigen binding proteins) include antigen binding proteins and antigen binding protein-FGF21 fusions binding to the same epitope as the reference antigen binding proteins or antigen binding protein-FGF21 fusions and antigen binding proteins or antigen binding protein-FGF21 fusions binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antigen binding protein or antigen binding protein-FGF21 fusion for steric hindrance to occur. Additional details regarding methods for determining competitive binding are provided in the examples herein. Usually, when a competing antigen binding protein is present in excess, it will inhibit specific binding of a reference antigen binding protein or antigen binding protein-FGF21 fusion to a common antigen by at least 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%. In some instance, binding is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

The term “antigen” refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antigen binding protein or antigen binding protein-FGF21 fusion (including, *e.g.*, an antibody or immunological functional fragment thereof), and additionally is capable of being used in an animal to produce antibodies capable of binding to that antigen. An antigen can possess one or more epitopes that are capable of interacting with different antigen binding proteins, *e.g.*, antibodies.

The term “epitope” is the portion of a molecule that is bound by an antigen binding protein or antigen binding protein-FGF21 fusion (for example, an antibody). The term includes any determinant capable of specifically binding to an antigen binding protein or antigen binding protein-FGF21 fusion, such as an antibody. An epitope can be contiguous or non-contiguous (*e.g.*, (i) in a single-chain polypeptide, amino acid residues that are not contiguous to one another in the polypeptide sequence but that within in context of the molecule are bound by the antigen binding protein or antigen binding protein-FGF21 fusion, or (ii) in a multimeric receptor comprising two or more individual components, *e.g.*, FGFR1c, FGFR2c, FGFR3c or FGFR4, and β -Klotho, amino acid residues that are present on one or more of the individual components, but which are still bound by the antigen binding protein or antigen binding protein-FGF21 fusion). In certain embodiments, epitopes can be mimetic in that they comprise a three dimensional structure that is similar to an epitope used to generate the antigen binding protein or antigen binding protein-FGF21 fusion, yet comprise none or only some of the amino acid residues found in that epitope used to generate the antigen binding protein or antigen binding protein-FGF21 fusion. Most often, epitopes reside

on proteins, but in some instances can reside on other kinds of molecules, such as nucleic acids. Epitope determinants can include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and can have specific three dimensional structural characteristics, and/or specific charge characteristics. Generally, antigen binding proteins or antigen binding protein-FGF21 fusions specific for a particular target antigen will preferentially recognize an epitope on the target antigen in a complex mixture of proteins and/or macromolecules.

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 (*i.e.*, 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.

In calculating percent identity, the sequences being compared are aligned in a way that gives the largest match between the sequences. The computer program used to determine percent identity can be, for example, the GCG program package, which includes GAP (Devereux *et al.*, (1984) *Nucl. Acid Res.* 12:387; Genetics Computer Group, University of Wisconsin, Madison, WI). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are 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 3x 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.

Recommended parameters for determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following:

Algorithm: Needleman *et al.*, 1970, *J. Mol. Biol.* 48:443-453;

Comparison matrix: BLOSUM 62 from Henikoff *et al.*, 1992, *supra*;

Gap Penalty: 12 (but with no penalty for end gaps)

Gap Length Penalty: 4

Threshold of Similarity: 0

Certain alignment schemes for aligning two amino acid sequences can result in matching of only a short region of the two sequences, and this small aligned region can 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 at least 50 contiguous amino acids of the target polypeptide.

As used herein, “substantially pure” means that the described species of molecule is the predominant species present, that is, on a molar basis it is more abundant than any other individual species in the same mixture. In certain embodiments, a substantially pure molecule is a composition wherein the object species comprises at least 50% (on a molar basis) of all macromolecular species present. In other embodiments, a substantially pure composition will comprise at least 80%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98% or 99% of all macromolecular species present in the composition. In other embodiments, the object species is purified to essential homogeneity wherein contaminating species cannot be detected in the composition by conventional detection methods and thus the composition consists of a single detectable macromolecular species.

The terms “treat” and “treating” refer to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination,

neuropsychiatric exams, and/or a psychiatric evaluation. For example, certain methods presented herein successfully treat diabetes, obesity and dyslipidemia, either prophylactically or as an acute treatment, and/or decrease plasma glucose levels and circulating triglyceride and cholesterol levels and/or ameliorate a symptom associated with type 2 diabetes, obesity or dyslipidemia.

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 diabetes, obesity or dyslipidemia. 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 state (*e.g.*, diabetes, obesity or dyslipidemia) or symptoms, particularly a state or symptoms associated with the disease state, or otherwise prevent, hinder, retard or reverse the progression of the disease state or any other undesirable symptom associated with the disease 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 diabetes, obesity or dyslipidemia or associated symptoms. The full therapeutic or prophylactic effect does not necessarily occur by administration of one dose, and can occur only after administration of a series of doses. Thus, a therapeutically or prophylactically effective amount can be administered in one or more administrations.

The term “amino acid” is employed per its normal meaning in the art. The twenty naturally-occurring amino acids and their abbreviations follow conventional usage. *See, e.g.*, Immunology-A Synthesis, 2nd Edition, (E. S. Golub and D. R. Green, eds.), Sinauer Associates: Sunderland, Mass. (1991), incorporated herein by reference for any purpose. Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural or non-naturally occurring amino acids such as α,α -disubstituted amino acids, N-alkyl amino acids, and other unconventional amino acids can also be suitable components for polypeptides and are included in the term “amino acid.” Examples of non-naturally amino acids (which can be substituted for any naturally-occurring amino acid found in any sequence disclosed herein, as desired) include: 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and

imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino-terminal (or “N-terminal”) direction and the right-hand direction is the carboxyl-terminal (or “C-terminal”) direction, in accordance with standard usage and convention. The term “amino acid” also encompasses non-naturally occurring amino acids. A non-limiting list of examples of non-naturally occurring amino acids that can be inserted into an antigen binding protein or antigen binding protein-FGF21 fusion sequence or substituted for a wild-type residue in an antigen binding sequence includes β -amino acids, homoamino acids, cyclic amino acids and amino acids with derivatized side chains. Examples include (in the L-form or D-form; abbreviated as in parentheses): citrulline (Cit), homocitrulline (hCit), N α -methylcitrulline (NMeCit), N α -methylhomocitrulline (N α -MeHoCit), ornithine (Orn), N α -Methylornithine (N α -MeOrn or NMeOrn), sarcosine (Sar), homolysine (hLys or hK), homoarginine (hArg or hR), homoglutamine (hQ), N α -methylarginine (NMeR), N α -methyllleucine (N α -MeL or NMeL), N-methylhomolysine (NMeHoK), N α -methylglutamine (NMeQ), norleucine (Nle), norvaline (Nva), 1,2,3,4-tetrahydroisoquinoline (Tic), Octahydroindole-2-carboxylic acid (Oic), 3-(1-naphthyl)alanine (1-Nal), 3-(2-naphthyl)alanine (2-Nal), 1,2,3,4-tetrahydroisoquinoline (Tic), 2-indanylglycine (IgI), para-iodophenylalanine (pI-Phe), para-aminophenylalanine (4AmP or 4-Amino-Phe), 4-guanidino phenylalanine (Guf), glycyllsine (abbreviated “K(N ϵ -glycyl)” or “K(glycyl)” or “K(gly)”), nitrophenylalanine (nitrophe), aminophenylalanine (aminophe or Amino-Phe), benzylphenylalanine (benzylphe), γ -carboxyglutamic acid (γ -carboxyglu), hydroxyproline (hydroxypro), p-carboxyl-phenylalanine (Cpa), α -aminoadipic acid (Aad), N α -methyl valine (NMeVal), N- α -methyl leucine (NMeLeu), N α -methylnorleucine (NMeNle), cyclopentylglycine (Cpg), cyclohexylglycine (Chg), acetylarginine (acetylarg), α , β -diaminopropionic acid (Dpr), α , γ -diaminobutyric acid (Dab), diaminopropionic acid (Dap), cyclohexylalanine (Cha), 4-methyl-phenylalanine (MePhe), β , β -diphenyl-alanine (BiPhA), aminobutyric acid (Abu), 4-phenyl-phenylalanine (or biphenylalanine; 4Bip), α -amino-isobutyric acid (Aib), beta-alanine, beta-aminopropionic acid, piperidinic acid, aminocaproic acid, aminoheptanoic acid, aminopimelic acid, desmosine, diaminopimelic acid, N-ethylglycine, N-ethylasparagine, hydroxylysine, allo-hydroxylysine, isodesmosine, allo-isoleucine, N-methylglycine, N-methylisoleucine, N-methylvaline, 4-hydroxyproline (Hyp), γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, ω -methylarginine, 4-

Amino-O-Phthalic Acid (4APA), and other similar amino acids, and derivatized forms of any of those specifically listed.

GENERAL OVERVIEW

FGF21 is a secreted polypeptide that is a member of a subfamily of fibroblast growth factors (FGFs). Transgenic mice overexpressing FGF21 exhibit metabolic phenotypes of slow growth rate, low plasma glucose as well as triglyceride levels, and an absence of age-associated type 2 diabetes, islet hyperplasia, and obesity. Pharmacological administration of recombinant FGF21 protein in diabetic rodent models, results in normalized levels of plasma glucose, reduced triglyceride and cholesterol levels, improved glucose tolerance and insulin sensitivity. In addition, FGF21 reduces body weight and body fat by increasing energy expenditure, physical activity, and metabolic rate.

It has been suggested that a complex comprising β -klotho and fibroblast growth factor receptor 1c (FGFR1c) can elicit an *in vivo* effect similar to the effect induced by FGF21. Based on this observation bispecific antibodies and antigen binding protein-FGF21 fusions were designed based on an immunoglobulin (IgG) scaffold. The disclosed bispecific antigen binding proteins bind specifically to β -klotho via the Fab regions and also to FGFR1c via the C_H3 loop of the Fc region. The antigen binding protein-FGF21 fusions provided herein comprise or the antigen binding protein component and a FGF21 component; the antigen binding protein component binds to β -Klotho via the Fab regions of the antigen binding component and associates with FGFR1c, FGFR2c, FGFR3c and/or FGFR4 via the FGF21 component of the fusion. In another embodiment, the antigen binding protein component of an antigen binding protein-FGF21 fusion can associate with FGFR1c, FGFR2c, FGFR3c and/or FGFR4 via the Fab regions of the antigen binding component and with β -Klotho via the FGF21 component of the fusion. The specificity of an antigen binding protein-FGF21 fusion will depend on whether the N- or C-terminal of the FGF21 component is truncated and on the specificity of the antigen binding component.

In the antigen binding proteins disclosed herein the β -klotho binding sites are positioned on the Fab domains, which are then joined to an Fc region comprising FGFR1c-binding peptides situated in the CH3 loop of the Fc region.

Antigen binding proteins that bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, are provided herein, as well as antigen binding protein-FGF21 fusions. A unique property of the antigen binding proteins and antigen binding

protein-FGF21 fusions disclosed herein is the agonistic nature of these proteins, specifically the ability to induce FGF21-like signaling, in the case of antigen binding proteins by binding to β -Klotho via the Fab region and associating with FGFR1c via the peptide inserted in the the native Fc region and in the case of in the case of antigen binding protein-FGF21 fusions by associating with either (a) β -Klotho via the Fab region of the antigen binding protein component and with FGFR1c, FGFR2c, FGFR3c, and/or FGFR4 via the FGF21 component or (b) FGFR1c, FGFR2c, FGFR3c and/or FGFR4 via the Fab region of the antigen binding protein component and β -Klotho via the FGF21 component.

More remarkably and specifically, some of the antigen binding proteins and antigen binding protein-FGF21 fusions disclosed herein induce FGF21-like signaling in several *in vitro* cell-based assays, including the ELK-luciferase reporter assay of Examples 5 and 11 under the following conditions (1) the binding to and activity of the FGF21 receptor is β -Klotho dependent; (2) the activity is selective to FGFR1c/ β -Klotho complex; (3) the binding to the FGFR1c/ β -Klotho triggers FGF21-like signaling pathways and (4) the potency (EC50) is comparable to a wild-type FGF21 standard comprising the mature form of SEQ ID NO:2, as measured in the following cell-based assays: (1) the recombinant FGF21 receptor mediated luciferase-reporter cell assay of Examples 5 and 11; and (2) the ERK-phosphorylation in the recombinant FGF21 receptor mediated cell assay of Examples 5 and 11. The disclosed antigen binding proteins and antigen binding protein-FGF21 fusions, therefore, are expected to exhibit activities *in vivo* that are consistent with the natural biological function of FGF21. This property makes the disclosed antigen binding proteins and antigen binding protein-FGF21 fusions viable therapeutics for the treatment of metabolic diseases such as type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, metabolic syndrome and broadly any disease or condition in which it is desirable to mimic or augment the *in vivo* effects of FGF21.

The antigen binding proteins and antigen binding protein-FGF21 fusions provided are polypeptides into which one or more complementarity determining regions (CDRs), as described herein, are embedded and/or joined. In some antigen binding proteins, the CDRs are embedded into a "framework" region, which orients the CDR(s) such that the proper antigen binding properties of the CDR(s) is achieved. In general, the antigen binding proteins and antigen binding protein-FGF21 fusions that are provided can facilitate or enhance the interaction between FGFR1c and β -Klotho, and can substantially induce FGF21-like signaling.

Certain antigen binding proteins and antigen binding protein-FGF21 fusions described herein are antibodies or are derived from antibodies. In certain embodiments, the polypeptide structure of the antigen binding proteins is based on antibodies, including, but not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as “antibody mimetics”), chimeric antibodies, humanized antibodies, human antibodies, antibody fusions (sometimes referred to herein as “antibody conjugates”), and fragments thereof. The various structures are further described herein below.

The antigen binding proteins and antigen binding protein-FGF21 fusions provided herein have been demonstrated to bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, and particularly the human forms of FGFR1c and/or β -Klotho to varying degrees. The antigen binding proteins and antigen binding protein-FGF21 fusions that are provided mimic the natural *in vivo* biological activity of FGF21. As a consequence, the antigen binding proteins and antigen binding protein-FGF21 fusions provided herein are capable of activating FGF21-like signaling activity to varying degrees. In particular, antigen binding proteins and antigen binding protein-FGF21 fusions binding to these epitopes can have one or more of the following activities *in vivo*: induction of FGF21-like signal transduction pathways, lowering blood glucose levels, lowering circulating lipid levels, improving metabolic parameters and other physiological effects induced *in vivo* by the formation of the ternary complex of FGFR1c, β -Klotho and FGF21, for example in conditions such as type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

The antigen binding proteins and antigen binding protein-FGF21 fusions that are disclosed herein have a variety of utilities. Some of the antigen binding proteins and antigen binding protein-FGF21 fusions, for instance, are useful in specific binding assays, in the affinity purification of FGFR1c and/or β -Klotho, in particular human FGFR1c and/or β -Klotho, or ligands of these proteins, and in screening assays to identify other agonists of FGF21-like signalling activity.

The antigen binding proteins and antigen binding protein-FGF21 fusions that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are disclosed herein can be used in a variety of treatment applications, as explained herein. For example, certain antigen binding proteins and antigen binding protein-FGF21 fusions are useful for treating conditions associated with FGF21-like signaling

processes in a patient, such as reducing, alleviating, or treating type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome. Other uses for the antigen binding proteins and antigen binding protein-FGF21 fusions include, for example, diagnosis of diseases or conditions associated with β -Klotho, FGFR1c, FGFR2c, FGFR3c, FGFR4 or FGF21, and screening assays to determine the presence or absence of these molecules. The antigen binding proteins and antigen binding protein-FGF21 fusions described herein may be useful in treating conditions, symptoms and/or the pathology associated with decreased FGF21-like signalling activity. Exemplary conditions include, but are not limited to, diabetes, obesity, NASH and dyslipidemia.

FGF21

The antigen binding proteins and antigen binding protein-FGF21 fusions disclosed herein can induce FGF21-mediated signaling, as defined herein, to varying degrees. *In vivo*, the mature form of FGF21 is the active form of the molecule. The nucleotide sequence encoding full length FGF21 is provided; the nucleotides encoding the signal sequence are underlined.

ATG GAC TCG GAC GAG ACC GGG TTC GAG CAC TCA GGA CTG
TGG GTT TCT GTG CTG GCT GGT CTT CTG CTG GGA GCC TGC CAG
GCA CAC CCC ATC CCT GAC TCC AGT CCT CTC CTG CAA TTC GGG
 GGC CAA GTC CGG CAG CGG TAC CTC 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 AGC CCC GAA AGT CTC
 CTG CAG CTG AAA GCC TTG AAG CCG GGA GTT ATT CAA ATC
 TTG GGA GTC AAG ACA TCC AGG TTC CTG TGC CAG CGG CCA
 GAT GGG GCC CTG TAT GGA TCG CTC CAC TTT GAC CCT GAG
 GCC TGC AGC TTC CGG GAG CTG CTT CTT GAG GAC GGA TAC
 AAT GTT TAC CAG TCC GAA GCC CAC GGC CTC CCG CTG CAC
 CTG CCA GGG AAC AAG TCC CCA CAC CGG GAC CCT GCA CCC
 CGA GGA CCA GCT CGC TTC CTG CCA CTA CCA GGC CTG CCC
 CCC GCA CCC CCG GAG CCA CCC GGA ATC CTG GCC CCC CAG
 CCC CCC GAT GTG GGC TCC TCG GAC CCT CTG AGC ATG GTG
 GGA CCT TCC CAG GGC CGA AGC CCC AGC TAC GCT TCC TGA
 (SEQ ID NO: 1)

The amino acid sequence of full length FGF21 is provided; the amino acids that make up the signal sequence are underlined:

MDSDETGFESGLWVSVLAGLLLGACQAHPIPDSS
 PLLQFGGQVRQRYLYTDDAQQT^{EA}HL^{EIR}EDGTV
 GGAADQSPESLLQLKALKPGVIQILGVKTSRFLCQ
 RPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEA

HGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPAPP
 EPPGILAPQPPDVGSSDPLSMVGPSQGRSPSYAS
 (SEQ ID NO: 2)

Thus, the mature form of FGF21 comprises the amino acid sequence:

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEI
 REDGTVGGAADQSPESELLQLKALKPGVILGVKTSRFLCQRPD
 GALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNK
 SPHRDPAPRGPARFLPLPGLPPA **P**PEPPGILAPQPPDVGSSDPLSMVGPSQGRS
 PSYAS (SEQ ID NO: 341)

A truncated form of FGF21 comprising residues 1-169 comprises the amino acid sequence :

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIRE
 DGTGTVGGAADQSPESLLQLKALKPGVILGVKTSRFLCQRPD
 GALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNK
 SPHRDPAPRGPARFLPLPGLPPA PPEPPGILAPQPPDVGSSDPLSMV
 (SEQ ID NO: 342)

A truncated form of FGF21 comprising residues 1-170 comprises the amino acid sequence :

HPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHLEIRE
 DGTGTVGGAADQSPESLLQLKALKPGVILGVKTSRFLCQRPD
 GALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGNK
 SPHRDPAPRGPARFLPLPGLPPA PPEPPGILAPQPPDVGSSDPLSMVG
 (SEQ ID NO: 343)

FGF21 can exist in at least two different forms, which differ from one another at position 146 (underlined and in bold in SEQ ID NO: 341 above); in one form the residue at this position is a proline as in SEQ ID NO:341 and in another form it is a leucine. Throughout the present disclosure, unless indicated otherwise, the term FGF21 encompasses these and any other known or discovered isoforms of SEQ ID NO:341).

As described herein, an FGF21 can also include fragments. As used herein, the terms are used interchangeably to mean a protein, in particular and unless otherwise specified, a human protein, that upon association with β -Klotho and FGFR1c, FGFR2c, FGFR3c and/or FGFR4 induces FGF21-like signaling activity.

FGFR1c

The antigen binding proteins and the antigen binding protein component of the antigen binding protein-FGF21 fusions disclosed herein bind to or associate with FGFR1c, in particular human FGFR1c, when associated with β -Klotho, to varying degrees. The nucleotide sequence encoding human FGFR1c (GenBank Accession Number NM_023110) is provided:

ATGTGGAGCTGGAAGTGCCTCCTCTTCTGGGCTGTGCTGGTCACAG
 CCACACTCTGCACCGCTAGGCCGTCCCCGACCTTGCCTGAACAAGC
 CCAGCCCTGGGGAGCCCCTGTGGAAGTGGAGTCCTTCCTGGTCCAC
 CCCGGTGACCTGCTGCAGCTTCGCTGTCGGCTGCGGGACGATGTGC
 AGAGCATCAACTGGCTGCGGGACGGGGTGCAGCTGGCGGAAAGCA
 ACCGCACCCGCATCACAGGGGAGGAGGTGGAGGTGCAGGACTCCG
 TGCCCGCAGACTCCGGCCTCTATGCTTGCGTAACCAGCAGCCCCTC
 GGGCAGTGACACCACCTACTTCTCCGTCAATGTTTCAGATGCTCTCC
 CCTCCTCGGAGGATGATGATGATGATGACTCCTCTTCAGAGGA
 GAAAGAAACAGATAACACCAAACCAAACCGTATGCCCGTAGCTCC
 ATATTGGACATCACCAGAAAAGATGGAAAAGAAATTGCATGCAGT
 GCCGGCTGCCAAGACAGTGAAGTTCAAATGCCCTTCCAGTGGGACA
 CCAAACCCAACACTGCGCTGGTTGAAAAATGGCAAAGAATTCAAA
 CCTGACCACAGAATTGGAGGCTACAAGGTCCGTTATGCCACCTGGA
 GCATCATAATGGACTCTGTGGTGCCCTCTGACAAGGGCAACTACAC
 CTGCATTGTGGAGAATGAGTACGGCAGCATCAACCACACATACCA
 GCTGGATGTCGTGGAGCGGTCCCCTCACCGGCCCATCCTGCAAGCA
 GGGTTGCCCCGCCAACAACAAACAGTGGCCCTGGGTAGCAACGTGGAG
 TTCATGTGTAAGGTGTACAGTGACCCGCAGCCGCACATCCAGTGGC
 TAAAGCACATCGAGGTGAATGGGAGCAAGATTGGCCCAGACAACC
 TGCCTTATGTCCAGATCTTGAAGACTGCTGGAGTTAATACCACCGA
 CAAAGAGATGGAGGTGCTTCACTTAAGAAATGTCTCCTTTGAGGAC
 GCAGGGGAGTATACGTGCTTGGCGGGTAACTCTATCGGACTCTCCC
 ATCACTCTGCATGGTTGACCGTTCTGGAAGCCCTGGAAGAGAGGCC
 GGCAGTGATGACCTCGCCCCTGTACCTGGAGATCATCATCTATTGC
 ACAGGGGCCTTCCTCATCTCCTGCATGGTGGGGTCGGTCATCGTCT
 ACAAGATGAAGAGTGGTACCAAGAAGAGTGACTTCCACAGCCAGA

TGGCTGTGCACAAGCTGGCCAAGAGCATCCCTCTGCGCAGACAGGT
AACAGTGTCTGCTGACTCCAGTGCATCCATGAACTCTGGGGTTCTT
CTGGTTCGGCCATCACGGCTCTCCTCCAGTGGGACTCCCATGCTAG
CAGGGGTCTCTGAGTATGAGCTTCCCGAAGACCCTCGCTGGGAGCT
GCCTCGGGACAGACTGGTCTTAGGCAAACCCCTGGGAGAGGGCTG
CTTTGGGCAGGTGGTGTGTCAGAGGCTATCGGGCTGGACAAGGA
CAAACCCAACCGTGTGACCAAAGTGGCTGTGAAGATGTTGAAGTC
GGACGCAACAGAGAAAGACTTGTCTCAGACCTGATCTCAGAAATGGA
GATGATGAAGATGATCGGGAAGCATAAGAATATCATCAACCTGCT
GGGGGCCTGCACGCAGGATGGTCCCTTGTATGTCATCGTGGAGTAT
GCCTCCAAGGGCAACCTGCGGGAGTACCTGCAGGCCCCGGAGGCCC
CCAGGGCTGGAATACTGCTACAACCCCAGCCACAACCCAGAGGAG
CAGCTCTCCTCCAAGGACCTGGTGTCTGCGCCTACCAGGTGGCCC
GAGGCATGGAGTATCTGGCCTCCAAGAAGTGCATACACCGAGACC
TGGCAGCCAGGAATGTCCTGGTGACAGAGGACAATGTGATGAAGA
TAGCAGACTTTGGCCTCGCACGGGACATTCACCACATCGACTACTA
TAAAAAGACAACCAACGGCCGACTGCCTGTGAAGTGGATGGCACC
CGAGGCATTATTTGACCGGATCTACACCCACCAGAGTGATGTGTGG
TCTTTCGGGGTGCTCCTGTGGGAGATCTTCACTCTGGGCGGCTCCCC
ATACCCCGGTGTGCCTGTGGAGGAACTTTTCAAGCTGCTGAAGGAG
GGTCACCGCATGGACAAGCCCAGTAACTGCACCAACGAGCTGTAC
ATGATGATGCGGGACTGCTGGCATGCAGTGCCCTCACAGAGACCCA
CCTTCAAGCAGCTGGTGGAAGACCTGGACCGCATCGTGGCCTTGAC
CTCCAACCAGGAGTACCTGGACCTGTCCATGCCCCTGGACCAGTAC
TCCCCCAGCTTTCCCGACACCCGGAGCTCTACGTGCTCCTCAGGGG
AGGATTCCGTCTTCTCTCATGAGCCGCTGCCCCGAGGAGCCCTGCCT
GCCCCGACACCCAGCCCAGCTTGCCAATGGCGGACTCAAACGCCG
CTGA (SEQ ID NO: 3).

The amino acid sequence of human FGFR1c (GenBank Accession Number NP_075598) is provided:

MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHP
GDLLQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPA
DSGLYACVTSSPSGSDTTYFSVNVSDALPSSDDDDDDSSSEEKETD

NTKPNRMPVAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTRL
 WLKNGKEFKPDHRIGGYKVRYATWSIIMDSVVP SDKGNYTCIVENEY
 GSINHTYQLDVVERSHPRPILQAGLPANKTVALGSNVEFMCKVYSDPQ
 PHIQWLKHIEVNGSKIGPDNLPYVQILKTAGVNTTDKEMEVLHLRNVS
 FEDAGEYTCLAGNSIGLSHHS AWLTVLEALEERPAVMTSPLYLEIIYC
 TGAFLISCMVGSVIVYKMKSGTKKSD FHSQMAVHKLAKSIPLRRQVT
 VSADSSASMNSGVLLVRPSRLSSSGTPMLAGVSEYELPEDPRWELPRD
 RLVLGKPLGEGCFGQVVLAE AIGLDKDKPNRVTKVAVKMLKSDATE
 KDLSDLISEMEMMMKMIGKHKN IINLLGACTQDGPLYVIVEYASKGNLR
 EYLQARRPPGLEYCYNPSHN PEEQLSSKDLVSCAYQVARGMEYLASK
 KCIHRDLAARNVLVTEDNVMKIAD FGLARDIHHIDYYKKTNGRLPV
 KWMAPEALFDRIYTHQSDVWSFGVLLWEIFTLGGSPYPGVPVEELFKL
 LKEGHRMDKPSNCTNELYMMMRDC WHAVPSQRPTFKQLVEDLDRIV
 ALTSNQEYLDLSMPLDQYSPSFPD TRSSTCSSGEDSVFSHEPLPEEPCLP
 RHPAQLANGGLKRR (SEQ ID NO: 4).

The antigen binding proteins and the antigen binding protein component of the antigen binding protein-FGF21 fusions described herein bind or associate with the extracellular portion of FGFR1c to varying degrees which, in some embodiments, may be bound to or associated with β -Klotho. An example of an extracellular region of FGFR1c is:

MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPGDLL
 QLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGLYACVT
 SSPSGSDTTYFSVNVSDALPSEDDDDDDSSSEEKETDNTKPNRMPVAPYW
 TSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTRLWLKNGKEFKPDHRIGGYK
 VRYATWSIIMDSVVP SDKGNYTCIVENEYGSINHTYQLDVVERSHPRPILQAG
 LPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKIGPDNLPYVQILKT
 AGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLSHHS AWLTVLEALEER
 PAVMTSPLY
 (SEQ ID NO: 5).

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 β -Klotho and FGF21 induces FGF21-like signaling activity.

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.

β -Klotho

The antigen binding proteins and the antigen binding protein component of the antigen binding protein-FGF21 fusions disclosed herein bind to the extracellular domain of β -Klotho to varying degrees, in particular to human β -Klotho. The nucleotide sequence encoding full-length human β -Klotho (GenBank Accession Number NM_175737) is provided:

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ATGAAGCCAGGCTGTGCGGCAGGATCTCCAGGGAATGAATGGATT
TTCTTCAGCACTGATGAAATAACCACACGCTATAGGAATACAATGT
CCAACGGGGGATTGCAAAGATCTGTCATCCTGTCAGCACTTATTCT
GCTACGAGCTGTTACTGGATTCTCTGGAGATGGAAGAGCTATATGG
TCTAAAAATCCTAATTTTACTCCGGTAAATGAAAGTCAGCTGTTTCT
CTATGACACTTTCCCTAAAAACTTTTTCTGGGGTATTGGGACTGGA
GCATTGCAAGTGGAAGGGAGTTGGAAGAAGGATGGAAAAGGACCT
TCTATATGGGATCATTTTCATCCACACACACCTTAAAAATGTCAGCA
GCACGAATGGTTCCAGTGACAGTTATATTTTTCTGGAAAAAGACTT
ATCAGCCCTGGATTTTATAGGAGTTTCTTTTTATCAATTTTCAATTT
CCTGGCCAAGGCTTTTCCCCGATGGAATAGTAACAGTTGCCAACGC
AAAAGGTCTGCAGTACTACAGTACTCTTCTGGACGCTCTAGTGCTT
AGAAACATTGAACCTATAGTTACTTTATACCACTGGGATTTGCCTTT
GGCACTACAAGAAAAAATATGGGGGGTGGAAAAATGATACCATAAT
AGATATCTTCAATGACTATGCCACATACTGTTTCCAGATGTTTGGG
GACCGTGTCAAATATTGGATTACAATTCACAACCCATATCTAGTGG
CTTGGCATGGGTATGGGACAGGTATGCATGCCCCTGGAGAGAAGG
GAAATTTAGCAGCTGTCTACACTGTGGGACACAACCTTGATCAAGGC
TCACTCGAAAGTTTGGCATAACTACAACACACATTTCCGCCCACAT
CAGAAGGGTTGGTTATCGATCACGTTGGGATCTCATTGGATCGAGC
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CAAACCGGTCGGAAAACACGATGGATATATTCAAATGTCAACAAT
CCATGGTTTCTGTGCTTGGATGGTTTGCCAACCCTATCCATGGGGAT
GGCGACTATCCAGAGGGGATGAGAAAGAAGTTGTTCTCCGTTCTAC
CCATTTTCTCTGAAGCAGAGAAGCATGAGATGAGAGGCACAGCTG
ATTTCTTTGCCTTTTCTTTTGGACCCAACAACCTTCAAGCCCCTAAAC
ACCATGGCTAAAATGGGACAAAATGTTTCACTTAATTTAAGAGAAG
CGCTGAACTGGATTAAACTGGAATACAACAACCCTCGAATCTTGAT
TGCTGAGAATGGCTGGTTCACAGACAGTCGTGTGAAAACAGAAGA
CACCACGGCCATCTACATGATGAAGAATTTCTCAGCCAGGTGCTT
CAAGCAATAAGGTTAGATGAAATACGAGTGTTTGGTTATACTGCCT
GGTCTCTCCTGGATGGCTTTGAATGGCAGGATGCTTACACCATCCG
CCGAGGATTATTTTATGTGGATTTTAACAGTAAACAGAAAGAGCGG
AAACCTAAGTCTTCAGCACACTACTACAAACAGATCATACGAGAA
AATGGTTTTTCTTTAAAAGAGTCCACGCCAGATGTGCAGGGCCAGT
TTCCCTGTGACTTCTCCTGGGGTGTCACTGAATCTGTTCTTAAGCCC
GAGTCTGTGGCTTCGTCCCCACAGTTCAGCGATCCTCATCTGTACGT
GTGGAACGCCACTGGCAACAGACTGTTGCACCGAGTGGAAGGGGT
GAGGCTGAAAACACGACCCGCTCAATGCACAGATTTTGTAAACATC
AAAAACAACCTTGAGATGTTGGCAAGAATGAAAGTCACCCACTAC
CGGTTTGCTCTGGATTGGGCCTCGGTCCTTCCCCTGGCAACCTGTC
CGCGGTGAACCGACAGGCCCTGAGGTACTACAGGTGCGTGGTCAG
TGAGGGGCTGAAGCTTGGCATCTCCGCGATGGTCAACCCTGTATTAT
CCGACCCACGCCCACCTAGGCCTCCCCGAGCCTCTGTTGCATGCCG
ACGGGTGGCTGAACCCATCGACGGCCGAGGCCTTCCAGGCCTACG
CTGGGCTGTGCTTCCAGGAGCTGGGGGACCTGGTGAAGCTCTGGAT
CACCATCAACGAGCCTAACCGGCTAAGTGACATCTACAACCGCTCT
GGCAACGACACCTACGGGGCGGCGCACAACTGCTGGTGGCCCAC
GCCCTGGCCTGGCGCCTCTACGACCGGCAGTTCAGGCCCTCACAGC
GCGGGGCCGTGTCGCTGTCGCTGCACGCGGACTGGGCGGAACCCG
CCAACCCCTATGCTGACTCGCACTGGAGGGCGGCCGAGCGCTTCCT
GCAGTTCGAGATCGCCTGGTTCGCCGAGCCGCTCTTCAAGACCGGG
GACTACCCCGCGGCCATGAGGGAATACATTGCCTCCAAGCACCGA
CGGGGGCTTTCCAGCTCGGCCCTGCCGCGCCTACCGAGGCCGAAA
GGAGGCTGCTCAAGGGCACGGTCGACTTCTGCGCGCTCAACCACTT

CACCACTAGGTTCGTGATGCACGAGCAGCTGGCCGGCAGCCGCTAC
GACTCGGACAGGGACATCCAGTTTCTGCAGGACATCACCCGCCTGA
GCTCCCCACGCGCCTGGCTGTGATTCCCTGGGGGGGTGCGCAAGCT
GCTGCGGTGGGTCCGGAGGAACACTACGGCGACATGGACATTTACATC
ACCGCCAGTGGCATCGACGACCAGGCTCTGGAGGATGACCGGCTC
CGGAAGTACTACCTAGGGAAGTACCTTCAGGAGGTGCTGAAAGCA
TACCTGATTGATAAAGTCAGAATCAAAGGCTATTATGCATTCAAAC
TGGCTGAAGAGAAATCTAAACCCAGATTTGGATTCTTCACATCTGA
TTTTAAAGCTAAATCCTCAATACAATTTTACAACAAAGTGATCAGC
AGCAGGGGGCTTCCCTTTTGAGAACAGTAGTTCTAGATGCAGTCAGA
CCCAAGAAAATACAGAGTGCACTGTCTGCTTATTCCTTGTGCAGAA
GAAACCACTGATATTCCTGGGTTGTTGCTTCTTCTCCACCCTGGTTC
TACTCTTATCAATTGCCATTTTTCAAAGGCAGAAGAGAAGAAAGTT
TTGGAAAGCAAAAAAATTACAACACATACCATTAAAGAAAGGCAA
GAGAGTTGTTAGCTAA (SEQ ID NO: 6).

The amino acid sequence of full length human β -Klotho (GenBank Accession Number NP_783864) is provided:

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRA
VTGFSGDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVE
GSWKKDGKGPSIWDHFIHHLKNVSSTNGSSDSYIFLEKDLSALDFIGV
SFYQFSISWPRLFPDGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYH
WDLPLALQEKYGGWKNDTIIDIFNDYATYCFQMFGDRVKYWITIHP
YLVAWHGYGTGMHAPGEKGNLAAVYTVGHNLIAHASKVWHNYNTH
FRPHQKGWLSITLGSHWIEPNRSENTMDIFKCQQSMVSVLGWFANPIH
GDGDYPEGMRKKLFSVLPIFSEAEKHEMRGTADFFAFSFGPNNFKPLN
TMAKMGQNVSLNLREALNWIKLEYNNPRILIAENGWFTDSRVKTEDT
TAIYMMKNFLSQVLQAIRLDEIRVFGYTAWSLLDGFEWQDAYTIRGL
FYVDFNSKQKERKPKSSAHYYKQIIRENGFSLKESTPDVQQGFPCDFS
WGVTESVLKPESVASSPQFSDPHLYVWNATGNRLLHRVEGVRLKTRP
AQCTDFVNIKKQLEMLARMKVTHYRFALDWASVLPTGNLSAVNRQA
LRYRYRCVVSEGLKLGISAMVTLYYPHTAHLGLPEPLLHADGWLNPST
AEAFQAYAGLCFQELGDLVKLWITINEPNRLSDIYNRSGNDTYGAAHN

LLVAHALAWRLYDRQFRPSQRGAVSLSLHADWAEPANPYADSHWRA
 AERFLQFEIAWFAEPLFKTGDYPAAMREYIASKHRRGLSSSALPRLTEA
 ERRLKGTVDFCALNHFTTRFVMHEQLAGSRYDSDRDIQFLQDITRLS
 SPTRLAVIPWGVVRKLLRWVRRNYGDMDIYITASGIDDQALEDDRLRK
 YYLGKYLQEVVKAYLIDKVRIKGYAFAKLAEKSKPRFGFFTSDFKAK
 SSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLVQKKPLIFLGC
 CFFSTLVLLLSIAIFQRQKRRKFWKAKNLQHIPLKKGKRVVS (SEQ ID
 NO: 7).

An example of an extracellular region of β -Klotho is:

MKPGCAAGSPGNEWIFFSTDEITTRYRNTMSNGGLQRSVILSALILLRAVTGFS
 GDGRAIWSKNPNFTPVNESQLFLYDTFPKNFFWGIGTGALQVEGSWKKDGK
 GPSIWDHFIHHLKNVSSTNGSSDSYIFLEKDLSALDFIGVSFYQFSISWPRLFP
 DGIVTVANAKGLQYYSTLLDALVLRNIEPIVTLYHWDLPALQEKYGGWKN
 DTIIDIFNDYATYCFQMFGDRVKYWITIHNPYLVAWHGYGTGMHAPGEKGN
 LAAVYTVGHNLKAHSAKSVWHNYNTHFRPHQKGWLSITLGSHWIEPNRSENT
 MDIFKCQQSMVSVLGWFANPIHGDGDYPEGMRKKLFSVLPIFSEAEKHEMRG
 TADFFAFSFGPNNFKPLNTMAKMGQNVSLNLREALNWIKLEYNNPRILIAEN
 GWFTDSRVKTEDTTAIYMMKNFLSQVLQAIRLDEIRVFGYTAWSLLDGFEWQ
 DAYTIRRGFLFYVDFNSKQKERKPKSSAHYYKQIIRENGFSLKESTPDVQGGQFP
 CDFSWGVTESVLKPESVASSPQFSDPHLYVWNATGNRLLHRVEGVRLKTRPA
 QCTDFVNIKKQLEMLARMKVTHYRFALDWASVLPTGNLSAVNRQALRYR
 CVVSEGLKLGISAMVTLYYPHTAHLGLPEPLLHADGWLNPNSTAEAFQAYAGL
 CFQELGDLVKLWITINEPNRLSDIYNRSGNDTYGAAHNLLVAHALAWRLYDR
 QFRPSQRGAVSLSLHADWAEPANPYADSHWRAAERFLQFEIAWFAEPLFKTG
 DYPAAMREYIASKHRRGLSSSALPRLTEAERRLKGTVDFCALNHFTTRFVM
 HEQLAGSRYDSDRDIQFLQDITRLSSPTRLAVIPWGVVRKLLRWVRRNYGDMD
 IYITASGIDDQALEDDRLRKYYLGKYLQEVVKAYLIDKVRIKGYAFAKLAEK
 SKPRFGFFTSDFKAKSSIQFYNKVISSRGFPFENSSSRCSQTQENTECTVCLFLV
 QKKP (SEQ ID NO: 8).

As described herein, β -Klotho proteins can also include fragments. As used herein, these terms are used interchangeably to mean a co-receptor, in particular and unless otherwise

specified, a human co-receptor, that upon association with FGFR1c, FGFR2c, FGFR3c or FGFR4 and FGF21 induces FGF21-like signaling activity.

The term β -Klotho also includes post-translationally modified forms of the β -Klotho amino acid sequence, for example, glycosylation at N-linked glycosylation sites. Thus, the antigen binding proteins and antigen binding protein-FGF21 fusions can bind to or be generated from proteins glycosylated at one or more of these positions.

Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusions that Specifically Bind β -Klotho or β -Klotho and One or More of FGFR1c, FGFR2c, FGFR3c, FGFR4c

A variety of antigen binding proteins and antigen binding protein-FGF21 fusions useful for modulating FGF21-like signaling are provided. These agents include, for instance, antigen binding proteins and antigen binding protein-FGF21 fusions that contain an antigen binding domain (*e.g.*, single chain antibodies, domain antibodies, immunoadhesions, and polypeptides with an antigen binding region) and specifically bind to β -Klotho or, when a FGFR-binding peptide is present, both β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c or FGFR4, in particular human FGFR1c, FGFR2c, FGFR3c or FGFR4 and human β -Klotho. Some of the agents are useful, for example, in mimicking the signaling effect generated *in vivo* by the association of an FGF receptor (*e.g.*, FGFR1c, FGFR2c, FGFR3c or FGFR4) with β -Klotho and with FGF21, and can thus be used to enhance or modulate one or more activities associated with FGF21-like signaling.

In general, the antigen binding proteins and the antigen binding protein component of the antigen binding protein-FGF21 fusions that are provided typically comprise one or more CDRs as described herein (*e.g.*, 1, 2, 3, 4, 5 or 6) and can also comprise a FGFR-binding peptide. In some instances, the antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion comprises (a) a polypeptide structure and (b) one or more CDRs that are inserted into and/or joined to the polypeptide structure. The polypeptide structure can take a variety of different forms. For example, the polypeptide structure can be, or comprise, the framework of a naturally occurring antibody, or fragment or variant thereof, or can be completely synthetic in nature. Examples of various antigen binding protein structures and the antigen binding protein component of antigen binding protein-FGF21 fusions are further described herein. In particular embodiments, the polypeptide structure of an antigen binding protein or the antigen binding protein component

of an antigen binding protein-FGF21 fusion comprises a FGFR-binding peptide, which can be integrated at any point in the heavy chain, such as in the CH2 and CH3 loops.

In certain embodiments, the polypeptide structure of the antigen binding proteins and the antigen binding protein component of antigen binding protein-FGF21 fusions is an antibody or is derived from an antibody, including, but not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as “antibody mimetics”), chimeric antibodies, humanized antibodies, antibody fusions (sometimes referred to as “antibody conjugates”), and portions or fragments of each, respectively. In some instances, the antigen binding protein is an immunological fragment of an antibody (*e.g.*, a Fab, a Fab’, a F(ab’)₂, or a scFv). The polypeptide structure of an antigen binding protein can comprise a CH3 region, which has been further engineered to comprise a peptide component that is not normally found in the wild-type CH3 sequence, such as a FGFR-binding peptide. Alternatively, an antigen binding protein-FGF21 fusion can comprise a truncated form of FGF21 fused to an antigen binding protein. These various structures are further described and defined herein.

Certain of the antigen binding proteins and the antigen binding protein component of antigen binding protein-FGF21 fusions provided herein specifically bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In one embodiment, an antigen binding protein or the antigen binding protein component of antigen binding protein-FGF21 fusion specifically binds to both human FGFR1c comprising the amino acid sequence of SEQ ID NO:5 (the extracellular region of FGFR1c) and human β -Klotho comprising the amino acid sequence of SEQ ID NO:8 (the extracellular region of β -Klotho), and in another embodiment an antigen binding protein or the antigen binding protein component of antigen binding protein-FGF21 fusion specifically binds to both human FGFR1c comprising the amino acid sequence of SEQ ID NO:5 and human β -Klotho having the amino acid sequence of SEQ ID NO:8 and the antigen binding protein or antigen binding protein-FGF21 fusion induces FGF21-like signaling. It is noted that, an antigen binding protein or antigen binding protein-FGF21 fusion of the present disclosure can, but need not, induce FGF21-like signaling and still form an aspect of the disclosed invention.

Antigen Binding Protein and Antigen Binding Protein-FGF21 Fusion Structure

Some of the antigen binding proteins and antigen binding protein components of antigen binding protein-FGF21 fusions that specifically bind β -Klotho or β -Klotho and one

or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are provided herein comprise a structure typically associated with naturally occurring antibodies. The structural units of these antibodies typically comprise one or more tetramers, each composed of two identical couplets of polypeptide chains, though some species of mammals also produce antibodies having only a single heavy chain. In a typical antibody, each pair or couplet includes one full-length “light” chain (in certain embodiments, about 25 kDa) and one full-length “heavy” chain (in certain embodiments, about 50-70 kDa). Each individual immunoglobulin chain is composed of several “immunoglobulin domains”, each consisting of roughly 90 to 110 amino acids and expressing a characteristic folding pattern. These domains are the basic units of which antibody polypeptides are composed. The amino-terminal portion of each chain typically includes a variable domain that is responsible for antigen recognition. The carboxy-terminal portion is more conserved evolutionarily than the other end of the chain and is referred to as the “constant region” or “C region”. Human light chains generally are classified as kappa and lambda light chains, and each of these contains one variable domain and one constant domain. Heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon chains, and these define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subtypes, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM subtypes include IgM, and IgM2. IgA subtypes include IgA1 and IgA2. In humans, the IgA and IgD isotypes contain four heavy chains and four light chains; the IgG and IgE isotypes contain two heavy chains and two light chains; and the IgM isotype contains five heavy chains and five light chains. The heavy chain C region typically comprises one or more domains that can be responsible for effector function. The number of heavy chain constant region domains will depend on the isotype. Each IgG heavy chain, for example, contains three C region domains known as C_H1, C_H2 and C_H3. The antibodies that are provided can have any of these isotypes and subtypes. In certain embodiments, an antigen binding protein or antigen binding protein component of an antigen binding protein-FGF21 fusion that specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c or FGFR4 is an antibody of the IgG1, IgG2, or IgG4 subtype, and which can comprise an FGFR-binding peptide integrated into the constant region of the heavy chain(s).

In full-length light and heavy chains, the variable and constant regions are joined by a “J” region of about twelve or more amino acids, with the heavy chain also including a “D” region of about ten more amino acids. *See, e.g.,* Fundamental Immunology, 2nd ed., Ch. 7 (Paul, W., ed.) 1989, New York: Raven Press (hereby incorporated by reference in its entirety

for all purposes). The variable regions of each light/heavy chain pair typically form the antigen binding site.

One example of an IgG2 heavy chain constant domain of an exemplary monoclonal antibody, which comprises wild type CH2 and CH3 loops, that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 has the amino acid sequence:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ
ID NO: 9).

which is encoded by the nucleotide sequence:

gcctccaccaagggcccatcggtcttccccctggcgccctgctccaggagcacctccgagagcacagcggcc
ctgggctgcctggtcaaggactacttccccgaaccggtgacggtgctggaactcaggcgctctgaccagcg
gcgtgcacaccttcccagctgtcctacagtctcaggactctactccctcagcagcggtgacctgccctcca
gcaacttcggcacccagacctacacctgcaacgtagatcacaagcccagcaacaccaaggtggacaagaca
gttgagcgcaaagtgtgtcgtgagtgcccaccgtgcccagcaccacctgtggcaggaccgtcagtcttctcttc
ccccaaaaccaaggacacctcatgatctcccgaccctgaggtcacgtgcgtggtggtggacgtgagc
cacgaagaccccgaggtccagttcaactggtacgtggacggcggtggaggtgcataatgccaagacaaagcca
cgggaggagcagttcaacagcacgttccgtgtggtcagcgctcctcaccgttgccaccaggactggctgaacg
gcaaggagtacaagtgaaggtctccaacaaaggcctcccagcccccatcgagaaaaccatctccaaaacca
aagggcagccccgagaaccacaggtgtacacctgcccccatcccgaggagatgaccaagaaccaggt
cagcctgacctgcctggtcaaaggcttctaccccagcgacatcgccgtggagtgaggagcaatgggcagcc
ggagaacaactacaagaccacacctcccatgctggactccgacggctccttctctctacagcaagctcaccg
tggaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccacta
cacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 10)

In another aspect, a heavy chain of any isotype can but need not comprise a FGFR-binding peptide, which can be integrated into the constant region of the heavy chain. Any

FGFR-binding peptide can be inserted into a heavy chain, including those FGFR-binding peptides disclosed herein, for example in Table 4A. The FGFR-binding peptide can be integrated into any region of the heavy chain constant region, including the CH2 or CH3 loop regions of the heavy chain. Examples of heavy chains that comprise a FGFR-binding peptide are listed in Table 5A.

One particular example of a IgG2 heavy chain comprising a FGFR-binding peptide has the amino acid sequence:

QVQLVESGGGVVQPGRSLRLSCAASRFSFSRYGMHWVRQAPGKGLE
 WVAVIWF DGRNQYYADSVKGRFTISRDN SKNTLFLQMNSLRVEDTAV
 YYCARDHPVVGTSFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGG
 TAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
 TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL
 GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
 VHNAKTKPREEQYQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
 APIEKTISKAKGQPREPQVYTLPPSRDELGGCYQAWGYYVCGGTKNQ
 VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL
 TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:
 11);

which is encoded by the nucleotide sequence:

cagggtgcagttggtggagctctgggggaggcgtggtccagcctgggaggtccctgagactctcctgtgcagcgt
 ctagattctccttcagtagatatggcatgcactgggtccgccaggtccaggcaaggggctggagtgggtggc
 agttatatggtttgatggaagaaatcaatactatgcagactccgtgaaggggcgattcaccatctccagagacaat
 tccaagaatacgtgtttctgcaaatgaacagcctgagagtcgaggacacggctgtgtattactgtgcgagagat
 caccagtagttggtacgagctttgactactggggccagggaaccctggtcaccgtctctagtgcctccaccaa
 gggcccatcggctcttccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcct
 ggtcaaggactacttccccgaaccggtgacgggtgctgtggaactcaggcgccctgaccagcggcgtgcacac
 ctccccggctgtcctacagtctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttggg
 caccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagaaagttgagcccaa
 atcttgtgacaaaactcacacatgccaccgtgccagcacctgaactcctggggggaccgtcagtcttctctt
 cccccaaaacccaaggacaccctcatgatctcccgaccctgaggtcacatgcgtggtggtggacgtgag
 ccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagcc
 gcgggaggagcagtagcagacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
 tggcaaggagtacaagtgaaggtctccaacaaagccctccagcccccatcgagaaaaccatctccaaagc

caaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggatgagctgggtggttgctacca
 ggcctggggctactacgtgtgcggtggtaccaagaaccaggtcagcctgacctgcctgggtcaaaggcttctatc
 ccagcgacatcgccgtggagtgaggagagcaatgggcagccggagaacaactacaagaccacgcctcccgt
 gctggactccgacggctccttcttctctatagcaagctcaccgtggacaagagcaggtggcagcaggggaac
 gtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggt
 aaa (SEQ ID NO: 12)

One example of a kappa light constant domain of an exemplary monoclonal antibody that binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 has the amino acid sequence:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL
 QSGNSQESVTEQDSKDSSTLSKADYEKHKVYACEVTHQGLS
 SPVTKSFNRGEC (SEQ ID NO: 13).

which is encoded by the nucleotide sequence:

cgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgtgtg
 gtgcctgctgaataacttctatcccagagaggccaaagtacagtgggaaggtggataacgccctccaatcgggta
 actcccaggagagtgctcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctg
 agcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtc
 acaaagagcttcaacaggggagagtg (SEQ ID NO: 14)

One example of a lambda light constant domain of an exemplary monoclonal antibody that binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 has the amino acid sequence:

GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSP
 VKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST
 VEKTVAPTECS (SEQ ID NO: 15)

which is encoded by the nucleotide sequence:

ggtcagcccaaggccaaccccactgtcactctgttcccgcctcctctgaggagctccaagccaacaaggcca
 cactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctggaaggcagatggcagccccgtc
 aaggcgggagtgaggaccaccaaaccctccaaacagagcaacaacaagtacgcggccagcagctacctga

gcctgacgcccgagcagtggaagtccacagaagctacagctgccaggtcacgcatgaagggagcaccgtg
gagaagacagtggcccctacagaatgttca (SEQ ID NO: 16)

Variable regions of immunoglobulin chains generally exhibit the same overall structure, comprising relatively conserved framework regions (FR) joined by three hypervariable regions, more often called “complementarity determining regions” or CDRs. The CDRs from the two chains of each heavy chain/light chain pair typically are aligned by the framework regions to form a structure that binds specifically with a specific epitope on the target protein (*e.g.*, β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4). From N-terminal to C-terminal, naturally-occurring light and heavy chain variable regions both typically conform with the following order of these elements: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. A numbering system has been devised for assigning numbers to amino acids that occupy positions in each of these domains. This numbering system is defined in Kabat Sequences of Proteins of Immunological Interest (1987 and 1991, NIH, Bethesda, MD), or Chothia & Lesk, 1987, *J. Mol. Biol.* 196:901-917; or Chothia *et al.*, 1989, *Nature* 342:878-883, or AHO any of which can be employed to describe the regions of the disclosed antigen binding proteins.

The various heavy chain and light chain variable regions provided herein are depicted in Tables 2A and 2B. Each of these variable regions can be attached to the disclosed heavy and light chain constant regions to form a complete antibody heavy and light chain, respectively. Further, each of the heavy and light chain sequences can be combined to form a complete antibody structure. It should be understood that the heavy chain and light chain variable regions provided herein can also be attached to other constant domains having different sequences than the exemplary sequences listed above.

Specific examples of some of the full length light and heavy chains of the antibodies that are provided and their corresponding amino acid sequences are summarized in Tables 1A and 1B. Table 1A shows exemplary light chain sequences, and Table 1B shows exemplary heavy chain sequences. The heavy chains presented in Table 1B do not comprise a FGFR-binding peptide; heavy chains comprising a FGFR-binding peptide are presented in Table 5A.

Table 1A – Exemplary Antibody Light Chain Sequences

SEQ ID NO:	Designation	Contained in Clone	Amino Acid Sequence
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SEQ ID NO:	Designation	Contained in Clone	Amino Acid Sequence
17	L1	1A2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVYSDGNTY LSWLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGAGT DFTLKISRVEADDVGIYYCMQAIEFPWTFGQGTQVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
18	L2	2G10	QSVLTQPPSVSAAPGQKVTVSCSGSSSNIGNNYVSW YQQLPGTAPKLLIYDNNKRPSGIPDRFSGSGSKSGTSAT LGITGLQTGDEAEYYCGTWDSSLSVVAFGGGTKLT VLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADGSPVKAGVETTKPSKQSNNKYAAS SYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC S
19	L3	14E8	DIQMTQSPSSLSASVGDRVTITCQASQDINNYLNWY QQKLGKAPKLLIYDTSNLETGVPSRFSGSGFGTDFTF TISSLQPEDIATYYCQQYDNLFTFGQGTRLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
21	L5	25B10	QTVVTQEPSFSVSPGGTVTLTCGVSSGSVSTRYYPS WYQQTPGQAPRTLINSTNTRSSGVPDRFSGSILGNKA ALTITGAQADDESDFCVLYMGSGIWVFGGGTKLT VLGQPKANPTVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADGSPVKAGVETTKPSKQSNNKYAAS SYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC S
22	L6	3B4	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHYDGNT YLSWLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGA GTDFTLKISRVEAEDVGIYYCMQALEFPWTFGQGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC
23	L7	1B5	DIVMTQTPLTSPVTLGQPASISCRSSQSLVHYDGNT YLSWLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGA GTDFTLKISRVEAEDVGIYYCMQALEFPWTFGQGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC
24	L8	10H3	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHYDGNTY LSWLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGAGT DFTLKISRVA AEDVGIYYCMQALEFPWTFGQGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS TLTSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C

SEQ ID NO:	Designation	Contained in Clone	Amino Acid Sequence
25	L9	9D10	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNNYVSWY QQLPGTAPKLLIYDNNRRPSGIPDRFSGSKSGTSATL GITGLQTGDEADYYCGTWDSSLSAVVFGGGTKLTV LGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADGSPVKAGVETTKPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
26	L10	3F4	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNNYVSWY QQLPGTAPKLLIYDNNRRPSGIPDRFSGSKSGTSATL GITGLQTGDEADYYCETWDSSLSAGVFGGGTKLTV LGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADGSPVKAGVETTKPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
27	L11	8F9	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNNYVSWY QQLPGTAPKLLIYDNNRRPSGIPDRFSGSKSGTSATL GITGLQTGDEADYYCGTWDSSLSAVVFGGGTKLTV LGQPKANPTVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADGSPVKAGVETTKPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Table 1B – Exemplary Antibody Heavy Chain Sequences

SEQ ID NO:	Designation	Contained in Clone	Sequence
28	H1	1A2	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQ GRVTMTRDTSISTAYMELSRLRSDDTAVYYCARD ATSGWFDYWGGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK

SEQ ID NO:	Designation	Contained in Clone	Sequence
29	H2	2G10	QVQLVESGGGVVQPGRSLRLSCAASRFSFSRYGM HWVRQAPGKGLEWVAVIWFDGRNQYYADSVKG RFTISRDNSKNTLFLQMNSLRVEDTAVYYCARDHP VVGTSFDYWGGQGLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK
30	H3	14E8	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGM HWVRQAPGKGLEWVAVIGYDGSYKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGS NWNYYGGSFDYWGGQGLVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
32	H5	25B10	EVQLLESGGGLVQPEGSLRLSCAASGFTFSIYAMS WVRQAPGKGLEWVSDISGRGGYTYADSVKGRF TISRDNSKNTLYLQMNSLRADDTAVYYCAKDRSI AVAGPFDWFVGQGLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK

SEQ ID NO:	Designation	Contained in Clone	Sequence
33	H6	3B4	QVQLVQSGAEVKKPGASVKVSCKASGYTFTAYY MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQ GRVTMTRDTSIRTAYMELSWLRSDDTAVYYCARD ATSGWFDIWGQGTPVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVD HKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
34	H7	1B5	QVQLVQSGAEVKKPGASVKVSCKASGYTFTAYY MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQ GRVTMTRDTSIRTAYMELSWLRSDDTAVYYCARD ATSGWFDFFWGQGTPVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVD HKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
35	H8	10H3	QVQLVQSGAEVRKPGASVKVSCKASGYTFTAYY MHWVRQAPGQGLEWMGWINPYSGGTNSAQKFQ GRVTMTRDTSISTAYMELSWLRSDDTAVYYCARD ATSGWFDFFWGQGLTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVD HKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Designation	Contained in Clone	Sequence
36	H9	9D10	QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYGM HWVRQAPGKGLEWVAVIWYDGRNEYADSVKG RFTISRDN SKNTLYLRMNSLRAEDTAVYYCARDH PVAGTSFDYWGQGT LVT VSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VVH QDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
37	H10	3F4	QVQLVESGGGVVQPGRSLRLSCAASGFIFRSYGMH WVRQAPGKGLEWVAVISYDGSNKYYADSVKGRF TISRDN SKNTLYLQMNSLRAEDTAVYYCARDHPV AGTSFDYWGQGT LVT VSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DH KPSNTKVDKTVERKCCVECPCPAPPVAGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTFRVVS VLT VVH QD WLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
38	H11	8F9	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGM HWVRQAPGKGLEWVAVIWYDGRNKYHADSVKG RFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDH PVAGTSFDYWGQGT LVT VSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VVH QDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Again, each of the exemplary heavy chains (H1, H2, H3 etc.) listed in Table 1B, or alternatively each of the exemplary heavy chains comprising a FGFR-binding protein listed in Table 5A can be combined with any of the exemplary light chains shown in Table 1A to form an antibody. Examples of such combinations include H1 combined with any of L1

through L11; H2 combined with any of L1 through L11; H3 combined with any of L1 through L11, any heavy chain comprising a FGFR-binding peptide (e.g., those shown in Table 5) combined with any of L1 through L11, any heavy chain comprising a FGFR-binding peptide (e.g., those shown in Table 5) combined with any of L1 through L11, and so on. In some instances, the antibodies include at least one heavy chain and one light chain from those listed in Tables 1A, 1B and 5A. In some instances, the antibodies comprise two different heavy chains and two different light chains listed in Tables 1A, 1B and 5A. In other instances, the antibodies contain two identical light chains and two identical heavy chains. As an example, an antibody or immunologically functional fragment thereof can include two H1 heavy chains and two L1 light chains, or two H2 heavy chains and two L2 light chains, or two H3 heavy chains and two L3 light chains and other similar combinations of pairs of light chains and pairs of heavy chains as listed in Tables 1A, 1B and 5A.

Other antigen binding proteins and the antigen binding protein component of the antigen binding protein-FGF21 fusions that are provided herein comprise variants of antibodies formed by combination of the heavy and light chains shown in Tables 1A, 1B and 5A and comprise light and/or heavy chains that each have at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to the amino acid sequences of these chains. In some instances, such antibodies include at least one heavy chain and one light chain, whereas in other instances the variant forms contain two identical light chains and two identical heavy chains.

Variable Domains of Antigen Binding Proteins and the Antigen Binding Protein Component of Antigen Binding Protein-FGF21 Fusions

Also provided are antigen binding proteins and the antigen binding protein components of antigen binding protein-FGF21 fusions that contain an antibody heavy chain variable region selected from the group consisting of V_{H1} - V_{H11} as shown in Table 2B and/or an antibody light chain variable region selected from the group consisting of V_{L1} - V_{L11} as shown in Table 2A, and immunologically functional fragments, derivatives, muteins and variants of these light chain and heavy chain variable regions.

Antigen binding proteins and antigen binding protein-FGF21 fusions of this type can generally be designated by the formula " V_{HX}/V_{LY} ," where "x" corresponds to the number of heavy chain variable regions and "y" corresponds to the number of the light chain variable regions.

Table 2A - Exemplary Antibody Variable Light (V_L) Chains

Contained in Clone	Designa- tion	SEQ ID NO.	Amino Acid Sequence
1A2	V_L1	39	DIVMTQTPLSSPVTLGQPASISCRSSQSLVYSDGNT YLSWLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGA GTDFTLKISRVEADDVGIYYCMQAIEFPWTFGQGT QVEIKR
2G10	V_L2	40	QSVLTQPPSVSAAPGQKVTVSCSGSSSNIGNNYVS WYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGT SATLGITGLQTGDEAEYYCGTWDSSLSVVAFGGG TKLTVLG
14E8	V_L3	41	DIQMTQSPSSLSASVGDRVITTCQASQDINNYLNW YQQKLGKAPKLLIYDTSNLETGVPSRFSGSGFGTD FTFTISSLQPEDIATYYCQQYDNLFTFGQGTRLEIK R
25B10	V_L5	43	QTVVTQEPSFSVSPGGTVTLTGCVSSGSVSTRYYPS WYQQTPGQAPRTLINSTNTRSSGVPDRFSGSILGN KAALTITGAQADDESDFCVLYMGSGIWVFGGGT KLTVLG
3B4	V_L6	44	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHYDGNT YLSWLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGA GTDFTLKISRVEAEDVGIYYCMQALEFPWTFGQGT KVEIK
1B5	V_L7	45	DIVMTQTPLTSPVTLGQPASISCRSSQSLVHYDGNT YLSWLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGA GTDFTLKISRVEAEDVGIYYCMQALEFPWTFGQGT KVEIK
10H3	V_L8	46	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHYDGNT YLSWLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGA GTDFTLKISRVAEDVGIYYCMQALEFPWTFGQG TKVEIK
9D10	V_L9	47	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVS WYQQLPGTAPKLLIYDNNRRPSGIPDRFSGSKSGT SATLGITGLQTGDEADYYCGTWDSSLSAVVFGGG TKLTVL
3F4	V_L10	48	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVS WYQQLPGTAPKLLIYDNNNRPSGIPDRFSGSKSGT SATLGITGLQTGDEADYYCETWDSSLSAGVFGGG TKLTVL
8F9	V_L11	49	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVS WYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGT SATLGITGLQTGDEADYYCGTWDSSLSAVVFGGG TKLTVL

Table 2B – Exemplary Antibody Variable Heavy (V_H) Chains

Contained in Clone	Designa- tion	SEQ ID NO.	Amino Acid Sequence
1A2	V_H 1	50	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQ GRVTMTRDTSISTAYMELSRRLRSDDTAVYYCARD ATSGWFDYWGQGTLVTVSS
2G10	V_H2	51	QVQLVESGGGVVQPGRSLRLSCAASRFSFSRYGM HWVRQAPGKGLEWVAVIWFDGRNQYYADSVKG RFTISRDNSKNTLFLQMNSLRVEDTAVYYCARDHP VVGTSFDYWGQGTLVTVSS
14E8	V_H3	52	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGM HWVRQAPGKGLEWVAVIGYDGSYKYYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDG SNWNYGGSFDYWGQGTLVTVSS
25B10	V_H5	54	EVQLLESGGGLVQPEGSLRLSCAASGFTFSIYAMS WVRQAPGKGLEWVSDISGRGGYTYADSVKGRF TISRDNSKNTLYLQMNSLRADDTAVYYCAKDRSI AVAGPFDFWGQGTLVTVSS
3B4	V_H6	55	QVQLVQSGAEVKKPGASVKVSCKASGYTFTAYY MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQ GRVTMTRDTSIRTAYMELSWLRSDDTAVYYCARD ATSGWFDFWGQGTPVTVSS
1B5	V_H7	56	QVQLVQSGAEVKKPGASVKVSCKASGYTFTAYY MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQ GRVTMTRDTSIRTAYMELSWLRSDDTAVYYCARD ATSGWFDFWGQGTPVTVSS
10H3	V_H8	57	QVQLVQSGAEVRKPGASVKVSCKASGYTFTAYY MHWVRQAPGQGLEWMGWINPYSGGTNSAQKFQ GRVTMTRDTSISTAYMELSWLRSDDTAVYYCARD ATSGWFDFWGQGTLVTVSS
9D10	V_H9	58	QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYGM HWVRQAPGKGLEWVAVIWYDGRNEYADSVKG RFTISRDNSKNTLYLRMNSLRAEDTAVYYCARDH PVAGTSFDYWGQGTLVTVSS
3F4	V_H10	59	QVQLVESGGGVVQPGRSLRLSCAASGFIFRSYGM HWVRQAPGKGLEWVAVISYDGSNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDHP VAGTSFDYWGQGTLVTVSS
8F9	V_H11	60	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGM HWVRQAPGKGLEWVAVIWYDGRNKYHADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDH PVAGTSFDYWGQGTLVTVSS

Table 2C - Coding Sequence for Antibody Variable Light (V_L) Chains

Contained in Clone	Designa- tion	SEQ ID NO.	Coding Sequence
1A2	V _L 1	61	gatattgtgatgaccagactccactctcctcacctgtcacccttggacagccgg cctccatctcctgcaggtctagtcaaagcctcgtatacagtgatggaaacaccta cttgagttggcttcagcagaggccaggccagcctccaagactcctaatttataag atttctaaccgggttctctgggggtcccagacagattcagtggcagtggggcaggg acagatttcacactgaaaatcagcaggggtggaagctgacgatgtcgggatttatt actgcatgcaagctatagaatttccgtggacgttcggccaagggacccaggtg gaaatcaaacgt
2G10	V _L 2	62	cagtctgtgtgacgcagccgccctcagtgctcgcggccccaggacagaaggt caccgtctcctgctctggaagcagctccaacattgggaataattatgtatcctgt accagcaactcccaggaacagccccaaactcctcatttatgacaataataagc gaccctcagggtattcctgaccgattctctggctccaagtctggcacgtcagcca ccctgggcatcaccggactccagactggggacgaggccgagtattactgcgg aacatgggatagcagcctgagtggttggtgcattcggcggaggggaccaagctga ccgtcctaggt
14E8	V _L 3	63	gacatccagatgaccagctcctcctcctgtctgcatctgtaggagacaga gtcaccatcacttgccaggcgagtcaggacattaacaattatttaaattggtatca gcagaaactagggaagccctaaagctcctgatctacgatacatccaatttga aacaggggtcccatcaagggtcagtggaagtggatttgggacagattttactttc accatcagcagcctgcagcctgaagatattgcaacatattactgtcaacagtatg ataatctcttcaccttcggccaagggacacgactggagattaaacgt
25B10	V _L 5	65	cagactgtggtgaccagaggccatcgttctcagtgctccctggaggggacagt cacactcacttggtgctgagctctggctcagtcctactaggtactacccagct ggtaccagcagaccccaggccaggctccacgcacgctcatcaacagcacaaa cactcgtcttctgggggtccctgatcgttctctggctccatccttgggaacaaag ctgccctcaccatcacggggggcccaggcagatgatgaatctgattatttctgtgt gctgtatatgggtagtggcatttgggtgttcggcggaggggaccaagctgaccgt cctaggt
3B4	V _L 6	66	gatattgtgatgaccagactccactctcctcacctgtcacccttggacagccgg cctccatctcctgcaggtctagtcaaagcctcgttactatgatggaaacacctac ttgagttggcttcagcagaggccaggccagcctccaagactcctaatttataaga tttctaaccgggttctctgggggtcccagacagattcagtggcagtggggcaggg cagatttcacactgaaaatcagcaggggtggaagctgaggatgtcgggatttatta ctgcatgcaagctctagaatttccgtggacgttcggccaagggaccaaggtgg aatcaaaa
1B5	V _L 7	67	gatattgtgatgaccagactccactcactcacctgtcacccttggacagccgg cctccatctcctgcaggtctagtcaaagcctcgttactatgatggaaacacctac ttgagttggcttcagcagaggccaggccagcctccaagactcctaatttataaga tttctaaccgggttctctgggggtcccagacagattcagtggcagtggggcaggg cagatttcacactgaaaatcagcaggggtggaagctgaggatgtcgggatttatta ctgcatgcaagctctagaatttccgtggacgttcggccaagggaccaaggtgg aatcaaaa

Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
10H3	V _L 8	68	gatattgtgatgaccagactccactctcctcacctgtcacccttggacagccgg cctccatctcctgcaggtctagtcaaagcctcgttactatgatggaaacacctac ttgagttggcttcagcagaggccaggccagcctccaagactcctaatttataaga tttctaaccggttctctgggggtcccagacagattcagtggcagtggggcaggga cagatttcacactgaaaatcagcaggggtggcagctgaggatgtcgggatttatta ctgcatgcaagctctagaatttccgtggacgttcggccaagggaaccaaggtgg aatcaaa
9D10	V _L 9	69	cagtctgtgttgacgcagccgccctcagtgtctgcggccccaggacagaaggt caccatctcctgctctggaagcagctccaacattgggaataattatgtatcctggt accagcagctcccagggaacagccccaaactcctcatttatgacaataataggc gacctcagggaattcctgaccgattctctggctccaagtctggcacgtcagcca ccctgggcatcaccggactccagactggggacgaggccgattattactgcgga acatgggatagcagcctgagtgtgtgtgttcggcggagggaaccaagctga ccgtccta
3F4	V _L 10	70	cagtctgtgttgacgcagccgccctcagtgtctgcggccccaggacagaaggt caccatctcctgctctggaagcagctccaacattgggaataattatgtatcctggt accagcagctcccagggaacagccccaaactcctcatttatgacaataataacc gacctcagggaattcctgaccgattctctggctccaagtctggcacgtcagcca ccctgggcatcaccggactccagactggggacgaggccgattattactgcgaa acatgggatagcagcctgagtgtgtgtgttcggcggagggaaccaagctga ccgtccta
8F9	V _L 11	71	cagtctgtgttgacgcagccgccctcagtgtctgcggccccaggacagaaggt caccatctcctgctctggaagcagctccaacattgggaataattatgtatcctggt accagcaactcccagggaacagccccaaactcctcatttatgacaataataagc gacctcagggaattcctgaccgattctctggctccaagtctggcacgtcagcca ccctgggcatcaccggactccagactggggacgaggccgattattactgcgga acttgggatagcagcctgagtgtgtgtgttcggcggagggaaccaagctgac cgtccta

Table 2D - Coding Sequence for Antibody Variable Heavy (V_H) Chains

Contained in Clone	Designation	SEQ ID NO.	Coding Sequence
1A2	V _H 1	72	caggtgcaactggtgcagtctggggctgaggtgaagaagcctggggcctcag tgaaggtctcctgcaaggcttctggatacaccttcaccggctactatatgcactg ggtgcgacagggcccctggacaagggttgagtggatgggatggatcaaccct aacagtgggtggcacaactctgcacagaagtttcagggcagggtcaccatgac cagggaacgtccatcagcacagcctacatggagctgagcaggctgagatct gacgacacggccgtgtattactgtgcaagagatgcgaccagtggtgtgttgac tactggggccagggaaccctggtcaccgtctctagt

Contained in Clone	Designa- tion	SEQ ID NO.	Coding Sequence
2G10	V _H 2	73	caggtgcagttggtggagtctgggggagggcgtggtccagcctgggaggtccc tgagactctcctgtgcagcgtctagattctccttcagtagatatggcatgcactgg gtccgccagggtccaggcaaggggctggagtgggtggcagttatatggtttga tggaagaaatcaatactatgcagactccgtgaaggggcgattcaccatctccag agacaattccaagaatacgtgtttctgcaaatgaacagcctgagagtcgagga cacggctgtgtattactgtgcgagagatcacccagtagttggtacgagctttgac tactggggccagggaaccctggtcaccgtctctagt
14E8	V _H 3	74	caggtgcaactggtggagtctgggggagggcgtggtccagcctgggaggtccc tgagactctcctgtgcagcgtctggattcaccttcagtagctatggcatgcactgg gtccgccagggtccaggcaaggggctggagtgggtggcagttatagggtatg atggaagtataaatactatgcagactccgtgaagggccgattcaccatctccag agacaattccaagaacacgctatatctgcaaatgaacagcctgagagccgagg acacggctgtgtattactgtgcgagagatgggtctaactggaactacgggggtt cttttgactactggggccagggaaccctggtcaccgtctctagt
25B10	V _H 5	76	gaggtgcagctgttggagtctgggggagggcttggtacagccggaggggtccc tgagactctcctgtgcagcctctggattcaccttagcatctatgcatgagctgg gtccgccagggtccagggaaggggctggagtgggtctcagatattagtggtcg tggtggttacacatactacgcagactccgtgaagggccggttcaccatctccag agacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgacg acacggccgtatattactgtgcgaaagatcggagtatagcagtggttggtcctt tgacttctggggccagggaaccctggtcaccgtctctagt
3B4	V _H 6	77	caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcag tgaaggtctcctgcaaggcttctggatacaccttcaccgcctactatatgcactgg gtgcgacaggcccctggacaagggcttgagtggatgggatggatcaacccta acagtgggtggcacaaactctgcacagaagtttcagggcagggtcaccatgacc agggacacgtccatcagaacagcctacatggagttgagctggctgagatctga cgacacggccgtgtattattgtgcgagagatgcgaccagtggctggtttgacat ctggggccagggaaccccggtcaccgtctctca
1B5	V _H 7	78	caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcag tgaaggtctcctgcaaggcttctggatacaccttcaccgcctactatatgcactgg gtgcgacaggcccctggacaagggcttgagtggatgggatggatcaacccta acagtgggtggcacaaactctgcacagaagtttcagggcagggtcaccatgacc agggacacgtccatcagaacagcctacatggagttgagctggctgagatctga cgacacggccgtgtattactgtgcgagagatgcgaccagtggctggtttgactt ctggggccagggaaccccggtcaccgtctctca
10H3	V _H 8	79	caggtgcagctggtgcagtctggggctgaggtgaggaagcctggggcctcag tgaaggtctcctgcaaggcttctggatacaccttcaccgcctactatatgcactgg gtgcgacaggcccctggacaagggcttgagtggatgggatggatcaacccta cagtgggtggcacaaactctgcacagaagtttcagggcagggtcaccatgacca gggacacgtccatcagcacagcctacatggagttgagctggctgagatctgac gacacggccgtgtattactgtgcgagagatgcgaccagtggctggtttgacttct ggggccagggaaccctggtcaccgtctctca

Contained in Clone	Designa- tion	SEQ ID NO.	Coding Sequence
9D10	V _H 9	80	caggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccc tgagactctcctgtgcagcgtctggattcaccttcagaagctatggcatgcaactg ggccgccaggctccaggcaaggggctggagtgggtggcagttatatggtatg atggaaggaatgaatactatgcagactccgtgaagggccgattcaccatctcca gagacaattccaagaatacgtgtatctgcgaatgaacagtctgagagccgag gacacggctgtgtattactgtgcgagagatcacccagtagctggtacgagcttt gactactggggccagggaaccctggtcaccgtctctca
3F4	V _H 10	81	caggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccc tgagactctcctgtgcagcctctggattcatcttcaggagctatggcatgcaactg gtccgccaggctccaggcaaggggctggagtgggtggcagttatatcatatga tggaagtaataaatactatgcagactccgtgaagggccgattcaccatctccag agacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgagg acacggctgtctattactgtgcgagagatcacccagtggtgtacacctcttga ctactggggccagggaaccctggtcaccgtctctca
8F9	V _H 11	82	caggtgcagctggtggagtctgggggaggcgtggtccagcctgggaggtccc tgagactctcctgtgcagcgtctggattcaccttcagtagctatggcatgcaactg gtccgccaggctccaggcaaggggctggagtgggtggcagttatatggtatg atggaagaaataaataccatgcagactccgtgaagggccgattcaccatctcca gagacaattccaagaacacgctatatctgcaaatgaacagcctgagagccgag gacacggctgtgtattactgtgcgagagatcacccagtagctggtacgagcttt gactactggggccagggaaccctggtcaccgtctctca

Each of the heavy chain variable regions listed in Table 2B can be combined with any of the light chain variable regions shown in Table 2A to form an antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion. Examples of such combinations include V_H1 combined with any of V_L1-V_L11; V_H2 combined with any of V_L1-V_L11; V_H3 combined with any of V_L1-V_L11 ; and so on.

In some instances, the antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion includes at least one heavy chain variable region and/or one light chain variable region from those listed in Tables 2A and 2B. In some instances, the antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion includes at least two different heavy chain variable regions and/or light chain variable regions from those listed in Table 2B. An example of such an antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion comprises (a) one V_H1, and (b) one of V_H2-V_H11 . Another example comprises (a) one V_H2, and (b) one of V_H1 or V_H3-V_H11. Again another example comprises (a) one V_H3, and (b) one of V_H1, V_H2, or V_H5 or V_H11, etc.

Again another example of such an antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion comprises (a) one V_L1 , and (b) one of V_L2 - V_L11 . Again another example of such an antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion comprises (a) one V_L2 , and (b) one of V_L1 , or V_L3 - V_L11 , etc. Again another example of such an antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion comprises (a) one V_L3 , and (b) one of V_L1 , V_L2 , or V_L4 - V_L11 , etc.

The various combinations of heavy chain variable regions can be combined with any of the various combinations of light chain variable regions.

In other instances, the antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion contains two identical light chain variable regions and/or two identical heavy chain variable regions. As an example, the antigen binding protein or the antigen binding protein component of an antigen binding protein-FGF21 fusion can be an antibody or immunologically functional fragment that includes two light chain variable regions and two heavy chain variable regions in combinations of pairs of light chain variable regions and pairs of heavy chain variable regions as listed in Tables 2A and 2B.

Some antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that are provided comprise a heavy chain variable domain comprising a sequence of amino acids that differs from the sequence of a heavy chain variable domain selected from V_H1 - V_H11 at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, with the deletions, insertions and/or substitutions resulting in no more than 15 amino acid changes relative to the foregoing variable domain sequences. The heavy chain variable region in some antigen binding proteins and some antigen binding protein components of antigen binding protein-FGF21 fusions comprise a sequence of amino acids that has at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 99% sequence identity to the amino acid sequences of the heavy chain variable region of V_H1 - V_H11 .

Certain antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components comprise a light chain variable domain comprising a sequence of amino acids that differs from the sequence of a light chain variable domain selected from V_L1 - V_L11 at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of

one amino acid, with the deletions, insertions and/or substitutions resulting in no more than 15 amino acid changes relative to the foregoing variable domain sequences. The light chain variable region in some antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components comprise a sequence of amino acids that has at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 99% sequence identity to the amino acid sequences of the light chain variable region of V_L1-V_L11.

In additional instances, antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components comprise the following pairings of light chain and heavy chain variable domains: V_L1 with V_H1, V_L2 with V_H2, V_L3 with V_H3, V_L4 with V_H4, V_L5 with V_H5, V_L6 with V_H6, V_L7 with V_H7, V_L8 with V_H8, V_L9 with V_H9, V_L10 with V_H10, V_L11 with V_H11. In some instances, the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components in the above pairings can comprise amino acid sequences that have 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with the specified variable domains.

Still other antigen binding proteins and antigen binding protein components of an antigen binding protein-FGF21 fusions, *e.g.*, antibodies or immunologically functional fragments, include variant forms of a variant heavy chain and a variant light chain as just described.

Antigen Binding Protein and Antigen Binding Protein-FGF21 Fusion Antigen Binding Protein Component CDRs

The antigen binding proteins and antigen binding protein components of antigen binding protein-FGF21 fusions disclosed herein are polypeptides into which one or more CDRs are grafted, inserted and/or joined. An antigen binding protein or antigen binding protein component of an antigen binding protein-FGF21 fusion can have 1, 2, 3, 4, 5 or 6 CDRs. An antigen binding protein or antigen binding protein component of an antigen binding protein-FGF21 fusion thus can have, for example, one heavy chain CDR1 (“CDRH1”), and/or one heavy chain CDR2 (“CDRH2”), and/or one heavy chain CDR3 (“CDRH3”), and/or one light chain CDR1 (“CDRL1”), and/or one light chain CDR2 (“CDRL2”), and/or one light chain CDR3 (“CDRL3”). Some antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components include both a CDRH3 and a CDRL3. Specific heavy and light chain CDRs are identified in Tables 3A and 3B, respectively.

Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody can be identified using any of the numbering systems known to those of skill in the art, such as the system described by Kabat et al. in *Sequences of Proteins of Immunological Interest*, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991, *see also* Chothia and Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia *et al.*, 1989, *Nature* 342: 877-883. Certain antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that are disclosed herein comprise one or more amino acid sequences that are identical or have substantial sequence identity to the amino acid sequences of one or more of the CDRs presented in Table 3A (CDRHs) and Table 3B (CDRLs).

Table 3A - Exemplary CDRH Sequences

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
1A2	83	V _H 1	CDRH1-1	GYVMH
2G10	84	V _H 2	CDRH1-2	RYGMH
14E8	85	V _H 3	CDRH1-3	SYGMH
25B10	87	V _H 5	CDRH1-5	IYAMS
3B4	88	V _H 6	CDRH1-6	AYYMH
1B5	88	V _H 7	CDRH1-7	AYYMH
10H3	88	V _H 8	CDRH1-8	AYYMH
9D10	85	V _H 9	CDRH1-9	SYGMH
3F4	85	V _H 10	CDRH1-10	SYGMH
8F9	85	V _H 11	CDRH1-11	SYGMH
1A2	89	V _H 1	CDRH2-1	WINPNSGGTNSAQKFQG
2G10	90	V _H 2	CDRH2-2	VIWFDGRNQYYADSVKG
14E8	91	V _H 3	CDRH2-3	VIGYDGSYKYYADSVKG
25B10	93	V _H 5	CDRH2-5	DISGRGGYTTYADSVKG
3B4	89	V _H 6	CDRH2-6	WINPNSGGTNSAQKFQG
1B5	89	V _H 7	CDRH2-7	WINPNSGGTNSAQKFQG
10H3	94	V _H 8	CDRH2-8	WINPYSGGTNSAQKFQG
9D10	95	V _H 9	CDRH2-9	VIWYDGRNEYADSVKG
3F4	96	V _H 10	CDRH2-10	VISYDGSNKYYADSVKG
8F9	97	V _H 11	CDRH2-11	VIWYDGRNKYHADSVKG

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
1A2	98	V _H 1	CDRH3-1	GWFDY
2G10	99	V _H 2	CDRH3-2	GTSFDY
14E8	100	V _H 3	CDRH3-3	YGGSFYD
25B10	102	V _H 5	CDRH3-5	VAGPFDF
3B4	103	V _H 6	CDRH3-6	GWFDI
1B5	104	V _H 7	CDRH3-7	GWFDY
10H3	104	V _H 8	CDRH3-8	GWFDY
9D10	105	V _H 9	CDRH3-9	GTSFDY
3F4	105	V _H 10	CDRH3-10	GTSFDY
8F9	105	V _H 11	CDRH3-11	GTSFDY

Table 3B - Exemplary CDRL Sequences

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
1A2	106	V _L 1	CDRL1-1	RSSQSLVYSDGNTYLS
2G10	107	V _L 2	CDRL1-2	SGSSSNIGNNYVS
14E8	108	V _L 3	CDRL1-3	QASQDINNYLN
25B10	110	V _L 5	CDRL1-5	GVSSGSVSTRYYPS
3B4	111	V _L 6	CDRL1-6	RSSQSLVHYDGNTYLS
1B5	111	V _L 7	CDRL1-7	RSSQSLVHYDGNTYLS
10H3	111	V _L 8	CDRL1-8	RSSQSLVHYDGNTYLS
9D10	107	V _L 9	CDRL1-9	SGSSSNIGNNYVS
3F4	107	V _L 10	CDRL1-10	SGSSSNIGNNYVS
8F9	107	V _L 11	CDRL1-11	SGSSSNIGNNYVS
1A2	112	V _L 1	CDRL2-1	KISNRFS
2G10	113	V _L 2	CDRL2-2	DNNKRP
14E8	114	V _L 3	CDRL2-3	DTSNLET
25B10	116	V _L 5	CDRL2-5	STNTRSS
3B4	112	V _L 6	CDRL2-6	KISNRFS
1B5	112	V _L 7	CDRL2-7	KISNRFS
10H3	112	V _L 8	CDRL2-8	KISNRFS
9D10	117	V _L 9	CDRL2-9	DNNRRPS

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
3F4	118	V _L 10	CDRL2-10	DNNNRPS
8F9	119	V _L 11	CDRL2-11	DNNKRPS
1A2	120	V _L 1	CDRL3-1	MQAIEFPWT
2G10	121	V _L 2	CDRL3-2	GTWDSSLSVVA
14E8	122	V _L 3	CDRL3-3	QQYDNLFT
25B10	124	V _L 5	CDRL3-5	VLYMGSGIWV
3B4	125	V _L 6	CDRL3-6	MQALEFPWT
1B5	125	V _L 7	CDRL3-7	MQALEFPWT
10H3	125	V _L 8	CDRL3-8	MQALEFPWT
9D10	126	V _L 9	CDRL3-9	GTWDSSLSAVV
3F4	127	V _L 10	CDRL3-10	ETWDSSLSAGV
8F9	126	V _L 11	CDRL3-11	GTWDSSLSAVV

Table 3C – Coding Sequences for CDRHs

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
1A2	128	V _H 1	CDRH1-1	ggctactatatgcac
2G10	129	V _H 2	CDRH1-2	agatatggcatgcac
14E8	130	V _H 3	CDRH1-3	agctatggcatgcac
25B10	132	V _H 5	CDRH1-5	atctatgccatgagc
3B4	133	V _H 6	CDRH1-6	gcctactatatgcac
1B5	133	V _H 7	CDRH1-7	gcctactatatgcac
10H3	133	V _H 8	CDRH1-8	gcctactatatgcac
9D10	130	V _H 9	CDRH1-9	agctatggcatgcac
3F4	130	V _H 10	CDRH1-10	agctatggcatgcac
8F9	130	V _H 11	CDRH1-11	agctatggcatgcac
1A2	134	V _H 1	CDRH2-1	tggatcaaccctaacagtgggtggcacaactctgcacagaagtttcagggc
2G10	135	V _H 2	CDRH2-2	ttatatggtttgatggaagaaatcaatactatgcagactccgtgaagggg
14E8	136	V _H 3	CDRH2-3	gttatagggtatgatggaagttataaatactatgcagactccgtgaagggc
25B10	138	V _H 5	CDRH2-5	gatattagtggtcgtgggtggttacacatactacgcagactccgtgaagggc

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
3B4	134	V _H 6	CDRH2-6	tggatcaaccctaacagtgggtggcaciaaactctgcacagaagtttcagggc
1B5	134	V _H 7	CDRH2-7	tggatcaaccctaacagtgggtggcaciaaactctgcacagaagtttcagggc
10H3	139	V _H 8	CDRH2-8	tggatcaacccttacagtgggtggcaciaaactctgcacagaagtttcagggc
9D10	140	V _H 9	CDRH2-9	gttatatggtatgatggaaggaatgaatactatgcagactccgtgaagggc
3F4	141	V _H 10	CDRH2-10	gttatatcatatgatggaagtaataaatactatgcagactccgtgaagggc
8F9	142	V _H 11	CDRH2-11	gtcatatggtatgatggaagaaataaataccatgcagactccgtgaagggc
1A2	143	V _H 1	CDRH3-1	ggctggtttgactac
2G10	144	V _H 2	CDRH3-2	ggtacgagctttgactac
14E8	145	V _H 3	CDRH3-3	tacgggggttctttgactac
25B10	147	V _H 5	CDRH3-5	gtggctggtcctttgacttc
3B4	148	V _H 6	CDRH3-6	ggctggttgacatc
1B5	149	V _H 7	CDRH3-7	ggctggttgacttc
10H3	149	V _H 8	CDRH3-8	ggctggttgacttc
9D10	144	V _H 9	CDRH3-9	ggtacgagctttgactac
3F4	150	V _H 10	CDRH3-10	ggtacctcctttgactac
8F9	144	V _H 11	CDRH3-11	ggtacgagctttgactac

Table 3D – Coding Sequences for CDRLs

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
1A2	151	V _L 1	CDRL1-1	aggtctagtcaaagcctcgatacagtgatggaacacctacttgagt
2G10	152	V _L 2	CDRL1-2	tctggaagcagctccaacattgggaataattatgtatcc
14E8	153	V _L 3	CDRL1-3	caggcgagtcaggacattaacaattatttaa
25B10	155	V _L 5	CDRL1-5	ggcgtgagctctggctcagtctctactaggtactaccccg
3B4	156	V _L 6	CDRL1-6	aggtctagtcaaagcctcgctcactatgatggaacacctacttgagt
1B5	156	V _L 7	CDRL1-7	aggtctagtcaaagcctcgctcactatgatggaacacctacttgagt
10H3	156	V _L 8	CDRL1-8	aggtctagtcaaagcctcgctcactatgatggaacacctacttgagt
9D10	152	V _L 9	CDRL1-9	tctggaagcagctccaacattgggaataattatgtatcc
3F4	152	V _L 10	CDRL1-10	tctggaagcagctccaacattgggaataattatgtatcc

Clone	SEQ ID NO:	Contained in Reference	Designation	Sequence
8F9	152	V _L 11	CDRL1-11	tctggaagcagctccaacattgggaataattatgtatcc
1A2	157	V _L 1	CDRL2-1	aagatttctaaccggttctct
2G10	158	V _L 2	CDRL2-2	gacaataataagegaccc
14E8	159	V _L 3	CDRL2-3	gatacatccaatttggaaca
25B10	161	V _L 5	CDRL2-5	agcacaacactcgtcttct
3B4	157	V _L 6	CDRL2-6	aagatttctaaccggttctct
1B5	157	V _L 7	CDRL2-7	aagatttctaaccggttctct
10H3	157	V _L 8	CDRL2-8	aagatttctaaccggttctct
9D10	162	V _L 9	CDRL2-9	gacaataataggcgaccctca
3F4	163	V _L 10	CDRL2-10	gacaataataaccgaccctca
8F9	164	V _L 11	CDRL2-11	gacaataataaggcgaccctca
1A2	165	V _L 1	CDRL3-1	atgcaagctatagaatttccgtggacg
2G10	166	V _L 2	CDRL3-2	ggaacatgggatagcagcctgagtgttggtgca
14E8	167	V _L 3	CDRL3-3	caacagtatgataatctcttcacc
25B10	169	V _L 5	CDRL3-5	gtgctgtatatgggtagtggcatttgggtg
3B4	170	V _L 6	CDRL3-6	atgcaagctctagaatttccgtggacg
1B5	170	V _L 7	CDRL3-7	atgcaagctctagaatttccgtggacg
10H3	170	V _L 8	CDRL3-8	atgcaagctctagaatttccgtggacg
9D10	171	V _L 9	CDRL3-9	ggaacatgggatagcagcctgagtgtgtggtg
3F4	172	V _L 10	CDRL3-10	gaaacatgggatagcagcctgagtgtgtgggtg
8F9	173	V _L 11	CDRL3-11	ggaacttgggatagcagcctgagtgtgtggta

The structure and properties of CDRs within a naturally occurring antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components (*e.g.*, antibodies) has been described, *supra*. Briefly, in a traditional antibody, the CDRs are embedded within a framework in the heavy and light chain variable region where they constitute the regions responsible for antigen binding and recognition. A variable region comprises at least three heavy or light chain CDRs, (*see, e.g.* Kabat *et al.*, 1991, *Sequences of Proteins of Immunological Interest*, Public Health Service N.I.H., Bethesda, MD; *see also* Chothia and Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia *et al.*, 1989, *Nature* 342: 877-883), within a framework region (designated framework regions 1-4, FR1, FR2, FR3, and FR4, by Kabat *et al.*, 1991, *supra*; *see also* Chothia and Lesk, 1987, *supra*). The CDRs

provided herein, however, can not only be used to define the antigen binding domain of an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component, but they can be embedded in a variety of other polypeptide structures, as described herein.

In one aspect, the CDRs provided are (a) a CDRH selected from the group consisting of (i) a CDRH1 selected from the group consisting of SEQ ID NO:83-88; (ii) a CDRH2 selected from the group consisting of SEQ ID NO:89-97; (iii) a CDRH3 selected from the group consisting of SEQ ID NO:98-105; and (iv) a CDRH of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, two, or one amino acids; (B) a CDRL selected from the group consisting of (i) a CDRL1 selected from the group consisting of SEQ ID NO:106-111; (ii) a CDRL2 selected from the group consisting of SEQ ID NO:112-119; (iii) a CDRL3 selected from the group consisting of SEQ ID NO:120-127; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, two, or one amino acids amino acids.

In another aspect, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes 1, 2, 3, 4, 5, or 6 variant forms of the CDRs listed in Tables 3A and 3B, each having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to a CDR sequence listed in Tables 3A and 3B. Some antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components include 1, 2, 3, 4, 5, or 6 of the CDRs listed in Tables 3A and 3B, each differing by no more than 1, 2, 3, 4 or 5 amino acids from the CDRs listed in these tables.

In still another aspect, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the following associations of CDRL1, CDRL2 and CDRL3: SEQ ID NOs:106, 112 and 120; SEQ ID NOs: 107, 113, 121; SEQ ID NO: 108, 114, 122; SEQ ID NOs: 110, 116, 124; SEQ ID NOs: 111, 112, 125; SEQ ID NOs: 111, 112, 127; SEQ ID NOs: 111, 112, 125; SEQ ID NOs: 107, 117, 126; SEQ ID NOs: 107, 118, 127 and SEQ ID NOs: 107, 119, 126.

In an additional aspect, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the following associations of CDRH1, CDRH2 and CDRH3: SEQ ID NOs:83, 89, and 98; SEQ ID NOs 84, 90, 99; SEQ ID NOs: 85, 91, 100; SEQ ID NOs: 87, 93, 102; SEQ ID NOs:88, 89, 103; SEQ ID NOs: 88, 89, 104; SEQ ID NOs: 88, 94, 104; SEQ ID NOs: 85, 95, 105; SEQ ID NOs: 85, 96, 105; and SEQ ID NOs: 85, 97, 105.

In another aspect, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the following associations of CDRL1, CDRL2 and CDRL3 with CDRH1, CDRH2 and CDRH3: SEQ ID NOs:106, 112 and 120 and SEQ ID NOs:83, 89, and 98; SEQ ID NOs: 107, 113, 121 and SEQ ID NOs 84, 90, 99; SEQ ID NO: 108, 114, 122 and SEQ ID NOs: 85, 91, 100; SEQ ID NOs: 110, 116, 124 and SEQ ID NOs: 87, 93, 102; SEQ ID NOs: 111, 112, 125 and SEQ ID NOs:88, 89, 103; SEQ ID NOs: 111, 112, 127 and SEQ ID NOs: 88, 89, 104; SEQ ID NOs: 111, 112, 125 and SEQ ID NOs: 88, 94, 104; SEQ ID NOs: 107, 117, 126 and SEQ ID NOs: 85, 95, 105; SEQ ID NOs: 107, 118, 127 and SEQ ID NOs: 85, 96, 105; and SEQ ID NOs: 107, 119, 126 and SEQ ID NOs: 85, 97, 105.

Consensus Sequences

In yet another aspect, the CDRs disclosed herein include consensus sequences derived from groups of related antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components, particularly monoclonal antibodies. 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 each of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3.

Consensus sequences were determined using standard phylogenic analyses of the CDRs corresponding to the V_H and V_L of the disclosed antibodies, some of which specifically binds β -Klotho one or of FGFR1c, FGFR2c, FGFR3c, and FGFR4. The consensus sequences were determined by keeping the CDRs contiguous within the same sequence corresponding to a V_H or V_L.

Light Chain CDR3

Group 1

MQA I EFPWT (SEQ ID NO: 120)

MQA L EFPWT (SEQ ID NO: 125)

MQA X₁ EFPWT (SEQ ID NO: 174)

wherein X₁ is L or I

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Group 2

GTWDSSLS V V A (SEQ ID NO: 121)

GTWDSSLS A V V (SEQ ID NO: 126)

GTWDSSLS X₂ V X₃ (SEQ ID NO: 175)**wherein X₂ is V or A and X₃ is V or A**Group 3

QQYDNLFT (SEQ ID NO: 122)

Group 4

QQYGSAPLT (SEQ ID NO: 123)

Group 5

VLYMGSGIWV (SEQ ID NO: 124)

Group 6

ETWDSSLSAGV (SEQ ID NO: 127)

Light Chain CDR2Group 1

KISNRFS (SEQ ID NO: 112)

Group 2

DNN K RP (SEQ ID NO: 113)

DNN N RP S (SEQ ID NO: 118)

DNN R RP S (SEQ ID NO: 117)

DNN X₄ RP X₅ (SEQ ID NO: 176)**wherein X₄ is K, N or R and X₅ is S or absent**Group 3

DTSNLET (SEQ ID NO: 114)

Group 4

GASSRAT (SEQ ID NO: 115)

Group 5

STNTRSS (SEQ ID NO: 116)

Light Chain CDR1Group 1

RSSQSLV Y S DGNTYLS (SEQ ID NO: 106)

RSSQSLV H Y DGNTYLS (SEQ ID NO: 111)

RSSQSLV X₂₂ Y X₂₃ DGNTYLS (SEQ ID NO: 177)**wherein X₂₂ is H or absent and X₂₃ is S or absent.**Group 2

SGSSSNIGNNYVS (SEQ ID NO: 107)

Group 3

QASQDINNYLN (SEQ ID NO: 108)

Group 4

RASQSVSGNYLA (SEQ ID NO: 109)

Group 5

GVSSGSVSTRYYPS (SEQ ID NO: 110)

HEAVY CDR3Group 1

GWFD Y (SEQ ID NO: 98)

GWFD I (SEQ ID NO: 103)

GWFD F (SEQ ID NO: 104)

GWFD X₆ (SEQ ID NO: 178)**wherein X₆ is Y, I or F**Group 2

GTSFDY (SEQ ID NO: 99)

Group 3

YGGSFYDY (SEQ ID NO: 100)

Group 4

MVYVLDY (SEQ ID NO: 101)

Group 5

VAGPFDF (SEQ ID NO: 102)

HEAVY CDR2Group 1

WINP N SGGTNSAQKFQG (SEQ ID NO: 89)

WINP N SGGTNSAQKFQG (SEQ ID NO: 89)

WINP N SGGTNSAQKFQG (SEQ ID NO: 89)

WINP Y SGGTNSAQKFQG (SEQ ID NO: 94)

WINP X₇ SGGTNSAQKFQG (SEQ ID NO: 179)**wherein X₇ is N or Y**Group 2

VI W F DG R N Q YYADSVKG (SEQ ID NO: 90)

VI G Y DG S Y K YYADSVKG (SEQ ID NO: 91)

VI G Y DG S Y K YYADSVKG (SEQ ID NO: 91)

VI X₈ X₉ DG X₁₀ X₁₁ X₁₂ YYADSVKG (SEQ ID NO: 180)**wherein X₈ is W or G; X₉ is F or Y; X₁₀ is R or S; X₁₁ is N or Y and X₁₂ is Q or K**Group 3

A ISG S G V S TYYADSVKG (SEQ ID NO: 92)

D ISG R G G Y TYYADSVKG (SEQ ID NO: 93)

X₁₃ ISG X₁₄ G X₁₅ X₁₆ TYYADSVKG (SEQ ID NO: 181)**wherein X₁₃ is A or D; X₁₄ is S or R; X₁₅ is V or G; and X₁₆ is S or Y**Group 4

VI W YDGRNEY Y ADSVKG (SEQ ID NO: 95)

VI S YDGSNKY Y ADSVKG (SEQ ID NO: 96)

VI W YDGRNKY H ADSVKG (SEQ ID NO: 97)

VI X₁₇ YDGRNKY X₁₈ ADSVKG (SEQ ID NO: 182)

wherein X₁₇ is W or S and X₁₈ is Y or H.

HEAVY CDR1

Group 1

G Y Y M H (SEQ ID NO: 83)

R Y G M H (SEQ ID NO: 84)

S Y G M H (SEQ ID NO: 85)

T Y A M S (SEQ ID NO: 86)

I Y A M S (SEQ ID NO: 87)

A Y Y M H (SEQ ID NO: 88)

X₁₉ Y X₂₀ M X₂₁ (SEQ ID NO: 183)

wherein X₁₉ is A, G, R, S, T or I, X₂₀ is Y, G or A and X₂₁ is H or S.

In some cases the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises at least one heavy chain CDR1, CDR2, or CDR3 having one of the above consensus sequences. In some cases, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises at least one light chain CDR1, CDR2, or CDR3 having one of the above consensus sequences. In other cases, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises at least two heavy chain CDRs according to the above consensus sequences, and/or at least two light chain CDRs according to the above consensus sequences. In still other cases, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises at least three heavy chain CDRs according to the above consensus sequences, and/or at least three light chain CDRs according to the above consensus sequences.

FGFR-binding Peptides

Peptides that specifically bind to an FGFR, *e.g.*, FGFR1c, FGFR2c, FGFR3c, or FGFR4 are also provided. Such peptides can form an element of a heavy chain, which in turn can form an element of an antigen binding protein, such as an antibody that specifically binds to β -Klotho. The insertion can change the antibody's specificity from specificity for a single

target into the ability to associate and/or specifically bind with two or more different targets. In various embodiments, the disclosed peptides are inserted into a CH2 or CH3 loop region of an Fc region of a heavy chain, as described herein.

Peptide libraries were screened, and ELISA experiments were performed to determine binding, which resulted in a number of peptides that bind to an FGFR, *e.g.*, FGFR1c. Table 4A discloses exemplary FGFR1c-binding peptides that were identified (also see Figure 12):

Table 4A - Exemplary FGFR-binding Peptides

Identifier	Amino Acid Sequence	SEQ ID NO
SR1	TRLWKYWV	184
SR2	RRLYIFWE	185
SR3	YKAWGYVYV	186
SR4	YQAWGYVYV	187
SR5	YQAWGYLV	188
SR6	YQAWGYFV	189
SR7	FTWVFWNV	190
SR8	YQVWGYFV	191
SR9	YKWLKWNL	192
SR10	RRLYIFEW	193
SR11	WAERGG	194
SR12	GGWAVGRI	195
SR13	YKYLFWV	196
SR14	YKYLSYWV	197
SR15	YKTAWYWK	198
SR16	YVFHKWWV	199
SR17	YVFYLWWK	200
SR18	YRWLHWHV	201
SR19	YKFLFWHA	202
SR20	RRQWGFV	203
SR21	YSAWSFV	204
SR22	LARWGFV	205
SR23	YDAWGYWV	206
SR24	WRKYHFWVS	207
SR25	KRLYGLFWYD	208
SR26	KKHWSSLFFE	209
SR27	KAWPYSWEAV	210
Rm26	EWYCGVLFNCQQ	211
Rm27	HFGCGVIFNCVSD	212
Rm33	WELCASGYGWCYLH	213
Rm37	APSCKSYIGFGLYHCWDG	214
Rm40	HFKCGMGLFECADP	215

Table 4B – Exemplary FGFR-binding Peptide Coding Sequences

Identifier	Coding Sequence	SEQ ID NO
SR1	acgaggctttggaagtattgggtg	216
SR2	aggaggttgatatattttgggag	217
SR3	tataaggcgtgggggtattatgtg	218
SR4	tattaggcgtgggggtattatgtg	219
SR5	tattaggcgtgggggtatttgggtg	220
SR6	taccaggcttgggggtacttcgtt	221
SR7	ttcactggggtttctggaacgtt	222
SR8	taccaggtttgggggtacttcgtt	223
SR9	tacaaatggctgaaatggaacctg	224
SR10	aggaggttgatatattttgggag	225
SR11	tgggcggagaggggtggt	226
SR12	gggggggtgggcggttgggcgtatt	227
SR13	tacaaatacctggttttctgggtt	228
SR14	tacaaatacctgtcttactgggtt	229
SR15	tacaaaactgcttggtactggaaa	230
SR16	tatgtgtttcataagtgggtgggtt	231
SR17	tacgtttctacctgtggtggaaa	232
SR18	taccgttggtgcattggcatgtt	233
SR19	tacaaattcctgttctggcacgct	234
SR20	aggaggcagtgggggttttgggtt	235
SR21	tactctgcttggcttttctgggtt	236
SR22	ttggctaggtgggggttttgggtt	237
SR23	tatgatgcgtgggggtattgggtg	238
SR24	tggcgtaaatactaccatttctgggtttct	239
SR25	aaacgtctgtacggtctgttctggtacgac	240
SR26	aaaaaacattggtcttctctgttcttcgaa	241
SR27	aaagcttggccgtactcttgggaagctgtt	242
Rm26	gagtgggtactgcggcgtgctgttcaactgccagcag	243
Rm27	cattttggttgcggtgttatttttaattgtgtttctgat	244
Rm33	tgggagctttgtgcttctgggtatggttgggtgctatcttcat	245
Rm37	gctccttcttgcaagtcttatattggttttgggtctttatcattgttgggatggt	246
Rm40	cacttcaagtgcggcatgggcctgttcgagtgcgccgacccc	247

Full-length Heavy Chains Comprising a FGFR-binding Peptide

Having provided exemplary heavy chain variable regions, in another aspect, a heavy chain of an antigen binding protein comprising a FGFR-binding peptide, such as a peptide disclosed in Table 4A, is provided. In this aspect, the FGFR-binding peptide is inserted into the primary sequence of the heavy chain and forms an integrated component of the heavy

chain. The FGFR-binding peptide can be located at any point in the heavy chain; in one example the FGFR-binding peptide is located in a CH2 or CH3 loop of the heavy chain.

An FGFR-binding peptide can be flanked on the N, C or both termini by flanking residues. Flanking residues, such as glycine residues, can provide a level of flexibility that is conducive to the formation of a disulfide bond between the flanking cysteine residues. In one example, an FGFR-binding peptide, such as those shown in Table 4A, can be flanked on the N terminus by GGC residues and on the C terminus by CGG residues. Flanking sequences can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 residues.

Table 5A – Exemplary Antibody Heavy Chains Comprising a FGFR-binding Peptide

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide SEQ ID NO	Sequence Identifier	SEQ ID NO	Amino Acid Sequence
1A2-SR4	SR4	187	H1-SR4	248	QVQLVQSGAEVKKPGASVKV SCKASGYTFTGYMHVVRQ APGQGLEWMGWNPNSGGT NSAQKFQGRVTMTRDTSISTA YMELSRRLRSDDTAVYYCARD ATSGWFDYWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEV HNAKTKPREEQYQSTYRVVS VLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELGGCYQAW GYIVCGGTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide SEQ ID NO	Sequence Identifier	SEQ ID NO	Amino Acid Sequence
2G10-SR4	SR4	187	H2-SR4	249	QVQLVESGGGVVQPGRSLRL SCAASRFSFSRYGMHWVRQA PGKGLEWVAVIWFDGRNQY YADSVKGRFTISRDN SKNTLF LQMNSLRVEDTAVYYCARD HPVVGTSFDYWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVTV DVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYQSTYRVV SVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELGGCYQA WGYYVCGGTKNQVSLTCLV KGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide SEQ ID NO	Sequence Identifier	SEQ ID NO	Amino Acid Sequence
14E8-SR4	SR4	187	H3-SR4	250	QVQLVESGGGVVQPGRSLRL SCAASGFTFSSYGMHWVRQA PGKGLEWVAVIGYDGSYKYY ADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARDGS NWN YGGSFDYWGQGT LVTV SSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYQSTYR VVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELGGCY QAWGY YVCGGTKNQVSLTC LVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDS DGSFFLYSK LTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide SEQ ID NO	Sequence Identifier	SEQ ID NO	Amino Acid Sequence
25B10-SR4	SR4	187	H5-SR4	252	EVQLLESGGGLVQPEGSLRLS CAASGFTFSIYAMSWVRQAP GKGLEWVSDISGRGGYTYYA DSVKGRFTISRDN SKNTLYLQ MNSLRADDTAVYYCAKDRSI AVAGPFD FWGQGT LVTVSSA STKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVT VSWNS GALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEV HNAKTKPREEQYQSTYRVVS VLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELGGCYQAW GYYVCGGTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNY KTTTPVLDS DGSFFLYSKLTV DKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide SEQ ID NO	Sequence Identifier	SEQ ID NO	Amino Acid Sequence
1A2-Rm26	Rm26	211	H1-Rm26	253	QVQLVQSGAEVKKPGASVKV SCKASGYTFTGYMHVVRQ APGQGLEWMGWNPNSGGT NSAQKFQGRVTMTRDTSISTA YMELSRRLRSDDTAVYYCARD ATSGWFDYWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEV HNAKTKPREEQYQSTYRVVS VLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELGGEWYCG VLFNCQQGGTKNQVSLTCLV KGFYPSDIAVEWESNGQPEN NYKTTTPVLDSFGSFLYSKL TVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide SEQ ID NO	Sequence Identifier	SEQ ID NO	Amino Acid Sequence
1A2-Rm40	Rm40	215	H1-Rm40	254	QVQLVQSGAEVKKPGASVKV SCKASGYTFTGYMHVVRQ APGQGLEWMGWNPNSGGT NSAQKFQGRVTMTRDTSISTA YMELSRRLRSDDTAVYYCARD ATSGWFDYWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVD VSHEDPEVKFNWYVDGVEV HNAKTKPREEQYQSTYRVVS VLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELGGHFKCG MGLFECADPGGTKNQVSLTC LVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSK LTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide SEQ ID NO	Sequence Identifier	SEQ ID NO	Amino Acid Sequence
2G10-Rm26	Rm26	211	H2-Rm26	255	QVQLVESGGGVVQPGRSLRL SCAASRFSFSRYGMHWVRQA PGKGLEWVAVIWFDGRNQY YADSVKGRFTISRDN SKNTLF LQMNSLRVEDTAVYYCARD HPVVGTSFDYWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVTV DVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYQSTYRVV SVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELGGEWY CGVLFNCQQGGTKNQVSLTC LVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDS DGSFFLYSK LTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide SEQ ID NO	Sequence Identifier	SEQ ID NO	Amino Acid Sequence
2G10-Rm40	Rm40	215	H2-Rm40	256	QVQLVESGGGVVQPGRSLRL SCAASRFSFSRYGMHWVRQA PGKGLEWVAVIWFDGRNQY YADSVKGRFTISRDN SKNTLF LQMNSLRVEDTAVYYCARD HPVVGTSFDYWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVTV DVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYQSTYRVV SVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELGGHFKC GMGLFECADPGGTKNQVSLT CLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK

Table 5B - Coding Sequence for Antibody Heavy Chains Comprising a FGFR-binding Peptide

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide DNA SEQ ID NO	Sequence Identifier	SEQ ID NO	Coding Sequence
1A2-SR4	SR4	219	H1-SR4	257	cagggtgcaactggtgcagctctggggctgaggtgaa gaagcctggggcctcagtgaaggtctcctgcaagg cttctggatacaccttcaccggctactatatgcactgg gtgcgacaggccccctggacaagggttgagtggat gggatggatcaaccctaacagtgggtggcacaact ctgcacagaagtttcagggcagggtcaccatgacc agggacacgtccatcagcacagcctacatggagct gagcaggctgagatctgacgacacggcctgtatta ctgtgcaagagatgcgaccagtggctggttgacta ctggggccagggaaccctggtcaccgtctctagtgc ctccaccaaggggcccatcggtcttccccctggcacc ctcctccaagagcacctctgggggcacagcggccc tgggctgcctggtcaaggactacttccccgaaccgg tgacggtgtcgtggaactcaggcgcctgaccagc ggcgtgcacaccttcccggctgtctacagtcctca ggactctactccctcagcagcgtggtgaccgtgccc tccagcagcttgggcacccagacctacatctgcaac gtgaatcacaagcccagcaacaccaaggtggacaa gaaagttgagcccaaatcttgtgacaaaactcacac atgcccaccgtgcccagcacctgaactcctggggg gaccgtcagttcttcttcccccaaaaccaagg acacctcatgatctcccgaccctgaggtcatat gcgtggtggtggacgtgagccacgaagacctga ggtcaagttcaactggtacgtggacggcgtggaggt gcataatgccaagacaaagccgaggaggagcag taccagagcacgtaccgtgtggtcagcgtcctcacc gtcctgcaccaggactggctgaatggcaaggagta caagtgcagggtctccaacaaagccctcccagccc ccatcgagaaaaccatctccaaagccaaagggcag ccccgagaaccacaggtgtacaccctgccccatc ccgggatgagctgggtggttctaccaggcctggg gtactacgtgtgcgggtgtaccaagaaccaggtca gcctgacctgctggtcaaaggcttctatccagcg acatgccgtggagtgggagagcaatgggcagcc ggagaacaactacaagaccacgcctcccgtgtgg actccgacggctccttcttctctatagcaagtcacc gtggacaagagcaggtggcagcaggggaacgtct tctcatgctccgtgatgcatgaggctctgcacaacca ctacacgcagaagagcctctccctgtctccgggtaa a

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide DNA SEQ ID NO	Sequence Identifier	SEQ ID NO	Coding Sequence
2G10-SR4	SR4	219	H2-SR4	258	cagggtgcagttggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctagattctccttcagtagatatggcatgcactgggtccgccaggctccaggcaaggggctggagtgggtggcagttatatggttgatggaagaaatcaatactatgcagactccgtgaaggggcgattcaccatctccagagacaattccaagaatacgtgtttctgcaaatgaacagcctgagagtcgaggacacggctgtgtattactgtgcgagagatcacccagtagttggtacgagctttgactactggggccagggaaccctggtcaccgtctctagtgcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcggcccctgggctgcctggtcaaggactactccccgaaccggtgacgggtgcgtggaactcaggcgccctgaccaggcgtgcacacctccccggtgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgcccctcagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaa gaaagttgagcccaaattcttgacaaaactcacacatgcccaccgtgcccagcacctgaactcctggggg gaccgtcagtcttctcttccccccaaaacccaaggacacctcatgatctcccggaccttgaggtcacatgcgtgggtggtggacgtgagccacgaagaccctga ggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcag taccagagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagta caagtgaagggtctccaacaaagccctcccagccc ccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacacctgccccatc ccgggatgagctgggtggttgctaccaggcctggg gctactacgtgtgcggtggtaccaagaaccaggtcagcctgacctgcctggtcaaaaggcttctatcccagcg acatcgccgtggagtgggagagcaatgggcagcc ggagaacaactacaagaccacgcctcccggtgtgg actccgacggctccttcttctctatagcaagtcaccgtggacaagagcaggtggcagcaggggaacgtct tctcatgctccgtgatgcatgaggctctgcacaacca ctacacgcagaagagcctctccctgtctccgggtaa a

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide DNA SEQ ID NO	Sequence Identifier	SEQ ID NO	Coding Sequence
14E8-SR4	SR4	219	H3-SR4	259	cagggtgcaactgggtggagtctgggggaggcgtggt ccagcctgggaggtccctgagactctcctgtgcagc gtctggattcaccttcagtagctatggcatgcactgg gtccgccaggctccaggcaaggggctggagtggg tggcagttatagggtatgatggaagttataaatactat gcagactccgtgaagggccgattcaccatctccaga gacaattccaagaacacgctatatctgcaaatgaac agcctgagagccgaggacacggctgtgtattactgt gcgagagatgggtctaactggaactacgggggttct tttgactactggggccagggaaccctggtcaccgtc tctagtgcctccaccaagggcccatcggtcttcccc tggcacccctcctccaagagcacctctgggggcaca gcggccctgggctgcctggtcaaggactacttcccc gaaccggtgacggtgtcgtggaactcaggcgcct gaccagcggcgtgcacaccttcccggctgtcctaca gtcctcaggactctactccctcagcagcgtggtgac cgtgccctccagcagcttgggcacccagacctacat ctgcaacgtgaatcacaagcccagcaacaccaagg tggacaagaaagttgagcccaatcttgtgacaaaa ctcacacatgccaccgtgccagcacctgaactcc tggggggaccgtcagtcttctcttcccccaaaac ccaaggacaccctcatgatctccggaccctgag gtcacatgcgtggtggtggacgtgagccacgaaga ccctgaggtcaagttaactggtacgtggacggcgt ggaggtgcataatgccaagacaaagccgaggag gagcagtagcagagcacgtaccgtgtggtcagcgt cctcaccgtcctgcaccaggactggctgaatggcaa ggagtacaagtgaaggtctccaacaaagccctcc cagcccccatcgagaaaaccatctcaaagccaaa gggcagccccgagaaccacaggtgtacacctgc cccatcccgggatgagctgggtggttgctaccag gcctggggctactacgtgtgcggtggtaccaagaa ccaggtcagcctgacctgcctggtcaaaggcttctat cccagcgacatcgccgtggagtgggagagcaatg ggcagccggagaacaactacaagaccacgcctcc cgtgctggactccgacggctccttcttctctatagca agctcaccgtggacaagagcaggtggcagcaggg gaacgttctctcatgctccgtgatgcatgaggctctg cacaaccactacacgcagaagagcctctccctgtct ccgggtaaa

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide DNA SEQ ID NO	Sequence Identifier	SEQ ID NO	Coding Sequence
25B10-SR4	SR4	219	H5-SR4	261	gaggtgcagctgttgagctctgggggaggcttggtacagccggaggggtccctgagactctcctgtgcagcctctggattcacctttagcatctatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagatattagtggctcgtgggtgttacacatactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgacgacacggcgtatattactgtgcgaaagatcggagtatagcagtggctggctctttgacttctggggccagggaaccctggtcaccgtctctagtgcctccaccaagggcccatcggctctccccctggcaccctcctccaagagcacctctgggggcacagcggcctgggctgcctgggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgcctgacagcggcgtgcacaccttcccggctgtcctacagctcagaggactctactccctcagcagcgtgggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggaacaagaaagttgagcccaaattcttgacaaaactcacatgcccaccgtgccagcacctgaactcctgggggaccgtcagtcttcttccccccaaaaccgaaggacacctcatgatctcccggaccttgaggtcacatgcgtgggtgggtgacgtgagccacgaagacctgaggtcaagtcaactggtacgtggacggcgtggaaggtcataatgccaagacaaagccgcgggaggagcagtaccagagcacgtaccgtgtggtcagcgtcctcaccgtctgcaccaggactggctgaatggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacacctgccccatccccggatgagctgggtggtgtaccaggcctgggctactacgtgtgcggtggtaccaagaaccaggtcagcctgacctgcctgggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtctggactccgacggctccttcttctctatagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide DNA SEQ ID NO	Sequence Identifier	SEQ ID NO	Coding Sequence
1A2-Rm26	Rm26	243	H1-Rm26	262	cagggtgcaactgggtgcagtctggggctgaggtgaa gaagcctggggcctcagtgaaggtctctgcaagg cttctggatacaccttcaccggctactatatgactgg gtgcgacagggcccctggacaagggcttgagtggat gggatggatcaaccctaacagtgggtggcacaaact ctgcacagaagtttcagggcagggtcacatgacc agggacacgtccatcagcacagcctacatggagct gagcaggctgagatctgacgacacggccgtgtatta ctgtgcaagagatgcgaccagtggctggttgacta ctggggccagggaaacctggtcaccgtctctagtgc ctccaccaagggcccatcggtcttcccctggcacc ctcctccaagagcacctctgggggcacagcggccc tgggctgcctgggtcaaggactactccccgaaccgg tgacgggtgctgtggaactcaggcgcctgaccagc ggcgtgcacaccttcccggctgtcctacagtctca ggactctactccctcagcagcgtggtgaccgtgccc tccagcagcttgggcacccagacctacatctgcaac gtgaatcacaagcccagcaacaccaaggtggacaa gaaagttgagcccaaattcttgacaaaactcacac atgcccaccgtgccagcacctgaactcctggggg gaccgtcagtcttcttcttcccccaaaacccaagg acacctcatgatctcccggaccttgaggtcacat gcgtgggtggtggacgtgagccacgaagacctga ggtcaagttcaactggtacgtggacggcgtggaggt gcataatgccaagacaaagccgcgggaggagcag taccagagcacgtaccgtgtgtcagcgtcctcacc gtcctgcaccaggactggctgaatggcaaggagta caagtgcaagggtctccaacaaagccctcccagccc ccatcgagaaaaccatctccaaagccaaagggcag ccccgagaaccacaggtgtacacctgccccatc ccgggatgagctgggtggtgagtggactgcggcg tgctgttcaactgccagcagggtggtaccaagaacc aggtcagcctgacctgctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggagagcaatggg cagccggagaacaactacaagaccagcctccgt gtggactccgacggctccttcttctctatagcaag ctcaccgtggacaagagcaggtggcagcagggga acgtcttctcatgctccgtgatgcatgaggctctgca caaccactacgcagaagagcctctccctgtctcc gggtaaa

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide DNA SEQ ID NO	Sequence Identifier	SEQ ID NO	Coding Sequence
1A2-Rm40	Rm40	247	H1-Rm40	263	cagggtgcaactgggtgcagtctggggctgaggtgaa gaagcctggggcctcagtgaaggtctctgcaagg cttctggatacaccttcaccggctactatatgactgg gtgcgacaggcccctggacaagggttgagtggat gggatggatcaaccctaacagtgggtggcacaaact ctgcacagaagtttcagggcagggtcaccatgacc agggacacgtccatcagcacagcctacatggagct gagcaggctgagatctgacgacacggcctgtatta ctgtgcaagagatgcgaccagtggctggttgacta ctggggccagggaaccctggtcaccgtctctagtgc ctccaccaaggggcccatcggtcttcccctggcacc ctcctccaagagcacctctgggggcacagcggccc tgggctgcctgggtcaaggactacttccccgaaccgg tgacgggtgctgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtctca ggactctactccctcagcagcgtggtgaccgtgccc tccagcagcttgggcaccagacctacatctgcaac gtgaatcacaagcccagcaacaccaaggtggacaa gaaagttgagcccaaattcttgacaaaactcacac atgcccaccgtgccagcacctgaactcctggggg gaccgtcagtcttctcttcccccaaaacccaagg acacctcatgatctcccggaccttgaggtcacat gcgtgggtggtggacgtgagccacgaagaccctga ggtcaagttcaactggtacgtggacggcgtggaggt gcataatgccaagacaaagccgcgggaggagcag taccagagcacgtaccgtgtgtcagcgtcctcacc gtcctgcaccaggactggctgaatggcaaggagta caagtgcaagggtctccaacaaagccctcccagccc ccatcgagaaaaccatctccaaagccaaagggcag ccccgagaaccacaggtgtacacctgccccatc ccgggatgagctgggtgggtcacttcaagtgcggcat gggcctgttcgagtgcgccgacccgggtgtacca agaaccaggtcagcctgacctgcctgggtcaaaggc ttctatcccagcgacatcgccgtggagtgggagagc aatgggcagccggagaacaactacaagaccacgc ctcccgtgtggactccgacggctccttcttctctat agcaagctcaccgtggacaagagcaggtggcagc aggggaacgtcttctcatgctccgtgatgcatgagg ctctgcacaaccactacgcgagaagagcctctccc tgtctccgggtaaa

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide DNA SEQ ID NO	Sequence Identifier	SEQ ID NO	Coding Sequence
2G10-Rm26	Rm26	243	H2-Rm26	264	cagggtgcagttggtggagtctgggggagggcgtggtccagcctgggaggtccctgagactctcctgtgcagcgtctagattctccttcagtagatatggcatgcactgggtccgccaggctccaggcaaggggctggagtgggtggcagttatatggtttgatggaagaaatcaatactatgcagactccgtgaaggggcgattcaccatctccagagacaattccaagaatacgtgtttctgcaaatgaacagcctgagagtcgaggacacggctgtgtattactgtgcgagagatcacccagtagttggtacgagctttgactactggggccagggaaccctggtcaccgtctctagtgcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggcccctgggctgcctggtcaaggactactccccgaaccggtgacgggtgctgtggaactcaggcgcctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgcccctcagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaa gaaagttgagcccaaattcttgacaaaactcacacatgcccaccgtgcccagcacctgaactcctggggg gaccgtcagttcttcttccccccaaaacccaaggacacctcatgatctcccggaccttgaggtcacatgcgtgggtggtggacgtgagccacgaagaccctga ggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcag taccagagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagta caagtgcaagggtctccaacaaagccctcccagccc catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacacctgccccatc ccgggatgagctgggtggtgagtgggtactgcggcg tgctgttcaactgccagcagggtggtaccaagaacc aggtcagcctgacctgctgtcctgcaaggcttctatcc agcgacatcgccgtggagtgggagagcaatgggcagccggagaaactacaagaccacgcctcccgt gctggactccgacggctccttcttctctatagcaagctcaccgtggacaagagcaggtggcagcagggga acgtcttctcatgctccgtgatgcagaggtctgca caaccactacacgcagaagagcctctccctgtctcc gggtaaa

Clone	FGFR-binding Peptide Identifier	FGFR-binding Peptide DNA SEQ ID NO	Sequence Identifier	SEQ ID NO	Coding Sequence
2G10-Rm40	Rm40	247	H2-Rm40	265	cagggtgcagttggtggagtctgggggaggcgtggt ccagcctgggaggtccctgagactctcctgtgcagc gtctagattctcctcagtagatatggcatgcactggg tccgccaggctccaggcaaggggctggagtgggt ggcagttatatggttgatggaagaaatcaatactatg cagactccgtgaaggggcgattaccatctccaga gacaattccaagaatacgtgtttctgcaaatgaaca gcctgagagtcgaggacacggctgtgtattactgtg cgagagatcacccagtagttggtacgagctttgacta ctggggccagggaaccctggtcaccgtctctagtgc ctccaccaaggggcccatcggtcttcccctggcacc ctcctccaagagcacctctgggggcacagcggccc tgggctgcctggtcaaggactactccccgaaccgg tgacggtgtcgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtctca ggactctactccctcagcagcgtggtgaccgtgccc tccagcagcttgggcacccagacctacatctgcaac gtgaatcacaagcccagcaacaccaaggtggacaa gaaagttgagcccaaatcttgacaaaactcacac atgcccaccgtgccagcacctgaactcctggggg gaccgtcagtcttcttcttcccccaaaacccaagg acacctcatgatctcccggaccttgaggtcacat gcgtggtggtggacgtgagccacgaagacctga ggtcaagtcaactggtacgtggacggcgtggaggt gcataatgccaagacaaagccgaggagagcag taccagagcacgtaccgtgtggtcagcgtcctcacc gtcctgcaccaggactggctgaatggcaaggagta caagtgcagggtctccaacaaagccctcccagccc ccatcgagaaaaccatctccaaagccaaagggcag ccccgagaaccacaggtgtacacctgccccatc ccgggatgagctgggtggtcacttcaagtgcggcat gggcctgttcgagtgcgcccacccgggtgtacca agaaccaggtcagcctgacctggtggtcaaaggc tttatcccagcgacatcgccgtggagtgggagagc aatgggcagccggagaacaactacaagaccacgc ctcccgtgtggactccgacggctccttcttctctat agcaagctcaccgtggacaagagcaggtggcagc aggggaacgtcttctcatgctccgtgatgcatgagg ctctgcacaaccactacgcagaagagcctctccc tgtctccgggtaaa

Exemplary Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusion Antigen Binding Protein Components

According to one aspect, an isolated antigen binding protein comprising (A) one or more heavy chain complementarity determining regions (CDRHs) selected from the group consisting of: (i) a CDRH1 selected from the group consisting of SEQ ID NO:83-88; (ii) a CDRH2 selected from the group consisting of SEQ ID NO:89-97; (iii) a CDRH3 selected from the group consisting of SEQ ID NO: 98-105; and (iv) a CDRH of (i), (ii) and (iii) that

contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, two or one amino acids; (B) one or more light chain complementary determining regions (CDRLs) selected from the group consisting of: (i) a CDRL1 selected from the group consisting of SEQ ID NO:106-111; (ii) a CDRL2 selected from the group consisting of SEQ ID NO:112-119; (iii) a CDRL3 selected from the group consisting of SEQ ID NO: 120-127; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, two or one amino acids; or (C) one or more heavy chain CDRHs of (A) and one or more light chain CDRLs of (B).

In another embodiment, the CDRHs have at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 83-105, and/or the CDRLs have at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 106-127. In a further embodiment, the VH is selected from the group consisting of SEQ ID NO: 72-82, and/or the VL is selected from the group consisting of SEQ ID NO: 61-71.

According to one aspect, an isolated antigen binding protein comprising (A) one or more variable heavy chains (VHs) selected from the group consisting of: (i) SEQ ID NO: 72-82; and (ii) a VH of (i) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, four, two or one amino acids; (B) one or more variable light chains (VLs) selected from the group consisting of: (i) SEQ ID NO:61-71, and (ii) a VL of (i) that contains one or more amino acid substitutions, deletions or insertions of no more than five, four, three, two or one amino acids; or (C) one or more variable heavy chains of (A) and one or more variable light chains of (B).

In another embodiment, the variable heavy chain (VH) has at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO:72-82, and/or the variable light chain (VL) has at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 61-71.

In one aspect, also provided is an antigen binding protein and antigen binding protein-FGF21 fusion antigen binding protein component that associates with an epitope comprising amino acid residues from FGFR1c, FGFR2c, FGFR3c or FGFR4, when associated with β -Klotho. In one particular embodiment the epitope comprises amino acid residues from FGFR1c.

In one aspect, also provided is an antigen binding protein and antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds to an epitope comprising amino acid residues from β -Klotho.

In another aspect, also provided is an isolated antigen binding protein and antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds to an epitope comprising amino acid residues from both β -Klotho and amino acid residues from FGFR1c, FGFR2c, FGFR3c, or FGFR4.

In yet another embodiment, the isolated antigen binding protein and antigen binding protein-FGF21 fusion antigen binding protein component described hereinabove comprises a first amino acid sequence comprising at least one of the CDRH consensus sequences disclosed herein, and a second amino acid sequence comprising at least one of the CDRL consensus sequences disclosed herein. In one aspect, the first amino acid sequence comprises at least two of the CDRH consensus sequences, and/or the second amino acid sequence comprises at least two of the CDRL consensus sequences.

In certain embodiments, the first and the second amino acid sequence are covalently bonded to each other.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:98, the CDRH2 of SEQ ID NO:89, and the CDRH1 of SEQ ID NO:83, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:120, the CDRL2 of SEQ ID NO: 112, and the CDRL1 of SEQ ID NO:106.

In another embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:99, the CDRH2 of SEQ ID NO:90, and the CDRH1 of SEQ ID NO:84, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:121, the CDRL2 of SEQ ID NO:113, and the CDRL1 of SEQ ID NO:107.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:100, the CDRH2 of SEQ ID NO:91, and the CDRH1 of SEQ ID

NO:85, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:122, the CDRL2 of SEQ ID NO:114, and the CDRL1 of SEQ ID NO:108.

In another embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:102, the CDRH2 of SEQ ID NO:93, and the CDRH1 of SEQ ID NO:87, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:124, the CDRL2 of SEQ ID NO:116, and the CDRL1 of SEQ ID NO:110.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:103, the CDRH2 of SEQ ID NO:89, and the CDRH1 of SEQ ID NO:88, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:125, the CDRL2 of SEQ ID NO:112, and the CDRL1 of SEQ ID NO:111.

In another embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:104, the CDRH2 of SEQ ID NO:89, and the CDRH1 of SEQ ID NO:88, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:127, the CDRL2 of SEQ ID NO:112, and the CDRL1 of SEQ ID NO:111.

In another embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:104, the CDRH2 of SEQ ID NO:94, and the CDRH1 of SEQ ID NO:88, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:125, the CDRL2 of SEQ ID NO:112, and the CDRL1 of SEQ ID NO:111.

In a further embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes

the CDRH3 of SEQ ID NO:105, the CDRH2 of SEQ ID NO:95, and the CDRH1 of SEQ ID NO:85, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:126, the CDRL2 of SEQ ID NO:117, and the CDRL1 of SEQ ID NO:107.

In another embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:105, the CDRH2 of SEQ ID NO:96, and the CDRH1 of SEQ ID NO:85, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:127, the CDRL2 of SEQ ID NO:118, and the CDRL1 of SEQ ID NO:107.

In another embodiment, the first amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component includes the CDRH3 of SEQ ID NO:105, the CDRH2 of SEQ ID NO:97, and the CDRH1 of SEQ ID NO:85, and/or the second amino acid sequence of the isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprises the CDRL3 of SEQ ID NO:126, the CDRL2 of SEQ ID NO:119, and the CDRL1 of SEQ ID NO:107.

In a further embodiment, the antigen binding protein comprises at least one CDRH sequence of heavy chain sequences H1-H11 as shown in Table 3A, or 1A2-SR4, 2G10-SR4, 14E8-SR4, 25B10-SR4, 1A2-Rm26, 1A2-Rm40, 2G10-Rm26, 2G10-Rm40 as shown in Table 5A. In again a further embodiment, the antigen binding protein comprises at least one CDRL sequence of light chain sequences L1-L11 as shown in Table 3B.

In again a further embodiment, the antigen binding protein comprises at least two CDRH sequences of heavy chain sequences H1-H11 as shown in Table 3A, or 1A2-SR4, 2G10-SR4, 14E8-SR4, 25B10-SR4, 1A2-Rm26, 1A2-Rm40, 2G10-Rm26, 2G10-Rm40 as shown in Table 5A, and at least two CDRL sequences of light chain sequences L1-L11 as shown in Table 3B.

In again another embodiment, the antigen binding protein comprises the CDRH1, CDRH2, and CDRH3 sequences of heavy chain sequences H1-H11 as shown in Table 3A, or 1A2-SR4, 2G10-SR4, 14E8-SR4, 25B10-SR4, 1A2-Rm26, 1A2-Rm40, 2G10-Rm26, 2G10-Rm40 as shown in Table 5A. In yet another embodiment, the antigen binding protein

comprises the CDRL1, CDRL2, and CDRL3 sequences of light chain sequences L1-L11 as shown in Table 3B.

In yet another embodiment, the antigen binding protein comprises all six CDRs of L1 and H1, or L2 and H2, or L3 and H3, or L4 and H4, or L5 and H5, L6 and H6, L7 and H7, L8 and H8, L9 and H9, L10 and H10 or L11 and H11 or the six CDRs of 1A2-SR4, 2G10-SR4, 14E8-SR4, 25B10-SR4, 1A2-Rm26, 1A2-Rm40, 2G10-Rm26 and 2G10-Rm40, as shown in Tables 6A, 6B and 6C.

Table 6A – Heavy Chain Sequences Without a FGFR-Binding Peptide

Clone	Full Heavy (H#)	Full Heavy SEQ ID NO	Variable Heavy (VH#)	Variable Heavy SEQ ID NO	CDRH1 SEQ ID NO	CDRH2 SEQ ID NO	CDRH3 SEQ ID NO
1A2	H1	28	V _H 1	50	83	89	98
2G10	H2	29	V _H 2	51	84	90	99
14E8	H3	30	V _H 3	52	85	91	100
25B10	H5	32	V _H 5	54	87	93	102
3B4	H6	33	V _H 6	55	88	89	103
1B5	H7	34	V _H 7	56	88	89	104
10H3	H8	35	V _H 8	57	88	94	104
9D10	H9	36	V _H 9	58	85	95	105
3F4	H10	37	V _H 10	59	85	96	105
8F9	H11	38	V _H 11	60	85	97	105

Table 6B – Light Chain Sequences

CLone	Full Light (L#)	Full Light SEQ ID NO	Variable Light (VH#)	Variable Light SEQ ID NO	CDRL1 SEQ ID NO	CDRL2 SEQ ID NO	CDRL3 SEQ ID NO
1A2	L1	17	V _L 1	61	106	112	120
2G10	L2	18	V _L 2	62	107	113	121

CLone	Full Light (L#)	Full Light SEQ ID NO	Variable Light (VH#)	Variable Light SEQ ID NO	CDRL1 SEQ ID NO	CDRL2 SEQ ID NO	CDRL3 SEQ ID NO
14E8	L3	19	V _L 3	63	108	114	122
25B10	L5	21	V _L 5	65	110	116	124
3B4	H6	22	V _L 6	66	111	112	125
1B5	H7	23	V _L 7	67	111	112	127
10H3	H8	24	V _L 8	68	111	112	125
9D10	H9	25	V _L 9	69	107	117	126
3F4	H10	26	V _L 10	70	107	118	127
8F9	H11	27	V _L 11	71	107	119	126

Table 6C – Heavy Chain Sequences Comprising a FGFR-binding Peptide

Clone	FGFR-binding Peptide Identifier	Full Heavy SEQ ID NO	Variable Heavy (VH#)	Variable Heavy SEQ ID NO	CDRH1 SEQ ID NO	CDRH2 SEQ ID NO	CDRH3 SEQ ID NO
1A2-SR4	SR4	28	V _H 1	50	83	89	98
2G10-SR4	SR4	29	V _H 2	51	84	90	99
14E8-SR4	SR4	30	V _H 3	52	85	91	100
25B10-SR4	SR4	32	V _H 5	54	87	93	102
1A2-Rm26	Rm26	28	V _H 1	50	83	89	98
1A2-Rm40	Rm40	28	V _H 1	50	83	89	98
2G10-Rm26	Rm26	29	V _H 2	51	84	90	99
2G10-Rm40	Rm40	29	V _H 2	51	84	90	99

In one aspect, the isolated antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 provided herein can be a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof.

In another embodiment, the antibody fragment of the isolated antigen-binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components provided herein can be a Fab fragment, a Fab' fragment, an F(ab')₂ fragment, an Fv fragment, a diabody, or a single chain antibody molecule.

In a further embodiment, an isolated antigen binding protein and antigen binding protein-FGF21 fusion antigen binding protein components provided herein that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 is a human antibody and can be of the IgG1-, IgG2- IgG3- or IgG4-type.

In another embodiment, an isolated antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 comprises just a light or a heavy chain polypeptide as set forth in Tables 1 and 5. In some embodiments, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 consists just of a variable light or variable heavy domain such as those listed in Table 2. Such antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can be PEGylated with one or more PEG molecules, for examples PEG molecules having a molecular weight selected from the group consisting of 5K, 10K, 20K, 40K, 50K, 60K, 80K, 100K or greater than 100K.

In yet another aspect, the isolated antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 provided herein can be coupled to a labeling group and can compete for binding to the extracellular portion of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with an antigen binding protein of one of the isolated antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components provided herein. In one embodiment, the isolated antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein

components provided herein can reduce blood glucose levels, decrease triglyceride and cholesterol levels or improve other glycemic parameters and cardiovascular risk factors when administered to a patient.

As will be appreciated, for any antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component comprising more than one CDR from the depicted sequences, any combination of CDRs independently selected from the depicted sequences is useful. Thus, antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components with one, two, three, four, five or six of independently selected CDRs can be generated. However, as will be appreciated, specific embodiments generally utilize combinations of CDRs that are non-repetitive, *e.g.*, antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components are generally not made with two CDRH2 regions, etc.

Some of the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are provided herein are discussed in more detail below.

Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusion Antigen Binding Protein Components and Binding Epitopes and Binding Domains

When an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component is said to bind an epitope on β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, or the extracellular domain thereof, for example, what is meant is that the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component specifically binds to a specified portion of β -Klotho or a specified portion of a complex comprising β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In some embodiments, *e.g.*, in certain cases where the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component binds only β -Klotho, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component can specifically bind to a polypeptide consisting of the specified residues (*e.g.*, a specified segment of β -Klotho). In other embodiments, *e.g.*, in certain cases where an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component interacts with both β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4, the antigen binding protein or

antigen binding protein-FGF21 fusion antigen binding protein component will bind residues, sequences of residues, or regions in both β -Klotho and FGFR1c, FGFR2c, FGFR3c or FGFR4, depending on which receptor the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component recognizes. In still other embodiments the antigen binding protein and antigen binding protein-FGF21 fusion antigen binding protein components will bind residues, sequence or residues or regions of a complex comprising β -Klotho and FGFR1c. In any of the foregoing embodiments, such an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component typically does not need to contact every residue of β -Klotho and/or one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Nor does every single amino acid substitution or deletion within β -Klotho and/or FGFR1c, FGFR2c, FGFR3c or FGFR4, or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, or the extracellular domain of the recited proteins or complexes necessarily significantly affect binding affinity.

Epitope specificity and the binding domain(s) of an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component can be determined by a variety of methods. Some methods, for example, can use truncated portions of an antigen. Other methods utilize antigen mutated at one or more specific residues, such as by employing an alanine scanning or arginine scanning-type approach or by the generation and study of chimeric proteins in which various domains, regions or amino acids are swapped between two proteins, or by protease protection assays.

Competing Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusion Antigen Binding Protein Components

In another aspect, antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components are provided that compete with one of the exemplified antibodies or functional fragments binding to an epitope described herein for specific binding to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Such antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can also bind to the same epitope as one of the herein exemplified antigen binding proteins or antigen binding protein-FGF21 fusion antigen binding protein components, or an overlapping epitope. Antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components and fragments thereof that compete with or bind to the same epitope as the exemplified antigen binding proteins and

antigen binding protein-FGF21 fusion antigen binding protein components are expected to show similar functional properties. The exemplified antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein component and fragments thereof include those with the heavy and light chains, variable region domains V_L1 - V_L11 and V_H1 - V_H11 , and the CDRs included in Tables 1 and 3, respectively. Thus, as a specific example, the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that are provided include those that compete with an antibody or fragment having:

- (a) all 6 of the CDRs listed for an antibody as listed in Table 3;
- (b) a V_H and a V_L selected from V_L1 - V_L11 and V_H1 - V_H11 for an antibody as listed in Table 2; or
- (c) two light chains and two heavy chains as specified for an antibody as listed in Tables 1 and 5.

Thus, in one embodiment, the present disclosure provides antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that compete for binding to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with a reference antibody, wherein the reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H0 or L11H11.

In another embodiment, the present disclosure provides human antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that compete for binding to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with a reference antibody, wherein the reference antibody is 1A2, 2G10, 14E8, 25B10, 3B4, 1B5, 10H3, 9D10, 3F4 or 8F9.

In a further embodiment, an isolated human antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component is provided that specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with substantially the same K_d as a reference antibody; initiates FGF21-like signaling in an *in vitro* ELK-Luciferase assay to the same degree as a reference antibody; lowers blood glucose; lowers serum lipid levels; and/or competes for binding with said reference antibody to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, wherein the reference antibody is selected from the group consisting of 1A2, 2G10, 14E8, 25B10, 3B4, 1B5, 10H3, 9D10, 3F4 or 8F9.

The ability to compete with an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component can be determined using any suitable assay, in which 1A2, 2G10, 14E8, 25B10, 3B4, 1B5, 10H3, 9D10, 3F4, 8F9, 1A2-SR4, 2G10-SR4, 14E8-SR4, 25B10-SR4, 1A2-Rm26, 1A2-Rm40, 2G10-Rm26, or 2G10-Rm40 can be used as the reference antibody.

Monoclonal Antibodies

The antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that are provided include monoclonal antibodies that bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, and induce FGF21-like signaling to various degrees. Monoclonal antibodies can be produced using any technique known in the art, *e.g.*, by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, *e.g.*, by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XXO Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

In some instances, a hybridoma cell line is produced by immunizing an animal (*e.g.*, a transgenic animal having human immunoglobulin sequences) with a FGFR1c, β -Klotho or FGFR1c and/or β -Klotho immunogen (*e.g.*, a soluble complex comprising the extracellular domains of FGFR1c, FGFR2c, FGFR3c or FGFR4 and/or β -Klotho as shown in Examples 2, and 3 membranes on which the extracellular domains of FGFR1c, FGFR2c, FGFR3c or FGFR4 and/or β -Klotho are expressed, as shown in Examples 1 and 3 or whole cells expressing FGFR1c and/or β -Klotho, as shown in Examples 1 and 3); harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; establishing hybridoma cell lines from the hybridoma cells, and identifying a hybridoma cell line that produces an antibody that specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 (*e.g.*, as

described herein) and can induce FGF21-like signaling (*e.g.*, as described in Examples 5-7). Such hybridoma cell lines, and the monoclonal antibodies produced by them, form aspects of the present disclosure.

Monoclonal antibodies secreted by a hybridoma cell line can be purified using any technique known in the art. Hybridomas or mAbs can be further screened to identify mAbs with particular properties, such as the ability to induce FGF21-like signaling. Examples of such screens are provided herein.

Chimeric and Humanized Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusion Antigen Binding Protein Components

Chimeric and humanized antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components (*e.g.*, antibodies, such as monoclonal antibodies) based upon the disclosed sequences are also provided. Monoclonal antibodies for use as therapeutic agents can be modified in various ways prior to use. One example is a chimeric antibody, which is an antibody composed of protein segments from different antibodies that are covalently joined to produce functional immunoglobulin light or heavy chains or immunologically functional portions thereof. Generally, a portion of the heavy chain and/or light chain is identical with or homologous to a corresponding sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. For methods relating to chimeric antibodies, *see*, for example, United States Patent No. 4,816,567; and Morrison *et al.*, 1985, *Proc. Natl. Acad. Sci. USA* 81:6851-6855, which are hereby incorporated by reference. CDR grafting is described, for example, in United States Patent No. 6,180,370, No. 5,693,762, No. 5,693,761, No. 5,585,089, and No. 5,530,101.

Generally, the goal of making a chimeric antibody is to create a chimera in which the number of amino acids from the intended patient species is maximized. One example is the “CDR-grafted” antibody, in which the antibody comprises one or more complementarity determining regions (CDRs) from a particular species or belonging to a particular antibody class or subclass, while the remainder of the antibody chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. For use in humans, the variable region or selected CDRs from a rodent antibody often are grafted into a human antibody, replacing the naturally-occurring variable regions or CDRs of the human antibody.

One useful type of chimeric antibody is a “humanized” antibody. Generally, a humanized antibody is produced from a monoclonal antibody raised initially in a non-human animal. Certain amino acid residues in this monoclonal antibody, typically from non-antigen recognizing portions of the antibody, are modified to be homologous to corresponding residues in a human antibody of corresponding isotype. Humanization can be performed, for example, using various methods by substituting at least a portion of a rodent variable region for the corresponding regions of a human antibody (*see, e.g.*, United States Patent No. 5,585,089, and No. 5,693,762; Jones *et al.*, 1986, *Nature* 321:522-525; Riechmann *et al.*, 1988, *Nature* 332:323-27; Verhoeyen *et al.*, 1988, *Science* 239:1534-1536).

In one aspect, the CDRs of the light and heavy chain variable regions of the antibodies provided herein (*see* Tables 3 and 6) are grafted to framework regions (FRs) from antibodies from the same, or a different, phylogenetic species. For example, the CDRs of the heavy and light chain variable regions V_H1, V_H2, V_H3, V_H4 or V_H5 and/or V_L1, V_L2, V_L3, V_L4 or V_L5 can be grafted to consensus human FRs. To create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences can be aligned to identify a consensus amino acid sequence. In other embodiments, the FRs of a heavy chain or light chain disclosed herein are replaced with the FRs from a different heavy chain or light chain. In one aspect, rare amino acids in the FRs of the heavy and light chains of an antigen binding protein (*e.g.*, an antibody) that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 are not replaced, while the rest of the FR amino acids are replaced. A “rare amino acid” is a specific amino acid that is in a position in which this particular amino acid is not usually found in an FR. Alternatively, the grafted variable regions from the one heavy or light chain can be used with a constant region that is different from the constant region of that particular heavy or light chain as disclosed herein. In other embodiments, the grafted variable regions are part of a single chain Fv antibody.

In certain embodiments, constant regions from species other than human can be used along with the human variable region(s) to produce hybrid antibodies.

Fully Human Antibodies

Fully human antibodies are also provided by the instant disclosure. Methods are available for making fully human antibodies specific for a given antigen without exposing human beings to the antigen (“fully human antibodies”). One specific means provided for implementing the production of fully human antibodies is the “humanization” of the mouse

humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated is one means of producing fully human monoclonal antibodies (mAbs) in mouse, an animal that can be immunized with any desirable antigen. Using fully human antibodies can minimize the immunogenic and allergic responses that can sometimes be caused by administering mouse or mouse-derived mAbs to humans as therapeutic agents.

Fully human antibodies can be produced by immunizing transgenic animals (typically mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production. Antigens for this purpose typically have six or more contiguous amino acids, and optionally are conjugated to a carrier, such as a hapten. *See, e.g., Jakobovits et al., (1993) Proc. Natl. Acad. Sci. USA 90:2551-2555; Jakobovits et al., (1993) Nature 362:255-258; and Bruggermann et al., (1993) Year in Immunol. 7:33.* In one example of such a method, transgenic animals are produced by incapacitating the endogenous mouse immunoglobulin loci encoding the mouse heavy and light immunoglobulin chains therein, and inserting into the mouse genome large fragments of human genome DNA containing loci that encode human heavy and light chain proteins. Partially modified animals, which have less than the full complement of human immunoglobulin loci, are then cross-bred to obtain an animal having all of the desired immune system modifications. When administered an immunogen, these transgenic animals produce antibodies that are immunospecific for the immunogen but have human rather than murine amino acid sequences, including the variable regions. For further details of such methods, *see, for example, WO96/33735 and WO94/02602.* Additional methods relating to transgenic mice for making human antibodies are described in United States Patent No. 5,545,807; No. 6,713,610; No. 6,673,986; No. 6,162,963; No. 5,545,807; No. 6,300,129; No. 6,255,458; No. 5,877,397; No. 5,874,299 and No. 5,545,806; in PCT publications WO91/10741, WO90/04036, and in EP 546073B1 and EP 546073A1.

The transgenic mice described above, referred to herein as “HuMab” mice, contain a human immunoglobulin gene minilocus that encodes unrearranged human heavy ([μ , mu] and [γ , gamma]) and [κ , kappa] light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ [mu] and κ [kappa] chain loci (Lonberg *et al.*, 1994, *Nature* 368:856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or [κ , kappa] and in response to immunization, and the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity

human IgG [κ , kappa] monoclonal antibodies (Lonberg *et al.*, *supra.*; Lonberg and Huszar, (1995) *Intern. Rev. Immunol.* 13: 65-93; Harding and Lonberg, (1995) *Ann. N.Y Acad. Sci.* 764:536-546). The preparation of HuMab mice is described in detail in Taylor *et al.*, (1992) *Nucleic Acids Research* 20:6287-6295; Chen *et al.*, (1993) *International Immunology* 5:647-656; Tuailon *et al.*, (1994) *J. Immunol.* 152:2912-2920; Lonberg *et al.*, (1994) *Nature* 368:856-859; Lonberg, (1994) *Handbook of Exp. Pharmacology* 113:49-101; Taylor *et al.*, (1994) *International Immunology* 6:579-591; Lonberg and Huszar, (1995) *Intern. Rev. Immunol.* 13:65-93; Harding and Lonberg, (1995) *Ann. N.Y Acad. Sci.* 764:536-546; Fishwild *et al.*, (1996) *Nature Biotechnology* 14:845-851; the foregoing references are hereby incorporated by reference in their entirety for all purposes. See, further United States Patent No. 5,545,806; No. 5,569,825; No. 5,625,126; No. 5,633,425; No. 5,789,650; No. 5,877,397; No. 5,661,016; No. 5,814,318; No. 5,874,299; and No. 5,770,429; as well as United States Patent No. 5,545,807; International Publication Nos. WO 93/1227; WO 92/22646; and WO 92/03918, the disclosures of all of which are hereby incorporated by reference in their entirety for all purposes. Technologies utilized for producing human antibodies in these transgenic mice are disclosed also in WO 98/24893, and Mendez *et al.*, (1997) *Nature Genetics* 15:146-156, which are hereby incorporated by reference. For example, the HCo7 and HCo12 transgenic mice strains can be used to generate antigen binding proteins (*e.g.*, antibodies) that bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and induce FGF21-like signalling. Further details regarding the production of human antibodies using transgenic mice are provided in the examples herein.

Using hybridoma technology, antigen-specific human mAbs with the desired specificity can be produced and selected from the transgenic mice such as those described above. Such antibodies can be cloned and expressed using a suitable vector and host cell, or the antibodies can be harvested from cultured hybridoma cells.

Fully human antibodies can also be derived from phage-display libraries (as disclosed in Hoogenboom *et al.*, (1991) *J. Mol. Biol.* 227:381; and Marks *et al.*, (1991) *J. Mol. Biol.* 222:581). Phage display techniques mimic immune selection through the display of antibody repertoires on the surface of filamentous bacteriophage, and subsequent selection of phage by their binding to an antigen of choice. One such technique is described in PCT Publication No. WO 99/10494 (hereby incorporated by reference), which describes the isolation of high affinity and functional agonistic antibodies for MPL- and msk-receptors using such an approach.

Bispecific or Bifunctional Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusion Antigen Binding Protein Components

The antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that are provided also include bispecific and bifunctional antibodies that include one or more CDRs or one or more variable regions as described herein. A bispecific or bifunctional antibody can be, in some instances, an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. *See, e.g.,* Songsivilai and Lachmann, 1990, *Clin. Exp. Immunol.* 79:315-321; Kostelny *et al.*, 1992, *J. Immunol.* 148:1547-1553. In one embodiment, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component of the instant disclosure can bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, which can lead to the activation of FGF21-like activity as measured by the FGF21-like functional and signaling assays described in Examples 5-7.

Antigen Binding Protein-FGF21 Fusions

It has been demonstrated that the N-terminus of FGF-21 provides specificity for the FGF receptor, while the C-terminus of FGF-21 provides specificity for β -Klotho. Accordingly, antigen binding protein-FGF21 fusions can be designed that mimic the signaling ability of mature FGF21 and can comprise (a) an antigen binding protein component that has specificity for β -Klotho and (b) an FGF21 component comprising a variable length of the N-terminal end of an FGF21 polypeptide sequence that retains specificity for an FGF21 receptor. Alternatively, an antigen binding protein-FGF21 fusion can comprise (a) an antigen binding protein component that has specificity for one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4 and (b) an FGF21 component comprising a variable length of the C-terminal end of an FGF21 polypeptide sequence that retains specificity for β -Klotho. Optionally, linkers can be included to join the FGF21 component to the antigen binding protein component. Thus, in another aspect of the present disclosure, antigen binding protein-FGF21 fusions are provided.

In one embodiment an antigen binding protein-FGF21 fusion comprises (a) an antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of

FGFR1c, FGFR2c, FGFR3c, and FGFR4; and (b) an FGF21 component, which comprises a truncated form of FGF21. In some embodiments, the antigen binding protein-FGF21 fusion comprises an antigen binding protein component that specifically binds to human β -Klotho and is fused to an FGF21 component comprising a truncated form of human FGF21. In some embodiments, the antigen binding protein component is selected from the antigen binding proteins of Tables 1-3 and 6. In some embodiments the FGF21 component comprises between 25 and 180 amino acids of SEQ ID NO:341. In one particular embodiment the antigen binding protein component is antibody 2G10 and the FGF21 component comprises residues 1-170 of FGF21 (SEQ ID NO: 343).

The FGF21 component of a fusion can be joined directly to the antigen binding protein component of the fusion at the N-terminus of either the heavy or the light chain of the antigen binding protein component. In other embodiments the FGF21 component of a fusion can be directly joined to the antigen binding protein component of the fusion at the C-terminus of the heavy chain of the antigen binding protein component. Optionally, a linker can be employed to join the components of a fusion together, either at the N or C-terminus of the heavy chain of an antigen binding protein or the N-terminus of the light chain of an antigen binding protein.

The disclosed antigen binding protein-FGF21 fusions may exhibit a variety of characteristics such as (i) *in vivo* potency similar or equal to the full length mature form of FGF21; (ii) high binding affinity and specificity to an FGF21 receptor or β -Klotho; (iii) decreased immunogenicity due to the presence of the native sequences of truncated FGF-21; and (iv) the extended half-life typical of an antibody.

The Antigen Binding Protein Component

An antigen binding protein component of an antigen binding protein-FGF21 fusion comprises a protein that specifically binds (a) β -Klotho, (b) one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, or (c) β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. The specificity of the antigen binding protein will depend on the overall architecture of the fusion, although all designs will preferably produce a fusion that mimics the signaling activity of FGF21. Any of the antigen binding protein formats described herein can be employed in a fusion, such as antibodies, hemibodies, Fab fragments, etc. The antigen binding proteins and elements thereof (*e.g.*, heavy chains, light chains,

variable regions and CDRs) provided in Tables 1-3 and 6 can serve as antigen binding components of an antigen binding protein-FGF21 fusion.

In one embodiment the antigen binding protein component specifically binds β -Klotho. In this embodiment the FGF21 component of the fusion will specifically associate with one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and will comprise an N-terminally truncated form of FGF21. The antigen binding component can also bind one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in addition to β -Klotho.

In another embodiment the antigen binding protein component specifically binds one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In this embodiment that FGF21 component of the fusion will specifically associate with β -Klotho and will comprise a C-terminally truncated form of FGF21. The antigen binding protein component can also bind to β -Klotho in addition to one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

When the antigen binding component is an antibody, the antibody can comprise an antibody provided herein, such as those described in Tables 1-3 and 6, such as those secreted from clones 1A2, 2G10, 14E8, 25B10, 3B4, 1B5, 10H3, 9D10, 3F4, and 8F9. Antibodies comprising one or more of the disclosed CDRs, including Fab fragments and variable regions, can also be employed in an antigen binding protein component.

The FGF-21 Component

The FGF21 component of the antigen binding protein-FGF21 fusion can comprise any length of FGF21 that is at least 25 amino acids in length.

In various embodiments, the FGF21 component of an antigen binding protein comprises a fragment of FGF21 (SEQ ID NO:341), comprising between 25 and 180 amino acids, for example 180, 179, 178, 177, 176, 175, 174, 173, 172, 171, 170, 169, 168, 167, 166, 165, 160, 155, 150, 145, 140, 135, 130, 125, 120, 115, 110, 105, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30 or 25 amino acids. The FGF21 component can be a fragment of SEQ ID NO:341 that has been truncated from the N-terminus, C-terminus or both the C-terminus to generate the fragment comprising between 25 and 180 amino acids.

In some embodiments, the FGF21 component can comprise an FGF21 sequence (e.g., SEQ ID NO:341) which has been truncated on the C-terminal end. For example the FGF21 component can comprise residues 1-180, 1-179, 1-178, 1-177, 1-176, 1-175, 1-174, 1-173, 1-172, 1-171, 1-170, 1-169, 1-168, 1-167, 1-166, 1-165, 1-160, 1-155, 1-150, 1-145, 1-140, 1-

135, 1-130, 1-125, 1-120, 1-115, 1-110, 1-105, 1-100, 1-95, 1- 90, 1- 85, 1-80, 1-75, 1-70, 1-65, 1-60, 1-55, 1-50, 1-45, 1-40, 1-35, 1-30 or 1-25 of SEQ ID NO:341.

In other embodiments the FGF21 component can comprise an FGF21 sequence (e.g., SEQ ID NO:341) which has been truncated on the N-terminal end. For example the FGF21 component can comprise residues 2-181, 3-181, 4-181, 5-181, 6-181, 7-181, 8-181, 9-181, 10-181, 11-181, 12-181, 13-181, 14-181, 15-181, 20-181, 25-181, 30-181, 35-181, 40-181, 45-181, 50-181, 55-181, 60-181, 65-181, 70-181, 75-181, 80-181, 85-181, 90-181, 95-181, 100-181, 105-181, 110-181, 115-181, 120-181, 125-181, 130-181, 135-181, 140-181, 145-181, 150-181, 155-181, 160-181 or 165-181.

In still other embodiments the FGF21 component can comprise an FGF21 sequence (e.g., SEQ ID NO:341) which has been truncated on both the N- and C-terminal ends. For example the FGF21 component can comprise 2-181, 3-180, 4-179, 5-178, 6-177, 7-176, 8-175, 9-174, 10-173, 11-172, 12-171, 13-170, 14-165, 15-160, 20-155, 25-150, 30-145, 35-140, 40-135, 45-130, 50-125, 55-120, 60-115, 65-110, 70-105 or 75-100.

Linkers

The antigen binding protein component of a fusion can, but need not, be associated with the FGF21 component of the fusion via a linker sequence. Examples of linkers are provided here and can comprise peptides, polysaccharides, PEG and other types of polymers. Examples of suitable peptide linkers are described in United States Patent Nos. 4,751,180 and 4,935,233. In particular embodiments a peptide linker comprises a Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 344) motif repeated two or more times. Thus, a linker can comprise, for example, (G₄S)₃ (SEQ ID NO: 336), (G₄S)₆ (SEQ ID NO: 337), (G₄S)₉ (SEQ ID NO: 338), (G₄S)₁₂ (SEQ ID NO: 339), or (G₄S)₁₅ (SEQ ID NO: 340). Other examples of polymeric linkers include PEG molecules, such as PEG 20, PEG 40 or PEG 60.

The disclosed antigen binding protein-FGF21 fusions can be expressed and purified using standard laboratory techniques as described herein, for example in Example 17. The fusions can be expressed as a single full length protein or they can be expressed in components and subsequently joined via a chemical reaction. Standard purification techniques, such as Protein A, size exclusion and ion exchange chromatography, can be employed to isolate an antigen binding protein-FGF21 fusion.

Other Forms of Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusion

Antigen Binding Protein Components

Some of the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are provided can comprise variant forms of the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components disclosed herein (*e.g.*, those comprising one or more of the sequences listed in Tables 1-3 and 6).

In various embodiments, the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components disclosed herein can comprise one or more non-naturally occurring amino acids. For instance, some of the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can have one or more non-naturally occurring amino acid substitutions in one or more of the heavy or light chains, variable regions or CDRs listed in Tables 1-3 and 6. Examples of non-naturally amino acids (which can be substituted for any naturally-occurring amino acid found in any sequence disclosed herein, as desired) include: 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxyl-terminal direction, in accordance with standard usage and convention. A non-limiting lists of examples of non-naturally occurring amino acids that can be inserted into an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component primary amino acid sequence or substituted for a wild-type residue in an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component sequence include β -amino acids, homoamino acids, cyclic amino acids and amino acids with derivatized side chains. Examples include (in the L-form or D-form; abbreviated as in parentheses): citrulline (Cit), homocitrulline (hCit), N α -methylcitrulline (NMeCit), N α -methylhomocitrulline (N α -MeHoCit), ornithine (Orn), N α -Methylornithine (N α -MeOrn or NMeOrn), sarcosine (Sar), homolysine (hLys or hK), homoarginine (hArg or hR), homoglutamine (hQ), N α -methylarginine (NMeR), N α -methyllleucine (N α -MeL or NMeL), N-methylhomolysine (NMeHoK), N α -methylglutamine (NMeQ), norleucine (Nle), norvaline (Nva), 1,2,3,4-tetrahydroisoquinoline (Tic), Octahydroindole-2-carboxylic acid (Oic), 3-(1-

naphthyl)alanine (1-Nal), 3-(2-naphthyl)alanine (2-Nal), 1,2,3,4-tetrahydroisoquinoline (Tic), 2-indanylglycine (Igl), para-iodophenylalanine (pI-Phe), para-aminophenylalanine (4AmP or 4-Amino-Phe), 4-guanidino phenylalanine (Guf), glycyllysine (abbreviated “K(N ϵ -glycyl)” or “K(glycyl)” or “K(gly)”), nitrophenylalanine (nitrophe), aminophenylalanine (aminophe or Amino-Phe), benzylphenylalanine (benzylphe), γ -carboxyglutamic acid (γ -carboxyglu), hydroxyproline (hydroxypro), p-carboxyl-phenylalanine (Cpa), α -aminoadipic acid (Aad), N α -methyl valine (NMeVal), N- α -methyl leucine (NMeLeu), N α -methylnorleucine (NMeNle), cyclopentylglycine (Cpg), cyclohexylglycine (Chg), acetylarginine (acetylarg), α , β -diaminopropionic acid (Dpr), α , γ -diaminobutyric acid (Dab), diaminopropionic acid (Dap), cyclohexylalanine (Cha), 4-methyl-phenylalanine (MePhe), β , β -diphenyl-alanine (BiPhA), aminobutyric acid (Abu), 4-phenyl-phenylalanine (or biphenylalanine; 4Bip), α -amino-isobutyric acid (Aib), beta-alanine, beta-aminopropionic acid, piperidinic acid, aminocaproic acid, aminoheptanoic acid, aminopimelic acid, desmosine, diaminopimelic acid, N-ethylglycine, N-ethylasparagine, hydroxylysine, allo-hydroxylysine, isodesmosine, allo-isoleucine, N-methylglycine, N-methylisoleucine, N-methylvaline, 4-hydroxyproline (Hyp), γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, ω -methylarginine, 4-Amino-O-Phthalic Acid (4APA), and other similar amino acids, and derivatized forms of any of those specifically listed.

Additionally, the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can have one or more conservative amino acid substitutions in one or more of the heavy or light chains, variable regions or CDRs listed in Tables 1-6. Naturally-occurring amino acids can be divided into classes 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.

Conservative amino acid substitutions can involve exchange of a member of one of these classes with another member of the same class. Conservative amino acid substitutions can encompass non-naturally occurring amino acid residues, which are typically incorporated

by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties.

Non-conservative substitutions can involve the exchange of a member of one of the above classes for a member from another class. Such substituted residues can be introduced into regions of the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that are homologous with human antibodies, or into the non-homologous regions of the molecule.

In making such changes, according to certain embodiments, the hydropathic index of amino acids can be considered. The hydropathic profile of a protein is calculated by assigning each amino acid a numerical value ("hydropathy index") and then repetitively averaging these values along the peptide chain. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

The importance of the hydropathic profile in conferring interactive biological function on a protein is understood in the art (*see, e.g., Kyte et al., 1982, J. Mol. Biol.* 157:105-131). It is known that certain amino acids can be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ± 2 is included. In some aspects, those which are within ± 1 are included, and in other aspects, those within ± 0.5 are included.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigen-binding or immunogenicity, that is, with a biological property of the protein.

The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 $\pm$ 1); glutamate (+3.0 $\pm$ 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 $\pm$ 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8);

isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5) and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ± 2 is included, in other embodiments, those which are within ± 1 are included, and in still other embodiments, those within ± 0.5 are included. In some instances, one can also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as “epitopic core regions.”

Exemplary conservative amino acid substitutions are set forth in Table 7.

Table 7 - Conservative Amino Acid Substitutions

Original Residue	Exemplary Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

A skilled artisan will be able to determine suitable variants of the disclosed antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components as set forth herein using well-known techniques. One skilled in the art can

identify suitable areas of the molecules that can be changed without destroying activity by targeting regions not believed to be important for activity. The skilled artisan also will be able to identify residues and portions of the molecules that are conserved among similar polypeptides. In further embodiments, even areas that can be important for biological activity or for structure can be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues important for activity or structure in similar proteins. One skilled in the art can opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

One skilled in the art can also analyze the 3-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of such information, one skilled in the art can predict the alignment of amino acid residues of an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component (e.g., an antibody) with respect to its three dimensional structure. One skilled in the art can choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues can be involved in important interactions with other molecules. Moreover, one skilled in the art can generate test variants containing a single amino acid substitution at each desired amino acid residue. These variants can then be screened using assays for FGF21-like signaling (e.g., as described in the Examples provided herein), thus yielding information regarding which amino acids can be changed and which must not be changed. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acid positions where further substitutions should be avoided either alone or in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See, Moult, (1996) *Curr. Op. in Biotech.* 7:422-427; Chou *et al.*, (1974) *Biochem.* 13:222-245; Chou *et al.*, (1974) *Biochemistry* 113:211-222; Chou *et al.*, (1978) *Adv. Enzymol. Relat. Areas Mol. Biol.* 47:45-148; Chou *et al.*, (1979) *Ann. Rev. Biochem.* 47:251-276; and Chou *et al.*, (1979) *Biophys. J.* 26:367-384. Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins that have a sequence identity of greater than 30%, or similarity

greater than 40% can have similar structural topologies. The growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See, Holm *et al.*, (1999) *Nucl. Acid. Res.* 27:244-247. It has been suggested (Brenner *et al.*, (1997) *Curr. Op. Struct. Biol.* 7:369-376) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate.

Additional methods of predicting secondary structure include “threading” (Jones, (1997) *Curr. Opin. Struct. Biol.* 7:377-387; Sippl *et al.*, (1996) *Structure* 4:15-19), “profile analysis” (Bowie *et al.*, (1991) *Science* 253:164-170; Gribskov *et al.*, (1990) *Meth. Enzym.* 183:146-159; Gribskov *et al.*, (1987) *Proc. Nat. Acad. Sci.* 84:4355-4358), and “evolutionary linkage” (See, Holm, (1999) *supra*; and Brenner, (1997) *supra*).

In some embodiments, amino acid substitutions can be made in the disclosed antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter ligand or antigen binding affinities, and/or (4) confer or modify other physicochemical or functional properties on such polypeptides. For example, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) can be made in the sequences disclosed herein.

In other embodiments, substitutions can be made in that portion of the disclosed antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that lies outside the domain(s) forming intermolecular contacts). In such embodiments, conservative amino acid substitutions can be used that do not substantially change the structural characteristics of the parent sequence (*e.g.*, one or more replacement amino acids that do not disrupt the secondary structure that characterizes the parent or native antigen binding protein). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed.), 1984, W. H. New York: Freeman and Company; *Introduction to Protein Structure* (Branden and Tooze, eds.), 1991, New York: Garland Publishing; and Thornton *et al.*, (1991) *Nature* 354:105, which are each incorporated herein by reference.

Additional preferred antigen binding protein and antigen binding protein-FGF21 fusion antigen binding protein components variants include cysteine variants wherein one or more cysteine residues in the parent or native amino acid sequence are deleted from or

substituted with another amino acid (*e.g.*, serine). Cysteine variants are useful, *inter alia* when antibodies must be refolded into a biologically active conformation. Cysteine variants can have fewer cysteine residues than the native antibody, and typically have an even number to minimize interactions resulting from unpaired cysteines.

The heavy and light chains, variable regions domains and CDRs that are disclosed can be used to prepare polypeptides that contain an antigen binding region that can specifically bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and induce FGF21-like signaling. For example, one or more of the CDRs listed in Tables 3 and 6 can be incorporated into a molecule (*e.g.*, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component) covalently or noncovalently to make an immunoadhesion. An immunoadhesion can incorporate the CDR(s) as part of a larger polypeptide chain, can covalently link the CDR(s) to another polypeptide chain, or can incorporate the CDR(s) noncovalently. The CDR(s) enable the immunoadhesion to bind specifically to a particular antigen of interest (*e.g.*, β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 or an epitope thereon).

The heavy and light chains, variable regions domains and CDRs that are disclosed can be used to prepare antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that contain an antigen binding region that can specifically bind to one or more of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and induce FGF21-like signaling. For example, one or more of the CDRs listed in Tables 3 and 6 can be incorporated into a molecule (*e.g.*, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component) that is structurally similar to a “half” antibody comprising the heavy chain, the light chain of an antigen binding protein paired with a Fc fragment so that the antigen binding region is monovalent (like a Fab fragment) but with a dimeric Fc moiety.

Mimetics (*e.g.*, “peptide mimetics” or “peptidomimetics”) based upon the variable region domains and CDRs that are described herein are also provided. These analogs can be peptides, non-peptides or combinations of peptide and non-peptide regions. *See, e.g.*, Fauchere, 1986, *Adv. Drug Res.* 15:29; Veber and Freidinger, 1985, *TINS* p. 392; and Evans *et al.*, 1987, *J. Med. Chem.* 30:1229, which are incorporated herein by reference for any purpose. Peptide mimetics that are structurally similar to therapeutically useful peptides can be used to produce a similar therapeutic or prophylactic effect. Such compounds are often developed with the aid of computerized molecular modeling. Generally, peptidomimetics are

proteins that are structurally similar to an antibody displaying a desired biological activity, such as, in the context of the instant disclosure, the ability to specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, but which have one or more peptide linkages optionally replaced by a linkage selected from: -CH₂NH-, -CH₂S-, -CH₂-CH₂-, -CH-CH-(cis and trans), -COCH₂-, -CH(OH)CH₂-, and -CH₂SO-, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) can be used in certain embodiments to generate more stable proteins. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation can be generated by methods known in the art (see, *e.g.*, Rizo and Gierasch, 1992, *Ann. Rev. Biochem.* 61:387), incorporated herein by reference), for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

Derivatives of the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are described herein are also provided. The derivatized antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can comprise any molecule or substance that imparts a desired property to the antibody or fragment, such as increased half-life in a particular use. The derivatized antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component can comprise, for example, a detectable (or labeling) moiety (*e.g.*, a radioactive, colorimetric, antigenic or enzymatic molecule, a detectable bead (such as a magnetic or electrodense (*e.g.*, gold) bead), or a molecule that specifically binds to another molecule (*e.g.*, biotin or streptavidin)), a therapeutic or diagnostic moiety (*e.g.*, a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component for a particular use (*e.g.*, administration to a subject, such as a human subject, or other *in vivo* or *in vitro* uses). Examples of molecules that can be used to derivatize an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component include albumin (*e.g.*, human serum albumin (HSA)) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can be prepared using techniques well known in the art. Certain antigen binding proteins and antigen binding

protein-FGF21 fusion antigen binding protein components include a PEGylated single chain polypeptide as described herein. In one embodiment, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component is conjugated or otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyrrolidone), polyethylene glycols, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols.

Other derivatives include covalent or aggregative conjugates of the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are disclosed herein with other proteins or polypeptides, such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an antigen binding protein that induce FGF21-like signaling. For example, the conjugated peptide can be a heterologous signal (or leader) polypeptide, *e.g.*, the yeast alpha-factor leader, or a peptide such as an epitope tag. An antigen binding protein-containing fusion protein of the present disclosure can comprise peptides added to facilitate purification or identification of an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 (*e.g.*, poly-His). An antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 also can be linked to the FLAG peptide as described in Hopp *et al.*, 1988, *Bio/Technology* 6:1204; and United States Patent No. 5,011,912. The FLAG peptide is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody (mAb), enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, MO).

Multimers that comprise one or more antigen binding proteins or antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 form another aspect of the present disclosure. Multimers can take the form of covalently-linked or non-covalently-linked dimers, trimers, or higher multimers. Multimers comprising two or more antigen binding proteins or antigen binding protein-FGF21 fusion antigen binding protein

components that bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 and which induce FGF21-like signaling are contemplated for use as therapeutics, diagnostics and for other uses as well, with one example of such a multimer being a homodimer. Other exemplary multimers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc.

One embodiment is directed to multimers comprising multiple antigen binding proteins or antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are joined *via* covalent or non-covalent interactions between peptide moieties fused to an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Such peptides can be peptide linkers (spacers), or peptides that have the property of promoting multimerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote multimerization of antigen binding proteins attached thereto, as described in more detail herein.

In particular embodiments, the multimers comprise from two to four antigen binding proteins or antigen binding protein-FGF21 fusion antigen binding protein components that bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. The antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein components moieties of the multimer can be in any of the forms described above, *e.g.*, variants or fragments. Preferably, the multimers comprise antigen binding proteins or antigen binding protein-FGF21 fusion antigen binding protein components that have the ability to specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, *e.g.*, by Ashkenazi *et al.*, (1991) *Proc. Natl. Acad. Sci. USA* 88:10535; Byrn *et al.*, (1990) *Nature* 344:677; and Hollenbaugh *et al.*, 1992 "Construction of Immunoglobulin Fusion Proteins", in *Current Protocols in Immunology*, Suppl. 4, pages 10.19.1-10.19.11.

One embodiment is directed to a dimer comprising two fusion proteins created by fusing an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

One suitable Fc polypeptide, described in PCT application WO 93/10151 and United States Patent. No. 5,426,048 and No. 5,262,522, is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein described in United States Patent No. 5,457,035, and in Baum *et al.*, (1994) *EMBO J.* 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

In other embodiments, the variable portion of the heavy and/or light chains of a antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component, such as disclosed herein, can be substituted for the variable portion of an antibody heavy and/or light chain.

Alternatively, the oligomer can be a fusion protein comprising multiple antigen binding proteins or antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, with or without peptide linkers (spacer peptides). Among

the suitable peptide linkers are those described in United States Patent. No. 4,751,180 and No. 4,935,233.

Another method for preparing oligomeric derivatives comprising that antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz *et al.*, (1988) *Science* 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe *et al.*, (1994) *FEBS Letters* 344:191, hereby incorporated by reference. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow *et al.*, (1994) *Semin. Immunol.* 6:267-278. In one approach, recombinant fusion proteins comprising an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component fragment or derivative that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 is fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric antigen binding protein fragments or derivatives that form are recovered from the culture supernatant.

In certain embodiments, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component has a K_D (equilibrium binding affinity) of less than 1 pM, 10 pM, 100 pM, 1 nM, 2 nM, 5 nM, 10 nM, 25 nM or 50 nM.

Another aspect provides an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component (or portion thereof) having a half-life of at least one day *in vitro* or *in vivo* (e.g., when administered to a human subject). In one embodiment, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component has a half-life of at least three days. In another embodiment, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component (or portion thereof) has a half-life of four days or longer. In another embodiment, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component (or portion thereof) has a half-life of eight days or longer. In another embodiment, the

antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component (or portion thereof) is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antigen binding protein. In another embodiment, an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 contains point mutations to increase serum half life, such as described in WO 00/09560, published Feb. 24, 2000, incorporated by reference.

Glycosylation

An antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can have a glycosylation pattern that is different or altered from that found in the native species. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (*e.g.*, the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine can also be used.

Addition of glycosylation sites to the antigen binding protein is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration can also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component amino acid sequence can be altered through changes at the DNA level, particularly by mutating the

DNA encoding the target polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the antigen binding protein is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) can be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330 and in Aplin and Wriston, (1981) *CRC Crit. Rev. Biochem.*, pp. 259-306.

Removal of carbohydrate moieties present on the starting antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component can be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin *et al.*, (1987) *Arch. Biochem. Biophys.* 259:52 and by Edge *et al.*, (1981) *Anal. Biochem.* 118:131. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura *et al.*, (1987) *Meth. Enzymol.* 138:350. Glycosylation at potential glycosylation sites can be prevented by the use of the compound tunicamycin as described by Duskin *et al.*, (1982) *J. Biol. Chem.* 257:3105. Tunicamycin blocks the formation of protein-N-glycoside linkages.

Hence, aspects of the present disclosure include glycosylation variants of antigen binding proteins NS antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 wherein the number and/or type of glycosylation site(s) has been altered compared to the amino acid sequences of the parent polypeptide. In certain embodiments, antigen binding protein and antigen binding protein-FGF21 fusion antigen binding protein component variants comprise a greater or a lesser number of N-linked glycosylation sites than the native sequence. An N-linked glycosylation site is characterized

by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X can be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions that eliminate or alter this sequence will prevent addition of an N-linked carbohydrate chain present in the native polypeptide. For example, the glycosylation can be reduced by the deletion of an Asn or by substituting the Asn with a different amino acid. In other embodiments, one or more new N-linked sites are created. Antibodies typically have a N-linked glycosylation site in the Fc region.

Labels and Effector Groups

In some embodiments, an antigen binding protein that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 comprises one or more labels. The term “labeling group” or “label” means any detectable label. Examples of suitable labeling groups include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), fluorescent groups (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic groups (*e.g.*, horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labeling group is coupled to the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art and can be used as seen fit.

The term “effector group” means any group coupled to an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that acts as a cytotoxic agent. Examples for suitable effector groups are radioisotopes or radionuclides (*e.g.*, ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I). Other suitable groups include toxins, therapeutic groups, or chemotherapeutic groups. Examples of suitable groups include calicheamicin, auristatins, geldanamycin and cantansine. In some embodiments, the effector group is coupled to the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component *via* spacer arms of various lengths to reduce potential steric hindrance.

In general, labels fall into a variety of classes, depending on the assay in which they are to be detected: (a) isotopic labels, which can be radioactive or heavy isotopes; (b) magnetic labels (*e.g.*, magnetic particles); (c) redox active moieties; (d) optical dyes; enzymatic groups (*e.g.* horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase); (e) biotinylated groups; and (f) predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags, etc.). In some embodiments, the labeling group is coupled to the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art.

Specific labels include optical dyes, including, but not limited to, chromophores, phosphors and fluorophores, with the latter being specific in many instances. Fluorophores can be either “small molecule” fluoers, or proteinaceous fluoers.

By “fluorescent label” is meant any molecule that can be detected *via* its inherent fluorescent properties. Suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade Blue, Texas Red, IAEDANS, EDANS, BODIPY FL, LC Red 640, Cy 5, Cy 5.5, LC Red 705, Oregon green, the Alexa-Fluor dyes (Alexa Fluor 350, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680), Cascade Blue, Cascade Yellow and R-phycoerythrin (PE) (Molecular Probes, Eugene, OR), FITC, Rhodamine, and Texas Red (Pierce, Rockford, IL), Cy5, Cy5.5, Cy7 (Amersham Life Science, Pittsburgh, PA). Suitable optical dyes, including fluorophores, are described in MOLECULAR PROBES HANDBOOK by Richard P. Haugland, hereby expressly incorporated by reference.

Suitable proteinaceous fluorescent labels also include, but are not limited to, green fluorescent protein, including a Renilla, Ptilosarcus, or Aequorea species of GFP (Chalfie *et al.*, (1994) *Science* 263:802-805), EGFP (Clontech Labs., Inc., Genbank Accession Number U55762), blue fluorescent protein (BFP, Quantum Biotechnologies, Inc., Quebec, Canada; Stauber, (1998) *Biotechniques* 24:462-471; Heim *et al.*, (1996) *Curr. Biol.* 6:178-182), enhanced yellow fluorescent protein (EYFP, Clontech Labs., Inc.), luciferase (Ichiki *et al.*, (1993) *J. Immunol.* 150:5408-5417), β galactosidase (Nolan *et al.*, (1988) *Proc. Natl. Acad. Sci. U.S.A.* 85:2603-2607) and Renilla (WO92/15673, WO95/07463, WO98/14605,

WO98/26277, WO99/49019, United States Patents No. 5292658, No. 5418155, No. 5683888, No. 5741668, No. 5777079, No. 5804387, No. 5874304, No. 5876995, No. 5925558).

Preparation of Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusion Antigen Binding Protein Components

Non-human antibodies that are provided can be, for example, derived from any antibody-producing animal, such as mouse, rat, rabbit, goat, donkey, or non-human primate (such as monkey (*e.g.*, cynomolgus or rhesus monkey) or ape (*e.g.*, chimpanzee)). Non-human antibodies can be used, for instance, in *in vitro* cell culture and cell-culture based applications, or any other application where an immune response to the antibody does not occur or is insignificant, can be prevented, is not a concern, or is desired. In certain embodiments, the antibodies can be produced by immunizing with full-length β -Klotho (Example 1), with the extracellular domain of β -Klotho (Example 2), with whole cells expressing β -Klotho, with membranes prepared from cells expressing β -Klotho (Example 1), with fusion proteins, *e.g.*, Fc fusions comprising β -Klotho (or extracellular domains thereof) fused to Fc, or other methods known in the art, *e.g.*, as described in the Examples presented herein. Alternatively, non-human antibodies can be raised by immunizing with amino acids which are segments of β -Klotho that form part of the epitope to which certain antibodies provided herein bind. The antibodies can be polyclonal, monoclonal, or can be synthesized in host cells by expressing recombinant DNA.

Fully human antibodies can be prepared as described herein by immunizing transgenic animals containing human immunoglobulin loci or by selecting a phage display library that is expressing a repertoire of human antibodies.

The monoclonal antibodies (mAbs) can be produced by a variety of techniques, including conventional monoclonal antibody methodology, *e.g.*, the standard somatic cell hybridization technique of Kohler and Milstein, (1975) *Nature* 256:495. Alternatively, other techniques for producing monoclonal antibodies can be employed, for example, the viral or oncogenic transformation of B-lymphocytes. One suitable animal system for preparing hybridomas is the murine system, which is a well-established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. For such procedures, B cells from immunized mice are fused with a suitable immortalized fusion partner, such as a murine myeloma cell line. If desired, rats or other mammals besides can be immunized instead of mice and B cells from such animals can be

fused with the murine myeloma cell line to form hybridomas. Alternatively, a myeloma cell line from a source other than mouse can be used. Fusion procedures for making hybridomas also are well known. SLAM technology can also be employed in the production of antibodies.

The single chain antibodies that are provided can be formed by linking heavy and light chain variable domain (Fv region) fragments *via* an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) can be prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (V_L and V_H). The resulting polypeptides can fold back on themselves to form antigen binding monomers, or they can form multimers (*e.g.*, dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt *et al.*, (1997) *Prot. Eng.* 10:423; Kortt *et al.*, (2001) *Biomol. Eng.* 18:95-108). By combining different V_L and V_H-comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum *et al.*, (2001) *Biomol. Eng.* 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Pat. No. 4,946,778; Bird, (1988) *Science* 242:423; Huston *et al.*, (1988) *Proc. Natl. Acad. Sci. U.S.A.* 85:5879; Ward *et al.*, (1989) *Nature* 334:544, de Graaf *et al.*, (2002) *Methods Mol. Biol.* 178:379-387. Single chain antibodies derived from antibodies provided herein include, but are not limited to scFvs comprising the variable domain combinations of the heavy and light chain variable regions depicted in Tables 2A-2D, or combinations of light and heavy chain variable domains which include CDRs depicted in Tables 3 and 6.

Antibodies provided herein that are of one subclass can be changed to antibodies from a different subclass using subclass switching methods. Thus, IgG antibodies can be derived from an IgM antibody, for example, and *vice versa*. Such techniques allow the preparation of new antibodies that possess the antigen binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques can be employed. Cloned DNA encoding particular antibody polypeptides can be employed in such procedures, *e.g.*, DNA encoding the constant domain of an antibody of the desired isotype. See, *e.g.*, Lantto *et al.*, (2002) *Methods Mol. Biol.* 178:303-316.

Accordingly, the antibodies that are provided include those comprising, for example, the variable domain combinations described, *supra*, having a desired isotype (for example, IgA, IgG1, IgG2, IgG3, IgG4, IgE, and IgD) as well as Fab or F(ab')₂ fragments thereof. Moreover, if an IgG4 is desired, it can also be desired to introduce a point mutation (CPSCP-

>CPPCP (SEQ ID NOS 266-267, respectively) in the hinge region as described in Bloom *et al.*, (1997) *Protein Science* 6:407, incorporated by reference herein) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies.

Moreover, techniques for deriving antibodies having different properties (*i.e.*, varying affinities for the antigen to which they bind) are also known. One such technique, referred to as chain shuffling, involves displaying immunoglobulin variable domain gene repertoires on the surface of filamentous bacteriophage, often referred to as phage display. Chain shuffling has been used to prepare high affinity antibodies to the hapten 2-phenyloxazol-5-one, as described by Marks *et al.*, (1992) *BioTechnology* 10:779.

Conservative modifications can be made to the heavy and light chain variable regions described in Table 2, or the CDRs described in Table 3 (and corresponding modifications to the encoding nucleic acids) to produce an antigen binding protein having functional and biochemical characteristics. Methods for achieving such modifications are described above.

Antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c and FGFR4 can be further modified in various ways. For example, if they are to be used for therapeutic purposes, they can be conjugated with polyethylene glycol (PEGylated) to prolong the serum half-life or to enhance protein delivery. Alternatively, the V region of the subject antibodies or fragments thereof can be fused with the Fc region of a different antibody molecule. The Fc region used for this purpose can be modified so that it does not bind complement, thus reducing the likelihood of inducing cell lysis in the patient when the fusion protein is used as a therapeutic agent. In addition, the subject antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components or functional fragments thereof can be conjugated with human serum albumin to enhance the serum half-life of the antibody or fragment thereof. Another useful fusion partner for the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components or fragments thereof is transthyretin (TTR). TTR has the capacity to form a tetramer, thus an antibody-TTR fusion protein can form a multivalent antibody which can increase its binding avidity.

Alternatively, substantial modifications in the functional and/or biochemical characteristics of the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components described herein can be achieved by creating substitutions in the amino acid sequence of the heavy and light chains that differ significantly

in their effect on maintaining (a) the structure of the molecular 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 bulkiness of the side chain. A “conservative amino acid substitution” can involve a substitution of a native amino acid residue with a nonnative residue that has little or no effect on the polarity or charge of the amino acid residue at that position. *See*, Table 7, presented herein. Furthermore, any native residue in the polypeptide can also be substituted with alanine, as has been previously described for alanine scanning mutagenesis.

Amino acid substitutions (whether conservative or non-conservative) of the subject antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can be implemented by those skilled in the art by applying routine techniques. Amino acid substitutions can be used to identify important residues of the antigen binding proteins provided herein, or to increase or decrease the affinity of these antigen binding proteins for β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 or for modifying the binding affinity of other antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components described herein.

Methods of Expressing Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusion Antigen Binding Protein Components

Expression systems and constructs in the form of plasmids, expression vectors, transcription or expression cassettes that comprise at least one polynucleotide as described above are also provided herein, as well as host cells comprising such expression systems or constructs.

The antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components provided herein can be prepared by any of a number of conventional techniques. For example, antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be produced by recombinant expression systems, using any technique known in the art. *See, e.g.*, Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Kennet et al. (eds.) Plenum Press, New York (1980); and Antibodies: A Laboratory Manual, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1988).

Antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can be expressed in hybridoma cell lines (*e.g.*, in particular antibodies can be expressed in hybridomas) or in cell lines other than hybridomas. Expression constructs encoding the antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components can be used to transform a mammalian, insect or microbial host cell. Transformation can be performed using any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus or bacteriophage and transducing a host cell with the construct by transfection procedures known in the art, as exemplified by United States Patent No. 4,399,216; No. 4,912,040; No. 4,740,461; No. 4,959,455. The optimal transformation procedure used will depend upon which type of host cell is being transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, mixing nucleic acid with positively-charged lipids, and direct microinjection of the DNA into nuclei.

Recombinant expression constructs typically comprise a nucleic acid molecule encoding a polypeptide comprising one or more of the following: one or more CDRs provided herein; a light chain constant region; a light chain variable region; a heavy chain constant region (*e.g.*, C_H1, C_H2 and/or C_H3); and/or another scaffold portion of an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component. These nucleic acid sequences are inserted into an appropriate expression vector using standard ligation techniques. In one embodiment, the heavy or light chain constant region is appended to the C-terminus of an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4-specific heavy or light chain variable regions and is ligated into an expression vector. The vector is typically selected to be functional in the particular host cell employed (*i.e.*, the vector is compatible with the host cell machinery, permitting amplification and/or expression of the gene to occur). In some embodiments, vectors are used that employ protein-fragment complementation assays using protein reporters, such as dihydrofolate reductase (*see*, for example, U.S. Pat. No. 6,270,964, which is hereby incorporated by reference). Suitable expression vectors can be purchased, for example, from Invitrogen Life Technologies or BD Biosciences (formerly "Clontech").

Other useful vectors for cloning and expressing the antibodies and fragments include those described in Bianchi and McGrew, (2003) *Biotech. Biotechnol. Bioeng.* 84:439-44, which is hereby incorporated by reference. Additional suitable expression vectors are discussed, for example, in *Methods Enzymol.*, vol. 185 (D. V. Goeddel, ed.), 1990, New York: Academic Press.

Typically, expression vectors used in any of the host cells will contain sequences for plasmid maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as “flanking sequences” in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element. Each of these sequences is discussed below.

Optionally, the vector can contain a “tag”-encoding sequence, *i.e.*, an oligonucleotide molecule located at the 5’ or 3’ end of an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component coding sequence; the oligonucleotide sequence encodes polyHis (such as hexaHis (SEQ ID NO: 268)), or another “tag” such as FLAG[®], HA (hemagglutinin influenza virus), or myc, for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification or detection of the antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein components from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified antigen binding protein by various means such as using certain peptidases for cleavage.

Flanking sequences can be homologous (*i.e.*, from the same species and/or strain as the host cell), heterologous (*i.e.*, from a species other than the host cell species or strain), hybrid (*i.e.*, a combination of flanking sequences from more than one source), synthetic or native. As such, the source of a flanking sequence can be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

Flanking sequences useful in the vectors can be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein will have been previously

identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence can be known. Here, the flanking sequence can be synthesized using the methods described herein for nucleic acid synthesis or cloning.

Whether all or only a portion of the flanking sequence is known, it can be obtained using polymerase chain reaction (PCR) and/or by screening a genomic library with a suitable probe such as an oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence can be isolated from a larger piece of DNA that can contain, for example, a coding sequence or even another gene or genes. Isolation can be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagen[®] column chromatography (Chatsworth, CA), or other methods known to the skilled artisan. The selection of suitable enzymes to accomplish this purpose will be readily apparent to one of ordinary skill in the art.

An origin of replication is typically a part of those prokaryotic expression vectors purchased commercially, and the origin aids in the amplification of the vector in a host cell. If the vector of choice does not contain an origin of replication site, one can be chemically synthesized based on a known sequence, and ligated into the vector. For example, the origin of replication from the plasmid pBR322 (New England Biolabs, Beverly, MA) is suitable for most gram-negative bacteria, and various viral origins (*e.g.*, SV40, polyoma, adenovirus, vesicular stomatitis virus (VSV), or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not needed for mammalian expression vectors (for example, the SV40 origin is often used only because it also contains the virus early promoter).

A transcription termination sequence is typically located 3' to the end of a polypeptide coding region and serves to terminate transcription. Usually, a transcription termination sequence in prokaryotic cells is a G-C rich fragment followed by a poly-T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using methods for nucleic acid synthesis such as those described herein.

A selectable marker gene encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, *e.g.*, ampicillin, tetracycline,

or kanamycin for prokaryotic host cells; (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from complex or defined media. Specific selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene. Advantageously, a neomycin resistance gene can also be used for selection in both prokaryotic and eukaryotic host cells.

Other selectable genes can be used to amplify the gene that will be expressed. Amplification is the process wherein genes that are required for production of a protein critical for growth or cell survival are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and promoterless thymidine kinase genes. Mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selectable gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the medium is successively increased, thereby leading to the amplification of both the selectable gene and the DNA that encodes another gene, such as an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. As a result, increased quantities of a polypeptide such as an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component are synthesized from the amplified DNA.

A ribosome-binding site is usually necessary for translation initiation of mRNA and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be expressed.

In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system, one can manipulate the various pre- or pro-sequences to improve glycosylation or yield. For example, one can alter the peptidase cleavage site of a particular signal peptide, or add prosequences, which also can affect glycosylation. The final protein product can have, in the -1 position (relative to the first amino acid of the mature protein), one or more additional amino acids incident to expression, which can not have been totally removed. For example, the final protein product can have one or two amino acid residues found in the peptidase cleavage site, attached to the amino-terminus. Alternatively, use of

some enzyme cleavage sites can result in a slightly truncated form of the desired polypeptide, if the enzyme cuts at such area within the mature polypeptide.

Expression and cloning will typically contain a promoter that is recognized by the host organism and operably linked to the molecule encoding an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Promoters are untranscribed sequences located upstream (*i.e.*, 5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, uniformly transcribe a gene to which they are operably linked, that is, with little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is operably linked to the DNA encoding heavy chain or light chain comprising an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component by removing the promoter from the source DNA by restriction enzyme digestion and inserting the desired promoter sequence into the vector.

Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, retroviruses, hepatitis-B virus, and Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, for example, heat-shock promoters and the actin promoter.

Additional promoters which can be of interest include, but are not limited to: SV40 early promoter (Benoist and Chambon, (1981) *Nature* 290:304-310); CMV promoter (Thornsen *et al.*, (1984) *Proc. Natl. Acad. U.S.A.* 81:659-663); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, (1980) *Cell* 22:787-797); herpes thymidine kinase promoter (Wagner *et al.*, (1981) *Proc. Natl. Acad. Sci. U.S.A.* 78:1444-1445); promoter and regulatory sequences from the metallothioneine gene (Prinster *et*

al., (1982) *Nature* 296:39-42); and prokaryotic promoters such as the beta-lactamase promoter (Villa-Kamaroff *et al.*, (1978) *Proc. Natl. Acad. Sci. U.S.A.* 75:3727-3731); or the tac promoter (DeBoer *et al.*, (1983) *Proc. Natl. Acad. Sci. U.S.A.* 80:21-25). Also of interest are the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: the elastase I gene control region that is active in pancreatic acinar cells (Swift *et al.*, (1984) *Cell* 38:639-646; Ornitz *et al.*, (1986) *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409; MacDonald, (1987) *Hepatology* 7:425-515); the insulin gene control region that is active in pancreatic beta cells (Hanahan, (1985) *Nature* 315:115-122); the immunoglobulin gene control region that is active in lymphoid cells (Grosschedl *et al.*, (1984) *Cell* 38:647-658; Adames *et al.*, (1985) *Nature* 318:533-538; Alexander *et al.*, (1987) *Mol. Cell. Biol.* 7:1436-1444); the mouse mammary tumor virus control region that is active in testicular, breast, lymphoid and mast cells (Leder *et al.*, (1986) *Cell* 45:485-495); the albumin gene control region that is active in liver (Pinkert *et al.*, (1987) *Genes and Devel.* 1 :268-276); the alpha-feto-protein gene control region that is active in liver (Krumlauf *et al.*, (1985) *Mol. Cell. Biol.* 5:1639-1648; Hammer *et al.*, (1987) *Science* 253:53-58); the alpha 1-antitrypsin gene control region that is active in liver (Kelsey *et al.*, (1987) *Genes and Devel.* 1:161-171); the beta-globin gene control region that is active in myeloid cells (Mogam *et al.*, (1985) *Nature* 315:338-340; Kollias *et al.*, (1986) *Cell* 46:89-94); the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain (Readhead *et al.*, (1987) *Cell* 48:703-712); the myosin light chain-2 gene control region that is active in skeletal muscle (Sani, (1985) *Nature* 314:283-286); and the gonadotropic releasing hormone gene control region that is active in the hypothalamus (Mason *et al.*, (1986) *Science* 234:1372-1378).

An enhancer sequence can be inserted into the vector to increase transcription of DNA encoding light chain or heavy chain comprising an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 by higher eukaryotes. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent, having been found at positions both 5' and 3' to the transcription unit. Several enhancer sequences available from mammalian genes are known (*e.g.*, globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus is used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the

polyoma enhancer, and adenovirus enhancers known in the art are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer can be positioned in the vector either 5' or 3' to a coding sequence, it is typically located at a site 5' from the promoter. A sequence encoding an appropriate native or heterologous signal sequence (leader sequence or signal peptide) can be incorporated into an expression vector, to promote extracellular secretion of the antibody. The choice of signal peptide or leader depends on the type of host cells in which the antibody is to be produced, and a heterologous signal sequence can replace the native signal sequence. Examples of signal peptides that are functional in mammalian host cells include the following: the signal sequence for interleukin-7 (IL-7) described in US Patent No. 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman *et al.*, (1984) *Nature* 312:768; the interleukin-4 receptor signal peptide described in EP Patent No. 0367 566; the type I interleukin-1 receptor signal peptide described in U.S. Patent No. 4,968,607; the type II interleukin-1 receptor signal peptide described in EP Patent No. 0 460 846.

The expression vectors that are provided can be constructed from a starting vector such as a commercially available vector. Such vectors can, but need not, contain all of the desired flanking sequences. Where one or more of the flanking sequences described herein are not already present in the vector, they can be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking sequences are well-known to one skilled in the art.

After the vector has been constructed and a nucleic acid molecule encoding light chain, a heavy chain, or a light chain and a heavy chain component(s) of an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 has been inserted into the proper site of the vector, the completed vector can be inserted into a suitable host cell for amplification and/or polypeptide expression. The transformation of an expression vector for an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component into a selected host cell can be accomplished by well-known methods including transfection, infection, calcium phosphate co-precipitation, electroporation, microinjection, lipofection, DEAE-dextran mediated transfection, or other known techniques. The method selected will in part be a function of the type of host cell to be used. These methods and other suitable methods are well-known to the skilled artisan, and are set forth, for example, in Sambrook *et al.*, (2001), *supra*.

A host cell, when cultured under appropriate conditions, synthesizes an antigen binding protein or antigen binding protein-FGF21 fusion antigen binding protein component that can subsequently be collected from the culture medium (if the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity (such as glycosylation or phosphorylation) and ease of folding into a biologically active molecule.

Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and a number of other cell lines. In certain embodiments, cell lines can be selected through determining which cell lines have high expression levels and constitutively produce antigen binding proteins and antigen binding protein-FGF21 fusion antigen binding protein components that specifically bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c or FGFR4. In another embodiment, a cell line from the B cell lineage that does not make its own antibody but has a capacity to make and secrete a heterologous antibody can be selected. The ability to induce FGF21-like signaling can also form a selection criterion.

Uses Of Antigen Binding Proteins and Antigen Binding Protein-FGF21 Fusions For Diagnostic And Therapeutic Purposes

The antigen binding proteins and antigen binding protein-FGF21 fusions disclosed herein are useful for detecting the presence of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in biological samples and identification of cells or tissues that produce β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. For instance, the antigen binding proteins and antigen binding protein-FGF21 fusions disclosed herein can be used in diagnostic assays, *e.g.*, binding assays to detect and/or quantify β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 expressed in a tissue or cell. Antigen binding proteins and antigen binding protein-FGF21 fusions that specifically bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be used in treatment of diseases related to FGF21-like signaling in a patient in need thereof, such as type 2 diabetes, obesity, dyslipidemia, NASH,

cardiovascular disease, and metabolic syndrome. By forming a signaling complex comprising an antigen binding protein or antigen binding protein-FGF21 fusions, β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4, the natural *in vivo* activity of FGF21, which associates with an FGFR such as FGFR1c, FGFR2c, FGFR3c, FGFR4 and β -Klotho *in vivo* to initiate signaling, can be mimicked and/or enhanced, leading to therapeutic effects.

Indications

A disease or condition associated with human FGF21 includes any disease or condition whose onset in a patient is caused by, at least in part, the induction of FGF21-like signaling, which is initiated *in vivo* by the formation of a complex comprising FGFR1c, FGFR2c, FGFR3c or FGFR4, β -Klotho and FGF21. The severity of the disease or condition can also be decreased by the induction of FGF21-like signaling. Examples of diseases and conditions that can be treated with the antigen binding proteins include type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

The antigen binding proteins and antigen binding protein-FGF21 fusions described herein can be used to treat type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome, or can be employed as a prophylactic treatment administered, *e.g.*, 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, thereby providing an improved glycemic and cardiovascular risk factor profile.

Diagnostic Methods

The antigen binding proteins and antigen binding protein-FGF21 fusions described herein can be used for diagnostic purposes to detect, diagnose, or monitor diseases and/or conditions associated with FGFR1c, FGFR2c, FGFR3c, FGFR4, β -Klotho, FGF21 or combinations thereof. Also provided are methods for the detection of the presence of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in a sample using classical immunohistological methods known to those of skill in the art (*e.g.*, Tijssen, 1993, *Practice and Theory of Enzyme Immunoassays*, Vol 15 (Eds R.H. Burdon and P.H. van Knippenberg, Elsevier, Amsterdam); Zola, (1987) *Monoclonal Antibodies: A Manual of Techniques*, pp. 147-158 (CRC Press, Inc.); Jalkanen *et al.*, (1985) *J. Cell. Biol.* 101:976-985;

Jalkanen *et al.*, (1987) *J. Cell Biol.* 105:3087-3096). The detection of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be performed *in vivo* or *in vitro*.

Diagnostic applications provided herein include use of the antigen binding proteins and antigen binding protein-FGF21 fusions to detect expression of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. Examples of methods useful in the detection of the presence of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA).

For diagnostic applications, the antigen binding protein or antigen binding protein-FGF21 fusion typically will be labeled with a detectable labeling group. Suitable labeling groups include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), fluorescent groups (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic groups (*e.g.*, horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labeling group is coupled to the antigen binding protein *via* spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art and can be used.

In another aspect, an antigen binding protein or antigen binding protein-FGF21 fusion can be used to identify a cell or cells that express β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4. In a specific embodiment, the antigen binding protein or antigen binding protein-FGF21 fusion is labeled with a labeling group and the binding of the labeled antigen binding protein or antigen binding protein-FGF21 fusion to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 is detected. In a further specific embodiment, the binding of the antigen binding protein or antigen binding protein-FGF21 fusion to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 detected *in vivo*. In a further specific embodiment, the antigen binding protein or antigen binding protein-FGF21 fusion is isolated and measured using techniques known in the art. *See, for example, Harlow and Lane, (1988) Antibodies: A Laboratory Manual*, New York: Cold Spring Harbor (ed. 1991 and periodic supplements);

John E. Coligan, ed., (1993) Current Protocols In Immunology New York: John Wiley & Sons.

Another aspect provides for detecting the presence of a test molecule that competes for binding to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with the antigen binding proteins and antigen binding protein-FGF21 fusions provided, as disclosed herein. An example of one such assay could involve detecting the amount of free antigen binding protein or antigen binding protein-FGF21 fusion in a solution containing an amount of β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in the presence or absence of the test molecule. An increase in the amount of free antigen binding protein or antigen binding protein-FGF21 fusion (*i.e.*, the antigen binding protein or antigen binding protein-FGF21 fusion not bound to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4) would indicate that the test molecule is capable of competing for binding to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 with the antigen binding protein or antigen binding protein-FGF21 fusion. In one embodiment, the antigen binding protein or antigen binding protein-FGF21 fusion is labeled with a labeling group. Alternatively, the test molecule is labeled and the amount of free test molecule is monitored in the presence and absence of an antigen binding protein or antigen binding protein-FGF21 fusion.

Methods of Treatment: Pharmaceutical Formulations, Routes of Administration

Methods of using the antigen binding proteins and antigen binding protein-FGF21 fusions are also provided. In some methods, an antigen binding protein or antigen binding protein-FGF21 fusion is provided to a patient. The antigen binding protein or antigen binding protein-FGF21 fusion induces FGF21-like signaling.

Pharmaceutical compositions that comprise a therapeutically effective amount of one or a plurality of the disclosed antigen binding proteins and antigen binding protein-FGF21 fusions and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant are also provided. In addition, methods of treating a patient by administering such pharmaceutical composition are included. The term "patient" includes human patients.

Acceptable formulation materials are nontoxic to recipients at the dosages and concentrations employed. In specific embodiments, pharmaceutical compositions comprising a therapeutically effective amount of human antigen binding proteins or antigen binding

protein-FGF21 fusions that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 are provided.

In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, the pharmaceutical composition can contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as Pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. *See, Remington's Pharmaceutical Sciences*, 18th Edition, (A.R. Gennaro, ed.), 1990, Mack Publishing Company.

In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. *See, for example, Remington's Pharmaceutical Sciences, supra.* In certain embodiments, such compositions can influence the physical state, stability, rate of *in vivo* release and rate of *in vivo* clearance of the antigen binding proteins disclosed.

In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition can be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier can be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In specific embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and can further include sorbitol or a suitable substitute. In certain embodiments, compositions comprising antigen binding proteins or antigen binding protein-FGF21 fusions that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (Remington's Pharmaceutical Sciences, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, an antigen binding protein or antigen binding protein-FGF21 fusion that bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be formulated as a lyophilizate using appropriate excipients such as sucrose.

The pharmaceutical compositions can be selected for parenteral delivery. Alternatively, the compositions can be selected for inhalation or for delivery through the digestive tract, such as orally. Preparation of such pharmaceutically acceptable compositions is within the skill of the art.

The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

When parenteral administration is contemplated, the therapeutic compositions can be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired antigen binding protein or antigen binding protein-FGF21 fusion in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the antigen binding protein is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that can provide controlled or sustained release of the product which can be

delivered *via* depot injection. In certain embodiments, hyaluronic acid can also be used, having the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices can be used to introduce the desired antigen binding protein or antigen binding protein-FGF21 fusion.

Certain pharmaceutical compositions are formulated for inhalation. In some embodiments, antigen binding proteins or antigen binding protein-FGF21 fusions that bind to β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 are formulated as a dry, inhalable powder. In specific embodiments, antigen binding protein or antigen binding protein-FGF21 fusion inhalation solutions can also be formulated with a propellant for aerosol delivery. In certain embodiments, solutions can be nebulized. Pulmonary administration and formulation methods therefore are further described in International Patent Application No. PCT/US94/001875, which is incorporated by reference and describes pulmonary delivery of chemically modified proteins. Some formulations can be administered orally. Antigen binding proteins or antigen binding protein-FGF21 fusions that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 that are administered in this fashion can be formulated with or without carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In certain embodiments, a capsule can be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of an antigen binding protein or antigen binding protein-FGF21 fusion. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders can also be employed.

Some pharmaceutical compositions comprise an effective quantity of one or a plurality of human antigen binding proteins or antigen binding protein-FGF21 fusions that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in a mixture with non-toxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving antigen binding proteins or antigen binding protein-FGF21 fusions that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. *See*, for example, International Patent Application No. PCT/US93/00829, which is incorporated by reference and describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations can include semipermeable polymer matrices in the form of shaped articles, *e.g.*, films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides (as disclosed in U.S. Patent No. 3,773,919 and European Patent Application Publication No. EP 058481, each of which is incorporated by reference), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, 1983, *Biopolymers* 2:547-556), poly (2-hydroxyethyl-methacrylate) (Langer *et al.*, 1981, *J. Biomed. Mater. Res.* 15:167-277 and Langer, 1982, *Chem. Tech.* 12:98-105), ethylene vinyl acetate (Langer *et al.*, 1981, *supra*) or poly-D(-)-3-hydroxybutyric acid (European Patent Application Publication No. EP 133,988). Sustained release compositions can also include liposomes that can be prepared by any of several methods known in the art. *See, e.g.*, Eppstein *et al.*, 1985, *Proc. Natl. Acad. Sci. U.S.A.* 82:3688-3692; European Patent Application Publication Nos. EP 036,676; EP 088,046 and EP 143,949, incorporated by reference.

Pharmaceutical compositions used for *in vivo* administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes. When the composition is lyophilized, sterilization using this method can be conducted either prior to or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

In certain embodiments, cells expressing a recombinant antigen binding protein as disclosed herein is encapsulated for delivery (*see, Invest. Ophthalmol Vis Sci* (2002) 43:3292-3298 and *Proc. Natl. Acad. Sciences USA* (2006) 103:3896-3901).

In certain formulations, an antigen binding protein or antigen binding protein-FGF21 fusion has a concentration of at least 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml or 150 mg/ml. Some formulations contain a buffer, sucrose and polysorbate. An example of a formulation is one containing 50-100 mg/ml of antigen binding protein, 5-20 mM sodium acetate, 5-10% w/v sucrose, and 0.002 – 0.008% w/v polysorbate. Certain, formulations, for instance, contain 65-75 mg/ml of an antigen binding protein in 9-11 mM sodium acetate buffer, 8-10% w/v sucrose, and 0.005-0.006% w/v polysorbate. The pH of certain such formulations is in the range of 4.5-6. Other formulations have a pH of 5.0-5.5 (*e.g.*, pH of 5.0, 5.2 or 5.4).

Once the pharmaceutical composition has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, crystal, or as a dehydrated or lyophilized powder. Such formulations can be stored either in a ready-to-use form or in a form (*e.g.*, lyophilized) that is reconstituted prior to administration. Kits for producing a single-dose administration unit are also provided. Certain kits contain a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments, kits containing single and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes) are provided. The therapeutically effective amount of an antigen binding protein-containing pharmaceutical composition to be employed will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will vary depending, in part, upon the molecule delivered, the indication for which the antigen binding protein or antigen binding protein-FGF21 fusion is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect.

A typical dosage can range from about 1 µg/kg to up to about 30 mg/kg or more, depending on the factors mentioned above. In specific embodiments, the dosage can range from 10 µg/kg up to about 30 mg/kg, optionally from 0.1 mg/kg up to about 30 mg/kg, alternatively from 0.3 mg/kg up to about 20 mg/kg. In some applications, the dosage is from 0.5 mg/kg to 20 mg/kg. In some instances, an antigen binding protein is dosed at 0.3 mg/kg, 0.5mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, or 20 mg/kg. The dosage schedule in some treatment regimes is at a dose of 0.3 mg/kg qW, 0.5mg/kg qW, 1 mg/kg qW, 3 mg/kg qW, 10 mg/kg qW, or 20 mg/kg qW.

Dosing frequency will depend upon the pharmacokinetic parameters of the particular antigen binding protein or antigen binding protein-FGF21 fusion in the formulation used. Typically, a clinician administers the composition until a dosage is reached that achieves the desired effect. The composition can therefore be administered as a single dose, or as two or more doses (which can or can not contain the same amount of the desired molecule) over time, or as a continuous infusion *via* an implantation device or catheter. Appropriate dosages can be ascertained through use of appropriate dose-response data. In certain embodiments, the antigen binding proteins or antigen binding protein-FGF21 fusions can be administered to patients throughout an extended time period. Chronic administration of an antigen binding protein or antigen binding protein-FGF21 fusion minimizes the adverse immune or allergic response commonly associated with antigen binding proteins and antigen binding protein-FGF21 fusions that are not fully human, for example an antibody raised against a human antigen in a non-human animal, for example, a non-fully human antibody or non-human antibody produced in a non-human species.

The route of administration of the pharmaceutical composition is in accord with known methods, *e.g.*, orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain embodiments, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device.

The composition also can be administered locally *via* implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In certain embodiments, where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be *via* diffusion, timed-release bolus, or continuous administration.

It also can be desirable to use antigen binding protein or antigen binding protein-FGF21 fusion pharmaceutical compositions *ex vivo*. In such instances, cells, tissues or organs that have been removed from the patient are exposed to antigen binding protein or antigen binding protein-FGF21 fusion pharmaceutical compositions after which the cells, tissues and/or organs are subsequently implanted back into the patient.

In particular, antigen binding proteins or antigen binding protein-FGF21 fusions that specifically bind β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4 can be delivered by implanting certain cells that have been genetically engineered,

using methods such as those described herein, to express and secrete the polypeptide. In certain embodiments, such cells can be animal or human cells, and can be autologous, heterologous, or xenogeneic. In certain embodiments, the cells can be immortalized. In other embodiments, in order to decrease the chance of an immunological response, the cells can be encapsulated to avoid infiltration of surrounding tissues. In further embodiments, the encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

Combination Therapies

In another aspect, the present disclosure provides a method of treating a subject for diabetes with a therapeutic antigen binding protein or antigen binding protein-FGF21 fusion of the present disclosure, such as the fully human therapeutic antibodies described herein, together with one or more other treatments. In one embodiment, such a combination therapy achieves an additive or synergistic effect. The antigen binding proteins or antigen binding protein-FGF21 fusions can be administered in combination with one or more of the type 2 diabetes or obesity treatments currently available. These treatments for diabetes include biguanide (metformin), and sulfonylureas (such as glyburide, glipizide). Additional treatments directed at maintaining glucose homeostasis include PPAR gamma agonists (such as pioglitazone, rosiglitazone); glinides (such as meglitinide, repaglinide, and nateglinide); DPP-4 inhibitors (such as Januvia® and Onglyza®) and alpha glucosidase inhibitors (such as acarbose, voglibose).

Additional combination treatments for diabetes include injectable treatments such as insulin and incretin mimetics (such as Byetta®, Exenatide®), other GLP-1 (glucagon-like peptide) analogs such as liraglutide, other GLP-1R agonists and Symlin® (pramlintide).

Additional treatment directed at weight loss drugs include Meridia and Xenical.

EXAMPLES

The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting.

EXAMPLE 1

PREPARATION OF FGFR1c OVER EXPRESSING CELLS FOR USE AS AN ANTIGEN

Nucleic acid sequences encoding the full length human FGFR1c polypeptide (SEQ ID NO: 305; Figures 1a-b) and a separate sequence encoding the full length human β -Klotho polypeptide (SEQ ID NO: 308; Figures 2a-c) were subcloned into suitable mammalian cell expression vectors (*e.g.*, pcDNA3.1 Zeo, pcDNA3.1 Hyg (Invitrogen, Calsbad, CA) or pDSR α 20). The pDSR α 20 vector contains SV40 early promoter/enhancer for expressing the gene of interest and a mouse DHFR expression cassette for selection in CHO DHFR (-) host cells such as AM1 CHO (a derivative of DG44, CHO DHFR (-)).

AM-1 CHO cells were seeded at 1.5×10^6 cells per 100mm dish. After 24 hours, the cells were co-transfected with linearized DNAs of pDSR α 20/huFGFR1c and pDSR α 20/hu β -Klotho with FuGene6 (Roche Applied Science). The transfected cells were trypsinized 2 days after transfection and seeded into CHO DHFR selective growth medium containing 10% dialyzed FBS and without hypoxanthine/thymidine supplement. After 2 weeks, the resulting transfected colonies were trypsinized and pooled.

HEK293T cells were transfected with the full length huFGFR1c and hu β -Klotho in pcDNA3.1 series or pTT14 (an expression vector developed by Durocher, NRCC, with CMV promoter and EBV ori, similar to pTT5 and a puromycin selection marker) based vector and selected with the corresponding drugs following similar procedure as for the CHO transfection and selection.

The FGF21R (*i.e.*, FGFR1c and β -Klotho) transfected AM1 CHO or 293T cell pools were sorted repeatedly using Alexa 647-labeled FGF21. As a cell-surface staining reagent, FGF21 was labeled with Alexa 647-NHS following the method recommended by the manufacturer (Molecular Probes, Inc. Cat A 2006). The Alexa 647-labeled FGF21 showed specific staining of FGF21R receptor expressing cells and not the non-transfected parental cells (Figure 3). High expressing cells were collected at the end of the final sorting, expanded and frozen into vials. The AM-1/huFGF21R cells were prepared for immunization and the 293T/huFGF21R cells were used for titering mouse sera by FACS after immunization and in binding screens of the hybridoma supernatants by FMAT (see Example 4).

EXAMPLE 2

PREPARATION OF A SOLUBLE FGFR1c/ β -KLOTHO COMPLEX FOR USE AS ANTIGEN

Soluble FGF21 receptor constructs were generated in pTT14 or pcDNA3.1 expression vectors. The FGFR1c ECD-Fc construct (SEQ ID NO: 311, Figure 4) comprises the N-terminal extracellular domain of FGFR1c (amino acid residues #1 – 374; SEQ ID NO:5) fused to IgG1 Fc (SEQ ID NO: 20). The β -Klotho ECD-Fc construct (SEQ ID NO: 312, Figure 5) comprises the N-terminal extracellular domain of β -Klotho (amino acid residues #1-996; SEQ ID NO:8) fused to IgG1 Fc (SEQ ID NO: 20).

HEK293 cells (293F, Invitrogen) were transfected with human FGFR1c ECD-Fc/pTT5, human β -Klotho ECD-Fc/pTT14-puro and dGFP/pcDNA3.1-Neo and selected in the presence of the corresponding drugs followed by repeated FACS sorting based on dGFP expression. Cells were grown in serum-free Dulbecco's Modified Eagle Medium (DMEM) supplemented with nonessential amino acids in HyperFlasks (Corning) for 4 days and conditioned media (CM) harvested for purification.

The 293 CM was concentrated 6 fold and applied to Protein A FF equilibrated in PBS. The protein was eluted with Pierce Gentle Ag/Ab elution buffer. The Protein A pool was dialyzed against 20mM Tris-HCl, pH 7, 10mM NaCl and applied to SP HP at pH 7.0. The FGFR1c ECD-Fc was present in the flow-through and the heterodimer was eluted with linear gradient of 0- 0.4 M NaCl, 20 mM tris-HCl pH 7.0. N-terminus amino acid sequencing verified the purified soluble FGF21R to be a heterodimer composed of (1:1) ratio of FGFR1c ECD-Fc and betaKlotho ECD-Fc. The purified soluble FGF21R-Fc (Figure 6) was used as the antigen for immunization.

EXAMPLE 3

PREPARATION OF MONOCLONAL ANTIBODIES

Immunizations were conducted using one or more suitable forms of FGF21 receptor antigen, including: (1) cell bound receptor of CHO transfectants expressing full length human FGFR1c and β -Klotho at the cell surface, obtained by transfecting CHO cells with cDNA encoding a human full length FGFR1c polypeptide of SEQ ID NO: 305 (see also Figures 1a-b) and cDNA encoding a human β -Klotho polypeptide of SEQ ID NO: 308 (see also Figures 2a-c); (2) membrane extract from the aforementioned cells expressing the FGF21R receptor complex; or (3) soluble FGF21R receptor obtainable by co-expressing the

N-terminal extracellular domain (ECD) of FGFR1c (SEQ ID NO: 311; see also Figure 4) and the N-terminal extracellular domain (ECD) of β -Klotho (SEQ ID NO: 312; see also Figure 5) or (4) combinations thereof.

A suitable amount of immunogen (*i.e.*, 10 μ gs/mouse of soluble FGF21R or 3 - 4 x 10⁶ cells/mouse of stably transfected CHO cells or 150 μ gs/mouse of purified FGF21R membranes prepared from CHO cells stably expressing FGF21R) was used for initial immunization in XenoMouse™ according to the methods disclosed in U.S. Patent Application Serial No. 08/759,620, filed December 3, 1996 and International Patent Application Nos. WO 98/24893, and WO 00/76310, the disclosures of which are hereby incorporated by reference. Following the initial immunization, subsequent boost immunizations of immunogen (5 μ g/mouse of soluble FGF21R or 1.7 x 10⁶ FGF21R transfected cells/mouse or 75 μ gs of purified FGF21R membranes) were administered on a schedule and for the duration necessary to induce a suitable anti-FGF21R titer in the mice. Titers were determined by a suitable method, for example, by enzyme immunoassay, fluorescence activated cell sorting (FACS), or by other methods (including combinations of enzyme immunoassays and FACS).

Animals exhibiting suitable titers were identified, and lymphocytes were obtained from draining lymph nodes and, if necessary, pooled for each cohort. Lymphocytes were dissociated from lymphoid tissue by grinding in a suitable medium (for example, Dulbecco's Modified Eagle Medium; DMEM; obtainable from Invitrogen, Carlsbad, CA) to release the cells from the tissues, and suspended in DMEM. B cells were selected and/or expanded using standard methods, and fused with suitable fusion partner, for example, nonsecretory myeloma P3X63Ag8.653 cells (American Type Culture Collection CRL 1580; Kearney et al, *J. Immunol.* 123, 1979, 1548-1550), using techniques that were known in the art.

In one suitable fusion method, lymphocytes were mixed with fusion partner cells at a ratio of 1:4. The cell mixture was gently pelleted by centrifugation at 400 x g for 4 minutes, the supernatant decanted, and the cell mixture gently mixed (for example, by using a 1 ml pipette). Fusion was induced with PEG/DMSO (polyethylene glycol/dimethyl sulfoxide; obtained from Sigma-Aldrich, St. Louis MO; 1 ml per million of lymphocytes). PEG/DMSO was slowly added with gentle agitation over one minute followed, by one minute of mixing. IDMEM (DMEM without glutamine; 2 ml per million of B cells), was then added over 2 minutes with gentle agitation, followed by additional IDMEM (8 ml per million B-cells) which was added over 3 minutes.

The fused cells were pelleted (400 x g 6 minutes) and resuspended in 20 ml Selection media (for example, DMEM containing Azaserine and Hypoxanthine [HA] and other supplemental materials as necessary) per million B-cells. Cells were incubated for 20-30 minutes at 37°C and then resuspended in 200 ml selection media and cultured for three to four days in T175 flasks prior to 96 well plating.

Cells were distributed into 96-well plates using standard techniques to maximize clonality of the resulting colonies. After several days of culture, supernatants were collected and subjected to screening assays as detailed in the examples below, including confirmation of binding to human FGF21 receptor, specificity and/or cross-species reactivity. Positive cells were further selected and subjected to standard cloning and subcloning techniques. Clonal lines were expanded *in vitro*, and the secreted human antibodies obtained for analysis.

In this manner, mice were immunized with either cells or membranes expressing full length FGF21R cells, or soluble FGF21R extracellular domain, with a range of 11-17 immunizations over a period of approximately one to three and one-half months. Several cell lines secreting FGF21R-specific antibodies were obtained, and the antibodies were further characterized. The sequences thereof are presented herein and in the Sequence Listing, and results of various tests using these antibodies are provided.

EXAMPLE 4

SELECTION OF BINDING ANTIBODIES BY FMAT

After 14 days of culture, hybridoma supernatants were screened for FGF21R-specific monoclonal antibodies by Fluorometric Microvolume Assay Technology (FMAT) by screening against either the CHO AM1/huFGF21R cell line or recombinant HEK293 cells that were transfected with human FGF21R and counter-screening against parental CHO or HEK293 cells. Briefly, the cells in Freestyle media (Invitrogen) were seeded into 384-well FMAT plates in a volume of 50 µL/well at a density of 4,000 cells/well for the stable transfectants, and at a density of 16,000 cells/well for the parental cells, and cells were incubated overnight at 37°C. 10 µL/well of supernatant was then added, and the plates were incubated for approximately one hour at 4°C, after which 10 µL/well of anti-human IgG-Cy5 secondary antibody was added at a concentration of 2.8 µg/ml (400ng/ml final concentration). Plates were then incubated for one hour at 4°C, and fluorescence was read using an FMAT Cellular Detection System (Applied Biosystems).

In total, over 3,000 hybridoma supernatants were identified as binding to the FGF21 receptor expressing cells but not to parental cells by the FMAT method. These supernatants were then tested in the FGF21 functional assays as described below.

EXAMPLE 5

SELECTION OF ANTIBODIES THAT INDUCE FGF21-LIKE SIGNALING

Experiments were performed to identify functional antibodies that mimic wild-type FGF21 activity (*e.g.*, the ability to induce FGF21-like signaling) using a suitable FGF21 reporter assay. The disclosed FGF21 reporter assay measures activation of FGFR signaling via a MAPK pathway readout. β -Klotho is a co-receptor for FGF21 signaling, and although it is believed not to have any inherent signaling capability due to its very short cytoplasmic domain, it is required for FGF21 to induce signaling through FGFRs.

5.A ELK-Luciferase Reporter Assay

ELK-luciferase assays were performed using a recombinant human 293T kidney cell or CHO cell system. Specifically, the host cells were engineered to over-express β -Klotho and luciferase reporter constructs. The reporter constructs contain sequences encoding GAL4-ELK1 and 5xUAS-Luc, a luciferase reporter driven by a promoter containing five tandem copies of the Gal4 binding site. Activation of the FGF21 receptor complex in these recombinant reporter cell lines induces intracellular signal transduction, which in turn leads to ERK and ELK phosphorylation. Luciferase activity is regulated by the level of phosphorylated ELK, and is used to indirectly monitor and quantify FGF21 activity.

In one example, CHO cells were transfected sequentially using the Lipofectamine 2000 transfection reagent (Invitrogen) according to the manufacturer's protocol with the receptor constructs expressing β -Klotho, FGFR1c and the reporter plasmids: 5x Gal4-Luciferase (minimal TK promoter with 5xGal4 binding sites upstream of luciferase) and Gal4-ELK1. Gal4-ELK1 binds to the Gal4 binding sites and activates transcription when it is phosphorylated by ERK. Luciferase transcription, and thereby the corresponding enzymatic activity in this context is regulated by the level of phosphorylated ELK1, and is used to indirectly monitor and quantify FGF21 activity.

Clone 2E10 was selected as the FGF21 luciferase reporter cell line based on the optimal assay window of 10-20 fold with native FGF21 exhibiting an EC50 in the single nM range.

For the assay, the ELK-luciferase reporter cells were plated in 96 well assay plates, and serum starved overnight. FGF21 or test samples were added for 6 hours at 37 degrees. The plates were then allowed to cool to room temperature and the luciferase activity in the cell lysates was measured with Bright-Glo (Promega).

5.B ERK-Phosphorylation Assay

Alternative host cell lines, specifically a L6 (a rat myoblastic cell line), was developed and employed to identify antibodies with FGF21-like signaling activity. The rat L6 cell line is a desirable host cell line for the activity assay because it is known to express minimal levels of endogenous FGF receptors. The L6 cells do not respond to FGF21 even when transfected with β -Klotho expression vector and therefore provides a cleaner background. (Kurosu et al., (2007) J. Biol. Chem. 282, 26687-26695).

L6 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum and penicillin/streptomycin. Cells were transfected with plasmids expressing β Klotho and individual FGFR using the Lipofectamine 2000 transfection reagent (Invitrogen) according to the manufacturer's protocol.

Analysis of FGF signaling in L6 cells was performed as described in the literature (Kurosu et al., (2007) J. Biol. Chem. 282, 26687–26695). Cell cultures were collected 10 min after the treatment of FGF21 or test molecules and snap frozen in liquid nitrogen, homogenized in the lysis buffer and subjected to western blot analysis using an anti-phospho-p44/42 MAP kinase (ERK1/2) antibody and an anti-ERK antibody (Cell Signaling). The percent of phosphorylated ERK versus total ERK protein was determined in this way.

In addition, the factor-dependent mouse BaF3 cell-based proliferation assay used frequently for cytokine receptors can also be developed and applied.

Among the hybridoma supernatants tested in the CHO cell (clone 2E10) based human FGF21 ELK-luciferase reporter assay, over 30 were identified as positive (> 5% of the activity of FGF21) when compared to 20nM FGF21 as the positive control. Antibodies were then purified from the conditioned media of the hybridoma cultures of these positives and tested again in the CHO cell based ELK-luciferase reporter assay. (Figure 7) showed the representative antibodies in the dose-responsive potency assay with estimated EC50 less than 1 μ g/ml (or 6.7nM). The activities were confirmed in the L6 cell based ERK1/2-phosphorylation assay (Figure 8) with EC50 less than 10 nM which is consistent to the ELK-luciferase assay in the CHO stable cell line 2E10.

EXAMPLE 6**ELISA OF FGFR1c BINDERS**

Peptides that bind to FGFR1c were identified and examined in an ELISA assay. Subsequently, human FGFR1c (hu-FGFR1c), and murine FGFR1c (mu-FGFR1c) were expressed and purified. Anti-M13-HRP was purchased from GE healthcare (Piscataway, NJ). Maxisorp 96 well plates (Thermo Fisher Scientific; Rockford, IL) were coated with 2 µg/ml hu-FGFR1c and mu-FGFR1c in PBS respectively. Plates were then incubated at 4°C overnight and blocked in 2% MPBS at room temperature for 1 h the next day. Plates were then incubated for 1 h with samples diluted in 2% MPBS and washed 3 times with PBST (Tween20) after 1 h incubation. Anti-M13-HRP was diluted 1:10000 in 2% MPBS and added to each well then incubated for 1 h. After 1 h incubation, plates were washed 3 times with 300 µl PBST. Lumiglo chemiluminescent reagent (KPL; Gaithersburg, MD) was added and luminescence was measured using Perkin Elmer Envision reader (Perkin Elmer; Waltham, MA).

EXAMPLE 7**CONSTRUCTION OF BISPECIFIC FGF21 MIMETIC ANTIGEN BINDING
PROTEINS**

Vector pTT5 SNS (National Research Council of Canada, Ottawa, Canada) was used for heavy chains. The N-linked glycosylation site in IgG1 was removed by overlap PCR as follows using Novagen (Darmstadt, Germany) Hot Start KOD PCR kit 71086. The reaction contained 30.5 µl H₂O, 2.5 µl DMSO, 5 µl 10× buffer #1, 5 µl dNTPs for final concentration of 0.2 mM, 2 µl MgCl₂ (catalog number 71153) for final concentration of 1 mM, 1 µl template DNA prepared by Qiagen spin Mini-prep (Valencia, CA), 1.5 µl each of forward and reverse oligos at 10 pmol/µl for a final concentration of 0.3 µM each, and 1 µl KOD Hot Start DNA Polymerase. The reaction was thermocycled 94 °C 2 min, then 30 cycles of [94 °C for 15 sec, 45 °C for 30 sec, and 68 °C for 3 min]. Two initial PCR reactions were performed to introduce the mutation. The primer pair sequences were GGAGGAGCAGTACCAGAGCACGTACCGTGTGGTCAGCGTC (SEQ ID NO: 269) with CTTCCGAGTGAGAGACAC (SEQ ID NO: 270) and CAGCTGGCGTAATAGCGAAG (SEQ ID NO: 271) with TGCTCTGGTACTGCTCCTCCCGCGGCTTTGTCTTGGCATTATG (SEQ ID NO: 272). The PCR products were gel purified using a Qiagen spin column kit (Valencia, CA) and then

added together in an overlap PCR reaction using primers CTTCCGAGTGAGAGACAC (SEQ ID NO: 273) and CAGCTGGCGTAATAGCGAAG (SEQ ID NO: 274). The final PCR product was gel purified and used to replace the original fragment in the pTT5 SNS vector using restriction sites *BsmBI* and *NotI*. Quick Ligase kit from New England Biolabs (Ipswich, MA) and TOP10 chemically competent cells from Invitrogen (Carlsbad, California) were used for cloning and then the DNA constructs were purified and sequence-verified.

Heavy chain CDRs were PCRed and cloned into this vector using *BssHII* and *BsmBI* and primers AAAAAAGGCACTAGAGACGGTGACCAGGGTTCC (SEQ ID NO: 275) and TTTTTTTTGC GCGCTGTCAGGTGCAACTGGTGCAGTC (SEQ ID NO: 276) for 1A2 or primers AAAAAAGGCACTAGAGACGGTGACCAGGGTTCC (SEQ ID NO: 277) and TTTTTTTTGC GCGCTGTCAGGTGCAGTTGGTGGAGTC (SEQ ID NO: 278) for 2G10.

1A2 light chain was cloned into pTT5 Kappa using *BssHII* and *BsiWI* and primers TTTTTTTTGC GCGCTGTGATATTGTGATGACCCAGAC (SEQ ID NO: 279) and AAAAAACGTACGTTTGATTTCACCTGGGTCC (SEQ ID NO: 280).

2G10 light chain was cloned into pTT5 Lambda using *BssHII* and *BsmBI* and primers TTTTTTTTGC GCGCTGTCAGTCTGTGTTGACGCAGCC (SEQ ID NO: 281) and TTTTTTCGTCTCTGACCTAGGACGGTCAGCTTGGTCC (SEQ ID NO: 282).

All oligos (see Table 8) were diluted to 10 μ M in water. 9 μ l UB and LA oligos were used for 5' internal phosphorylation. A mixture (1 μ l) of 90% NEB PNK buffer (Ipswich, MA) and 10% NEB PNK (Ipswich, MA) was added. The mixture was incubated at 37 °C for 10 min and then at 60 °C for 20 min (in a PCR machine). 9 μ l of the complimentary oligo was then added. All oligo pairs were cycled at 95 °C for 20 sec, then decreased 0.1 °C/sec to 50 °C (a 7:30 min ramp). Both pairs of oligos were mixed and "stitched" at 55 °C for 20 sec, using a 5 min ramp to 25 °C (a 0.1 °C/sec decrease). 150 μ l of 5 mM Tris-HCl pH 8.5/0.1 mM EDTA was then added to the linker prep. The linker was ligated into pTT5-1A2 or 2G10 which had been digested with *BsrGI* and *SexAI* and gel purified.

TABLE 8
Oligos Used in Constructing Antigen Binding Proteins

Oligo #	Oligo Name	Sequence	SEQ ID NO
5412-51	R26 UA	GTA CAC CCT GCC CCC ATC CCG GGA TGA GCT GGG TGG TGA GTG GTA CTG CGG CGT	283

Oligo #	Oligo Name	Sequence	SEQ ID NO
5412-52	R26 UB	GCT GTT CAA CTG CCA GCA GGG TGG TAC CAA GAA	284
5412-53	R26 LB	CCT GGT TCT TGG TAC CAC CCT GCT GGC AGT TGA ACA GCA CGC CGC AGT ACC ACT C	285
5412-54	R26 LA	ACC ACC CAG CTC ATC CCG GGA TGG GGG CAG GGT	286
5412-63	R40 UA	GTA CAC CCT GCC CCC ATC CCG GGA TGA GCT GGG TGG TCA CTT CAA GTG CGG CA	287
5412-64	R40 UB	TGG GCC TGT TCG AGT GCG CCG ACC CCG GTG GTA CCA AGA A	288
5412-65	R40 LB	CCT GGT TCT TGG TAC CAC CGG GGT CGG CGC ACT CGA ACA GGC CCA TGC CGC ACT TGA AGT	289
5412-50	R40 LA	GAC CAC CCA GCT CAT CCC GGG ATG GGG GCA GGG T	290
5448-38	SR4 UA	GTA CAC CCT GCC CCC ATC CCG GGA TG AGC TGG GTG GTT GCT ACC A	291
5448-40	SR4 UB	GGC CTG GGG CTA CTA CGT GTG CGG TGG TAC CAA GAA	292
5448-39	SR4 LB	CCT GGT TCT TGG TAC CAC CGC ACA CGT AGT AGC CCC AGG CCT GGT AGC AAC CAC CCA GC	293

Oligo #	Oligo Name	Sequence	SEQ ID NO
4619-60	SR4 LA	TCA TCC CGG GAT GGG GGC AGG GT	294

FGFR1c binder SR4 was also added to the N-terminus of 1A2 or 2G10 as follows: A PCR reaction was done on the heavy chain plasmid using primers AAAAAAGGCACTAGAGACGGTGACCAGGGTTCC (SEQ ID NO: 295) and TCAGGCGTGGGGCTATTATGTGTGCGGAGGCGGAGGAGGCCAGGTGCAACTGGT GCAGTC (SEQ ID NO: 296). One μ l of this reaction was then used as a template for PCR with primers AAAAAAGGCACTAGAGACGGTGACCAGGGTTCC (SEQ ID NO: 297) and

TCAGGCGTGGGGCTATTATGTGTGCGGAGGCGGAGGAGGCCAGGTGCAGTTGGT GGAGTC (SEQ ID NO: 298). This PCR provided a SR4-CDR fragment that was then purified using a Qiagen PCR Clean Up Kit (Valencia, CA) and ligated into pTT5-IgG1 Aglyco BssHII to BsmBI.

SR4 was also added to the C-terminus of 1A2 or 2G10 as follows: A PCR reaction was done on pTT5-IgG1 Aglyco using primers CGGCGTGGAGGTGCATAATG (SEQ ID NO: 299) and AATAGCCCCACGCCTGATAGCAGCCTCCTCCGCCTCCTTTACCCGGAGACAGGGAGAG (SEQ ID NO: 300). One μ l of this reaction was then used as a template for PCR with primers CGGCGTGGAGGTGCATAATG (SEQ ID NO: 301) and GATGTCGAGGCGGCCGCTCAGCCGCCGCACACATAATAGCCCCACGCCTGATAG (SEQ ID NO: 302). This PCR provided an IgG1-SR4 fragment that was then purified using a Qiagen PCR Clean Up Kit (Valencia, CA) and ligated into pTT5-IgG1 Aglyco SacII to NotI. Before ligation, the vector was dephosphorylated in a 30 min reaction using a Roche rAPid AP kit (Mannheim, Germany).

EXAMPLE 8

EXPRESSION OF BISPECIFIC FGF21 MIMETIC ANTIGEN BINDING PROTEINS

The bispecific FGF21 mimetics antigen binding proteins in the pTT5 vector were expressed transiently in serum-free suspension adapted 293-6E cells maintained in FreeStyle medium (Invitrogen Corporation, Carlsbad, CA) supplemented with (25 μ g/ml) geneticin (Invitrogen) and 0.1% Pluronic F68 (Invitrogen). Transfections were performed as 1L cultures. Briefly, the cell inoculum was grown to 1.1×10^6 cells/ml in a 3L fernbach shake

flask (Corning, Inc.). The shake flask culture was maintained on an Innova 2150 shaker platform (News Brunswick Scientific, Edison, NJ) at 65 RPM which was placed in a humidified incubator maintained at 37°C and 5% CO₂. At the time of transfection, the 293-6E cells were diluted to 1.0×10^6 cells/ml. The transfection complexes were formed in 100 ml FreeStyle medium. 1 mg plasmid DNA was first added to the medium followed by 3 ml of FuGene HD transfection reagent (Roche Applied Science, Indianapolis, IN). The transfection complex was incubated at room temperature for approximately 15 minutes and then added to the cells in the shake flask. Twenty-hour hours post transfection, 20% (w/v) of peptone TN1 (OrganoTechnie S.A., TeknieScience, QC, Canada) was added to reach a final concentration of 0.5% (w/v). The transfection/expression was performed for 4-7 days, after which the conditioned medium was harvested by centrifugation at 4,000 RPM for 60 minutes at 4°C.

EXAMPLE 9

PURIFICATION OF ANTIGEN BINDING PROTEINS FROM TRANSIENT CELL CULTURE

The FGF21 mimetic antigen binding proteins were purified from transient cell culture as follows. All purification processes were carried out at room temperature or 4°C. One purification scheme was used to purify various bispecific FGF21 mimetic antibodies and used affinity chromatography.

9.A

Protein A Chromatography

The host cell culture fluid (CCF) was loaded onto Protein G chromatography media in the form of a column, Protein A High Performance (GE Healthcare, formerly Amersham Biosciences), equilibrated in PBS.

After loading, the Protein A column was washed with PBS until the absorbance at 280 nm of the flow-through returned to baseline. The antibodies were then eluted from the column using 10 mM Acetate, pH 3.5 and immediately neutralized by adding 80 µL of a stock solution of 1 M Tris Base per mL of elution volume. The absorbance at 280 nm of the eluate was monitored and fractions containing protein were collected to make the Protein A pool.

9.B

Formulation and Concentration

Following purification, the antibodies were formulated in DPBS (8.1 mM NaHPO₄-H₂O, 138 mM NaCl₂, 1.2 mM KH₂PO₄, 2.7 mM KCL pH 7.4) by dialysis using 10,000 MWCO membranes (Pierce Slide-A-Lyzer). If measuring concentration of the antibodies were necessary, a centrifugal device (Macrocep, Pall) with a 10,000 MWCO membrane was used. Following formulation the antibodies were filtered through a sterile 0.2 µm filter and stored at 4°C or frozen.

EXAMPLE 10

ELISA OF THE BISPECIFIC FGF21 MIMETICS ANTIBODIES

Biotin-hu-β-Klotho-His, biotin-mu-βKlotho-His, hu-FGFR1c-His, and mu-FGFR1c-Fc were expressed and purified. Anti-Fc-HRP was purchased from Thermo Fisher Scientific (Rockford, IL). Neutravidin 96 well plates (Thermo Fisher Scientific; Rockford, IL) were coated with 2 µg/ml biotin-hu-β-Klotho-His or biotin-mu-β-Klotho-His in PBS (Invitrogen; Carlsbad, CA). Maxisorp 96 well plates (Thermo Fisher Scientific; Rockford, IL) were coated with 2µg/ml hu-FGFR1c-His or mu-FGFR1c-Fc in PBS. Plates were then incubated at 4°C overnight. Plates were blocked in 2% milk-PBS at room temperature for 1 hour. Each well was then incubated 1 hour with samples diluted in 2% milk-PBS. Plates were washed 3 times with 300 µl PBS/0.1% Tween20 (Invitrogen; Carlsbad, CA and Sigma-Aldrich; St. Louis, MO). Anti-hu-Fc-HRP was diluted 1:10000 in 2% milk-PBS and added to each well. Plates were again washed 3 times with 300 µl PBS/0.1% Tween20. Lumiglo reagent (KPL; Gaithersburg, MD) was added and luminescence was measured (Perkin Elmer; Waltham, MA).

EXAMPLE 11

LUCIFERASE ASSAYS OF THE BISPECIFIC FGF21 MIMETICS ANTIBODIES

AM1D cells expressing FGFR1c, Elk and Luciferase with or without βKlotho were constructed. FGF21 was expressed and purified. AM1D cells expressing FGFR1c, βKlotho, Elk, and Luciferase were maintained in DMEM media (Invitrogen; Carlsbad, CA) supplemented with 10% dialyzed fetal bovine serum (Invitrogen; Carlsbad, CA), 200 µg/ml Hygromycin B (Invitrogen; Carlsbad, CA), 4 µg/ml Puromycin (Invitrogen; Carlsbad, CA), Penicillin-Streptomycin-Glutamine (Invitrogen; Carlsbad, CA), Sodium Pyruvate (Invitrogen;

Carlsbad, CA), and MEM non-essential amino acids (Invitrogen; Carlsbad, CA). AMID cells expressing FGFR1c, Elk, and Luciferase were maintained in DMEM media supplemented with 10% dialyzed fetal bovine serum, 400 µg/ml Hygromycin B, 6 µg/ml Puromycin, HT Supplement (Invitrogen; Carlsbad, CA), Penicillin-Streptomycin-Glutamine, Sodium Pyruvate, and MEM non-essential amino acids.

Cells were plated at a density of 3×10^4 cells/well in a 96 half well plate (Corning; Lowell, MA) in F-12 media (Invitrogen; Carlsbad, CA) containing 0.1% BSA (Sigma-Aldrich; St. Louis, MO) for a total volume of 30 µl/well. The cells were then incubated at 37°C for 20-22 hours. Samples were diluted in PBS (Invitrogen; Carlsbad, CA) and 15 µl was added to each well. Cells were then incubated at 37°C for 15 minutes. Human FGF21 was diluted in F-12 media and 5 µl was added to the cells for a final concentration of 3nM. Cells were then incubated at 37°C for 5-7 hours. Luciferase reagent (Perkin Elmer; Waltham, MA) was added and luminescence was measured (Perkin Elmer; Waltham, MA).

EXAMPLE 12

KINETIC STUDY OF THE ANTI-β-KLOTHO ANTIBODIES

Biotinylated hu-β-klotho was prepared. Affinity measurement of purified anti-β-klotho antibodies was performed using Octet QK (fortéBIO Inc., Menlo Park, CA) following the vendor's protocol. Streptavidin High Binding FA Biosensors were incubated for 1 h with biotinylated hu-β-klotho at 100 nM in Kinetic buffer (fortéBIO Inc., Menlo Park, CA) for antigen coating and in Kinetic buffer for 1 min for establishing the baseline. The biosensors were incubated with a control IgG at 2 µg/ml in Kinetic buffer for 15 min to measure association, and then in Kinetic buffer for 15 min to measure dissociation. Affinity data was derived using the built-in analysis software.

EXAMPLE 13

EPITOPE BINNING OF ANTI-β-KLOTHO ANTIBODIES

While off-line, columns of Streptavidin High Binding FA Biosensors can be incubated in biotinylated hu-β-klotho at 100 nM in Kinetic buffer (fortéBIO Inc., Menlo Park, CA), for 1 hour for antigen coating, then in Kinetic buffer for 2 min, followed by incubation with the anti-β-klotho antibodies, different for each column, at 11 µg/ml in Kinetic buffer for 2.5 hours. The antibodies for the first load can be Ab1 in column 1, Ab2 in column 2, etc. In the beginning, sensors in each column can be preloaded with a specific first-loaded IgG, and incubated with different test IgGs in different wells at 11 µg/ml for 30

minutes. The order for 2nd-load IgGs are Ab1 in well A, Ab2 in well B, etc. Binding signals of 2nd IgGs can be recorded as the read out.

EXAMPLE 14

ARGININE SCANNING

As described herein, FGF21 mimetic antigen binding proteins and antigen binding protein-FGF21 fusions that bind human β -Klotho or both β -Klotho and one of FGFR1c, FGFR2c, FGFR3c, or FGFR4, *i.e.*, FGFR1c, were created and characterized. To determine the neutralizing determinants on human FGFR1c and/or β -Klotho that these various antigen binding proteins and antigen binding protein-FGF21 fusions bind, a number of mutant FGFR1c and/or β -Klotho proteins can be constructed having arginine substitutions at select amino acid residues of human FGFR1c and/or β -Klotho. Arginine scanning is an art-recognized method of evaluating where antibodies, or other proteins, bind to another protein, see, *e.g.*, Nanevich *et al.*, (1995) *J. Biol. Chem.* 270:37, 21619-21625 and Zupnick *et al.*, (2006) *J. Biol. Chem.* 281:29, 20464-20473. In general, the arginine sidechain is positively charged and relatively bulky as compared to other amino acids, which can disrupt antibody binding to a region of the antigen where the mutation is introduced. Arginine scanning is a method that determines if a residue is part of a neutralizing determinant and/or an epitope.

Various amino acids distributed throughout the human FGFR1c and/or β -Klotho extracellular domains can be selected for mutation to arginine. The selection can be biased towards charged or polar amino acids to maximize the possibility of the residue being on the surface and reduce the likelihood of the mutation resulting in misfolded protein. Using standard techniques known in the art, sense and anti-sense oligonucleotides containing the mutated residues can be designed based on criteria provided by Stratagene Quickchange[®] II protocol kit (Stratagene/Agilent, Santa Clara, CA). Mutagenesis of the wild-type (WT) FGFR1c and/or β -Klotho sequences can be performed using a Quickchange[®] II kit (Stratagene). Chimeric constructs can be engineered to encode a FLAG-histidine tag (six histidines (SEQ ID NO: 268)) on the carboxy terminus of the extracellular domain to facilitate purification via the poly-His tag.

Multiplex analysis using the Bio-Plex Workstation and software (BioRad, Hercules, CA) can be performed to determine neutralizing determinants on human FGFR1c and/or β -Klotho by analyzing exemplary human FGFR1c and/or β -Klotho mAbs differential binding to arginine mutants versus wild-type FGFR1c and/or β -Klotho proteins. Any number of bead

codes of pentaHis-coated beads ("penta-His" disclosed as SEQ ID NO: 303) (Qiagen, Valencia, CA) can be used to capture histidine-tagged protein. The bead codes can allow the multiplexing of FGFR1c and/or β -Klotho arginine mutants and wild-type human FGFR1c and/or β -Klotho.

To prepare the beads, 100 μ l of wild-type FGFR1c and/or β -Klotho and FGFR1c and/or β -Klotho arginine mutant supernatants from transient expression culture are bound to penta-His-coated beads ("penta-His" disclosed as SEQ ID NO: 303) overnight at 4°C or 2 hours at room temperature with vigorous shaking. The beads are then washed as per the manufacturer's protocol and the bead set pooled and aliquoted into 2 or 3 columns of a 96-well filter plate (Millipore, Bellerica, MA, product #MSBVN1250) for duplicate or triplicate assay points, respectively. 100 μ l anti-FGFR1c and/or anti- β -Klotho antigen binding protein in 4-fold dilutions are added to the wells, incubated for 1 hour at room temperature, and washed. 100 μ l of a 1:100 dilution of PE-conjugated anti-human IgG Fc (Jackson Labs., Bar Harbor, ME, product #109-116-170) is added to each well, incubated for 1 hour at room temperature and washed. Beads are resuspended in 1% BSA, shaken for 3 minutes, and read on the Bio-Plex workstation. Antibody binding to FGFR1c and/or β -Klotho arginine mutant protein is compared to antibody binding to the human FGFR1c and/or β -Klotho wild-type from the same pool. A titration of antibody over approximately a 5 log scale can be performed. Median Fluorescence Intensity (MFI) of FGFR1c and/or β -Klotho arginine mutant proteins can be graphed as a percent of maximum wild-type human FGFR1c and/or β -Klotho signal. Those mutants for which signal from all the antigen binding proteins are below a cut-off value, *e.g.*, 30% of wild-type FGFR1c and/or β -Klotho can be deemed to be either of too low a protein concentration on the bead due to poor expression in the transient culture or possibly misfolded and can be excluded from analysis. Mutations (*i.e.*, arginine substitutions) that increase the EC50 for the FGFR1c and/or β -Klotho antigen binding protein by a cut-off value, *e.g.*, 3-fold or greater (as calculated by, *e.g.*, GraphPad Prism[®]) can be considered to have negatively affected FGFR1c and/or β -Klotho antigen binding protein binding. Through these methods, neutralizing determinants and epitopes for various FGFR1c and/or β -Klotho antigen binding proteins can be elucidated.

EXAMPLE 15

CONSTRUCTION OF CHIMERIC RECEPTORS

In another method of determining the activation determinants on human FGFR1c and/or β -Klotho that these various antigen binding proteins and antigen binding protein-FGF21 fusions bind, specific chimeric FGFR1c and/or β -Klotho proteins comprising sequences from human and mouse proteins can be constructed, expressed in transient or stable 293 or CHO cells as described before and tested. For example, a chimeric FGF21 receptor can be constructed comprising native human FGFR1c, FGFR2C, FGFR3c or FGFR4, in one example FGFR1c, paired with chimeric human or mouse β -Klotho in which selected regions or sequences on the human β -Klotho are systematically replaced by the corresponding mouse-specific residues (see, *e.g.*, Figure 2). Similarly, native human β -Klotho paired is with chimeric human/mouse FGFR1c, FGFR2c, FGFR3c or FGFR4, in one example FGFR1c, in which selected regions or sequences on the human FGFR1c are systematically replaced by the corresponding mouse-specific residues. The critical sequences involved in the binding and/or activity of the antigen binding proteins can be derived through binding assay or activity measurements described herein or known in the art, based on the chimeric FGF21 receptors.

EXAMPLE 16

PROTEASE PROTECTION ANALYSIS

Regions of the human FGF21 receptor bound by the antigen binding proteins and antigen binding protein-FGF21 fusions that bind human FGF21 receptor, *e.g.*, FGFR1c, β -Klotho or a complex comprising FGFR1c and β -Klotho can be identified by fragmenting human FGF21 receptor into peptides with specific proteases, *e.g.*, AspN, Lys-C, chymotrypsin or trypsin. The sequence of the resulting human FGF21 receptor peptides (*i.e.*, both disulfide- and non-disulfide-containing peptide fragments from FGFR1c and β -Klotho portions) can then be determined. In one example, soluble forms of a human FGF21 receptor complex, *e.g.*, a complex comprising the FGFR1c ECD-Fc and β -Klotho ECD-Fc heterodimer described herein, can be digested with AspN (which cleaves after aspartic acid and some glutamic acid residues at the amino end) by incubating about 100 μ g of soluble FGF21 receptor at 1.0 mg/ml in 0.1M sodium phosphate (pH 6.5) for 20 hrs at 37°C with 2 μ g of AspN.

A peptide profile of the AspN digests can then be generated on HPLC chromatography while a control digestion with a similar amount of antibody is expected to be essentially resistant to AspN endoproteinase. A protease protection assay can then be performed to determine the proteolytic digestion of human FGF21 receptor in the presence of the antigen binding proteins. The general principle of this assay is that binding of an antigen binding protein or antigen binding protein-FGF21 fusion to the FGF21 receptor can result in protection of certain specific protease cleavage sites and this information can be used to determine the region or portion of FGF21 receptor where the antigen binding protein or antigen binding protein-FGF21 fusion binds.

Briefly, the peptide digests can be subjected to HPLC peptide mapping; the individual peaks are collected, and the peptides are identified and mapped by on-line electrospray ionization LC-MS (ESI-LC-MS) analyses and/or by N-terminal sequencing. HPLC analyses for these studies can be performed using a narrow bore reverse-phase C18 column (Agilent Technologies) for off-line analysis and using a capillary reverse phase C18 column (The Separation Group) for LC-MS. HPLC peptide mapping can be performed with a linear gradient from 0.05% trifluoroacetic acid (mobile phase A) to 90% acetonitrile in 0.05% trifluoroacetic acid. Columns can be developed at desirable flow rate for narrow bore HPLC for off-line or on-line LC-MS analyses, and for capillary HPLC for on-line LC-MS analyses.

Sequence analyses can be conducted by on-line LC-MS/MS and by Edman sequencing on the peptide peaks recovered from HPLC. On-line ESI LC-MS analyses of the peptide digest can be performed to determine the precise mass and sequence of the peptides that are separated by HPLC. The identities of selected peptides present in the peptide peaks from the protease digestion can thus be determined.

EXAMPLE 17

ANTIGEN BINDING PROTEIN-FGF21 FUSIONS

The C-terminus of FGF21 has been reported to be the critical motif for β -Klotho binding specificity (Wu, et al., *J. Biol. Chem.* 283, 33304–33309 (2008)). A cluster of highly protease-susceptible cleavage sites have been identified near the C-terminus of FGF21 based on *in vivo* testing, specifically between Pro171 and Ser 172. Cleavage at this cluster of residues diminishes the binding to β -Klotho and inactivated FGF21 *in vivo*. The series of antigen binding protein-FGF21 fusions disclosed herein were designed to replace the native β -Klotho binding motif in FGF21 with a high affinity antigen binding protein.

A series of ten antigen binding protein-FGF21 fusions were generated comprising (a) an antigen binding protein component that specifically binds β -Klotho or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4; and (b) an FGF21 component comprising FGF21 or a fragment thereof. The ten antigen binding protein-FGF21 fusions were engineered with the goal that the antigen binding protein component would specifically bind human β -Klotho and the FGF21 component would associate with FGFR1c, ultimately forming a complex that can initiate FGF21-induced signaling. Thus, the fusions were designed as FGF21 mimetics.

The fusions were tested in *in vitro* activity assays as described below.

17.A.

Construction

Ten specific antigen binding protein fusions were generated. These fusions each comprised the anti- β -Klotho antibody 2G10 (as described in Tables 1-3 and 6) fused to residues 1-169 (SEQ ID NO: 342) or 1-170 of mature FGF21 (SEQ ID NO: 343) in various orientations via a linker (i.e., (G₄S)₁₅ (SEQ ID NO: 340), (G₄S)₁₂ (SEQ ID NO: 339), (G₄S)₉ (SEQ ID NO: 338), (G₄S)₆ (SEQ ID NO: 337), and (G₄S)₃ (SEQ ID NO: 336)), and are shown below.

The antigen binding protein fusions generated, which are presented from N- to C-terminus, included:

- (a) FGF21(1-169)-(G₄S)₃-2G10 (SEQ ID NOs:315 (coding sequence) and 316 (amino acid sequence));
- (b) FGF21(1-169)-(G₄S)₆-2G10 (SEQ ID NOs:319 (coding sequence) and 320 (amino acid sequence));
- (c) FGF21(1-169)-(G₄S)₉-2G10 (SEQ ID NOs:321 (coding sequence) and 322 (amino acid sequence));
- (d) FGF21(1-169)-(G₄S)₁₂-2G10 (SEQ ID NOs:323 (coding sequence) and 324 (amino acid sequence));
- (e) FGF21(1-169)-(G₄S)₁₅-2G10 (SEQ ID NOs:325 (coding sequence) and 326 (amino acid sequence));
- (f) 2G10-(G₄S)₃-FGF21(1-170) (SEQ ID NOs:317 (coding sequence) and 318 (amino acid sequence));

- (g) 2G10-(G₄S)₆-FGF21(1-170) (SEQ ID NOs:327 (coding sequence) and 328 (amino acid sequence));
- (h) 2G10-(G₄S)₉- FGF21(1-170) (SEQ ID NOs:329 (coding sequence) and 330 (amino acid sequence));
- (i) 2G10-(G₄S)₁₂-FGF21(1-170) (SEQ ID NOs:331 (coding sequence) and 332 (amino acid sequence)); and
- (j) 2G10-(G₄S)₁₅-FGF21(1-170) (SEQ ID NOs:333 (coding sequence) and 334 (amino acid sequence)).

The antigen binding protein fusions were constructed as follows:

Construction of FGF21(1-169)-(G₄S)₃-2G10 Coding Sequence (SEQ ID NOs:316)

A nucleic acid sequence encoding amino acids 1-197 of full-length wild type human FGF21 (SEQ ID NO:2), *i.e.*, the signal sequence and residues 1-169 of the mature form of FGF21 (SEQ ID NO:342)), was amplified with two primers, attaching a Sall restriction site as well as a Kozak sequence on the 5' end and two copies of a (G₄S)₃ linker (SEQ ID NO: 336) plus a BamHI restriction site on the 3' end.

The anti- β -Klotho antibody 2G10 mature form (*i.e.*, minus signal peptide) was amplified using two primers. The first primer attached a BamHI site as well as one copy of a (G₄S)₃ linker (SEQ ID NO: 336) on the 5' end and the second primer added a NotI restriction site after the stop codon.

The FGF21-containing PCR fragment was digested with Sall and BamHI restriction enzymes, likewise the anti- β -Klotho antibody 2G10 PCR fragment was digested with BamHI and NotI restriction enzymes. Both fragments, as well as a pTT5 expression plasmid fragment digested with Sall and NotI, were gel purified and the resulting fragments ligated to obtain pTT5 - Human FGF21 (1-197 (*i.e.*, residues 1-169 plus the 28 residue signal sequence)) – (G₄S)₃ - anti- β -Klotho antibody 2G10.

Construction of FGF21(1-169)-(G₄S)₆-2G10 (SEQ ID NO:320), FGF21(1-169)-(G₄S)₉-2G10 (SEQ ID NO:322), FGF21(1-169)-(G₄S)₁₂-2G10 (SEQ ID NO:324), FGF21(1-169)-(G₄S)₁₅-2G10 (SEQ ID NO:326) Coding Sequences

Using the transient expression clone pTT5 – Human FGF21 (1-197) – (G₄S)₃ - anti- β -Klotho antibody 2G10, all subsequent clones were made with larger linkers. Taking

advantage of the unique BamHI restriction site within the (G₄S)₃ linker (SEQ ID NO: 336) as well as the overall clone, two phosphorylated and annealed oligomers coding for an additional (G₄S)₃ linker (SEQ ID NO: 336) were inserted. These annealed oligomers contained BamHI compatible ends that allowed ligation into a BamHI linearized fragment of pTT5 - Human FGF21 (1-197) – (G₄S)₃ - anti-β-Klotho antibody 2G10 clone. In this process, only one BamHI restriction site at one end of the annealed ligomers was regenerated, yielding pTT5 - Human FGF21 (1-197) – (G₄S)₆ - anti-β-Klotho antibody 2G10. Similarly, the pTT5 - Human FGF21 – (G₄S)₆ - anti-β-Klotho antibody 2G10 clone was used to produce the (G₄S)₉ version. Ultimately, the (G₄S)₁₅ clone was produced from a (G₄S)₁₂ clone.

Construction of 2G10-(G₄S)₃ -FGF21(1-170) (SEQ ID NO:318) Coding Sequence

A nucleic acid sequence encoding the full length anti-β-Klotho antibody 2G10 mature form (plus signal peptide) but lacking the terminal lysine was amplified using two primers. The first primer attached a SalI restriction site as well as a Kozak sequence on the 5' end and two copies of a (G₄S)₃ linker (SEQ ID NO: 336) plus a BamHI restriction site on the 3' end.

A nucleic acid sequence encoding amino acids 1-170 of the mature form of FGF21 (SEQ ID NO:343) was amplified with two primers. The first primer attached a BamHI site as well as one copy of a (G₄S)₃ linker (SEQ ID NO: 336) on the 5' end and the second primer added a NotI restriction site after the stop codon.

The anti-β-Klotho antibody 2G10 containing PCR fragment was digested with SalI and BamHI restriction enzymes, likewise the FGF21 PCR fragment was digested with BamHI and NotI restriction enzymes. Both fragments as well as a pTT5 expression plasmid fragment digested with SalI and NotI were gel purified and the resulting fragments ligated to obtain pTT5 - anti-β-Klotho antibody 2G10 – (G₄S)₃ - human FGF21 (1-170).

Construction of 2G10-(G₄S)₆ -FGF21(1-170) (SEQ ID NO:328), 2G10-(G₄S)₉ - FGF21(1-170) (SEQ ID NO:330), 2G10-(G₄S)₁₂ -FGF21 (1-170) (SEQ ID NO:332), 2G10-(G₄S)₁₅ - FGF21 (1-170) (SEQ ID NO:334) Coding Sequences

Using the transient expression clone pTT5 - anti-β-Klotho antibody 2G10 – (G₄S)₃ - human FGF21 (1-170), all subsequent clones were made with larger linkers. Taking advantage of the unique BamHI restriction site within the (G₄S)₃ linker (SEQ ID NO: 336) as well as the overall clone, two phosphorylated and annealed oligomers coding for an

additional (G₄S)₃ linker (SEQ ID NO: 336) were inserted. These annealed oligomers contained BamHI compatible ends that allowed ligation into a BamHI linearized fragment of pTT5 - anti-β-Klotho antibody 2G10 – (G₄S)₃ - human FGF21 (1-170). In this process, only one BamHI restriction site at one end of the annealed ligomers was regenerated, yielding pTT5 - anti-β-Klotho antibody 2G10 – (G₄S)₆ - human FGF21 (1-170). Similarly, the pTT5 - anti-β-Klotho antibody 2G10 – (G₄S)₆ - human FGF21 (1-170) clone was used to produce the (G₄S)₉ version. Ultimately, the (G₄S)₁₅ clone was produced from a (G₄S)₁₂ clone.

17.B.

Expression and Purification

cDNA encoding each of the fusions proteins was generated and inserted into a pTT5 expression vector, with desK 2G10 heavy chain used in the C-terminal fusions.

The constructs were expressed in transiently transfected 293 cells. The human embryonic kidney 293 cell line stably expressing Epstein Barr virus Nuclear Antigen-1 (293-6E cells) was obtained from the National Research Council (Montreal, Canada). Cells were maintained as serum-free suspension cultures using F17 medium (Invitrogen, Carlsbad, CA) supplemented with 6mM L-glutamine (Invitrogen, Carlsbad, CA), 1.1% F-68 Pluronic (Invitrogen, Carlsbad, CA) and 50 ug/ul Geneticin (Invitrogen, Carlsbad, CA). The suspension cell cultures were maintained in Erlenmeyer shake flask cultures. The culture flasks were shaken at 65 rpm at 37°C in a humidified, 5% CO₂ atmosphere. Cells were routinely passaged by dilution to 3.0e5 viable cells/ml on Mondays and Wednesdays and to 1.5e5 viable cells/ml on Fridays for a period of three months before being replaced with a freshly thawed vial of cells.

Stock solutions (1mg/ml) of 25-kDa linear PEI_{max} (Polysciences, Warrington, PA) were prepared in water, acidified with HCl to pH 2.0 until dissolved, then neutralized with NaOH, sterilized by filtration (0.2 μm), aliquoted, and stored at -20°C until used. Tryptone N1 was obtained from OrganoTechni S.A. (TekniScience, QC, Canada). Stock solutions (20%, w/v) were prepared in Freestyle medium (Invitrogen, Carlsbad, CA), sterilized by filtration through 0.2 μm filters, and stored at 4°C until use.

For transfection, cells were diluted to 1.1e6 cells/ml. The transfection mixture of DNA and PEI_{max} was prepared in fresh medium at 10% of the culture volume. The transfection mixtures consisted of 500ug of DNA per ml of culture followed by 3ug of

PEI max per μg of DNA and were incubated for 10 minutes before being added to the cell culture. Cultures were typically harvested 6-7 days post-transfection.

The conditioned media was harvested and the fusions were purified using Protein A chromatography (MabSelect Sure, Millipore) at pH 3.5. The elution pools were titrated to around pH 7.0 and the buffer was then exchanged into PBS.

17.C.

Binding Assays

The fusions were assayed for binding to both human and mouse β -Klotho using an ELISA format. As shown in Figure 16, all of the fusions were observed to bind to human β -Klotho, and Figure 17 demonstrates that all of the fusions were observed to bind to murine β -Klotho. The observed binding was independent of the relative orientation of the FGF21 component with respect to the 2G10 antibody component.

17.D.

In vitro Activity Assays

The fusions were then tested in a luciferase assay using AM1D reporter cells expressing β -Klotho and FGFR1c. Figure 18 demonstrates that all of the fusions are active in the reporter assay. Additionally Figure 18 demonstrates that while the observed activity is independent of linker length, the relative orientation of the FGF21 component with respect to the 2G10 antibody component of the fusion is significant. More particularly, it was observed that fusions in which the antibody component of the fusion is located at the N-terminus of the fusion showed a higher level of activity than those fusions in which the antibody component is located at the C-terminus of the overall fusion.

The fusions were then tested in a luciferase assay using AM1D reporter cells expressing β -Klotho and FGFR1c. When the fusion proteins were incubated with 3nM FGF21 none of the fusions demonstrated any detectable antagonistic activity, as shown in Figure 19. Additionally, Figure 20 demonstrates that the fusions did not interact with human α -Klotho, confirming the specificity of the fusions for β -Klotho. Moreover, no activity was detected in the luciferase assay using AM1D reporter cells expressing β -Klotho and FGFR1c in the absence of β -Klotho.

17.E.

Conclusions

Summarily, the results of the experiments presented in this Example 17 indicate that the antigen binding protein-FGF21 fusions that were generated (a) specifically bind human β -Klotho and induce FGF21-mediated activity; and (b) do not induce FGF21-mediated activity in the absence of human β -Klotho.

The disclosed fusion proteins combine the benefits of natural FGF21 activity while deleting a proteolysis-sensitive region of the C-terminus, which otherwise leads to inactivation of FGF21 through degradation. The β -Klotho binding antibody provided target specific binding with a higher affinity than FGF21 alone. In particular, the binding affinity of FGF21 to β -Klotho is in the range of 10 – 20nM whereas the binding affinity for β -Klotho specific antibodies is typically in the sub-nanomolar or picomolar range. This highly enhanced affinity is expected to improve the *in vivo* targeting efficiency. Furthermore, in contrast to the fast clearance of exogenously administered FGF21 observed *in vivo* ($t_{1/2} < 30\text{min}$), these antibody-based fusion proteins are expected to exhibit an extended half-life of days or weeks, reminiscent of a typical antibody *in vivo*. These beneficial attributes combine make the disclosed fusion proteins uniquely suited for a therapeutic role.

Each reference cited herein is incorporated by reference in its entirety for all that it teaches and for all purposes.

The present disclosure is not to be limited in scope by the specific embodiments described herein, which are intended as illustrations of individual aspects of the disclosure, and functionally equivalent methods and components form aspects of the disclosure. Indeed, various modifications of the disclosure, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

1. An isolated antigen binding protein comprising one or more of:
 - (a) a light chain CDR3 comprising one or more of:
 - (i) a light chain CDR3 sequence that differs by no more than two amino acid additions, substitutions, deletions and combinations thereof from a CDR3 sequence of L1-L11, SEQ ID NOs:17-27;
 - (ii) MQAX₁EFPWT (SEQ ID NO: 174);
 - (iii) GTWDSSLX₂VX₃ (SEQ ID NO: 175);
 - (iv) QQYDNLFT (SEQ ID NO: 122);
 - (v) QQYGSAPLT (SEQ ID NO: 123);
 - (vi) VLYMGSGIWV (SEQ ID NO: 124);
 - (vii) ETWDSSLSAGV (SEQ ID NO: 127);

wherein

X₁ is L or I;
 X₂ is V or A; and
 X₃ is V or A;

- (b) a heavy chain CDR3 comprising one or more of:
 - (i) a heavy chain CDR3 sequence that differs by no more than one amino acid additions, substitutions, deletions, and or combinations thereof from a CDR3 sequence of H1-H11, SEQ ID NOs:28-38;
 - (ii) GWFDX₆ (SEQ ID NO: 178);
 - (iii) GTSFDY (SEQ ID NO: 99);
 - (iv) YGGSFDY (SEQ ID NO: 100);
 - (v) MVYVLDY (SEQ ID NO: 101);
 - (vi) VAGPFDF (SEQ ID NO: 102);

wherein

X₆ is Y, I or F; and

- (c) the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b); and wherein the antigen binding protein specifically binds β -Klotho.

2. The antigen binding protein of claim 1, wherein the antigen binding protein further comprises one or more of:

- (a) a light chain CDR1 comprising one or more of:
 - (i) a light chain CDR1 sequence that differs by no more than two amino acid additions, substitutions, deletions, and combinations thereof, from a CDR1 sequence of L1-L11, SEQ ID NOs:17-27;
 - (ii) RSSQSLVX₂₂ YX₂₃DGNTYLS (SEQ ID NO: 177);
 - (iii) SGSSSNIGNNYVS (SEQ ID NO: 107);
 - (iv) QASQDINNYLN (SEQ ID NO: 108);
 - (v) RASQSVSGNYLA (SEQ ID NO: 109);
 - (vi) GVSSGSVSTRYYPS (SEQ ID NO: 110);

wherein

X₂₂ is H or absent; and

X₂₃ is S or absent;

- (b) a light chain CDR2 comprising one or more of:
 - (i) a light chain CDR2 sequence that differs by no more than two amino acid additions, substitutions, deletions, and combinations thereof, from a CDR2 sequence of L1-L11, SEQ ID NOs:17-27;
 - (ii) KISNRFS (SEQ ID NO: 112);
 - (iii) DNNX₄RPX₅ (SEQ ID NO: 176);
 - (iv) DTSNLET (SEQ ID NO: 114);
 - (v) GASSRAT (SEQ ID NO: 115);
 - (vi) STNTRSS (SEQ ID NO: 116);

wherein

X₄ is K, N or R; and

X₅ is S or absent; and

- (c) a heavy chain CDR1 comprising one or more of:
 - (i) a heavy chain CDR1 sequence that differs by no more than three amino acid additions, substitutions, deletions, and combinations thereof, from a CDR1 sequence of H1-H11, SEQ ID NOs:28-38;
 - (ii) X₁₉YX₂₀MX₂₁

wherein

X_{19} is A, G, R, S, T, or I;

X_{20} is Y, G or A; and

X_{21} is H or S;

- (d) a heavy chain CDR2 comprising one or more of:
 - (i) a heavy chain CDR2 sequence that differs by no more than five amino acid additions, substitutions, and /or deletions from a CDR2 sequence of H1-H11, SEQ ID NOs:28-38;
 - (ii) WINPX₇SGGTNSAQKFQG (SEQ ID NO: 179);
 - (iii) VIX₈X₉DGX₁₀X₁₁X₁₂YYADSVKG (SEQ ID NO: 180);
 - (iv) X₁₃ISGX₁₄GX₁₅X₁₆TYADSVKG (SEQ ID NO: 181);
 - (v) VIX₁₇YDGRNKYX₁₈ADSVKG (SEQ ID NO: 182);

wherein

X_7 is N or Y;

X_8 is W or G;

X_9 is F or Y;

X_{10} is R or S

X_{11} is N or Y;

X_{12} is Q or K;

X_{13} is A or D;

X_{14} is S or R;

X_{15} is V or G;

X_{16} is S or Y;

X_{17} is W or S; and

X_{18} is Y or H;

- (e) the light chain CDR1 of (a) and the light chain CDR2 of (b);
- (f) the light chain CDR1 of (a) and the heavy chain CDR1 of (c);
- (g) the light chain CDR1 of (a) and the heavy chain CDR2 of (d);
- (h) the light chain CDR1 (b) and the heavy chain CDR1 of (c);
- (i) the heavy chain CDR1 of (c) and the heavy chain CDR2 of (d);
- (j) the light chain CDR2 of (b) and the heavy chain CDR2 of (d);

- (k) the light chain CDR1 of (a), the light chain CDR2 of (b), and the heavy chain CDR1 of (c);
- (l) the light chain CDR2 of (b), the heavy CDR1 of (c), and the heavy chain CDR2 of (d);
- (m) the light chain CDR1 of (a), the heavy chain CDR1 of (c), and the heavy chain CDR2 of (d); and
- (n) the light chain CDR1 of (a), the light chain CDR2 of (b), the heavy chain CDR2 of (c), and the heavy chain CDR2 of (d),

wherein said antigen binding protein specifically binds β -Klotho.

3. The antigen binding protein of claim 1, wherein the antigen binding protein comprises one or more of:

- (a) a light chain variable domain comprising:
 - (i) a light chain CDR1 comprising one or more of SEQ ID NOs:106-111;
 - (ii) a light chain CDR2 comprising one or more of SEQ ID NOs:112-119;
 - (iii) a light chain CDR3 comprising one or more of SEQ ID NOs:120-127;
 and
- (b) a heavy chain variable domain comprising:
 - (i) a heavy chain CDR1 comprising one or more of SEQ ID NOs: 83-88;
 - (ii) a heavy chain CDR2 comprising one or more of SEQ ID NOs: 89-97;
 and
 - (iii) a heavy chain CDR3 comprising one or more of SEQ ID NOs:98-105;
 or
- (c) the light chain variable domain of (a) and the heavy chain variable domain of (b),

wherein the antigen binding protein specifically binds β -Klotho.

4. The antigen binding protein of claim 1, wherein the antigen binding protein comprises one or more of:

- (a) a light chain variable domain comprising one or more of:
 - (i) amino acids having a sequence at least 80% identical to a light chain variable domain sequence comprising one or more of L1-L11, SEQ ID NOs:17-27;

- (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L11, SEQ ID NOs:17-27;
- (b) a heavy chain variable domain comprising one or more of:
 - (i) a sequence of amino acids that is at least 80% identical to a heavy chain variable domain sequence of H1-H11 of SEQ ID NOs:28-38;
 - (ii) a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H11, SEQ ID NOs: 28-38; and
- (c) the light chain variable domain of (a) and the heavy chain variable domain of (b);

wherein the antigen binding protein specifically binds β -Klotho.

5. The isolated antigen binding protein of claim 4, wherein the antigen binding protein comprises one or more of:

- (a) a light chain variable domain sequence comprising one or more of L1-L11 of SEQ ID NOs:17-27;
- (b) a heavy chain variable domain sequence comprising one or more of H1-H11 of SEQ ID NOs: 28-38; and
- (c) the light chain variable domain of (a) and the heavy chain variable domain of (b),

wherein the antigen binding protein specifically binds to β -Klotho.

6. The antigen binding protein of claim 5, wherein the light chain variable domain and a heavy chain variable domain are selected from the group of combinations consisting of: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10 and L11H11, wherein the antigen binding protein specifically binds to β -Klotho.

7. The antigen binding protein of claim 6, wherein the antigen binding protein comprises:

- (a) the light chain constant sequence of SEQ ID NO: 13;
- (b) the light chain constant sequence of SEQ ID NO:15;
- (c) the heavy chain constant sequence of SEQ ID NO: 9; and

- (d) the light chain constant sequence of SEQ ID NO: 13 or SEQ ID NO: 15 and the heavy chain constant sequence of SEQ ID NO: 9.

8. The antigen binding protein of claim 1, wherein the antigen binding protein comprises a human antibody, a humanized antibody, chimeric antibody, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an F(fa')x fragment, a domain antibody, an IgD antibody, an IgE antibody, an IgM antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, an IgG4 antibody, or an IgG4 antibody having at least one mutation in the hinge region.

- 9. The antigen binding protein of claim 1, that, when bound to β -Klotho:
 - (a) binds to β -Klotho with substantially the same K_d as a reference antibody;
 - (b) induces FGF21-like signaling of 10 % or greater than the signaling induced by a wild-type FGF21 standard comprising the mature form of SEQ ID NO:2 as measured in an ELK-luciferase reporter assay;
 - (c) exhibits an EC50 of 10nM or less of FGF21-like signaling in an assay selected from the group consisting of:
 - (i) a FGFR1c/ β Klotho-mediated *in vitro* recombinant cell-based assay;
 - (d) exhibits an EC50 of less than 10nM of agonistic activity on FGFR1c in the presence of β -Klotho in an *in vitro* recombinant FGFR1c receptor mediated reporter assay; and
 - (e) an EC50 of greater than 1 μ M of agonistic activity on FGFR1c in the absence of β -Klotho in an *in vitro* recombinant FGFR1c receptor mediated reporter assay; and
 - (f) competes for binding with a reference antibody to β -Klotho,

wherein the reference antibody comprises one or more of the following combinations of light chain and heavy chain variable domain sequences: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10 and L11H11.

- 10. The antigen binding protein of claim 9, that, when bound to β -Klotho:
 - (a) lowers blood glucose in an animal model;
 - (b) lowers serum lipid levels in an animal model; or

(c) (a) and (b).

11. A pharmaceutical composition comprising the antigen binding protein of claim 1 or 9 in admixture with a pharmaceutically acceptable carrier thereof.

12. An isolated nucleic acid comprising a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of the antigen binding protein of claim 4.

13. The isolated nucleic acid of claim 12, wherein the sequence is selected from L1-L11, SEQ ID NOs:17-27; H1-H11, SEQ ID NOs: 28-38, or both.

14. An expression vector comprising the nucleic acid of claim 13.

15. An isolated cell comprising the nucleic acid of claim 13.

16. The isolated cell of claim 15, comprising an expression vector comprising the nucleic acid.

17. A method of producing an antigen binding protein that specifically binds to β -Klotho comprising incubating the host cell of claim 16 under conditions that allow it to express the antigen binding protein.

18. A polypeptide comprising one or more of: TRLWKYWV (SEQ ID NO: 184); RRLYIFWE (SEQ ID NO: 185); YKAWGYV (SEQ ID NO: 186); YQAWGYV (SEQ ID NO: 187); YQAWGYLV (SEQ ID NO: 188); YQAWGYFV (SEQ ID NO: 189); FTWVFWNV (SEQ ID NO: 190); YQVWGYFV (SEQ ID NO: 191); YKWLKWNL (SEQ ID NO: 192); RRLYIFEW (SEQ ID NO: 193); WAERGG (SEQ ID NO: 194); GGWAVGRI (SEQ ID NO: 195); YKYLFWV (SEQ ID NO: 196); YKYLFWV (SEQ ID NO: 197); YKTAWYWK (SEQ ID NO: 198); YVFHKWWV (SEQ ID NO: 199); YVFYLWWK (SEQ ID NO: 200); YRWLHWHV (SEQ ID NO: 201); YKFLFWHA (SEQ ID NO: 202); RRQWGFV (SEQ ID NO: 203); YSAWSFWV (SEQ ID NO: 204); LARWGFV (SEQ ID NO: 205); YDAWGYWV (SEQ ID NO: 206); WRKYHFWVS (SEQ ID NO: 207);

KRLYGLFWYD (SEQ ID NO: 208); KKHWSLFFE (SEQ ID NO: 209); KAWPYSWEAV (SEQ ID NO: 210); EWYCGVLFNCQQ (SEQ ID NO: 211); HFGCGVIFNCVSD (SEQ ID NO: 212); WELCASGYGWCYLH (SEQ ID NO: 213); APSCKSYIGFGLYHCWDG (SEQ ID NO: 214); and HFKCGMGLFECADP (SEQ ID NO: 215).

19. An antigen binding protein of any of claims 1-10, wherein the heavy chain further comprises a peptide that specifically binds to one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4.

20. The antigen binding protein heavy chain of claim 19, wherein the peptide comprises one or more of: TRLWKYWV (SEQ ID NO: 184); RRLYIFWE (SEQ ID NO: 185); YKAWGYYV (SEQ ID NO: 186); YQAWGYYV (SEQ ID NO: 187); YQAWGYLV (SEQ ID NO: 188); YQAWGYFV (SEQ ID NO: 189); FTWVFWNV (SEQ ID NO: 190); YQVWGYFV (SEQ ID NO: 191); YKWLKWNL (SEQ ID NO: 192); RRLYIFEW (SEQ ID NO: 193); WAERGG (SEQ ID NO: 194); GGWAVGRI (SEQ ID NO: 195); YKYLFWV (SEQ ID NO: 196); YKYSYWV (SEQ ID NO: 197); YKTAWYWK (SEQ ID NO: 198); YVFHKWWV (SEQ ID NO: 199); YVFYLWWK (SEQ ID NO: 200); YRWLHWHV (SEQ ID NO: 201); YKFLFWHA (SEQ ID NO: 202); RRQWGFV (SEQ ID NO: 203); YSAWSFWV (SEQ ID NO: 204); LARWGFV (SEQ ID NO: 205); YDAWGYWV (SEQ ID NO: 206); WRKYHFWVS (SEQ ID NO: 207); KRLYGLFWYD (SEQ ID NO: 208); KKHWSLFFE (SEQ ID NO: 209); KAWPYSWEAV (SEQ ID NO: 210); EWYCGVLFNCQQ (SEQ ID NO: 211); HFGCGVIFNCVSD (SEQ ID NO: 212); WELCASGYGWCYLH (SEQ ID NO: 213); APSCKSYIGFGLYHCWDG (SEQ ID NO: 214); and HFKCGMGLFECADP (SEQ ID NO: 215).

21. The antigen binding protein heavy chain of claim 20, wherein the heavy chain comprises a CH2 loop, a CH3 loop or both a CH2 and a CH3 loop.

22. The heavy chain of claim 21, wherein the heavy chain comprises a CH3 loop.

23. The heavy chain of claim 22, wherein the CH3 loop comprises the peptide.

24. The heavy chain of claim 21, wherein the heavy chain comprises a CH2 loop.

25. The heavy chain of claim 24, wherein the CH2 loop comprises the peptide.
26. An antigen binding protein comprising the heavy chain of claim 23 or 25.
27. A pharmaceutical composition comprising the antigen binding protein of claim 19 in admixture with a pharmaceutically acceptable carrier thereof.
28. An isolated nucleic acid comprising a polynucleotide sequence encoding the light chain variable domain, the heavy chain variable domain, or both, of the antigen binding protein of claim 19.
29. The isolated nucleic acid of claim 28, wherein the sequence is selected from L1-L11, SEQ ID NOs:17-27; H1-H11, SEQ ID NOs: 28-38, or both.
30. An expression vector comprising the nucleic acid of claim 29.
31. An isolated cell comprising the nucleic acid of claim 29.
32. The isolated cell of claim 31, comprising an expression vector comprising the nucleic acid.
33. A method of producing an antigen binding protein that specifically binds to β -Klotho comprising incubating the host cell of claim 32 under conditions that allow it to express the antigen binding protein.
34. An antigen binding protein-FGF21 fusion comprising:
 - (a) an antigen binding component; and
 - (b) an FGF21 component.
35. The antigen binding protein-FGF21 fusion of claim 34, wherein the antigen binding component comprises an antigen binding protein of claim 1.

36. The antigen binding protein-FGF21 fusion of claim 34, wherein the FGF21 component comprises at least 25 consecutive residues of SEQ ID NO:341.

37. The antigen binding protein-FGF21 fusion of claim 36, wherein the FGF21 component comprises one of (a) SEQ ID NO:342 or (b) SEQ ID NO:343.

38. The antigen binding protein-FGF21 fusion of claim 34, further comprising a linker.

39. The antigen binding protein-FGF21 fusion of claim 34, wherein

- (a) the antigen binding component comprising SEQ ID NOS:18 and 29;

and

- (b) an FGF21 component comprising one of:
 - (i) SEQ ID NO: 342; and
 - (ii) SEQ ID NO: 343.

40. The antigen binding protein-FGF21 fusion of claim 39, wherein the antigen binding component is joined to the FGF21 component by a linker selected from the group consisting of (G₄S)₃, (SEQ ID NO: 336) (G₄S)₆ (SEQ ID NO: 337), (G₄S)₉ (SEQ ID NO: 338), (G₄S)₁₂ (SEQ ID NO: 339) and (G₄S)₁₅ (SEQ ID NO: 340).

41. The antigen binding protein-FGF21 fusion of claim 39, wherein the FGF21 component is joined to the heavy chain of the antigen binding component.

42. The antigen binding protein-FGF21 fusion of claim 41, wherein the heavy chain comprises one or more of: SEQ ID NOs:316, 320, 322, 324, 326, 318, 328, 330, 332 and 334.

43. The antigen binding protein-FGF21 fusion of claim 39, wherein the FGF21 component is joined to the light chain of the antigen binding component.

44. The antigen binding protein of claim 34, that, when bound to β -Klotho, or β -Klotho and one or more of FGFR1c, FGFR2c, FGFR3c, and FGFR4:

- (a) lowers blood glucose in an animal model;
- (b) lowers serum lipid levels in an animal model; and
- (c) (a) and (b).

45. An isolated nucleic acid encoding the light chain, the heavy chain or both of the antigen binding component of claim 34, wherein the nucleic acid comprises:

- (a) L1-L11, SEQ ID NOs:17-27;
- (b) H1-H11, SEQ ID NOs: 28-38; or
- (c) SEQ ID NOs: 316, 320, 322, 324, 326, 318, 328, 330, 332 or 334.

46. An expression vector comprising the nucleic acid of claim 45.

47. An isolated cell comprising the nucleic acid of claim 46.

48. The isolated cell of claim 47, comprising an expression vector comprising the nucleic acid.

49. A pharmaceutical composition comprising an antigen binding protein-FGF21 fusion of claim 34, further comprising a pharmaceutically acceptable carrier.

50. A method of preventing or treating a condition in a subject in need of such treatment comprising administering a therapeutically effective amount of the composition of claim 49 to the subject, wherein the condition is treatable by lowering blood glucose.

51. The method of claim 49, wherein the condition is selected from type 2 diabetes, obesity, dyslipidemia, NASH, cardiovascular disease, and metabolic syndrome.

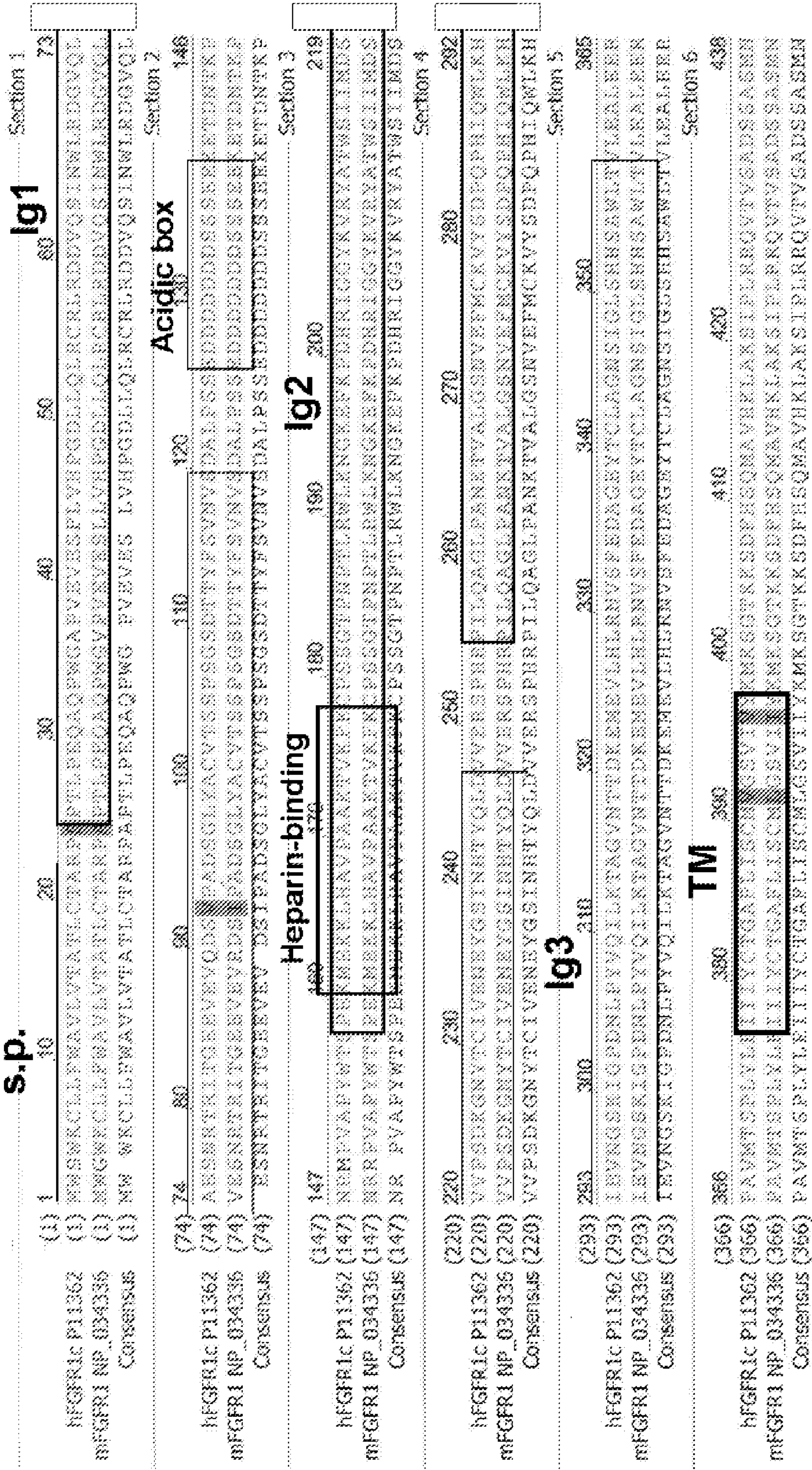


Figure 1a

Protein kinase domain												Section 7
(439)	439	450	460	470	480	490	500	510	520	530	540	554
hFGFR1c P11362 (439)	SOVLLV	PPSRLSSG	STPMLAGV	SEYELPED	FNWELPRER	IVLGRPLGGGGG	QGVVLA	ATGLD	EDFPNR	VTKV		
mFGFR1 NP_034336 (439)	SOVLLV	PPSRLSSG	STPMLAGV	SEYELPED	FPNSELPRER	IVLGRPLGGGGG	QGVVLA	ATGLD	EDFPNR	VTKV		
Consensus (439)	SOVLLV	PPSRLSSG	STPMLAGV	SEYELPED	FPNSELPRER	IVLGRPLGGGGG	QGVVLA	ATGLD	EDFPNR	VTKV		
Section 8												
(512)	512	520	530	540	550	560	570	580	590	600	610	624
hFGFR1c P11362 (512)	AVKML	SSDAT	TEKDL	SDLI	SEMMNN	NIIGX	HNII	INLLG	ACTQ	DGFL	VIV	YAS
mFGFR1 NP_034336 (512)	AVKML	SSDAT	TEKDL	SDLI	SEMMNN	NIIGX	HNII	INLLG	ACTQ	DGFL	VIV	YAS
Consensus (512)	AVKML	SSDAT	TEKDL	SDLI	SEMMNN	NIIGX	HNII	INLLG	ACTQ	DGFL	VIV	YAS
Section 9												
(585)	585	590	600	610	620	630	640	650	660	670	680	694
hFGFR1c P11362 (585)	YNP	SHN	PP	EEQ	LS	SKDLV	SCAYQ	VAR	GN	SEY	LA	SKK
mFGFR1 NP_034336 (585)	YNP	SHN	PP	EEQ	LS	SKDLV	SCAYQ	VAR	GN	SEY	LA	SKK
Consensus (585)	YNP	SHN	PP	EEQ	LS	SKDLV	SCAYQ	VAR	GN	SEY	LA	SKK
Section 10												
(658)	658	670	680	690	700	710	720	730	740	750	760	774
hFGFR1c P11362 (658)	TNG	RLP	VKN	MA	PE	AL	DR	IY	TN	QSD	VNS	F
mFGFR1 NP_034336 (658)	TNG	RLP	VKN	MA	PE	AL	DR	IY	TN	QSD	VNS	F
Consensus (658)	TNG	RLP	VKN	MA	PE	AL	DR	IY	TN	QSD	VNS	F
Section 11												
(731)	731	740	750	760	770	780	790	800	810	820	830	844
hFGFR1c P11362 (731)	MNM	RDC	WH	AV	PS	QR	PT	FK	QL	V	ED	L
mFGFR1 NP_034336 (731)	MNM	RDC	WH	AV	PS	QR	PT	FK	QL	V	ED	L
Consensus (731)	MNM	RDC	WH	AV	PS	QR	PT	FK	QL	V	ED	L
Section 12												
(804)	804	810	820	830	840	850	860	870	880	890	900	914
hFGFR1c P11362 (804)	EP	CL	PR	HP	AC	LAN	G	GL	NR			
mFGFR1 NP_034336 (804)	EP	CL	PR	HP	AC	LAN	G	GL	NR			
Consensus (804)	EP	CL	PR	HP	AC	LAN	G	GL	NR			

Figure 1b

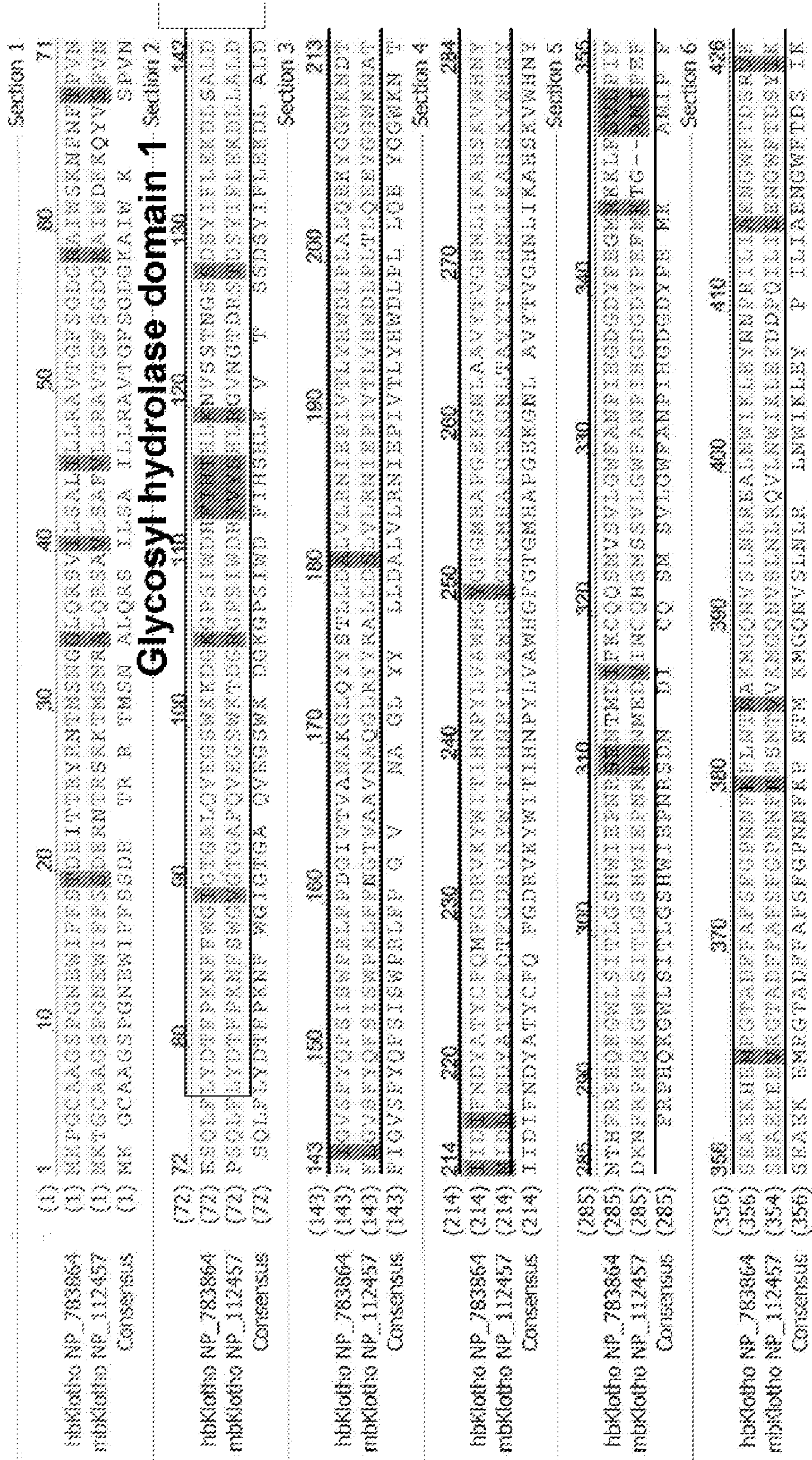
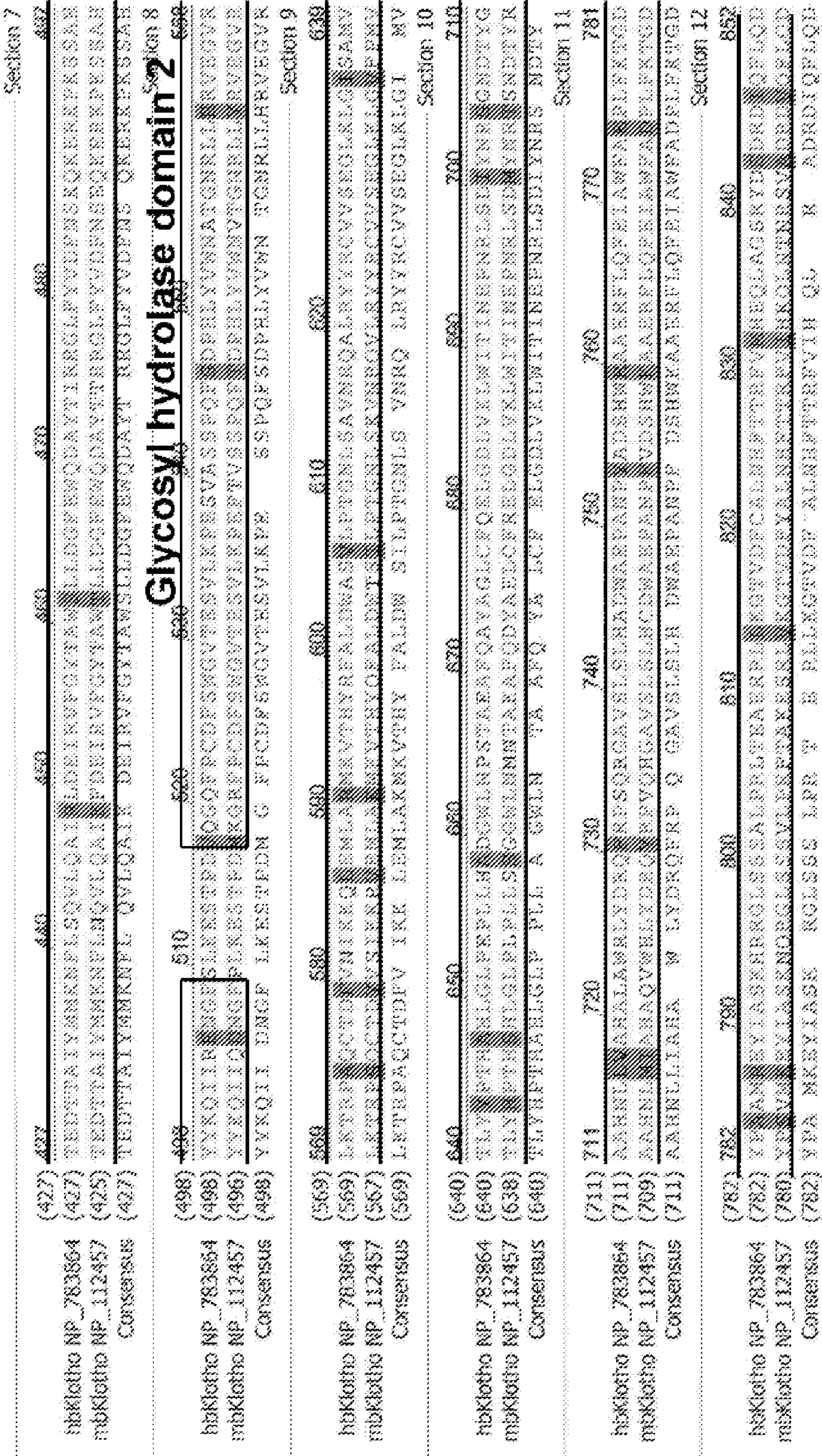


Figure 2a



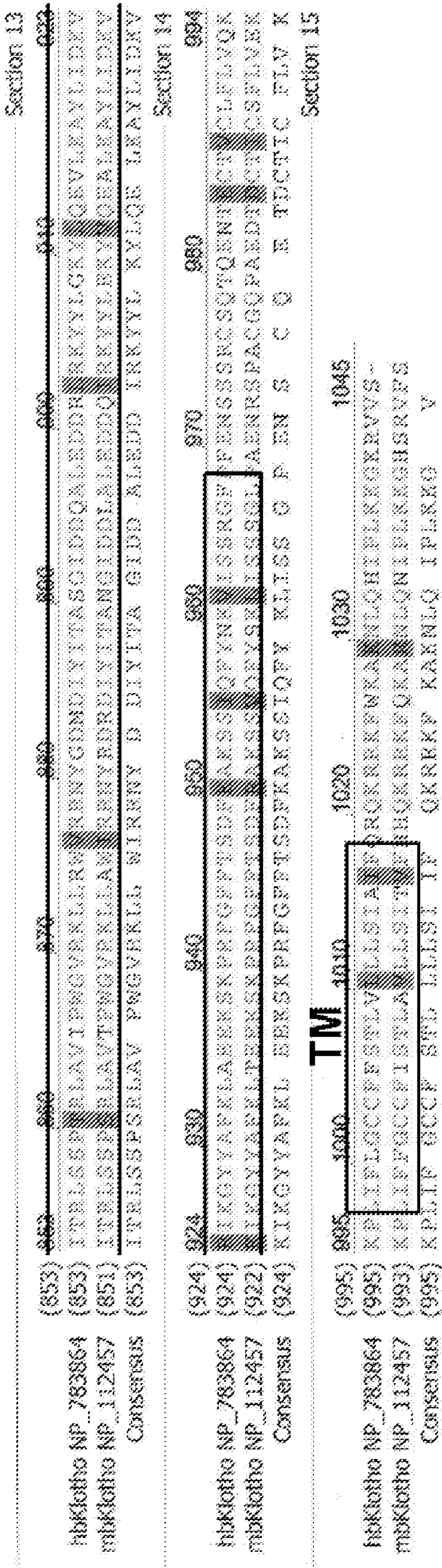


Figure 2c

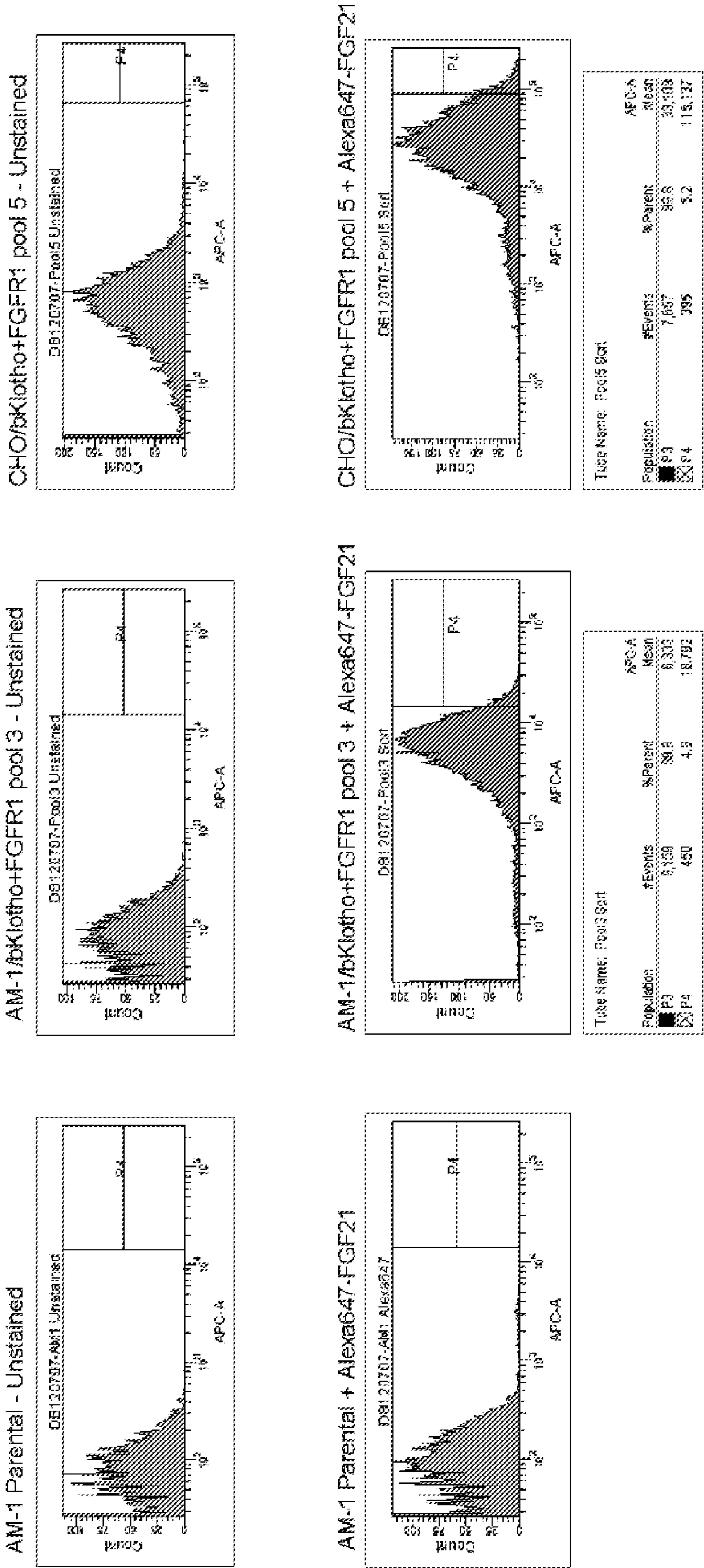


Figure 3

DPSPTLPEQAQPWGAPEVESFLVHPGDLLQLRCRLRDDVQSI
NWL RDGVQLAESNRTRITGEEVEVQDSVPADSGLYACVTSSPS
GSDTTYFSVNVSDALPSS EDDDDSSSEEKETDNTKPNRM
PVAPYWTSP EKM EKKLH AVPA AKTVKFKCPS SGT PNTLRWLK
NGKEFKPDHRIGGYKVRYATWSIMDSVVP SDKGNYTCIVENEY
GSINHTYQLDVVERSPHRPILQAGLPANKTV ALG SNVEFMCKV
YSDPQPHIQWLKHIEVNGSKIGPDNLPYVQILKTAGVNTTDKEM
EVLHLRNVSFEDAGEYTCLAGNSIGLSHSAWLTVLEALEERPA
VMTSPLY gaggggdkthtcppcpapellggpsvflfpkpkdtlmisrtpevtcvv dv
shedpevkfnwyvdgvevhnaktkpreeqynstyrsvltvlhqdwlngkeykckvs
nkalpapietiskakgqprepqvytlppsrdeltknqvsitclvkgfypsdiavewesng
qpennnykttpbvldsdgsfflyskltvdksrwqqgnvfscsvmhealhhhtqkslslsp
gk

Figure 4

FSGDGRAI WSKNPNEFTPV NESQLFLYDT FPKNFFWGIG TGAHQVEGSW
 KKDGKGPSIW DHFIHTHLKN VSSSTNGSSDS YIFLEKDL SALDFIGVSFYQ
 FSISWPRLFP DGIVTVANAK GLOYYSTLLD ALVLRNIEPI VTLYHWDLPL
 ALQEKYGGWK NDTIIDIFND YATYCFQMFG DRVKYWITH NPYLVAWHGY
 GTGMHAPGEK GNLAAYTVG HNLKAHSAKV WHNYNTHFRP HQKGWLSITL
 GSHWIEPNRS ENTMDIFKCC QSMVSVLGWF ANPIHGDGDY PEGMRKKLFS
 VLPIFSEAEK HEMRGTADEFF AFSFGPNNEK PLNTMAKMGQ NVSLNREAL
 NNIKLEYNNP RILIAENGWF TDSRVKTEDT TAIYMMKNFL SQVLOAIRLD
 EIRVFGYTAW SLLDGFIEWQD AYTIIRRGLEY VDFNSKQKER KPKSSAHYYK
 QIRENGFSL KESTPDVQGG FPCDFSWGVT ESVLKPESVA SSPQFSDPHL
 YVWNATGNRL LHRVEGVRLK TRPAQCTDEFV NIKKQLEMLA RMKVTHYRFA
 LDWASVLPTG NLSAVNRQAL RYYRCVWSEG LKLGISAMVT LYYPTHAHLG
 LPEPLLHADG WLNPSAEAF QAYAGLCFQE LGDLVKLWIT INEPNRLSDI
 YNRSNGNDTYG AAHNLLVAHA LAWRLYDRQF RPSQRGAVSL SLHADWAEPA
 NPYADSHWRA AERFLQFEIA WFAEPLFKTG DYPAAMREYI ASKHRRGLSS
 SALPRLTEAE RRLKGTVD F CALNHFTTRF VMHEQLAGSR YSDRDIOFL
 QDITRLSSPT RLAVIPWGV R KLLRWVRRNY GMDIYITAS GIDDOALEDD
 RL RKYVLGKY LQEV LKAYLI DKVRIKGYA FKLAEKSKP RFGFTSDFK
 AKSSIQFYNK VISSRGFPFE NSSRCSQIQ ENTTECTVCLF LVQKKP

gggggdkthtcp pc papellggpsvflppkpkdt misrtpevtcvvdvshedpevkfnwyvdgvevhnaktkpre
 eqynstyrvsvltv hqdwlngkeyckvsnkalpapietkiskakgqprepqvytlppsrde ltknqvs lclvkgfyps
 diavewesngqpennnyktpbvldsdgssflyskltvdksrwqqgnvfscsvmhealhnhytqkslsisp gk

Figure 5

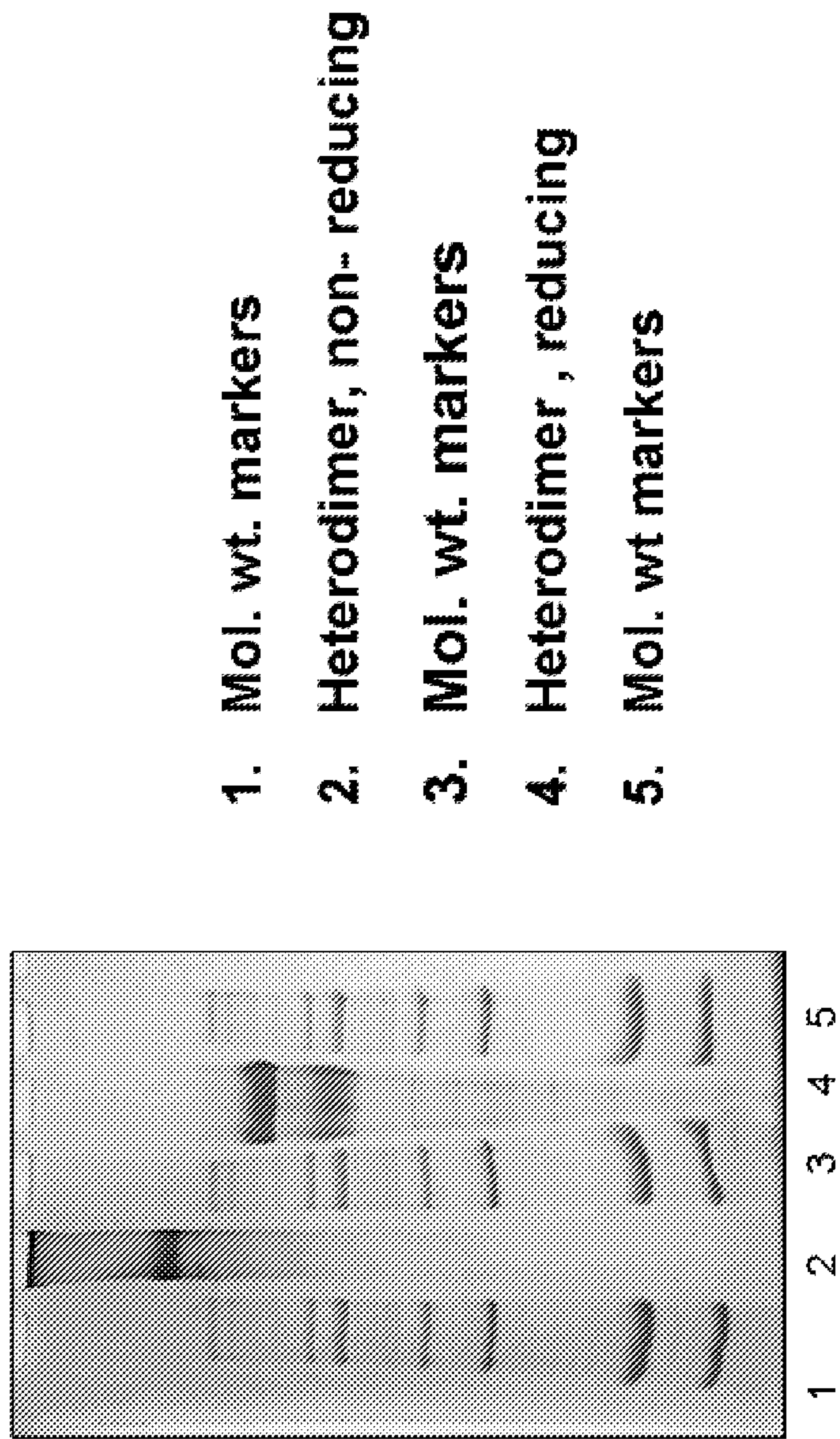


Figure 6

Line	Clone	pl (Q->pyroGlu, desk)/isotype
10H3(=3E10)	1	8.42/IgG2_K
1A2	1	8.16/IgG2_K
1B5	1	8.44/IgG2_K
3B4	1	8.44/IgG2_K
9D10	1	8.59/IgG2_L
3F4	1	8.15/IgG2_L
1C10	1	8.44/IgG2_L
2G10	1	8.76/IgG2_L
8F9	1	8.6/IgG2_L

Figure 7

1315	1C	: DVMQCTPZLSEVVLGQPAS18	BSQSGLVHTZNTTSLMLQCRSGQPERLLIYXINRP	SGVEDRPFSGSAGSTDTIKIRVKAEDVSTY	---WCALEPFRPTFGQCRKVEIK
1316	1C	: DVMQCTPZLSEVVLGQPAS18	BSQSGLVHTZNTTSLMLQCRSGQPERLLIYXINRP	SGVEDRPFSGSAGSTDTIKIRVKAEDVSTY	---WCALEPFRPTFGQCRKVEIK
1317	1C	: DVMQCTPZLSEVVLGQPAS18	BSQSGLVHTZNTTSLMLQCRSGQPERLLIYXINRP	SGVEDRPFSGSAGSTDTIKIRVKAEDVSTY	---WCALEPFRPTFGQCRKVEIK
1318	1C	: DVMQCTPZLSEVVLGQPAS18	BSQSGLVHTZNTTSLMLQCRSGQPERLLIYXINRP	SGVEDRPFSGSAGSTDTIKIRVKAEDVSTY	---WCALEPFRPTFGQCRKVEIK
1319	1C	: QSVLQ-PEVSVAAPGQKVPI8	---SNIENNYQSMYQCLPGTAERKLLIYDNNRP	SGIEDRPFSGSKSTGATIGTGLQGDGADY	BTGTHSISAGVFGSGGPHLTVL
1320	1C	: QSVLQ-PEVSVAAPGQKVPI8	---SNIENNYQSMYQCLPGTAERKLLIYDNNRP	SGIEDRPFSGSKSTGATIGTGLQGDGADY	BTGTHSISAGVFGSGGPHLTVL
1321	1C	: QSVLQ-PEVSVAAPGQKVPI8	---SNIENNYQSMYQCLPGTAERKLLIYDNNRP	SGIEDRPFSGSKSTGATIGTGLQGDGADY	BTGTHSISAGVFGSGGPHLTVL
1322	1C	: QSVLQ-PEVSVAAPGQKVPI8	---SNIENNYQSMYQCLPGTAERKLLIYDNNRP	SGIEDRPFSGSKSTGATIGTGLQGDGADY	BTGTHSISAGVFGSGGPHLTVL
1323	1C	: QSVLQ-PEVSVAAPGQKVPI8	---SNIENNYQSMYQCLPGTAERKLLIYDNNRP	SGIEDRPFSGSKSTGATIGTGLQGDGADY	BTGTHSISAGVFGSGGPHLTVL
1324	1C	: QSVLQ-PEVSVAAPGQKVPI8	---SNIENNYQSMYQCLPGTAERKLLIYDNNRP	SGIEDRPFSGSKSTGATIGTGLQGDGADY	BTGTHSISAGVFGSGGPHLTVL

[illegible][illegible]

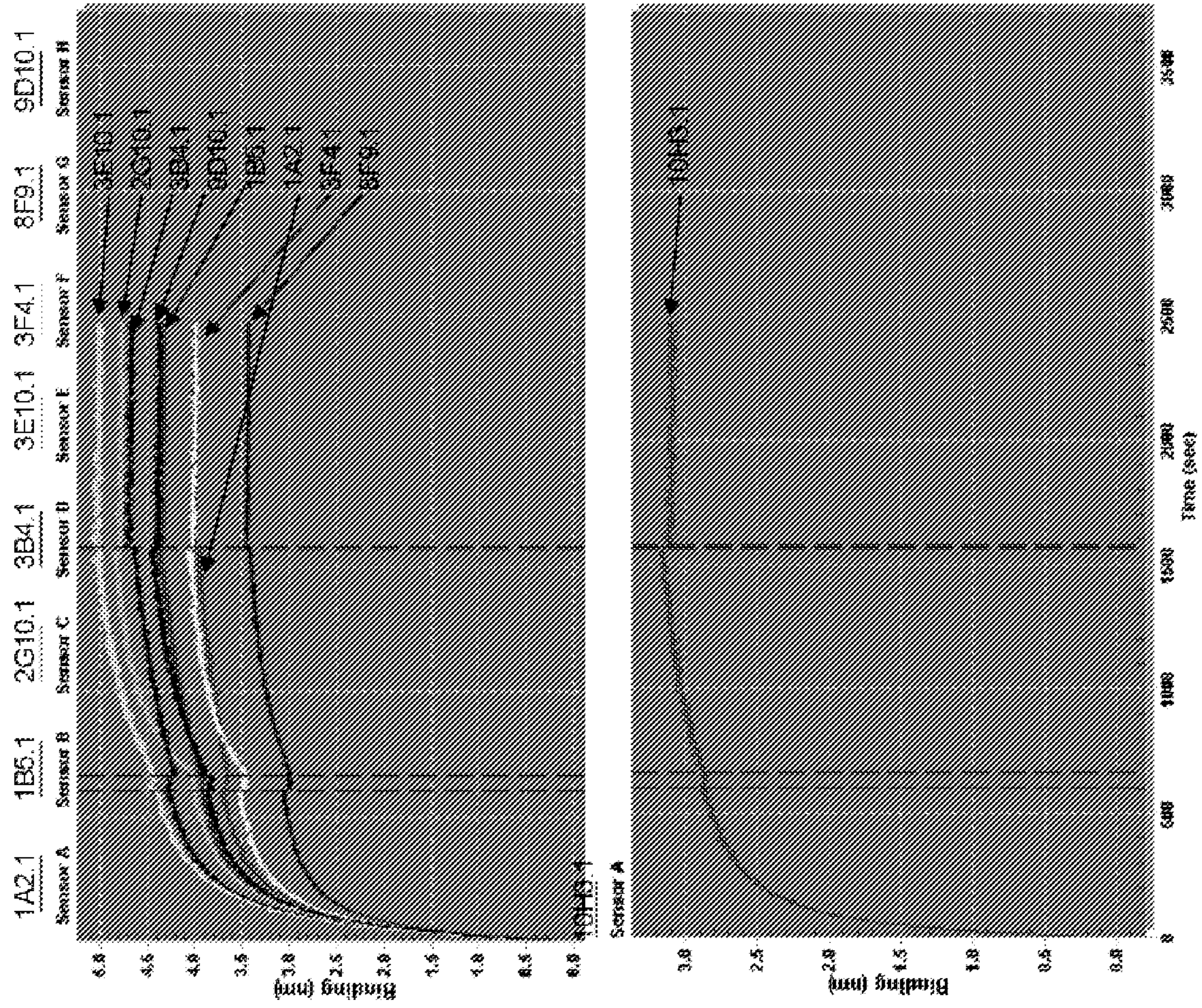


Figure 9A

Sensor	lgG	k _d		k _a		K _D	
		[1/s]		[1/Ms]		[M]	[nM]
A1	1A2.1	3.34E-05		1.56E+04		2.14E-09	2.14
B1	1B5.1	6.13E-05		1.06E+05		5.78E-10	0.58
C1	2G10.1	3.49E-05		2.71E+05		1.29E-10	0.13
D1	3B4.1	1.13E-04		1.86E+04		6.08E-09	6.08
E1	3E10.1	7.87E-05		1.32E+05		5.97E-10	0.60
F1	3F4.1	7.41E-05		2.64E+05		2.81E-10	0.28
G1	8F9.1	5.75E-05		1.36E+05		4.22E-10	0.42
H1	9D10.1	4.76E-05		1.60E+05		2.98E-10	0.30
A2	10H3.1	8.03E-05		1.43E+05		5.63E-10	0.56

Figure 9B

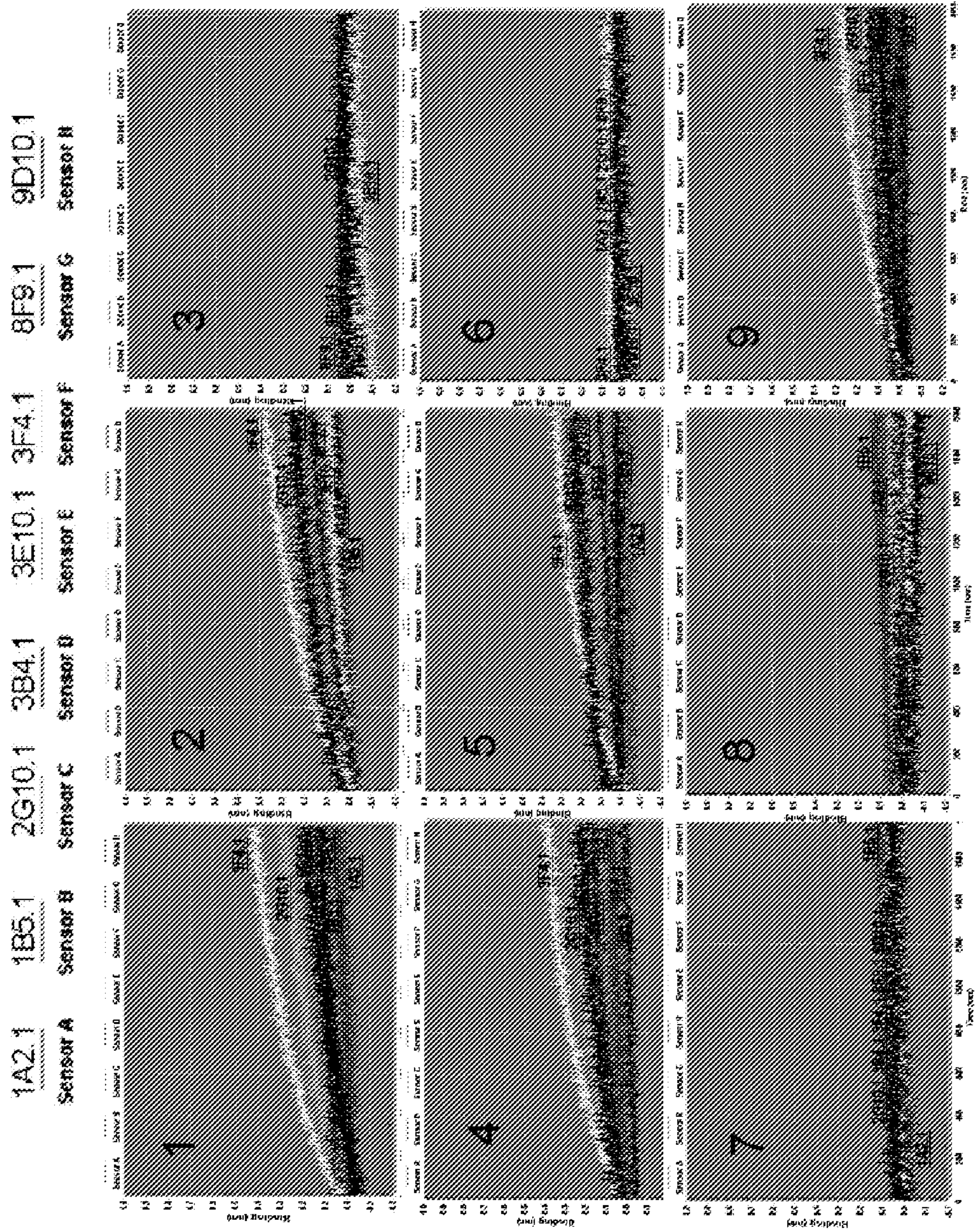


Figure 10

Ab ID		Kd (nM)						
3B4.1	Kappa	6.08						
1A2.1	Kappa	2.14						
1B5.1	Kappa	0.58						
10H3.1	Kappa	0.56						
9D10.1	Lambda	0.30						
2G10.1	Lambda	0.13						
3F4.1	Lambda	0.28						
8F9.1	Lambda	0.42						

Figure 11

Pb ID	aa sequences	Kd (nM)	ELISA	Agretopes
Rm26	EWYCGVLFNCQQ	1.02	Hu: ++ Mu: ++ Other: -	0
Rm27	HFGCGVIFNCVSD	1.08	Hu: ++ Mu: ++ Other: -	0
Rm33	WELCASGYGWCYLH	3.00	Hu: ++ Mu: ++ Other: -	0
Rm37	APSCKSYIGFGLYHCWDG	8.19	Hu: ++ Mu: ++ Other: -	0
Rm40	HFKCGMGLFECADP	1.44	Hu: ++ Mu: ++ Other: -	0
SR4	YQAWGYVW	0.46	Hu: ++ Mu: ++ Other: -	0

Figure 12

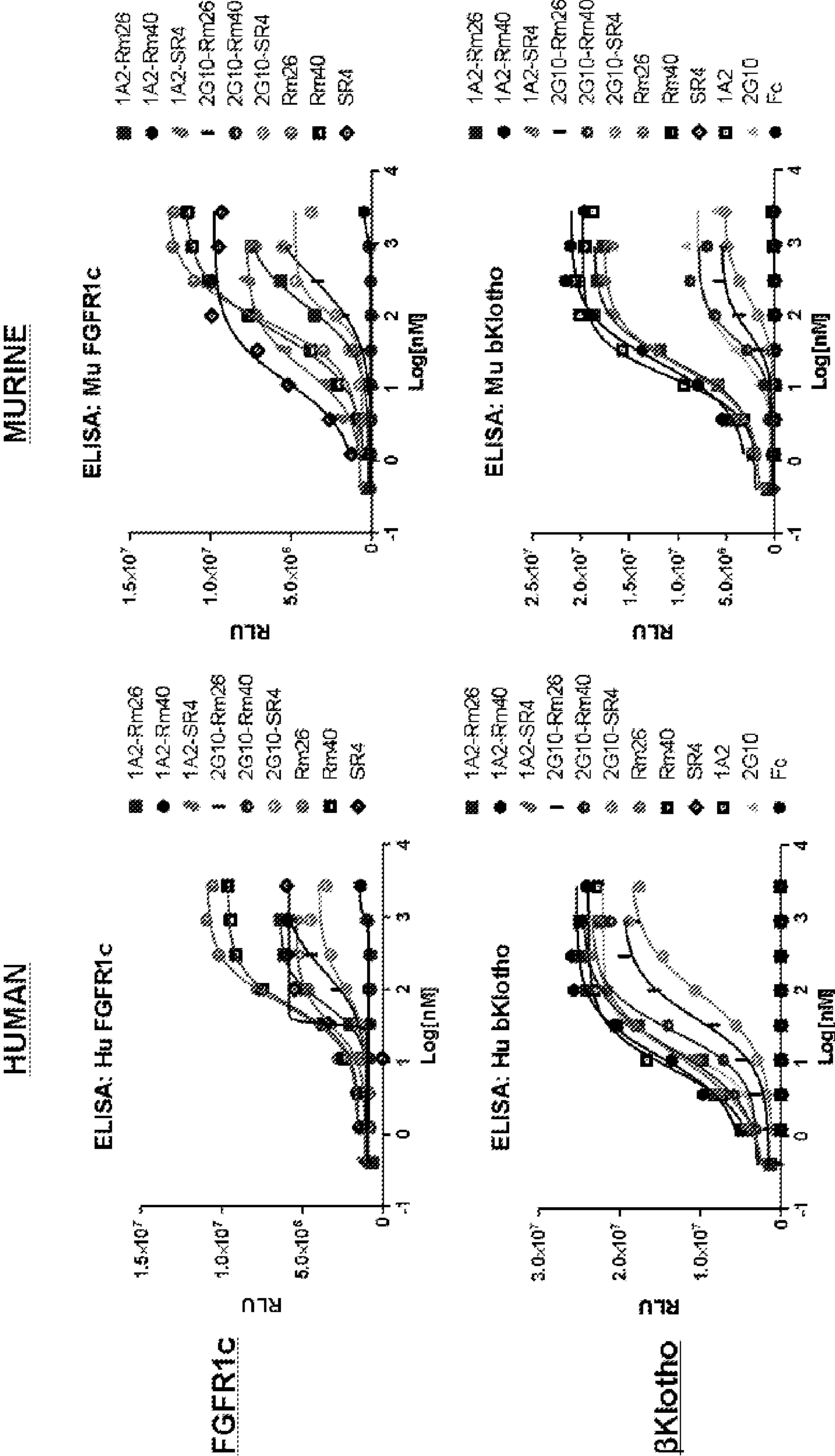


Figure 13

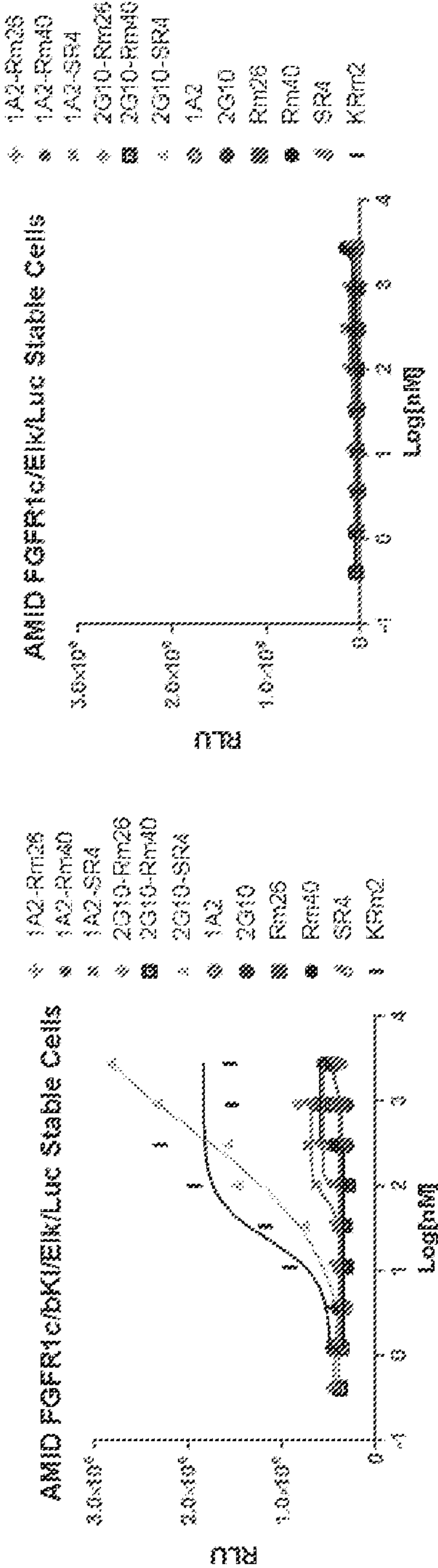


Figure 14

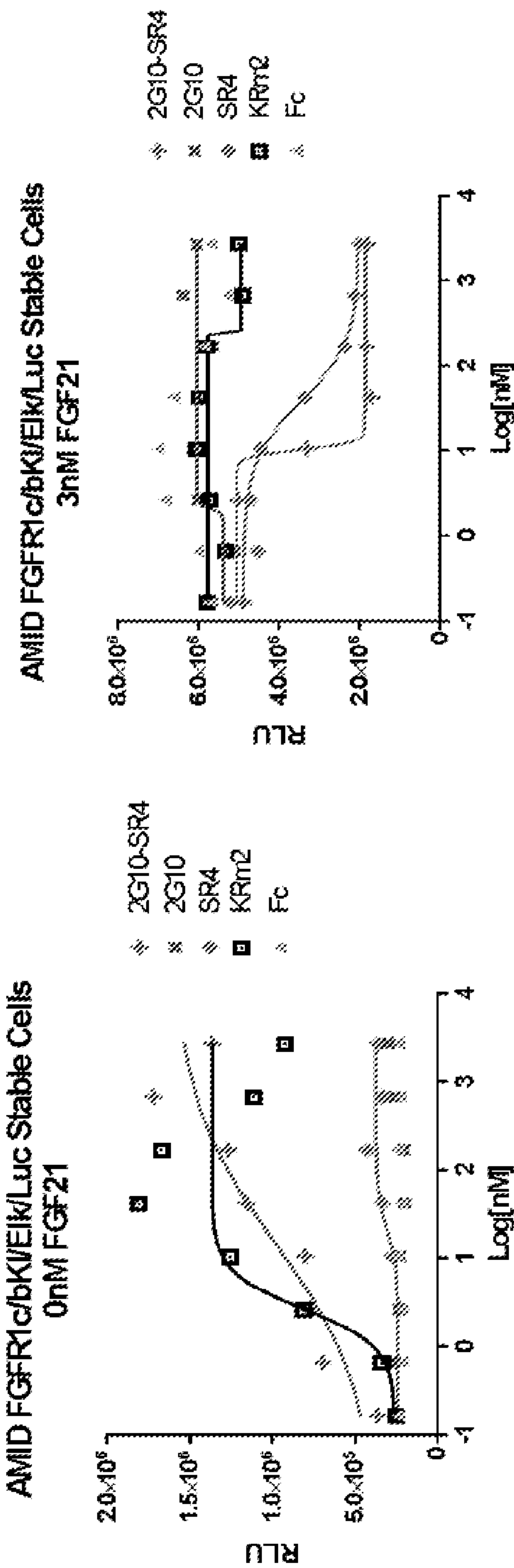


Figure 15

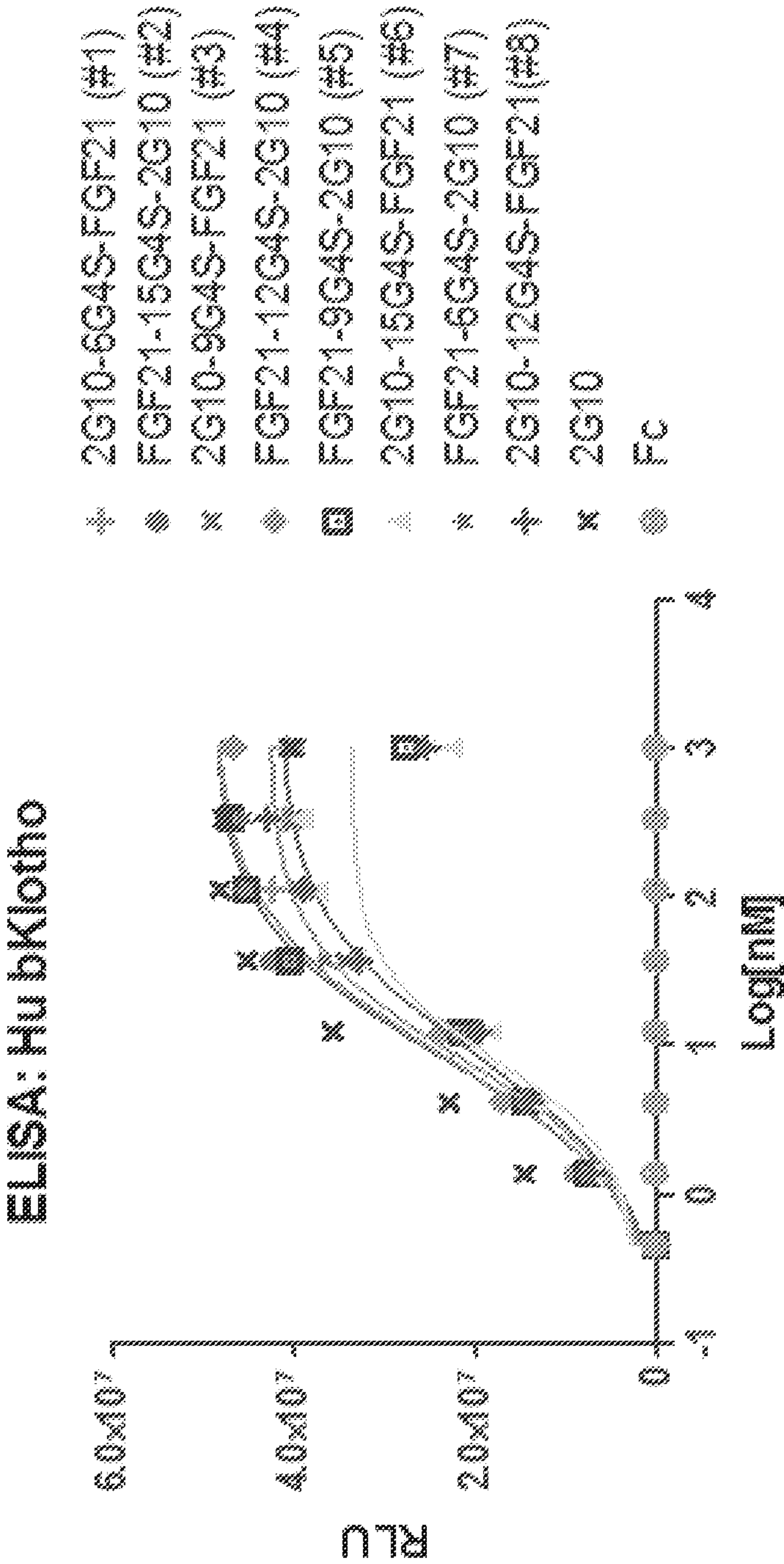


Figure 16

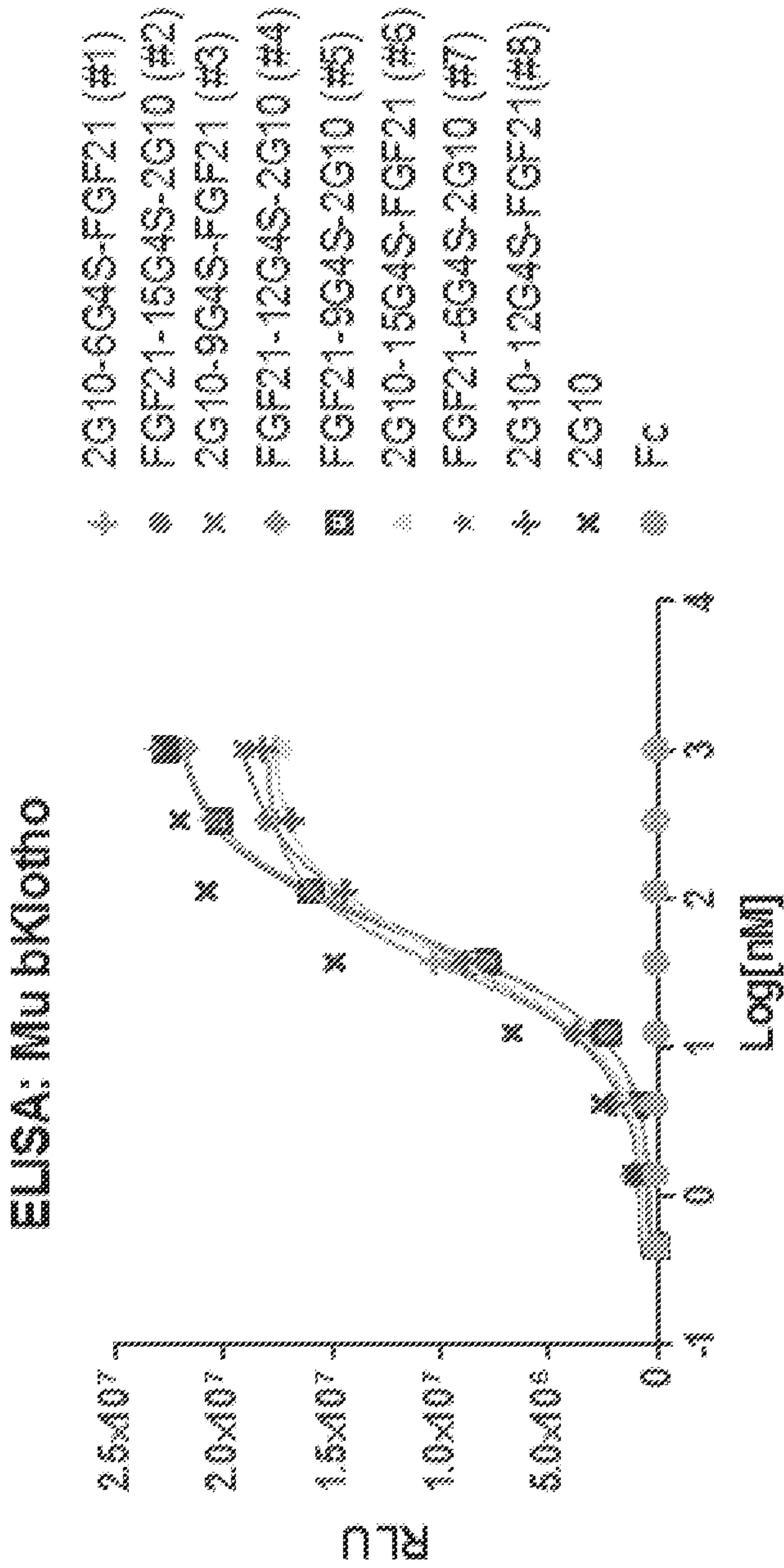


Figure 17

AND FGFR1c/bKlElk Luc Stable Cells
0nM FGF21

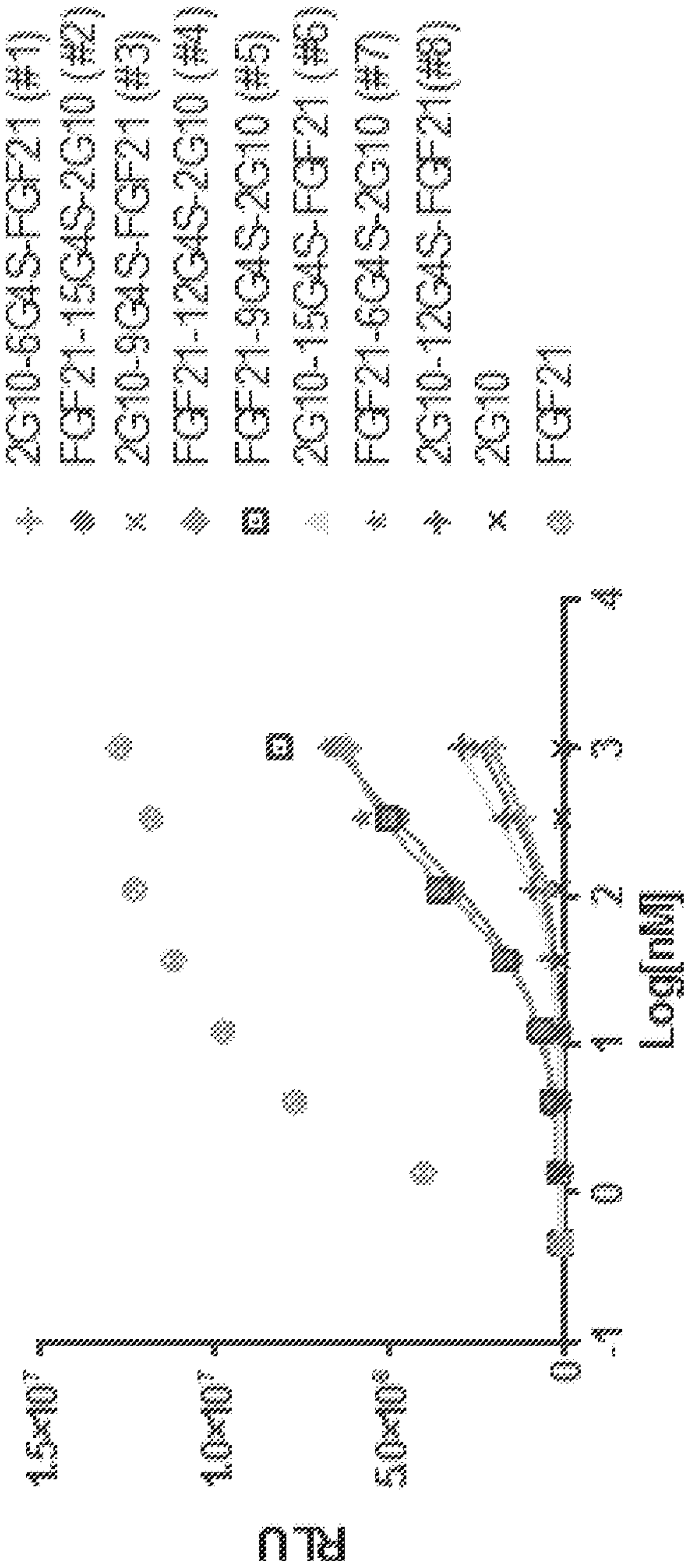


Figure 18

AMID FGFR1c/bK1/EK Luc Stable Cells
3nM FGF21

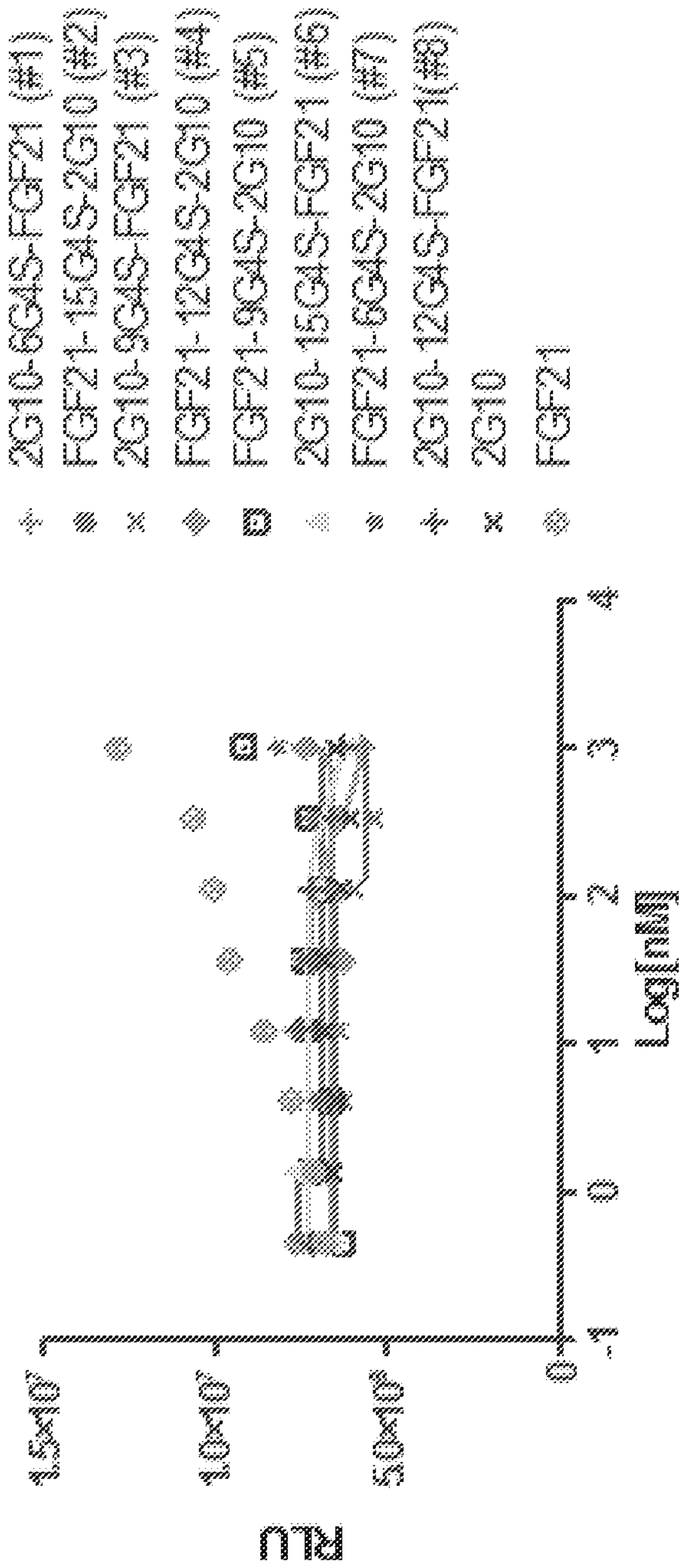


Figure 19

ANID aKlElk Luc Stable Cells
0nM FGF21

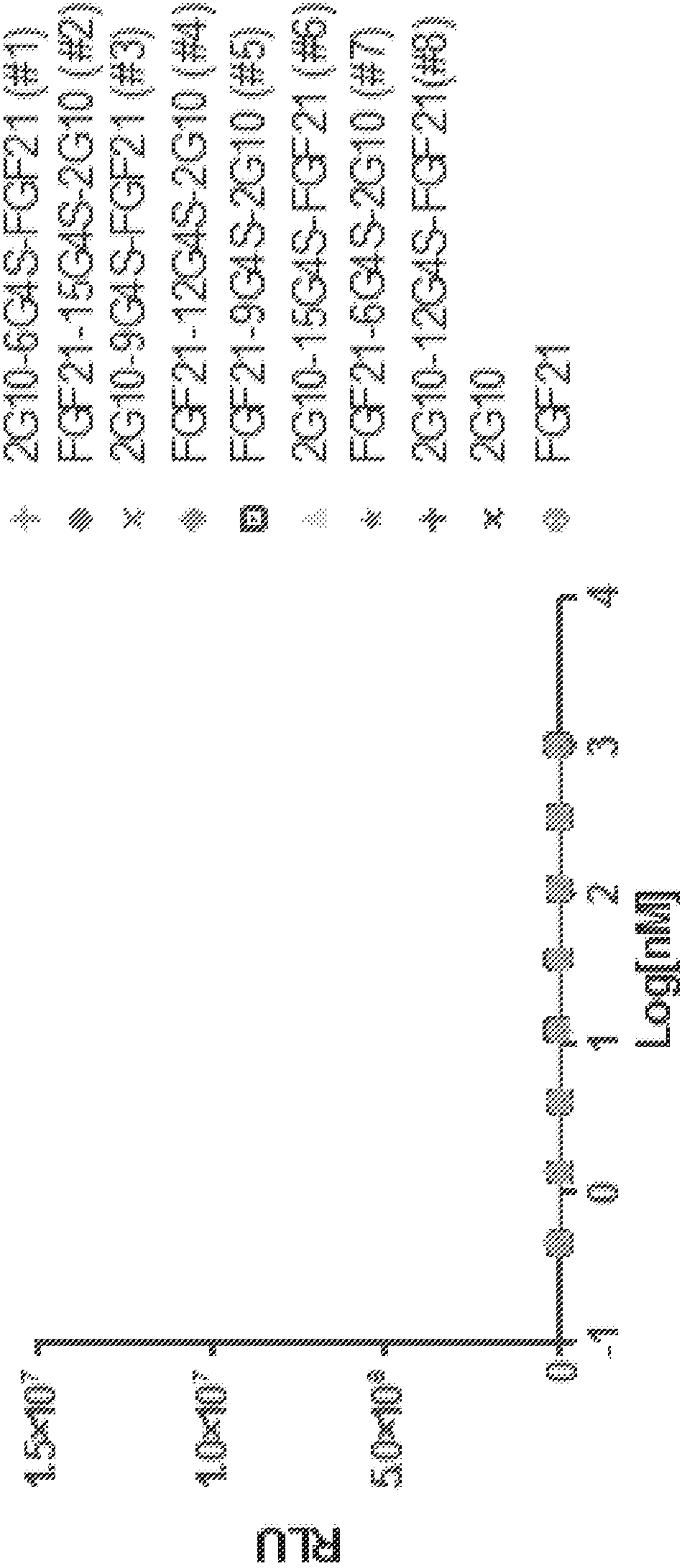


Figure 20

AMID FGFR1c/EK Luc Stable Cells 0nM FGF21

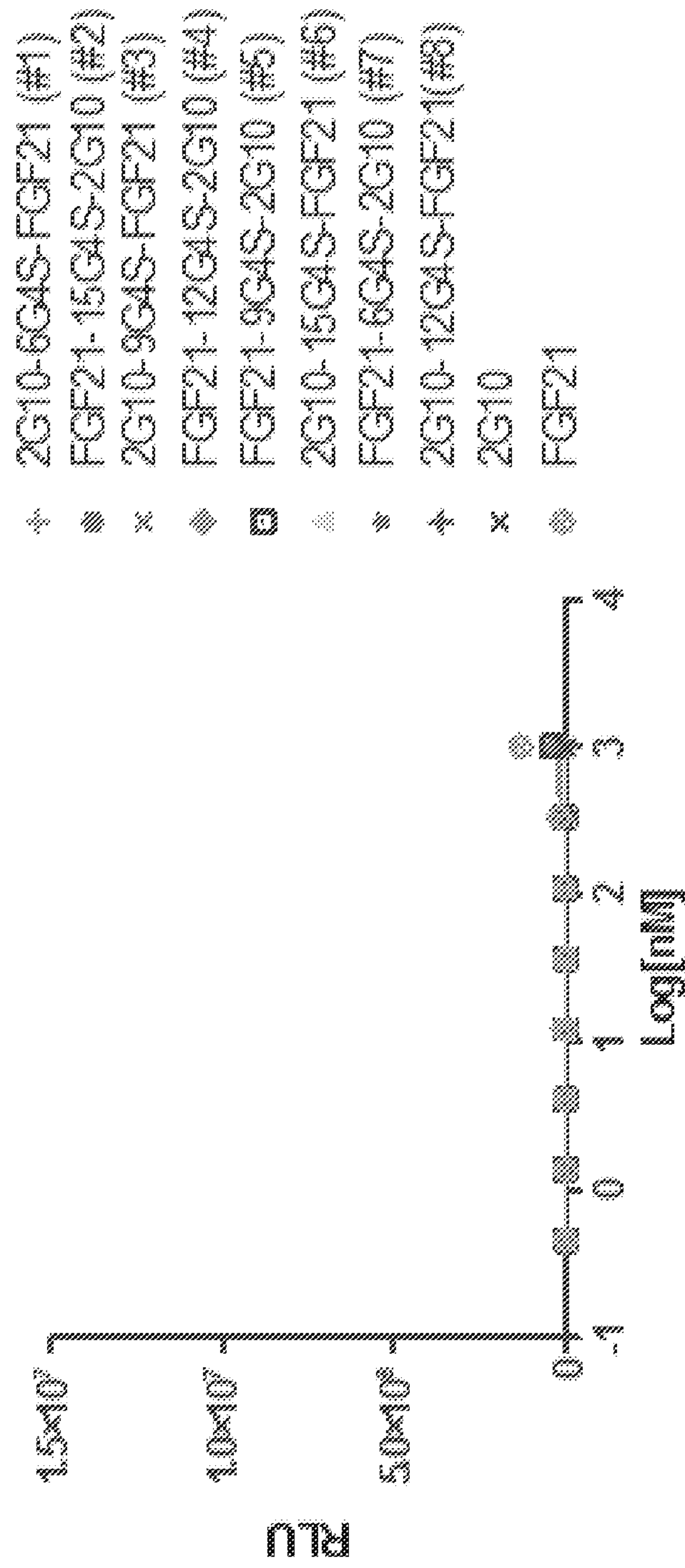


Figure 21