via activation of FGF Receptor (FGFR) 4 (Fu et al., *Endocrinology* 145, 2594-2603 (2004); Tomlinson et al., *Endocrinology* 143, 1741-1747 (2002); French et al., *PLoS One* 7, e36713 (2012)).

Recombinant monoclonal antibodies (Abs) can act as a powerful therapeutic modality as they can provide excellent target selectivity, pharmacokinetic profile, and other properties important for a pharmaceutical agent (Chan and Carter, *Nature reviews. Immunology* 10, 301-316 (2010)). For example, an antibody antagonist specific for FGFR1c was reported to induce weight loss in mice and monkeys (WO2005/037235) and agonistic antibody-mediated selective activation of FGFR1c is sufficient to recapitulate the insulin sensitization by FGF21 in diabetic mice (WO2012/158704; Wu et al. *Science Translational Med.* 3(113): 1-10 (2011)). Antibodies that bind to the KLB/FGFR1c complex have been proposed as activators/therapeutic agents (US 7,537,903; WO2011/071783; WO2012/158704). Others have investigated two alternative approaches to selectively activate the FGFR1c/KLB complex, such as a high affinity anti-KLB antibody called mimAb1 (Foltz et al. *Sci. Transl. Med.* 4: 162ra153 (2012)) and bispecific anti-FGFR1/KLB Avimer polypeptide C3201 linked to human serum albumin (HSA) (US 8,372,952).

Given the significant role for FGF19 and FGF21 in glucose metabolism, there remains a need in the art for the development of therapeutic molecules and methods to modulate FGF19 or FGF21-mediated activities.

SUMMARY

The present disclosure provides antibodies that bind to KLB, antibodies that bind to FGFR1, and bispecific antibodies that bind to both KLB and FGFR1, and methods of using the same. The ~~invention~~ disclosure is based, in part, on the discovery of bispecific antibodies that bind to both KLB and FGFR1, which selectively activate the FGFR1c/KLB receptor complex and induce the beneficial metabolic changes expected from the FGF21-like activity, including weight loss and improvement in glucose and lipid metabolism, without a significant impact on the liver and without a loss in bone mass.

In one aspect, there is provided an isolated bispecific antibody, or an antigen-binding portion thereof, that binds to beta-Klotho (KLB) and Fibroblast Growth Factor Receptor 1 (FGFR1).

In certain embodiments, the antibody is a bispecific antibody. For example, and not by way of limitation, an isolated antibody of the present ~~invention~~ disclosure can bind to both beta-Klotho (KLB) and Fibroblast Growth Factor Receptor 1 (FGFR1), wherein

heavy chain variable region includes amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 128, and the light chain variable region includes amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 130. In certain embodiments, the second antibody, or antigen binding portion thereof, includes a heavy chain variable region and a light chain variable region, where the heavy chain variable region includes amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 132, and the light chain variable region includes amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 134.

In one aspect, there is provided an isolated anti-KLB/anti-FGFR1 bispecific antibody comprising:

(a) a first antibody, or antigen binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 128, and the light chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 130; and

(b) a second antibody, or antigen binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 132, and the light chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 134.

In certain embodiments, an anti-KLB/anti-FGFR1 bispecific antibody of the present disclosure includes a first antibody, or antigen binding portion thereof, which includes a heavy chain region and a light chain region, where the heavy chain region includes amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 129, and the light chain region includes amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 131. In certain embodiments, the second antibody, or antigen binding portion thereof, includes a heavy chain region and a light chain region, where the heavy chain region includes amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 133, and the light chain region includes amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 135.

In one aspect, there is provided an isolated anti-KLB/anti-FGFR1 bispecific antibody comprising:

(a) a first antibody, or antigen binding portion thereof, comprising a heavy chain region and a light chain region, wherein the heavy chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 129, and the light chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 131; and

(b) a second antibody, or antigen binding portion thereof, comprising a heavy chain region and a light chain region, wherein the heavy chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 133, and the light chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 135.

In one aspect, there is provided an anti-beta-Klotho (KLB) antibody, or an antigen-binding portion thereof, comprising (a) HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-47 and, (b) HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93.

The present disclosure further provides an anti-KLB antibody that includes: (a) HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-15, (b) HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93, and (c) HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-31.

In certain embodiments, the anti-KLB antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-15, (b) HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-31, and (c) HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-47.

In certain embodiments, the anti-KLB antibody further comprises (a) HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-62, (b) HVR-L2 comprising an amino acid sequence selected from the group

consisting of SEQ ID NOs: 63-78, and (c) HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93.

In certain embodiments, the anti-KLB antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 12, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 59, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 75, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 90.

In certain embodiments, the anti-KLB antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 31, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 47, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 62, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 78, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 93.

In certain embodiments, the anti-KLB antibody comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130. In certain embodiments, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 129 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 131.

In one aspect, there is provided an anti-KLB antibody, or an antigen-binding portion thereof, that competitively inhibits binding of any antibody of the disclosure.

In another aspect, ~~the present disclosure~~there is providesd an anti-KLB antibody, or an antigen-binding portion thereof, comprising (a) a heavy chain variable region having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 128; (b) a light chain variable region having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 130; and (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

The present disclosure further provides antibodies that bind to FGFR1, *e.g.*, FGFR1c. For example, and not by way of limitation, an antibody of the present disclosure comprises a variable domain that binds to FGFR1. In certain embodiments, the antibody binds to a fragment of FGFR1 consisting of the amino acid sequence KLHAVPAAKTVKFKCP (SEQ ID NO: 143) or FKPDHRIGGYKVRY (SEQ ID NO: 144). In certain embodiments, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 136, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 137, (c) HVR-H3 comprising the amino acid sequence of

SEQ ID NO: 138, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 139, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 140, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 141. In certain embodiments, the antibody comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 134. In certain embodiments, the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 133 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 135. In certain embodiments, an antibody of the present disclosure binds to a fragment of FGFR1c consisting of the amino acid sequence KLHAVPAAKTVKFKCP (SEQ ID NO: 143) or FKPDHRIGGYKVRY (SEQ ID NO: 144).

In certain embodiments, an antibody of the present disclosure is a monoclonal antibody. In certain embodiments, the antibody is a human, humanized, or chimeric antibody. In certain embodiments, the antibody has reduced effector function.

In another aspect, ~~the present disclosure~~there is provides~~d~~ an isolated nucleic acid encoding an antibody of the present disclosure. In ~~certain embodiments~~another aspect, ~~the present disclosure~~there is provides~~d~~ a host cell comprising a nucleic acid of the present disclosure. In ~~certain embodiments~~yet another aspect, ~~the present disclosure~~there is provides~~d~~ a method of producing an antibody comprising culturing a host cell of the present disclosure so that the antibody is produced. In certain embodiments, this method further comprises recovering the antibody from the host cell.

~~The present disclosure further provides~~In one aspect, there is provided a pharmaceutical formulation ~~that includes~~comprising one or more antibodies of the ~~invention~~ disclosure and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical formulation comprises an additional therapeutic agent.

In one aspect, there is provided an antibody of disclosure for use as a medicament; for use in activating a KLB/FGFR1 receptor complex; for treatment of a metabolic disorder or for use in treating a disorder selected from the group consisting of polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY), and aging and related diseases such as Alzheimer's disease, Parkinson's disease and ALS, Bardet-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, Cohen syndrome, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), Carpenter syndrome, MOMO syndrome, Rubinstein-Taybi syndrome, fragile X syndrome and Börjeson-Forssman-Lehman syndrome.

In ~~another aspect~~one embodiment, the present disclosure provides an antibody of the ~~invention~~ disclosure for use as a medicament. In certain embodiments, the antibody is for use in treating metabolic disorders, *e.g.*, polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY). In certain embodiments, the antibody is for use in treating type 2

diabetes. In certain embodiments, the antibody is for use in treating obesity. In certain embodiments, the present disclosure provides an antibody for use in treating Bardet-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, Cohen syndrome, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), Carpenter syndrome, MOMO syndrome, Rubinstein-Taybi syndrome, fragile X syndrome and Börjeson-Forssman-Lehman syndrome. In certain embodiments, the present disclosure provides an antibody for use in activating a KLB/FGFR1 receptor complex, *e.g.*, a KLB/FGFR1c receptor complex.

In one aspect, there is provided use of the antibody of the disclosure in the manufacture of a medicament for activating a KLB/FGFR1 receptor complex; for treating a metabolic disorder or for treating a disorder selected from the group consisting of polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY), and aging and related diseases such as Alzheimer's disease, Parkinson's disease and ALS, Bardet-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, Cohen syndrome, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), Carpenter syndrome, MOMO syndrome, Rubinstein-Taybi syndrome, fragile X syndrome and Börjeson-Forssman-Lehman syndrome.

In ~~another aspect~~one embodiment, the present disclosure provides the use of an antibody, disclosed herein, in the manufacture of a medicament for treatment of metabolic disorders, *e.g.*, polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY), and aging and related diseases such as Alzheimer's disease, Parkinson's disease and ALS. In certain embodiments, the metabolic disorder is type 2 diabetes. In certain embodiments, the metabolic disorder is obesity. In certain embodiments, the manufacture is of a medicament for activating a KLB/FGFR1c receptor complex.

In ~~another aspect~~one embodiment, the present disclosure provides a method of treating an individual having a disease selected from the group consisting of polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY), and aging and related diseases such as Alzheimer's disease, Parkinson's disease and ALS, the method comprising administering to the individual an effective amount of one or more antibodies of the present disclosure. In certain embodiments, the disease is diabetes, *e.g.*, type 2 diabetes. In certain embodiments, the disease is obesity. In certain embodiments, the present disclosure provides a method of treating an individual having a disease and/or disorder selected from the group consisting of Bardet-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, Cohen syndrome, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), Carpenter syndrome, MOMO syndrome, Rubinstein-Taybi syndrome, fragile X syndrome and Börjeson-Forssman-

Lehman syndrome. In certain embodiments, the method further includes administering an additional therapeutic agent to the individual. In certain embodiments, a method using one or more antibodies of the present disclosure does not affect liver function in an individual. In certain embodiments, the present disclosure provides a method for inducing weight loss comprising administering to an individual an effective amount of one or more antibodies of the present disclosure.

In another ~~aspect~~embodiment, the present disclosure provides a method of activating a KLB-FGFR1c receptor complex in an individual comprising administering to the individual an effective amount of an antibody of the present disclosure.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A depicts agonistic activity of anti-FGFR1 antibodies and antibody fragments.

Figure 1B depicts results of binding competition experiments using anti-FGFR1 antibodies.

Figure 1C depicts amino acid residues in FGFR1 important for binding by anti-FGFR1 antibodies of the presently disclosed subject matter. Figure 1C discloses SEQ ID NOs: 159, 159, 143 and 144, respectively, in order of appearance.

Figure 1D depicts the results of site-specific mutagenesis to determine amino acid residues important for binding by anti-FGFR1 antibodies of the presently disclosed subject matter.

Figure 1E depicts the results of site-specific mutagenesis to determine amino acid residues important for binding by anti-FGFR1 antibodies of the presently disclosed subject matter.

Figure 1F depicts residues important for binding on a space-filling model of FGFR1.

Figure 2A depicts the affinities of two anti-FGFR1 antibodies for FGFR1b and FGFR1c.

Figure 2B depicts binding of an anti-FGFR1 antibody to various FGFRs.

Figure 2C depicts an anti-FGFR1 antibody that acted as a specific agonist for FGFR1 in GAL-ELK1 (ETS-like transcription factor 1) based luciferase assay in L6 cells.

WHAT IS CLAIMED IS:

1. An isolated bispecific antibody, or an antigen-binding portion thereof, that binds to beta-Klotho (KLB) and Fibroblast Growth Factor Receptor 1 (FGFR1).

2. The antibody of claim 1, wherein the antibody, or an antigen-binding portion thereof, binds to the C-terminal domain of KLB.

3. The antibody of claim 1, wherein the antibody, or an antigen-binding portion thereof, binds to a fragment of KLB comprising the amino acid sequence set forth in SEQ ID NO: 142.

4. The antibody of any one of claims 1-3, wherein the antibody, or an antigen-binding portion thereof, binds to an FGFR1 epitope within a fragment of FGFR1c comprising the amino acid sequence set forth in SEQ ID NO: 143 or SEQ ID NO: 144.

5. The antibody of any one of claims 1-4, wherein the antibody, or an antigen-binding portion thereof, reduces blood glucose levels *in vivo*.

6. The antibody of any one of claims 1-5, wherein the antibody, or an antigen-binding portion thereof, does not significantly affect bone density.

7. The antibody of any one of claims 1-6, wherein the antibody, or an antigen-binding portion thereof, does not significantly affect the liver.

8. The antibody of any one of claims 1-7, wherein the antibody, or an antigen-binding portion thereof, induces ERK and MEK phosphorylation in the liver at significantly lower levels than FGF21 induces.

9. The antibody of any one of claims 1-8, wherein the antibody, or an antigen-binding portion thereof, binds to KLB with a K_d from 10^{-8} M to 10^{-13} M.

10. The antibody of any one of claims 1-9, wherein the antibody, or an antigen-binding portion thereof, binds to FGFR1c with a K_d from 10 nM to about 10 μM.

11. The antibody of any one of claims 1-10, wherein the antibody, or an antigen-binding portion thereof, is a monoclonal antibody.

12. The antibody of any one of claims 1-11, wherein the antibody, or an antigen-binding portion thereof, is a human, humanized, or chimeric antibody.

13. The antibody of any one of claims 1-12, wherein the antibody, or an antigen-binding portion thereof, comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids

having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 128, and a light chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 130.

14. The antibody of any one of claims 1-12, wherein the antibody, or an antigen-binding portion thereof, comprises:

(a) a heavy chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-15, and conservative substitutions thereof;

(b) a heavy chain variable region CDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-31, and conservative substitutions thereof;

(c) a heavy chain variable region CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-47, and conservative substitutions thereof;

(d) a light chain variable region CDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-62, and conservative substitutions thereof;

(e) a light chain variable region CDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 63-78, and conservative substitutions thereof; and

(f) a light chain variable region CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93, and conservative substitutions thereof.

15. The antibody of any one of claims 1-12, wherein the antibody, or an antigen-binding portion thereof, comprises:

(a) a heavy chain variable region CDR1 domain comprising an amino acid sequence at set forth in SEQ ID NO: 15, and conservative substitutions thereof;

(b) a heavy chain variable region CDR2 domain comprising an amino acid sequence at set forth in SEQ ID NO: 31, and conservative substitutions thereof;

(c) a heavy chain variable region CDR3 domain comprising an amino acid sequence at set forth in SEQ ID NO: 47, and conservative substitutions thereof;

(d) a light chain variable region CDR1 domain comprising an amino acid sequence at set forth in SEQ ID NO: 62, and conservative substitutions thereof;

(e) a light chain variable region CDR2 domain comprising an amino acid sequence at set forth in SEQ ID NO: 78, and conservative substitutions thereof; and

(f) a light chain variable region CDR3 domain comprising an amino acid sequence at set forth in SEQ ID NO: 93, and conservative substitutions thereof.

16. An anti-beta-Klotho antibody, or an antigen-binding portion thereof, comprising (a) HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-15, (b) HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93, and (c) HVR-H2 an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-31.

17. The antibody of claim 16, wherein the antibody, or an antigen-binding portion thereof, comprises (a) HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-15, (b) HVR-H2 an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-31, and (c) HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-47.

18. The antibody of claim 17, further comprising (a) HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-62, (b) HVR-L2 an amino acid sequence selected from the group consisting of SEQ ID NOs: 63-78, and (c) HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93.

19. The antibody of claim 18, wherein the antibody, or an antigen-binding portion thereof, comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 12, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 59, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 75, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 90.

20. The antibody of claim 18, wherein the antibody, or an antigen-binding portion thereof, comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 31, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 47, (d) HVR-L1

comprising the amino acid sequence of SEQ ID NO: 62, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 78, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 93.

21. The antibody of claim 20, wherein the antibody, or an antigen-binding portion thereof, comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130.

22. The antibody of claim 20, wherein the antibody, or an antigen-binding portion thereof, comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 129 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 131.

23. An anti-KLB antibody, or an antigen-binding portion thereof, that competitively inhibits binding of any antibody of claim 16-22.

24. The antibody of claim 23, wherein the antibody, or an antigen-binding portion thereof, binds the same epitope as the 12A11 or the 8C5 antibody.

25. The antibody of claim 23, wherein the antibody, or an antigen-binding portion thereof, binds to an epitope within the C-terminal domain of KLB.

26. The antibody of claim 25, wherein the antibody binds to a KLB epitope within a fragment of KLB consisting of the amino acid sequence SSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITAS (SEQ ID NO: 142).

27. An anti-KLB antibody, or an antigen-binding portion thereof, comprising (a) a heavy chain variable region having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 128; (b) a light chain variable region having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 130; and (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

28. The antibody of any one of claims 16-27, wherein the antibody is a bispecific antibody.

29. The antibody of claim 28, wherein the antibody comprises a variable domain that binds to FGFR1.

30. The antibody of claim 28, wherein FGFR1 is FGFR1c.

31. The antibody of claim 30, wherein the antibody binds to a fragment of FGFR1c consisting of the amino acid sequence KLHAVPAAKTVKFKCP (SEQ ID NO: 143) or FKPDHRIGGYKVRY (SEQ ID NO: 144).

32. The antibody of claim 30, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 136, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 137, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 138, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 139, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 140, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 141.

33. The antibody of claim 30, wherein the antibody comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 134.

34. The antibody of claim 30, wherein the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 133 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 135.

35. An isolated anti-KLB/anti-FGFR1 bispecific antibody comprising:

(a) a first antibody, or antigen binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 128, and the light chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 130; and

(b) a second antibody, or antigen binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 132, and the light chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 134.

36. An isolated anti-KLB/anti-FGFR1 bispecific antibody comprising:

(a) a first antibody, or antigen binding portion thereof, comprising a heavy chain region and a light chain region, wherein the heavy chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 129, and the light chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 131; and

(b) a second antibody, or antigen binding portion thereof, comprising a heavy chain region and a light chain region, wherein the heavy chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 133, and the light chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 135.

37. An isolated nucleic acid encoding the antibody of any one of claims 1-36.

38. A host cell comprising the nucleic acid of claim 37.

39. A method of producing an antibody comprising culturing the host cell of claim 38 so that the antibody is produced.

40. The method of claim 39, further comprising recovering the antibody from the host cell.

41. A pharmaceutical formulation comprising one or more antibodies of any one of claims 1-36 and a pharmaceutically acceptable carrier.

42. The pharmaceutical formulation of claim 41, further comprising an additional therapeutic agent.

43. The antibody of any one of claims 1-36 for use as a medicament.

44. The antibody of any one of claims 1-36 for use in treating a disorder selected from the group consisting of polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY), and aging and related diseases such as Alzheimer's disease, Parkinson's disease and ALS.

45. The antibody of any one of claims 1-36 for use in activating a KLB/FGFR1 receptor complex.

46. Use of the antibody of any one of claims 1-36 in the manufacture of a medicament for treatment of a metabolic disorder.

47. Use of the antibody of any one of claims 1-36 in the manufacture of a medicament for activating a KLB/FGFR1 receptor complex.

48. The use of claim 46, wherein the metabolic disorder is diabetes.

49. A method of treating an individual having a disease selected from the group consisting of polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), maturity onset diabetes of the young (MODY), and aging and related diseases such as Alzheimer's disease, Parkinson's disease and ALS, Bardet-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, Cohen syndrome, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), Carpenter syndrome, MOMO syndrome, Rubinstein-Taybi syndrome, fragile X syndrome and Börjeson-Forssman-Lehman syndrome, wherein the method comprises administering to the individual an effective amount of one or more antibodies of any one of claims 1-36.

50. The method of claim 49, wherein the disease is diabetes.

51. The method of claim 49, further comprising administering an additional therapeutic agent to the individual.

52. A method of activating a KLB-FGFR1 receptor complex in an individual comprising administering to the individual an effective amount of the antibody of any one of claims 1-36.

53. The antibody of any one of claims 1-36, wherein the antibody, or antigen binding portion thereof, activates the KLB-FGFR1c complex.

WHAT IS CLAIMED IS:

1. An isolated bispecific antibody, or an antigen-binding portion thereof, that binds to beta-Klotho (KLB) and Fibroblast Growth Factor Receptor 1 (FGFR1).

2. The antibody of claim 1, wherein the antibody, or an antigen-binding portion thereof, binds to the C-terminal domain of KLB or to a fragment of KLB comprising the amino acid sequence set forth in SEQ ID NO: 142.

3. The antibody of any one of claims 1-2, wherein the antibody, or an antigen-binding portion thereof, binds to an FGFR1 epitope within a fragment of FGFR1c comprising the amino acid sequence set forth in SEQ ID NO: 143 or SEQ ID NO: 144.

4. The antibody of any one of claims 1-3, wherein the antibody, or an antigen-binding portion thereof, (a) reduces blood glucose levels *in vivo*; (b) does not significantly affect bone density; or (c) does not significantly affect the liver.

5. The antibody of any one of claims 1-4, wherein the antibody, or an antigen-binding portion thereof, induces ERK and MEK phosphorylation in the liver at significantly lower levels than FGF21 induces.

6. The antibody of any one of claims 1-5, wherein the antibody, or an antigen-binding portion thereof, binds to KLB with a K_d from 10^{-8} M to 10^{-13} M or binds to FGFR1c with a K_d from 10 nM to about 10 μM.

7. The antibody of any one of claims 1-6, wherein the antibody, or an antigen-binding portion thereof, is a monoclonal antibody or is a human, humanized, or chimeric antibody.

8. The antibody of any one of claims 1-7, wherein the antibody, or an antigen-binding portion thereof, comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 128, and a light chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 130.

9. The antibody of any one of claims 1-7, wherein the antibody, or an antigen-binding portion thereof, comprises:

(a) a heavy chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-15, and conservative substitutions thereof;

(b) a heavy chain variable region CDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-31, and conservative substitutions thereof;

(c) a heavy chain variable region CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-47, and conservative substitutions thereof;

(d) a light chain variable region CDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-62, and conservative substitutions thereof;

(e) a light chain variable region CDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 63-78, and conservative substitutions thereof; and

(f) a light chain variable region CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93, and conservative substitutions thereof.

10. The antibody of any one of claims 1-9, wherein the antibody, or an antigen-binding portion thereof, comprises:

(a) a heavy chain variable region CDR1 domain comprising an amino acid sequence at set forth in SEQ ID NO: 15, and conservative substitutions thereof;

(b) a heavy chain variable region CDR2 domain comprising an amino acid sequence at set forth in SEQ ID NO: 31, and conservative substitutions thereof;

(c) a heavy chain variable region CDR3 domain comprising an amino acid sequence at set forth in SEQ ID NO: 47, and conservative substitutions thereof;

(d) a light chain variable region CDR1 domain comprising an amino acid sequence at set forth in SEQ ID NO: 62, and conservative substitutions thereof;

(e) a light chain variable region CDR2 domain comprising an amino acid sequence at set forth in SEQ ID NO: 78, and conservative substitutions thereof; and

(f) a light chain variable region CDR3 domain comprising an amino acid sequence at set forth in SEQ ID NO: 93, and conservative substitutions thereof.

11. An anti-beta-Klotho (KLB) antibody, or an antigen-binding portion thereof, comprising (a) HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-47 and, (b) HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93.

12. The antibody of claim 11, wherein the antibody, or an antigen-binding portion thereof, comprises (a) HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-15, (b) HVR-H2 an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-31, and (c) HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-47.

13. The antibody of claim 12, further comprising (a) HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-62, (b) HVR-L2 an amino acid sequence selected from the group consisting of SEQ ID NOs: 63-78, and (c) HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 79-93.

14. The antibody of claim 13, wherein the antibody, or an antigen-binding portion thereof, comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 12, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 28, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 59, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 75, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 90.

15. The antibody of claim 13, wherein the antibody, or an antigen-binding portion thereof, comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 15, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 31, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 47, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 62, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 78, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 93.

16. The antibody of claim 15, wherein the antibody, or an antigen-binding portion thereof, comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 130; or (a) a heavy chain comprising the

amino acid sequence of SEQ ID NO: 129 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 131.

17. An anti-KLB antibody, or an antigen-binding portion thereof, that competitively inhibits binding of any antibody of claim 11-16.

18. The antibody of claim 17, wherein the antibody, or an antigen-binding portion thereof, (a) binds the same epitope as the 12A11 or the 8C5 antibody; (b) binds to an epitope within the C-terminal domain of KLB; or (c) binds to a KLB epitope within a fragment of KLB consisting of the amino acid sequence SSPTRLAVIPWGVRKLLRWVRRNYGDMDIYITAS (SEQ ID NO: 142).

19. An anti-KLB antibody, or an antigen-binding portion thereof, comprising (a) a heavy chain variable region having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 128; (b) a light chain variable region having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 130; and (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

20. The antibody of any one of claims 11-19, wherein the antibody is a bispecific antibody.

21. The antibody of claim 20, wherein the antibody comprises a variable domain that binds to FGFR1.

22. The antibody of claim 21, wherein FGFR1 is FGFR1c.

23. The antibody of claim 22, wherein the antibody binds to a fragment of FGFR1c consisting of the amino acid sequence KLHAVPAAKTVKFKCP (SEQ ID NO: 143) or FKPDHRIGGYKVRY (SEQ ID NO: 144).

24. The antibody of claim 22 or 23, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 136, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 137, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 138, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 139, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 140, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 141.

25. The antibody of claim 22-24, wherein the antibody comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 134; or (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 133 and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 135.

26. An isolated anti-KLB/anti-FGFR1 bispecific antibody comprising:

(a) a first antibody, or antigen binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 128, and the light chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 130; and

(b) a second antibody, or antigen binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 132, and the light chain variable region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 134.

27. An isolated anti-KLB/anti-FGFR1 bispecific antibody comprising:

(a) a first antibody, or antigen binding portion thereof, comprising a heavy chain region and a light chain region, wherein the heavy chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 129, and the light chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 131; and

(b) a second antibody, or antigen binding portion thereof, comprising a heavy chain region and a light chain region, wherein the heavy chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 133, and the light chain region comprises amino acids having a sequence that is at least 95% identical to the sequence set forth in SEQ ID NO: 135.

28. An isolated nucleic acid encoding the antibody of any one of claims 1-27.

29. A host cell comprising the nucleic acid of claim 28.

30. A method of producing an antibody comprising culturing the host cell of claim 29 so that the antibody is produced.

31. The method of claim 30, further comprising recovering the antibody from the host cell.

32. A pharmaceutical formulation comprising one or more antibodies of any one of claims 1-27 and a pharmaceutically acceptable carrier.

33. The pharmaceutical formulation of claim 32, further comprising an additional therapeutic agent.

34. The antibody of any one of claims 1-27 for use as a medicament; for use in activating a KLB/FGFR1 receptor complex; for treatment of a metabolic disorder or for use in treating a disorder selected from the group consisting of polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY), and aging and related diseases such as Alzheimer's disease, Parkinson's disease and ALS, Bardet-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, Cohen syndrome, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), Carpenter syndrome, MOMO syndrome, Rubinstein-Taybi syndrome, fragile X syndrome and Börjeson-Forssman-Lehman syndrome.

35. The antibody of claim 34, wherein the disorder or metabolic disorder is diabetes.

36. Use of the antibody of any one of claims 1-27 in the manufacture of a medicament for activating a KLB/FGFR1 receptor complex; for treating a metabolic disorder or for treating a disorder selected from the group consisting of polycystic ovary syndrome (PCOS), metabolic syndrome (MetS), obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY), and aging and related diseases such as Alzheimer's disease, Parkinson's disease and ALS, Bardet-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, Cohen syndrome, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), Carpenter syndrome, MOMO syndrome, Rubinstein-Taybi syndrome, fragile X syndrome and Börjeson-Forssman-Lehman syndrome.

37. The use of claim 36, wherein the disorder or metabolic disorder is diabetes.

38. The antibody of any one of claims 1-27, wherein the antibody, or antigen binding portion thereof, activates the KLB-FGFR1c complex.