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 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, which binds to beta-Klotho (KLB) and Fibroblast Growth Factor Receptor 1 (FGFR1), wherein the bispecific antibody or antigen-binding portion thereof binds to a KLB epitope within a fragment of KLB consisting of the amino acid sequence set forth in SEQ ID NO: 142.

In certain embodiments, the antibody is a bispecific antibody. For example, and not by way of limitation, an isolated antibody of the present 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.

Disclosed is 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.

Disclosed is 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.

Disclosed is 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.

Disclosed is an anti-KLB antibody, or an antigen-binding portion thereof, that competitively inhibits binding of any antibody of the disclosure.

Disclosed is 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, there is provided an isolated nucleic acid encoding the bispecific antibody or antigen-binding portion thereof of the present disclosure. In another aspect, there is provided a host cell comprising a nucleic acid of the present disclosure. In yet another aspect, there is provided a method of producing an antibody comprising culturing a host cell of the present disclosure so that the antibody is produced and, optionally, recovering the antibody from the host cell. In certain embodiments, this method further comprises recovering the antibody from the host cell.

In one aspect, there is provided a pharmaceutical formulation comprising the bispecific antibody or antigen-binding portion thereof of the disclosure and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical formulation comprises an additional therapeutic agent.

In one aspect, there is provided the bispecific antibody or antigen-binding portion thereof of disclosure for use as a medicament; for use in treating a metabolic disorder or for use in treating a disorder selected from the group consisting of obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, and maturity onset diabetes of the young (MODY).

In one embodiment, the present disclosure provides an antibody of the 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 bispecific antibody or antigen-binding portion thereof of the disclosure in the manufacture of a medicament for treating a metabolic disorder or for treating a disorder selected from the group consisting of obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY).

In another aspect, there is provided use of the bispecific antibody or antigen-binding portion thereof of the disclosure in the manufacture of a medicament for reducing blood glucose or hepatic triglyceride levels in an individual having a disease selected from the group consisting of obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY).

In 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.

WHAT IS CLAIMED IS:

1. An isolated bispecific antibody, or an antigen-binding portion thereof, which binds to beta-Klotho (KLB) and Fibroblast Growth Factor Receptor 1 (FGFR1), wherein the bispecific antibody or antigen-binding portion thereof binds to a KLB epitope within a fragment of KLB consisting of the amino acid sequence set forth in SEQ ID NO: 142.

2. The isolated bispecific antibody or antigen-binding portion thereof of claim 1, which 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.

3. The isolated bispecific antibody or antigen-binding portion thereof of claim 1 or 2, which (a) reduces blood glucose levels *in vivo*; (b) does not significantly affect bone density; and/or (c) does not significantly affect the liver.

4. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-3,which induces ERK and MEK phosphorylation in the liver at significantly lower levels than FGF21 induces.

5. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-4, which binds to KLB with a K_d from 10^{-8} M to 10^{-13} M and/or binds to FGFR1c with a K_d from 10 nM to about 10 μM.

6. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-5, wherein the antibody, or an antigen-binding portion thereof, is a monoclonal antibody or is a human, humanized, or chimeric antibody.

7. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-6, comprising a first arm that comprises:

(a) a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises amino acids having the sequence set forth in SEQ ID NO: 128, and a light chain variable region comprises amino acids having the sequence set forth in SEQ ID NO: 130.

8. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-6, comprising a first arm that comprises:

(a) a heavy chain variable region comprising (i) a CDR1 (HVR-H1) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 12 and 15, and conservative substitutions thereof;

(ii) a CDR2 (HVR-H2) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 28 and 31, and conservative substitutions thereof;

(iii) a CDR3 (HVR-H3) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 39, 44 and 47, and conservative substitutions thereof; and/or

(b) a light chain variable region comprising (i) a CDR1 (HVR-L1) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 59 and 62, and conservative substitutions thereof;

(ii) a CDR2 (HVR-L2) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 70, 75 and 78, and conservative substitutions thereof; and

(iii) a CDR3 (HVR-L3) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 85, 90 and 93, and conservative substitutions thereof.

9. The isolated bispecific antibody of any one of claims 1-8, comprising a first arm that comprises:

(a) a heavy chain variable region CDR1 (HVR-H1) domain comprising the amino acid sequence at set forth in SEQ ID NO: 15, and conservative substitutions thereof;

(b) a heavy chain variable region CDR2 (HVR-H2) domain comprising the amino acid sequence at set forth in SEQ ID NO: 31, and conservative substitutions thereof;

(c) a heavy chain variable region CDR3 (HVR-H3) domain comprising the amino acid sequence at set forth in SEQ ID NO: 47, and conservative substitutions thereof;

(d) a light chain variable region CDR1 (HVR-L1) domain comprising the amino acid sequence at set forth in SEQ ID NO: 62, and conservative substitutions thereof;

(e) a light chain variable region CDR2 (HVR-L2) domain comprising the amino acid sequence at set forth in SEQ ID NO: 78, and conservative substitutions thereof; and

(f) a light chain variable region CDR3 (HVR-L3) domain comprising the amino acid sequence at set forth in SEQ ID NO: 93, and conservative substitutions thereof.

10. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-9, comprising a first arm that comprises:

(a) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 128 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 130, or

(b) a heavy chain region comprising the amino acid sequence set forth in SEQ ID NO: 129 and a light chain region comprising the amino acid sequence set forth in SEQ ID NO: 131.

11. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-10, comprising a second arm that comprises:

(a) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 132 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 134, or

(b) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 133 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 135.

12. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-9, comprising a second arm that comprises:

(a) a heavy chain variable region CDR1 (HVR-H1) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 136 and 152, and conservative substitutions thereof;

(b) a heavy chain variable region CDR2 (HVR-H2) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 137 and 153, and conservative substitutions thereof;

(c) a heavy chain variable region CDR3 (HVR-H3) domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 138 and 154, and conservative substitutions thereof;

(d) a light chain variable region CDR1 (HVR-L1) domain comprising the amino acid sequence set forth in SEQ ID NO: 139, and conservative substitutions thereof;

(e) a light chain variable region CDR2 (HVR-L2) domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and conservative substitutions thereof; and

(f) a light chain variable region CDR3 (HVR-L3) domain comprising the amino acid sequence set forth in SEQ ID NO: 141, and conservative substitutions thereof.

13. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-12, comprising a second arm that comprises:

(a) a heavy chain variable region CDR1 (HVR-H1) domain comprising the amino acid sequence set forth in SEQ ID NO: 136, and conservative substitutions thereof;

(b) a heavy chain variable region CDR2 (HVR-H2) domain comprising the amino acid sequence set forth in SEQ ID NO: 137, and conservative substitutions thereof;

(c) a heavy chain variable region CDR3 (HVR-H3) domain comprising the amino acid sequence set forth in SEQ ID NO: 138, and conservative substitutions thereof;

(d) a light chain variable region CDR1 (HVR-L1) domain comprising the amino acid sequence set forth in SEQ ID NO: 139, and conservative substitutions thereof;

(e) a light chain variable region CDR2 (HVR-L2) domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and conservative substitutions thereof; and

(f) a light chain variable region CDR3 (HVR-L3) domain comprising the amino acid sequence set forth in SEQ ID NO: 141, and conservative substitutions thereof.

14. An isolated nucleic acid encoding the bispecific antibody or antigen-binding portion thereof of any one of claims 1-13.

15. A host cell comprising the nucleic acid of claim 14.

16. A method of producing an antibody comprising culturing the host cell of claim 15 so that the antibody is produced and, optionally, recovering the antibody from the host cell.

17. A pharmaceutical formulation comprising the bispecific antibody or antigen-binding portion thereof of any one of claims 1-13 and a pharmaceutically acceptable carrier.

18. The pharmaceutical formulation of claim 17, further comprising an additional therapeutic agent.

19. The bispecific antibody or antigen-binding portion thereof of any one of claims 1-13 for use as a medicament; for use in treating a metabolic disorder or for use in treating a disorder selected from the group consisting of obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperlipidemia, hypertension, type 2 diabetes, non-type 2 diabetes, type 1 diabetes, and maturity onset diabetes of the young (MODY).

20. The bispecific antibody or antigen-binding portion thereof of claim 19, wherein the disorder or metabolic disorder is diabetes.

21. The bispecific antibody or antigen-binding portion thereof of claim 20, wherein the disorder or metabolic disorder is type II diabetes.

22. The bispecific antibody or antigen-binding portion thereof of claim 19, wherein the disorder or metabolic disorder is non-alcoholic steatohepatitis (NASH).

23. Use of the bispecific antibody or antigen-binding portion thereof of any one of claims 1-13 in the manufacture of a medicament for treating a metabolic disorder or for treating a disorder selected from the group consisting of obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY).

24. The use of claim 23, wherein the disorder or metabolic disorder is diabetes.

25. The use of claim of claim 24, wherein the disorder or metabolic disorder is type II diabetes.

26. The use of claim 24, wherein the disorder or metabolic disorder is non-alcoholic steatohepatitis (NASH).

27. Use of the bispecific antibody or antigen-binding portion thereof of any one of claims 1-13 in the manufacture of a medicament for reducing blood glucose or hepatic triglyceride levels in an individual having a disease selected from the group consisting of obesity, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, non-type 2 diabetes, type 1 diabetes, latent autoimmune diabetes (LAD), and maturity onset diabetes of the young (MODY).