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, comprises:

(a) a first arm comprising:

a heavy chain variable region CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a heavy chain variable region CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 31, a heavy chain variable region CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 47, a light chain variable region CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 62, a light chain variable region CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 78, and a light chain variable region CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 93; and

(b) a second arm comprising:

a heavy chain variable region CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136, a heavy chain variable region CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 137, a heavy chain variable region CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 138, a light chain variable region CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 139, a light chain variable region CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a light chain variable region CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 141.

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

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, comprises:

(a) a first arm comprising:

a heavy chain variable region CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 15, a heavy chain variable region CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 31, a heavy chain variable region CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 47, a light chain variable region CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 62, a light chain variable region CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 78, and a light chain variable region CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 93; and

(b) a second arm comprising:

a heavy chain variable region CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 136, a heavy chain variable region CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 137, a heavy chain variable region CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 138, a light chain variable region CDR1 domain comprising the amino acid sequence set forth in SEQ ID NO: 139, a light chain variable region CDR2 domain comprising the amino acid sequence set forth in SEQ ID NO: 140, and a light chain variable region CDR3 domain comprising the amino acid sequence set forth in SEQ ID NO: 141.

2. The isolated bispecific antibody or antigen-binding portion thereof of claim 1, wherein the bispecific antibody, or an antigen-binding portion thereof, is a monoclonal antibody or is a human, humanized, or chimeric antibody.

3. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-2, wherein the first arm comprises: (a) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 128 and (b) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 130.

4. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-3, wherein the first arm 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.

5. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-4, wherein the second arm comprises: (a) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 132 and (b) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 134.

6. The isolated bispecific antibody or antigen-binding portion thereof of any one of claims 1-5, wherein the second arm comprises: (a) a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 133 and (b) a light chain comprising the amino acid sequence set forth in SEQ ID NO: 135.

7. An isolated nucleic acid encoding the bispecific antibody or antigen-binding portion thereof of any one of claims 1-6.

8. A host cell comprising the nucleic acid of claim 7.

9. A method of producing an antibody comprising culturing the host cell of claim 8 so that the antibody is produced and, optionally, recovering the antibody from the host cell.

10. A pharmaceutical formulation comprising the bispecific antibody or antigen-binding portion thereof of any one of claims 1-6 and a pharmaceutically acceptable carrier.

11. The pharmaceutical formulation of claim 10, further comprising an additional therapeutic agent.

12. The bispecific antibody or antigen-binding portion thereof of any one of claims 1-6 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).

13. The bispecific antibody or antigen-binding portion thereof of claim 12, wherein the disorder or metabolic disorder is diabetes.

14. The bispecific antibody or antigen-binding portion thereof of claim 13, wherein the disorder or metabolic disorder is type 2 diabetes.

15. The bispecific antibody or antigen-binding portion thereof of claim 12, wherein the disorder or metabolic disorder is non-alcoholic steatohepatitis (NASH).

16. Use of the bispecific antibody or antigen-binding portion thereof of any one of claims 1-6 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).

17. The use of claim 16, wherein the disorder or metabolic disorder is diabetes.

18. The use of claim 16, wherein the disorder or metabolic disorder is type 2 diabetes.

19. The use of claim 16, wherein the disorder or metabolic disorder is non-alcoholic steatohepatitis (NASH).

20. Use of the bispecific antibody or antigen-binding portion thereof of any one of claims 1-6 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).