SUMMARY

The disclosureinvention is based, in part, on the discovery that activation of FGFR1 ameliorates diabetes. The disclosureinvention provides FGFR1 agonists, including agonist anti-FGFR1 antibodies and methods of using the same.

Disclosed isIn one aspect, the invention provides a method of treating a metabolic disease or condition in an individual, comprising administering to the individual an effective amount of an anti-fibroblast growth factor receptor-1 (FGFR1) agonist, wherein the metabolic disease is 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 fo the young (MODY). In some embodiments, the FGFR1 agonist does not activate FGFR2 or FGFR3. In some embodiments, the FGFR1 agonist is an anti-FGFR1 antibody. In some embodiments, the anti-FGFR1 antibody has two FGFR1-binding sites, e.g. a full-length antibody or a F(ab')2 fragment. In some embodiments, the antibody binds to peptide #26 KLHAVPAAKTVKFKCP (SEQ ID NO: 28) or peptide #28 FKPDHRIGGYKVRY (SEQ ID NO: 29). In some embodiments, the antibody binds to both peptide #26 and peptide #28. In some embodiments, the anti-FGFR1 antibody binds to both FGFR1b and FGFR1c. In some embodiments, the antibody is a bispecific antibody. In some embodiments, the bispecific antibody also binds to beta-Klotho.

In one aspect, there is provided an isolated antibody that binds to FGFR1, wherein the antibody is an agonist of FGFR1 activity and wherein the antibody binds to peptide #26 KLHAVPAAKTVKFKCP (SEQ ID NO: 28) or peptide #28 FKPDHRIGGYKVRY (SEQ ID NO: 29). Disclosed isIn another aspect, the invention provides an isolated antibody that binds to FGFR1, wherein the antibody is an agonist of FGFR1 activity. In some embodiments, the antibody is not an agonist of FGFR2 or FGFR3. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a human, humanized, or chimeric antibody. In some embodiments, the antibody comprises (a) HVR-H3 comprising an amino acid sequence selected from the group consisting of SSGYGGSDYAMDY (SEQ ID NO: 16), SGYGGSDYAMDY (SEQ ID NO: 17), EHFDAWVHYYVMDY (SEQ ID NO: 18), TGTDVMDY (SEQ ID NO: 19), and GTDVMDY (SEQ ID NO: 20), (b) HVR-L3 comprising

the amino acid sequence QQSYTTPPT (SEQ ID NO: 23), and (c) HVR-H2 comprising an amino acid sequence selected from the group consisting of $X_1X_2IX_3PX_4DGX_5TX_6YADSVKG$, wherein X_1 is A or G, X_2 is D or E, X_3 is D or Y, X_4 is N or Y, X_5 is A or D, and X_6 is D or Y (SEQ ID NO: 24) and $X_1IX_2PX_3DGX_4TX_5YADSVKG$, wherein X_1 is D or E, X_2 is D or Y, X_3 is N or Y, X_4 is A or D, and X_5 is D or Y (SEQ ID NO: 25). In some embodiments, the

antibody comprises (a) HVR-H1 comprising the amino acid sequence GFTFX$_1$X$_2$X$_3$X$_4$IX$_5$, wherein X$_1$ is S or T, X$_2$ is N or S, X$_3$ is N or T, X$_4$ is W or Y, X$_5$ is H or S (SEQ ID NO: 26), (b) HVR-H2 comprising an amino acid sequence selected from the group consisting of X$_1$X$_2$IX$_3$PX$_4$DGX$_5$TX$_6$YADSVKG, wherein X$_1$ is A or G, X$_2$ is D or E, X$_3$ is D or Y, X$_4$ is N or Y, X$_5$ is A or D, and X$_6$ is D or Y (SEQ ID NO: 24) and X$_1$IX$_2$PX$_3$DGX$_4$TX$_5$YADSVKG, wherein X$_1$ is D or E, X$_2$ is D or Y, X$_3$ is N or Y, X$_4$ is A or D, and X$_5$ is D or Y (SEQ ID NO: 25), and (c) HVR-H3 comprising an amino acid sequence selected from the group consisting of SSGYGGSDYAMDY (SEQ ID NO: 16), SGYGGSDYAMDY (SEQ ID NO: 17), EHFDAWVHYYVMDY (SEQ ID NO: 18), TGTDVMDY (SEQ ID NO: 19), and GTDVMDY (SEQ ID NO: 20). In some embodiments, the antibody comprises (a) HVR-H1 comprising the amino acid sequence GFTFTSTWIS (SEQ ID NO: 7), (b) HVR-H2 comprising an amino acid sequence selected from the group consisting of GEIDPYDGDTYYADSVKG (SEQ ID NO: 10) and EIDPYDGDTYYADSVKG (SEQ ID NO: 11), and (c) HVR-H3 comprising an amino acid sequence selected from the group consisting of SSGYGGSDYAMDY (SEQ ID NO: 16) and SGYGGSDYAMDY (SEQ ID NO: 17). In some embodiments, the antibody comprises (a) HVR-H1 comprising the amino acid sequence GFTFSNNYIH (SEQ ID NO: 8), (b) HVR-H2 comprising an amino acid sequence selected from the group consisting of ADIYPNDGDTDYADSVKG (SEQ ID NO: 12) and DIYPNDGDTDYADSVKG (SEQ ID NO: 13), and (c) HVR-H3 comprising the amino acid sequence EHFDAWVHYYVMDY (SEQ ID NO: 18). In some embodiments, the antibody comprises (a) HVR-H1 comprising the amino acid sequence GFTFTSNWIS (SEQ ID NO: 9), (b) HVR-H2 comprising an amino acid sequence selected from the group consisting of AEIDPYDGATDYADSVKG (SEQ ID NO: 14) and EIDPYDGATDYADSVKG (SEQ ID NO: 15), and (c) HVR-H3 comprising an amino acid sequence selected from the group consisting of TGTDVMDY (SEQ ID NO: 19) and GTDVMDY (SEQ ID NO: 20). In some embodiments, the antibody further comprises (a) HVR-L1 comprising the amino acid sequence RASQDVSTAVA (SEQ ID NO: 21); (b) HVR-L2 comprising the amino acid sequence SASFLYS (SEQ ID NO: 22); and (c) HVR-L3 comprising the amino acid sequence QQSYTTPPT (SEQ ID NO: 23). In some embodiments, the antibody comprises a VH sequence selected from the group consisting of SEQ ID NO: 2, 3 and 4. In some embodiments, the antibody comprises a VL sequence of SEQ ID NO: 6.

In some embodiments, the anti-FGFR1 antibody has two FGFR1-binding sites, e.g. a full-length antibody or a F(ab')2 fragment . In some embodiments, the antibody of the disclosure~~invention~~ is a multispecific antibody. In some embodiments, the antibody also binds to beta-

Klotho. In some embodiments, the antibody is an IgG1 antibody. In another aspect, there is provided an isolated nucleic acid encoding the antibody described herein. In some embodiments, the disclosure~~invention~~ provides an isolated nucleic acid encoding an antibody of the disclosure~~invention~~. In another aspect, there is~~In some embodiments, the invention~~ provides~~d~~ a host cell comprising the nucleic acid described herein~~of claim 21~~. In another aspect, there is~~In some embodiments, the invention~~ provides~~d~~ a method of producing an antibody comprising culturing the host cell described herein~~of claim 22~~ so that the antibody is produced. In some embodiments, the method further comprises recovering the antibody from the host cell.

In another aspect, there is~~some embodiments, the invention~~ provides~~d~~ a pharmaceutical formulation comprising an antibody described herein~~of the invention~~ and a pharmaceutically acceptable carrier.

In another aspect, there is~~some embodiments, the invention~~ provides~~d~~ an antibody described herein~~of the invention~~ for use as a medicament. In another aspect, there is provided~~some embodiments,~~ the antibody described herein~~of the invention is~~ for use in treating a metabolic disease or condition 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 fo the young (MODY). In another aspect, there is provided~~some embodiments,~~ the antibody described herein~~of the invention is~~ for use in sensitizing an individual to insulin.

In another aspect, there is provided use of the antibody described herein in the manufacture of a medicament for treatment of a metabolic disease or condition 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). In some embodiments, the disclosure~~invention~~ provides use of an antibody of the disclosure~~invention~~ in the manufacture of a medicament. In some embodiments, the medicament is for treatment of a metabolic disease or condition 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 fo the young (MODY). In another aspect, there is provided use of the antibody described herein in the manufacture of a medicament for sensitizing an individual to insulin. In some embodiments, the medicament is for sensitizing an individual to insulin.

In another aspect, there is provided use of the antibody described herein in the manufacture of a medicament for treating diabetes in an individual. In some embodiments, the disclosure~~invention~~ provides a method of treating diabetes in an individual, comprising administering to the individual an effective amount of an antibody of the disclosure~~invention~~. In some embodiments, the method further comprises administering to the individual another agent to treat diabetes provided that the other agent is not insulin. In some embodiments, the method further comprises administering to the individual an agent to treat cardiovascular disease.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A shows an ELISA measuring binding of anti-FGFR1 antibodies to purified FGFR ECD fragments.