CLAIMS

1. A compound comprising a modified oligonucleotide having the structure:

[oligo1]-[x-N]$_m$-x-[oligo2]

wherein:

oligo1 consists of 7 to 15 linked nucleosides and has a nucleobase sequence that is complementary to the nucleobase sequence of miR-103 and/or miR-107 with no more than 1 mismatch;

oligo2 consists of 7 to 15 linked nucleosides and has a nucleobase sequence that is complementary to the nucleobase sequence of miR-103 and/or miR-107 with no more than 1 mismatch;

each x is independently selected from a phosphodiester bond and a phosphorothioate bond;

each N is independently selected from a modified nucleoside and an unmodified nucleoside;

m is an integer from 1 to 5;

wherein at least one x is a phosphodiester bond.

2. The compound of claim 1, wherein the modified oligonucleotide consists of 15 to 32, 15 to 30, 15 to 28, 15 to 26, 15 to 24, or 15 to 22, or 15 to 20 nucleosides.

3. The compound of claim 1 or claim 2, wherein oligo1 has a nucleobase sequence that is 100% complementary to the nucleobase sequence of miR-103 and/or miR-107.

4. The compound of any one of the preceding claims, wherein oligo1 has a nucleobase sequence that is complementary to at least 6, at least 7, or 8 nucleotides of the seed region of miR-103 and/or miR-107.

5. The compound of any one of the preceding claims, wherein oligo2 has a nucleobase sequence that is 100% complementary to the nucleobase sequence of miR-103 and/or miR-107.

6. The compound of any one of the preceding claims, wherein oligo2 has a nucleobase sequence that is complementary to at least 6, at least 7, or 8 nucleotides of the seed region of miR-103 and/or miR-107.

7. The compound of any one of claims 1, 2, 4, and 6, wherein oligo1 has a mismatch with the first nucleotide at the 5' end of miR-103 and miR-107.

8. The compound of any one of claims 1, 2, 4, 6, and 7, wherein oligo2 has a mismatch with the first nucleotide at the 5' end of miR-103 and miR-107.

9. The compound of any one of the preceding claims, wherein at least 2 x are phosphodiester bonds, or wherein each x is a phosphodiester bond.

10. The compound of any one of the preceding claims, wherein at least one N is an unmodified nucleoside, or wherein each N is an unmodified nucleoside.

11. The compound of any one of the preceding claims, wherein m is 1, 2, 3, 4, or 5.

12. The compound of any one of the preceding claims, wherein the compound comprises a conjugate moiety linked to the 5' terminus or the 3' terminus of the modified oligonucleotide, or both.

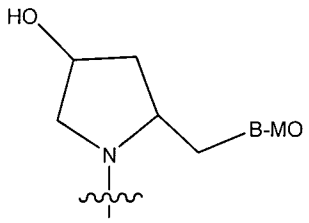
13. The compound of claim 12, wherein the compound comprises a conjugate moiety linked to the 5' terminus or the 3' terminus of the modified oligonucleotide, but not both.

14. The compound of claim 12 or claim 13, wherein the conjugate moiety comprises at least one ligand selected from a carbohydrate, cholesterol, a lipid, a phospholipid, an antibody, a lipoprotein, a hormone, a peptide, a vitamin, a steroid, and a cationic lipid.

15. The compound of any one of claims 12 to 14, wherein the compound has a structure selected from:

a) L_n-linker-MO
   wherein each L is, independently, a ligand and n is from 1 to 10; and MO is the modified oligonucleotide;
b) L_n-linker-X-MO
   wherein each L is, independently, a ligand and n is from 1 to 10; X is a phosphodiester linkage or a phosphorothioate linkage; and MO is the modified oligonucleotide; or
c) L_n-linker-X_1-N_m-X_2-MO
   wherein each L is, independently, a ligand and n is from 1 to 10; each N of N_m is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is the modified oligonucleotide.

16. The compound of claim 15, wherein the compound has the structure:



wherein:

B is selected from –O-, -S-, -N(R^N)-, –Z-P(Z')(Z")O-, –Z-P(Z')(Z")O-N_m-X-, and –Z-P(Z')(Z")O-N_m-Y-;

MO is the modified oligonucleotide;

R^N is selected from H, methyl, ethyl, propyl, isopropyl, butyl, and benzyl;

Z, Z', and Z" are each independently selected from O and S;

each N of N_m is, independently, a modified or unmodified nucleoside;

m is from 1 to 5;

X is selected from a phosphodiester linkage and a phosphorothioate linkage;

Y is a phosphodiester linkage; and

the wavy line indicates the connection to the rest of the linker and ligand(s).

17. The compound of claim 15 or claim 16, wherein X is a phosphodiester linkage.

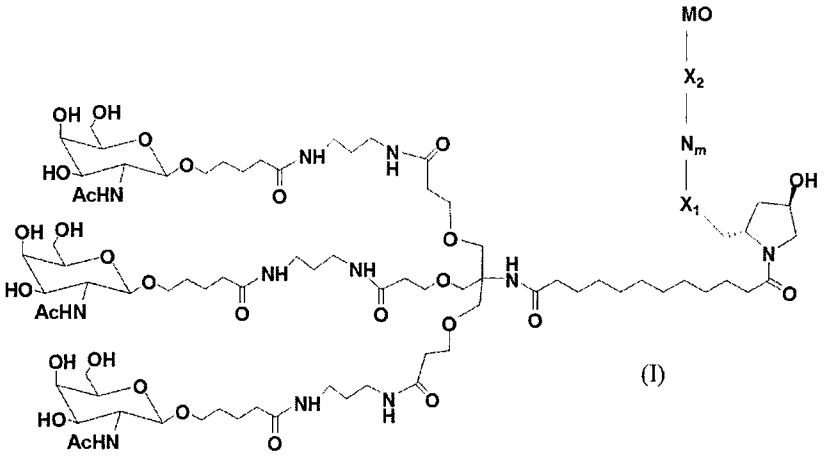
18. The compound of any one of claims 15 to 17, wherein n is from 1 to 5, 1 to 4, 1 to 3, or 1 to 2, or wherein n is 3.

19. The compound of any one of claims 15 to 18, wherein at least one ligand is selected from a carbohydrate, cholesterol, a lipid, a phospholipid, an antibody, a lipoprotein, a hormone, a peptide, a vitamin, a steroid, and a cationic lipid.

20. The compound of claim 19, wherein at least one ligand is a carbohydrate, wherein the carbohydrate is optionally selected from mannose, glucose, galactose, ribose, arabinose, fructose, fucose, xylose, D-mannose, L-mannose, D-galactose, L-galactose, D-glucose, L-glucose, D-ribose, L-ribose, D-arabinose, L-arabinose, D-fructose, L-fructose, D-fucose, L-fucose, D-xylose, L-xylose, alpha-D-mannofuranose, beta-D-mannofuranose, alpha-D-mannopyranose, beta-D-mannopyranose, alpha-D-glucofuranose, Beta-D-glucofuranose, alpha-D-glucopyranose, beta-D-glucopyranose, alpha-D-galactofuranose, beta-D-galactofuranose, alpha-D-galactopyranose, beta-D-galactopyranose, alpha-D-ribofuranose, beta-D-ribo-

furanose, alpha-D-ribopyranose, beta-D-ribopyranose, alpha-D-fructofuranose, alpha-D-fructopyranose, glucosamine, galactosamine, sialic acid, and N-acetylgalactosamine.

21. The compound of any one of claims 15 to 20, wherein the compound has the structure:



wherein each N of N_m is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is the modified oligonucleotide.

22. The compound of any one of the preceding claims, wherein oligo1 and/or oligo2 each consists of 7 to 15 linked nucleosides, 7 to 14 linked nucleosides, 7 to 13 linked nucleosides, 7 to 12 linked nucleosides, 7 to 11 linked nucleosides, 7 to 10 linked nucleosides, 8 to 15 linked nucleosides, 8 to 14 linked nucleosides, 8 to 13 linked nucleosides, 8 to 12 linked nucleosides, 8 to 11 linked nucleosides, 8 to 10 linked nucleosides, or 10 linked nucleosides.

23. The compound of claim 22, wherein oligo1 and/or oligo2 each comprises at least one nucleoside with a modified sugar moiety.

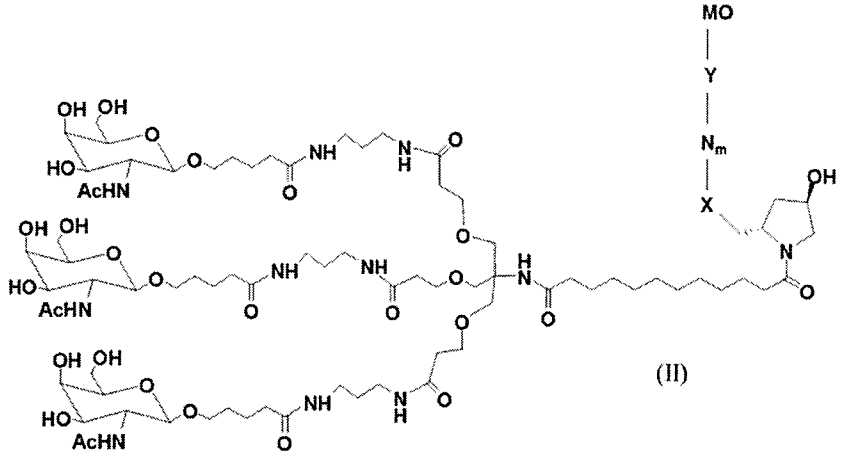
24. The compound of claim 22 or claim 23, wherein oligo1 and/or oligo2 each comprises at least one nucleoside with an unmodified sugar moiety.

25. The compound of any one of claims 22 to 24, wherein at least 4, at least 5, at least 6, at least 7, or at least 8 nucleosides of oligo1 and/or oligo2 have a modified sugar moiety, or wherein each nucleoside of oligo1 and/or oligo2 has a modified sugar moiety.

26. The compound of any one of claims 23 to 25, wherein each modified nucleoside is independently selected from a 2'-O-methyl sugar moiety, a 2'-O-methoxyethyl sugar moiety, a 2'-fluoro sugar moiety, and a bicyclic sugar moiety.

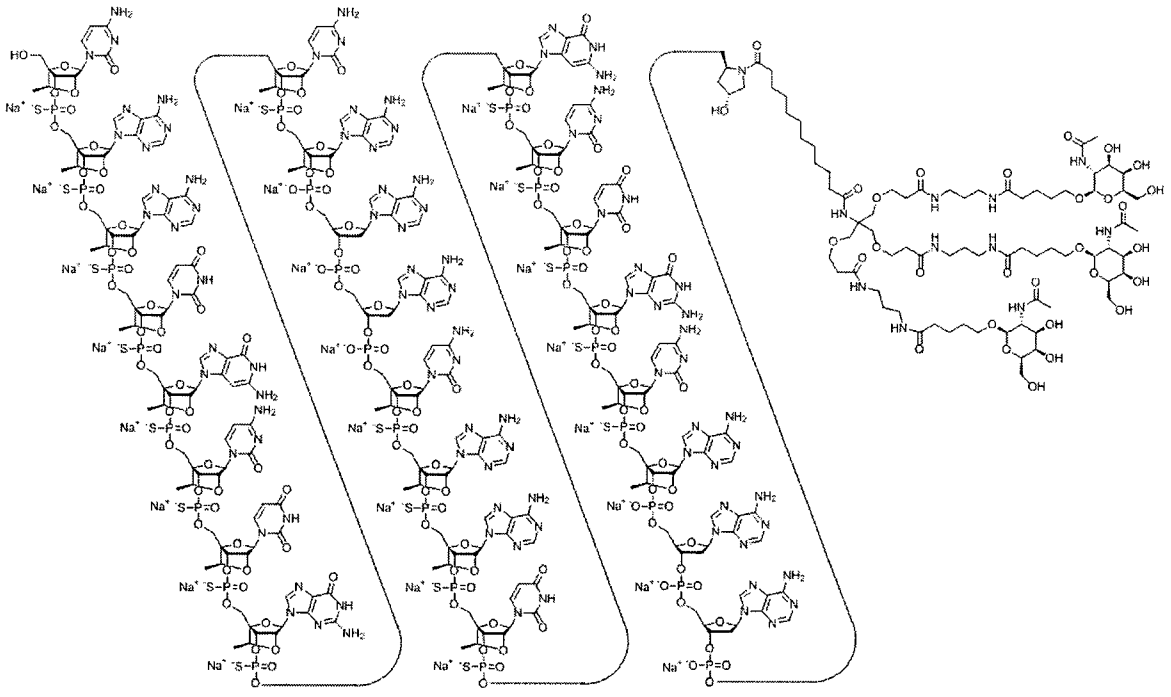
27. The compound of claim 26, wherein each bicyclic sugar moiety is independently selected from a cEt sugar moiety and an LNA sugar moiety.

28. A compound comprising the structure:



wherein X is a phosphodiester linkage; each N of N_m is a deoxyadenosine (A); m is 2; Y is a phosphodiester linkage; and MO is 5'-$C_SA_SA_SU_SG_SC_SU_SG_SC_SA_SAAC_SA_SA_SU_SG_SC_SU_SG_SC_SA_S$-3', wherein each nucleoside followed by a subscript "S" is a S-cEt nucleoside, each nucleoside not followed by a subscript is a deoxynucleoside, and each internucleoside linkage between two S-cEt nucleosides is a phosphorothioate linkage, and the remaining internucleoside linkages are phosphodiester linkages; and wherein Y is linked to the 3' terminus of MO.

29. A compound having the structure:



30. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable carrier.

31. The pharmaceutical composition of claim 30, which comprises 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg of the compound of claim 163.

32. The pharmaceutical composition of claim 30 or claim 31, which is an aqueous composition or a lyophilized composition.

33. A compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 for use in reducing a blood glucose level of a subject having an elevated blood glucose level or preventing or delaying the onset of an elevated blood glucose level in a subject at risk for developing an elevated glucose level.

34. A compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 for use in improving insulin sensitivity in a subject with insulin resistance or delaying the onset of

insulin resistance in a subject at risk for developing insulin resistance in a subject.

35. A compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 for use in improving glucose tolerance in a subject with impaired glucose tolerance.

36. A compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 for use in the treatment of at least one metabolic disorder in a subject or preventing or delaying the onset of at least one metabolic disorder in a subject, wherein the metabolic disorder is optionally selected from pre-diabetes, diabetes, metabolic syndrome, obesity, diabetic dyslipidemia, hyperlipdemia, hypertension, hypertriglyceridemia, hyperfattyacidemia, hypercholesterolemia, and hyperinsulinemia.

37. The compound of any one of claims 33 to 36, wherein the subject has fatty liver disease, wherein the fatty liver disease is optionally selected from non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease, alcoholic steatohepatitis, and non-alcoholic steatohepatitis (NASH).

38. A compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 for use in the treatment of fatty liver disease wherein the fatty liver disease is optionally selected from non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease, alcoholic steatohepatitis, and non-alcoholic steatohepatitis (NASH).

39. A compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 for use in reducing liver triglycerides.

40. The compound of any one of claims 33 to 35 and 37 to 39, wherein the subject has a metabolic disorder selected from among pre-diabetes, diabetes, metabolic syndrome, obesity, diabetic dyslipidemia, hyperlipdemia, hypertension, hypertriglyceridemia, hyperfattyacidemia, hypercholesterolemia, and hyper-insulinemia.

41. The compound of any one of claims 33 to 40, wherein the use in the specified treatment comprises at least one additional therapy.

42. The compound of claim 41, wherein the at least one additional therapy is a glucose-lowering agent or a lipid lowering agent, wherein the glucose-lowing agent is optionally selected from a PPAR agonist (gamma, dual, or pan), a dipeptidyl peptidase (IV) inhibitor, a GLP-I analog, insulin or an insulin analog,

an insulin secretagogue, a SGLT2 inhibitor, a human amylin analog, a biguanide, an alpha-glucosidase inhibitor, a meglitinide, a thiazolidinedione, and sulfonylurea.

43. Use of a compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 in the manufacture of a medicament for the treatment of blood glucose level in a subject by reducing the blood glucose level in a subject, or preventing the elevation of an elevated blood glucose level in a subject.

44. Use of a compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 in the manufacture of a medicament for the treatment of a metabolic disorder, wherein the metabolic disorder is optionally selected from among pre-diabetes, diabetes, metabolic syndrome, obesity, diabetic dyslipidemia, hyperlipdemia, hypertension, hypertriglyceridemia, hyperfattyacidemia, hypercholesterolemia, and hyperinsulinemia.

45. Use of a compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 in the manufacture of a medicament for the treatment of fatty liver disease in a subject.

46. Use of a compound of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 30 to 32 in the manufacture of a medicament for the treatment of a subject with insulin resistance, elevated blood glucose levels or elevated HbA1c levels.

47. The use of claim 45, wherein the fatty liver disease is selected from non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease, alcoholic steatohepatitis, and non-alcoholic steatohepatitis (NASH).

48. The use of any one of claims 43 to 47, wherein the medicament once taken reduces the level of liver triglycerides in a subject.