We claim:

1. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of ketohexokinase (KHK) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from the nucleotide sequence of nucleotides 1209-1229 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

2. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of ketohexokinase (KHK) in a cell,

wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding KHK, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-5.

3. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of ketohexokinase (KHK) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 943-965; 788-810; 734-756; 1016-1038; 1013-1035; 1149-1171; 574-596; 1207-1229 or 828-850 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

4. The dsRNA agent of any one of claims 1-3, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-252498.1, AD-252339.1, AD-252285.1, AD-252531.1, AD-254265.1, AD-254403.1, AD-252627.1, AD-252146.1, AD-252666.1 and AD-252379.1.

5. The dsRNA agent of any one of claims 1-4, wherein the dsRNA agent comprises at least one modified nucleotide.

6. The dsRNA agent of any one of claims 1-5, wherein all of the nucleotides of the sense strand comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

7. The dsRNA agent of any one of claims 4-6, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3’-terminal deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2’-amino-modified nucleotide, a 2’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, a nucleotide comprising a 5’-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

8. The dsRNA agent of any one of claims 4-6, wherein the modifications on the nucleotides are selected from the group consisting of LNA, HNA, GNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2′-deoxy, 2’-hydroxyl, and glycol; and combinations thereof.

9. The dsRNA of any one of claims 4-6, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), and, a vinyl-phosphonate nucleotide; and combinations thereof.

10. The dsRNA of any one of claims 4-6, wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.

11. The dsRNA of claim 10, wherein the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2’-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycerol nucleic acid (GNA).

12. The dsRNA agent of any one of claims 1-11, wherein the double stranded region is 19-30 nucleotide pairs in length.

13. The dsRNA agent of claim 12, wherein the double stranded region is 19-25 nucleotide pairs in length.

14. The dsRNA agent of claim 12, wherein the double stranded region is 19-23 nucleotide pairs in length.

15. The dsRNA agent of claim 12, wherein the double stranded region is 23-27 nucleotide pairs in length.

16. The dsRNA agent of claim 12, wherein the double stranded region is 21-23 nucleotide pairs in length.

17. The dsRNA agent of any one of claims 1-16, wherein each strand is independently no more than 30 nucleotides in length.

18. The dsRNA agent of any one of claims 1-17, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

19. The dsRNA agent of any one of claims 1-18, wherein the region of complementarity is at least 17 nucleotides in length.

20. The dsRNA agent of any one of claims 1-19, wherein the region of complementarity is between 19 and 23 nucleotides in length.

21. The dsRNA agent of any one of claims 1-18, wherein the region of complementarity is 19 nucleotides in length.

22. The dsRNA agent of any one of claims 1-21, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

23. The dsRNA agent of any one of claims 1-21, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

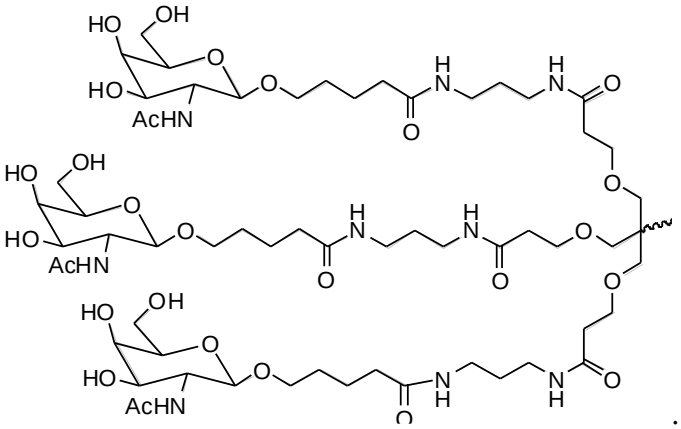
24. The dsRNA agent of any one of claims 1-23, further comprising a ligand.

25. The dsRNA agent of claim 24, wherein the ligand is conjugated to the 3’ end of the sense strand of the dsRNA agent.

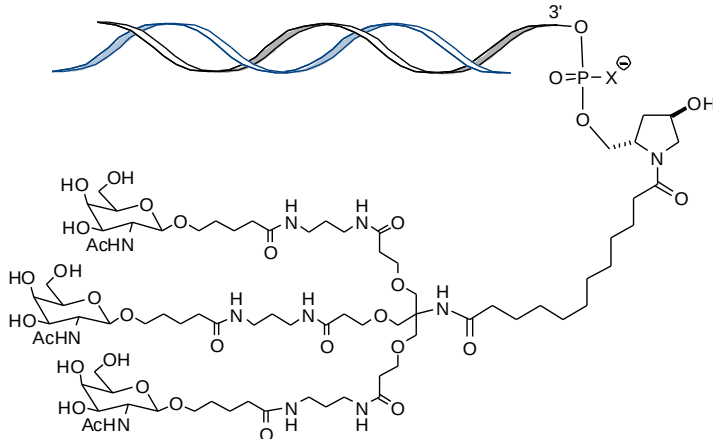
26. The dsRNA agent of claim 24 or 25, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

27. The dsRNA agent of any one of claims 24-26, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

28. The dsRNA agent of claim 26 or 27, wherein the ligand is



29. The dsRNA agent of claim 28, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

30. The dsRNA agent of claim 29, wherein the X is O.

31. The dsRNA agent of any one of claims 1-30, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

32. The dsRNA agent of claim 31, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

33. The dsRNA agent of claim 32, wherein the strand is the antisense strand.

34. The dsRNA agent of claim 32, wherein the strand is the sense strand.

35. The dsRNA agent of claim 31, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

36. The dsRNA agent of claim 35, wherein the strand is the antisense strand.

37. The dsRNA agent of claim 35, wherein the strand is the sense strand.

38. The dsRNA agent of claim 31, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand.

39. The dsRNA agent of claim 38, wherein the strand is the antisense strand.

40. The dsRNA agent of any one of claims 1-39, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

41. A cell containing the dsRNA agent of any one of claims 1-40.

42. A pharmaceutical composition for inhibiting expression of a gene encoding ketohexokinase (KHK) comprising the dsRNA agent of any one of claims 1-40.

43. The pharmaceutical composition of claim 42, wherein dsRNA agent is in an unbuffered solution.

44. The pharmaceutical composition of claim 43, wherein the unbuffered solution is saline or water.

45. The pharmaceutical composition of claim 42, wherein said dsRNA agent is in a buffer solution.

46. The pharmaceutical composition of claim 45, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

47. The pharmaceutical composition of claim 46, wherein the buffer solution is phosphate buffered saline (PBS).

48. Use of the dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47 in the manufacture of a medicament for inhibiting expression of a ketohexokinase (KHK) gene in a cell, wherein the cell is to be contacted with the dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47, thereby inhibiting expression of the KHK gene in the cell.

49. The use of claim 48, wherein the cell is within a subject.

50. The use of claim 49, wherein the subject is a human.

51. The use of claim 50, wherein the subject has a ketohexokinase (KHK)-associated disorder.

52. The use of any one of claims 48-51, wherein the cell that is to be contacted with the dsRNA agent inhibits the expression of ketohexokinase by at least 50%, 60%, 70%, 80%, 90%, or 95%.

53. The use of any one of claims 48-52, wherein inhibiting expression of ketohexokinase decreases ketohexokinase protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.

54. Use of the dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47 in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in ketohexokinase expression, wherein a therapeutically effective amount of the dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47 is to be administered to the subject, thereby treating the subject having the disorder that would benefit from reduction in ketohexokinase expression.

55. Use of the dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47 in the manufacture of a medicament for preventing at least one symptom in

a subject having a disorder that would benefit from reduction in ketohexokinase expression, wherein a prophylactically effective amount of the dsRNA agent of any one of claims 1-40, or the pharmaceutical composition of any one of claims 42-47 is to be administered to the subject, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in ketohexokinase expression.

56. The use of claim 54 or 55, wherein the disorder is a ketohexokinase-associated disorder.

57. The use of claim 56, wherein the KHK-associated disease comprises liver disease.

58. The use of claim 57, wherein the liver disease is non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

59. The use of claim 56, wherein the KHK-associated disease comprises dyslipidemia or abnormal lipid deposition or dysfunction.

60. The use of claim 59, wherein dyslipidemia comprises one or more of hyperlipidemia, high LDL cholesterol, low HDL cholesterol, hypertriglyceridemia, postprandial hypertriglyceridemia, adipocyte dysfunction, visceral adipose deposition, obesity, and metabolic syndrome.

61. The use of claim 56, wherein the KHK-associated disease comprises a disorder of glycemic control.

62. The use of claim 61, wherein the disorder of glycemic control comprises one or more of insulin resistance not related to immune response to insulin, type 2 diabetes, and glucose intolerance.

63. The use of claim 56, wherein the KHK-associated disease comprises kidney disease.

64. The use of claim 63, wherein the kidney disease comprises at least one of acute kidney disorder, tubular dysfunction, proinflammatory changes to the proximal tubules, and chronic kidney disease.

65. The use of claim 56, wherein the KHK-associated disease comprises cardiovascular disease.

66. The use of claim 65, wherein the cardiovascular disease comprises at least one of hypertension and endothelial cell dysfunction.

67. The use of any one of claims 54-66, wherein the subject is human.

68. The use of claim 67, wherein the subject has or is prone to compromised renal function.

69. The use of any one of claims 54-68, wherein the dsRNA agent is to be administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

70. The use of any one of claims 54-69, wherein the dsRNA agent is to be administered to the subject subcutaneously.

71. The use of any one of claims 54-70, wherein an agent for the treatment of a KHK-associated disease is to be further administered.

72. The use of any one of claims 54-71, further comprising determining the level of ketohexokinase in a sample(s) from the subject.

73. The use of claim 72, wherein the level of ketohexokinase in the subject sample(s) is a ketohexokinase protein level in a blood or serum sample(s).

74. The use of any one of claims 54-73, further comprising measuring a level of fructose metabolism in the subject.

75. The use of any one of claims 54-74, further comprising measuring a uric acid level in the subject.

76. The use of any one of claims 54-75, further comprising measuring a serum lipid level in the subject..

77. A kit comprising the dsRNA agent of any one of claims 1-40 or the pharmaceutical composition of any one of claims 42-47.

78. A vial comprising the dsRNA agent of any one of claims 1-40 or the pharmaceutical composition of any one of claims 42-47.

79. A syringe comprising the dsRNA agent of any one of claims 1-40 or the pharmaceutical composition of any one of claims 42-47.

80. The dsRNA agent of any one of claims 1-40 or the pharmaceutical composition of any one of claims 42-47 for use in therapy.