CLAIMS

1. A compound consisting of an antisense oligomer that is 16 to 22 contiguous nucleotides in length, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and wherein the antisense oligomer targets mRNA encoding PCSK9.
2. The compound of claim 1, wherein the LNA is oxy-LNA, thio-LNA, amino-5 LNA, 5'-methyl-LNA, ENA, cET, cMOE or a combination thereof.
3. The compound of claim 1, wherein the LNA is an stereoisomer in the beta-D- configuration or the alpha-L configuration.
4. The compound of claim 1, wherein the antisense oligomer comprises at least one cET unit.
5. The compound of claim 1, wherein the antisense oligomer comprises 2, 3, 4, 5, 6 or 7 LNA units.
6. The compound of claim 5, wherein every LNA unit in the antisense oligomer is a stereoisomer in the same configuration.
7. The compound of claim 5, wherein every LNA unit in the antisense oligomer is a beta-D-oxy LNA unit or every LNA unit in the antisense oligomer is an alpha-L-oxy-LNA unit.
8. The compound of claim 1, wherein the sequence of the antisense oligomer comprises at least one phosphorothioate, phosphorodithioate, or boranophosphate internucleoside linkage.
9. The compound of claim 8, wherein all the internucleoside linkages are phosphorothioate.
10. The compound of claim 8, wherein one or more of the internucleoside linkages comprises a chiral center in the R conformation and/or in the S conformation.
11. The compound of claim 1, wherein the compound and an oligomer of SEQ ID NO:31 can form a duplex with increased thermal stability with respect to a corresponding duplex comprising the corresponding antisense oligomer without LNA.
12. An antisense oligonucleotide conjugate comprising:

(i) an antisense oligomer that is 16 to 22 contiguous nucleotides, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, and wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and

(ii) at least one non-nucleotide or non-polynucleotide moiety covalently attached to said antisense oligomer directly or via a linker positioned between the contiguous oligomer sequence and the non-nucleotide or non-polynucleotide moiety,

wherein the antisense oligonucleotide conjugate targets mRNA encoding PCSK9.

13. The antisense oligonucleotide conjugate of claim 12, wherein the non-nucleotide or non-polynucleotide moiety is a liver targeting moiety that is attached to the 5'-end or to the 3'-end of the antisense oligomer.
14. The antisense oligonucleotide conjugate of claim 13, wherein the liver targeting moiety is linked to the antisense oligomer via a linker.
15. The antisense oligonucleotide conjugate of claim 13, wherein the liver targeting moiety comprises a carbohydrate conjugate moiety comprising a carbohydrate selected from the group consisting of galactose, lactose, N-acetylgalactosamine (GalNAc), mannose, mannose-6-phosphate, and combinations thereof.
16. The antisense oligonucleotide conjugate of claim 15, wherein the carbohydrate conjugate moiety is not a linear carbohydrate polymer.
17. The antisense oligonucleotide conjugate of claim 15, wherein the carbohydrate conjugate moiety is a carbohydrate group comprising 1, 2, 3, or 4 carbohydrate moieties.
18. The antisense oligonucleotide conjugate of claim 17, wherein the carbohydrate moieties are identical or non-identical.
19. The antisense oligonucleotide conjugate of claim 15, wherein the carbohydrate conjugate moiety comprises at least one asialoglycoprotein receptor targeting conjugate moiety.
20. The antisense oligonucleotide conjugate of claim 19, wherein the asialoglycoprotein receptor targeting conjugate moiety comprises a monovalent, divalent, trivalent, or tetravalent GalNAc cluster.

21. The antisense oligonucleotide conjugate of claim 20, wherein each GalNAc in the GalNAc cluster is attached to a branch point group via a spacer.
22. The antisense oligonucleotide conjugate of claim 21, wherein the branch point group comprises di-lysine.
23. The antisense oligonucleotide conjugate of claim 21, wherein the spacer comprises a PEG spacer.
24. The antisense oligonucleotide conjugate of claim 13, wherein the linker comprises a C6 to C12 amino alkyl group or a biocleavable phosphate nucleotide linker comprising between 1 to 6 nucleotides.
25. The antisense oligonucleotide conjugate of claim 20, wherein the trivalent GalNAc cluster comprises Conj 1, Conj 2, Conj 1a, or Conj 2a.
26. The antisense oligonucleotide conjugate of claim 12, wherein the non-nucleotide or non-polynucleotide moiety is covalently attached to the antisense oligomer via a covalent bond.
27. An antisense oligonucleotide conjugate of SEQ ID NO: 18 or SEQ ID NO:19



SEQ ID 18



SEQ ID 19

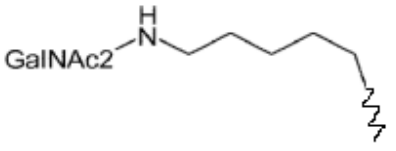
wherein

a superscript ^{L} identifies a beta-D-oxy LNA unit,

a ^{Me}C identifies a 5-methylcytosine unit,

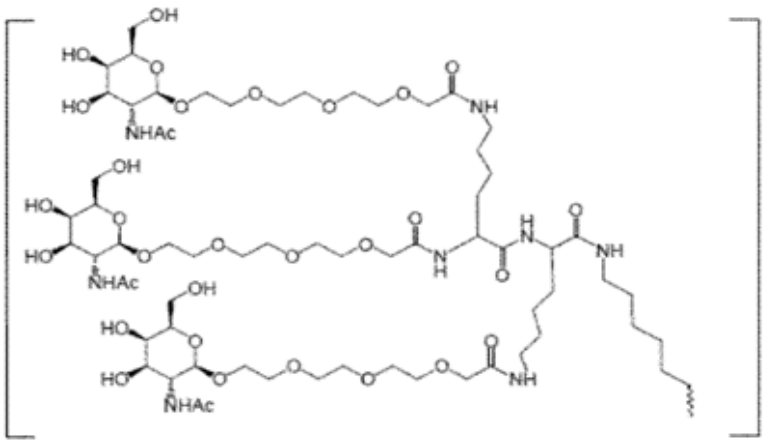
a subscript $_{s}$ identifies a phosphorothioate internucleoside linkage,

and wherein



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is a Conj 2a asialoglycoprotein receptor targeting conjugate moiety

Conj 2a= ,

and wherein the antisense oligonucleotide conjugate targets mRNA encoding PCSK9.

28. A pharmaceutical composition comprising a compound of claim 1 or an antisense oligonucleotide conjugate of claim 12 and a pharmaceutically acceptable diluent, carrier, salt, or adjuvant.

29. Use of a compound of any one of claims 1-11, an antisense oligonucleotide conjugate of any one of claims 12-27, or a pharmaceutical composition of claim 28 in the manufacture of a medicament for treating a disease or condition caused by abnormal expression levels and/or activity of PCSK9 in a subject in need thereof, wherein the abnormal levels and/or activity of PCSK9 are caused by a gene whose protein product is associated with or interacts with PCSK9, and wherein administration of the compound, antisense oligonucleotide conjugate, or pharmaceutical composition reduces the level of serum PCSK9 and/or reduces the level of serum LDL cholesterol.

30. The use of claim 29, wherein PCSK9 is

(i) a PCSK9 allelic variant;

(ii) a PCSK9 gain of function mutant; or,

(iii) an expression product of a mutant PCSK9 gene.

31. The use of claim 29, wherein the disease or condition is selected from the group consisting of atherosclerosis, hypercholesterolemia, HDL/LDL cholesterol imbalance, dyslipidemia, coronary artery disease (CAD), and coronary heart disease (CHD).

32. The use of claim 31, wherein the dyslipidemia is familial hyperlipidemia (FCHL) or acquired hyperlipidemia.
33. The use of claim 31, wherein the hypercholesterolemia is familiar hypercholesterolemia or statin resistant hypercholesterolemia.
34. The use of claim 29, wherein a second therapeutic agent selected from the group consisting of a statin, a bile sequestering resin, nicotinic acid, a fibric acid derivative, probucol, neomycin, dextrothyroxine, a plant stanol ester, a cholesterol absorption inhibitor, implitapide, an inhibitor of bile acid transporters, a regulator of hepatic CYP7a, an estrogen replacement therapeutic, and an anti-inflammatory is to be administered in the subject in need thereof.
35. The use of claim 34, wherein the statin is selected from the group consisting of lovastatin, cerivastatin, pravastatin, atorvastatin, simvastatin, rosuvastatin, and fluvastatin.
36. The use of claim 29, wherein the compound, antisense oligonucleotide conjugate, or pharmaceutical composition is to be administered intravenously or subcutaneously.
37. The use of claim 29, wherein the compound, antisense oligonucleotide conjugate, or pharmaceutical composition conjugate is to be administered as a single dose or as multiple doses.
38. Use of a compound of any one of claims 1-11, an antisense oligonucleotide conjugate of any one of claims 12-27, or a pharmaceutical composition of claim 28 in the manufacture of a medicament for treating a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, HDL/LDL cholesterol imbalance, coronary artery disease (CAD), or coronary heart disease (CHD) in a subject in need thereof.
39. An *in vitro* method of reducing expression levels and/or activity of PCSK9 in a cell comprising administering an effective amount of a compound of any one of claims 1-11, an antisense oligonucleotide conjugate of any one of claims 12-27, or a pharmaceutical composition of claim 28 to the cell.
40. Use of a compound of any one of claims 1-11, an antisense oligonucleotide conjugate of any one of claims 12-27, or a pharmaceutical composition of claim 28 in the manufacture of

a medicament for reducing expression levels and/or activity of PCSK9 in a subject in need thereof.

41. Use of a compound of any one of claims 1-11, an antisense oligonucleotide conjugate of any one of claims 12-27, or a pharmaceutical composition of claim 28 in the manufacture of a medicament for reducing cholesterol levels in a subject in need thereof.

42. A method of manufacturing a compound consisting of an antisense oligomer that is 16 to 26 contiguous nucleotides in length, the method comprising chemically synthesizing the compound using sequential solid phase oligonucleotide synthesis, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and wherein the antisense oligomer targets mRNA encoding PCSK9.

43. A method of manufacturing an antisense oligonucleotide conjugate comprising covalently attaching at least one non-nucleotide or non-polynucleotide moiety covalently to an antisense oligomer that is 16 to 26 contiguous nucleotides in length directly or via a linker positioned between the antisense oligomer sequence and the non-nucleotide or non-polynucleotide moiety, wherein the sequence of the antisense oligomer comprises a contiguous sequence 16 nucleotides in length which is 100% complementary to the sequence of SEQ ID NO: 31, wherein the antisense oligomer is a gapmer comprising at least one LNA unit, and wherein the antisense oligonucleotide conjugate targets mRNA encoding PCSK9.

44. The method of claim 43, wherein covalently attaching the at least one non-nucleotide or non-polynucleotide moiety to the antisense oligomer comprises:

(i) chemically synthesizing the antisense oligomer; and,

(ii) adding by chemical synthesis or conjugation the at least one non-nucleotide or non-polynucleotide moiety to the antisense oligonucleotide conjugate.

45. The method of claim 44, wherein adding by chemical synthesis or conjugation the at least one non-nucleotide or non-polynucleotide moiety to the antisense oligonucleotide conjugate comprises:

(i) incorporating by chemical synthesis or conjugation at least one non-nucleotide or non-polynucleotide moiety to the antisense oligonucleotide conjugate;

(ii) incorporating by chemical synthesis or conjugation at least one linker to the antisense oligonucleotide conjugate;

(iii) incorporating by chemical synthesis or conjugation at least one branching point to the antisense oligonucleotide conjugate;

(iv) incorporating by chemical synthesis or conjugation at least one spacer to the antisense oligonucleotide conjugate; or,

(v) a combination thereof.

46. The method of claim 45, wherein

(i) at least one linker is interposed between the antisense oligomer and a branching point.

(ii) at least one branching point is interposed between a linker and at least one non-nucleotide or non-polynucleotide moiety.

(iii) at least one, two, or three non-nucleotide or non-polynucleotide moieties are attached to a branching point.

(iv) at least one PEG spacer is interposed between a non-nucleotide or non-polynucleotide moieties and a branching point; or,

(v) any combination thereof.

47. The compound of any one of claims 1-11 or the method of claim 42, wherein the antisense oligomer is an intermediate in the synthesis of an antisense oligonucleotide conjugate comprising the antisense oligomer.

48. The compound of any one of claims 1-11, antisense oligonucleotide conjugate of any one of claims 12-27, pharmaceutical composition of claim 28, use of any one of claims 29-38, 40, 41, or method of any one of claims 39, 42 to 46, wherein the sequence of the antisense oligomer comprises or consists of SEQ ID NO*:* 26.

49. The compound of any one of claims 1-11, antisense oligonucleotide conjugate of any one of claims 12-27, pharmaceutical composition of claim 28, use of any one of claims 29-38, 40, 41, or method of any one of claims 39, 42 to 46, wherein the sequence of the antisense oligomer comprises or consists of SEQ ID NO: 2 or SEQ ID NO: 3.
50. The antisense oligonucleotide conjugate of any one of claims 12-27, pharmaceutical composition of claim 28, use of any one of claims 29-38, 40, 41, or method of any one of claims 39, 42 to 46, wherein the antisense oligonucleotide conjugate consists of SEQ ID NO: 18 or SEQ ID NO: 19.