Abstract:
Title: ANTISENSE OLIGOMERS AND CONJUGATES TARGETING PCSK9

The present invention relates to oligomeric compounds and conjugates thereof that target Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) mRNA in a cell, leading to reduced expression of PCSK9. Reduction of PCSK9 expression is beneficial for a range of medical disorders, such as hypercholesterolemia and related disorders.
1. An antisense oligonucleotide conjugate comprising
   a. an antisense oligomer (A) of between 12 - 22 nucleotides in length, which comprises a
      contiguous sequence of 10 - 16 nucleotides which are complementary to a corresponding
      length of SEQ ID NO 30 or 31 or 32 or 33 or 34 or 45, and
   b. at least one asialoglycoprotein receptor targeting conjugate moiety (C) covalently
      attached to said oligomer (A).
2. The oligonucleotide conjugate according to claim 0, wherein the antisense oligomer comprises
   a contiguous sequence selected from the group consisting of SEQ ID NO 25, 26, 27, 28, 29
   and 44.
3. The oligonucleotide conjugate according any one of claims 0 or 2, wherein the antisense
   oligomer targets PCSK9.
4. The oligonucleotide conjugate according to any one of the claims 0 to 3, wherein the antisense
   oligomer comprises a contiguous sequence selected from the group consisting of SEQ ID NO
   1, 2, 3, 4, 5, 6, 7, and 8.
5. The oligonucleotide conjugate according to any one of the claims 0 to 4, wherein the conjugate
   moiety (C) comprises an N-acetylgalactosamine (GalNAc), such as a mono-valent, di-valent,
   tri-valent of tetra-valent GalNAc.
6. The antisense oligonucleotide conjugate according to any one of claims 0 to 5, wherein the
   conjugate moiety (C) enhances delivery and/or uptake to liver cells.
7. The antisense oligonucleotide conjugate according to claim 0 to 6, wherein the conjugate
   moiety (C) comprises a trivalent GalNAc, such as those shown as Conj 1, 2, 3 or 4, or 1a, 2a,
   3a or 4a.
8. The antisense oligonucleotide conjugate according to claim 7, wherein the three GalNAc
   moieties are attached to a di-lysine branch point group via PEG spacers, such as those shown
   as Conj 1, 2, 1a or 2a.
9. The antisense oligonucleotide conjugate according to claim 7 or 7, wherein the conjugate
   moiety (C) comprises Conj 2a.
10. The antisense oligonucleotide conjugate according to any one of claims 0 to 9, which is
    selected from the group consisting of SEQ ID NO 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,
    21, 22, 23, and 24.
11. The antisense oligonucleotide conjugate according to any one of claims 0 to 10, wherein the antisense oligomer (A) is conjugated to the conjugate moiety (C) via a linker region positioned between the contiguous sequence of the oligomer and the conjugate moiety (B and/or Y).

12. The antisense oligonucleotide conjugate according to claim 11, wherein the linker is selected from a C6 to C12 amino alkyl groups.

13. The antisense oligonucleotide conjugate according to claim 11, wherein the linker is a biocleavable phosphate nucleotide linker comprising between 1 to 6 nucleotides.

14. An oligomer of between 12 - 22 nucleotides in length, which either comprises
   a. a contiguous sequence of 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31, or
   b. a contiguous sequence of 10 - 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 33 or 34 or 45.

15. The oligomer according to claim 14, which comprises a contiguous sequence selected from the group consisting of SEQ ID NO 26, 27, 28, 29 and 44.

16. The oligomer according any one of claims 14 or 15, wherein the oligomer targets PCSK9.

17. The oligomer according to any one of claims 14 to 16 wherein the contiguous sequence comprises affinity enhancing nucleotide analogues.

18. The oligomer according to any one of claims 14 to 17, which is a gapmer.

19. The oligomer according to any one of claims 14 to 18, wherein the oligomer comprises a contiguous sequence of 13, 14, 15 or 16 nucleotides.

20. The oligomer according to any one of claims 14 to 19, wherein the oligomer comprises one or more nucleoside linkages selected from the group consisting of phosphorothioate, phosphorodithioate and boranophosphate.

21. Then oligomer according to any one of claims 14 to 20, which comprises a contiguous sequence selected from the group consisting of SEQ ID NO 2, 3, 4, 5, 6, 7, and 8.

22. A pharmaceutical composition comprising the oligomer or antisense oligonucleotide conjugate according to any one of claims 0 to 21 and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

23. The oligomer or antisense oligonucleotide conjugate or pharmaceutical composition according to any one of claims 0 to 22, for use as a medicament, such as for the treatment of hypercholesterolemia or related disorder, such as a disorder selected from the group
consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, familiar hypercholesterolemia e.g. gain of function mutations in PCSK9, HDL/LDL cholesterol imbalance, dyslipidemias, e.g., familial hyperlipidemia (FCHL) or familial hypercholesterolemia (FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD).

24. The use of an oligomer or antisense oligonucleotide conjugate or pharmaceutical composition according to any one of the claims 0 to 22, for the manufacture of a medicament for the treatment of hypercholesterolemia or a related disorder, such as a disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, familial hypercholesterolemia e.g. gain of function mutations in PCSK9, HDL/LDL cholesterol imbalance, dyslipidemias, e.g., familial hyperlipidemia (FCHL) or familial hypercholesterolemia(FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD).

25. A method of treating hypercholesterolemia or a related disorder, such as a disorder selected from the group consisting atherosclerosis, hyperlipidemia, hypercholesterolemia, familial hypercholesterolemia e.g. gain of function mutations in PCSK9, HDL/LDL cholesterol imbalance, dyslipidemias, e.g., familial hypercholesterolemia(FHC), acquired hyperlipidemia, statin-resistant hypercholesterolemia, coronary artery disease (CAD), and coronary heart disease (CHD), said method comprising administering an effective amount of an oligomer or antisense oligonucleotide conjugate or pharmaceutical composition according to any one of the claims 0 to 22, to a patient suffering from, or likely to suffer from hypercholesterolemia or a related disorder.

26. A in vivo or in vitro method for the inhibition of PCSK9 in a cell which is expressing PCSK9, said method comprising administering an oligomer or antisense oligonucleotide conjugate or pharmaceutical composition according to any one of the claims 0 to 22 to said cell.