SUMMARY ~~OF INVENTION~~

The oligomer ~~of the invention~~ as described herein may comprise between 10 – 22, such as 12 - 18 nucleotides in length, which either comprises a) contiguous sequence of 10 – 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 33 or 34 or 45, or b) a contiguous sequence of 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31. In one aspect, there is provided an oligomer of between 12 - 22 nucleotides in length, which comprises a contiguous sequence of 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31.

The ~~invention~~ disclosure provides for an antisense oligonucleotide conjugate comprising the oligomer as described herein~~according to the invention~~, and at least one non-nucleotide or non-polynucleotide moiety covalently attached to said oligomer.

The ~~invention~~ disclosure also provides for an antisense oligonucleotide conjugate comprising the oligomer (A) ~~according to the~~ as described herein~~invention~~, and at least one non-nucleotide or non-polynucleotide moiety covalently attached to said oligomer (C), optionally via a linker region (B and/or Y) positioned between the contiguous sequence of the oligomer and the conjugate moiety.

In another aspect, there is provided 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).

In some embodiments, the ~~invention~~ disclosure also provides for an antisense oligonucleotide conjugate comprising an oligomer of 10 – 22, such as 12 - 18 nucleotides in length, wherein said oligomer comprises a) a contiguous sequence of 10 – 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 33 or 34, or 45 or b) a contiguous sequence of 16 nucleotides which are complementary to a corresponding length of SEQ ID NO 31.

The ~~invention~~ disclosure also provides for a compound selected from the group consisting of SEQ ID NO 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 16, 18, 19, 20, 21, 22, 23, and 24.

The ~~invention~~ disclosure provides for a pharmaceutical composition comprising the oligomer or the conjugate ~~according to the invention~~as described herein, and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

In another aspect, there is provided a pharmaceutical composition comprising the oligomer or antisense oligonucleotide conjugate as described herein and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

The ~~invention~~ disclosure provides for an oligomer or conjugate or pharmaceutical composition ~~according to the invention~~as described herein, 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).

In another aspect, there is provided the oligomer or antisense oligonucleotide conjugate or pharmaceutical composition as described herein, 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).

The ~~invention~~ disclosure provides for the use of an oligomer or conjugate or pharmaceutical composition ~~of the invention~~as described herein, 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, 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).

In another aspect, there is provided the use of an oligomer or antisense oligonucleotide conjugate or pharmaceutical composition as described herein, 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, 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).

The ~~invention~~ disclosure provides for a method of treating hypercholesterolemia or a related disorder, such as a disorder selected from the group consisting 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), said method comprising administering an effective amount of an oligomer or conjugate or pharmaceutical composition according to the invention, to a patient suffering from, or likely to suffer from hypercholesterolemia or a related disorder.

The ~~invention~~ disclosure provides for an *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 conjugate or pharmaceutical composition ~~according to the invention~~as described herein to said cell so as to inhibit PCSK9 in said cell.

In another aspect, there is provided an *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 as described herein to said cell.

The ~~invention~~ disclosure also provides for an oligomer ~~according to the invention~~as described herein, such as an LNA oligomer, comprising a contiguous region of 10 – 22, such as 12 – 18, such as 13, 14, 15, 16 or 17 phosphorothioate linked nucleosides, (i.e. region A, which typically is complementary to a corresponding region of the target sequence, such as SEQ ID NO 46) and further comprising between 1 and 6 DNA nucleosides which are contiguous with the LNA oligomer, wherein the inter-nucleoside linkages between the DNA, and/or adjacent to the DNA nucleoside(s), is physiologically labile, such as is / are phosphodiester linkages. Such an LNA oligomer may be in the form of a conjugate, as described herein, or may, for example be an intermediate to be used in a subsequent conjugation step. When conjugated, the conjugate may, for example be or comprise a sterol, such as cholesterol or tocopherol, or may be or

comprise a (non-nucleotide) carbohydrate, such as a GalNAc conjugate, or another conjugate as described herein.

The ~~invention~~ disclosure also provides a gapmer oligomer which comprises at least one cET, such as (S)-cET nucleotides, of between 10 – 22, such as 12 – 18, such as 13, 14, 15, 16 or 17 nucleotides in length, which targets (*i.e.* has a sequence which is complementary to a corresponding part of) human PCSK9.

BRIEF DESCRIPTION OF FIGURES

Figure 1: Examples of tri-GalNAc conjugates which may be used. Conjugates 1 – 4 illustrate 4 suitable GalNAc conjugate moieties, and conjugates 1a – 4a refer to the same conjugates with an additional linker moiety (Y) which is used to link the conjugate to the oligomer (region A or to

CLAIMS

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 1, 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 1 or 2, wherein the antisense oligomer targets PCSK9.
4. The oligonucleotide conjugate according to any one of the claims 1 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 1 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 1 to 5, wherein the conjugate moiety (C) enhances delivery and/or uptake to liver cells.
7. The antisense oligonucleotide conjugate according to claim 1 to 6, wherein the conjugate moiety (C) comprises a trivalent GalNAc.
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 8, wherein the conjugate moiety (C) comprises Conj 2a.
10. The antisense oligonucleotide conjugate according to any one of claims ~~0~~ 1 to 9, which is selected from the group consisting of SEQ ID NO 17, 18, 19, 20, 21, 22, 23, and 24.