

medicament for the treatment of a disease, disorder or condition associated with ANGPTL3 expression.

[0037] In some examples, the oligonucleotide of the disclosure, or the pharmaceutical composition of the disclosure, is for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with ANGPTL3 expression.

[0038] In a further example, the oligonucleotide of the present disclosure is provided in the form of a kit for treating a disease, disorder or condition associated with ANGPTL3 expression. In some examples, the kit comprises an oligonucleotide herein, and a pharmaceutically acceptable carrier. In some examples, the kit further includes a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with ANGPTL3 expression.

[0039] In some examples of the use or kits, the disease, disorder or condition associated with ANGPTL3 expression is selected from the group consisting of hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, NASH, NAFLD, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia.

[0040] In some examples of the use or kits, the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

[0040a] In one aspect, the present disclosure refers to an RNAi oligonucleotide for reducing angiopoietin-like protein 3 (ANGPTL3) expression, the RNAi oligonucleotide comprising a sense strand forming a duplex region with an antisense strand, wherein the antisense strand comprises a nucleotide sequence as set forth in sequence: 5'-UUAUUGUGAACAUUUUUAUGG -3' (SEQ ID NO: 2); and the sense strand comprises a nucleotide sequence as set forth in sequence: 5'-UGUAUAACCUUCCAUUUUGAGGUAAGCAGCCGAAAGGCUGC -3' (SEQ ID NO: 1).

[0040b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the RNAi oligonucleotide in the disclosure and a pharmaceutically acceptable carrier, delivery agent, or excipient.

[0040c] In yet another aspect, the present disclosure refers to an *in vitro* method for reducing ANGPTL3 expression in a cell or a population of cells wherein the method comprises: contacting the cell or the population of cells with the oligonucleotide in the disclosure or the pharmaceutical composition in the disclosure, wherein reducing ANGPTL3 expression

comprises reducing an amount or a level of ANGPTL3 mRNA, an amount or a level of ANGPTL3 protein, or both.

[0040d] In yet another aspect, the present disclosure refers to use of the RNAi oligonucleotide in the disclosure or the pharmaceutical composition in the disclosure, in the manufacture of a medicament for treating a disease, disorder, or condition associated with ANGPTL3 expression, wherein the disease, disorder, or condition associated with ANGPTL3 expression is selected from the group consisting of: hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia, optionally wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.

[0040e] In yet another aspect, the present disclosure refers to a kit comprising the oligonucleotide of the disclosure, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with ANGPTL3 expression.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] FIG. 1 provides a graph depicting the percent (%) of ANGPTL3 mRNA in HuH-7 cells transfected with the indicated DsiRNAs relative to the % of ANGPTL3 mRNA control mock-treated cells.

[0042] FIG. 2 provides a graph depicting the percent (%) of ANGPTL3 mRNA in HuH-7 cells transfected with the indicated DsiRNAs relative to the % of ANGPTL3 mRNA control mock-treated cells.

[0043] FIG. 3 provides a schematic depicting the structure and chemical modification patterns of generic GalNAc-conjugated ANGPTL3 oligonucleotides.

[0044] FIG. 4 provides a graph depicting the percent (%) of ANGPTL3 mRNA in liver samples from mice treated with the indicated GalNAc-conjugated ANGPTL3 oligonucleotides relative to mice treated with phosphate buffered saline (PBS).

CLAIMS

What is claimed is:

1. An RNAi oligonucleotide for reducing angiopoietin-like protein 3 (ANGPTL3) expression, the RNAi oligonucleotide comprising a sense strand forming a duplex region with an antisense strand, wherein:

the antisense strand comprises a nucleotide sequence as set forth in sequence: 5'-UUAAUUGUGAACAUUUUUAUGG -3' (SEQ ID NO: 2); and

the sense strand comprises a nucleotide sequence as set forth in sequence: 5'-UGUAUAACCUUCCAUUUUGAGGUAAGCAGCCGAAAGGCUGC -3' (SEQ ID NO: 1).

2. The RNAi oligonucleotide of claim 1, wherein the RNAi oligonucleotide comprises at least one modified nucleotide .

3. The RNAi oligonucleotide of claim 2, wherein all nucleotides of the oligonucleotide are modified.

4. The RNAi oligonucleotide of any one of claims 1-3, wherein at least one modified nucleotide comprises a 2' modification.

5. The RNAi oligonucleotide of claim 4, wherein the 2' modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid.

6. The RNAi oligonucleotide of claim 5, wherein the 2' modification is selected from the group consisting of 2'-fluoro (2'-F) and 2'-O-methyl (2'-OMe).

7. The RNAi oligonucleotide of any one of claims 1-6, wherein the RNAi oligonucleotide comprises at least one modified internucleotide linkage.

8. The RNAi oligonucleotide of claim 7, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

9. The RNAi oligonucleotide of any one of claims 1-8, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog.
10. The RNAi oligonucleotide of claim 9, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.
11. The RNAi oligonucleotide of claim 9, wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.
12. The RNAi oligonucleotide of any one of claims 1-11, wherein at least one nucleotide of the RNAi oligonucleotide is conjugated to one or more targeting ligands.
13. The RNAi oligonucleotide of claim 12, wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide or lipid.
14. The RNAi oligonucleotide of claim 12, wherein each targeting ligand comprises an N-acetylgalactosamine (GalNAc) moiety.
15. The RNAi oligonucleotide of claim 14, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.
16. The RNAi oligonucleotide of claim 15, wherein up to 4 nucleotides of a stem-loop of the RNAi oligonucleotide are each conjugated to a monovalent GalNAc moiety.
17. The RNAi oligonucleotide of any one of claims 1-16, wherein the sense strand is:
5'-
[mAs][mU][mA][mA][mA][mA][mA][fU][fG][fU][fU][mC][mA][mC][mA][mA][mU][mU]
[mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]-3' (SEQ ID NO: 132),
wherein:
mAs represents 2'-OMe modified adenosine with a 3'-phosphorothioate linkage;
mC represents 2'-OMe modified cytosine;
mA represents 2'-OMe modified adenosine;

mU represents 2'-OMe modified uridine;
 mG represents 2'-OMe modified guanosine;
 fG represents 2'-F modified guanosine;
 fA represents 2'-F modified adenosine;
 fG represents 2'-F modified uridine; and
 ademA-GalNAc represents 2'-aminodiethoxymethanol-Adenine-GalNAc.

18. The RNAi oligonucleotide of any one of claims 2-17, wherein the antisense strand is:

5'-[MePhosphonate-4O-mUs][fUs][fAs][fA][fU][mU][fG][mU][mG][fA][mA][mC][mA][fU][mU][mU][mU][mA][mUs][mGs][mG]-3' (SEQ ID NO: 133), wherein:

MePhosphonate-4O-mUs represents ;
 mC represents 2'-OMe modified cytosine;
 mA represents 2'-OMe modified adenosine;
 mU represents 2'-OMe modified uridine;
 mG represents 2'-OMe modified guanosine;
 fG represents 2'-F modified guanosine;
 fA represents 2'-F modified adenosine;
 fU represents 2'-F modified uridine;
 fGs represents 2'-F modified guanosine with a 3'-phosphorothioate linkage;
 fUs represents 2'-F modified uridine with a 3'-phosphorothioate linkage;
 mUs represents 2'-OMe modified uridine with a 3'-phosphorothioate linkage; and
 mGs represents 2'-OMe modified guanosine with a 3'-phosphorothioate linkage.

19. A pharmaceutical composition comprising:

- (i) the RNAi oligonucleotide of any one of claims 1-18; and
- (ii) a pharmaceutically acceptable carrier, delivery agent, or excipient.

20. The pharmaceutical composition of claim 19, wherein the pharmaceutically acceptable carrier comprises water.

21. The pharmaceutical composition of claim 19, wherein the pharmaceutically acceptable carrier comprises phosphate buffered saline.

22. An *in vitro* method for reducing ANGPTL3 expression in a cell or a population of cells, wherein the method comprises: contacting the cell or the population of cells with the oligonucleotide of any one of claims 1 to 18, or the pharmaceutical composition of claim 19, wherein reducing ANGPTL3 expression comprises reducing an amount or a level of ANGPTL3 mRNA, an amount or a level of ANGPTL3 protein, or both.
23. Use of the RNAi oligonucleotide of any one of claims 1 to 18, or the pharmaceutical composition of claim 19, in the manufacture of a medicament for treating a disease, disorder, or condition associated with ANGPTL3 expression, wherein the disease, disorder, or condition associated with ANGPTL3 expression is selected from the group consisting of: hypertriglyceridemia, obesity, hyperlipidemia, abnormal lipid and/or cholesterol metabolism, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, homozygous and heterozygous familial hypercholesterolemia, and statin-resistant hypercholesterolemia, optionally wherein the disease, disorder or condition associated with ANGPTL3 expression is cardiovascular disease, type II diabetes mellitus, hypertriglyceridemia, NASH, obesity, or a combination thereof.
24. The use of claim 23, wherein the RNAi oligonucleotide or pharmaceutical composition, is to be administered in combination with a second composition or therapeutic agent.
25. The RNAi oligonucleotide of any one of claims 1 to 18, or the pharmaceutical composition of claim 19, for use as a medicament.
26. A kit comprising the oligonucleotide of any one of claims 1 to 18, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with ANGPTL3 expression.