fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis (irreversible, advanced scarring of the liver), or SCAP related obesity. Accordingly, in one example, the present disclosure provides an RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is complementary to a SCAP mRNA sequence. In certain examples, the antisense strand comprises a region having at least 15 contiguous nucleotides from an antisense sequence listed in Table 1 or Table 2.

[0007a] In one aspect, the present disclosure refers to an RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having at least 15 contiguous nucleotides from an antisense sequence of SEQ ID NO:336 or 478, and wherein the RNAi construct inhibits the expression of SREBP Cleavage Activating Protein (SCAP).

[0007b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the RNAi construct as disclosued herein and a pharmaceutically acceptable carrier, excipient, or diluent.

[0007c] In another aspect, the present disclosure refers to the use of the RNAi construct as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject having a SCAP-associated disease, wherein said disease is selected from the group consisting of fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, hepatocellular carcinoma, liver fibrosis, obesity, myocardial infarction, heart failure, coronary artery disease, hypercholesterolemia, or nonalcoholic fatty liver disease (NAFLD).

[0007d] In another aspect, the present disclosure refers to an RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having at least 15 contiguous nucleotides from an antisense sequence of SEQ ID NO:336 or 478, for use in therapy.

[0008] In some examples, the sense strand of the RNAi constructs described herein comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region of about 15 to about 30 base pairs in length. In these and other examples, the sense and antisense strands each are about 15 to about 30 nucleotides in length. In some examples, the RNAi constructs comprise at least one blunt end. In other examples, the RNAi constructs comprise at least one nucleotide overhang. Such nucleotide overhangs may comprise at least 1 to 6 unpaired nucleotides and can be located at the 3' end of the sense strand, the 3' end of the antisense strand, or the 3' end of both the sense and antisense strand. In certain examples, the RNAi constructs comprise an overhang of two unpaired nucleotides at the 3' end of the sense strand and the 3' end of the antisense strand. In other examples, the RNAi constructs comprise an overhang of two unpaired nucleotides at the 3' end of the antisense strand and a blunt end of the 3' end of the sense strand/5' end of the antisense strand.

[0009] The RNAi constructs of the disclosure may comprise one or more modified nucleotides, including nucleotides having modifications to the ribose ring, nucleobase, or phosphodiester backbone. In some examples, the RNAi constructs comprise one or more 2'-modified nucleotides. Such 2'-modified nucleotides can include 2'-fluoro modified nucleotides, 2’-O-methyl modified nucleotides, 2’-O-methoxyethyl modified nucleotides, 2’-O-allyl modified nucleotides, bicyclic nucleic acids (BNA), glycol nucleic acids (GNAs), inverted bases (e.g. inverted adenosine) or combinations thereof In one particular example, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2’-O-methyl modified nucleotides, or combinations thereof. In some examples, all of the nucleotides in the sense and antisense strand of the RNAi construct are modified nucleotides.

[0010] In some examples, the RNAi constructs comprise at least one backbone modification, such as a modified internucleotide or internucleoside linkage. In certain

What is Claimed

1. An RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having at least 15 contiguous nucleotides from an antisense sequence of SEQ ID NO:336 or 478, and wherein the RNAi construct inhibits the expression of SREBP Cleavage Activating Protein (SCAP).

2. The RNAi construct of claim 1, wherein the antisense strand comprises a region that is complementary to a SCAP mRNA sequence.

3. The RNAi construct of any of the above claims, wherein the sense strand comprises a region having at least 15 contiguous nucleotides from an antisense sequence of SEQ ID NO:335 or 477.

4. The RNAi construct of any of the above claims, wherein the sense strand comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region of 15 to 30 base pairs in length.

5. The RNAi construct of claim 4, wherein the duplex region is 19 to 21 base pairs in length.

6. The RNAi construct of claim 5, wherein the duplex region is 19 base pairs in length.

7. The RNAi construct of any one of claims 4 to 6, wherein the sense strand and the antisense strand are each 19 to 27 nucleotides in length.

8. The RNAi construct of claim 7, wherein the sense strand and the antisense strand are each 21 to 25 nucleotides in length.

9. The RNAi construct of claim 8, wherein the sense strand and the antisense strand are each 21 to 23 nucleotides in length.

10. The RNAi construct of any one of claims 1 to 9, wherein the RNAi construct comprises at least one blunt end.

11. The RNAi construct of any one of claims 1 to 9, wherein the RNAi construct comprises at least one nucleotide overhang of 1 to 4 unpaired nucleotides.

12. The RNAi construct of claim 11, wherein the nucleotide overhang has 2 unpaired nucleotides.

13. The RNAi construct of claim 11 or 12, wherein the RNAi construct comprises a nucleotide overhang at the 3' end of the sense strand, the 3' end of the antisense strand, or the 3' end of both the sense strand and the antisense strand.

14. The RNAi construct of any one of claims 11 to 13**,** wherein the nucleotide overhang comprises a 5'-UU-3' dinucleotide or a 5'-dTdT-3' dinucleotide.

15. The RNAi construct of any one of claims 1 to 14, wherein the RNAi construct comprises at least one modified nucleotide.

16. The RNAi construct of claim 15, wherein the modified nucleotide is a 2'-modified nucleotide.

17. The RNAi construct of claim 15, wherein the modified nucleotide is a 2'-fluoro modified nucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-allyl modified nucleotide, a bicyclic nucleic acid (BNA), a glycol nucleic acid, an inverted base or combinations thereof.

18. The RNAi construct of claim 17, wherein the modified nucleotide is a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-fluoro modified nucleotide, or combinations thereof.

19. The RNAi construct of claim 15, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.

20. The RNAi construct of claim 19, wherein the modified nucleotides are 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, or combinations thereof.

21. The RNAi construct of any one of claims 1 to 20, wherein the RNAi construct comprises at least one phosphorothioate internucleotide linkage.

22. The RNAi construct of claim 21, wherein the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at the 3' end of the antisense strand.

23. The RNAi construct of claim 21, wherein the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3' and 5' ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages at the 5' end of the sense strand.

24. The RNAi construct of any one of claims 1 to 23, wherein the antisense strand comprises the antisense sequence of SEQ ID NO:336 or 478.

25. The RNAi construct of claim 24, wherein the sense strand comprises the sense sequence of SEQ ID NO:335 or 477.

26. The RNAi construct of any one of claims 1 to 25, wherein the RNAi construct is any one of the duplex compounds of D-1087 or D-2087.

27. The RNAi construct of any one of claims 1 to 26, wherein the RNAi construct reduces the expression level of SCAP in liver cells following incubation with the RNAi construct as compared to the SCAP expression level in liver cells that have been incubated with a control RNAi construct.

28. The RNAi construct of claim 27, wherein the liver cells are Hep3B cells.

29. The RNAi construct of claim 28, wherein the RNAi construct inhibits at least 10% of SCAP expression at 5 μM in Hep3B cells *in vitro.*

30. The RNAi construct of claim 28, wherein the RNAi construct inhibits SCAP expression in Hep3B cells with an IC50 of less than 1 nM.

31. A pharmaceutical composition comprising the RNAi construct of any one of claims 1 to 30 and a pharmaceutically acceptable carrier, excipient, or diluent.

32. Use of the RNAi construct of any one of claims 1 to 30 or the pharmaceutical composition of claim 31 in the manufacture of a medicament for treating a subject having a SCAP-associated disease, wherein said disease is selected from the group consisting of fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, hepatocellular carcinoma, liver fibrosis, obesity, myocardial infarction, heart failure, coronary artery disease, hypercholesterolemia, or nonalcoholic fatty liver disease (NAFLD).

33. The use of claim 32, wherein the expression level of SCAP in hepatocytes is reduced in the patient following that the RNAi construct is to be administered as compared to the SCAP expression level in a patient not receiving the RNAi construct.

34. The use of claim32, wherein that the RNAi construct of any one of claims 1 to 30 or the pharmaceutical composition of claim 31 results in a reduction of expression of a SCAP gene by at least 10%.

35. An RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having at least 15 contiguous nucleotides from an antisense sequence of SEQ ID NO:336 or 478, for use in therapy.