[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 examples, the RNAi constructs described herein comprise at least one phosphorothioate internucleotide linkage. In particular examples, the phosphorothioate internucleotide linkages may be positioned at the3' or 5' ends of the sense and/or antisense strands.

[0011] In some examples, the antisense strand and/or the sense strand of the RNAi constructs of the disclosure may comprise or consist of a sequence from the antisense and sense sequences listed in Tables 1 or 2. In certain examples, the RNAi construct may be any one of the duplex compounds listed in any one of Tables 1 to 2.

[0011a] 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 differing by no more than 3 nucleotides from~~consists of a nucleic acid sequence of SEQ ID NO: 648, 734, or 2, and wherein the RNAi construct inhibits the expression of Patatin-Like Phospholipase Domain Containing 3 (PNPLA3). In another aspect, the present disclosure refers to a pharmaceutical composition comprising the RNAi construct as disclosed herein and a pharmaceutically acceptable carrier, excipient, or diluent.

What is Claimed

1. An RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand ~~comprises a~~consists of ~~region having at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a~~ nucleic acid sequence of SEQ ID NO: 648, 734, or 2, and wherein the RNAi construct inhibits the expression of Patatin-Like Phospholipase Domain Containing 3 (PNPLA3).

2. The RNAi construct of claim 1, wherein the antisense strand comprises a region that is complementary to a PNPLA3 mRNA sequence.

3. The RNAi construct any of the above claims, wherein the sense strand ~~comprises a region having at least 15 contiguous nucleotides differing by no more than 3 nucleotides from an~~consists of a nucleic acid sequence of SEQ ID NO: 647, 733, or 1~~.~~.

4. The RNAi construct any of the above claims, wherein the construct preferentially inhibits a PNPLA3-rs738409 minor allele.

5. The RNAi construct of claim 4, wherein the construct has at least 10% greater inhibition of a PNPLA3-rs738409 minor allele as compared to the major allele.

6. The RNAi construct of any of the above claims, wherein the construct preferentially inhibits a PNPLA3-rs738408 minor allele.

7. The RNAi construct of claim 6, wherein the construct has at least 10% greater inhibition of a PNPLA3-rs738409-rs738408 double minor allele as compared to the major allele.

8. The RNAi construct 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 ~~about~~ 15 to ~~about~~ 30 base pairs in length.

9. The RNAi construct of claim 8, wherein the duplex region is 19 base pairs in length.

10. ~~The RNAi construct of any one of claims 8 or 9, wherein the sense strand and the antisense strand are each about 15 to about 30 nucleotides in length.~~

11. ~~The RNAi construct of claim 10, wherein the sense strand and the antisense strand are each about 19 to about 27 nucleotides in length.~~

~~12.~~10. The RNAi construct of any one of claims 1 to ~~11~~9, wherein the RNAi construct comprises at least one blunt end.

~~13.~~11. The RNAi construct of any one of claims 1 to ~~11~~9, wherein the RNAi construct comprises at least one nucleotide overhang of 1 to 4 unpaired nucleotides.

~~14.~~12. The RNAi construct of claim ~~13~~11, wherein the nucleotide overhang has 2 unpaired nucleotides.

~~15. The RNAi construct of claim 13 or 14, 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.~~

~~16.~~13. The RNAi construct of any one of claims 11 to 12~~13 to 15~~**,** wherein the nucleotide overhang comprises a 5'-UU-3' dinucleotide or a 5'-dTdT-3' dinucleotide.

~~17.~~14. The RNAi construct of any one of claims 1 to ~~16~~13, wherein the RNAi construct comprises at least one modified nucleotide, wherein the modified nucleotide is a 2'-modified nucleotide.

~~18. The RNAi construct of claim 17, wherein the modified nucleotide is a 2'-modified nucleotide.~~

~~19.~~15. The RNAi construct of claim ~~17~~14, 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.

~~20.~~16. The RNAi construct of claim ~~19~~15, 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.

~~21.~~17. The RNAi construct of claim ~~17~~14, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides, wherein the modified nucleotide is a 2'-modified nucleotide.

~~22.~~18. The RNAi construct of claim ~~21~~17, wherein the modified nucleotides are 2'-O-methylmodified nucleotides, 2'-fluoro modified nucleotides, or combinations thereof.

~~23.~~19. The RNAi construct of any one of claims 1 to ~~22~~18, wherein the RNAi construct comprises at least one phosphorothioate internucleotide linkage.

~~24.~~20. The RNAi construct of claim ~~23~~19, wherein the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at the 3' end of the antisense strand.

~~25.~~21. The RNAi construct of claim ~~23~~19, 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.

~~26.~~22. The RNAi construct of any one of claims 1 to ~~25~~21, wherein the RNAi construct ~~is D-1240, D1283, D-1000, D-2240, D-2238, or D-2000~~consists of a sense and antisense strand having SEQ ID Nos: 647 and 648; 733 and 734; 1 and 2; 1609 and 1610; 1695 and 1696; and 167 and 168.

~~27.~~23. The RNAi construct of any one of claims 1 to ~~26~~22, wherein the RNAi construct reduces the expression level of PNPLA3 in liver cells following incubation with the RNAi construct as compared to the PNPLA3 expression level in liver cells that have been incubated with a control RNAi construct.

~~28.~~24. The RNAi construct of claim ~~26~~23, wherein the liver cells are Hep3B or HepG2 cells.

~~29.~~25. The RNAi construct of any one of claims 1 to ~~28~~24, wherein the RNAi construct inhibits at least 10% of PNPLA3 expression at 5 nM in Hep3B cells *in vitro.*

~~30.~~26. The RNAi construct of any one of claims 1 to ~~28~~24, wherein the RNAi construct inhibits at least 10% of PNPLA3 expression at 5 nM in HepG2 cells *in vitro.*

~~31.~~27. The RNAi construct of any one of claims 1 to ~~28~~24, wherein the RNAi construct inhibits PNPLA3 expression in Hep3B cells with an IC50 of less than ~~about~~ 1 nM.

~~32.~~28. The RNAi construct of any one of claims 1 to ~~28~~24, wherein the RNAi construct inhibits PNPLA3 expression in HepG2 cells with an IC50 of less than ~~about~~ 1 nM.

~~33.~~29. A pharmaceutical composition comprising the RNAi construct of any one of claims 1 to ~~32~~28 and a pharmaceutically acceptable carrier, excipient, or diluent.