

HSD17B13, originally named SCDR9, was first cloned from a human liver cDNA library in 2007 (Liu et al. (2007) *Acta Biochim* 54:213-218). In 2008, Horiguchi identified HSD17B13 as a new LD-associated protein with expression mainly restricted to the liver (Horiguchi et al. (2008) *Biochem Biophys Res Commun* 370:235-238). Hepatic overexpression of HSD17B13 promotes lipid accumulation in the liver. HSD17B13 expression is markedly upregulated in patients and mice with non-alcoholic fatty liver disease (NAFLD) (Su et al. (2014) *PNAS* 111:11437-11442). Accordingly, novel therapeutics targeting HSD17B13 represents a novel approach to reducing HSD17B13 levels and treating hepatologic diseases, such as nonalcoholic fatty liver disease.

SUMMARY

[0004] The present disclosure is based, in part, on the design and generation of RNAi constructs that target the HSD17B13 mRNA and reduce expression of HSD17B13 in liver cells. The sequence specific inhibition of HSD17B13 expression is useful for treating or preventing conditions associated with HSD17B13 expression, such as liver-related diseases, such as, for example, simple fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis (irreversible, advanced scarring of the liver), or HSD17B13 related obesity. In one aspect, the present disclosure provides 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 an antisense sequence listed in Table 1 or 2, and wherein the RNAi construct inhibits the expression of 17 β -Hydroxysteroid dehydrogenase type 13 (HSD17B13). In another aspect, the present disclosure provides a pharmaceutical composition comprising the RNAi construct as described herein and a pharmaceutically acceptable carrier, excipient, or diluent. In yet another aspect, the present disclosure provides a use of the RNAi construct as described herein in the manufacture of a pharmaceutical composition for reducing the expression of HSD17B13 in a patient in need thereof.

[0004a] 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 HSD17B13 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.

[0005] 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.

[0006] 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'-deoxy 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.

[0007] 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 the 3' or 5' ends of the sense and/or antisense strands.

[0008] 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.

DETAILED DESCRIPTION OF THE INVENTION

[0009] The present invention is directed to compositions and methods for regulating the expression of the 17 β -Hydroxysteroid dehydrogenase type 13 (HSD17B13) gene. In some embodiments, the gene may be within a cell or subject, such as a mammal (e.g. a human). In some embodiments, compositions of the invention comprise RNAi constructs that target a HSD17B13 mRNA and reduce HSD17B13 expression in a cell or mammal. Such RNAi constructs are useful for treating or preventing various forms of liver-related diseases, such as,

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 differing by no more than 3 nucleotides from an antisense sequence listed in Table 1 or 2, and wherein the RNAi construct inhibits the expression of 17 β -Hydroxysteroid dehydrogenase type 13 (HSD17B13).
2. The RNAi construct of claim 1, wherein the antisense strand comprises a region that is complementary to a HSD17B13 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 differing by no more than 3 nucleotides from an antisense sequence listed in Table 1 or 2.
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 17 to 24 base pairs in length.
6. The RNAi construct of claim 4 or 5, wherein the sense strand and the antisense strand are each 15 to 30 nucleotides in length.
7. The RNAi construct of any one of claims 1 to 6, wherein the RNAi construct comprises at least one blunt end.
8. The RNAi construct of any one of claims 1 to 6, wherein the RNAi construct comprises at least one nucleotide overhang of 1 to 4 unpaired nucleotides.
9. The RNAi construct of claim 8, wherein the nucleotide overhang has 2 unpaired nucleotides.
10. The RNAi construct of claim 8 or 9, 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.
11. The RNAi construct of any one of claims 8 to 10, wherein the nucleotide overhang comprises a 5'-UU-3' dinucleotide or a 5'-dTdT-3' dinucleotide.
12. The RNAi construct of any one of claims 1 to 11, wherein the RNAi construct comprises at least one modified nucleotide.
13. The RNAi construct of claim 12, wherein the modified nucleotide is a 2'-modified nucleotide.

14. The RNAi construct of claim 12, 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.
15. The RNAi construct of claim 12, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.
16. The RNAi construct of any one of claims 1 to 15, wherein the RNAi construct comprises at least one phosphorothioate internucleotide linkage.
17. The RNAi construct of any one of claims 1 to 16, wherein the antisense strand comprises a sequence selected from the antisense sequences listed in Table 1 or Table 2.
18. The RNAi construct of claim 17, wherein the sense strand comprises a sequence selected from the sense sequences listed in Table 1 or Table 2.
19. The RNAi construct of any one of claims 1 to 18, wherein the RNAi construct is any one of the duplex compounds listed in any one of Tables 1 to 2.
20. The RNAi construct of any one of claims 1 to 19, wherein the RNAi construct reduces the expression level of HSD17B13 in liver cells following incubation with the RNAi construct as compared to the HSD17B13 expression level in liver cells that have been incubated with a control RNAi construct.
21. The RNAi construct of claim 16, wherein the liver cells are primary hepatocyte cells.
22. The RNAi construct of any one of claims 1 to 21, wherein the RNAi construct inhibits HSD17B13 expression in primary hepatocyte cells with an IC₅₀ of less than about 40 nM.
23. A pharmaceutical composition comprising the RNAi construct of any one of claims 1 to 22 and a pharmaceutically acceptable carrier, excipient, or diluent.
24. Use of the RNAi construct of any one of claims 1 to 23 in the manufacture of a pharmaceutical composition for reducing the expression of HSD17B13 in a patient in need thereof.
25. The use of claim 24, wherein the expression level of HSD17B13 in hepatocytes is reduced in the patient to be administered the RNAi construct as compared to the HSD17B13 expression level in a patient not to be administered the RNAi construct.