PH1, AGXT, and HAO1 are described in the following: Angel L. Pey, Armando Albert, and Eduardo Salido, "Protein Homeostasis Defects of Alanine-Glyoxylate Aminotransferase: New Therapeutic Strategies in Primary Hyperoxaluria Type I," BioMed Research International, vol. 2013, Article ID 687658, 15 pages, 2013. doi:10.1155/2013/687658; Cochat and Rumsby (2013) NEJM 369:7; Salido et al (2006) PNAS 103:18249; Baker et al (2004) American Journal of Physiology - Heart and Circulatory Physiology Published 1 October 2004Vol. 287no. 4, H1771-H1779DOI: 10.1152/ajpheart.00234.2004.

Summary

In one aspect, the present invention refers to a double stranded RNAi agent capable of inhibiting expression of HAO1 in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:1 SEQ ID NO:2, SEQ ID NO:5, or SEQ ID NO:6 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:3 SEQ ID NO:4, SEQ ID NO:7, or SEQ ID NO:8; wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein at least one of said modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, and a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group, and wherein said sense strand is conjugated to a ligand attached at the 3'-terminus.

In another aspect, the present invention refers to a double stranded RNAi agent capable of inhibiting expression of HAO1 in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of from any one of the nucleotide sequences of SEQ ID NO:1 SEQ ID NO:2, SEQ ID NO:5, or SEQ ID NO:6 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3

nucleotides from any one of the nucleotide sequences of SEQ ID NO:3 SEQ ID NO:4, SEQ ID NO:7, or SEQ ID NO:8, wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

In yet another aspect, the present invention refers to an RNAi agent selected from the group of RNAi agents listed in Table 1 or 2.

In yet another aspect, the present invention refers to the use of a double stranded RNAi agent in the manufacture of a medicament for treating a subject having Primary Hyperoxaluria 1 (PH1), wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of from any one of the nucleotide sequences of SEQ ID NO:1 SEQ ID NO:2, SEQ ID NO:5, or SEQ ID NO:6 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:3 SEQ ID NO:4, SEQ ID NO:7, or SEQ ID NO:8, wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoromodification, wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoromodification, wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and, wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

The present disclosure provides compositions comprising RNAi agents, *e.g.*, double-stranded iRNA agents, targeting HAO1. The present disclosure also provides methods using the compositions of the invention for inhibiting HAO1 expression and for treating HAO1 associated disorders, *e.g.*, PH1.

We claim:

1. A double stranded RNAi agent capable of inhibiting expression of HAO1 in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:1 SEQ ID NO:2, SEQ ID NO:5, or SEQ ID NO:6 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:3 SEQ ID NO:4, SEQ ID NO:7, or SEQ ID NO:8;

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides,

wherein at least one of said modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, and a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group, and

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus.

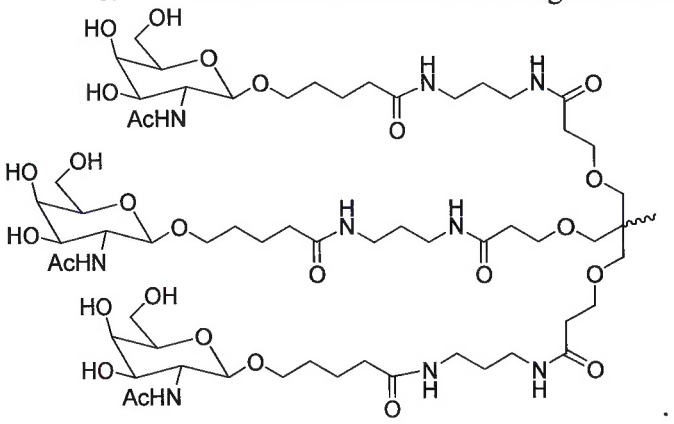
2. The double stranded RNAi agent of claim 1, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand are modified nucleotides.

3. The double stranded RNAi agent of claim 1, wherein said sense strand and said antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in Table 2.

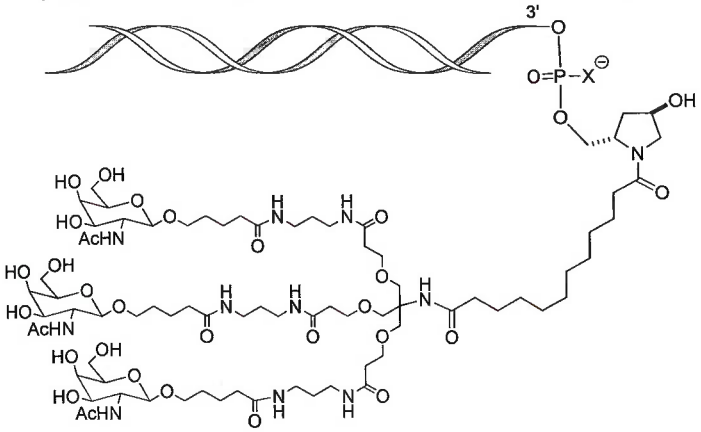
4. The double stranded RNAi agent of any claim 1, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

5. The double stranded RNAi agent of claim 1, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

6. The double stranded RNAi agent of claim 1, wherein the ligand is



7. The double stranded RNAi agent of claim 1, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

8. The double stranded RNAi agent of claim 1, wherein said agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

9. The double stranded RNAi agent of claim 8, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

10. The double stranded RNAi agent of claim 8, wherein said RNAi agent comprises 6-8 phosphorothioate internucleotide linkages.

11. The double stranded RNAi of claim 10, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and the sense strand comprises at least two phosphorothioate internucleotide linkages at either the 5'-terminus or the 3'-terminus.

12. The double stranded RNAi agent of claim 1, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

13. The double stranded RNAi agent of claim 1, wherein the RNAi agent is selected from the group consisting of AD-62994, AD-62933, and AD-65585.

14. A double stranded RNAi agent capable of inhibiting expression of HAO1 in a cell,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of from any one of the nucleotide sequences of SEQ ID NO:1 SEQ ID NO:2, SEQ ID NO:5, or SEQ ID NO:6 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:3 SEQ ID NO:4, SEQ ID NO:7, or SEQ ID NO:8,

wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

15. The double stranded RNAi agent of claim 14, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

16. An RNAi agent selected from the group of RNAi agents listed in Table 1 or 2.

17. The RNAi agent of claim 14, wherein the RNAi agent is selected from the group consisting of AD-62994, AD-62933, and AD-65585.

18. Use of a double stranded RNAi agent in the manufacture of a medicament for treating a subject having Primary Hyperoxaluria 1 (PH1),

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of from any one of the nucleotide sequences of SEQ ID NO:1 SEQ ID NO:2, SEQ ID NO:5, or SEQ ID NO:6 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NO:3 SEQ ID NO:4, SEQ ID NO:7, or SEQ ID NO:8,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoromodification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus,

wherein substantially all of the nucleotides of said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoromodification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and,

wherein said sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

19. The use of claim of claim 18, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

20. The use of claim 18, wherein the subject is a human.

21. The use of claim 18, wherein the double stranded RNAi agent is to be administered at a dose of 0.01 mg/kg to 10 mg/kg or 1 mg/kg to 10 mg/kg.

22. The use of claim 21, wherein the double stranded RNAi agent is to be administered at a dose of 0.1 mg/kg, 1.0 mg/kg, or 3.0 mg/kg.

23. The use of claim 21, wherein the double stranded RNAi agent is to be administered at a dose of 1 mg/kg to 10 mg/kg.

24. The use of claim 21, wherein the double stranded RNAi agent is to be administered subcutaneously.

25. The use of claim 21, wherein the double stranded RNAi agent is to be administered intravenously.

26. The use of claim 21, wherein said RNAi agent is to be administered in two or more doses.

27. The use of claim 26, wherein said RNAi agent is to be administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours.

28. The use of claim 26, wherein said RNAi agent is to be administered once a week for up to 2 weeks, up to 3 weeks, up to 4 weeks, up to 5 weeks, or longer.