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, 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.

Brief Description of the Drawings

Figure 1 shows the nucleotide sequence of *Homo sapiens* HAO1 mRNA (SEQ ID NO:1).

Figure 2 shows the nucleotide sequence of *Mus musculus* HAO1 mRNA (SEQ ID NO:2).

Figure 3A is a graph with the results of in vitro screening of GO (HAO) GalNac-siRNA conjugates in primary cynomologous monkey hepatocytes.

Figure 3B is a graph with the dose response curve of a GO (HAO) GalNac-siRNA conjugate in primary cynomologous monkey hepatocytes.

Figure 4A is a graph with the results of in vivo evaluation of GO (HAO) GalNac-siRNA conjugates in C57B6 mice after a single dose.

Figure 4B is a graph with the results of in vivo evaluation of GO (HAO) GalNac-siRNA conjugates in C57B6 mice after a repeat dose.

Figure 5A is a graph showing urinary oxalate levels in AGXT knock out (KO) mice after treatment with GO (HAO) GalNac-siRNA conjugates.

Figure 5B is a graph showing urinary glycolate levels in AGXT KO mice after treatment with GO (HAO) GalNac-siRNA conjugates.

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.

17. The double stranded RNAi agent of claim 16, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

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

19. The RNAi agent of claim 16, wherein the RNAi agent is selected from the group consisting of AD-62994, AD-62933, and AD-65585.

20. 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.

21. The use of claim of claim 20, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

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

23. The use of claim 20, wherein the double stranded RNAi agent is to be administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 1 mg/kg to about 10 mg/kg.

24. The use of claim 23, wherein the double stranded RNAi agent is to be administered at a dose of about 0.1 mg/kg, about 1.0 mg/kg, or about 3.0 mg/kg.

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

26. The use of claim 23, wherein the double stranded RNAi agent is to be administered subcutaneously.

27. The use of claim 23, wherein the double stranded RNAi agent is to be administered intravenously.

28. The use of claim 23, wherein said RNAi agent is to be administered in two or more doses.

29. The use of claim 28, 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.

30. The use of claim 28, 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.