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.

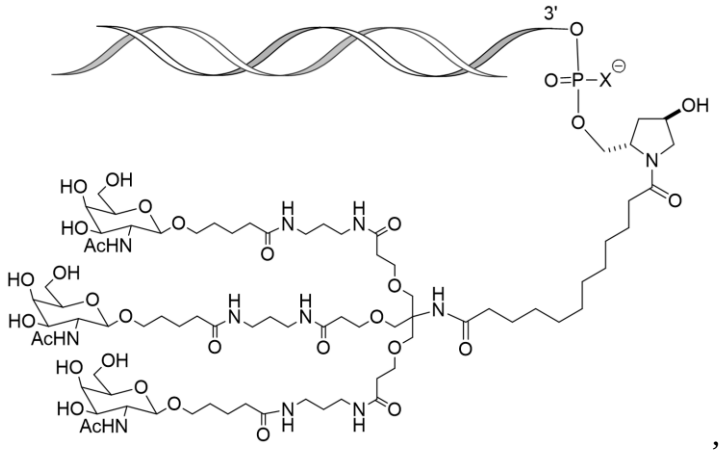
Summary of the Invention

In one aspect, provided herein is a double stranded RNAi agent that inhibits expression of hydroxyacid oxidase (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 antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'-UAUAUUUCCAGGAUGAAAGUCCA-3' (SEO ID NO: 706); wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a nucleotide modification, and wherein at least one strand is conjugated to a ligand.

In another aspect, provided herein is a double stranded RNAi agent that inhibits expression of hydroxyacid oxidase (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 the nucleotide sequence of GACUUUCAUCCUGGAAAUAUA (SEO ID NO: 589) and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence UAUAUUUCCAGGAUGAAAGUCCA (SEO ID NO: 706), wherein all of the nucleotides of said sense strand independently 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 all of the nucleotides of said antisense strand independently 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 a ligand which is one or more GalNAc derivatives.

In another aspect, provided herein is an *in vitro* method of inhibiting HAO1 expression in a cell, the method comprising: (a) contacting the cell with the double stranded RNAi agent as described herein, or the pharmaceutical composition as described herein; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a HAO1 gene, thereby inhibiting expression of the HAO1 gene in the cell.

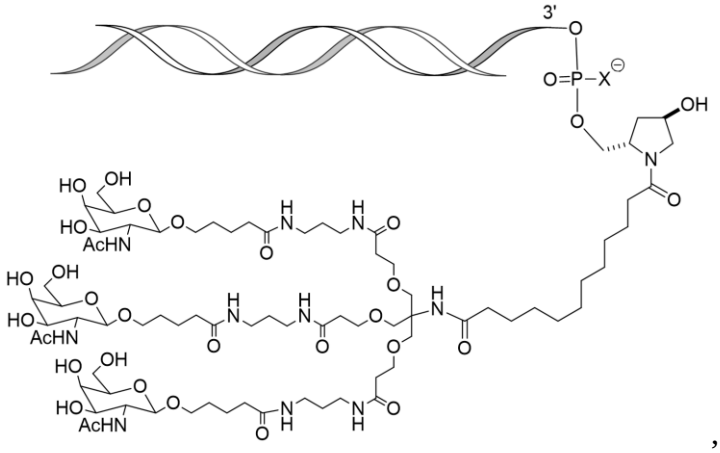
In another aspect, provided herein is a double stranded RNAi agent, or salt thereof, that inhibits expression of hydroxyacid oxidase (HAO1) in a cell, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises the nucleotide sequence of 5'- gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:213) and the antisense strand comprises the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:330), wherein a, g, c, and u are 2'-O-methyl (2'-OMe) modified A, G, C, and U nucleotides, respectively; Af, Gf, Cf, and Uf are 2'fluoro A, G, C, and U modified nucleotides, respectively; and s is a phosphorothioate linkage, wherein a ligand is conjugated to the 3' end of the sense strand as shown in the following schematic



, wherein X is O.

In another aspect, provided herein is a double stranded RNAi agent, or salt thereof, that inhibits expression of hydroxyacid oxidase (HAO1) in a cell, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand consists of the nucleotide sequence of 5'- gsascuuuCfaUfCfCfuggaaauaua-3' (SEQ ID NO:213) and the antisense strand consists of the nucleotide sequence 5'-usAfsuauUfuCfCfaggaUfgAfaagucscsa-3' (SEQ ID NO:330), wherein a, g, c, and u are 2'-O-methyl (2'-OMe) modified A, G, C, and U nucleotides, respectively; Af, Gf, Cf, and Uf are 2'fluoro A, G, C, and U modified nucleotides, respectively; and s is a phosphorothioate

linkage, wherein a ligand is conjugated to the 3' end of the sense strand as shown in the following schematic



, wherein X is O.

In another aspect, provided herein is an isolated cell containing the double stranded RNAi agent as described herein.

In another aspect, provided herein is a pharmaceutical composition comprising the double stranded RNAi agent as described herein.

In another aspect, provided herein is use of the double stranded RNAi agent as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject having an HAO1-associated disorder.

In another aspect, provided herein is the double stranded RNAi agent as described herein, or the pharmaceutical composition as described herein for use in therapy.

The present invention provides compositions comprising RNAi agents, *e.g.*, double-stranded iRNA agents, targeting HAO1. The present invention 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.