We claim:

1. A double stranded RNA (dsRNA) agent that inhibits expression of a serine peptidase inhibitor, clade A, member 1 (Serpina1) gene, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 19 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'– CUUCUUAAUGAUUGAACAAAA – 3' (SEQ ID NO: 417), and the antisense strand comprises at least 19 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5' –UUUUGUUCAAUCAUUAAGAAGAC – 3' (SEQ ID NO: 419),

wherein substantially all of the nucleotides of the antisense strand comprise a nucleotide modification,

wherein said antisense strand comprises at least one thermally destabilizing modification of the double stranded region located in position 4 to 8 from the 5'-end selected from the group consisting of an abasic modification, a mismatch with the opposing nucleotide in the opposing strand, a 2'-deoxy modification, and an acyclic nucleotide modification,

wherein the nucleotides at positions 2, 6, 8, 9, 14, and 16, or at positions 2, 6, 14, and 16, or at positions 2, 14, and 16 from the 5'-end of the antisense strand are 2'-F modified nucleotides,

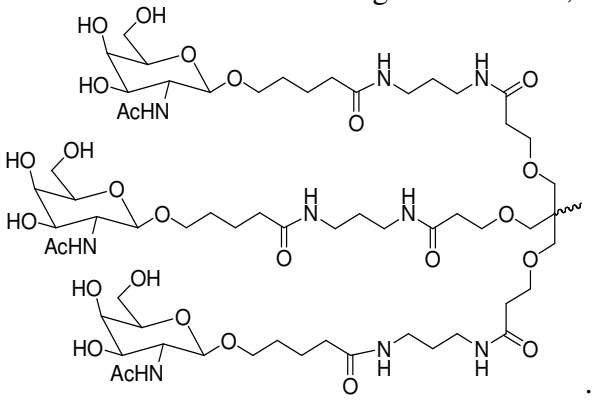
wherein substantially all of the nucleotides of the sense strand comprise a nucleotide modification,

wherein the nucleotides at positions 7, 9, 10, and 11, or at positions 7, 10, and 11 from the 5'-end of the sense strand are 2'-F modified nucleotides,

wherein said sense strand comprises an asialoglycoprotein (ASGPR) ligand, and

wherein each of the sense strand and the antisense strand are independently 19 to 25 nucleotides in length.

2. The dsRNA agent of claim 1, wherein the ASGPR ligand is:



.

3. The dsRNA agent of any one of claims 1-2, wherein each strand is independently 19 to 23 nucleotides in length.

4. The dsRNA agent of any one of claims 1-3, wherein the sense strand is 21 nucleotides in length, and the antisense strand is 23 nucleotides in length.

5. The dsRNA agent of claim 1, wherein the antisense strand comprises the nucleotide sequence 5’ – UUUUGUUCAAUCAUUAAGAAGAC – 3’ (SEQ ID NO: 419).

6. The dsRNA agent of claim 1, wherein the sense strand comprises the nucleotide sequence 5’ – CUUCUUAAUGAUUGAACAAAA – 3’ (SEQ ID NO: 417) and the antisense strand comprises the nucleotide sequence 5’ – UUUUGUUCAAUCAUUAAGAAGAC – 3’ (SEQ ID NO: 419).

7. The dsRNA agent of claim 6, wherein the sense strand comprises the nucleotide sequence 5’ - csusucuuAfaUfGfAfuugaacaaaa – 3’ (SEQ ID NO: 33) and the antisense strand comprises the nucleotide sequence 5’ – usUfsuugu(Tgn)caaucaUfuAfagaagsasc – 3’ (SEQ ID NO: 34) ,

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer.

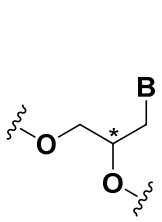
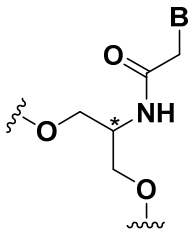
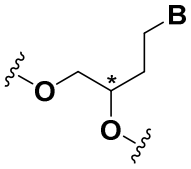
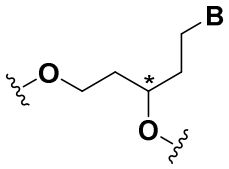
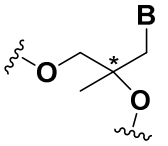
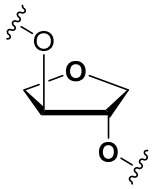
8. An isolated cell containing the dsRNA agent of any one of claims 1-7.

9. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-7.

10. Use of the pharmaceutical composition of claim 9 in the manufacture of a medicament for treating a Serpina1 deficiency variant-associated disorder selected from selected from the group consisting of chronic liver disease, liver inflammation, cirrhosis, liver fibrosis, and/or hepatocellular carcinoma.

11. The use of claim 10, wherein the Serpina1 associated disease is caused by intracellular accumulations of misfolded Serpina 1 protein, wherein the use comprises that a therapeutically effective amount of the pharmaceutical composition is to be administered to a subject in need thereof, wherein the administration of the pharmaceutical composition reduces the accumulation of misfolded Serpina 1 in the liver of the subject.

12. The dsRNA agent of claim 1, wherein the thermally destabilizing modification is selected from the group consisting of


,

,


,

, and

,

wherein B is nucleobase.

13. The dsRNA agent of claim 1 or 12, wherein the destabilizing modification is located in position 7 of the antisense strand.

14. The dsRNA agent of any one of claims 1, 12, and 13, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

15. The dsRNA of any one of claims 1 and 12-14, wherein all of the nucleotides of the antisense strand comprise a nucleotide modification selected from the group consisting of a thermally destabilizing modification, a 2'-F modification and a 2'-OMe modification;

all of the nucleotides of the sense strand comprise a nucleotide modification selected from the group consisting of a 2'-F modification and a 2'-OMe modification,
and

wherein the dsRNA agent has a melting temperature of from 40°C to 80°C.

16. The dsRNA agent of any one of claims 1 and 12-15, wherein the nucleotides at positions 2, 14, and 16 from the 5'-end of the antisense strand are 2'-F modified nucleotides.

17. The dsRNA agent of any one of claims 1 and 12-16, wherein the nucleotides at positions 7, 9, 10, and 11 from the 5'-end of the sense strand are 2'-F modified nucleotides

18. The dsRNA agent of any one of claims 1 and 12-17, wherein the antisense strand further comprises four phosphorothioate or methylphosphonate internucleotide linkages.

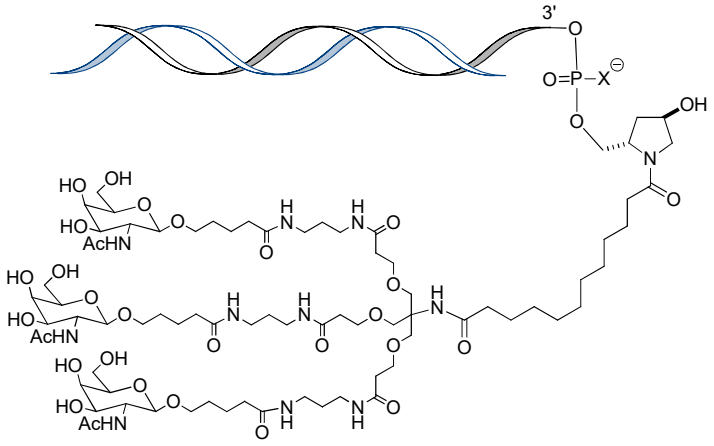
19. The dsRNA agent of claim 18, wherein the four phosphorothioate or methylphosphonate internucleotide linkages are located between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23 from the 5'-end.

20. The dsRNA agent of any one of claims 1 and 12-19, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

21. The dsRNA agent of any one of claims 1 and 12-19, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

22. The dsRNA agent of any one of claims 1, 3, 4 and 12-21, wherein the ASGPR ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

23. The dsRNA agent of claim 2, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

24. The dsRNA agent of claim 7, wherein the sense strand comprises the nucleotide sequence 5' - csusucuuAfaUfGfAfuugaacaaaaL96 – 3' (SEQ ID NO: 35) and the antisense strand comprises the nucleotide sequence 5' – usUfsuugu(Tgn)caaucaUfuAfagaagsasc – 3' (SEQ ID NO: 34),

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

25. The dsRNA agent of claim 24 ,wherein the sense strand consists of the nucleotide sequence 5' - csusucuuAfaUfGfAfuugaacaaaaL96 – 3' (SEQ ID NO: 35) and the antisense strand consists of the nucleotide sequence 5' – usUfsuugu(Tgn)caaucaUfuAfagaagsasc – 3' (SEQ ID NO: 34),

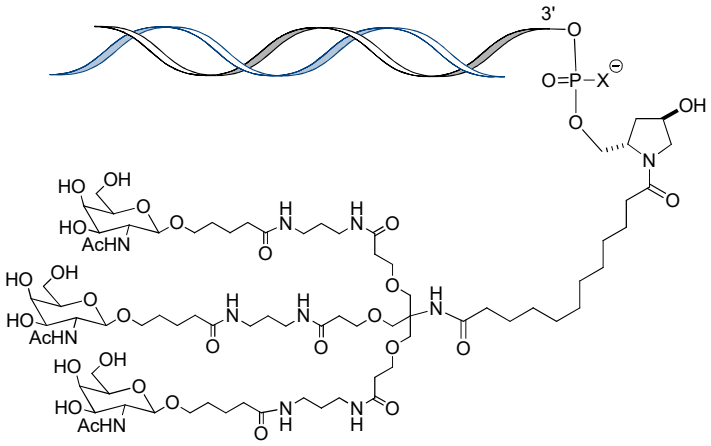
wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

26. The dsRNA agent of claim 7, wherein the sense strand comprises the nucleotide sequence 5' - csusucuuAfaUfGfAfuugaacaaaa – 3' (SEQ ID NO: 33) and the antisense strand

comprises the nucleotide sequence 5’ – usUfsuugu(Tgn)caaucaUfuAfagaagsasc – 3’ (SEQ ID NO: 34) ,

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and

wherein the 3’-end of the sense strand is conjugated to a ligand as shown in the following schematic



wherein X is O or S.

27. The pharmaceutical composition of claim 9, comprising the dsRNA agent and an unbuffered solution.

28. The pharmaceutical composition of claim 27, wherein the unbuffered solution is saline or water.

29. The pharmaceutical composition of claim 9, comprising the dsRNA agent and a buffer solution.

30. The pharmaceutical composition of claim 29, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

31. The pharmaceutical composition of claim 29, wherein the buffer solution is phosphate buffered saline (PBS).

32. A double stranded RNA (dsRNA) agent that inhibits expression of a serine peptidase inhibitor, clade A, member 1 (Serpina1) gene, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence 5' - csusucuuAfaUfGfAfuugaacaaaaL96 – 3' (SEQ ID NO: 35) and the antisense strand comprises the nucleotide sequence 5' – usUfsuugu(Tgn)caaucaUfuAfagaagsasc – 3' (SEQ ID NO: 34),

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

33. An isolated cell containing the dsRNA agent of claim 32.

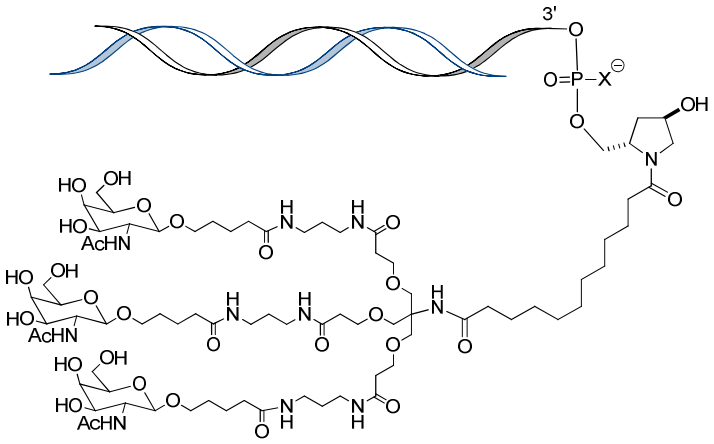
34. A pharmaceutical composition comprising the dsRNA agent of claim 32.

35. A double stranded RNA (dsRNA) agent that inhibits expression of a serine peptidase inhibitor, clade A, member 1 (Serpina1) gene, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence 5' - csusucuuAfaUfGfAfuugaacaaaa – 3' (SEQ ID NO: 33) and the antisense strand comprises the nucleotide sequence 5' – usUfsuugu(Tgn)caaucaUfuAfagaagsasc – 3' (SEQ ID NO: 34) ,

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and

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



wherein X is O.

36. An isolated cell containing the dsRNA agent of claim 35.

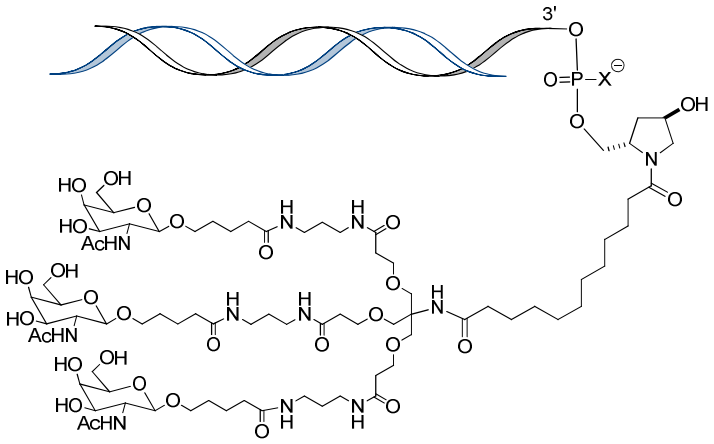
37. A pharmaceutical composition, comprising a double stranded RNA (dsRNA) agent that inhibits expression of a serine peptidase inhibitor, clade A, member 1 (Serpina1) gene,

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence 5' - csusucuuAfaUfGfAfuugaacaaaa – 3' (SEQ ID NO: 33) and the antisense strand comprises the nucleotide sequence 5' – usUfsuugu(Tgn)caaucaUfuAfagaagsasc – 3' (SEQ ID NO: 34) ,

wherein a, g, c, and u are 2′-O-methyl (2′-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2′-fluoro A, G, C and U, respectively; s is a phosphorothioate linkage; and (Tgn) is a thymidine-glycol nucleic acid (GNA) S-Isomer; and

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



wherein X is O.

38. An *in vitro* method of inhibiting Serpina1 expression in a cell, comprising contacting the cell with the dsRNA agent of any one of claims 1, 3, 4, 12-26, 32, and 36, or the pharmaceutical composition of any one of claims 9, 27-31, 34, and 37, thereby inhibiting expression of the Serpina1 gene in the cell.

39. The use of claim 10, wherein the double stranded RNAi agent is suitable for subcutaneous administration.

40. The use of claim 10, wherein the double stranded RNAi agent is suitable for intravenous administration.