We claim:

1. A double stranded RNAi agent for inhibiting expression of Serpina1 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, or SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, or SEQ ID NO:11, 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:15, SEQ ID NO:16, or SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:25 ,

wherein not more than 5 nucleotides of said sense strand are unmodified or do not 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 not more than 5 nucleotides of the antisense strand are unmodified or do not 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.

2. The double stranded RNAi agent of claim 1, wherein said RNAi agent comprises 15 or more nucleotides from the sense and antisense sequences selected from the group of RNAi agents listed in any one of Tables 1, 2, 5, 7, 8, and 9.

3. The double stranded RNAi agent of claim 1 or 2, wherein the double-stranded region is 15-30 nucleotide pairs in length.

4. The double stranded RNAi agent of claim 3, wherein the double-stranded region is 17-23 nucleotide pairs in length.

5. The double stranded RNAi agent of claim 3, wherein the double-stranded region is 17-25 nucleotide pairs in length.

6. The double stranded RNAi agent of claim 3, wherein the double-stranded region is 23-27 nucleotide pairs in length.

7. The double stranded RNAi agent of claim 3, wherein the double-stranded region is 19-21 nucleotide pairs in length.

8. The double stranded RNAi agent of claim 3, wherein the double-stranded region is 21-23 nucleotide pairs in length.

9. The double stranded RNAi agent of claim 1 or 2, wherein each strand has 15-30 nucleotides.

10. The double stranded RNAi agent of claim 1 or 2, wherein each strand has 19-30 nucleotides.

11. The double stranded RNAi agent of any one of claims 1 to 10, wherein one of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the seed region of the antisense strand.

12. The double stranded RNAi agent of claim 11, wherein the antisense strand comprises a universal base at the mismatched nucleotide.

13. The double stranded RNAi agent of claim 1 or 2, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

14. The double stranded RNAi agent of claim 2, wherein said RNAi agent consist of the sense and antisense nucleotide sequences selected from the group of RNAi nucleotide sequences listed in any one of Tables 1, 2, 5, 7, 8, and 9.

15. The double stranded RNAi agent of claim 1, wherein said sense strand comprises at least 19 contiguous nucleotides, differing by no more than 1 nucleotide, from the nucleotide sequence of CUUCUUAAUGAUUGAACAAAA (SEQ ID NO: 417) and said antisense strand comprises at least 19 contiguous nucleotides, differing by no more than 1 nucleotide, from the nucleotide sequence of UUUUGUUCAAUCAUUAAGAAGAC (SEQ ID NO: 419).

16. The double stranded RNAi agent of claim 1, wherein said sense strand comprises the nucleotide sequence of CUUCUUAAUGAUUGAACAAAA (SEQ ID NO: 417) and said antisense strand comprises at least 23 contiguous nucleotides, differing by no more than 1 nucleotide, from the nucleotide sequence of UUUUGUUCAAUCAUUAAGAAGAC (SEQ ID NO: 419).

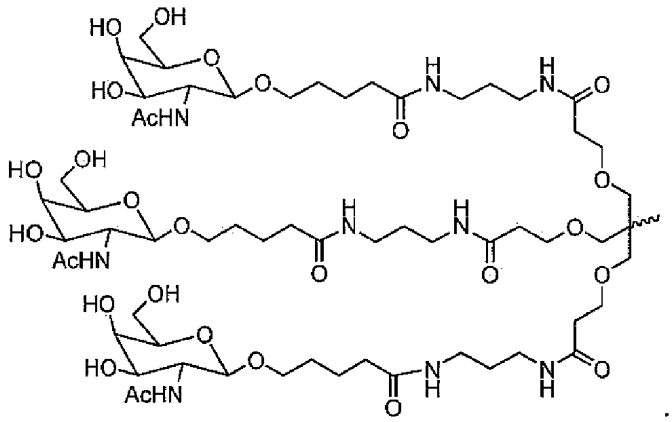
17. The double stranded RNAi agent of claim 1, wherein said sense strand consist of the nucleotide sequence of CUUCUUAAUGAUUGAACAAAA (SEQ ID NO: 417) and said antisense strand consist of 23 contiguous nucleotides, differing by no more than 1 nucleotide, from the nucleotide sequence of UUUUGUUCAAUCAUUAAGAAGAC (SEQ ID NO: 419).

18. The double stranded RNAi agent of claim 1, wherein said sense strand comprises at least 19 contiguous nucleotides, differing by no more than 1 nucleotide, from the nucleotide sequence of csusucuuaauGfAfuugaacaaaa (SEQ ID NO: 418) and said antisense strand comprises at least 19 contiguous nucleotides, differing by no more than 1 nucleotide, from the nucleotide sequence of usUfsuUfgUfuCfaAfucaUfuAfaGfaAfgsasc (SEQ ID NO: 420).

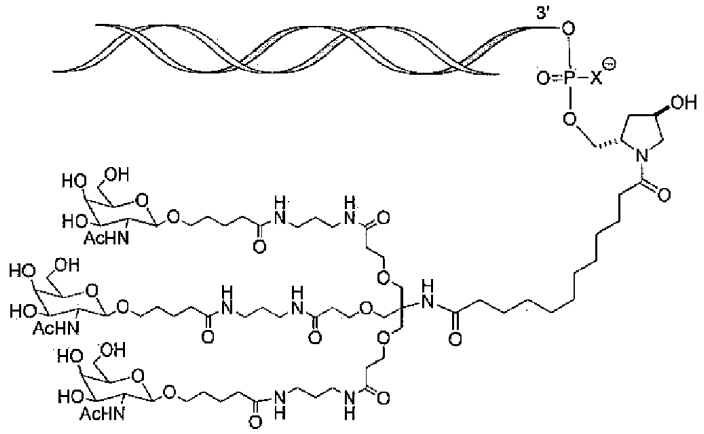
19. The double stranded RNAi agent of claim 1, wherein said sense strand comprises the nucleotide sequence of csusucuuaauGfAfuugaacaaaa (SEQ ID NO: 418) and said antisense strand comprises at least 23 contiguous nucleotides, differing by no more than 1 nucleotide, from the nucleotide sequence of usUfsuUfgUfuCfaAfucaUfuAfaGfaAfgsasc (SEQ ID NO: 420).

20. The double stranded RNAi agent of claim 1, wherein said sense strand consist of the nucleotide sequence of csusucuuaauGfAfuugaacaaaa (SEQ ID NO: 418) and said antisense strand consist of 23 contiguous nucleotides, differing by no more than 1 nucleotide, from the nucleotide sequence of usUfsuUfgUfuCfaAfucaUfuAfaGfaAfgsasc (SEQ ID NO: 420), and wherein the sense strand is conjugated to N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol Hyp-(GalNAc-alkyl)3.

21. The double stranded RNAi agent of any one of claims 1 to 19, wherein the GalNAc ligand is



22. The double stranded RNAi agent of claim 19 or 21, wherein the RNAi agent is conjugated to the GalNAc ligand as shown in the following schematic



wherein X is O or S.

23. The double stranded RNAi agent of claim 1, wherein said RNAi agent is selected from the group consisting of AD-58681 (SEQ ID NO: 217 and SEQ ID NO: 305), AD-59054

(SEQ ID NO: 221 and SEQ ID NO: 309), AD-61719 (SEQ ID NO: 425 and SEQ ID NO: 433), and AD-61444 (SEQ ID NO: 418 and SEQ ID NO: 420).

24. A cell containing the double stranded RNAi agent of any one of claims 1 to 23.

25. A pharmaceutical composition comprising the double stranded RNAi agent of any one of claims 1 to 23.

26. The pharmaceutical composition of claim 25, wherein RNAi agent is to be administered in an unbuffered solution.

27. The pharmaceutical composition of claim 26, wherein said unbuffered solution is saline or water.

28. The pharmaceutical composition of claim 25, wherein said siRNA is to be administered with a buffer solution.

29. The pharmaceutical composition of claim 28, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

30. The pharmaceutical composition of claim 28, wherein said buffer solution is phosphate buffered saline (PBS).

31. A method of inhibiting Serpina1 expression in a cell, the method comprising:

(a) contacting the cell *in vitro* with the double stranded RNAi agent of any one of claims 1 to 23, or the pharmaceutical composition of any one of claims 25 to 30; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a Serpina1 gene, thereby inhibiting expression of the Serpina1 gene in the cell.

32. The method of claim 31, wherein the Serpina1 expression is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, or about 100%.

33. The double stranded RNAi agent of any one of claims 1 to 23, or the pharmaceutical composition of any one of claims 25 to 30, for use in therapy.

34. Use of the double stranded RNAi agent of any one of claims 1 to 23, or the pharmaceutical composition of any one of claims 25 to 30, in the manufacture of a medicament for the treatment of a Serpina1-associated disorder in a subject, wherein the Serpina1-associated disorder is a liver disorder.

35. The use of claim 33 or 34, wherein the subject is a human.

36. The use of claim 33 or 35, wherein the liver disorder is selected from the group consisting of chronic liver disease, liver inflammation, cirrhosis, liver fibrosis, and/or hepatocellular carcinoma

37. The use of claim 33, wherein the double stranded RNAi agent is for administration at a dose of 0.01 mg/kg to 10 mg/kg or 0.5 mg/kg to 50 mg/kg.

38. The use of claim 37, wherein the double stranded RNAi agent is for administration at a dose of 10 mg/kg to 30 mg/kg.

39. The use of claim 37, wherein the double stranded RNAi agent is for administration at a dose of about 3 mg/kg.

40. The use of claim 37, wherein the double stranded RNAi agent is for administration at a dose of about 10 mg/kg.

41. The use of claim 37, wherein the double stranded RNAi agent is for administration at a dose of about 0.5 mg/kg twice per week.

42. The use of claim 38, wherein the double stranded RNAi agent is for administration at a dose of about 10 mg/kg every other week.

43. The use of claim 37, wherein the double stranded RNAi agent is for administration at a dose of about 0.5-1 mg/kg once per week.

44. The use of claim 37, wherein the double stranded RNAi agent is for subcutaneous administration.

45. The use of claim 37, wherein the double stranded RNAi agent is for intravenous administration.

46. The use of claim 37, wherein said RNAi agent is for administration in two or more doses.

47. The use of claim 46, wherein said RNAi agent is for administration 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.

48. Use of the double stranded RNAi agent of any one of claims 1 to 23, or the pharmaceutical composition of any one of claims 25 to 30, in the manufacture of a medicament for the inhibition of development of Serpina1-associated hepatocellular carcinoma in a subject.