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 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:15,

wherein said antisense strand comprises at least one thermally destabilizing modification of the double stranded region within the first 9 nucleotide positions of the 5′ region or a precursor thereof,

wherein said sense strand comprises an ASGPR ligand, and

wherein each of the sense strand and the antisense strand are independently 14 to 40 nucleotides in length.

2. 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, said antisense strand comprising a region of complementarity to an mRNA encoding Serpina1, wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:15,

wherein said antisense strand comprises at least one thermally destabilizing modification within the first 9 nucleotide positions of the 5′ region or a precursor thereof,

wherein said sense strand comprises an ASGPR ligand,

wherein each of the sense strand and the antisense strand are independently 14 to 40 nucleotides in length.

3. The dsRNA agent according to claim 1 or 2, wherein the dsRNA agent comprises at least four nucleotides comprising a 2’-fluoro modification.

4. The dsRNA agent according to claim 1 or 2, having the following characteristics:

a) the thermally destabilizing modification is located in position 4-8 of the 5′ region of the antisense strand;

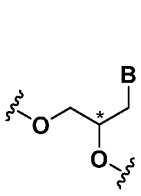
b) each of the sense and antisense strands independently comprise at least two nucleotides comprising a 2’-fluoro modification; and

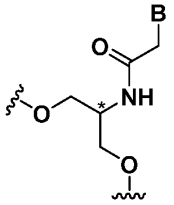
c) an ASGPR ligand attached to either end of the sense strand.

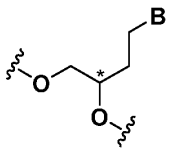
5. The dsRNA agent according to claim 1 or 2, wherein the antisense strand has at least two of the following characteristics:
a) the thermally destabilizing modification is located in position 4 to 8 of the antisense strand;
b) at least two nucleotides comprise a 2'-fluoro modification;
c) a phosphorothioate internucleotide linkage between nucleotide positions 1 and 2 (counting from the 5' end);
d) a length of 18 to 35 nucleotides.

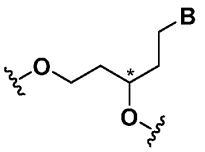
6. The dsRNA agent according to claim 1 or 2, wherein the sense strand has at least one of the following characteristics:
a) the ASGPR ligand attached to either end of the sense strand;
b) at least two nucleotides comprise a 2'-fluoro modification;
c) the double stranded region spans at least 19 nucleotide positions and wherein the thermally destabilizing modification is located within said double stranded region.

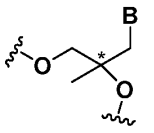
7. The dsRNA agent according to claim 1 or 2, wherein the thermally destabilizing modification is selected from the group consisting of

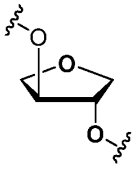


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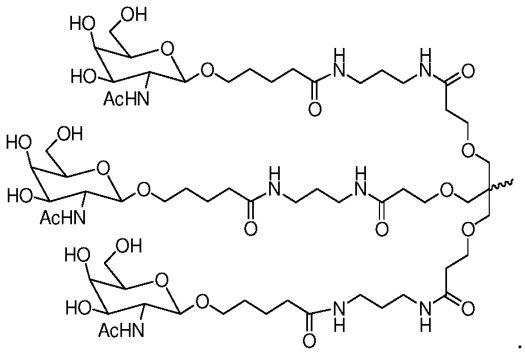
,

wherein B is nucleobase.

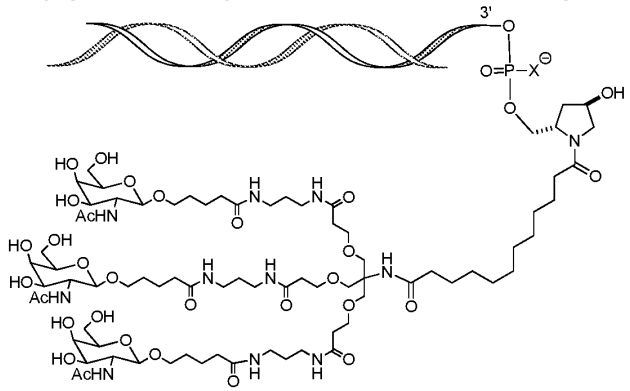
8. The dsRNA agent according to 1 or 2, wherein the destabilizing modification is located in position 7 of the antisense strand.

9. The dsRNA agent acccording to claim 1 or 2, wherein the ASGPR ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

10. The dsRNA agent of claim 9, wherein the ASGPR ligand is:



11. The double stranded RNAi agent of claim 10, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

12. A double stranded RNA molecule that inhibits expression of a serine peptidase inhibitor, clade A, member 1 (Serpina1) target gene sequence, comprising a sense strand and an antisense strand,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:15,

wherein the antisense strand comprises at least one thermally destabilizing modification within the first 9 nucleotide positions of the 5′ region,

wherein each of the sense strand and the antisense strand are independently 14 to 40 nucleotides in length, and

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

13. A double stranded RNA molecule that inhibits expression of a serine peptidase inhibitor, clade A, member 1 (Serpina1) target gene sequence, comprising a sense strand and an antisense strand, said antisense strand comprising a region of complementarity to an mRNA encoding Serpina1, wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:15,

wherein the antisense strand comprises at least one thermally destabilizing modification within the first 9 nucleotide positions of the 5′ region,

wherein each of the sense strand and the antisense strand are independently 14 to 40 nucleotides in length, and

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

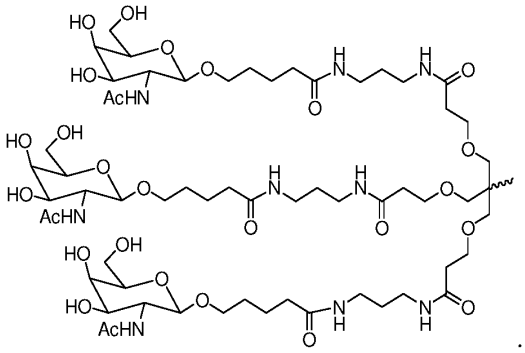
14. The dsRNA agent of claim 12 or 13, wherein the dsRNA has a melting temperature of from about 55°C to about 67°C.

15. The dsRNA agent of claim 14, wherein the dsRNA has a melting temperature of from about 60°C to about 67°C.

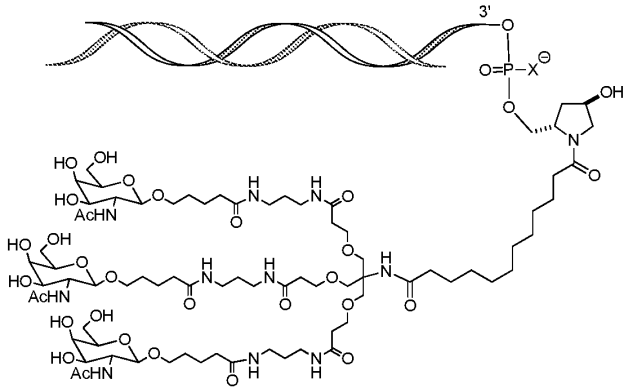
16. The dsRNA agent of any one of claims 12-14, further comprising an ASGPR ligand.

17. The dsRNA agent of claim 16, wherein the ASGPR ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

18. The dsRNA agent of claim 17, wherein the ASGPR ligand is:



19. The double stranded RNAi agent of claim 18, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

20. The dsRNA of any one of claims 1-19, wherein the dsRNA further has at least one of the following characteristics:
(i) the antisense strand comprises 2, 3, 4, 5 or 6 nucleotides comprising a 2'-fluoro modifications;
(ii) the antisense strand comprises 1, 2, 3 or 4 phosphorothioate internucleotide linkages;
(iii) the sense strand is conjugated with a ligand;
(iv) the sense strand comprises 2, 3, 4 or 5 nucleotides comprising a 2'-fluoro modification;
(v) the sense strand comprises 1, 2, 3 or 4 phosphorothioate internucleotide linkages;
(vi) the dsRNA comprises at least four nucleotides comprising a 2'-fluoro modification;
(vii) the dsRNA comprises a double stranded region region of 12-40 nucleotide pairs in length; and
(viii) a blunt end at 5'end of the antisense strand.

21. The dsRNA agent of any one of claims 1-4 or 7-20, wherein each strand has 15-30 nucleotides.

22. The ddRNA agent of any one of claims 1-4 or 7-20, wherein each strand has 19-30 nucleotides.

23. The dsRNA agent of any one of claims 1-20, wherein the sense strand has 21 nucleotides, and the antisense strand has 23 nucleotides.

24. The dsRNA agent of claim 2, wherein the antisense strand comprises a region of complementarity comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 1440-1480 of SEQ ID NO:1.

25. The dsRNA agent of claim 2, wherein the region of complemntarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5' – UUUUGUUCAAUCAUUAAGAAGAC – 3' (SEQ ID NO: 419).

26. The dsRNA agent of claim 1 or 2, 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).

27. The dsRNA agent of claim 1 or 2, 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.

28. A double stranded RNA (dsRNA) molecule 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.

29. A vector containing the dsRNA agent of any one of claims 1-28.

30. A cell containing the dsRNA agent of any one of claims 1-28.

31. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-28.

32. The pharmaceutical composition of claim 31, wherein RNAi agent is administered in an unbuffered solution.

33. The pharmaceutical composition of claim 32, wherein said unbuffered solution is saline or water.

34. The pharmaceutical composition of claim 31, wherein said siRNA is administered with a buffer solution.

35. The pharmaceutical composition of claim 34, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

36. The pharmaceutical composition of claim 34, wherein said buffer solution is phosphate buffered saline (PBS).

37. A method of inhibiting Serpina1 expression in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-28, the vector of claim 29, or the pharmaceutical composition of any one of claims 31-36, thereby inhibiting expression of the Serpina1 gene in the cell.

38. The method of claim 37, wherein said cell is within a subject.

39. The method of claim 38, wherein the subject is a human.

40. The method of any one of claims 37-39, 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%.

41. A method of treating a subject having a Serpina1 associated disease, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-28, the vector of claim 29, or the pharmaceutical composition of any one of claims 31-36, thereby treating said subject.

42. The method of claim 41, wherein the subject is a human.

43. The method of claim 41, wherein the Serpina1 associated disease is a liver disorder.

44. The method of claim 43, wherein the liver disorder is selected from the group consisting of chronic liver disease, liver inflammation, cirrhosis, liver fibrosis, and/or hepatocellular carcinoma.

45. The method of claim 41, wherein the double stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

46. The method of claim 45, wherein the double stranded RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

47. The method of claim 41, wherein the double stranded RNAi agent is administered subcutaneously.

48. The method of claim 41, wherein the double stranded RNAi agent is administered intravenously.

49. The method of claim 41, wherein said RNAi agent is administered in two or more doses.

50. A method of inhibiting development of hepatocellular carcinoma in a subject having a Serpina1 deficiency variant, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-28, the vector of claim 29, or the pharmaceutical composition of any one of claims 31-36, thereby inhibiting development of hepatocellular carcinoma in the subject.

51. The method of claim 50, wherein the subject is a primate or rodent.

52. The method of claim 50, wherein the subject is a human.

53. The method of claim 50, wherein the double stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

54. The method of claim 53, wherein the double stranded RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

55. The method of claim 50, wherein said RNAi agent is administered in two or more doses.

56. The method of claim 50, wherein the double stranded RNAi agent is administered subcutaneously.

57. The method of claim 50, wherein the double stranded RNAi agent is administered intravenously.

58. A method of reducing the accumulation of misfolded Serpina1 in the liver of a subject having a Serpina1 deficiency variant, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-28, the vector of claim 29, or the pharmaceutical composition of any one of claims 31-36, thereby reducing the accumulation of misfolded Serpina1 in the liver of the subject.

59. The method of claim 58, wherein the subject is a primate or rodent.

60. The method of claim 58, wherein the subject is a human.

61. The method of claim 58, wherein the double stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

62. The method of claim 61, wherein the double stranded RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

63. The method of claim 58, wherein said RNAi agent is administered in two or more doses.

64. The method of claim 58, wherein the double stranded RNAi agent is administered subcutaneously.

65. The method of claim 58, wherein the double stranded RNAi agent is administered intravenously.