**We claim:**

1. A double stranded ribonucleic acid (dsRNA) agent, or salt thereof, for inhibiting expression of transthyretin (TTR) in a cell,

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

wherein the nucleotide sequence of the sense strand differs by no more than 4 bases from the nucleotide sequence 5'-csasagagUfaUfUfCfcauuuuuacu-3' of SEQ ID NO: 21 and the nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'-asGfsuaaAfaauggaaUfaCfucuugsgsu-3' of SEQ ID NO: 22,

wherein a, c, g, and u are 2′-O-methyl (2′-OMe) A, C, G, and U, respectively; Af, Cf, Gf and Uf are 2′-fluoro A, C, G and U, respectively; s is a phosphorothioate linkage, and

wherein at least one strand is conjugated to a ligand.

2. The dsRNA agent, or salt thereof, of claim 1, wherein the nucleotide sequence of the sense strand differs by no more than 3 bases from the nucleotide sequence 5'-csasagagUfaUfUfCfcauuuuuacu-3' of SEQ ID NO: 21 and the nucleotide sequence of the antisense strand differs by no more than 3 bases from the nucleotide sequence 5'-asGfsuaaAfaauggaaUfaCfucuugsgsu-3' of SEQ ID NO: 22.

3. The dsRNA agent, or salt thereof, of claim 1, wherein the nucleotide sequence of the sense strand differs by no more than 2 bases from the nucleotide sequence 5'-csasagagUfaUfUfCfcauuuuuacu-3' of SEQ ID NO: 21 and the nucleotide sequence of the antisense strand differs by no more than 2 bases from the nucleotide sequence 5'-asGfsuaaAfaauggaaUfaCfucuugsgsu-3' of SEQ ID NO: 22.

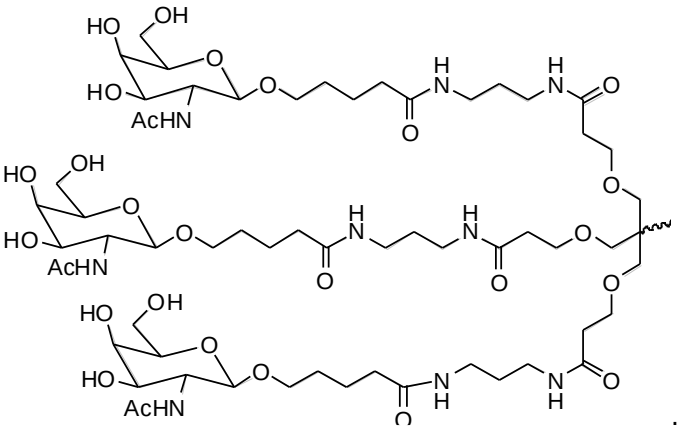
4. The dsRNA agent, or salt thereof, of claim 1, wherein the nucleotide sequence of the sense strand differs by no more than 1 base from the nucleotide sequence 5'-csasagagUfaUfUfCfcauuuuuacu-3' of SEQ ID NO: 21 and the nucleotide sequence of the antisense strand differs by no more than 1 base from the nucleotide sequence 5'-asGfsuaaAfaauggaaUfaCfucuugsgsu-3' of SEQ ID NO: 22.

5. The dsRNA agent, or salt thereof, of claim 1, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

6. The dsRNA agent, or salt thereof, of claim 1, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

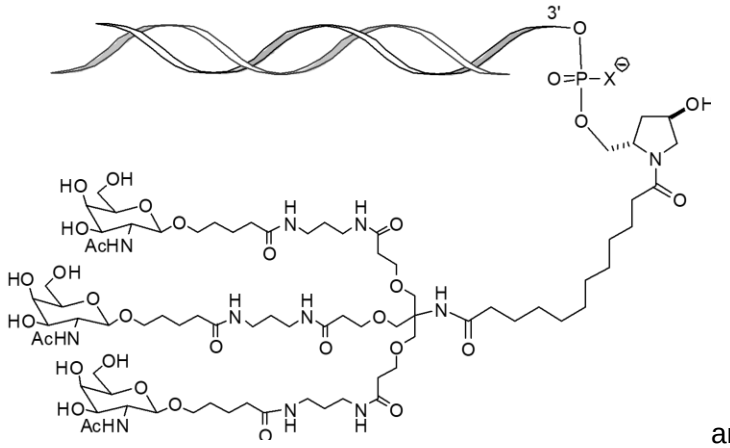
7. The dsRNA agent, or salt thereof, of claim 1, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

8. The dsRNA agent, or salt thereof, of claim 7, wherein the ligand is



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9. The dsRNA agent, or salt thereof, of claim 8, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

10. The dsRNA agent, or salt thereof, of claim 9, wherein X is O.

11. A double stranded ribonucleic acid (dsRNA) agent, or salt thereof, for inhibiting expression of transthyretin (TTR) in a cell,

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'-csasagagUfaUfUfCfcauuuuuacu-3' of SEQ ID NO: 21 and the antisense strand comprises the nucleotide sequence 5'-asGfsuaaAfaauggaaUfaCfucuugsgsu-3' of SEQ ID NO: 22,

wherein a, c, g, and u are 2′-O-methyl (2′-OMe) A, C, G, and U, respectively; Af, Cf, Gf and Uf are 2′-fluoro A, C, G and U, respectively; s is a phosphorothioate linkage, and wherein at least one strand is conjugated to a ligand.

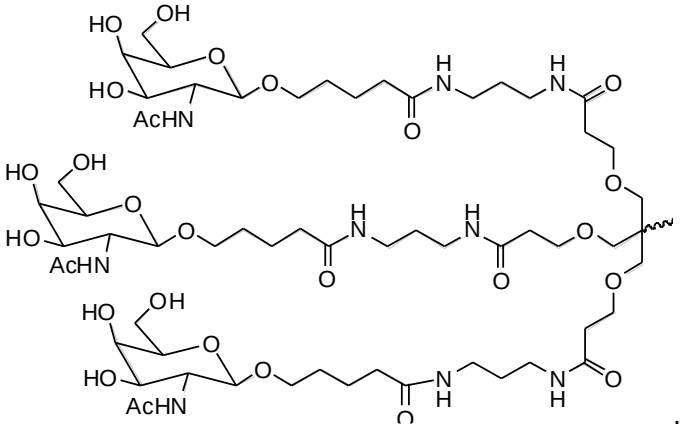
12. The dsRNA agent, or salt thereof, of claim 11, wherein the sense strand consists of the nucleotide sequence 5'-csasagagUfaUfUfCfcauuuuuacu-3' of SEQ ID NO: 21 and the antisense strand consists of the nucleotide sequence 5'-asGfsuaaAfaauggaaUfaCfucuugsgsu-3' of SEQ ID NO: 22.

13. The dsRNA agent, or salt thereof, of claim 11, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

14. The dsRNA agent, or salt thereof, of claim 11, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

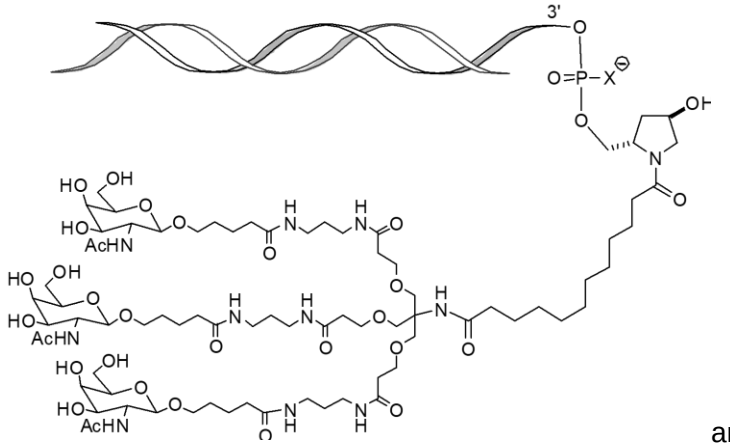
15. The dsRNA agent, or salt thereof, of claim 11, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

16. The dsRNA agent, or salt thereof, of claim 15, wherein the ligand is




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17. The dsRNA agent, or salt thereof, of claim 16, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

18. The dsRNA agent, or salt thereof, of claim 17, wherein X is O.

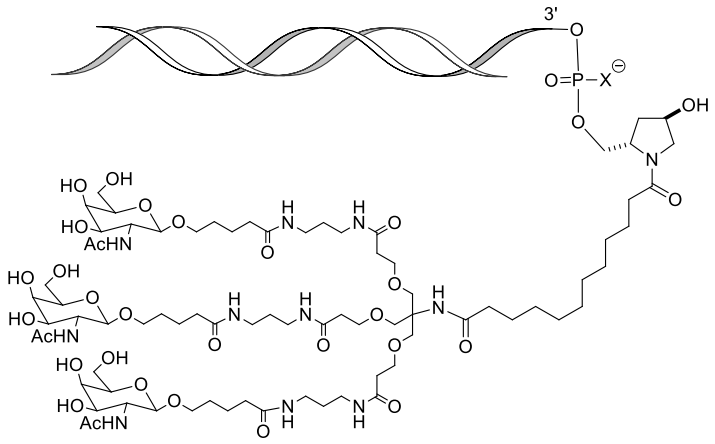
19. A double stranded ribonucleic acid (dsRNA) agent, or salt thereof, for inhibiting expression of transthyretin (TTR) in a cell,

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'-csasagagUfaUfUfCfcauuuuuacu-3' of SEQ ID NO: 21 and the antisense strand comprises the nucleotide sequence 5'-asGfsuaaAfaauggaaUfaCfucuugsgsu-3' of SEQ ID NO: 22,

wherein a, c, g, and u are 2′-O-methyl (2′-OMe) A, C, G, and U, respectively; Af, Cf, Gf and Uf are 2′-fluoro A, C, G and U, respectively; s is a phosphorothioate linkage, and

wherein the dsRNA agent is conjugated to a ligand as shown in the following schematic



, wherein X is O.

20. The dsRNA agent, or salt thereof, of claim 19, wherein the sense strand consists of the nucleotide sequence 5'-csasagagUfaUfUfCfcauuuuuacu-3' of SEQ ID NO: 21 and the antisense

strand consists of the nucleotide sequence 5’-asGfsuaaAfaauggaaUfaCfucuugsgsu-3’ of SEQ ID NO: 22.

21. A cell containing the dsRNA agent, or salt thereof, of any one of claims 1-20.

22. A pharmaceutical composition for inhibiting expression of a gene encoding transthyretin (TTR) comprising the dsRNA agent, or salt thereof, of any one of claims 1-20, and a pharmaceutically acceptable carrier.

23. The pharmaceutical composition of claim 22, wherein dsRNA agent, or salt thereof, is in an unbuffered solution.

24. The pharmaceutical composition of claim 23, wherein the unbuffered solution is saline or water.

25. The pharmaceutical composition of claim 22, wherein the dsRNA agent, or salt thereof, is in a buffer solution.

26. The pharmaceutical composition of claim 25, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

27. The pharmaceutical composition of claim 25, wherein the buffer solution is phosphate buffered saline (PBS).

28. The pharmaceutical composition of claim 22, wherein dsRNA agent is in a salt form.

29. The pharmaceutical composition of claim 22, wherein dsRNA agent is in a sodium salt form.

30. The pharmaceutical composition of claim 22, wherein dsRNA agent is in a free acid form.

31. An *in vitro* method of inhibiting expression of a transthyretin (TTR) gene in a cell, the method comprising contacting the cell with the dsRNA agent, or salt thereof, of any one of claims 1-20, or the pharmaceutical composition of any one of claims 21-30, thereby inhibiting expression of the TTR gene in the cell.

32. Use of the dsRNA agent, or salt thereof, of any one of claims 1-20, or the pharmaceutical composition of any one of claims 21-30, in the manufacture of a medicament for the treatment of a TTR-associated disease in a subject or a subject at risk for developing a TTR-associated disease.

33. The use of claim 32, wherein the subject is a human.

34. The use of claim 32 or 33, wherein said subject is a subject suffering from a TTR-associated disease.

35. The use of claim 32 or 33, wherein said subject is a subject at risk for developing a TTR-associated disease.

36. The use of any one of claims 32-35, wherein said subject carries a TTR gene mutation that is associated with the development of a TTR-associated disease.

37. The use of any one of claims 32-36, wherein said TTR-associated disease is selected from the group consisting of senile systemic amyloidosis (SSA), systemic familial amyloidosis, familial amyloidotic polyneuropathy (FAP), familial amyloidotic cardiomyopathy (FAC), leptomeningeal/Central Nervous System (CNS) amyloidosis, and hyperthyroxinemia.

38. The use of any one of claims 32-36, wherein said TTR-associated disease is an ocular disease.

39. The use of claim 38, wherein said ocular disease is Stargardt’s disease, diabetic retinopathy, or age-related macular degeneration (AMD).

40. The use of any one of claims 32-36, wherein said TTR-associated disease is a metabolic disorder.

41. The use of claim 40, wherein the metabolic disorder is a disorder of glucose and lipid homeostasis.

42. The use of claim 41, wherein the disorder of glucose and lipid homeostasis is insulin resistance associated with type II diabetes

43. The use of any one of claims 32-36, wherein said TTR-associated disease is a cardiovascular disease.

44. The use of any one of claims 32-43, wherein said subject has a transthyretin-mediated amyloidosis (ATTR amyloidosis) and said use reduces an amyloid TTR deposit in said subject.

45. The use of claim 44, wherein the ATTR is hereditary ATTR (h-ATTR).

46. The use of claim 44, wherein the ATTR is non-hereditary ATTR (wt ATTR).

47. The use of any one of claims 32-46, wherein the dsRNA agent, or salt thereof, or the pharmaceutical composition is to be administered to the subject and improves at least one indicia of neurological impairment, quality of life, ongoing nerve damage, or cardiovascular impairment in the subject.

48. The use of any one of claims 32-47, wherein the dsRNA agent, or salt thereof, or the pharmaceutical composition is to be administered to the human subject by subcutaneous administration or intravenous administration.

49. The use of claim 48, wherein the subcutaneous administration is self-administration.

50. The use of claim 49, wherein the self-administration is via a pre-filled syringe or auto-injector syringe.

51. The use of any one of claims 32-50, further comprising assessing the level of TTR mRNA expression or TTR protein expression in a sample derived from the human subject.

52. The dsRNA agent, or salt thereof, of any one of claims 1-20, or the pharmaceutical composition of any one of claims 21-30 for use in therapy.