identical modifications on three consecutive nucleotides, including one such motif at or near the cleavage site of the agents, show surprisingly enhanced TTR gene silencing activity. When a single such chemical motif is present in the agent, it is preferred to be at or near the cleavage region for enhancing of the gene silencing activity. Cleavage region is the region surrounding the cleavage site, *i.e.*, the site on the target mRNA at which cleavage occurs.

Accordingly, ~~in one aspect,~~ the present disclosure features RNAi agents, e.g., double stranded RNAi agents, for inhibiting expression of a transthyretin (TTR). The double stranded RNAi agent includes a sense strand complementary to an antisense strand. The antisense strand includes a region complementary to a part of an mRNA encoding transthyretin. Each strand has 14 to 30 nucleotides, and the double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$

(III).

In Formula III, i, j, k, and l are each independently 0 or 1; p, p′, q, and q′ are each independently 0-6; each N_a and N_a' independently represents an oligonucleotide sequence including 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence including at least two differently modified nucleotides; each N_b and N_b' independently represents an oligonucleotide sequence including 0-10 nucleotides which are either modified or unmodified or combinations thereof; each n_p, n_p', n_q, and n_q' independently represents an overhang nucleotide; XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represents one motif of three identical modifications on three consecutive nucleotides; modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′. In some embodiments, the sense strand is conjugated to at least one ligand, *e.g.*, at least one ligand, *e.g.*, at least one ligand attached to the 3' end of the sense strand. In other embodiments, the ligand may be conjugated to the antisense strand.

In some embodiments, i is 1; j is 1; or both i and j are 1.

In some embodiments, k is 1; l is 1; or both k and l are 1.

wherein lowercase nucleotides (a, u, g, c) indicate 2'-O-methyl nucleotides; Nf (e.g., Af) indicates a 2'-fluoro nucleotide; s indicates a phosphothiorate linkage; L96 indicates a $GalNAc_3$ ligand.

In one aspect, the present disclosure relates to double stranded RNAi agent comprising a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding transthyretin (TTR), wherein each strand has about 14 to about 30 nucleotides, wherein said double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$

(III)

wherein:

$j = 1$; and i, k, and l are 0;

p' is 2; p, q, and q' are 0;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 2-10 nucleotides which are modified nucleotides selected from the group consisting of 2'-fluoro nucleotide modifications and 2'-O-methyl nucleotide modifications;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-7 nucleotides which are modified nucleotides selected from the group consisting of 2'-fluoro nucleotide modifications and 2'-O-methyl nucleotide modifications;

n_p' represents an overhang nucleotide;

YYY, ZZZ, and Y'Y'Y' each independently represent one motif of three identical modifications on three consecutive nucleotides, wherein the Y nucleotides contain a 2'-fluoro modification, the Y' nucleotides contain a 2'-O-methyl modification, and the Z nucleotides contain a 2'-O-methyl modification;

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another aspect, the present disclosure features a cell containing the double stranded RNAi agent as defined above. The RNAi agent may inhibit expression of TTR.

In a further aspect, the present disclosure features a pharmaceutical composition comprising an RNAi agent as defined above. The RNAi agent may inhibit expression of TTR. In some embodiments, the pharmaceutical composition is a solution comprising the RNAi agent. In some embodiments, the solution comprising the RNAi agent is an unbuffered solution, e.g., saline solution or water. In other embodiments, the solution is a buffered solution, e.g., a solution of phosphate buffered saline (PBS). In other embodiments, the pharmaceutical composition is a liposome or a lipid formulation. In some embodiments, the lipid formulation comprises a XTC or MC3.

The present disclosure features methods of inhibiting expression of transthyretin (TTR) in a cell. The methods include contacting a cell with an RNAi agent, e.g., a double stranded RNAi agent, in an amount effective to inhibit expression of TTR in the cell, thereby inhibiting expression of TTR in the cell. In yet another aspect, the present disclosure features an RNAi agent as defined above or a pharmaceutical composition as defined above for use in inhibiting expression of transthyretin (TTR) in a cell, wherein said RNAi agent or pharmaceutical composition is in an amount effective to inhibit expression of said TTR in said cell.

In some embodiments, the expression of TTR is inhibited by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%.

In other embodiments, the cell is contacted *in vitro* with the RNAi agent. In other embodiments, the cell is present within a subject. In preferred embodiments, the subject is a human.

In further embodiments, the subject is a subject suffering from a TTR-associated disease and the effective amount is a therapeutically effective amount. In other embodiments, the subject is a subject at risk for developing a TTR-associated disease and the effective amount is a prophylactically effective amount. In some embodiments,

In some embodiments, the RNAi agent is administered in a solution. In some such embodiments, the siRNA is administered in an unbuffered solution. In one embodiment, the siRNA is administered in saline or water. In other embodiments, the siRNA is administred with a buffer solution, such as an acetate buffer, a citrate buffer, a prolamine buffer, a carbonate buffer, or a phosphate buffer or any combination thereof. In some embodiments, the buffer solution is phosphate buffered saline (PBS).

The present disclosure provides a method of inhibiting expression of transthyretin (TTR) in a cell, including contacting a cell with an RNAi agent, e.g., a double stranded RNAi agent, in an amount effective to inhibit expression of TTR in the cell. In one embodiment, the double stranded RNAi agent is selected from the group of agents listed in Table 1, thereby inhibiting expression of transthyretin (TTR) in the cell. ~~In another aspect, the present disclosure provides a double stranded RNAi agent for use in inhibiting expression of transthyretin (TTR) in a cell, said double stranded RNAi agent being in an amount effective to inhibit expression of TTR in said cell, wherein said double stranded RNAi agent is selected from the group of RNAi agents listed in Table 1.~~

The present disclosure provides a method of inhibiting expression of transthyretin (TTR) in a cell, including contacting a cell with an RNAi agent, e.g., a double stranded RNAi agent, in an amount effective to inhibit expression of TTR in the cell. In one embodiment, the double stranded RNAi agent is selected from the group consisting of AD-51544, AD-51545, AD-51546, and AD-51547, thereby inhibiting expression of transthyretin (TTR) in the cell. ~~In another aspect, the present disclosure provides a double stranded RNAi agent for use in inhibiting expression of transthyretin (TTR) in a cell, said double stranded RNAi agent being in an amount effective to inhibit expression of TTR in said cell, wherein said double stranded RNAi agent is selected from the group consisting of AD-51544, AD-51545, AD-51546, and AD-51547. In another aspect, the present disclosure provides a double stranded RNAi agent for use in inhibiting expression of transthyretin (TTR) in a cell, said double stranded RNAi agent being in an amount effective to inhibit expression of TTR in said cell, wherein said double stranded RNAi agent is AD-51547.~~

The present disclosure provides a method of treating or preventing a TTR-associated disease in a subject, including administering to the subject a therapeutically effective amount or a prophylactically effective amount of an RNAi agent, e.g., a double stranded RNAi agent. In one embodiment, the double stranded RNAi agent is selected from the group of agents listed in Table 1, thereby treating or preventing a TTR-associated disease in the subject. ~~In a further aspect, the present disclosure provides a double stranded RNAi agent for use in treating or preventing a TTR-associated disease in a subject, wherein said double stranded RNAi agent is selected from the group of agents listed in Table 1.~~

The present disclosure provides a method of treating or preventing a TTR-associated disease in a subject, including administering to the subject a therapeutically effective amount or a prophylactically effective amount of an RNAi agent, e.g., a double stranded RNAi agent. In one embodiment, the double stranded RNAi

agent is selected from the group consisting of AD-51544, AD-51545, AD-51546, and AD-51547, thereby treating or preventing a TTR-associated disease in the subject. ~~In yet another aspect, the present disclosure provides a double stranded RNAi agent for use in treating or preventing a TTR-associated disease in a subject, , wherein said double stranded RNAi agent is selected from the group consisting of AD-51544, AD-51545, AD-51546, and AD-51547. In yet another aspect, the present disclosure provides a double stranded RNAi agent for use in treating or preventing a TTR-associated disease in a subject, wherein said double stranded RNAi agent is AD-51547.~~

~~In further aspects, t~~The disclosure provides kits for performing the methods of the disclosure. In another aspect, there is provided a kit for use in treating or preventing a TTR-associated disease in a subject, comprising a RNAi agent as defined herein, and instructions for use The disclosure provides a kit for performing a method of inhibiting expression of transthyretin (TTR) in a cell comprising contacting a cell with an RNAi agent, e.g., a double stranded RNAi agent, in an amount effective to inhibit expression of said TTR in said cell, thereby inhibiting the expression of TTR in the cell. The kit comprises an RNAi agent and instructions for use and, optionally, means for administering the RNAi agent to the subject.

The present disclosure is further illustrated by the following detailed description and drawings.

Brief Description of the Drawings

Figure 1 is a graph depicting that administering to mice a single subcutaneous dose of a GalNAc-conjugated RNAi agent targeting TTR resulted in dose-dependent suppression of TTR mRNA.

Figure 2 is a graph depicting that administering to mice a single subcutaneous dose of 7.5 mg/kg or 30 mg/kg of a GalNAc conjugated RNAi agent targeting TTR resulted in long lasting suppression of TTR mRNA.

Figure 3 depicts the human TTR mRNA sequence.

Figure 4 is a graph depicting improved silencing activity of RNAi agents modified relative to the parent AD-45163.

Figure 5 is a graph depicting improved silencing activity of RNAi agents modified relative to the parent AD-45165.

Figure 6 is a graph depicting improved free uptake silencing following 4 hour incubation with RNAi agents modified relative to the parent AD-45163.

We claim:

1. A double stranded RNAi agent comprising a sense strand complementary to an antisense strand, wherein said antisense strand comprises a region complementary to part of an mRNA encoding transthyretin (TTR), wherein each strand has about 14 to about 30 nucleotides, wherein said double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X)$_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X'X'X')$_k$-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'- n_q' 5'

(III)

wherein:

j = 1; and i, ~~j,~~ k, and l are ~~each independently 0 or 1~~;

p' is 2; p, ~~p',~~ q, and q' are ~~each independently 0-6~~;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 2-10 ~~0-25~~ nucleotides which are ~~either~~ modified nucleotides selected from the group consisting of 2'-fluoro nucleotide modifications and 2'-O-methyl nucleotide modifications~~or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides~~;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-~~10~~ 7 nucleotides which are ~~either~~ modified nucleotides selected from the group consisting of 2'-fluoro nucleotide modifications and 2'-O-methyl nucleotide modifications~~or unmodified or combinations thereof~~;

~~each n_p, n_p', n_q, and n_q' independently~~ represents an overhang nucleotide;

~~XXX,~~ YYY, ZZZ, and ~~X'X'X',~~ Y'Y'Y'~~, and Z'Z'Z'~~ each independently represent one motif of three identical modifications on three consecutive nucleotides, wherein the Y nucleotides contain a 2'-fluoro modification, the Y' nucleotides contain a 2'-O-methyl modification, and the Z nucleotides contain a 2'-O-methyl modification;

~~modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and~~

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

2. The double stranded RNAi agent of claim 1, wherein the sense strand comprises the nucleobase sequence UGGGAUUUCAUGUAACCAAGA – 3' (SEQ ID NO:2211) and the antisense strand comprises the nucleotide sequence 5'-UCUUGGUUACAUGAAAUCCCAUC -3' (SEQ ID NO:2217)~~i is 1; j is 1; or both i and j are 1~~.

~~3. The RNAi agent of claim 1, wherein k is 1; l is 1; or both k and l are 1.~~

~~4. The RNAi agent of claim 1, wherein XXX is complementary to X'X'X', YYY is complementary to Y'Y'Y', and ZZZ is complementary to Z'Z'Z'.~~

~~5. The RNAi agent of claim 1, wherein the YYY motif occurs at or near the cleavage site of the sense strand.~~

~~6. The RNAi agent of claim 1, wherein the Y'Y'Y' motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end.~~

~~7. The RNAi agent of claim 6, wherein the Y' is 2'-O-methyl.~~

~~8. The RNAi agent of claim 1, wherein formula (III) is represented as formula (IIIa):~~

~~sense: 5' n_p-N_a-Y Y Y-N_b-Z Z Z-N_a-n_q 3'~~
~~antisense: 3' n_p'-N_a'-Y'Y'Y'-N_b'-Z'Z'Z'-N_a'-n_q' 5'~~
~~(IIIa)~~

~~wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.~~

~~9. The RNAi agent of claim 1, wherein formula (III) is represented as formula (IIIb):~~

~~sense: 5' n_p-N_a-X X X-N_b-Y Y Y-N_a-n_q 3'~~
~~antisense: 3' n_p'-N_a'-X'X'X'-N_b'-Y'Y'Y'-N_a'-n_q' 5'~~
~~(IIIb)~~

~~wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.~~

~~10. The RNAi agent claim 1, wherein formula (III) is represented as formula (IIIc):~~
~~sense: 5' n_p-N_a-X X X-N_b-Y Y Y-N_b-Z Z Z-N_a-n_q 3'~~

~~antisense: 3' n_p'-N_a'-X'X'X'-N_b'-Y'Y'Y'-N_b'-Z'Z'Z'-N_a'-n_q' 5'~~

~~(IIIc)~~

~~wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides and each N_a and N_a' independently represents an oligonucleotide sequence comprising 2-10 modified nucleotides.~~

~~11~~3. The RNAi agent of claim 1, wherein the duplex region is 15-30 nucleotide pairs in length.

~~12~~4. The RNAi agent of claim ~~11~~3, wherein the duplex region is 17-23 nucleotide pairs in length.

~~13~~5. The RNAi agent of claim ~~11~~3, wherein the duplex region is 17-25 nucleotide pairs in length.

~~14~~6. The RNAi agent of claim ~~11~~3, wherein the duplex region is 23-27 nucleotide pairs in length.

~~15~~7. The RNAi agent of claim ~~11~~3, wherein the duplex region is 19-21 nucleotide pairs in length.

~~16~~8. The RNAi agent of claim ~~13~~5, wherein the duplex region is 21-23 nucleotide pairs in length.

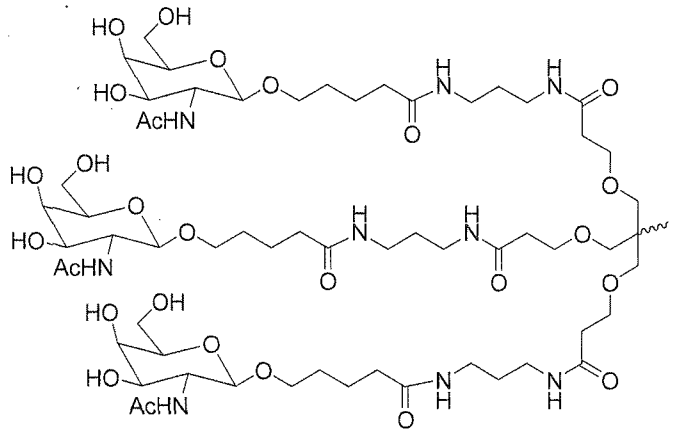
~~17~~9. The RNAi agent of claim 1, wherein each strand has 15-30 nucleotides.

~~18. The RNAi agent of claim 1, wherein the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and combinations thereof.~~

~~19. The RNAi agent of claim 18, wherein the modifications on the nucleotides are 2'-O-methyl,2'-fluoro or both.~~

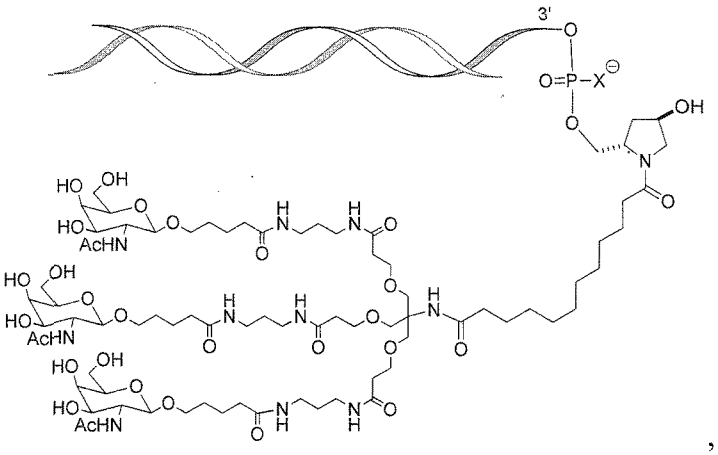
~~20~~10. The RNAi agent of claim 1, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

~~21~~11. The RNAi agent of claim 1, wherein the ligand is



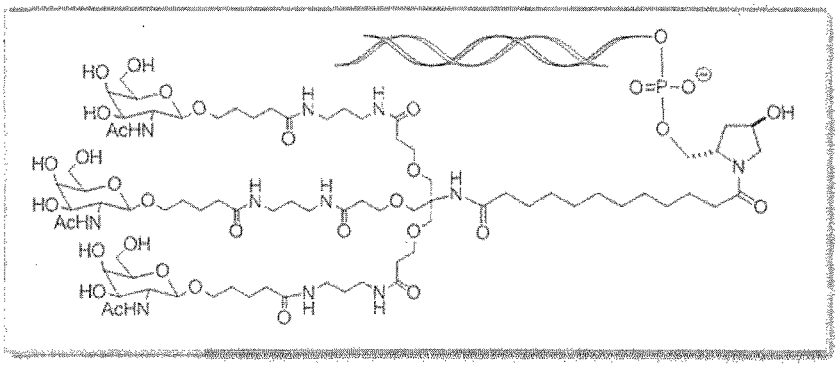
~~22~~12. The RNAi agent of claim 1, wherein the ligand is attached to the 3' end of the sense strand.

~~23~~13. The RNAi agent of claim ~~22~~12, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

~~24~~14. The RNAi agent of claim ~~23~~13, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



~~25~~15. The RNAi agent of claim 1 further comprising at least one phosphorothioate or methylphosphonate internucleotide linkage.

~~26~~16. The RNAi agent of claim ~~24~~15, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminal of one strand.

~~27~~17. The RNAi agent of claim ~~25~~16, wherein said strand is the antisense strand.

~~28~~18. The RNAi agent of claim ~~25~~16, wherein said strand is the sense strand.

~~29. The RNAi agent of claim 1, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.~~

~~30. The RNAi agent of claim 1, wherein the Y nucleotides contain a 2'-fluoro modification.~~

~~31. The RNAi agent of claim 1, wherein the Y' nucleotides contain a 2'-O-methyl modification.~~

~~32. The RNAi agent of claim 1, wherein p'>0.~~

~~33. The RNAi agent of claim 1, wherein p'=2.~~

~~34. The RNAi agent of claim 32, wherein q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA.~~

~~35. The RNAi agent of claim 32, wherein q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.~~

~~36. The RNAi agent of claim 32, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.~~

~~37. The RNAi agent of any one of claims 31-35, wherein at least one np' is linked to a neighboring nucleotide via a phosphorothioate linkage.~~

~~38. The RNAi agent of claim 36, wherein all np' are linked to neighboring nucleotides via phosphorothioate linkages.~~

~~39. The RNAi agent of claim 1 selected from the group of RNAi agents listed in Table 1.~~

~~40. The RNAi agent of claim 1 selected from the group consisting of AD-51544, AD-51545, AD-51546, and AD-51547.~~

~~41. The RNAi agent of claim 39, wherein the RNAi agent is AD-51547.~~

~~42~~19. A cell containing the double stranded RNAi agent of any one of claims 1 to ~~40~~18.

~~43~~20. A pharmaceutical composition comprising an RNAi agent of any one of claims 1 to ~~40~~18.

~~44~~21. The pharmaceutical composition of claim ~~42~~20, wherein RNAi agent is administered in an unbuffered solution.

~~45~~22. The pharmaceutical composition of claim ~~43~~21, wherein said unbuffered solution is saline or water.

~~46~~23. The pharmaceutical composition of claim ~~42~~20, wherein said siRNA is administered with a buffer solution.

~~47~~24. The pharmaceutical composition of claim ~~45~~23, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

4825. The pharmaceutical composition of claim 4624, wherein said buffer solution is phosphate buffered saline (PBS).

~~49. The pharmaceutical composition of claim 43, wherein said pharmaceutical composition is a liposome.~~

~~50. The pharmaceutical composition of claim 43, wherein said pharmaceutical composition is a lipid formulation.~~

5126. An RNAi agent of any one of claims 1 to 41 18 or a pharmaceutical composition of any one of claims 43 20 to 50 25 for use in inhibiting expression of transthyretin (TTR) in a cell, wherein said RNAi agent or pharmaceutical composition is in an amount effective to inhibit expression of said TTR in said cell.

~~52. The RNAi agent or pharmaceutical composition of claim 51, wherein expression of said TTR is inhibited by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%.~~

~~53. The RNAi agent or pharmaceutical composition of claim 51, wherein said cell is contacted *in vitro* with said RNAi agent.~~

~~54. The RNAi agent or pharmaceutical composition of claim 51, wherein said cell is present within a subject.~~

~~55. The RNAi agent or pharmaceutical composition of claim 54, wherein said subject is a human.~~

~~56. The RNAi agent or pharmaceutical composition of claim 54, wherein said subject is suffering from a TTR-associated disease and said effective amount is a therapeutically effective amount.~~

~~57. The RNAi agent or pharmaceutical composition of claim 54, wherein said subject is a subject at risk for developing a TTR-associated disease and said effective amount is a prophylactically effective amount.~~

~~58. The RNAi agent or pharmaceutical composition of claim 57, wherein said subject carries a TTR gene mutation that is associated with the development of a TTR-associated disease.~~

~~59. The RNAi agent or pharmaceutical composition of claim 56 or 57, 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.~~

~~60. The RNAi agent or pharmaceutical composition of claim 54, wherein said subject has a TTR-associated amyloidosis and said method reduces an amyloid TTR deposit in said subject.~~

~~61. The RNAi agent or pharmaceutical composition of claim 54, wherein said RNAi agent is formulated for administration to said subject by an administration means selected from the group consisting of subcutaneous, intravenous, intramuscular, intrabronchial, intrapleural, intraperitoneal, intraarterial, lymphatic, cerebrospinal, and any combinations thereof.~~

~~62. The RNAi agent or pharmaceutical composition of claim 54, wherein said RNAi agent is formulated for administration to said subject via subcutaneous, intramuscular or intravenous administration.~~

~~63. The RNAi agent or pharmaceutical composition of claim 62, wherein said subcutaneous administration comprises administration via a subcutaneous pump or subcutaneous depot.~~

~~64. The RNAi agent or pharmaceutical composition of claim 54, wherein said RNAi agent is formulated for administration to said subject, such that said RNAi agent is delivered to a specific site within said subject.~~

~~65. The RNAi agent or pharmaceutical composition of claim 64, wherein said site is selected from the group consisting of liver, choroid plexus, retina, and pancreas.~~

~~66. The RNAi agent or pharmaceutical composition of claim 64, wherein said site is the liver.~~

~~67. The RNAi agent or pharmaceutical composition of claim 64, wherein delivery of said RNAi agent is mediated by an asialoglycoprotein receptor (ASGP-R) present in hepatocytes.~~

~~68. The RNAi agent or pharmaceutical composition of claim 54, wherein said RNAi agent is formulated for administration at a dose of 0.05-50 mg/kg.~~

~~69. The RNAi agent or pharmaceutical composition of claim 54, wherein said RNAi agent is formulated for administration in two or more doses.~~

70. The RNAi agent or pharmaceutical composition of claim 69, wherein said RNAi agent is formulated 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.

71. The RNAi agent or pharmaceutical composition of claim 54, wherein the level of TTR mRNA expression or TTR protein expression is assessed in a sample derived from the subject.

72. The RNAi agent or pharmaceutical composition of claim 54, wherein administration of said RNAi agent does not result in an inflammatory response in said subject as assessed based on the level of a cytokine or chemokine selected from the group consisting of G-CSF, IFN-γ, IL-10, IL-12 (p70), IL1β, IL-1ra, IL-6, IL-8, IP-10, MCP-1, MIP-1α, MIP-1β, TNFα, and any combinations thereof, in a sample from said subject.

73. The RNAi agent or pharmaceutical composition of claim 54, wherein said RNAi agent is formulated for administration using a pharmaceutical composition.

74. The RNAi agent or pharmaceutical composition of claim 73, wherein said siRNA is formulated for administration in an unbuffered solution.

75. The RNAi agent or pharmaceutical composition of claim 74, wherein said unbuffered solution is saline or water.

76. The RNAi agent or pharmaceutical composition of claim 73, wherein said siRNA is formulated for administration with a buffer solution.

77. The RNAi agent or pharmaceutical composition of claim 76, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

78. The RNAi agent or pharmaceutical composition of claim 77, wherein said buffer solution is phosphate buffered saline (PBS).

79. The RNAi agent or pharmaceutical composition of claim 73, wherein said pharmaceutical composition is a liposome.

~~80~~27. An RNAi agent of any one of claims 1 to ~~41~~ 18 or a pharmaceutical composition of any one of claims ~~43~~ 20 to ~~50~~ 25 for use in treating or preventing a TTR-associated disease in a subject.

~~81~~28. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein TTR expression in a sample derived from said subject is inhibited by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%.

~~82~~29. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said subject is a human.

~~83~~30. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said subject is a subject suffering from a TTR-associated disease.

~~84~~31. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said subject is a subject at risk for developing a TTR-associated disease.

~~85~~32. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said subject carries a TTR gene mutation that is associated with the development of a TTR-associated disease.

~~86~~33. The RNAi agent or pharmaceutical composition of claim ~~80~~27, 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.

~~87~~34. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said subject has a TTR-associated amyloidosis and said method reduces an amyloid TTR deposit in said subject.

~~88~~35. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said RNAi agent is formulated for administration to said subject by an administration means selected from the group consisting of subcutaneous, intravenous, intramuscular, intrabronchial, intrapleural, intraperitoneal, intraarterial, lymphatic, cerebrospinal, and any combinations thereof.

~~89~~36. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said RNAi agent is formulated for administration to said subject via subcutaneous, intramuscular or intravenous administration.

~~90~~37. The RNAi agent or pharmaceutical composition of claim ~~89~~36, wherein said subcutaneous administration comprises administration via a subcutaneous pump or subcutaneous depot.

~~91~~38. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said RNAi agent is formulated for administration to said subject, such that said RNAi agent is delivered to a specific site within said subject.

~~92~~39. The RNAi agent or pharmaceutical composition of claim ~~91~~38, wherein said site is selected from the group consisting of liver, choroid plexus, retina, and pancreas.

~~93~~40. The RNAi agent or pharmaceutical composition of claim ~~91~~-38 wherein said site is the liver.

~~94~~41. The RNAi agent or pharmaceutical composition of claim ~~91~~38, wherein delivery of said RNAi agent is mediated by an asialoglycoprotein receptor (ASGP-R) present in hepatocytes.

~~95~~42. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said RNAi agent is formulated for administration at a dose of 0.05-50 mg/kg.

~~96~~43. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein said RNAi agent is formulated for administration in two or more doses.

~~97~~44. The RNAi agent or pharmaceutical composition of claim ~~96~~43, wherein said RNAi agent is formulated 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.

~~98~~45. The RNAi agent or pharmaceutical composition of claim ~~80~~27, wherein the level of TTR mRNA expression or TTR protein expression is assessed in a sample derived from the subject.

~~99. The RNAi agent or pharmaceutical composition of claim 80, wherein administration of said RNAi agent does not result in an inflammatory response in said subject as assessed based on the level of a cytokine or chemokine selected from the group consisting of G-CSF, IFN-γ, IL-10, IL-12 (p70), IL1β, IL-1ra, IL-6, IL-8, IP-10, MCP-1, MIP-1α, MIP-1β, TNFα, and any combinations thereof, in a sample from said subject.~~

~~10046~~. The RNAi agent or pharmaceutical composition of claim ~~8027~~, wherein said RNAi agent is formulated for administration using a pharmaceutical composition.

~~10147~~. The RNAi agent or pharmaceutical composition of claim ~~10046~~, wherein said siRNA is formulated for administration in an unbuffered solution.

~~10248~~. The RNAi agent or pharmaceutical composition of claim ~~10147~~, wherein said unbuffered solution is saline or water.

~~10349~~. The RNAi agent or pharmaceutical composition of claim ~~10046~~, wherein said siRNA is formulated for administration with a buffer solution.

~~10450~~. The RNAi agent or pharmaceutical composition of claim ~~10349~~, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

~~10551~~. The RNAi agent or pharmaceutical composition of claim ~~10450~~, wherein said buffer solution is phosphate buffered saline (PBS).

~~10652~~. The RNAi agent or pharmaceutical composition of claim ~~10046~~, wherein said pharmaceutical composition is a liposome.

~~107. A double stranded RNAi agent for use in inhibiting expression of transthyretin (TTR) in a cell, said double stranded RNAi agent being in an amount effective to inhibit expression of TTR in said cell, wherein said double stranded RNAi agent is selected from the group of RNAi agents listed in Table 1.~~

~~108. A double stranded RNAi agent for use in inhibiting expression of transthyretin (TTR) in a cell, said double stranded RNAi agent being in an amount effective to inhibit expression of TTR in said cell, wherein said double stranded RNAi agent is selected from the group consisting of AD-51544, AD-51545, AD-51546, and AD-51547.~~

~~109. A double stranded RNAi agent for use in inhibiting expression of transthyretin (TTR) in a cell, said double stranded RNAi agent being in an amount effective to inhibit expression of TTR in said cell, wherein said double stranded RNAi agent is AD-51547.~~

~~110. A a double stranded RNAi agent for use in treating or preventing a TTR-associated disease in a subject, wherein said double stranded RNAi agent is selected from the group of agents listed in Table 1.~~

~~111. A double stranded RNAi agent for use in treating or preventing a TTR-associated disease in a subject, , wherein said double stranded RNAi agent is selected from the group consisting of AD-51544, AD-51545, AD-51546, and AD-51547.~~

~~112. A double stranded RNAi agent for use in treating or preventing a TTR-associated disease in a subject, wherein said double stranded RNAi agent is AD-51547.~~

~~113~~53. A kit for use in treating or preventing a TTR-associated disease in a subject~~performing the method of claim 46~~, comprising

a) ~~said~~ a RNAi agent of any one of claims 1 to 18, and

b) instructions for use.

~~114. A kit for performing the method of claim 74, comprising~~

~~a) said RNAi agent,~~

~~b) instructions for use, and~~

~~c) optionally, means for administering said RNAi agent to said subject.~~