thyroxine with TTR due to a mutant TTR molecule with increased affinity for thyroxine. See, *e.g.*, Moses *et al.* (1982) *J. Clin. Invest.*, 86, 2025-2033.

Abnormal amyloidogenic proteins may be either inherited or acquired through somatic mutations. Guan, J. *et al.* (Nov. 4, 2011) Current perspectives on cardiac amyloidosis, *Am J Physiol Heart Circ Physiol*, doi:10.1152/ajpheart.00815.2011. Transthyretin associated ATTR is the most frequent form of hereditary systemic amyloidosis. Lobato, L. (2003) *J. Nephrol.*, 16:438-442. TTR mutations accelerate the process of TTR amyloid formation and are the most important risk factor for the development of ATTR. More than 85 amyloidogenic TTR variants are known to cause systemic familial amyloidosis. TTR mutations usually give rise to systemic amyloid deposition, with particular involvement of the peripheral nervous system, although some mutations are associated with cardiomyopathy or vitreous opacities. *Ibid.*

The V30M mutation is the most prevalent TTR mutation. See, *e.g.*, Lobato, L. (2003) *J Nephrol*, 16:438-442. The V122I mutation is carried by 3.9% of the African American population and is the most common cause of FAC. Jacobson, D.R. et al. (1997) *N. Engl. J. Med.* 336 (7): 466–73. It is estimated that SSA affects more than 25% of the population over age 80. Westermark, P. et al. (1990) *Proc. Natl. Acad. Sci. U.S.A.* **87** (7): 2843–5.

Accordingly, there is a need in the art for effective treatments for TTR-associated diseases.

Summary ~~of the Invention~~

The present ~~invention~~ disclosure provides RNAi agents, e.g., double stranded RNAi agents, targeting the Transthyretin (TTR) gene. The present disclosure ~~invention~~ also provides methods of inhibiting expression of TTR and methods of treating or preventing a TTR-associated disease in a subject using the RNAi agents, e.g. double stranded RNAi agents, of the invention. The present disclosure ~~invention~~ is based, at least in part, on the discovery that RNAi agents that comprise particular chemical modifications show a superior ability to inhibit expression of TTR. Agents including a certain pattern of chemical modifications (*e.g.*, an alternating pattern) and a ligand are shown herein to be effective in silencing the activity of the TTR gene. Furthermore, agents including one or more motifs of three

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

In a further aspect, the present disclosure ~~invention~~ features a pharmaceutical composition comprising an RNAi agent as defined above. The RNAi agent may inhibit ~~for inhibiting~~ 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 ~~In yet another aspect, the~~ present disclosure ~~invention~~ 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 using a pharmaceutical composition.

In preferred 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 water. In other embodiments, the siRNA is administered 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).

In another embodiment, the pharmaceutical composition is a liposome or a lipid formulation comprising SNALP or XTC. In one embodiment, the lipid formulation comprises an MC3.

~~In another aspect, the~~ The disclosure ~~invention~~ provides methods of treating or preventing a TTR-associated disease in a subject. The methods include administering to the subject a therapeutically effective amount or prophylactically effective amount of an RNAi agent, e.g., a double stranded RNAi agent, thereby treating or preventing the TTR-associated disease in the subject. In another aspect, the disclosure provides an RNAi agent as defined above or a pharmaceutical composition as defined above for use in treating or preventing a TTR-associated disease in a subject.

In some embodiments, TTR expression in a sample derived from the 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% or at least about 70% at least about 80%, or at least about 90%.

In some embodiments, the subject is a human.

In some embodiments, the subject is a subject suffering from a TTR-associated disease. In other embodiments, the subject is a subject at risk for developing a TTR-associated disease.

In some embodiments, the subject is a subject who carries s a TTR gene mutation that is associated with the development of a TTR-associated disease.

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 ~~In another aspect, the~~ present ~~invention~~ 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 ~~aspect~~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.

~~In another aspect, the~~ The present ~~invention~~ 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~~aspect~~, 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 ~~In a further aspect, the~~ present ~~invention~~ 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 ~~aspect~~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 ~~In yet another aspect, the~~ present ~~invention~~ 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 ~~aspect~~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, the ~~invention~~ disclosure provides kits for performing the methods of the disclosure~~invention~~. The disclosure ~~In one aspect, the invention~~ 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 ~~invention~~ 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.

48. The pharmaceutical composition of claim 47, 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.

51. An ~~method of inhibiting expression of a transthyretin (TTR) in a cell comprising contacting said cell with an~~ RNAi agent of any one of claims 1 to 41 or ~~with~~ a pharmaceutical composition of any one of claims 43 to 50 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~~, thereby inhibiting expression of said transthyretin (TTR) in said cell~~.

52. The ~~method~~ 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 ~~method~~ of claim 51, wherein said cell is contacted *in vitro* with said RNAi agent.

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

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

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

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

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

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

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

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

70. The RNAi agent or pharmaceutical composition ~~method~~ of claim 69, wherein said RNAi agent is formulated for administration ~~administered~~ 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 ~~method~~ of claim 54, wherein ~~further comprising assessing~~ 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 ~~method~~ of claim 54, wherein ~~administering~~ 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 ~~method~~ of claim 54, wherein said RNAi agent is formulated for administration ~~administered~~ using a pharmaceutical composition.

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

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

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

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

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

80. An ~~method of treating or preventing a TTR-associated disease in a subject, comprising administering to said subject a therapeutically effective amount or a prophylactically effective amount of an~~ RNAi agent of any one of claims 1 to 41 or a pharmaceutical composition of any one of claims 43 to 50 for use in ~~, thereby~~ treating or preventing ~~said~~ a TTR-associated disease in ~~said~~ a subject.

81. The RNAi agent or pharmaceutical composition ~~method~~ of claim 80, 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. The RNAi agent or pharmaceutical composition ~~method~~ of claim 80, wherein said subject is a human.

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

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

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

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

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

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

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

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

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

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

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

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

97. The RNAi agent or pharmaceutical composition ~~method~~ of claim 96, wherein said RNAi agent is formulated for administration ~~administered~~ 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. The RNAi agent or pharmaceutical composition ~~method~~ of claim 80, wherein ~~further comprising assessing~~ 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 ~~method~~ of claim 80, wherein ~~administering~~ 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.

100. The RNAi agent or pharmaceutical composition ~~method~~ of claim 80, wherein said RNAi agent is formulated for administration ~~administered~~ using a pharmaceutical composition.

101. The RNAi agent or pharmaceutical composition ~~method~~ of claim 100, wherein said siRNA is formulated for administration ~~administered~~ in an unbuffered solution.

102. The RNAi agent or pharmaceutical composition ~~method~~ of claim 101, wherein said unbuffered solution is saline or water.

103. The RNAi agent or pharmaceutical composition ~~method~~ of claim 100, wherein said siRNA is formulated for administration ~~administered~~ with a buffer solution.

104. The RNAi agent or pharmaceutical composition ~~method~~ of claim 103, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

105. The RNAi agent or pharmaceutical composition ~~method~~ of claim 104, wherein said buffer solution is phosphate buffered saline (PBS).

106. The RNAi agent or pharmaceutical composition ~~method~~ of claim 100, wherein said pharmaceutical composition is a liposome.

107. A ~~method of inhibiting expression of transthyretin (TTR) in a cell, comprising contacting said cell with 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~~, thereby inhibiting expression of transthyretin (TTR) in said cell~~.

108. A ~~method of inhibiting expression of transthyretin (TTR) in a cell, comprising contacting said cell with 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~~, thereby inhibiting expression of transthyretin (TTR) in said cell~~.

109. A ~~method of inhibiting expression of transthyretin (TTR) in a cell, comprising contacting said cell with 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~~, thereby inhibiting expression of transthyretin (TTR) in said cell~~.

110. A ~~method of treating or preventing a TTR-associated disease in a subject, comprising administering to said subject a therapeutically effective amount or a prophylactically effective amount of~~ 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~~, thereby treating or preventing a TTR-associated disease in said subject~~.

111. A ~~method of treating or preventing a TTR-associated disease in a subject, comprising administering to said subject a therapeutically effective amount or a prophylactically effective amount of 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~~, thereby treating or preventing a TTR-associated disease in said subject~~.

112. A ~~method of treating or preventing a TTR-associated disease in a subject, comprising administering to said subject a therapeutically effective amount or a prophylactically effective amount of 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~~, thereby treating or preventing a TTR-associated disease in said subject~~.

113. A kit for performing the method of claim 46, comprising

a) said RNAi agent, 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.