In addition, elevated RBP4 in the circulation of type 2 diabetic patients was reported many years ago (Basualdo C, *et al.*, (1997). *J. Am. Coll. Nutr.* 16, 39–45; Abahusain *et al.*, (1999). *Eur. J. Clin. Nutr.* 53, 630–635) and transgenic overexpression of RBP4 or injection of human RBP4 in normal mice were shown to cause insulin resistance. In contrast, genetic deletion of RBP4 or lowering of circulating RBP4 levels had the opposite effect and protected mice from developing insulin resistance (Yang, Q., *et al*. (2005). *Nature* 436, 356–362). In addition, positive associations were documented for circulating RBP4 or RBP4 expression levels with established cardiovascular disease (CVD) risk factors, including metabolic syndrome, overall/central obesity, dyslipidemia, inflammatory markers, and hypertension (Qi Q, *et al., J Clin Endocrinol Metab*. 2007; 92:4827–4834; Ingelsson E, *et al., Atherosclerosis*. 2009; 206:239–244). As indicated above, TTR regulates RBP4 and, thus, decreasing TTR results in a decrease in RBP4.

Any available current treatments for TTR-associated diseases such ocular diseases, *e.g.*, Stargardt's disease, diabetic retinopathy, age-related macular degeneration (AMD), *e.g.*, dry AMD and wet AMD; a metabolic disorder, *e.g.*, a disorder of glucose and lipid homeostasis, *e.g.*, insulin resistance associated with type II diabetes, and a cardiovascular disease, are not fully effective and may result in serous side effects, such as conjunctival hemorrhage, increased eye pressure, infection, retinal detachment and eye inflammation. Similarly, current treatments for metabolic diseases, including dieting, exercise, and medications to help control blood pressure, cholesterol and blood sugar levels, are not always effecive.

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

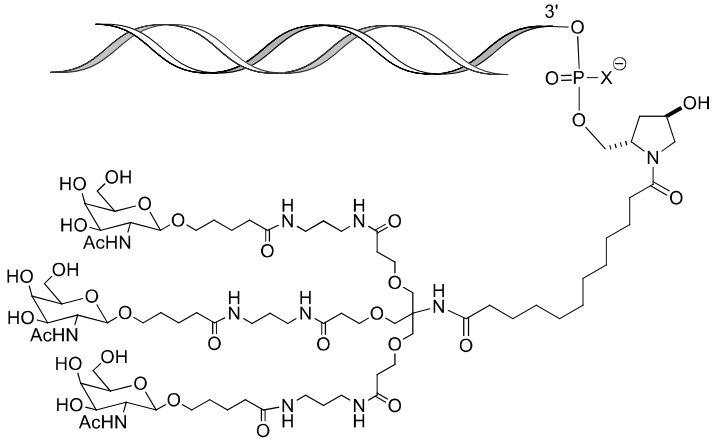
SUMMARY OF THE INVENTION

In one aspect, provided herein is 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.

In another aspect, provided herein is 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.

In another aspect, provided herein is 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.

In another aspect, provided herein is a cell containing the dsRNA agent, or salt thereof, as described herein.

In another aspect, provided herein is a pharmaceutical composition for inhibiting expression of a gene encoding transthyretin (TTR) comprising the dsRNA agent, or salt thereof, as described herein, and a pharmaceutically acceptable carrier.

In another aspect, provided herein is 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, as described herein, or the pharmaceutical composition as described herein, thereby inhibiting expression of the TTR gene in the cell.

In another aspect, provided herein is use of the dsRNA agent, or salt thereof, as described herein, or the pharmaceutical composition as described herein, 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.

In another aspect, provided herein is the dsRNA agent, or salt thereof, as described herein, or the pharmaceutical composition as described herein for use in therapy.

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding transthyretin (TTR). The TTR gene may be within a cell, *e.g.*, a cell within a subject, such as a human subject. The present

invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of an TTR gene and/or for treating a subject who would benefit from inhibiting or reducing the expression of an TTR gene, *e.g.*, a subject suffering or prone to suffering from an TTR-associated disorder, *e.g.*, senile systemic amyloidosis (SSA), systemic familial amyloidosis, familial amyloidotic polyneuropathy (FAP), familial amyloidotic cardiomyopathy (FAC), leptomeningeal/Central Nervous System (CNS) amyloidosis, hyperthyroxinemia, an ocular disease, *e.g.*, Stargardt's disease, diabetic retinopathy, age-related macular degeneration (AMD), *e.g.*, dry AMD and wet AMD; a metabolic disorder, *e.g.*, a disorder of glucose and lipid homeostasis, *e.g.*, insulin resistance associated with type II diabetes, and a cardiovascular disease.

Accordingly, in one aspect, the invention provides a double stranded ribonucleic acid (dsRNA) agent 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