

ANGIOPOIETIN-LIKE 3 (ANGPTL3) iRNA COMPOSITIONS AND METHODS OF USE THEREOF

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/156,476, filed on March 4, 2021, and U.S. Provisional Application No. 63/308,668, filed on February 10, 2022. The entire contents of each of the foregoing applications are incorporated herein by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 28, 2022, is named 121301_15120_SL.txt and is 316,668 bytes in size.

BACKGROUND OF THE INVENTION

Angiopietin-like 3 (ANGPTL3) is a member of the angiopietin-like family of secreted factors that regulates lipid metabolism and that is predominantly expressed in the liver (Koishi, R. *et al.*, (2002) *Nat. Genet.* 30(2):151-157). ANGPTL3 dually inhibits the catalytic activities of lipoprotein lipase (LPL), which catalyzes the hydrolysis of triglycerides, and of endothelial lipase (EL), which hydrolyzes high density lipoprotein (HDL) phospholipids. In hypolipidemic, yet obese, KK/Snk mice, a reduction in ANGPTL3 expression has a protective effect against hyperlipidemia and atherosclerosis by promoting the clearance of triglycerides (Ando *et al.*, (2003) *J. Lipid Res.*, 44:1216-1223). Human ANGPTL3 plasma concentrations positively correlate with plasma HDL cholesterol and HDL phospholipid levels (Shimamura *et al.*, (2007) *Arterioscler. Thromb. Vasc. Biol.*, 27:366-372).

Disorders of lipid metabolism can lead to elevated levels of serum lipids, such as triglycerides and/or cholesterol. Elevated serum lipids are strongly associated with high blood pressure, cardiovascular disease, diabetes and other pathologic conditions. Hypertriglyceridemia is an example of a lipid metabolism disorder that is characterized by high blood levels of triglycerides. It has been associated with atherosclerosis, even in the absence of high cholesterol levels (hypercholesterolemia). When triglyceride concentrations are excessive (*i.e.*, greater than 1000 mg/dl or 12 mmol/l), hypertriglyceridemia can also lead to pancreatitis. Hyperlipidemia is another example of a lipid metabolism disorder that is characterized by elevated levels of any one or all lipids and/or lipoproteins in the blood. Current treatments for disorders of lipid metabolism, including dieting, exercise and treatment with statins and other drugs, are not always effective. Accordingly, there is a need in the art for alternative treatments for subjects having disorders of lipid metabolism.

SUMMARY OF THE INVENTION

In one aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable

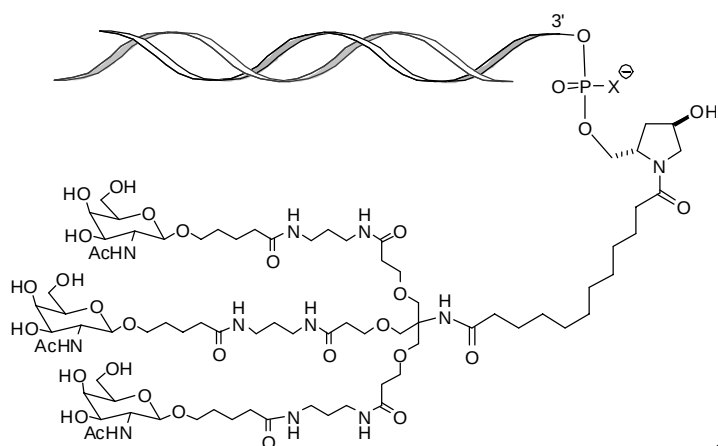
salt thereof, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 19 contiguous nucleotides of the nucleotide sequence 5'-

AAGCUCCUUCUUUUUAUUGUU-3' of SEQ ID NO:46 and the antisense strand comprises at least 21 contiguous nucleotides of the nucleotide sequence of 5'- AACAAUAAAAAGAAGGAGCUUGG-3' of SEQ ID NO:661, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification, and wherein at least one of the modifications is a 2'-deoxy-nucleotide modification.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable salt thereof, comprising 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'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'-asdAscAdAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19, wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-asdAscAdAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19, wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region, wherein the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'-asasgcuccuUfCfUfuuuuauuguu-3' of SEQ ID NO:20 and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'-asdAscAdAudAaaaadGaAfggagcuusgsg-3' of SEQ ID NO:19, wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; dA and dG, are 2'-deoxy A and G, respectively; Af, Cf and Uf are 2'-fluoro (2'-F) A, C and U, respectively; and s is a phosphorothioate linkage, and wherein a ligand is conjugated to the 3'-end of the sense strand as



shown in the following schematic
wherein X is O.

In another aspect, provided herein is a pharmaceutical composition for inhibiting expression of a gene encoding ANGPTL3 comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein.

In another aspect, an *in vitro* method of inhibiting expression of an Angiopoietin-like 3 (ANGPTL3) gene in a cell, comprising contacting the cell with any of the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein, thereby inhibiting expression of the ANGPTL3 gene in the cell.

In another aspect, provided herein is use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in Angiopoietin-like 3 (ANGPTL3) expression.

In another aspect, provided herein is use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein in the manufacture of a first medicament and use of an additional therapeutic agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treatment of an ANGPTL3-associated disorder.

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

In another aspect, provided herein is the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein, and an additional therapeutic agent for use in therapy.

The present invention provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding Angiopoietin-like 3