

Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Angiopoietin-like 3 (ANGPTL3), wherein the dsRNA agent comprises a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to an ANGPTL3 RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-5, and optionally comprising a targeting ligand,

optionally, wherein the region of complementarity to an ANGPTL3 RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by no more than 3 nucleotides from one of the antisense sequences listed in one of Tables 1-5.

2. The dsRNA agent of claim 1, wherein the antisense strand of dsRNA is at least substantially complementary to any one of a target region of SEQ ID NO: 235 and is provided in any one of Tables 1-5,

optionally, wherein the antisense strand of dsRNA is fully complementary to any one of a target region of SEQ ID NO: 235 and is provided in any one of Tables 1-5.

3. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-5, wherein the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent; or

wherein the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent.

4. The dsRNA agent of claim 1, wherein the dsRNA agent comprises an antisense strand sequence set forth in any one of Tables 1-5,

optionally, wherein the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-5.

5. The dsRNA of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide,

optionally, wherein all or substantially all of the nucleotides of the antisense strand are modified nucleotides,

optionally wherein the at least one modified nucleotide comprises: a 2'-O-methyl nucleotide, 2'-Fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-Ome nucleotide, inverted 2'-deoxy nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

6. The dsRNA agent of claim 5, comprises an E-vinylphosphonate nucleotide at the 5' end of the antisense strand,

optionally, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage,

optionally, wherein the sense strand comprises at least one phosphorothioate internucleoside linkage;

optionally, wherein the antisense strand comprises at least one phosphorothioate internucleoside linkage;

optionally, wherein the sense strand comprises 1, 2, 3, 4, 5, or 6, phosphorothioate internucleoside linkages;

optionally, wherein the antisense strand comprises 1, 2, 3, 4, 5, or 6, phosphorothioate internucleoside linkages,

optionally wherein all or substantially all of the nucleotides of the sense strand and the antisense strand are modified nucleotides,

optionally wherein the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-5, and

optionally, wherein the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-5.

7. The dsRNA agent of claim 1, wherein the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 16 and 23 nucleotides in length,

optionally wherein the region of complementarity is 19-21 nucleotides in length,

optionally wherein each strand is no more than 30 nucleotides in length;

optionally, wherein each strand is no more than 25 nucleotides in length; and

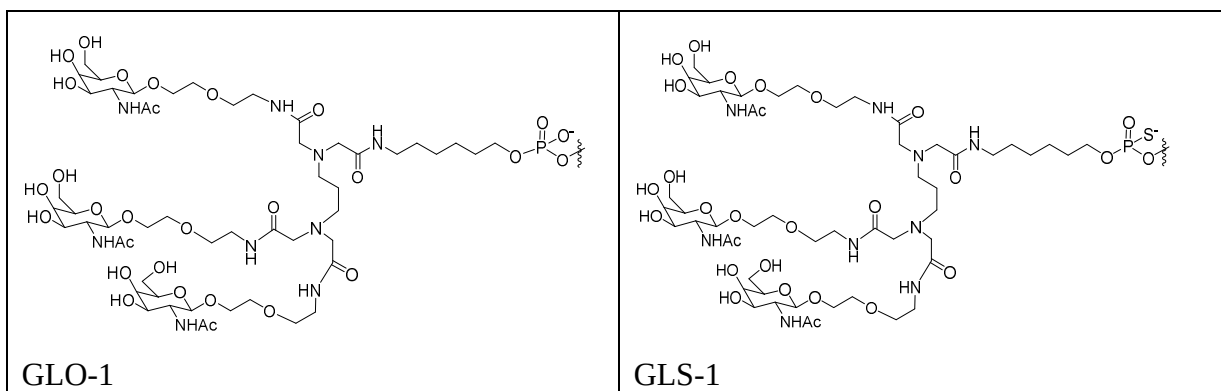
optionally, wherein each strand is no more than 23 nucleotides in length.

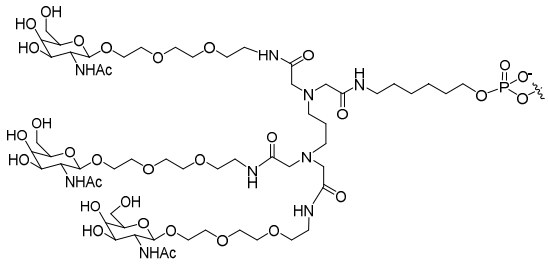
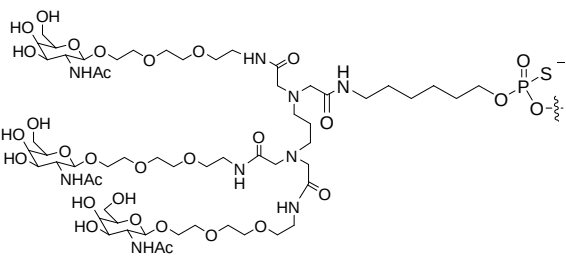
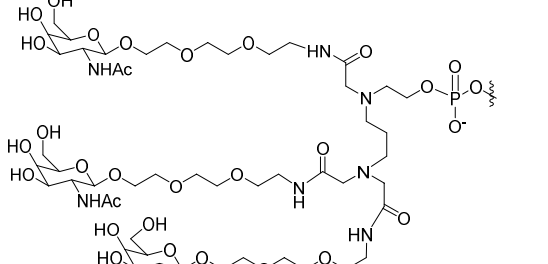
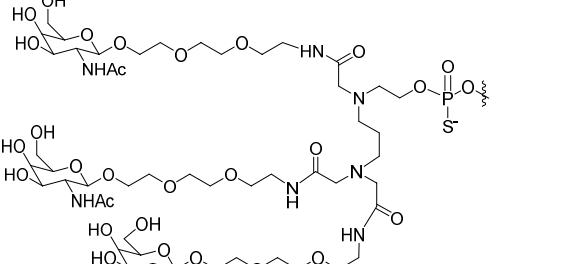
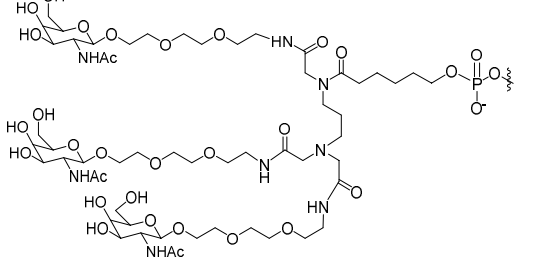
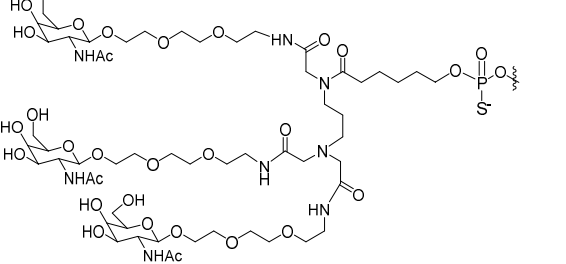
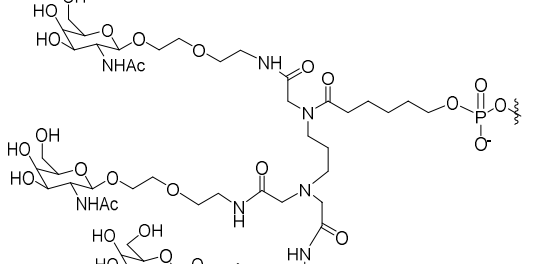
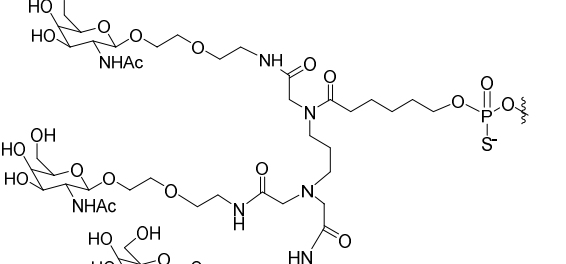
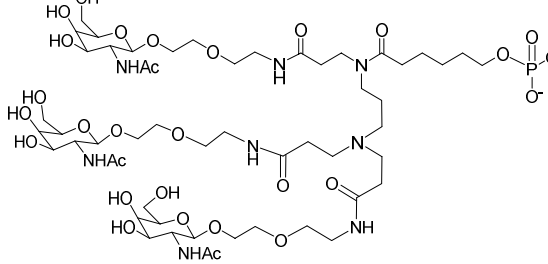
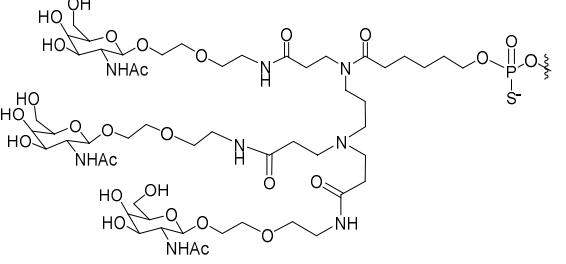
8. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups;

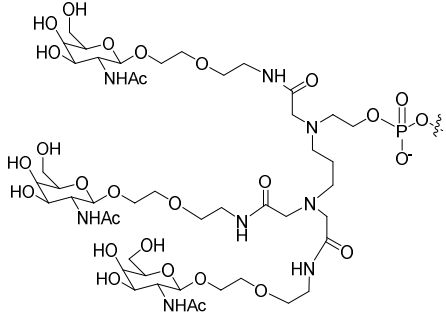
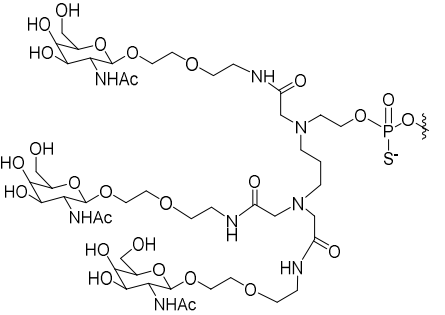
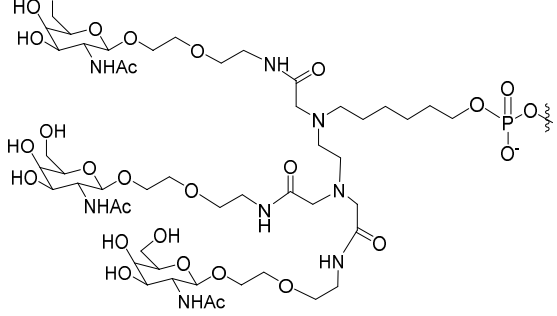
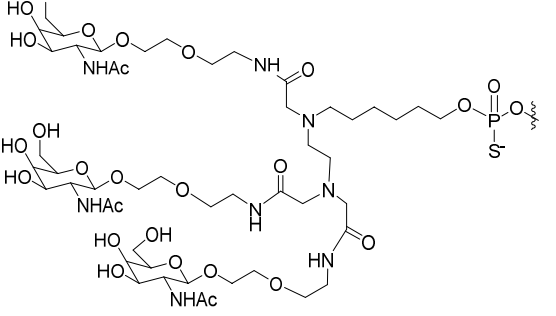
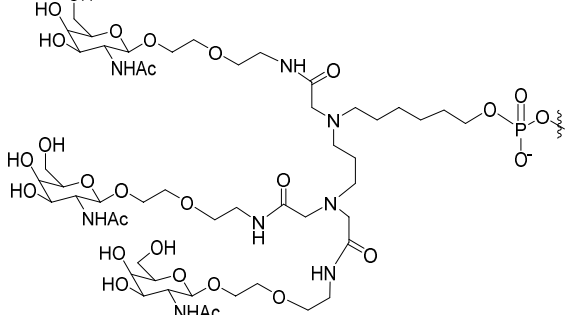
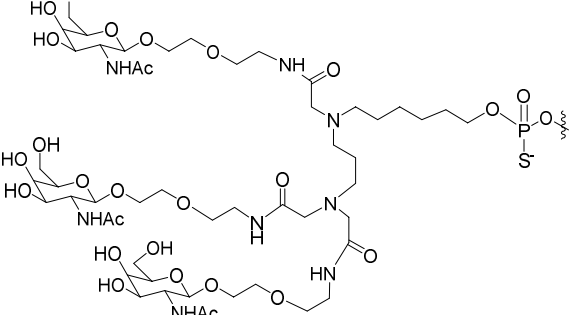
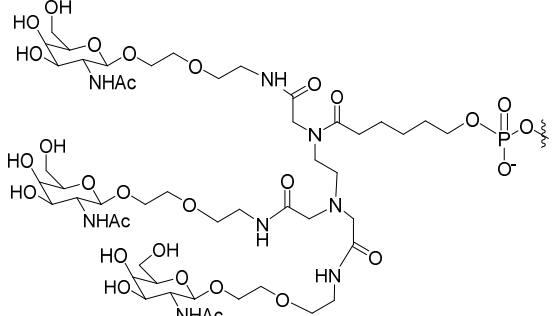
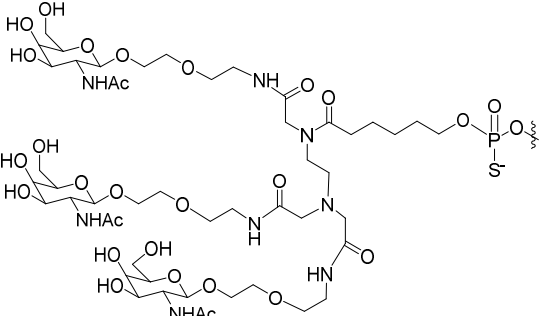
optionally, wherein the one or more targeting groups or linking groups are conjugated to the sense strand,

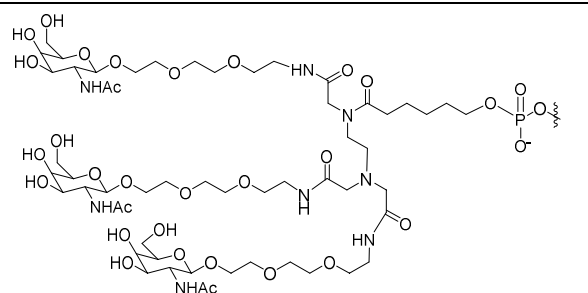
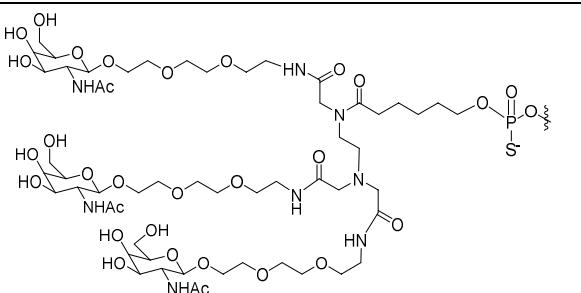
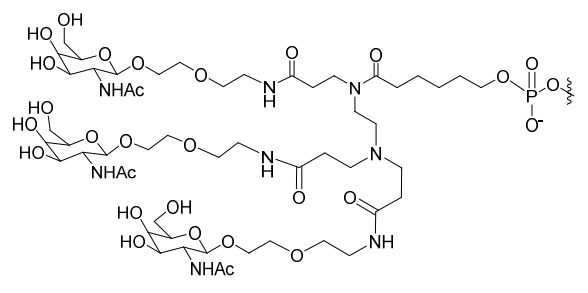
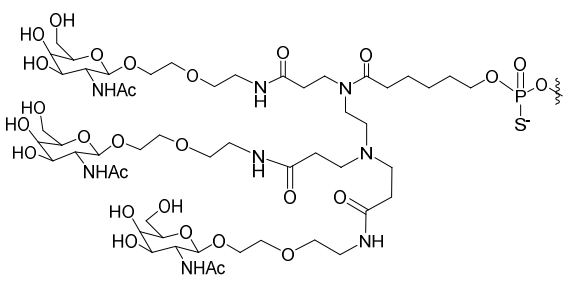
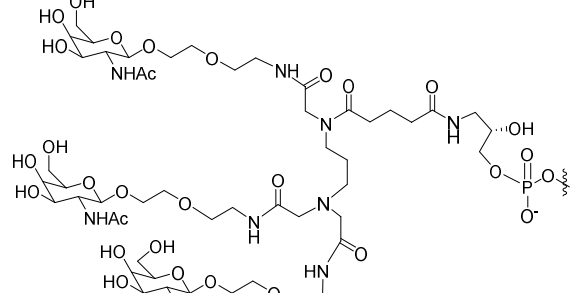
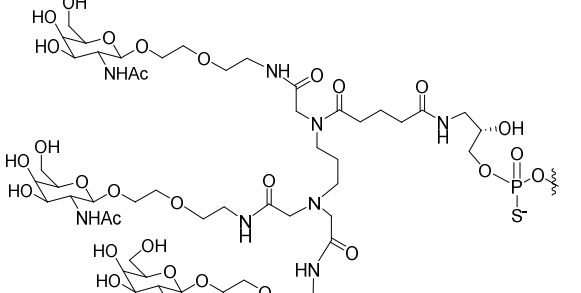
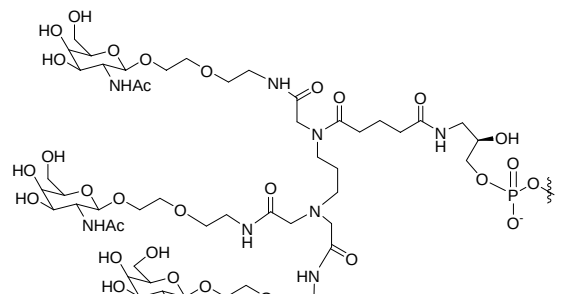
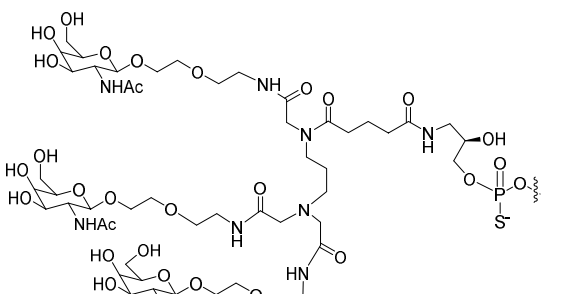
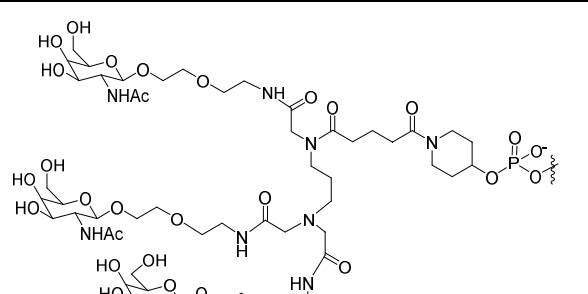
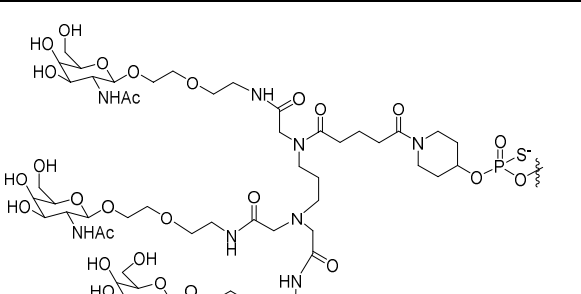
optionally, wherein the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc); and

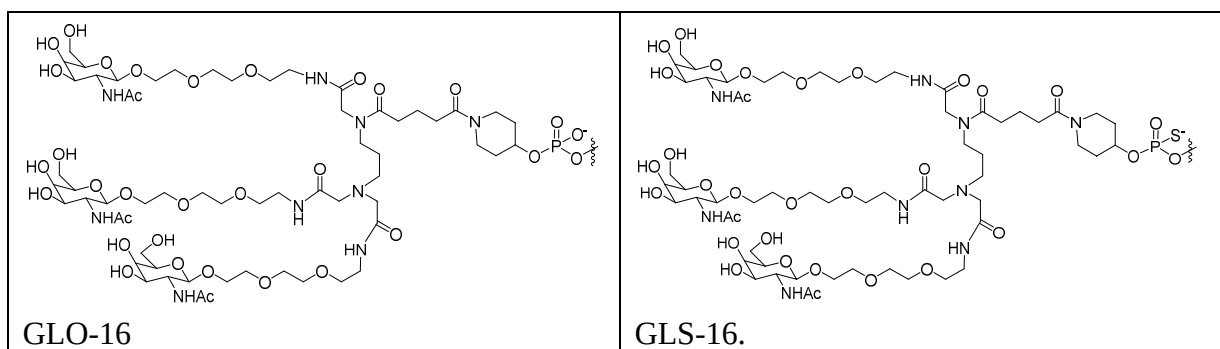
optionally wherein the targeting group has a structure:



 GLO-2	 GLS-2
 GLO-3	 GLS-3
 GLO-4	 GLS-4
 GLO-5	 GLS-5
 GLO-6	 GLS-6

 GLO-7	 GLS-7
 GLO-8	 GLS-8
 GLO-9	 GLS-9
 GLO-10	 GLS-10

 GLO-11	 GLS-11
 GLO-12	 GLS-12
 GLO-13	 GLS-13
 GLO-14	 GLS-14
 GLO-15	 GLS-15



9. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5'-terminal end of the sense strand, and/or
the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand.
10. The dsRNA agent of claim 1, wherein the antisense strand comprises one inverted abasic residue at 3'-terminal end,
optionally, wherein the sense strand comprises one or two inverted abasic residues at 3' or/and 5' terminal end.
11. The dsRNA agent of claim 1, wherein the dsRNA agent has two blunt ends; or
wherein at least one strand comprises a 3' overhang of at least 1 or 2 nucleotides.
12. A composition comprising a dsRNA agent of any one of claims 1-11,
optionally further comprising a pharmaceutically acceptable carrier;
optionally further comprising one or more additional therapeutic agents,
optionally wherein the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial;
optionally, wherein the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.
13. A method of inhibiting the expression of an ANGPTL3 gene in a cell *in vitro*, comprising:

(i) preparing a cell comprising an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-11 or a composition of claim 12, optionally, further comprising: (ii) maintaining the cell prepared in (i) for a time sufficient to obtain degradation of the mRNA transcript of an ANGPTL3 gene, thereby inhibiting expression of the ANGPTL3 gene in the cell.

14. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-11, or the composition of claim 12 for use in treating a disease or condition associated with the presence of ANGPTL3 protein;

optionally, wherein the disease or condition is one or more of: hyperlipidemia, hypertriglyceridemia, abnormal lipid and/or cholesterol metabolism, homozygous and heterozygous familial hypercholesterolemia, statin resistant hypercholesterolemia, cardiometabolic disease, obesity, atherosclerosis, type II diabetes mellitus, cardiovascular disease, coronary artery disease, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, pancreatitis caused by hypertriglyceridemia;

optionally, the composition further comprises one or more ANGPTL3 antisense polynucleotides, or a non-ANGPTL3 dsRNA therapeutic agent;

optionally, the non-ANGPTL3 dsRNA therapeutic agent is one of more of: (i) a statin; (ii) one or more of an antibody, antisense oligonucleotide (ASO), and a PCSK9 siRNA molecule capable of reducing PCSK9 expression; (iii) a therapeutic agent capable of reducing lipid accumulation in a subject, and (iv) a therapeutic agent capable of reducing cholesterol levels and/or accumulation in a subject.

15. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-11, or the composition of claim 12 for use in decreasing a level of ANGPTL3 protein in a subject compared to a baseline pre-treatment level of ANGPTL3 protein in the subject or altering a physiological characteristic of an ANGPTL3-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the ANGPTL3-associated disease or condition in the subject;

optionally, the physiological characteristic is one or more of: the subject's serum lipid level, the subject's HDL level, the subjects HDL : LDL ratio, the subject's serum triglyceride level, and the amount of fat in the subject's liver.