CLAIMS

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), wherein the dsRNA agent including a sense strand and an antisense strand, wherein the antisense strand comprises a region of complementarity to an mRNA encoding HMGCR which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of the antisense sequences listed in any one of Tables 1-3;

or, said antisense strand comprises a region of complementarity to an mRNA encoding HMGCR which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 1-3;

or, the antisense strand of dsRNA is substantially or fully complementary to any one of a target region of SEQ ID NO: 1, and the sense strand sequence is at least substantially complementary to or fully complementary to the antisense strand sequence in the dsRNA agent; wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-3.

2. The dsRNA agent of claim 1, wherein the dsRNA agent satisfies any one or more of the following:
(1) the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3;
(2) the dsRNA agent comprises at least one modified nucleotide; and
(3) all or substantially all of the nucleotides of the sense strand and/or the antisense strand are modified nucleotides.

3. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein:
the sense strand is complementary to the antisense strand, wherein the antisense strand comprises

a region complementary to part of an mRNA encoding HMGCR, wherein:

each strand is about 15 to about 30 nucleotides in length, wherein the sense strand sequence may be represented by formula (I):

$5'\text{-}(N'_L)_{n'}\ N'_L N'_L\ N'_{N1}\ N'_{N2}\ N'_{N3}\ N'_{N4}\ N'_L\ N'_F\ N'_L\ N'_{N5} N'_{N6}\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3'$ (I)

wherein:

each N'_F represents a 2'-fluoro-modified nucleotide;

each N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, and N'_{N6} independently represents a modified or unmodified nucleotide;

each N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide;

and m′ and n′ are each independently an integer of 0 to 7;

or,

the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HMGCR, wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand sequence may be represented by formula (II):

$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_L\ N_{M4}\ N_L\ N_{M5}\ N_{M6}\ N_L\ N_{M7}\ N_{M8}\ N_L\ N_F\ N_L\text{-}5'$(II)

wherein:

each N_F represents a 2'-fluoro-modified nucleotide;

each N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7} and N_{M8} independently represents a modified or unmodified nucleotide;

each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide;

and n is an integer of 0 to 7;

or,

the sense strand and the antisense strand form a dsRNA duplex, wherein said sense strand complementary to the antisense strand, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HMGCR, wherein the region of complementarity comprises at least 15 contiguous nucleotides, wherein the dsRNA duplex represented by formula

(III):

sense: 5′-$(N'_L)_{n'}$ $N'_L N'_L N'_L N'_{N1} N'_{N2} N'_{N3} N'_L N'_F N'_L N'_{N4} N'_{N5} N'_{N6} N'_L N'_L N'_L (N'_L)_{m'}$-3′

antisense: 3′-$(N_L)_n$ $N_{M1} N_L N_{M2} N_L N_F N_L N_{M3} N_L N_{M4} N_L N_{M5} N_{M6} N_L N_{M7} N_{M8} N_L N_F N_L$-5′

(III)

wherein:

each strand is independently about 17 to about 30 nucleotides in length;

each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide;

N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, N_{M8}, N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, and N'_{N6} each independently represents a modified or unmodified nucleotide;

each N_L and N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide;

and m′, n′ and n are each independently an integer of 0 to 7.

4. The dsRNA agent of claim 2 or 3, wherein the one or more modified nucleotides are independently selected from the group consisting of: a 2’-O-methyl nucleotide, a 2’-Fluoro nucleotide, a 2’-deoxy nucleotide, a 2’3’-seco nucleotide mimic, a locked nucleotide, an unlocked nucleic acid nucleotide (UNA), a glycol nucleic acid nucleotide (GNA), a 2’-F-Arabino nucleotide, a 2’-methoyxyethyl nucleotide, an abasic nucleotide, an ribitol, inverted nucleotide, an inverted abasic nucleotide, an isomannide nucleotide, an inverted 2’-Ome nucleotide, an inverted 2’-deoxy nucleotide, a 2’-amino-modified nucleotide, a 2’-alkyl-modified nucleotide, a mopholino nucleotide, a 3’-OMe nucleotide, a nucleotide comprising a 5’-phosphorothioate group, a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2’-amino-modified nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

5. The dsRNA agent of any one of claims 1-4, wherein the dsRNA agent satisfies any one or more of the following:

(1) the dsRNA comprising an E-vinylphosphonate nucleotide at the 5′ end of the guide strand;

(2) the dsRNA agent comprises at least one phosphorothioate internucleoside linkage;

(3) the sense strand comprises at least one phosphorothioate internucleoside linkage;
(4) the antisense strand comprises at least one phosphorothioate internucleoside linkag;
(5) the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages;
(6) the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.

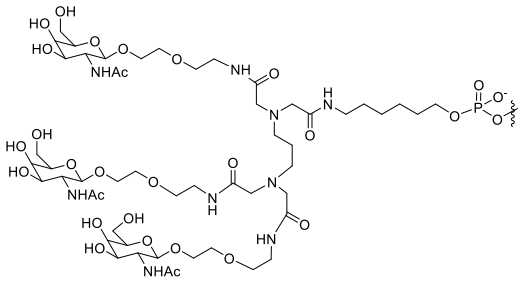
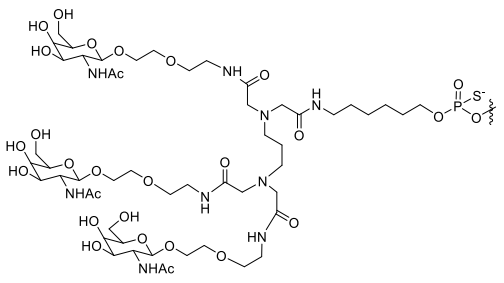
6. The dsRNA agent of any one of claims 1-5, wherein the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3;
and/or, the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3;

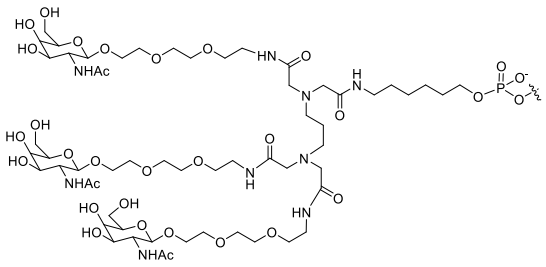
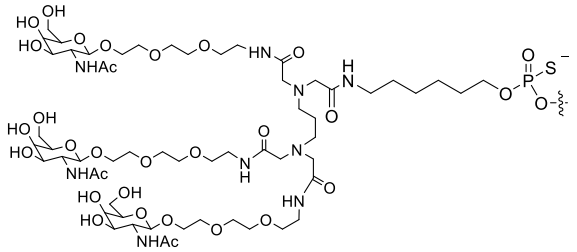
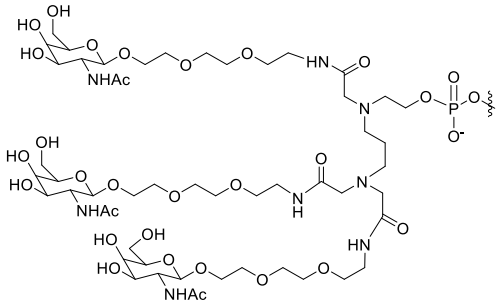
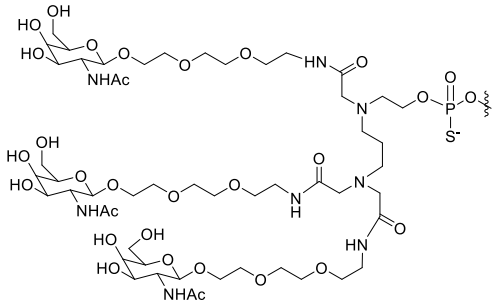
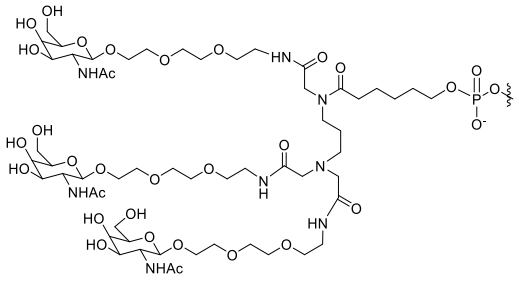
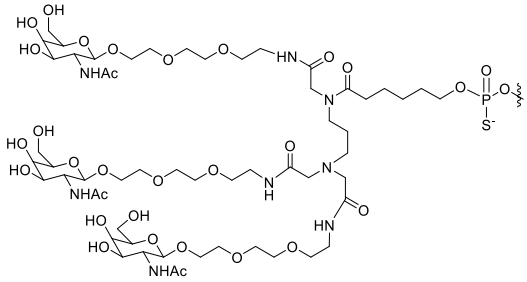
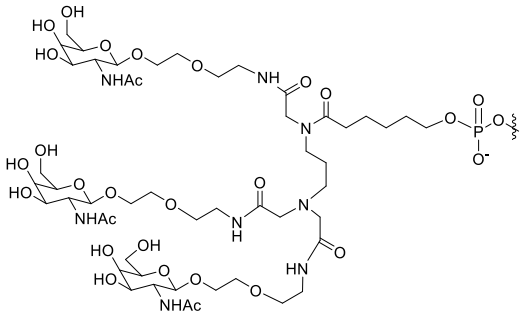
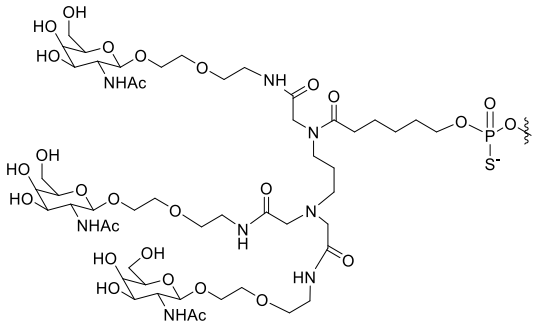
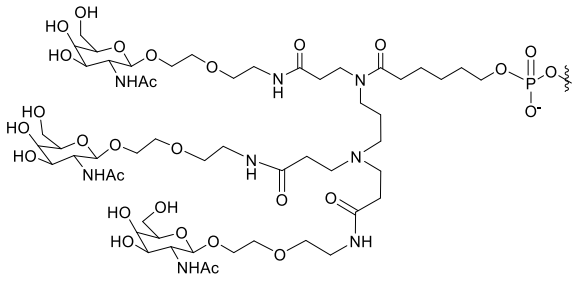
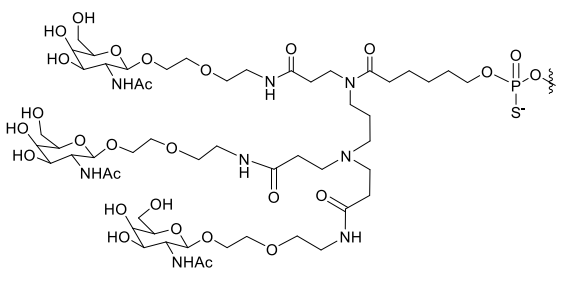
and/or, the sense strand is complementary or substantially complementary to the antisense strand for a region of 16-23, or 19-21 nucleotides in length.

7. The dsRNA agent of any one of claims 1-6, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups;
preferably, the one or more targeting groups or linking groups are conjugated to the sense strand;

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

and/or, the targeting group has a structure:

 GLO-1	 GLS-1*

 GLO-2	 GLS-2*
 GLO-3	 GLS-3*
 GLO-4	 GLS-4*
 GLO-5	 GLS-5*
	

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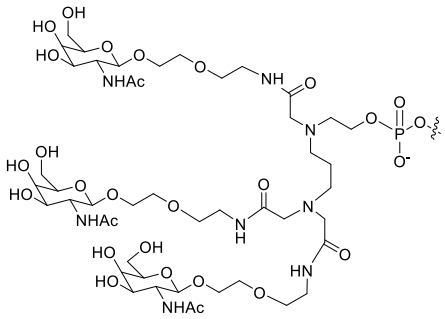
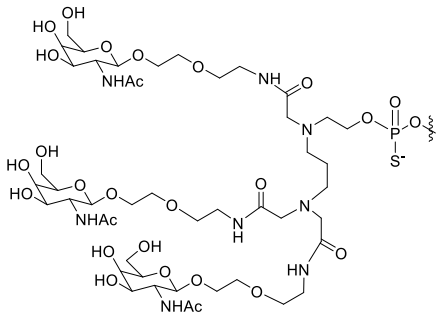
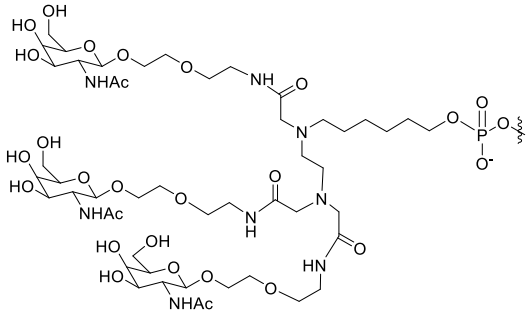
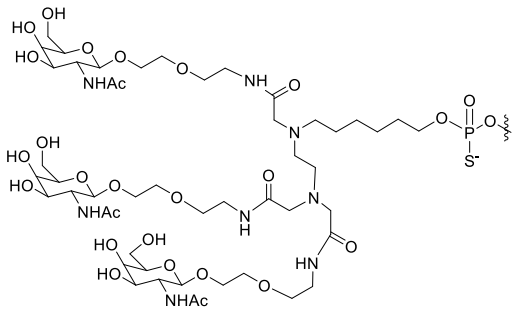
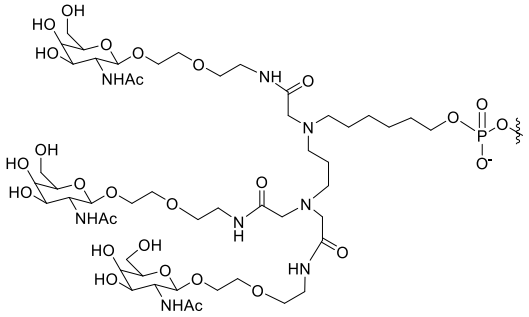
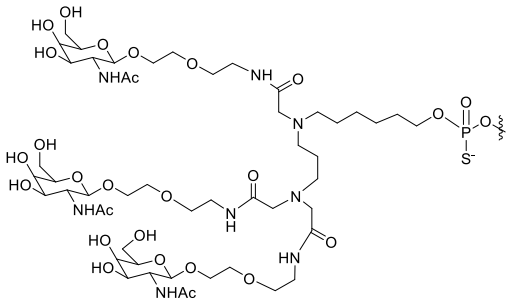
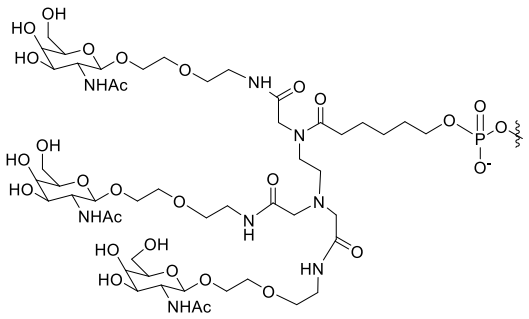
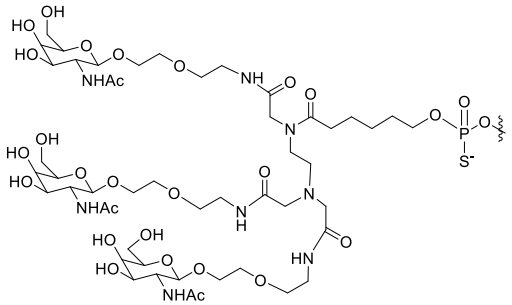
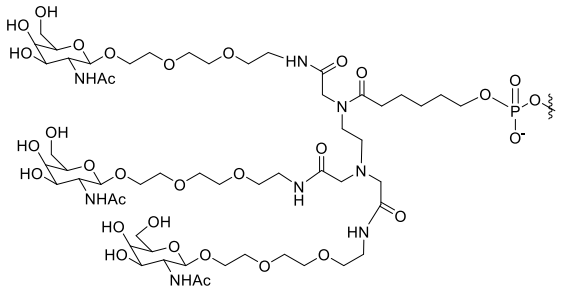
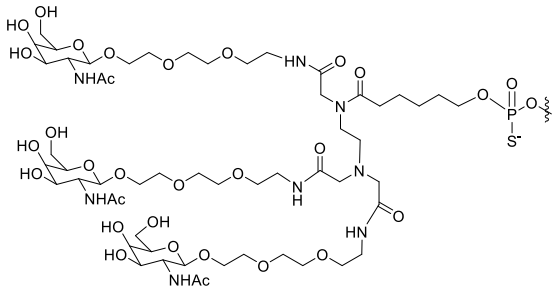
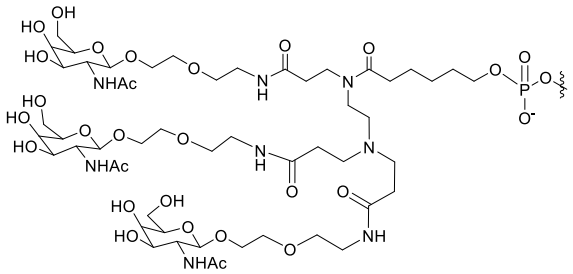
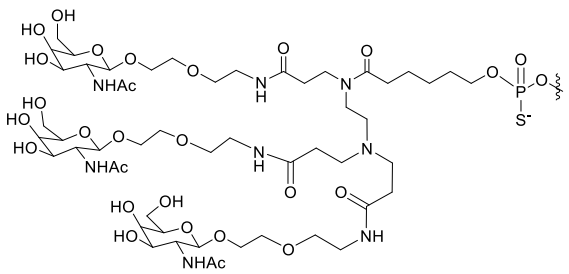
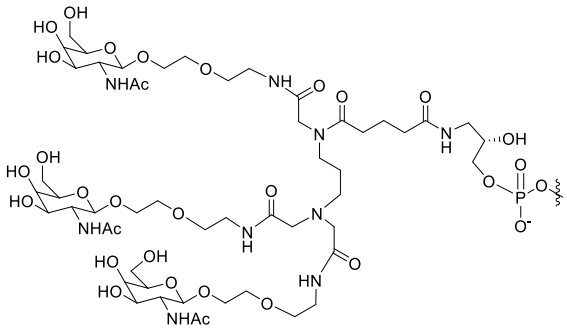
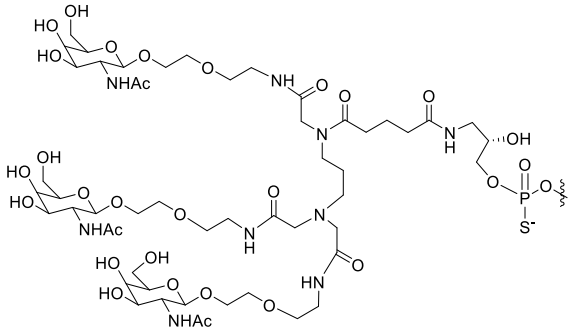
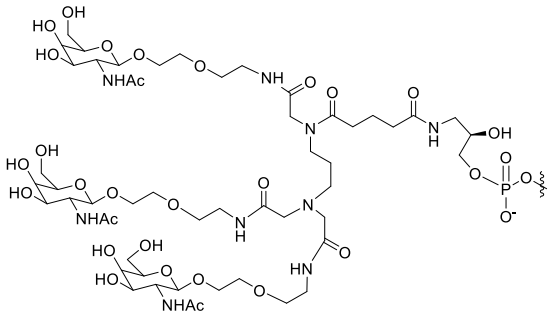
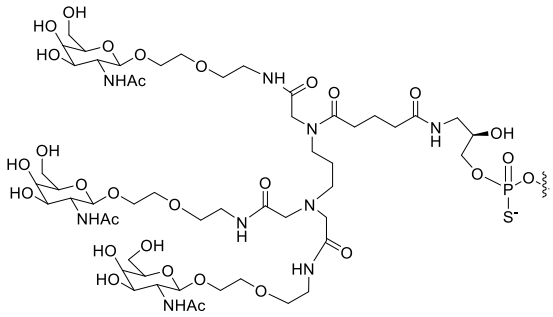
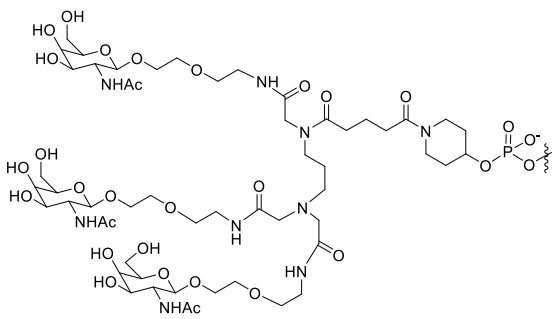
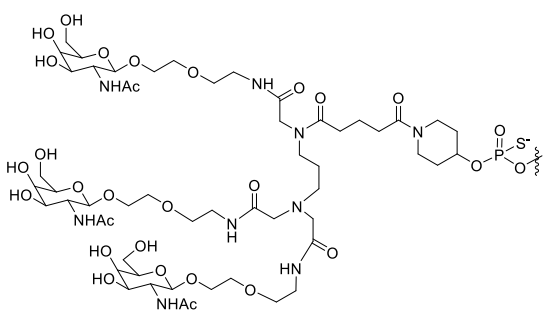
 GLO-7	 GLS-7*
 GLO-8	 GLS-8*
 GLO-9	 GLS-9*
 GLO-10	 GLS-10*

 GLO-11	 GLS-11*
 GLO-12	 GLS-12*
 GLO-13	 GLS-13*
 GLO-14	 GLS-14*
	

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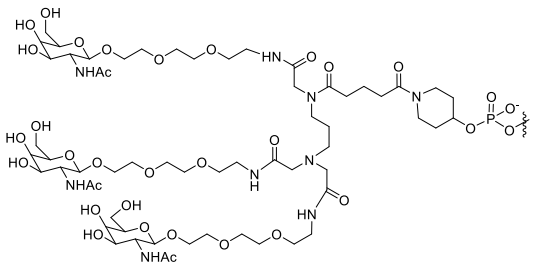	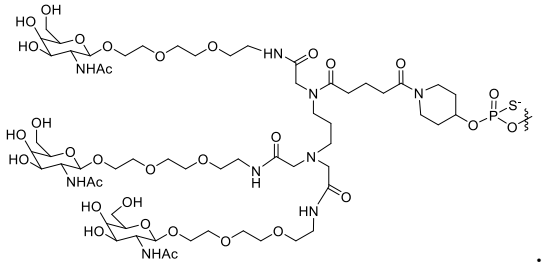
GLO-16	GLS-16*

8. The dsRNA agent of any one of claims 1-7, wherein the dsRNA agent satisfies any one or more of the following:

(1) the dsRNA agent comprises a targeting group that is conjugated to the 5’-terminal end of the sense strand;

(2) the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand;

(3) the antisense strand comprises one inverted abasic residue at 3’-terminal end;

(4) the sense strand comprises one or two inverted abasic residues or imann residues at 3’ or/and 5’ terminal end;

(5) the dsRNA agent has two blunt ends;

(6) at least one strand comprises a 3’ overhang of at least 1 nucleotide; and

(7) at least one strand comprises a 3’ overhang of at least 2 nucleotides.

9. A composition comprising a dsRNA agent of any one of claims 1-8;

preferably, the composition further comprises a pharmaceutically acceptable carrier;

more preferably, the composition further comprises one or more additional therapeutic agents;

for example, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial; and/or, the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

10. An *in vitro* method of inhibiting the expression of an HMGCR gene in a cell, comprising:

(i) preparing a cell comprising an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-8 or a composition of claim 9;

preferably, the method further comprises
(ii) maintaining the cell prepared in (i) for a time sufficient to obtain degradation of the mRNA transcript of an HMGCR gene, thereby inhibiting expression of the HMGCR gene in the cell; and/or, the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously or by IV administration.

11. The method of claim 10, further comprising assessing inhibition of the HMGCR gene, following the administration of the dsRNA agent to the subject, wherein a means for the assessing comprises:

(i) determining one or more physiological characteristics of an HMGCR-associated disease or condition in the subject and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition and/or to a control physiological characteristic of the HMGCR-associated disease or condition,
wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the HMGCR gene in the subject;

preferably, the determined physiological characteristic is one or more of: the HMGCR mRNA level, the HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-

density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum;

more preferably, a reduction in one or more of the subject's HMGCR mRNA level, the HMGCR protein level in the subject, and/or a decrease in one or more of cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum indicates reduction of HMGCR gene expression in the subject.

12. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-8, or the composition of claim 9 for use in treating a disease or condition associated with the presence of HMGCR protein, , to inhibit HMGCR gene expression;
preferably, the disease or condition is one or more of: hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, congestive heart disease (CHD) and atherosclerosis, atherosclerosis, dyslipidemia, acute pancreatitis associated with hypertriglyceridemia, chylomicron syndrom, familial chylomicronemia, Apo-E deficiency or resistance, LPL deficiency or hypoactivity, familial partial lipodystrophy type 1 (FPLD1), polycystic ovarian syndrome related to insulin resistance, renal transplantation, nephrotic syndrome, Cushing's syndrome, acromegaly, systemic lupus erythematosus, dysglobulinemia, lipodystrophy, glycogenosis type I, and Addison's disease, or other disorders of lipid metabolism related to HMGCR;

more preferably, the method further comprises administering an additional therapeutic regimen to the subject;
even more preferably, the additional therapeutic regimen comprises: administering to the subject one or more HMGCR antisense polynucleotides of the invention, administering to the subject a non-HMGCR dsRNA therapeutic agent, and a behavioral modification in the subject;
for example, the non-HMGCR dsRNA therapeutic agent is one of more of: a statin, a bile

sequestering agent, a VLDL secretion inhibitor, a lipophilic antioxidant, an acyl- CoA cholesterol acyl transferase inhibitor, a farnesoid X receptor antagonist, a sterol regulatory binding protein cleavage activating protein (SCAP) activator, a microsomal triglyceride transfer protein (MTP) inhibitor, an ApoE-related peptide, a cholesteryl ester transfer protein (CETP) inhibitor, a therapeutic antibody against HMGCR, and a combination of any of the foregoing.

13. The double-stranded ribonucleic acid (dsRNA) agent or the composition for use of claim 12, wherein the dsRNA agent is administered to the subject subcutaneously or by IV administration;

and/or, the method further comprises determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject;
preferably, a means of determining an efficacy of the treatment in the subject comprises:

(i) determining one or more physiological characteristics of the HMGCR-associated disease or condition in the subject and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition
wherein the comparison indicates one or more of a presence, absence, and level of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject;
more preferably, the determined physiological characteristic is: the HMGCR mRNA level, the HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum; or
a reduction in one or more of the HMGCR mRNA level, the HMGCR protein level in the subject, and/or a decrease in one or more of cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum indicates the presence of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent

to the subject.

14. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-8, or the composition of claim 9 for use in decreasing a level of HMGCR protein in a subject in need thereof compared to a baseline pre-treatment level of HMGCR protein in the subject, , to decrease the level of HMGCR gene expression

preferably, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

15. The double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-8, or the composition of claim 9 for use in altering a physiological characteristic of an HMGCR-associated disease or condition in a subject in need thereof compared to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition in the subject, to alter the physiological characteristic of the HMGCR-associated disease or condition in the subject;
preferably, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration;

and/or, the physiological characteristic is one or more of: the HMGCR mRNA level, the HMGCR protein level in the subject, cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum.