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(54) **Title:** TREATMENT OF ANGPTL4 RELATED DISEASES

(57) **Abstract:** Provided are compositions comprising an oligonucleotide that targets Angiopoietin-like 4 (ANGPTL4). The oligonucleotide may include a small interfering RNA (siRNA) or an antisense oligonucleotide (ASO). Oligonucleotide modification patterns are included that may be used to improve their stability or efficacy. Also provided herein are methods of treating a cardiometabolic disorder by providing an oligonucleotide that targets ANGPTL4 to a subject in need thereof. Some embodiments include treating a subject with hepatic steatosis or another cardiometabolic disorder.

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TREATMENT OF ANGPTL4 RELATED DISEASES

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. US 63/197,921, filed June 7, 2021. The entire content of the priority application is expressly incorporated herein by reference.

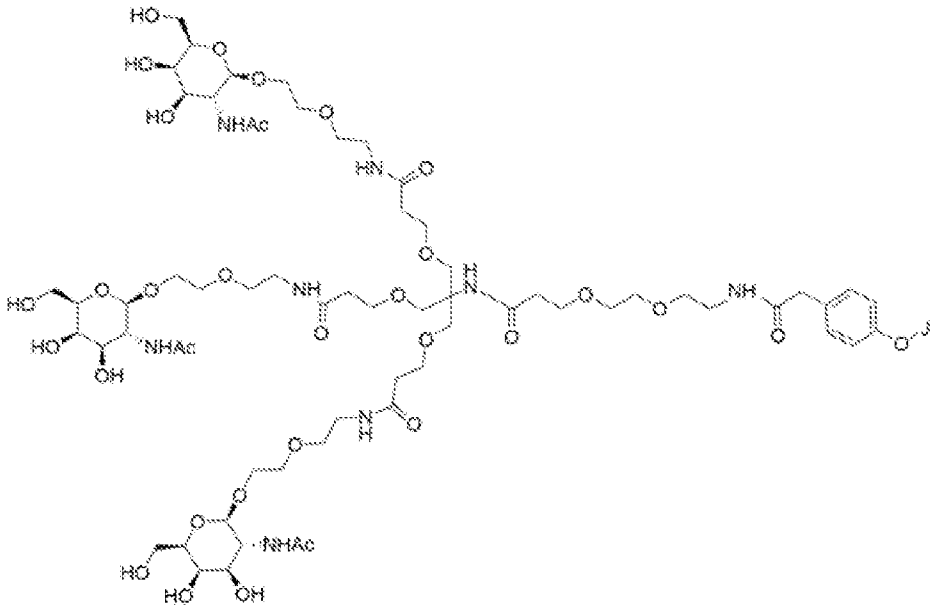
BACKGROUND

[0002] Cardiometabolic disorders are becoming increasingly abundant, and may affect a large proportion of the population. Improved therapeutics are needed for treating these disorders.

SUMMARY

[0003] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets ANGPTL4. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets ANGPTL4 and comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand. In some embodiments, the sense strand comprises modification pattern 8S. In some embodiments, the sense strand comprises modification pattern 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, or 16S. In some embodiments, the sense strand comprises modification pattern 7S, 8S, or 9S. In some embodiments, the antisense strand comprises modification pattern 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the antisense strand comprises modification pattern 10AS or 11AS. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity; wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand; and wherein the sense strand comprises modification pattern 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, or 16S; or wherein or the antisense strand comprises modification pattern 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. Disclosed herein, in some embodiments, are compositions that target ANGPTL4. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity; wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand comprising modification pattern 7S, 8S, or 9S, and/or an antisense strand comprising modification pattern 10AS or 11AS. Disclosed herein, in some embodiments, are

compositions comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity; wherein any one of the following is true with regard to a strand of the oligonucleotide: all purines comprise 2' fluoro modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines, all purines comprise 2' methyl modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines, all purines comprise 2' fluoro modified purines, and all pyrimidines comprise 2' methyl modified pyrimidines, all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines, all pyrimidines comprise 2' methyl modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines, or all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise 2' methyl modified purines. In some embodiments, the increase or decrease is by about 10% or more, as compared to prior to administration. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases a liver steatosis measurement in the subject. In some embodiments, the decrease is by about 10% or more, as compared to prior to administration. In some embodiments, the oligonucleotide comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, or 11AS. In some embodiments, the oligonucleotide comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 16S, 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS.In some embodiments, any one of the following is true with regard to a strand of the oligonucleotide: all purines comprise 2' fluoro modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines, all purines comprise 2' methyl modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines, all purines comprise 2' fluoro modified purines, and all pyrimidines comprise 2' methyl modified pyrimidines, all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines, all pyrimidines comprise 2' methyl modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines, or all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise 2' methyl modified purines. In some embodiments, the composition comprises an siRNA. In some embodiments, the composition comprises an antisense oligonucleotide (ASO). In some embodiments, the oligonucleotide comprises a N-acetylgalactosamine (GalNAc) moiety attached to a 5' or 3' end of the oligonucleotide. In some embodiments, the

composition comprises:  ,

wherein J comprises the oligonucleotide, and wherein J comprises an optional phosphate or phosphorothioate linking to the oligonucleotide. Disclosed herein, in some embodiments, are compositions comprising an siRNA comprising a sense strand comprising a GalNAc moiety attached at a 5' or 3' end and the nucleotide sequence of SEQ ID NO: 14005 or 14299, and an antisense strand having the nucleotide sequence of SEQ ID NO: 14298 or 14153. In some embodiments, the sense strand comprises the nucleotide sequence of SEQ ID NO: 14005. In some embodiments, the sense strand comprises the nucleotide sequence of SEQ ID NO: 14299. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 14298. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 14153.

[0004] Disclosed herein, in some embodiments, are methods of reducing an ANGPTL4 protein or mRNA measurement in the liver of a subject, comprising administering an effective amount of a composition described herein. In some embodiments, the subject is a primate. Disclosed herein, in some embodiments, are methods of treating a subject having a liver disease, comprising administering an effective amount of a composition described herein. In some embodiments, the liver disease comprises nonalcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

DETAILED DESCRIPTION

[0005] Oligonucleotides that target the expression of genes involved in cardiometabolic diseases may be useful for treating such diseases. Cardiometabolic diseases may often be exacerbated or result from obesity, which may affect a large percent of the population. Such diseases may include nonalcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), and may be characterized by liver steatosis. Oligonucleotides may be targeted to the liver using a moiety such as a N-acetylgalactosamine (GalNAc) moiety, and then combat the disease by targeting the mRNA of a gene involved in the disease. Additionally, specific nucleic acid modification patterns may be used to improve oligonucleotide stability or effectiveness.

[0006] Identification of which genes are involved in cardiometabolic diseases may be useful for determining which genes to target for treating these diseases. Large-scale human genetic data can improve the success rate of pharmaceutical discovery and development. A Genome Wide Association Study (GWAS) may detect associations between genetic variants and traits in a population sample. A GWAS may enable better understanding of the biology of disease, and provide applicable treatments. A GWAS can utilize genotyping and/or sequencing data, and often involves an evaluation of millions of genetic variants that are relatively evenly distributed across the genome. The most common GWAS design is the case-control study, which involves comparing variant frequencies in cases versus controls. If a variant has a significantly different frequency in cases versus controls, that variant is said to be associated with disease. Association statistics that may be used in a GWAS are p-values, as a measure of statistical significance; odds ratios (OR), as a measure of effect size; or beta coefficients (beta), as a measure of effect size. Researchers often assume an additive genetic model and calculate an allelic odds ratio, which is the increased (or decreased) risk of disease conferred by each additional copy of an allele (compared to carrying no copies of that allele). An additional concept in design and interpretation of GWAS is that of linkage disequilibrium, which is the non-random association of alleles. The presence of linkage disequilibrium can obfuscate which variant is "causal."

[0007] Functional annotation of variants and/or wet lab experimentation can identify the causal genetic variant identified via GWAS, and in many cases may lead to the identification of disease-causing genes. In particular, understanding the functional effect of a causal genetic variant (for example, loss of protein function, gain of protein function, increase in gene expression, or decrease in gene expression) may allow that variant to be used as a proxy for therapeutic modulation of the target gene, or to gain insight into potential therapeutic efficacy and safety of a therapeutic that modulates that target.

[0008] Identification of such gene-disease associations has provided insights into disease biology and may be used to identify novel therapeutic targets for the pharmaceutical industry. In order to translate the therapeutic insights derived from human genetics, disease biology in patients may be exogenously 'programmed' into replicating the observation from human genetics. There are several potential options for therapeutic modalities that may be brought to bear in translating therapeutic targets identified via human genetics into novel medicines. These may include well established therapeutic modalities such as small molecules and monoclonal antibodies, maturing modalities such as oligonucleotides, and emerging modalities such as gene therapy and gene editing. The choice of therapeutic modality can depend on several factors including the location of a target (for example, intracellular, extracellular, or secreted), a relevant tissue (for example, liver) and a relevant indication.

[0009] Cardiovascular and metabolic diseases are leading causes of death, accounting for about one-third of all deaths globally. Angiopoietin-like proteins (ANGPTLs) are regulators of lipoprotein metabolism and may serve as therapeutic targets for modulation of lipid levels and cardiometabolic disease risk. ANGPTLs are a family of eight proteins with some functional similarities to angiopoietins. They typically have a characteristic structure that includes an N-terminal coiled-coil domain that mediates homo-oligomerization and a C-terminal fibrinogen domain involved in signaling.

[0010] Angiopoietin-like 4 (ANGPTL4; UniProt ID Q9BY76) is an endogenous inhibitor of lipoprotein lipase (LPL), an enzyme that hydrolyzes triglycerides contained in triglyceride-rich lipoproteins (TRLs) such as chylomicrons and very low-density lipoproteins. ANGPTL4 is a secreted protein that in humans is often most highly expressed in the liver and adipose tissue. After cellular secretion, ANGPTL4 is often cleaved to 37kD C-terminal and 15kD N-terminal fragment, and these oligomerized N-terminal fragments inhibit LPL. In some embodiments, ANGPTL4 is glycosylated. In some embodiments, ANGPTL4 has a coiled-coil N-terminal domain. In some embodiments, ANGPTL4 has a fibrinogen-like C-terminal domain.

[0011] Circulating triglycerides are strong and independent positive predictors of cardiovascular disease risk and all-cause mortality, and are also positively correlated with plasma glucose levels, risk of diabetes, metabolic syndrome, and pancreatitis. Additionally, mutations in TRL genes may cause hereditary disorders including familial chylomicronemia syndrome and familial hypertriglyceridemia. Here, it is shown that genetic variants that cause inactivation of ANGPTL4 in humans are associated with decreased triglycerides, increased HDL and decreased risk of diabetes and cardiovascular disease. Therefore, inhibition of ANGPTL4 may serve as a therapeutic strategy for treatment of a range of cardiometabolic diseases.

[0012] Disclosed herein are compositions comprising an oligonucleotide that targets Angiopoietin-like 4 (ANGPTL4). The oligonucleotide may include a small interfering RNA (siRNA) or an antisense oligonucleotide (ASO). The oligonucleotide may be useful for treating a cardiometabolic disease such as one that involves steatosis of an organ such as liver. Specific modifications are included in the disclosure that may aid in stability and overall effectiveness. Further, the oligonucleotide may be targeted to the liver by use of a moiety such as a GalNAc moiety. Also provided herein are methods of treating a metabolic or cardiovascular disorder by providing an oligonucleotide that targets ANGPTL4 to a subject in need thereof. The oligonucleotide may treat the disorder by reducing steatosis, or another mechanism.

I. COMPOSITIONS

[0013] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide. In some embodiments, the composition comprises an oligonucleotide that targets Angiopoietin-like 4 (ANGPTL4). In some embodiments, the composition consists of an oligonucleotide that targets ANGPTL4. In some embodiments, the oligonucleotide reduces ANGPTL4 mRNA or protein expression in the subject. The oligonucleotide may include a small interfering RNA (siRNA) or an antisense oligonucleotide (ASO). In some embodiments, a composition described herein is used in a method of treating a disorder in a subject in need thereof. Some embodiments relate to a composition comprising an oligonucleotide for use in a method of treating a disorder as described herein. Some embodiments relate to use of a composition comprising an oligonucleotide, in a method of treating a disorder as described herein. In some embodiments, the composition is useful for treating a liver disease such as nonalcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), or another metabolic disorder.

[0014] In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases ANGPTL4 mRNA levels in a cell or tissue. In some embodiments, the cell is a hepatocyte. In some embodiments, the tissue is liver or adipose tissue. In some embodiments, the ANGPTL4 mRNA levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the ANGPTL4 mRNA levels are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the ANGPTL4 mRNA levels are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the ANGPTL4 mRNA levels are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the ANGPTL4 mRNA levels are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the ANGPTL4 mRNA levels are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the ANGPTL4 mRNA levels are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0015] In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating ANGPTL4 protein levels in a cell or tissue. In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases ANGPTL4 protein levels in a fluid such as blood, serum or plasma. In some embodiments, the ANGPTL4 protein levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the ANGPTL4 protein levels are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the ANGPTL4 protein levels are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the ANGPTL4 protein levels are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the ANGPTL4 protein levels are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the ANGPTL4 protein levels are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the ANGPTL4 protein levels are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0016] In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides. In some embodiments, the triglycerides are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the triglycerides are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the triglycerides are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, or about 90% or more, as compared to prior to administration. In some embodiments, the triglycerides are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the triglycerides are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the triglycerides are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the triglycerides are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, or by a range defined by any of the two aforementioned percentages.

[0017] In some embodiments the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating cholesterol. In some embodiments, the circulating cholesterol comprises circulating total cholesterol. In some embodiments, the circulating cholesterol is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the circulating cholesterol is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the circulating cholesterol is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, or about 90% or more, as compared to prior to administration. In some embodiments, the cholesterol is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the cholesterol is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the cholesterol is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the circulating cholesterol is decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, or by a range defined by any of the two aforementioned percentages.

[0018] In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount increases circulating high-density lipoproteins (HDL). In some embodiments, the circulating HDL are increased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the circulating HDL are increased by about 10% or more, as compared to prior to administration. In some

embodiments, the circulating HDL are increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100% or more as compared to prior to administration. In some embodiments, the circulating HDL are increased by about 200% or more, about 300% or more, about 400% or more, about 500% or more, about 600% or more, about 700% or more, about 800% or more, about 900% or more, or about 1000% or more, as compared to prior to administration. In some embodiments, the HDL is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the HDL is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the HDL is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% as compared to prior to administration. In some embodiments, the HDL is decreased by no more than about 200%, no more than about 300%, no more than about 400%, no more than about 500%, no more than about 600%, no more than about 700%, no more than about 800%, no more than about 900%, or no more than about 1000%, as compared to prior to administration. In some embodiments, the circulating HDL are increased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 200% 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000%, or by a range defined by any of the two aforementioned percentages.

[0019] In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating glucose. In some embodiments, the circulating glucose is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the circulating glucose is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the circulating glucose is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, or about 90% or more, as compared to prior to administration. In some embodiments, the glucose is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the glucose is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the glucose is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the circulating glucose is decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, or by a range defined by any of the two aforementioned percentages.

[0020] In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount increases insulin sensitivity. In some embodiments, the insulin sensitivity is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the insulin sensitivity is

increased by about 10% or more, as compared to prior to administration. In some embodiments, the insulin sensitivity is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, or more as compared to prior to administration. In some embodiments, the insulin sensitivity is increased by about 200% or more, about 300% or more, about 400% or more, about 500% or more, about 600% or more, about 700% or more, about 800% or more, about 900% or more, or about 1000% or more, as compared to prior to administration. In some embodiments, the insulin sensitivity is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the insulin sensitivity is increased by no more than about 10%, as compared to prior to administration. In some embodiments, the insulin sensitivity is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% as compared to prior to administration. In some embodiments, the insulin sensitivity is increased by no more than about 200%, no more than about 300%, no more than about 400%, no more than about 500%, no more than about 600%, no more than about 700%, no more than about 800%, no more than about 900%, or no more than about 1000%, as compared to prior to administration. In some embodiments, the insulin sensitivity is increased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 200% 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000%, or by a range defined by any of the two aforementioned percentages.

[0021] In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating insulin. In some embodiments, the circulating insulin is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the circulating insulin is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the circulating insulin is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, or about 90% or more, as compared to prior to administration. In some embodiments, the insulin is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the insulin is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the insulin is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the circulating insulin is decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, or by a range defined by any of the two aforementioned percentages.

[0022] In some embodiments, the composition comprises an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases a liver steatosis measurement. In some

embodiments, the liver steatosis measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the liver steatosis measurement is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the liver steatosis measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the insulin is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the insulin is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the insulin is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, or no more than about 90%, as compared to prior to administration. In some embodiments, the liver steatosis measurement is decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

A. siRNAs

[0023] In some embodiments, the composition comprises an oligonucleotide that targets Angiopoietin-like 4 (ANGPTL4), wherein the oligonucleotide comprises a small interfering RNA (siRNA). In some embodiments, the composition comprises an oligonucleotide that targets Angiopoietin-like 4 (ANGPTL4), wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand. In some embodiments, the sense strand comprises RNA. In some embodiments, the antisense strand comprises RNA.

[0024] In some embodiments, the siRNA comprises a sense strand and an antisense strand, the antisense strand being complementary with no more than 2 mismatches to a portion of a nucleic acid having the nucleoside sequence of SEQ ID NO: 13936, and each strand having 12 to 30 nucleotides. In some embodiments, the siRNA comprises a sense strand and an antisense strand, the antisense strand being complementary with no more than 2 mismatches to a portion of a nucleic acid having the nucleoside sequence of SEQ ID NO: 13935, and each strand having 12 to 30 nucleotides.

[0025] In some embodiments, the siRNA comprises a sense strand and an antisense strand, the antisense strand being 100% complementary to a portion of a nucleic acid having the nucleoside sequence of SEQ ID NO: 13936, and each strand having 12 to 30 nucleotides. In some embodiments, the siRNA comprises a sense strand and an antisense strand, the antisense strand being 100% complementary to a portion of a nucleic acid having the nucleoside sequence of SEQ ID NO: 13935, and each strand having 12 to 30 nucleotides.

[0026] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand is 10-30 nucleosides in length. In some embodiments, the composition comprises a sense strange that is at least about 10, 11, 12, 13, 14, 15, 15, 17, 18,19, 20, 21,

22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. The sense strand may be 12-30 or 14-30 nucleosides in length. In some embodiments, the composition comprises an antisense strand is 10-30 nucleosides in length. In some embodiments, the composition comprises an antisense strange that is at least about 10, 11, 12, 13, 14, 15, 15, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. The antisense strand may be 12-30 or 14-30 nucleosides in length.

[0027] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of a full-length human ANGPTL4 mRNA sequence such as SEQ ID NO: 13935. In some embodiments, at least one of the sense strand and the antisense strand comprise a nucleoside sequence comprising at least about 10, 11, 12, 13, 14, 15, 15, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more contiguous nucleosides of one of SEQ ID NO: 13935.

[0028] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of a full-length human ANGPTL4 pre-mRNA sequence SEQ ID NO: 13936. In some embodiments, at least one of the sense strand and the antisense strand comprise a nucleoside sequence comprising at least about 10, 11, 12, 13, 14, 15, 15, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more contiguous nucleosides of one of SEQ ID NO: 13936.

[0029] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a double-stranded RNA duplex. In some embodiments, the first base pair of the double-stranded RNA duplex is an AU base pair.

[0030] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the sense strand further comprises a 5' overhang. In some embodiments, the 5'

overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. The sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977 may include sequence of any one of SEQ ID NOs: 1-1854. The sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977 may include sequence of any one of SEQ ID NOs: 13970-13977.

[0031] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977.

[0032] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand sequence comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the antisense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. The sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985 may include sequence of any one of SEQ ID NOs: 1855-3708. The sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985 may include sequence of any one of SEQ ID NOs: 13978-13985.

[0033] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985.

[0034] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 19mer in a human ANGPTL4 mRNA. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, a 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a human ANGPTL4 mRNA.

[0035] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 17mer in a non-human primate ANGPTL4 mRNA. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, a 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a non-human primate ANGPTL4 mRNA.

[0036] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 19mer in a human ANGPTL4 mRNA, or a combination thereof. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, and 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a human ANGPTL4 mRNA.

[0037] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 20 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 10 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 30 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 40 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 50 human off-targets, with no more than 2 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 10 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 20 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 30 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 40 human off-targets, with no more than 3 mismatches in the antisense strand. In some embodiments, the siRNA binds with a human ANGPTL4 mRNA and less than or equal to 50 human off-targets, with no more than 3 mismatches in the antisense strand.

[0038] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, siRNA binds with a human ANGPTL4 mRNA target site that does not harbor an SNP, with a minor allele frequency (MAF) greater or equal to 1% (pos. 2-18). In some embodiments, the MAF is greater or equal to about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20%.

[0039] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 32, 33, 34, 35, 36, 56, 57, 58, 59, 61, 62, 63, 64, 79, 80, 84, 111, 112, 116, 117, 118, 119, 120, 121, 125, 126, 127, 128, 129, 149, 150, 152, 153, 154, 157, 158, 159, 161, 164, 165, 166, 167, 168, 169, 172, 174, 175, 177, 196, 198, 199, 210, 211, 212, 214, 215, 216, 217, 218, 219, 221, 222, 223, 228, 230, 231, 240, 241, 245, 246, 250, 252, 253, 254, 255, 260, 261, 262, 263, 265, 266, 271, 272, 274, 280, 282, 289, 290, 291, 292, 293, 299, 304, 321, 323, 325, 326, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 342, 347, 349, 350, 352, 353, 356, 377, 380, 382, 386, 388, 391, 392, 393, 394, 397, 398, 399, 402, 404, 405, 411, 412, 413, 414, 415, 417, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 435, 481, 484, 506, 509, 517, 519, 520, 565, 570, 571, 572, 589, 607, 608, 610, 611, 612, 616, 617, 620, 623, 635, 637, 640, 643, 653, 672, 673, 674, 675, 676, 677, 678, 679, 681, 682, 683, 684, 686, 687, 689, 692, 695, 830, 834, 841, 842, 843, 844, 850, 851, 852, 853, 854, 856, 857, 859, 866, 868, 871, 872, 876, 887, 888, 890, 892, 893, 894, 897, 900, 902, 907, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 925, 945, 968, 1001, 1002, 1005, 1006, 1009, 1010, 1011, 1013, 1028, 1032, 1037, 1052, 1053, 1054, 1055, 1057, 1058, 1064, 1112, 1122, 1124, 1126, 1127, 1133, 1134, 1136, 1137, 1147, 1148, 1149, 1151, 1153, 1154, 1155, 1157, 1158, 1161, 1162, 1163, 1164, 1165, 1166, 1171, 1172, 1175, 1181, 1182, 1184, 1248, 1249, 1252, 1253, 1259, 1276, 1285, 1310, 1315, 1338, 1343, 1347, 1348, 1349, 1350, 1351, 1352, 1378, 1405, 1407, 1413, 1414, 1415, 1416, 1417, 1418, 1429, 1430, 1448, 1477, 1487, 1488, 1489, 1493, 1494, 1519, 1523, 1538, 1556, 1561, 1563, 1564, 1565, 1570, 1571, 1572, 1580, 1581, 1589, 1597, 1598, 1601, 1602, 1603, 1604, 1605, 1606, 1610, 1611, 1613, 1614, 1617, 1693, 1699, 1701, 1702, 1703, 1722, 1740, 1741, 1742, 1745, 1747, 1748, 1749, 1751, 1754, 1755, 1779, 1780, 1784, 1787, 1788, 1798, 1799, 1800, 1801, 1802, or 1803, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1886, 1887, 1888, 1889, 1890, 1910, 1911, 1912, 1913, 1915, 1916, 1917, 1918, 1933, 1934, 1938, 1965, 1966, 1970, 1971, 1972, 1973, 1974, 1975, 1979, 1980, 1981, 1982, 1983, 2003, 2004, 2006, 2007, 2008, 2011, 2012, 2013, 2015, 2018, 2019, 2020, 2021, 2022, 2023, 2026, 2028, 2029, 2031, 2050, 2052, 2053, 2064, 2065, 2066, 2068, 2069, 2070, 2071, 2072, 2073, 2075, 2076, 2077, 2082, 2084, 2085, 2094, 2095, 2099, 2100, 2104, 2106, 2107, 2108, 2109, 2114, 2115, 2116, 2117, 2119, 2120, 2125, 2126, 2128, 2134, 2136, 2143, 2144, 2145, 2146, 2147, 2153, 2158, 2175, 2177, 2179, 2180, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2191, 2192, 2193, 2196, 2201, 2203, 2204, 2206, 2207, 2210, 2231, 2234, 2236, 2240,

2242, 2245, 2246, 2247, 2248, 2251, 2252, 2253, 2256, 2258, 2259, 2265, 2266, 2267, 2268, 2269, 2271, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2289, 2335, 2338, 2360, 2363, 2371, 2373, 2374, 2419, 2424, 2425, 2426, 2443, 2461, 2462, 2464, 2465, 2466, 2470, 2471, 2474, 2477, 2489, 2491, 2494, 2497, 2507, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2535, 2536, 2537, 2538, 2540, 2541, 2543, 2546, 2549, 2684, 2688, 2695, 2696, 2697, 2698, 2704, 2705, 2706, 2707, 2708, 2710, 2711, 2713, 2720, 2722, 2725, 2726, 2730, 2741, 2742, 2744, 2746, 2747, 2748, 2751, 2754, 2756, 2761, 2765, 2766, 2767, 2768, 2769, 2770, 2771, 2772, 2773, 2774, 2775, 2776, 2779, 2799, 2822, 2855, 2856, 2859, 2860, 2863, 2864, 2865, 2867, 2882, 2886, 2891, 2906, 2907, 2908, 2909, 2911, 2912, 2918, 2966, 2976, 2978, 2980, 2981, 2987, 2988, 2990, 2991, 3001, 3002, 3003, 3005, 3007, 3008, 3009, 3011, 3012, 3015, 3016, 3017, 3018, 3019, 3020, 3025, 3026, 3029, 3035, 3036, 3038, 3102, 3103, 3106, 3107, 3113, 3130, 3139, 3164, 3169, 3192, 3197, 3201, 3202, 3203, 3204, 3205, 3206, 3232, 3259, 3261, 3267, 3268, 3269, 3270, 3271, 3272, 3283, 3284, 3302, 3331, 3341, 3342, 3343, 3347, 3348, 3373, 3377, 3392, 3410, 3415, 3417, 3418, 3419, 3424, 3425, 3426, 3434, 3435, 3443, 3451, 3452, 3455, 3456, 3457, 3458, 3459, 3460, 3464, 3465, 3467, 3468, 3471, 3547, 3553, 3555, 3556, 3557, 3576, 3594, 3595, 3596, 3599, 3601, 3602, 3603, 3605, 3608, 3609, 3633, 3634, 3638, 3641, 3642, 3652, 3653, 3654, 3655, 3656, or 3657, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions.

[0040] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 32, 33, 34, 35, 36, 56, 57, 58, 59, 61, 62, 63, 64, 79, 80, 84, 111, 112, 116, 117, 118, 119, 120, 121, 125, 126, 127, 128, 129, 149, 150, 152, 153, 154, 157, 158, 159, 161, 164, 165, 166, 167, 168, 169, 172, 174, 175, 177, 196, 198, 199, 210, 211, 212, 214, 215, 216, 217, 218, 219, 221, 222, 223, 228, 230, 231, 240, 241, 245, 246, 250, 252, 253, 254, 255, 260, 261, 262, 263, 265, 266, 271, 272, 274, 280, 282, 289, 290, 291, 292, 293, 299, 304, 321, 323, 325, 326, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 342, 347, 349, 350, 352, 353, 356, 377, 380, 382, 386, 388, 391, 392, 393, 394, 397, 398, 399, 402, 404, 405, 411, 412, 413, 414, 415, 417, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 435, 481, 484, 506, 509, 517, 519, 520, 565, 570, 571, 572, 589, 607, 608, 610, 611, 612, 616, 617, 620, 623, 635, 637, 640, 643, 653, 672, 673, 674, 675, 676, 677, 678, 679, 681, 682, 683, 684, 686, 687, 689, 692, 695, 830, 834, 841, 842, 843, 844, 850, 851, 852, 853, 854, 856, 857, 859, 866, 868, 871, 872, 876, 887, 888, 890, 892, 893, 894, 897, 900, 902, 907, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 925, 945, 968, 1001, 1002, 1005, 1006, 1009, 1010, 1011, 1013, 1028, 1032, 1037, 1052, 1053, 1054, 1055, 1057, 1058, 1064, 1112, 1122, 1124, 1126, 1127, 1133, 1134, 1136, 1137, 1147, 1148, 1149, 1151, 1153, 1154, 1155, 1157, 1158, 1161, 1162, 1163, 1164, 1165, 1166, 1171, 1172, 1175, 1181, 1182, 1184, 1248, 1249, 1252, 1253, 1259, 1276, 1285, 1310, 1315, 1338, 1343, 1347, 1348, 1349, 1350, 1351, 1352, 1378, 1405, 1407, 1413, 1414, 1415, 1416, 1417, 1418, 1429, 1430, 1448, 1477, 1487, 1488, 1489, 1493, 1494, 1519, 1523, 1538, 1556, 1561, 1563, 1564, 1565, 1570, 1571, 1572, 1580, 1581, 1589, 1597, 1598, 1601, 1602, 1603, 1604, 1605, 1606, 1610, 1611, 1613, 1614, 1617, 1693, 1699, 1701, 1702, 1703, 1722, 1740, 1741, 1742, 1745, 1747, 1748, 1749, 1751, 1754, 1755, 1779, 1780, 1784, 1787, 1788, 1798, 1799, 1800,

1801, 1802, or 1803; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1886, 1887, 1888, 1889, 1890, 1910, 1911, 1912, 1913, 1915, 1916, 1917, 1918, 1933, 1934, 1938, 1965, 1966, 1970, 1971, 1972, 1973, 1974, 1975, 1979, 1980, 1981, 1982, 1983, 2003, 2004, 2006, 2007, 2008, 2011, 2012, 2013, 2015, 2018, 2019, 2020, 2021, 2022, 2023, 2026, 2028, 2029, 2031, 2050, 2052, 2053, 2064, 2065, 2066, 2068, 2069, 2070, 2071, 2072, 2073, 2075, 2076, 2077, 2082, 2084, 2085, 2094, 2095, 2099, 2100, 2104, 2106, 2107, 2108, 2109, 2114, 2115, 2116, 2117, 2119, 2120, 2125, 2126, 2128, 2134, 2136, 2143, 2144, 2145, 2146, 2147, 2153, 2158, 2175, 2177, 2179, 2180, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2191, 2192, 2193, 2196, 2201, 2203, 2204, 2206, 2207, 2210, 2231, 2234, 2236, 2240, 2242, 2245, 2246, 2247, 2248, 2251, 2252, 2253, 2256, 2258, 2259, 2265, 2266, 2267, 2268, 2269, 2271, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2289, 2335, 2338, 2360, 2363, 2371, 2373, 2374, 2419, 2424, 2425, 2426, 2443, 2461, 2462, 2464, 2465, 2466, 2470, 2471, 2474, 2477, 2489, 2491, 2494, 2497, 2507, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2535, 2536, 2537, 2538, 2540, 2541, 2543, 2546, 2549, 2684, 2688, 2695, 2696, 2697, 2698, 2704, 2705, 2706, 2707, 2708, 2710, 2711, 2713, 2720, 2722, 2725, 2726, 2730, 2741, 2742, 2744, 2746, 2747, 2748, 2751, 2754, 2756, 2761, 2765, 2766, 2767, 2768, 2769, 2770, 2771, 2772, 2773, 2774, 2775, 2776, 2779, 2799, 2822, 2855, 2856, 2859, 2860, 2863, 2864, 2865, 2867, 2882, 2886, 2891, 2906, 2907, 2908, 2909, 2911, 2912, 2918, 2966, 2976, 2978, 2980, 2981, 2987, 2988, 2990, 2991, 3001, 3002, 3003, 3005, 3007, 3008, 3009, 3011, 3012, 3015, 3016, 3017, 3018, 3019, 3020, 3025, 3026, 3029, 3035, 3036, 3038, 3102, 3103, 3106, 3107, 3113, 3130, 3139, 3164, 3169, 3192, 3197, 3201, 3202, 3203, 3204, 3205, 3206, 3232, 3259, 3261, 3267, 3268, 3269, 3270, 3271, 3272, 3283, 3284, 3302, 3331, 3341, 3342, 3343, 3347, 3348, 3373, 3377, 3392, 3410, 3415, 3417, 3418, 3419, 3424, 3425, 3426, 3434, 3435, 3443, 3451, 3452, 3455, 3456, 3457, 3458, 3459, 3460, 3464, 3465, 3467, 3468, 3471, 3547, 3553, 3555, 3556, 3557, 3576, 3594, 3595, 3596, 3599, 3601, 3602, 3603, 3605, 3608, 3609, 3633, 3634, 3638, 3641, 3642, 3652, 3653, 3654, 3655, 3656, or 3657.

[0041] In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 32, 33, 34, 35, 36, 56, 57, 58, 59, 61, 62, 63, 64, 79, 80, 84, 111, 112, 116, 117, 118, 119, 120, 121, 125, 126, 127, 128, 129, 149, 150, 152, 153, 154, 157, 158, 159, 161, 164, 165, 166, 167, 168, 169, 172, 174, 175, 177, 196, 198, 199, 210, 211, 212, 214, 215, 216, 217, 218, 219, 221, 222, 223, 228, 230, 231, 240, 241, 245, 246, 250, 252, 253, 254, 255, 260, 261, 262, 263, 265, 266, 271, 272, 274, 280, 282, 289, 290, 291, 292, 293, 299, 304, 321, 323, 325, 326, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 342, 347, 349, 350, 352, 353, 356, 377, 380, 382, 386, 388, 391, 392, 393, 394, 397, 398, 399, 402, 404, 405, 411, 412, 413, 414, 415, 417, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 435, 481, 484, 506, 509, 517, 519, 520, 565, 570, 571, 572, 589, 607, 608, 610, 611, 612, 616, 617, 620, 623, 635, 637, 640, 643, 653, 672, 673, 674, 675, 676, 677, 678, 679, 681, 682, 683, 684, 686, 687, 689, 692, 695, 830, 834, 841, 842, 843, 844, 850, 851, 852, 853, 854, 856, 857, 859, 866, 868, 871, 872, 876, 887, 888, 890, 892, 893, 894, 897, 900, 902, 907, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 925, 945, 968, 1001, 1002, 1005, 1006, 1009, 1010, 1011, 1013, 1028, 1032, 1037, 1052, 1053, 1054, 1055, 1057, 1058, 1064, 1112, 1122, 1124, 1126, 1127, 1133, 1134, 1136, 1137, 1147, 1148, 1149, 1151,

1153, 1154, 1155, 1157, 1158, 1161, 1162, 1163, 1164, 1165, 1166, 1171, 1172, 1175, 1181, 1182, 1184, 1248, 1249, 1252, 1253, 1259, 1276, 1285, 1310, 1315, 1338, 1343, 1347, 1348, 1349, 1350, 1351, 1352, 1378, 1405, 1407, 1413, 1414, 1415, 1416, 1417, 1418, 1429, 1430, 1448, 1477, 1487, 1488, 1489, 1493, 1494, 1519, 1523, 1538, 1556, 1561, 1563, 1564, 1565, 1570, 1571, 1572, 1580, 1581, 1589, 1597, 1598, 1601, 1602, 1603, 1604, 1605, 1606, 1610, 1611, 1613, 1614, 1617, 1693, 1699, 1701, 1702, 1703, 1722, 1740, 1741, 1742, 1745, 1747, 1748, 1749, 1751, 1754, 1755, 1779, 1780, 1784, 1787, 1788, 1798, 1799, 1800, 1801, 1802, or 1803, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1886, 1887, 1888, 1889, 1890, 1910, 1911, 1912, 1913, 1915, 1916, 1917, 1918, 1933, 1934, 1938, 1965, 1966, 1970, 1971, 1972, 1973, 1974, 1975, 1979, 1980, 1981, 1982, 1983, 2003, 2004, 2006, 2007, 2008, 2011, 2012, 2013, 2015, 2018, 2019, 2020, 2021, 2022, 2023, 2026, 2028, 2029, 2031, 2050, 2052, 2053, 2064, 2065, 2066, 2068, 2069, 2070, 2071, 2072, 2073, 2075, 2076, 2077, 2082, 2084, 2085, 2094, 2095, 2099, 2100, 2104, 2106, 2107, 2108, 2109, 2114, 2115, 2116, 2117, 2119, 2120, 2125, 2126, 2128, 2134, 2136, 2143, 2144, 2145, 2146, 2147, 2153, 2158, 2175, 2177, 2179, 2180, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2191, 2192, 2193, 2196, 2201, 2203, 2204, 2206, 2207, 2210, 2231, 2234, 2236, 2240, 2242, 2245, 2246, 2247, 2248, 2251, 2252, 2253, 2256, 2258, 2259, 2265, 2266, 2267, 2268, 2269, 2271, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2289, 2335, 2338, 2360, 2363, 2371, 2373, 2374, 2419, 2424, 2425, 2426, 2443, 2461, 2462, 2464, 2465, 2466, 2470, 2471, 2474, 2477, 2489, 2491, 2494, 2497, 2507, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2535, 2536, 2537, 2538, 2540, 2541, 2543, 2546, 2549, 2684, 2688, 2695, 2696, 2697, 2698, 2704, 2705, 2706, 2707, 2708, 2710, 2711, 2713, 2720, 2722, 2725, 2726, 2730, 2741, 2742, 2744, 2746, 2747, 2748, 2751, 2754, 2756, 2761, 2765, 2766, 2767, 2768, 2769, 2770, 2771, 2772, 2773, 2774, 2775, 2776, 2779, 2799, 2822, 2855, 2856, 2859, 2860, 2863, 2864, 2865, 2867, 2882, 2886, 2891, 2906, 2907, 2908, 2909, 2911, 2912, 2918, 2966, 2976, 2978, 2980, 2981, 2987, 2988, 2990, 2991, 3001, 3002, 3003, 3005, 3007, 3008, 3009, 3011, 3012, 3015, 3016, 3017, 3018, 3019, 3020, 3025, 3026, 3029, 3035, 3036, 3038, 3102, 3103, 3106, 3107, 3113, 3130, 3139, 3164, 3169, 3192, 3197, 3201, 3202, 3203, 3204, 3205, 3206, 3232, 3259, 3261, 3267, 3268, 3269, 3270, 3271, 3272, 3283, 3284, 3302, 3331, 3341, 3342, 3343, 3347, 3348, 3373, 3377, 3392, 3410, 3415, 3417, 3418, 3419, 3424, 3425, 3426, 3434, 3435, 3443, 3451, 3452, 3455, 3456, 3457, 3458, 3459, 3460, 3464, 3465, 3467, 3468, 3471, 3547, 3553, 3555, 3556, 3557, 3576, 3594, 3595, 3596, 3599, 3601, 3602, 3603, 3605, 3608, 3609, 3633, 3634, 3638, 3641, 3642, 3652, 3653, 3654, 3655, 3656, or 3657, or a nucleic acid sequence thereof having 1 or 2 nucleoside additions at the 3' end. For example, the nucleic acid sequence may have 2 uracil nucleoside additions at the 3' end. The nucleic acid sequence may have 1 uracil nucleoside addition at the 3' end. The nucleic acid sequence may have more than 2 nucleoside additions at the 3' end.

[0042] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 33, 34, 35, 36, 56, 121, 272, 280, 282, 289, 290, 291, 292, 293, 321, 323, 326, 328, 329, 330, 331, 332,

333, 334, 335, 337, 338, 339, 342, 347, 349, 411, 412, 430, 431, 435, 481, 484, 509, 517, 519, 520, 565, 620, 635, 637, 640, 830, 834, 841, 842, 843, 844, 850, 871, 872, 876, 887, 888, 894, 897, 902, 945, 1001, 1002, 1005, 1037, 1133, 1134, 1137, 1149, 1151, 1153, 1154, 1155, 1157, 1158, 1161, 1162, 1164, 1165, 1166, 1171, 1172, 1248, 1249, 1315, 1338, 1343, 1347, 1348, 1429, 1430, 1570, 1571, 1572, 1610, 1611, 1617, 1780, 1784, or 1787; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1887, 1888, 1889, 1890, 1910, 1975, 2126, 2134, 2136, 2143, 2144, 2145, 2146, 2147, 2175, 2177, 2180, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2191, 2192, 2193, 2196, 2201, 2203, 2265, 2266, 2284, 2285, 2289, 2335, 2338, 2363, 2371, 2373, 2374, 2419, 2474, 2489, 2491, 2494, 2684, 2688, 2695, 2696, 2697, 2698, 2704, 2725, 2726, 2730, 2741, 2742, 2748, 2751, 2756, 2799, 2855, 2856, 2859, 2891, 2987, 2988, 2991, 3003, 3005, 3007, 3008, 3009, 3011, 3012, 3015, 3016, 3018, 3019, 3020, 3025, 3026, 3102, 3103, 3169, 3192, 3197, 3201, 3202, 3283, 3284, 3424, 3425, 3426, 3464, 3465, 3471, 3634, 3638, or 3641.

[0043] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 32, 33, 34, 35, 36, 56, 57, 58, 59, 61, 62, 63, 64, 79, 80, 112, 116, 117, 118, 119, 120, 125, 126, 127, 128, 129, 149, 150, 152, 153, 157, 158, 159, 161, 164, 165, 166, 167, 168, 169, 172, 174, 175, 196, 199, 211, 212, 214, 215, 216, 217, 218, 219, 221, 222, 223, 228, 230, 231, 240, 241, 245, 246, 250, 252, 253, 254, 255, 260, 261, 262, 263, 265, 266, 271, 272, 274, 280, 289, 290, 291, 292, 293, 299, 304, 321, 323, 325, 326, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 342, 347, 349, 350, 352, 353, 356, 380, 382, 386, 388, 391, 392, 393, 394, 397, 398, 399, 402, 404, 405, 411, 412, 413, 414, 415, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 435, 484, 517, 519, 520, 565, 570, 571, 572, 607, 608, 610, 611, 612, 616, 617, 620, 635, 637, 640, 672, 673, 674, 675, 676, 677, 678, 679, 681, 682, 683, 684, 686, 687, 689, 692, 695, 830, 841, 842, 843, 844, 850, 851, 852, 853, 854, 856, 857, 866, 868, 871, 872, 876, 887, 888, 890, 892, 893, 894, 902, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 945, 1001, 1002, 1005, 1006, 1009, 1010, 1011, 1013, 1028, 1032, 1052, 1053, 1054, 1055, 1057, 1058, 1112, 1122, 1124, 1126, 1127, 1133, 1134, 1147, 1148, 1149, 1151, 1153, 1154, 1155, 1157, 1158, 1161, 1162, 1164, 1165, 1166, 1175, 1182, 1184, 1252, 1253, 1259, 1276, 1285, 1310, 1315, 1343, 1347, 1348, 1349, 1350, 1351, 1405, 1407, 1413, 1414, 1415, 1416, 1417, 1418, 1429, 1430, 1448, 1519, 1523, 1556, 1561, 1563, 1564, 1565, 1571, 1572, 1580, 1581, 1589, 1597, 1601, 1602, 1603, 1604, 1605, 1606, 1611, 1613, 1614, 1693, 1699, 1701, 1702, 1703, 1722, 1740, 1741, 1742, 1745, 1747, 1748, 1749, 1751, 1754, 1755, 1779, 1780, 1784, 1788, 1798, 1799, 1801, 1802, or 1803; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1886, 1887, 1888, 1889, 1890, 1910, 1911, 1912, 1913, 1915, 1916, 1917, 1918, 1933, 1934, 1966, 1970, 1971, 1972, 1973, 1974, 1979, 1980, 1981, 1982, 1983, 2003, 2004, 2006, 2007, 2011, 2012, 2013, 2015, 2018, 2019, 2020, 2021, 2022, 2023, 2026, 2028, 2029, 2050, 2053, 2065, 2066, 2068, 2069, 2070, 2071, 2072, 2073, 2075, 2076, 2077, 2082, 2084, 2085, 2094, 2095, 2099, 2100, 2104, 2106, 2107, 2108, 2109, 2114, 2115, 2116, 2117, 2119, 2120, 2125, 2126, 2128, 2134, 2143, 2144, 2145, 2146, 2147, 2153, 2158, 2175, 2177, 2179, 2180, 2182, 2183, 2184, 2185, 2186, 2187,

2188, 2189, 2191, 2192, 2193, 2196, 2201, 2203, 2204, 2206, 2207, 2210, 2234, 2236, 2240, 2242, 2245, 2246, 2247, 2248, 2251, 2252, 2253, 2256, 2258, 2259, 2265, 2266, 2267, 2268, 2269, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2289, 2338, 2371, 2373, 2374, 2419, 2424, 2425, 2426, 2461, 2462, 2464, 2465, 2466, 2470, 2471, 2474, 2489, 2491, 2494, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2535, 2536, 2537, 2538, 2540, 2541, 2543, 2546, 2549, 2684, 2695, 2696, 2697, 2698, 2704, 2705, 2706, 2707, 2708, 2710, 2711, 2720, 2722, 2725, 2726, 2730, 2741, 2742, 2744, 2746, 2747, 2748, 2756, 2765, 2766, 2767, 2768, 2769, 2770, 2771, 2772, 2773, 2774, 2775, 2776, 2799, 2855, 2856, 2859, 2860, 2863, 2864, 2865, 2867, 2882, 2886, 2906, 2907, 2908, 2909, 2911, 2912, 2966, 2976, 2978, 2980, 2981, 2987, 2988, 3001, 3002, 3003, 3005, 3007, 3008, 3009, 3011, 3012, 3015, 3016, 3018, 3019, 3020, 3029, 3036, 3038, 3106, 3107, 3113, 3130, 3139, 3164, 3169, 3197, 3201, 3202, 3203, 3204, 3205, 3259, 3261, 3267, 3268, 3269, 3270, 3271, 3272, 3283, 3284, 3302, 3373, 3377, 3410, 3415, 3417, 3418, 3419, 3425, 3426, 3434, 3435, 3443, 3451, 3455, 3456, 3457, 3458, 3459, 3460, 3465, 3467, 3468, 3547, 3553, 3555, 3556, 3557, 3576, 3594, 3595, 3596, 3599, 3601, 3602, 3603, 3605, 3608, 3609, 3633, 3634, 3638, 3642, 3652, 3653, 3655, 3656, or 3657.

[0044] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 33, 34, 35, 36, 56, 272, 280, 289, 290, 291, 292, 293, 321, 323, 326, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 342, 347, 349, 411, 412, 430, 431, 435, 484, 517, 519, 520, 565, 620, 635, 637, 640, 830, 841, 842, 843, 844, 850, 871, 872, 876, 887, 888, 894, 902, 945, 1001, 1002, 1005, 1133, 1134, 1149, 1151, 1153, 1154, 1155, 1157, 1158, 1161, 1162, 1164, 1165, 1166, 1315, 1343, 1347, 1348, 1429, 1430, 1571, 1572, 1611, 1780, or 1784; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1887, 1888, 1889, 1890, 1910, 2126, 2134, 2143, 2144, 2145, 2146, 2147, 2175, 2177, 2180, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2191, 2192, 2193, 2196, 2201, 2203, 2265, 2266, 2284, 2285, 2289, 2338, 2371, 2373, 2374, 2419, 2474, 2489, 2491, 2494, 2684, 2695, 2696, 2697, 2698, 2704, 2725, 2726, 2730, 2741, 2742, 2748, 2756, 2799, 2855, 2856, 2859, 2987, 2988, 3003, 3005, 3007, 3008, 3009, 3011, 3012, 3015, 3016, 3018, 3019, 3020, 3169, 3197, 3201, 3202, 3283, 3284, 3425, 3426, 3465, 3634, or 3638.

[0045] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 32, 36, 56, 57, 58, 61, 62, 79, 80, 117, 119, 125, 126, 128, 149, 152, 157, 158, 159, 161, 165, 166, 167, 168, 169, 174, 196, 211, 212, 217, 218, 219, 230, 231, 245, 246, 253, 260, 261, 262, 271, 272, 280, 289, 291, 292, 293, 304, 321, 323, 325, 326, 328, 330, 331, 332, 333, 334, 337, 338, 342, 347, 349, 352, 353, 356, 380, 382, 386, 388, 391, 392, 394, 399, 413, 414, 415, 422, 423, 424, 425, 426, 435, 517, 519, 520, 565, 571, 607, 608, 612, 617, 620, 635, 640, 672, 673, 674, 675, 678, 679, 681, 683, 684, 687, 692, 842, 843, 850, 851, 854, 866, 868, 876, 892, 893, 902, 911, 912, 913, 914, 916, 919, 945, 1001, 1002, 1006, 1010, 1028, 1052, 1053, 1054, 1055, 1057, 1112, 1124, 1127, 1147, 1149, 1151, 1153, 1155, 1157, 1164,

1175, 1182, 1184, 1259, 1276, 1285, 1315, 1343, 1349, 1350, 1351, 1405, 1407, 1413, 1415, 1418, 1564, 1571, 1581, 1589, 1597, 1601, 1602, 1603, 1604, 1605, 1606, 1613, 1614, 1693, 1701, 1722, 1740, 1745, 1751, 1755, 1801, 1802, or 1803, or 3638; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1886, 1890, 1910, 1911, 1912, 1915, 1916, 1933, 1934, 1971, 1973, 1979, 1980, 1982, 2003, 2006, 2011, 2012, 2013, 2015, 2019, 2020, 2021, 2022, 2023, 2028, 2050, 2065, 2066, 2071, 2072, 2073, 2084, 2085, 2099, 2100, 2107, 2114, 2115, 2116, 2125, 2126, 2134, 2143, 2145, 2146, 2147, 2158, 2175, 2177, 2179, 2180, 2182, 2184, 2185, 2186, 2187, 2188, 2191, 2192, 2196, 2201, 2203, 2206, 2207, 2210, 2234, 2236, 2240, 2242, 2245, 2246, 2248, 2253, 2267, 2268, 2269, 2276, 2277, 2278, 2279, 2280, 2289, 2371, 2373, 2374, 2419, 2425, 2461, 2462, 2466, 2471, 2474, 2489, 2494, 2526, 2527, 2528, 2529, 2532, 2533, 2535, 2537, 2538, 2541, 2546, 2696, 2697, 2704, 2705, 2708, 2720, 2722, 2730, 2746, 2747, 2756, 2765, 2766, 2767, 2768, 2770, 2773, 2799, 2855, 2856, 2860, 2864, 2882, 2906, 2907, 2908, 2909, 2911, 2966, 2978, 2981, 3001, 3003, 3005, 3007, 3009, 3011, 3018, 3029, 3036, 3038, 3113, 3130, 3139, 3169, 3197, 3203, 3204, 3205, 3259, 3261, 3267, 3269, 3272, 3418, 3425, 3435, 3443, 3451, 3455, 3456, 3457, 3458, 3459, 3460, 3467, 3468, 3547, 3555, 3576, 3594, 3599, 3605, 3609, 3655, 3656, or 3657.

[0046] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, the sense strand comprises the nucleoside sequence of any one of SEQ ID 36, 56, 272, 280, 289, 291, 292, 293, 321, 323, 326, 328, 330, 331, 332, 333, 334, 337, 338, 342, 347, 349, 435, 517, 519, 520, 565, 620, 635, 640, 842, 843, 850, 876, 902, 945, 1001, 1002, 1149, 1151, 1153, 1155, 1157, 1164, 1315, 1343, or 1571; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID 1890, 1910, 2126, 2134, 2143, 2145, 2146, 2147, 2175, 2177, 2180, 2182, 2184, 2185, 2186, 2187, 2188, 2191, 2192, 2196, 2201, 2203, 2289, 2371, 2373, 2374, 2419, 2474, 2489, 2494, 2696, 2697, 2704, 2730, 2756, 2799, 2855, 2856, 3003, 3005, 3007, 3009, 3011, 3018, 3169, 3197, or 3425.

[0047] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 32, 36, 56, 58, 61, 62, 80, 117, 119, 126, 152, 154, 157, 158, 159, 161, 166, 169, 174, 177, 196, 211, 212, 217, 218, 230, 231, 245, 253, 260, 261, 271, 272, 280, 289, 293, 304, 328, 330, 331, 332, 333, 334, 337, 342, 347, 349, 353, 356, 386, 388, 391, 392, 394, 414, 415, 422, 423, 424, 426, 435, 520, 571, 608, 612, 617, 653, 672, 678, 679, 681, 683, 692, 842, 843, 851, 854, 859, 876, 892, 900, 913, 914, 919, 968, 1001, 1002, 1054, 1057, 1064, 1112, 1124, 1157, 1164, 1182, 1184, 1248, 1259, 1343, 1351, 1352, 1415, 1418, 1564, 1581, 1602, 1614, 1693, 1701, 1722, 1740, 1751, 1755, or 1787; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1886, 1890, 1910, 1912, 1915, 1916, 1934, 1971, 1973, 1980, 2006, 2008, 2011, 2012, 2013, 2015, 2020, 2023, 2028, 2031, 2050, 2065, 2066, 2071, 2072, 2084, 2085, 2099, 2107, 2114, 2115, 2125, 2126, 2134, 2143, 2147, 2158, 2182, 2184, 2185, 2186, 2187, 2188, 2191, 2196, 2201, 2203, 2207, 2210, 2240, 2242, 2245, 2246, 2248, 2268, 2269, 2276, 2277, 2278, 2280, 2289, 2374, 2425, 2462, 2466, 2471, 2507, 2526, 2532, 2533, 2535, 2537, 2546, 2696,

2697, 2705, 2708, 2713, 2730, 2746, 2754, 2767, 2768, 2773, 2822, 2855, 2856, 2908, 2911, 2918, 2966, 2978, 3011, 3018, 3036, 3038, 3102, 3113, 3197, 3205, 3206, 3269, 3272, 3418, 3435, 3456, 3468, 3547, 3555, 3576, 3594, 3605, 3609, or 3641.

[0048] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 36, 56, 272, 280, 289, 293, 328, 330, 331, 332, 333, 334, 337, 342, 347, 349, 435, 520, 842, 843, 876, 1001, 1002, 1157, 1164, or 1343; and/or the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOs: 1890, 1910, 2126, 2134, 2143, 2147, 2182, 2184, 2185, 2186, 2187, 2188, 2191, 2196, 2201, 2203, 2289, 2374, 2696, 2697, 2730, 2855, 2856, 3011, 3018, or 3197.

[0049] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset A. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0050] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 4**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 4**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 4**. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0051] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset B. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0052] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C, or a nucleic acid sequence thereof having 1 or 2

nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset C. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0053] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset D. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0054] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset E. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0055] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset F, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset F, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset F. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0056] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset G, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset G, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA of subset G. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. The siRNA may include one or more internucleoside linkages and/or one or more nucleoside modifications.

[0057] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 5**, or a nucleic acid sequence thereof having 3 or 4 nucleoside

substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 5**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 5**. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 5**. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 5**. In some embodiments, the siRNA is unmodified. In some embodiments, the sense strand sequence of an siRNA in **Table 5** comprises modification pattern 1S. In some embodiments, the sense strand sequence of an siRNA in **Table 5** comprises modification pattern 3S or 6S. In some embodiments, the sense strand sequence of an siRNA in **Table 5** comprises modification pattern 1AS. In some embodiments, the sense or antisense strand sequence of an siRNA in **Table 5** comprises modification pattern 4AS, 5AS, 7AS, or 8AS. In some embodiments, the sense strand sequence of an siRNA in **Table 5** comprises modification pattern 7S, 8S, or 9S. In some embodiments, the antisense strand sequence of an siRNA in **Table 5** comprises modification pattern 10AS or 11AS.

[0058] In some embodiments, the siRNA reduces an ANGPTL4 mRNA measurement by 10% or more, 20% or more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, or 90% or more, relative to a control. In some embodiments, the siRNA reduces an ANGPTL4 mRNA measurement by 10% or less, 20% or less, 30% or less, 40% or less, 50% or less, 60% or less, 70% or less, 80% or less, or 90% or less, relative to a control. In some embodiments, the reduction is in a cell line such as U-138 MG cells. In some embodiments, the reduction is in response to 1 nM of the siRNA. In some embodiments, the reduction is in response to 10 nM of the siRNA.

[0059] Some siRNAs in **Table 5** reduced an ANGPTL4 mRNA measurement by 10% or more, relative to a control. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of ETD00646, ETD00648, ETD00649, ETD00651, ETD00653, ETD00654, ETD00655, ETD00656, ETD00658, ETD00660, ETD00661, ETD00662, ETD00667, ETD00669, ETD00683, ETD00684, ETD00686, ETD00688, ETD00689, ETD00691, ETD00692, ETD00694, ETD00702, ETD00709, ETD00713, ETD00714, ETD00715, ETD00716, ETD00717, ETD00719, ETD00721, ETD00726, ETD00727, ETD00728, ETD00729, ETD00730, ETD00731, ETD00733, ETD00736, ETD00738, or ETD00743, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of ETD00646, ETD00648, ETD00649, ETD00651, ETD00653, ETD00654, ETD00655, ETD00656, ETD00658, ETD00660, ETD00661, ETD00662, ETD00667, ETD00669, ETD00683, ETD00684, ETD00686, ETD00688, ETD00689, ETD00691, ETD00692, ETD00694, ETD00702, ETD00709, ETD00713, ETD00714, ETD00715, ETD00716, ETD00717, ETD00719, ETD00721, ETD00726, ETD00727, ETD00728, ETD00729, ETD00730, ETD00731, ETD00733, ETD00736, ETD00738, or ETD00743, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of ETD00646, ETD00648, ETD00649, ETD00651, ETD00653, ETD00654, ETD00655,

ETD00656, ETD00658, ETD00660, ETD00661, ETD00662, ETD00667, ETD00669, ETD00683, ETD00684, ETD00686, ETD00688, ETD00689, ETD00691, ETD00692, ETD00694, ETD00702, ETD00709, ETD00713, ETD00714, ETD00715, ETD00716, ETD00717, ETD00719, ETD00721, ETD00726, ETD00727, ETD00728, ETD00729, ETD00730, ETD00731, ETD00733, ETD00736, ETD00738, or ETD00743. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of ETD00646, ETD00648, ETD00649, ETD00651, ETD00653, ETD00654, ETD00655, ETD00656, ETD00658, ETD00660, ETD00661, ETD00662, ETD00667, ETD00669, ETD00683, ETD00684, ETD00686, ETD00688, ETD00689, ETD00691, ETD00692, ETD00694, ETD00702, ETD00709, ETD00713, ETD00714, ETD00715, ETD00716, ETD00717, ETD00719, ETD00721, ETD00726, ETD00727, ETD00728, ETD00729, ETD00730, ETD00731, ETD00733, ETD00736, ETD00738, or ETD00743. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of ETD00646, ETD00648, ETD00649, ETD00651, ETD00653, ETD00654, ETD00655, ETD00656, ETD00658, ETD00660, ETD00661, ETD00662, ETD00667, ETD00669, ETD00683, ETD00684, ETD00686, ETD00688, ETD00689, ETD00691, ETD00692, ETD00694, ETD00702, ETD00709, ETD00713, ETD00714, ETD00715, ETD00716, ETD00717, ETD00719, ETD00721, ETD00726, ETD00727, ETD00728, ETD00729, ETD00730, ETD00731, ETD00733, ETD00736, ETD00738, or ETD00743. In some embodiments, the siRNA is unmodified.

[0060] The siRNA may comprise an unmodified version of a sense strand sequence of an siRNA listed in **Table 5**. In some embodiments, the siRNA of listed in **Table 5** comprises any sense strand sequence of a subset A siRNA that is cross-reactive with a NHP ANGPTL4 mRNA. The siRNA may comprise an unmodified version of an antisense strand sequence of an siRNA listed in **Table 5**. In some embodiments, the siRNA of listed in **Table 5** comprises any antisense strand sequence of a subset A siRNA that is cross-reactive with a NHP ANGPTL4 mRNA.

[0061] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 6**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 6**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 6**. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 6**. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 6**. In some embodiments, the siRNA is unmodified.

[0062] The siRNA may comprise an unmodified version of an antisense strand sequence of an siRNA listed in **Table 6**. In some embodiments, the siRNA comprises the sense strand sequence of SEQ ID NO: 32, 570, 571, 572, 589, 607, 759, 801, 1276, 1285, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1702, 1840, or 1842, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of SEQ ID NO: 32,

570, 571, 572, 589, 607, 759, 801, 1276, 1285, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1702, 1840, or 1842, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of SEQ ID NO: 32, 570, 571, 572, 589, 607, 759, 801, 1276, 1285, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1702, 1840, or 1842. The siRNA may include the sense strand sequence of SEQ ID NO: 32, 570, 571, 572, 589, 607, 759, 801, 1276, 1285, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1702, 1840, or 1842, and one or more internucleoside linkages and/or one or more nucleoside modifications. The siRNA may include the sense strand sequence of SEQ ID NO: 32, 570, 571, 572, 589, 607, 759, 801, 1276, 1285, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1702, 1840, or 1842, and a modification pattern described herein. For example, any of the sense strands comprising the sequence of SEQ ID NO: 32, 570, 571, 572, 589, 607, 759, 801, 1276, 1285, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1702, 1840, or 1842 may in some cases comprise modification pattern 1S, 2S, 3S, or 6S, or modification pattern 7S, 8S, or 9S.

[0063] The siRNA may comprise an unmodified version of an antisense strand sequence of an siRNA listed in **Table 6**. In some embodiments, the siRNA comprises the antisense strand sequence of SEQ ID NO: 1886, 2424, 2425, 2426, 2443, 2461, 2613, 2655, 3130, 3139, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3556, 3694, or 3696, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of SEQ ID NO: 1886, 2424, 2425, 2426, 2443, 2461, 2613, 2655, 3130, 3139, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3556, 3694, or 3696, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of SEQ ID NO: 1886, 2424, 2425, 2426, 2443, 2461, 2613, 2655, 3130, 3139, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3556, 3694, or 3696. The siRNA may include the antisense strand sequence of SEQ ID NO: 1886, 2424, 2425, 2426, 2443, 2461, 2613, 2655, 3130, 3139, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3556, 3694, or 3696, and one or more internucleoside linkages and/or one or more nucleoside modifications. The siRNA may include the antisense strand sequence of SEQ ID NO: 1886, 2424, 2425, 2426, 2443, 2461, 2613, 2655, 3130, 3139, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3556, 3694, or 3696, and a modification pattern described herein. For example, any of the antisense strands comprising the sequence of SEQ ID NO: 1886, 2424, 2425, 2426, 2443, 2461, 2613, 2655, 3130, 3139, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3556, 3694, or 3696 may comprise modification pattern 1AS, 3AS, 4AS, 5AS, 7AS, or 8AS, or modification pattern 10AS or 11AS.

[0064] Some siRNAs in **Table 6** reduced an ANGPTL4 mRNA measurement by 10% or more, relative to a control. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of ETD00915, ETD00916, ETD00917, ETD00921, ETD00924, ETD00925, ETD00926, ETD00927, ETD00928, ETD00929, ETD00930, ETD00931, ETD00932, ETD00933, or ETD00934, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of ETD00915, ETD00916, ETD00917, ETD00921, ETD00924, ETD00925, ETD00926, ETD00927, ETD00928, ETD00929, ETD00930, ETD00931, ETD00932, ETD00933, or ETD00934, or a nucleic acid sequence

thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of ETD00915, ETD00916, ETD00917, ETD00921, ETD00924, ETD00925, ETD00926, ETD00927, ETD00928, ETD00929, ETD00930, ETD00931, ETD00932, ETD00933, or ETD00934. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of ETD00915, ETD00916, ETD00917, ETD00921, ETD00924, ETD00925, ETD00926, ETD00927, ETD00928, ETD00929, ETD00930, ETD00931, ETD00932, ETD00933, or ETD00934. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of ETD00915, ETD00916, ETD00917, ETD00921, ETD00924, ETD00925, ETD00926, ETD00927, ETD00928, ETD00929, ETD00930, ETD00931, ETD00932, ETD00933, or ETD00934. In some embodiments, the siRNA is unmodified.

[0065] The siRNA may comprise a sense strand sequence of an siRNA that reduced an ANGPTL4 mRNA measurement by 10% or more, relative to a control, in **Table 5** or **Table 6**. In some embodiments, the siRNA comprises the sense strand sequence of any one of SEQ ID NOS: 14012, 14014, 14015, 14017, 14019, 14020, 14021, 14022, 14024, 14026, 14027, 14028, 14033, 14035, 14049, 14050, 14052, 14054, 14055, 14057, 14058, 14060, 14068, 14075, 14079, 14080, 14081, 14082, 14083, 14085, 14087, 14092, 14093, 14094, 14095, 14096, 14097, 14099, 14102, 14104, 14109, 14114, 14115, 14116, 14120, 14123, 14124, 14125, 14126, 14127, 14128, 14129, 14130, 14131, 14132, or 14133, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of any one of SEQ ID NOS: 14012, 14014, 14015, 14017, 14019, 14020, 14021, 14022, 14024, 14026, 14027, 14028, 14033, 14035, 14049, 14050, 14052, 14054, 14055, 14057, 14058, 14060, 14068, 14075, 14079, 14080, 14081, 14082, 14083, 14085, 14087, 14092, 14093, 14094, 14095, 14096, 14097, 14099, 14102, 14104, 14109, 14114, 14115, 14116, 14120, 14123, 14124, 14125, 14126, 14127, 14128, 14129, 14130, 14131, 14132, or 14133, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of any one of SEQ ID NOS: 14012, 14014, 14015, 14017, 14019, 14020, 14021, 14022, 14024, 14026, 14027, 14028, 14033, 14035, 14049, 14050, 14052, 14054, 14055, 14057, 14058, 14060, 14068, 14075, 14079, 14080, 14081, 14082, 14083, 14085, 14087, 14092, 14093, 14094, 14095, 14096, 14097, 14099, 14102, 14104, 14109, 14114, 14115, 14116, 14120, 14123, 14124, 14125, 14126, 14127, 14128, 14129, 14130, 14131, 14132, or 14133. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the sense strand of 14012, 14014, 14015, 14017, 14019, 14020, 14021, 14022, 14024, 14026, 14027, 14028, 14033, 14035, 14049, 14050, 14052, 14054, 14055, 14057, 14058, 14060, 14068, 14075, 14079, 14080, 14081, 14082, 14083, 14085, 14087, 14092, 14093, 14094, 14095, 14096, 14097, 14099, 14102, 14104, 14109, 14114, 14115, 14116, 14120, 14123, 14124, 14125, 14126, 14127, 14128, 14129, 14130, 14131, 14132, or 14133. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the sense strand of 14012, 14014, 14015, 14017, 14019, 14020, 14021, 14022, 14024, 14026, 14027, 14028, 14033, 14035, 14049, 14050, 14052, 14054, 14055,

14057, 14058, 14060, 14068, 14075, 14079, 14080, 14081, 14082, 14083, 14085, 14087, 14092, 14093, 14094, 14095, 14096, 14097, 14099, 14102, 14104, 14109, 14114, 14115, 14116, 14120, 14123, 14124, 14125, 14126, 14127, 14128, 14129, 14130, 14131, 14132, or 14133. In some embodiments, the siRNA is unmodified.

[0066] The siRNA may comprise an antisense strand sequence of an siRNA that reduced an ANGPTL4 mRNA measurement by 10% or more, relative to a control, in **Table 5** or **Table 6**. In some embodiments, the siRNA comprises the antisense strand sequence of any one of SEQ ID NOS: 14167, 14169, 14170, 14172, 14174, 14175, 14176, 14177, 14179, 14181, 14182, 14183, 14188, 14190, 14204, 14205, 14207, 14209, 14210, 14212, 14213, 14215, 14223, 14230, 14234, 14235, 14236, 14237, 14238, 14240, 14242, 14247, 14248, 14249, 14250, 14251, 14252, 14254, 14257, 14259, 14264, 14269, 14270, 14271, 14275, 14278, 14279, 14280, 14281, 14282, 14283, 14284, 14285, 14286, 14287, or 14288, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of any one of SEQ ID NOS: 14167, 14169, 14170, 14172, 14174, 14175, 14176, 14177, 14179, 14181, 14182, 14183, 14188, 14190, 14204, 14205, 14207, 14209, 14210, 14212, 14213, 14215, 14223, 14230, 14234, 14235, 14236, 14237, 14238, 14240, 14242, 14247, 14248, 14249, 14250, 14251, 14252, 14254, 14257, 14259, 14264, 14269, 14270, 14271, 14275, 14278, 14279, 14280, 14281, 14282, 14283, 14284, 14285, 14286, 14287, or 14288, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of any one of SEQ ID NOS: 14167, 14169, 14170, 14172, 14174, 14175, 14176, 14177, 14179, 14181, 14182, 14183, 14188, 14190, 14204, 14205, 14207, 14209, 14210, 14212, 14213, 14215, 14223, 14230, 14234, 14235, 14236, 14237, 14238, 14240, 14242, 14247, 14248, 14249, 14250, 14251, 14252, 14254, 14257, 14259, 14264, 14269, 14270, 14271, 14275, 14278, 14279, 14280, 14281, 14282, 14283, 14284, 14285, 14286, 14287, or 14288. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the antisense strand of 14167, 14169, 14170, 14172, 14174, 14175, 14176, 14177, 14179, 14181, 14182, 14183, 14188, 14190, 14204, 14205, 14207, 14209, 14210, 14212, 14213, 14215, 14223, 14230, 14234, 14235, 14236, 14237, 14238, 14240, 14242, 14247, 14248, 14249, 14250, 14251, 14252, 14254, 14257, 14259, 14264, 14269, 14270, 14271, 14275, 14278, 14279, 14280, 14281, 14282, 14283, 14284, 14285, 14286, 14287, or 14288. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the antisense strand of 14167, 14169, 14170, 14172, 14174, 14175, 14176, 14177, 14179, 14181, 14182, 14183, 14188, 14190, 14204, 14205, 14207, 14209, 14210, 14212, 14213, 14215, 14223, 14230, 14234, 14235, 14236, 14237, 14238, 14240, 14242, 14247, 14248, 14249, 14250, 14251, 14252, 14254, 14257, 14259, 14264, 14269, 14270, 14271, 14275, 14278, 14279, 14280, 14281, 14282, 14283, 14284, 14285, 14286, 14287, or 14288. In some embodiments, the siRNA is unmodified.

[0067] The siRNA may comprise an unmodified version of a sense strand sequence of an siRNA that reduced an ANGPTL4 mRNA measurement by 10% or more, relative to a control, in **Table 5** or **Table 6**. In some embodiments, the siRNA comprises the sense strand sequence of any one of SEQ ID NOS: 32,

33, 35, 36, 121, 280, 282, 289, 290, 292, 321, 323, 326, 332, 334, 484, 509, 519, 565, 570, 571, 620, 637, 640, 759, 834, 876, 1001, 1133, 1134, 1137, 1149, 1151, 1154, 1157, 1165, 1166, 1171, 1172, 1248, 1249, 1285, 1338, 1348, 1430, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1611, 1702, 1840, or 1842, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of any one of SEQ ID NOS: 32, 33, 35, 36, 121, 280, 282, 289, 290, 292, 321, 323, 326, 332, 334, 484, 509, 519, 565, 570, 571, 620, 637, 640, 759, 834, 876, 1001, 1133, 1134, 1137, 1149, 1151, 1154, 1157, 1165, 1166, 1171, 1172, 1248, 1249, 1285, 1338, 1348, 1430, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1611, 1702, 1840, or 1842, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of any one of SEQ ID NOS: 32, 33, 35, 36, 121, 280, 282, 289, 290, 292, 321, 323, 326, 332, 334, 484, 509, 519, 565, 570, 571, 620, 637, 640, 759, 834, 876, 1001, 1133, 1134, 1137, 1149, 1151, 1154, 1157, 1165, 1166, 1171, 1172, 1248, 1249, 1285, 1338, 1348, 1430, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1611, 1702, 1840, or 1842. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 32, 33, 35, 36, 121, 280, 282, 289, 290, 292, 321, 323, 326, 332, 334, 484, 509, 519, 565, 570, 571, 620, 637, 640, 759, 834, 876, 1001, 1133, 1134, 1137, 1149, 1151, 1154, 1157, 1165, 1166, 1171, 1172, 1248, 1249, 1285, 1338, 1348, 1430, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1611, 1702, 1840, or 1842, and one or more internucleoside linkages and/or one or more nucleoside modifications. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 32, 33, 35, 36, 121, 280, 282, 289, 290, 292, 321, 323, 326, 332, 334, 484, 509, 519, 565, 570, 571, 620, 637, 640, 759, 834, 876, 1001, 1133, 1134, 1137, 1149, 1151, 1154, 1157, 1165, 1166, 1171, 1172, 1248, 1249, 1285, 1338, 1348, 1430, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1611, 1702, 1840, or 1842, and a modification pattern described herein (e.g. modification pattern 1S, 2S, 3S, 4S, 5S, or 6S, or modification pattern 7S, 8S, or 9S).

[0068] The siRNA may comprise an unmodified version of an antisense strand sequence of an siRNA that reduced an ANGPTL4 mRNA measurement by 10% or more, relative to a control, in **Table 5** or **Table 6**. In some embodiments, the siRNA comprises the antisense strand sequence of any one of SEQ ID NOS: 1886, 1887, 1889, 1890, 1975, 2134, 2136, 2143, 2144, 2146, 2175, 2177, 2180, 2186, 2188, 2338, 2363, 2373, 2419, 2424, 2425, 2474, 2491, 2494, 2613, 2688, 2730, 2855, 2987, 2988, 2991, 3003, 3005, 3008, 3011, 3019, 3020, 3025, 3026, 3102, 3103, 3139, 3192, 3202, 3284, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3465, 3556, 3694, or 3696, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of any one of SEQ ID NOS: 1886, 1887, 1889, 1890, 1975, 2134, 2136, 2143, 2144, 2146, 2175, 2177, 2180, 2186, 2188, 2338, 2363, 2373, 2419, 2424, 2425, 2474, 2491, 2494, 2613, 2688, 2730, 2855, 2987, 2988, 2991, 3003, 3005, 3008, 3011, 3019, 3020, 3025, 3026, 3102, 3103, 3139, 3192, 3202, 3284, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3465, 3556, 3694, or 3696, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of any one of SEQ ID NOS: 1886, 1887, 1889, 1890, 1975, 2134, 2136, 2143, 2144, 2146, 2175, 2177, 2180, 2186, 2188, 2338, 2363, 2373, 2419, 2424, 2425, 2474,

2491, 2494, 2613, 2688, 2730, 2855, 2987, 2988, 2991, 3003, 3005, 3008, 3011, 3019, 3020, 3025, 3026, 3102, 3103, 3139, 3192, 3202, 3284, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3465, 3556, 3694, or 3696. The siRNA may include the antisense strand sequence of any one of SEQ ID NOS: 1886, 1887, 1889, 1890, 1975, 2134, 2136, 2143, 2144, 2146, 2175, 2177, 2180, 2186, 2188, 2338, 2363, 2373, 2419, 2424, 2425, 2474, 2491, 2494, 2613, 2688, 2730, 2855, 2987, 2988, 2991, 3003, 3005, 3008, 3011, 3019, 3020, 3025, 3026, 3102, 3103, 3139, 3192, 3202, 3284, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3465, 3556, 3694, or 3696, and one or more internucleoside linkages and/or one or more nucleoside modifications. The siRNA may include the antisense strand sequence of any one of SEQ ID NOS: 1886, 1887, 1889, 1890, 1975, 2134, 2136, 2143, 2144, 2146, 2175, 2177, 2180, 2186, 2188, 2338, 2363, 2373, 2419, 2424, 2425, 2474, 2491, 2494, 2613, 2688, 2730, 2855, 2987, 2988, 2991, 3003, 3005, 3008, 3011, 3019, 3020, 3025, 3026, 3102, 3103, 3139, 3192, 3202, 3284, 3343, 3344, 3418, 3434, 3435, 3443, 3451, 3465, 3556, 3694, or 3696, and a modification pattern described herein (e.g. any of modification patterns 1S-16S or 1AS-15AS).

[0069] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 7**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 7**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 7**. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 7**. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 7**. In some embodiments, the siRNA is unmodified.

[0070] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 8**. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 8**. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 8**. In some embodiments, the siRNA is unmodified.

[0071] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 10**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 10**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 10**. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the siRNA in

Table 10. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 10**. In some embodiments, the siRNA is unmodified.

[0072] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 15**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 15**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 15**. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 15**. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 15**. In some embodiments, the siRNA is unmodified.

[0073] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 16**, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 16**, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA in **Table 16**. In some embodiments, the siRNA comprises one or more of the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 16**. In some embodiments, the siRNA comprises the internucleoside linkages and/or nucleoside modifications of the siRNA in **Table 16**. In some embodiments, the siRNA is unmodified.

[0074] In some embodiments, the siRNA comprises the sense strand sequence of an siRNA in **Table 25A**, or a sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of an siRNA in **Table 25A**, or a sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of an siRNA in **Table 25A**. In some embodiments, the siRNA comprises the antisense strand sequence of an siRNA in **Table 25A**, or a sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of an siRNA in **Table 25A**, or a sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of an siRNA in **Table 25A**.

[0075] In some embodiments, the siRNA comprises the sense strand sequence of an siRNA in **Table 28A**, or a sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of an siRNA in **Table 28A**, or a sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand sequence of an siRNA in **Table 28A**. In some embodiments, the siRNA comprises the antisense strand sequence of an siRNA in **Table 28A**, or a sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of an siRNA in **Table 28A**, or a sequence thereof having 1 or 2 nucleoside

substitutions, additions, or deletions. In some embodiments, the siRNA comprises the antisense strand sequence of an siRNA in **Table 28A**.

[0076] In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA described herein such as in any Table included herein, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA described herein such as in any Table included herein, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises the sense strand and/or the antisense strand sequence of an siRNA described herein such as in any Table included herein.

[0077] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to any one of SEQ ID NOS: 13970-13973. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 13970-13973, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 13970-13973. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 13970-13973, and one or more internucleoside linkages and/or one or more nucleoside modifications. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 13970-13973, and a modification pattern described herein (e.g. modification pattern 1S, 2S, 3S, 4S, 5S, or 6S, or modification pattern 7S, 8S, or 9S). The sense strand may include an overhang (e.g. a 2 nucleotide overhang such as 2 uracil nucleotides).

[0078] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to any one of SEQ ID NOS: 13978-13981. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 13978-13981, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 13978-13981. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 13978-13981, and one or more internucleoside linkages and/or one or more nucleoside modifications. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 13978-13981, and a modification pattern described herein (e.g. any of modification patterns 1S-16S or 1AS-15AS). The antisense strand may include an overhang (e.g. a 2 nucleotide overhang such as 2 uracil nucleotides).

[0079] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to any one of SEQ ID NOS: 13974-13977. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 13974-13977, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 13974-13977. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 13974-13977, and one or more internucleoside linkages and/or one or more nucleoside modifications. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 13974-13977, and a modification pattern described herein (e.g. modification pattern 1S, 2S, 3S, 4S, 5S, or 6S, or modification pattern 7S, 8S, or 9S). The sense strand may include an overhang.

[0080] In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to any one of SEQ ID NOS: 13982-13985. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 13982-13985, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 13982-13985. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 13982-13985, and one or more internucleoside linkages and/or one or more nucleoside modifications. The siRNA may include the sense strand sequence of any one of SEQ ID NOS: 13982-13985, and a modification pattern described herein (e.g. any of modification patterns 1S-16S or 1AS-15AS). The antisense strand may include an overhang.

[0081] In some embodiments, the sense strand and/or antisense strand comprises a nucleoside sequence at least 85% identical to the sense strand and/or antisense strand of any one of EDT01062 to ETD01065, EDT01062.1 to ETD01065.1, EDT01062.2 to ETD01065.2, EDT01062.3 to ETD01065.3, EDT01062.4 to ETD01065.4, EDT01062.5 to ETD01065.5, EDT01062.6 to ETD01065.6, EDT01062.7 to ETD01065.7, or EDT01062.8 to ETD01065.8. In some embodiments, the sense strand and/or antisense strand comprises the sense strand and/or antisense strand of any one of EDT01062 to ETD01065, EDT01062.1 to ETD01065.1, EDT01062.2 to ETD01065.2, EDT01062.3 to ETD01065.3, EDT01062.4 to ETD01065.4, EDT01062.5 to ETD01065.5, EDT01062.6 to ETD01065.6, EDT01062.7 to ETD01065.7, or EDT01062.8 to ETD01065.8, or a sense strand and/or antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand and/or antisense strand comprises the sense strand and/or antisense strand of any one of EDT01062 to ETD01065, EDT01062.1 to ETD01065.1, EDT01062.2 to ETD01065.2, EDT01062.3 to ETD01065.3, EDT01062.4 to ETD01065.4, EDT01062.5 to ETD01065.5, EDT01062.6 to ETD01065.6, EDT01062.7 to ETD01065.7, or EDT01062.8 to ETD01065.8. The sense strand and/or antisense strand may comprise a GalNAc ligand. The sense strand and/or antisense strand may exclude any GalNAc ligand.

[0082] The sense strand may comprise the nucleoside sequence of SEQ ID NO: 13973, or a derivative thereof. In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 13973. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include the sense strand comprising a nucleoside sequence at least 85% identical to SEQ ID NO: 13973. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 13973, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973 derivative may include the sense strand comprising a nucleoside sequence having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 13973. The sense strand sequence may consist of the nucleotide sequence of SEQ ID NO: 13973. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include a GalNAc ligand (e.g. attached to a 3' or 5' end). The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include a 2 nucleotide overhang.

The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 1S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 2S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 3S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 4S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 5S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 6S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 7S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 8S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13973, or derivative thereof, may include modification pattern 9S.

[0083] The sense strand may comprise the nucleoside sequence of SEQ ID NO: 13977, or a derivative thereof. In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 13977. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include the sense strand comprising a nucleoside sequence at least 85% identical to SEQ ID NO: 13977. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 13977, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977 derivative may include the sense strand comprising a nucleoside sequence having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of SEQ ID NO: 13977. The sense strand sequence may consist of the nucleotide sequence of SEQ ID NO: 13977. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include a GalNAc ligand (e.g. attached to a 3' or 5' end). The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include a 2 nucleotide overhang. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 1S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 2S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 3S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 4S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 5S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 6S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 7S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 8S. The sense strand comprising the nucleoside sequence of SEQ ID NO: 13977, or derivative thereof, may include modification pattern 9S.

[0084] The antisense strand may comprise the nucleoside sequence of SEQ ID NO: 13981, or a derivative thereof. In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 13981. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include the antisense strand comprising a nucleoside sequence at least 85% identical to SEQ ID NO: 13981. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 13981, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981 derivative may include the antisense strand comprising a nucleoside sequence having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 13981. The antisense strand sequence may consist of the nucleotide sequence of SEQ ID NO: 13981. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include a GalNAc ligand (e.g. attached to a 3' or 5' end). The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include a 2 nucleotide overhang. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 1AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 2AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 3AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 4AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 5AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 6AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 7AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 8AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 9AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 10AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13981, or derivative thereof, may include modification pattern 11AS.

[0085] The antisense strand may comprise the nucleoside sequence of SEQ ID NO: 13985, or a derivative thereof. In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to SEQ ID NO: 13985. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include the antisense strand comprising a nucleoside sequence at least 85% identical to SEQ ID NO: 13985. In some embodiments, the antisense strand comprises the nucleoside sequence of SEQ ID NO: 13985, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985 derivative may include the antisense strand comprising a nucleoside sequence having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand

comprises the nucleoside sequence of SEQ ID NO: 13985. The antisense strand sequence may consist of the nucleotide sequence of SEQ ID NO: 13985. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include a GalNAc ligand (e.g. attached to a 3' or 5' end). The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include a 2 nucleotide overhang. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 1AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 2AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 3AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 4AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 5AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 6AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 7AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 8AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 9AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 10AS. The antisense strand comprising the nucleoside sequence of SEQ ID NO: 13985, or derivative thereof, may include modification pattern 11AS.

[0086] In some embodiments, the sense strand comprises a nucleoside sequence at least 85% identical to any one of SEQ ID NOS: 14006-14011. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 14006-14011, or a sense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the sense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 14006-14011. The sense strand may comprise a GalNAc ligand. In some embodiments, the antisense strand comprises a nucleoside sequence at least 85% identical to any one of SEQ ID NOS: 14158-14166. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 14158-14166, or an antisense strand sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the antisense strand comprises the nucleoside sequence of any one of SEQ ID NOS: 14158-14166. The antisense strand may comprise a GalNAc ligand.

[0087] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13970, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13970, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13970. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand

comprising the sequence of SEQ ID NO: 13978, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13978, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13978. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0088] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13971, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13971, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13971. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13979, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13979, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13979. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0089] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13972, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13972, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13972. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13980, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13980, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13980. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0090] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13973, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13973, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13973. In some embodiments, the sense strand comprises one or more internucleoside linkages

and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13981, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13981, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13981. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0091] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 1285, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 1285, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 1285. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 3139, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 3139, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 3139. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0092] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 1580, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 1580, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 1580. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 3434, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 3434, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 3434. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0093] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13974, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13974, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ

ID NO: 13974. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13982, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13982, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13982. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0094] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13975, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13975, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13975. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13983, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13983, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13983. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0095] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13976, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13976, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13976. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13984, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13984, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13984. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0096] In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or

deletions. In some embodiments, the siRNA comprises a sense strand comprising the sequence of SEQ ID NO: 13977. In some embodiments, the sense strand comprises one or more internucleoside linkages and/or nucleoside modifications. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13985, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13985, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the siRNA comprises an antisense strand comprising the sequence of SEQ ID NO: 13985. In some embodiments, the antisense strand comprises one or more internucleoside linkages and/or nucleoside modifications.

[0097] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a seed region that is not identical to a seed region of a human miRNA. In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a seed region that is not identical to a seed region of a human miRNA. In some embodiments, the siRNA is cross-reactive with a non-human primate (NHP) ANGPTL4 mRNA. For example, the antisense strand may bind to, or be complementary with, the NHP ANGPTL4 mRNA.

B. ASOs

[0098] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO is 12-30 nucleosides in length. In some embodiments, the ASO is 14-30 nucleosides in length. In some embodiments, the ASO is at least about 10, 11, 12, 13, 14, 15, 15, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. In some embodiments, the ASO is 15-25 nucleosides in length. In some embodiments, the ASO is 20 nucleosides in length.

[0099] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO) about 12-30 nucleosides in length and comprising a nucleoside sequence complementary to about 12-30 contiguous nucleosides of a full-length human ANGPTL4 mRNA sequence such as SEQ ID NO: 13935; wherein (i) the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier.

[0100] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and comprising a nucleoside sequence complementary to about 12-30 contiguous nucleosides of a full-length human ANGPTL4 mRNA sequence such as SEQ ID NO: 13936; wherein (i) the oligonucleotide

comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier.

[0101] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an ASO that comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3709-13934. In some embodiments, the ASO comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3709-13934, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions. In some embodiments, the ASO comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3709-13934, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions.

C. Oligonucleotide modifications

[0102] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier. In some embodiments, the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the modified internucleoside linkage comprises one or more phosphorothioate linkages. A phosphorothioate may include a nonbridging oxygen atom in a phosphate backbone of the oligonucleotide that is replaced by sulfur. Modified internucleoside linkages may be included in siRNAs or ASOs. Benefits of the modified internucleoside linkage may include decreased toxicity or improved pharmacokinetics.

[0103] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a modified internucleoside linkage, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages, or a range of modified internucleoside linkages defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 18 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises no more than 20 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises 2 or more modified internucleoside linkages, 3 or more modified internucleoside linkages, 4 or more modified internucleoside linkages, 5 or more modified internucleoside linkages, 6 or more modified internucleoside linkages, 7 or more modified internucleoside linkages, 8 or more modified internucleoside linkages, 9 or more modified internucleoside linkages, 10 or more modified internucleoside linkages, 11 or more modified internucleoside linkages, 12 or more modified internucleoside linkages, 13 or more modified internucleoside linkages, 14 or more modified

internucleoside linkages, 15 or more modified internucleoside linkages, 16 or more modified internucleoside linkages, 17 or more modified internucleoside linkages, 18 or more modified internucleoside linkages, 19 or more modified internucleoside linkages, or 20 or more modified internucleoside linkages.

[0104] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises the modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'- methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the modified nucleoside comprises a LNA. In some embodiments, the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid. In some embodiments, the modified nucleoside comprises HLA. In some embodiments, the modified nucleoside comprises CeNA. In some embodiments, the modified nucleoside comprises a 2'- methoxyethyl group. In some embodiments, the modified nucleoside comprises a 2'-O-alkyl group. In some embodiments, the modified nucleoside comprises a 2'-O-allyl group. In some embodiments, the modified nucleoside comprises a 2'-fluoro group. In some embodiments, the modified nucleoside comprises a 2'-deoxy group. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, a 2'-O- dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, or 2'-ara-F, or a combination thereof. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside. In some embodiments, the modified nucleoside comprises a 2'-deoxyfluoro nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-NMA nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-DMAEOE nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-aminopropyl (2'-O-AP) nucleoside. In some embodiments, the modified nucleoside comprises 2'-ara-F. In some embodiments, the modified nucleoside comprises one or more 2'fluoro modified nucleosides. In some embodiments, the modified nucleoside comprises a 2' O-alkyl modified nucleoside. Benefits of the modified nucleoside may include decreased toxicity or improved pharmacokinetics.

[0105] In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 modified nucleosides, or a range of nucleosides defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 19 modified nucleosides. In some embodiments, the oligonucleotide comprises no more than 21 modified nucleosides. In some embodiments, the oligonucleotide comprises 2 or more modified nucleosides, 3 or more modified nucleosides, 4 or more modified nucleosides, 5 or more modified nucleosides, 6 or more modified nucleosides, 7 or more modified nucleosides, 8 or more modified nucleosides, 9 or more modified nucleosides, 10 or more modified nucleosides, 11 or more modified nucleosides, 12 or more modified nucleosides, 13 or more modified nucleosides, 14 or more modified nucleosides, 15 or more modified nucleosides, 16 or more modified nucleosides, 17 or more modified nucleosides, 18 or more modified nucleosides, 19 or more modified nucleosides, 20 or more modified nucleosides, or 21 or more modified nucleosides.

[0106] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a moiety attached at a 3' or 5' terminus of the oligonucleotide. Examples of moieties include a hydrophobic moiety or a sugar moiety, or a combination thereof. In some embodiments, the oligonucleotide is an siRNA having a sense strand, and the moiety is attached to a 5' end of the sense strand. In some embodiments, the oligonucleotide is an siRNA having a sense strand, and the moiety is attached to a 3' end of the sense strand. In some embodiments, the oligonucleotide is an siRNA having an antisense strand, and the moiety is attached to a 5' end of the antisense strand. In some embodiments, the oligonucleotide is an siRNA having an antisense strand, and the moiety is attached to a 3' end of the antisense strand. In some embodiments, the oligonucleotide is an ASO, and the moiety is attached to a 5' end of the ASO. In some embodiments, the oligonucleotide is an ASO, and the moiety is attached to a 3' end of the ASO.

[0107] The oligonucleotide may include purines. Examples of purines include adenine (A) or guanine (G), or modified versions thereof. The oligonucleotide may include pyrimidines. Examples of pyrimidines include cytosine (C), thymine (T), or uracil (U), or modified versions thereof.

[0108] In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. 2'-O-methyl may include 2' O-methyl.

[0109] In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines.

[0110] In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines, and pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines, and pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines, and pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines, and pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the

oligonucleotide comprise 2'-O-methyl modified pyrimidines, and purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and purines of the oligonucleotide comprise 2' fluoro modified purines.

[0111] In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines, and all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines, and all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines, and all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines, and all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and all purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and all purines of the oligonucleotide comprise 2' fluoro modified purines.

[0112] In some cases, the oligonucleotide comprises a particular modification pattern. In some embodiments, position 9 counting from the 5' end of the of a strand of the oligonucleotide may have a 2'F modification. In some embodiments, when position 9 of a strand of the oligonucleotide is a pyrimidine, then all purines in a strand of the oligonucleotide have a 2'OMe modification. In some embodiments, when position 9 is the only pyrimidine between positions 5 and 11 of the sense stand, then position 9 is the only position with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only one other base between positions 5 and 11 of a strand of the oligonucleotide are pyrimidines, then both of these pyrimidines are the only two positions with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of a strand of the oligonucleotide are pyrimidines, and those two other pyrimidines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 pyrimidines between positions 5 and 11 of a strand of the oligonucleotide, then all combinations of pyrimidines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that a strand of the oligonucleotide does not have three 2'F modifications in a row. In some cases, a strand of the oligonucleotide of any of the siRNAs

comprises a modification pattern which conforms to any or all of these a strand of the oligonucleotide rules.

[0113] In some embodiments, when position 9 of a strand of the oligonucleotide is a purine, then all purines in a strand of the oligonucleotide have a 2'OMe modification. In some embodiments, when position 9 is the only purine between positions 5 and 11 of the sense stand, then position 9 is the only position with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only one other base between positions 5 and 11 of a strand of the oligonucleotide are purines, then both of these purines are the only two positions with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of a strand of the oligonucleotide are purines, and those two other purines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 purines between positions 5 and 11 of a strand of the oligonucleotide, then all combinations of purines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that a strand of the oligonucleotide does not have three 2'F modifications in a row. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to any or all of these a strand of the oligonucleotide rules.

[0114] In some cases, position 9 of a strand of the oligonucleotide can be a 2'deoxy. In these cases, 2'F and 2'OMe modifications may occur at the other positions of a strand of the oligonucleotide. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to these a strand of the oligonucleotide rules.

[0115] In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified pyrimidine. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, 1, 2, 3, 4, or 5 pyrimidines between positions 5 and 11 comprise a 2'flouro-modified pyrimidine, provided there are not three 2' fluoro-modified pyrimidines in a row. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified pyrimidine; all purines of the sense strand comprises 2'-O-methyl modified purines; 1, 2, 3, 4, or 5 pyrimidines between positions 5 and 11 comprise a 2'flouro-modified pyrimidine, provided there are not three 2' fluoro-modified pyrimidines in a row; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides.

[0116] In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified purine. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, 1, 2, 3, 4, or 5 purines between positions 5 and 11 comprise a 2'flouro-modified purine, provided there are not three 2' fluoro-modified purine in a row. In some embodiments, the odd-numbered

positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified purine; all pyrimidine of the sense strand comprises 2'-O-methyl modified pyrimidines; 1, 2, 3, 4, or 5 purines between positions 5 and 11 comprise a 2'flouro-modified purines, provided there are not three 2' fluoro-modified purines in a row; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, there are not three 2' fluoro-modified purines in a row. In some embodiments, there are not three 2' fluoro-modified pyrimidines in a row.

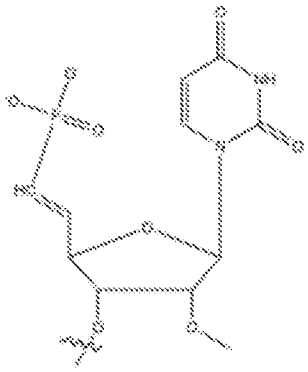
[0117] In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide. In some embodiments, positions 5, 7, and 8 of the sense strand comprise 2'fluoro-modifed nucleotides. In some embodiments, all pyrimidines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified pyrimidines and all purines in positions 10 to 21 of the comprise 2'-O-methyl modified purines or 2'fluoro-modified purines. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide; positions 5, 7, and 8 of the sense strand comprise 2'fluoro-modifed nucleotides; all pyrimidines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified pyrimidines and all purines in positions 10 to 21 of the comprise 2'-O-methyl modified purines or 2'fluoro-modified purines; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides.

[0118] In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide. In some embodiments, positions 5, 7, and 8 of the sense strand comprise 2'fluoro-modifed nucleotides. In some embodiments, all purines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified purines and all pyrimidines in positions 10 to 21 of the comprise 2'-O-methyl modified pyrimidines or 2'fluoro-modified pyrimidines. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide; positions 5, 7, and 8 of the sense strand comprise 2'fluoro-modifed nucleotides; all purines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified purines and all pyrimidines in positions 10 to 21 of the comprise 2'-O-methyl modified pyrimidines or 2'fluoro-modified pyrimidines; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotide.

[0119] In some embodiments, the moiety includes a negatively charged group attached at a 5' end of the oligonucleotide. This may be referred to as a 5'-end group. In some embodiments, the negatively charged group is attached at a 5' end of an antisense strand of an siRNA disclosed herein. The 5'-end group may be or include a 5'-end phosphorothioate, 5'-end phosphorodithioate, 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate, 5'-end cyclopropyl phosphonate, or a 5'-deoxy-5'-C-malonyl. The 5'-end group may comprise 5'-VP. In some embodiments, the 5'-VP comprises a trans-vinylphosphate or cis-vinylphosphate. The 5'-end group may include an extra 5' phosphate. A combination of 5'-end groups may be used.

[0120] In some embodiments, the oligonucleotide includes a negatively charged group. The negatively charged group may aid in cell or tissue penetration. The negatively charged group may be attached at a 5' or 3' end (e.g. a 5' end) of the oligonucleotide. This may be referred to as an end group. The end group may be or include a phosphorothioate, phosphorodithioate, vinylphosphonate, methylphosphonate, cyclopropyl phosphonate, or a deoxy-C-malonyl. The end group may include an extra 5' phosphate such as an extra 5' phosphate. A combination of end groups may be used.

[0121] In some embodiments, the oligonucleotide includes a phosphate mimic. In some embodiments, the phosphate mimic comprises vinyl phosphonate. In some embodiments, the vinyl phosphonate comprises a trans-vinylphosphate. In some embodiments, the vinyl phosphonate comprises a cis-vinylphosphate. An example of a nucleotide that includes a vinyl phosphonate is shown below.



5' vinylphosphonate 2' O Methyl Uridine

[0122] In some embodiments, the vinyl phosphonate increases the stability of the oligonucleotide. In some embodiments, the vinyl phosphonate increases the accumulation of the oligonucleotide in tissues. In some embodiments, the vinyl phosphonate protects the oligonucleotide from an exonuclease or a phosphatase. In some embodiments, the vinyl phosphonate improves the binding affinity of the oligonucleotide with the siRNA processing machinery.

[0123] In some embodiments, the oligonucleotide includes 1 vinyl phosphonate. In some embodiments, the oligonucleotide includes 2 vinyl phosphonates. In some embodiments, the oligonucleotide includes 3 vinyl phosphonates. In some embodiments, the oligonucleotide includes 4 vinyl phosphonates. In some embodiments, the antisense strand of the oligonucleotide comprises a vinyl phosphonate at the 5' end. In some embodiments, the antisense strand of the oligonucleotide comprises a vinyl phosphonate at the 3' end. In some embodiments, the sense strand of the oligonucleotide comprises a vinyl phosphonate at the

5' end. In some embodiments, the sense strand of the oligonucleotide comprises a vinyl phosphonate at the 3' end.

1. Hydrophobic moieties

[0124] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a hydrophobic moiety. The hydrophobic moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The hydrophobic moiety may include a lipid such as a fatty acid. The hydrophobic moiety may include a hydrocarbon. The hydrocarbon may be linear. The hydrocarbon may be non-linear. The hydrophobic moiety may include a lipid moiety or a cholesterol moiety, or a combination thereof.

[0125] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl, stearyl, or α-tocopherol, or a combination thereof.

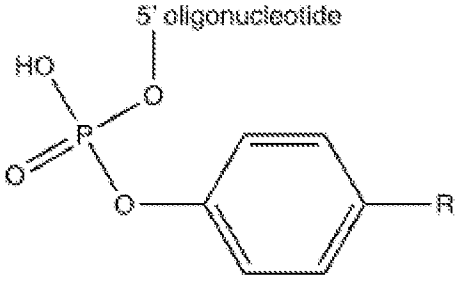
[0126] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a hydrophobic ligand or moiety. In some embodiments, the hydrophobic ligand or moiety comprises cholesterol. In some embodiments, the hydrophobic ligand or moiety comprises a cholesterol derivative. In some embodiments, the hydrophobic ligand or moiety is attached at a 3' terminus of the oligonucleotide. In some embodiments, the hydrophobic ligand or moiety s attached at a 5' terminus of the oligonucleotide. In some embodiments, the composition comprises a sense strand, and the hydrophobic ligand or moiety is attached to the sense strand (e.g. attached to a 5' end of the sense strand, or attached to a 3' end of the sense strand). In some embodiments, the composition comprises an antisense strand, and the hydrophobic ligand or moiety is attached to the antisense strand (e.g. attached to a 5' end of the antisense strand, or attached to a 3' end of the antisense strand). In some embodiments, the composition comprises a hydrophobic ligand or moiety attached at a 3' or 5' terminus of the oligonucleotide.

[0127] In some embodiments, a hydrophobic moiety is attached to the oligonucleotide (e.g. a sense strand and/or an antisense strand of a siRNA). In some embodiments, a hydrophobic moiety is attached at a 3' terminus of the oligonucleotide. In some embodiments, a hydrophobic moiety is attached at a 5' terminus of the oligonucleotide. In some embodiments, the hydrophobic moiety comprises cholesterol. In some embodiments, the hydrophobic moiety includes a cyclohexanyl.

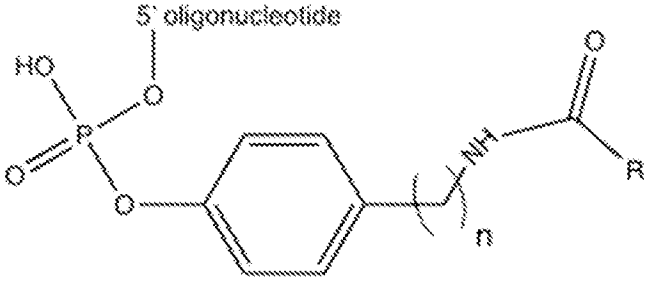
[0128] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, a lipid is attached at a 3' terminus of the oligonucleotide. In some embodiments, a lipid is attached at a 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl, stearyl, or α-tocopherol, or a combination thereof. In some embodiments, the lipid

comprises stearyl, lithocholyl, docosanyl, docosahexaenyl, or myristyl. In some embodiments, the lipid comprises cholesterol. In some embodiments, the lipid includes a sterol such as cholesterol. In some embodiments, the lipid comprises stearyl, t-butylphenol, n-butylphenol, octylphenol, dodecylphenol, phenyl n-dodecyl, octadecylbenzamide, hexadecylbenzamide, or octadecylcyclohexyl. In some embodiments, the lipid comprises phenyl para C12.

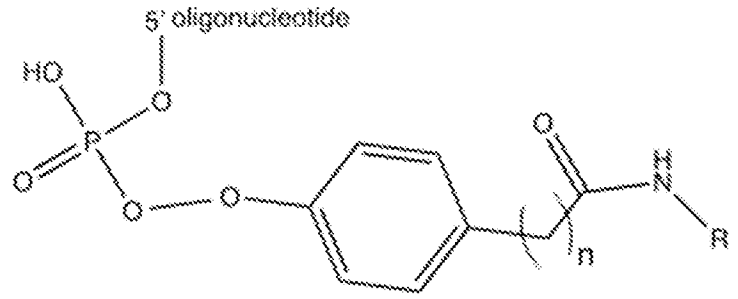
[0129] In some embodiments, the oligonucleotide comprises any aspect of the following structure:



[0130] In some embodiments, the oligonucleotide comprises any aspect of the following structure:



[0131] In some embodiments, the oligonucleotide comprises any aspect of the following structure:

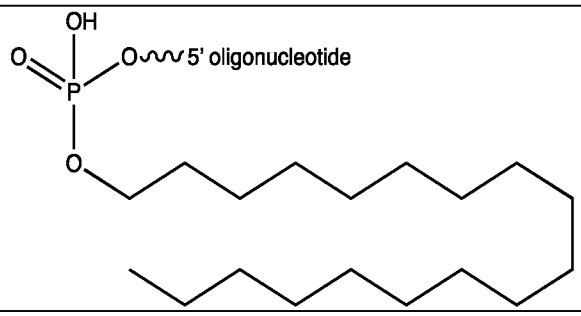
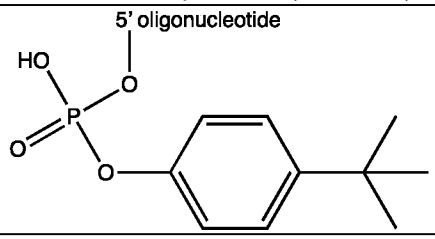
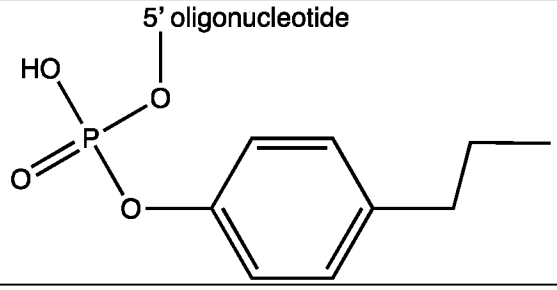
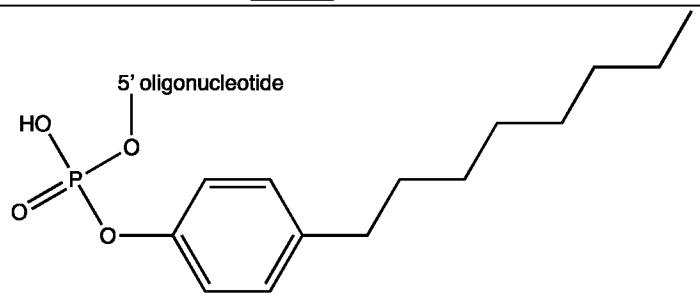
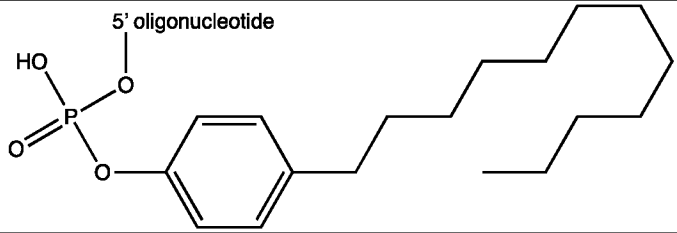


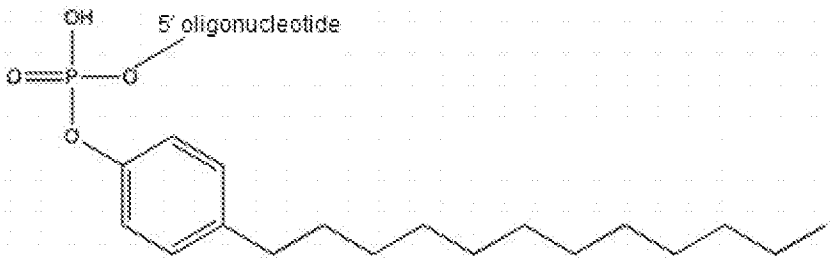
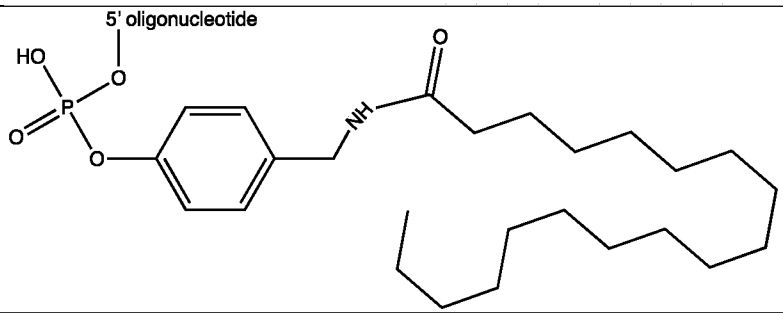
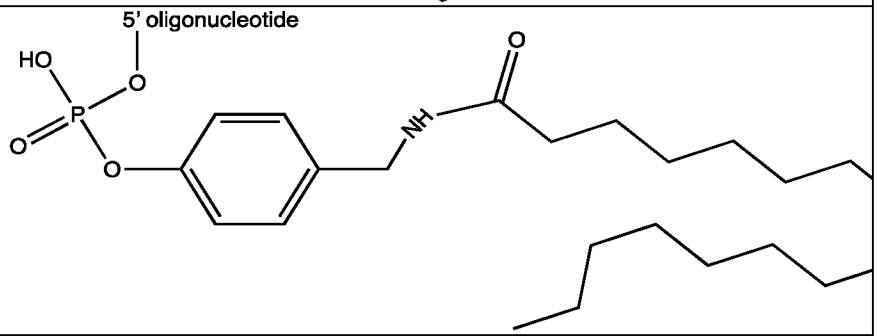
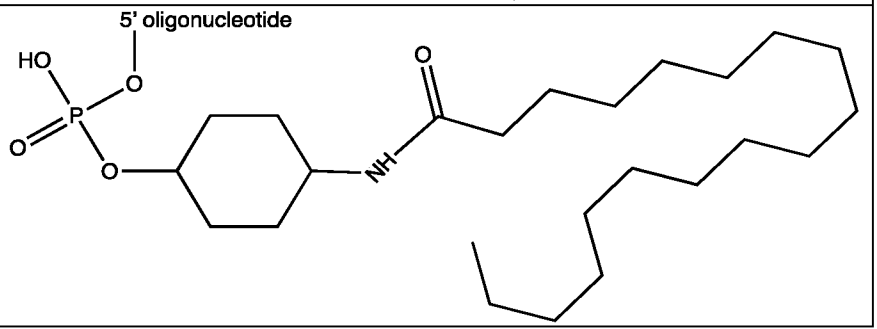
[0132] In some embodiments, the oligonucleotide comprises any aspect of the following structure: The aspect included in the oligonucleotide may include the entire structure, or may include the lipid moiety, of any of the structures shown. In some embodiments, n is 1-3. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, R is an alkyl group. In some embodiments, the alkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbons. In some embodiments, the alkyl group contains 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbons, or a range defined by any two of the aforementioned numbers of carbons. In some embodiments, the alkyl group contains 4-18 carbons. In some embodiments, the lipid moiety comprises an alcohol or ether.

[0133] In some embodiments, the lipid includes a fatty acid. In some embodiments, the lipid comprises a lipid depicted in **Table 1**. The example lipid moieties in **Table 1** are shown attached at a 5' end of an

oligonucleotide, in which the 5' terminal phosphate of the oligonucleotide is shown with the lipid moiety. In some embodiments, a lipid moiety in **Table 1** may be attached at a different point of attachment than shown. For example, the point of attachment of any of the lipid moieties in the table may be at a 3' oligonucleotide end. In some embodiments, the lipid is used for targeting the oligonucleotide to a non-hepatic cell or tissue.

Table 1: Hydrophobic moiety examples

Hydrophobic Moiety Description	Hydrophobic Moiety Name	Example Conjugation
stearyl	ETL3	
t-butylphenyl	ETL7	
n-butylphenyl	ETL8	
octylphenyl	ETL9	
dodecylphenyl	ETL10	

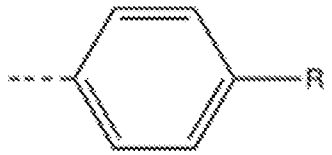
phenyl n-dodecyl	ETL12	
octadecylbenzamide	ETL13	
hexadecylbenzamide	ETL15	
octadecylcyclohexyl	ETL16	

[0134] In some embodiments, the lipid or lipid moiety includes 16 to 18 carbons. In some embodiments, the lipid includes 16 carbons. In some embodiments, the lipid includes 17 carbons. In some embodiments, the lipid includes 18 carbons. In some embodiments, the lipid moiety includes 16 carbons. In some embodiments, the lipid moiety includes 17 carbons. In some embodiments, the lipid moiety includes 18 carbons.

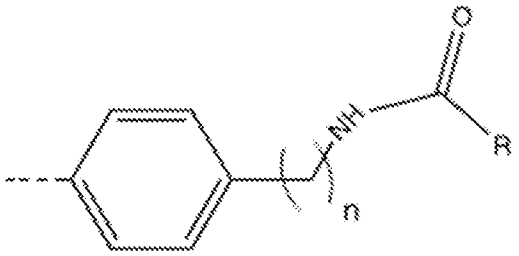
[0135] The hydrophobic moiety may include a linker that comprises a carbocycle. The carbocycle may be six-membered. Some examples of a carbocycle include phenyl or cyclohexyl. The linker may include a phenyl. The linker may include a cyclohexyl. The lipid may be attached to the carbocycle, which may in turn be attached at a phosphate (e.g. 5' or 3' phosphate) of the oligonucleotide. In some embodiments, the lipid or hydrocarbon, and the end of the sense are connected to the phenyl or cyclohexyl linker in the 1,4; 1,3; or 1,2 substitution pattern (e.g. the para, meta, or ortho phenyl configuration). In some embodiments, the lipid or hydrocarbon, and the end of the sense are connected to the phenyl or cyclohexyl linker in the 1,4 substitution pattern (e.g. the para phenyl configuration). The lipid may be

attached to the carbocycle in the 1,4 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the 1,3 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the 1,2 substitution pattern relative to the oligonucleotide. The lipid may be attached to the carbocycle in the ortho orientation relative to the oligonucleotide. The lipid may be attached to the carbocycle in the para orientation relative to the oligonucleotide. The lipid may be attached to the carbocycle in the meta orientation relative to the oligonucleotide.

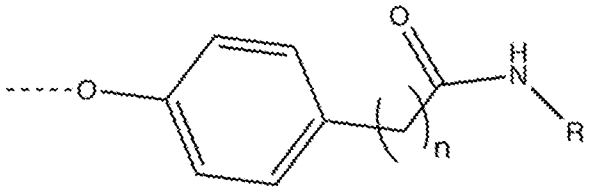
[0136] The lipid moiety may comprise or consist of the following structure



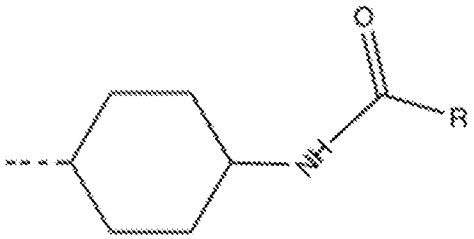
[0137] In some embodiments, the lipid moiety comprises or consists of the following structure:



[0138] In some embodiments, the lipid moiety comprises the following structure:



[0139] In some embodiments, the lipid moiety comprises or consist of the following structure:

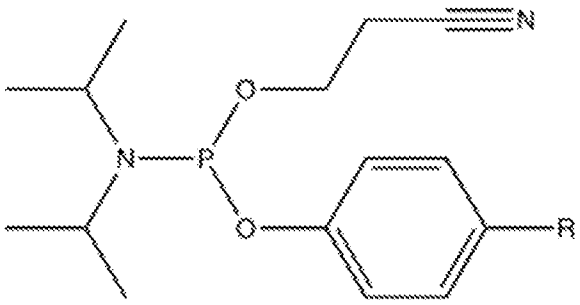


[0140] In some embodiments, the dotted line indicates a covalent connection. The covalent connection may between an end of the sense or antisense strand. For example, the connection may be to the 5' end of the sense strand. In some embodiments, n is 0-3. In some embodiments, n is 1-3. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, R is an alkyl group. In some embodiments, the alkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbons. In some embodiments, the alkyl group contains 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbons, or a range defined by any two of the aforementioned numbers of carbons. In some embodiments, R comprises or consists of an alkyl group containing 4-18 carbons.

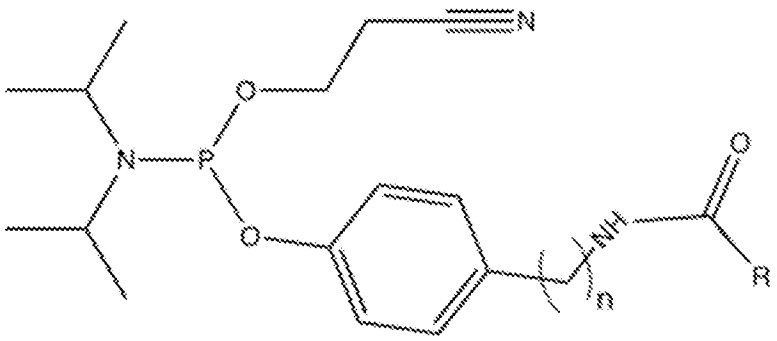
[0141] The lipid moiety may be attached at a 5' end of the oligonucleotide. The 5' end may have one phosphate linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have two phosphates linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have three phosphates linking the lipid moiety to a 5' carbon of a sugar of the oligonucleotide. The 5' end may have one phosphate connected to the 5' carbon of a sugar of the oligonucleotide, where the one phosphate is connected to the lipid moiety. The 5' end may have two phosphates connected to the 5' carbon of a sugar of the oligonucleotide, where the one of the two phosphates is connected to the lipid moiety. The 5' end may have three phosphates connected to the 5' carbon of a sugar of the oligonucleotide, where the one of the three phosphates is connected to the lipid moiety. The sugar may include a ribose. The sugar may include a deoxyribose. The sugar may be modified a such as a 2' modified sugar (e.g. a 2' O-methyl or 2' fluoro ribose). A phosphate of the 5' end may include a modification such as a sulfur in place of an oxygen. Two phosphates of the 5' end may include a modification such as a sulfur in place of an oxygen. Three phosphates of the 5' end may include a modification such as a sulfur in place of an oxygen.

[0142] In some embodiments, the oligonucleotide includes 1 lipid moiety. In some embodiments, the oligonucleotide includes 2 lipid moieties. In some embodiments, the oligonucleotide includes 3 lipid moieties. In some embodiments, the oligonucleotide includes 4 lipid moieties.

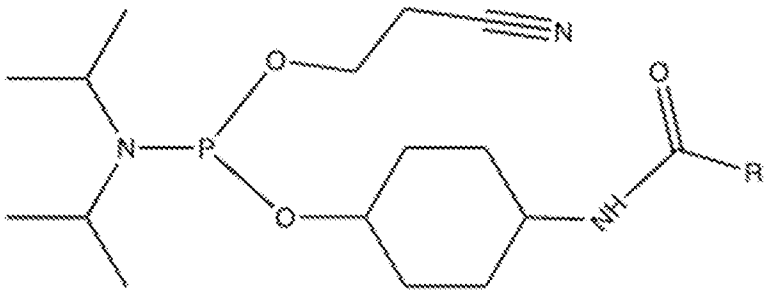
[0143] Some embodiments relate to a method of making an oligonucleotide comprising a hydrophobic conjugate. A strategy for making hydrophobic conjugates may include use of a phosphoramidite reagent based upon a 6-membered ring alcohol such as a phenol or cyclohexanol. The phosphoramidite may be reacted to a nucleotide to connect the nucleotide to the hydrophobic moiety, and thereby produce the hydrophobic conjugate. Some examples of phosphoramidite reagents that may be used to produce a hydrophobic conjugate are provided as follows:



,



, or



[0144] In some embodiments, n is 1-3. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, R is an alkyl group. In some embodiments, the alkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbons. In some embodiments, the alkyl group contains 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbons, or a range defined by any two of the aforementioned numbers of carbons. In some embodiments, R comprises or consists of an alkyl group containing 4-18 carbons. Any one of the phosphoramidite reagents may be reacted to a 5' end of an oligonucleotide to produce an oligonucleotide comprising a hydrophobic moiety. In some embodiments, the phosphoramidite reagents is reacted to a 5' end of a sense strand of an siRNA. The sense strand may then be hybridized to an antisense strand to form a duplex. The hybridization may be performed by incubating the sense and antisense strands in solution at a given temperature. The temperature may be gradually reduced. The temperature may comprise or include a temperature comprising an annealing temperature for the sense and antisense strands. The temperature may be below or include a temperature below the annealing temperature for the sense and antisense strands. The temperature may be below a melting temperature of the sense and antisense strands.

[0145] The lipid may be attached to the oligonucleotide by a linker. The linker may include a polyethyleneglycol (e.g. tetraethyleneglycol).

[0146] The modifications described herein may be useful for delivery to a cell or tissue, for example, extrahepatic delivery or targeting of an oligonucleotide composition. The modifications described herein may be useful for targeting an oligonucleotide composition to a cell or tissue.

2. Sugar moieties

[0147] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a sugar moiety. The sugar moiety may include an N-acetyl galactose moiety (e.g. an N-acetylgalactosamine (GalNAc) moiety), an N-acetyl glucose moiety (e.g. an N-acetylglucosamine (GlcNAc) moiety), a fucose moiety, or a mannose moiety. The sugar moiety may include 1, 2, 3, or more sugar molecules. The sugar moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The sugar moiety may include an N-acetyl galactose moiety. The sugar moiety may include an N-acetylgalactosamine (GalNAc) moiety. The sugar moiety may include an N-acetyl glucose moiety. The sugar moiety may include N-acetylglucosamine (GlcNAc) moiety. The sugar moiety may include a fucose moiety. The sugar moiety may include a mannose moiety. N-acetyl glucose, GlcNAc, fucose, or mannose may be useful for targeting macrophages when they target or bind a mannose receptor such as CD206. The sugar moiety may be useful for binding or targeting an

asialoglycoprotein receptor such as an asialoglycoprotein receptor of a hepatocyte. The GalNAc moiety may bind to an asialoglycoprotein receptor. The GalNAc moiety may target a hepatocyte.

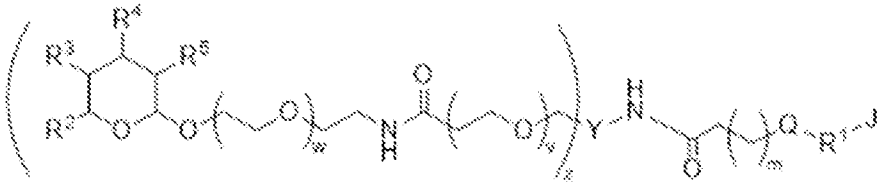
[0148] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) ligand for hepatocyte targeting. A "GalNAc ligand" may be refer to a ligand for an asialoglycoprotein receptor (e.g. on a hepatocyte) that comprises one or more GalNAc moieties. The GalNAc ligand may bind an asialoglycoprotein receptor (e.g. on a hepatocyte). The GalNAc ligand may comprise one or more GalNAc moieties. An example of a GalNAc moiety includes GalNAc attached to a linker. The GalNAc moiety may include 1, 2, 3, or more GalNAc molecules. The GalNAc ligand may comprise 3 GalNAc moieties. The GalNAc ligand may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or more GalNAc moieties.

[0149] The GalNAc ligand may be conjugated to the oligonucleotide. The GalNAc ligand may be conjugated to a 5' end of the oligonucleotide. The GalNAc ligand may be conjugated to a 3' end of the oligonucleotide. A first GalNAc ligand may be conjugated to a 5' end of the oligonucleotide, and a second GalNAc ligand may be conjugated to 3' end of the oligonucleotide. The GalNAc ligand may be conjugated to a 3' or 5' end of an ASO. The GalNAc ligand may be conjugated to a 3' or 5' end of a sense strand of an siRNA. The GalNAc ligand may be conjugated to a 3' end of a sense strand of an siRNA. The GalNAc ligand may be conjugated to a 5' end of a sense strand of an siRNA. The GalNAc ligand may be conjugated to a 3' or 5' end of an antisense strand of an siRNA. The GalNAc ligand may be conjugated to a 3' end of an antisense strand of an siRNA. The GalNAc ligand may be conjugated to a 5' end of an antisense strand of an siRNA. A first GalNAc ligand may be conjugated to a sense strand of an siRNA, and a second GalNAc ligand may be conjugated to an antisense strand of the siRNA.

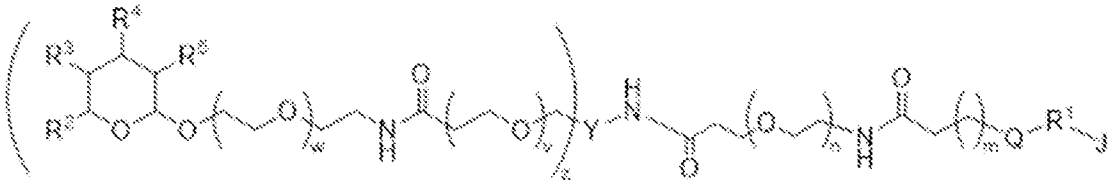
[0150] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) moiety. GalNAc may be useful for hepatocyte targeting. The GalNAc moiety may include a bivalent or trivalent branched linker. The oligo may be attached to 1, 2 or 3 GalNAcs through a bivalent or trivalent branched linker. The GalNAc moiety may include 1, 2, 3, or more GalNAc molecules. The GalNAc moiety may be attached at a 3' or 5' terminus of the oligonucleotide.

[0151] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) ligand for hepatocyte targeting. In some embodiments, the composition comprises GalNAc. In some embodiments, the composition comprises a GalNAc derivative. In some embodiments, the GalNAc ligand is attached at a 3' terminus of the oligonucleotide. In some embodiments, the GalNAc ligand is attached at a 5' terminus of the oligonucleotide. In some embodiments, the composition comprises a sense strand, and the GalNAc ligand is attached to the sense strand (e.g. attached to a 5' end of the sense strand, or attached to a 3' end of the sense strand). In some embodiments, the composition comprises an antisense strand, and the GalNAc ligand is attached to the antisense strand (e.g. attached to a 5' end of the antisense strand, or attached to a 3' end of the antisense strand). In some embodiments, the composition comprises a GalNAc ligand attached at a 3' or 5' terminus of the oligonucleotide.

[0152] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises a GalNAc moiety. The GalNAc moiety may be included in any formula, structure, or GalNAc moiety shown below. In some embodiments, described herein is a compound (e.g. oligonucleotide) represented by Formula (I) or (II):



(I), or



(II);

or a salt thereof, wherein

J is an oligonucleotide;

each w is independently selected from any value from 1 to 20;

each v is independently selected from any value from 1 to 20;

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

z is selected from any value from 1 to 3, wherein

if z is 3, Y is C

if z is 2, Y is CR^6, or

if z is 1, Y is $C(R^6)_2$;

Q is selected from:

C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$;

R^1 is a linker selected from:

-O-, -S-, $-N(R^7)-$, -C(O)-, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)C(O)N(R^7)-$, $-OC(O)N(R^7)-$, $-N(R^7)C(O)O-$, -C(O)O-, -OC(O)-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, $-OP(O)(OR^7)NR^7-$, $-OP(O)(N(R^7)_2)NR^7-$, $-OP(OR^7)O-$, $-OP(N(R^7)_2)O-$, $-OP(OR^7)N(R^7)-$, and $-OPN(R^7)_2NR^7-$;

each R^2 is independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

R^3 and R^4 are each independently selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^5 is independently selected from:

$-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)R^7$, $-C(O)OR^7$, and $-C(O)N(R^7)_2$;

each R^6 is independently selected from:

hydrogen;

halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^7 is independently selected from:

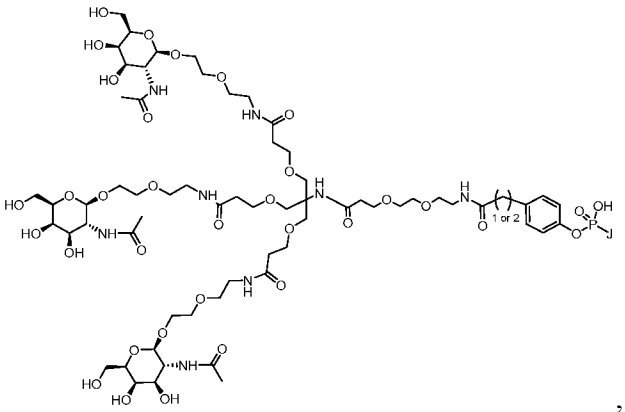
hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

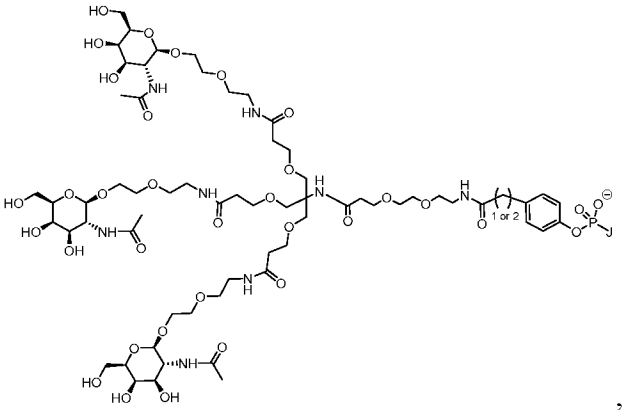
C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl.

In some embodiments, each w is independently selected from any value from 1 to 10. In some embodiments, each w is independently selected from any value from 1 to 5. In some embodiments, each w is 1. In some embodiments, each v is independently selected from any value from 1 to 10. In some embodiments, each v is independently selected from any value from 1 to 5. In some embodiments, each v is 1. In some embodiments, n is selected from any value from 1 to 10. In some embodiments, n is selected from any value from 1 to 5. In some embodiments, n is 2. In some embodiments, m is selected from any value from 1 to 10. In some embodiments, m is selected from any value from 1 to 5. In some embodiments, m is selected from 1 and 2. In some embodiments, z is 3 and Y is C. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more

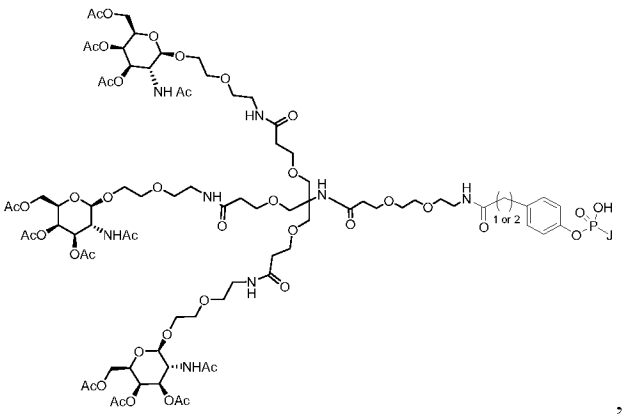
substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl. In some embodiments, Q is selected from cyclohexyl. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, $-OP(O)(OR^7)NR^7-$, $-OP(O)(N(R^7)_2)NR^7-$, $-OP(OR^7)O-$, $-OP(N(R^7)_2)O-$, $-OP(OR^7)N(R^7)-$, and $-OPN(R^7)_2-NR^7$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, and $-OP(OR^7)O-$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, and $-OP(OR^7)O-$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$ and $-OP(OR^7)O-$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from halogen, $-OR^7$, $-OC(O)R^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, and $-S(O)R^7$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^3 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, R^3 is selected from $-OR^7$ $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$. In some embodiments, R^3 is selected from $-OR^7$ - and $-OC(O)R^7$. In some embodiments, R^4 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, R^4 is selected from $-OR^7$ $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$. In some embodiments, R^4 is selected from $-OR^7$ - and $-OC(O)R^7$. In some embodiments, R^5 is selected from $-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, and $-N(R^7)C(O)OR^7$. In some embodiments, R^5 is selected from $-OC(O)R^7$ and $-N(R^7)C(O)R^7$. In some embodiments, each R^7 is independently selected from: hydrogen; and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, or 3- to 10-membered heterocycle. In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, and $-NH(C_{1-6}$ alkyl). In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, and -SH. In some embodiments, w is 1; v is 1; n is 2; m is 1 or 2; z is 3 and Y is C; Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, and C_{1-3} alkyl; R^1 is selected from $-OP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, and $-OP(OR^7)O-$; R^2 is C_1 alkyl substituted with -OH or $-OC(O)CH_3$;
R^3 is -OH or $-OC(O)CH_3$; R^4 is -OH or $-OC(O)CH_3$; and R^5 is $-NH(O)CH_3$. In some embodiments, the compound comprises:



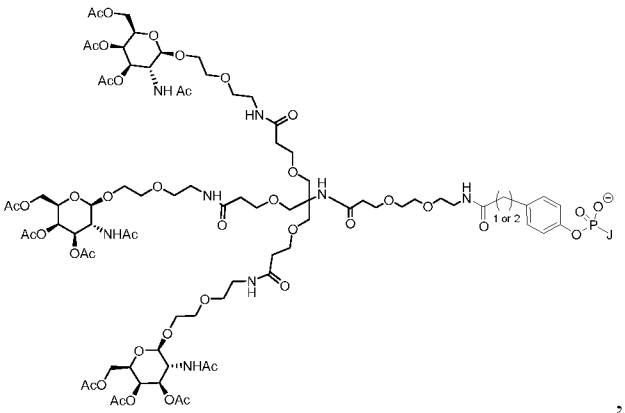
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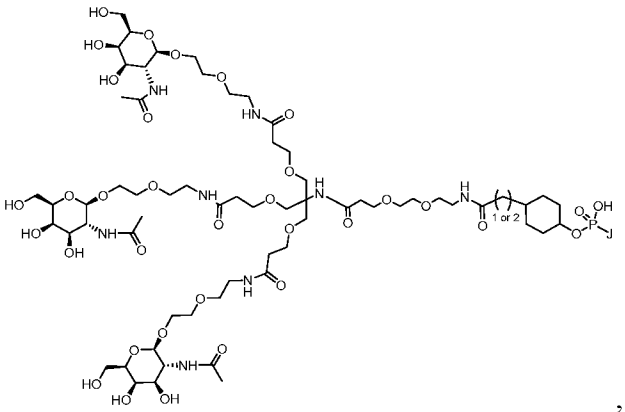
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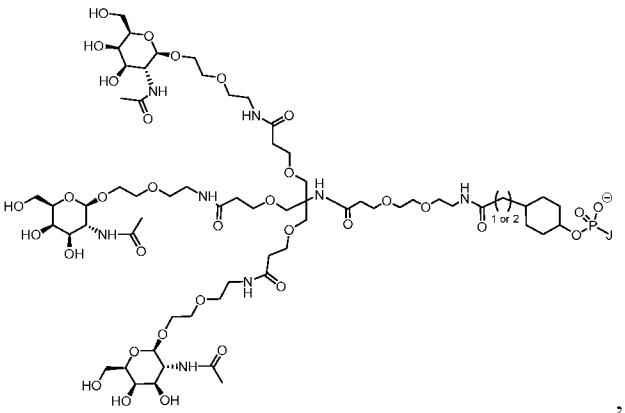
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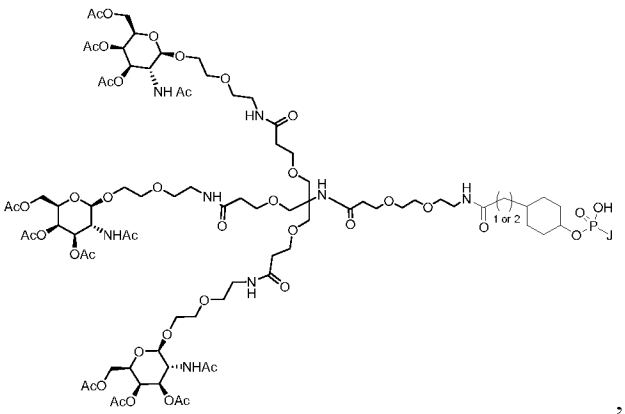
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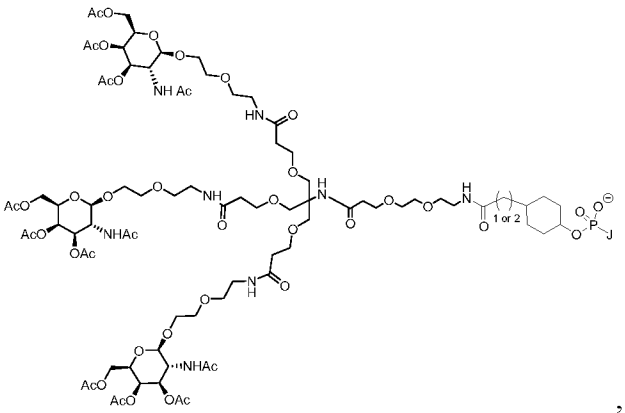
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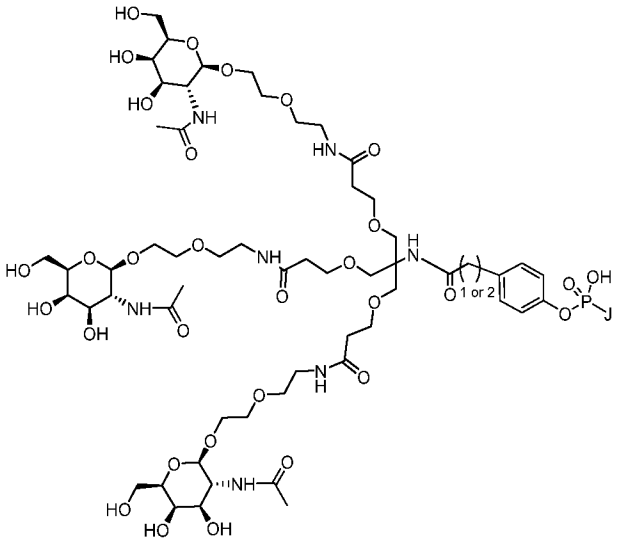
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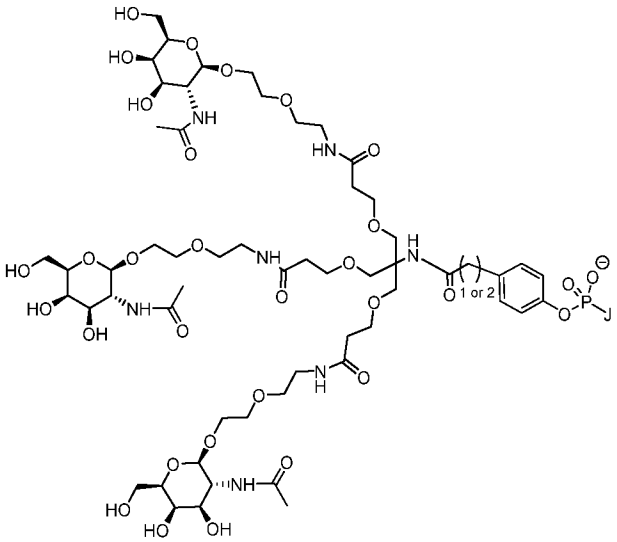
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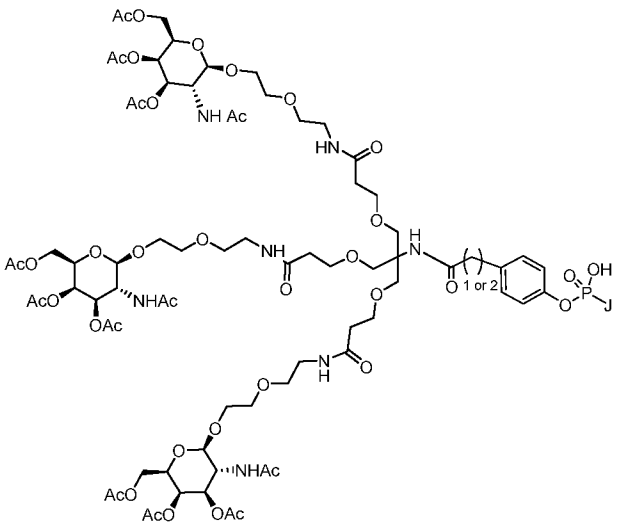
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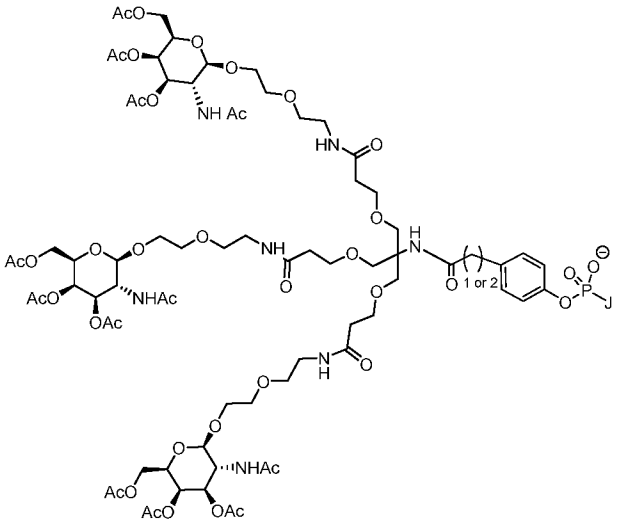
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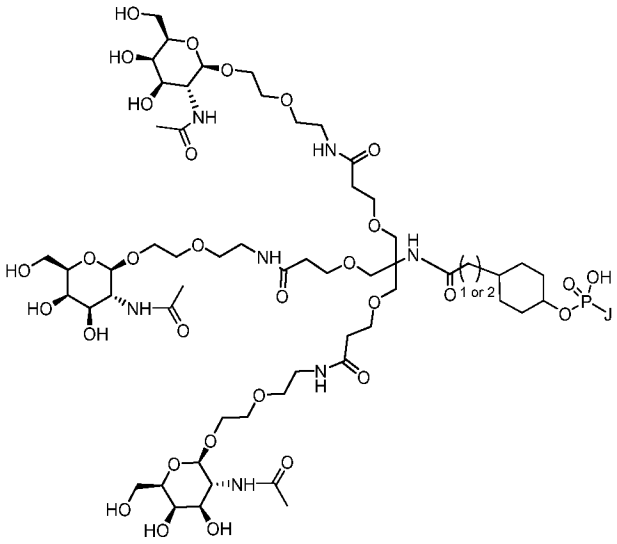
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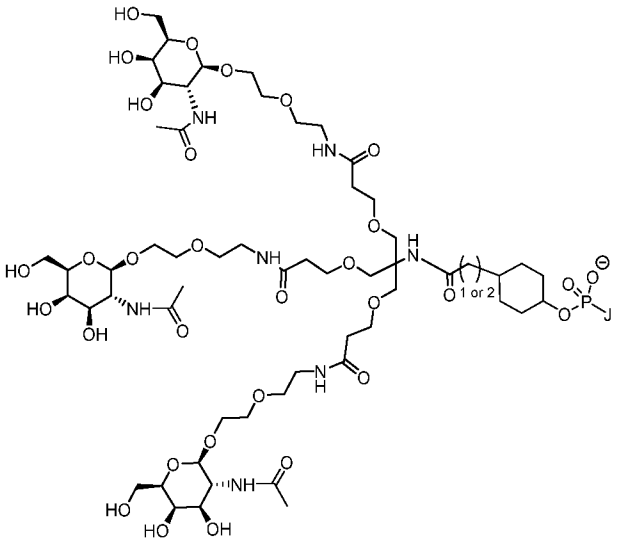
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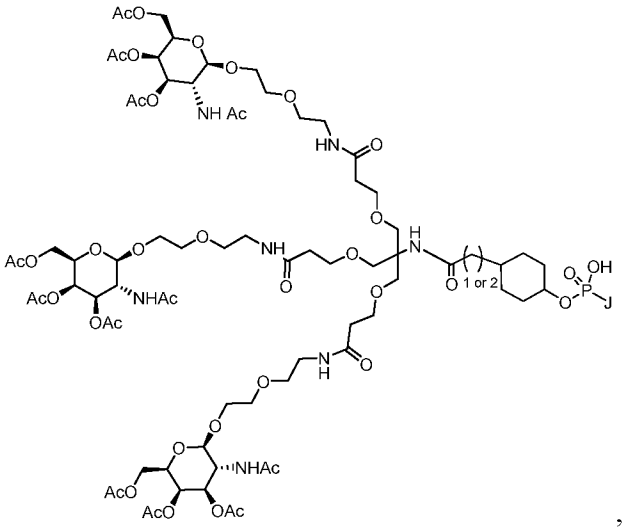
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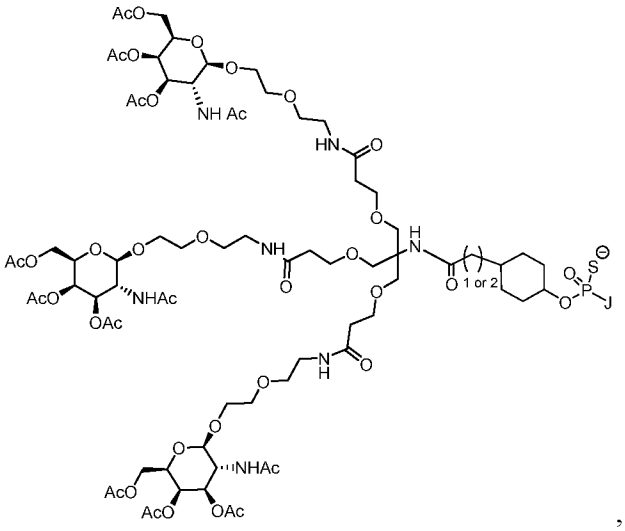
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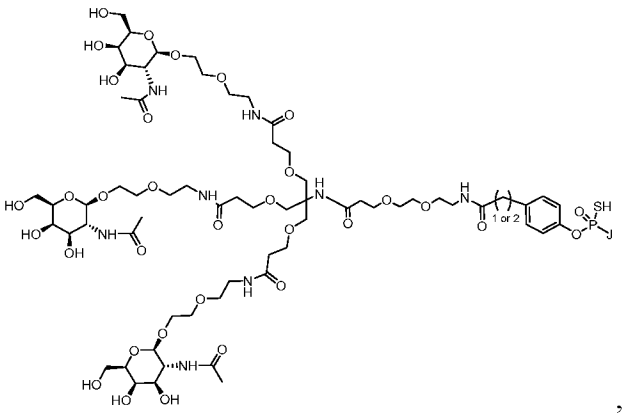
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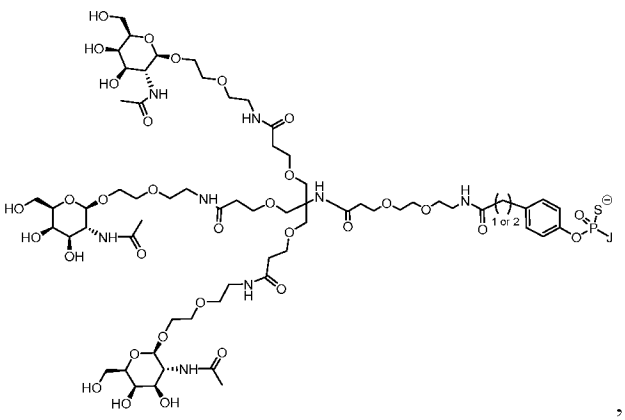
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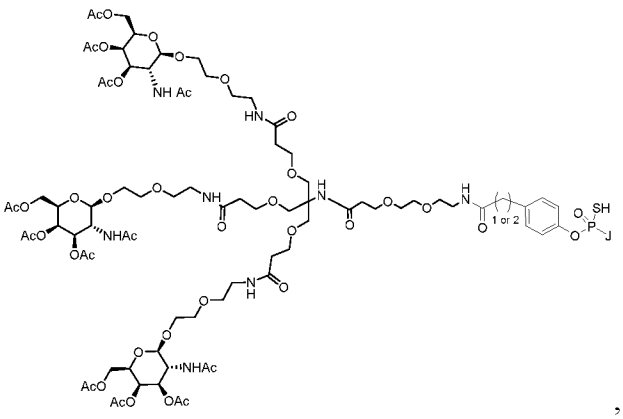
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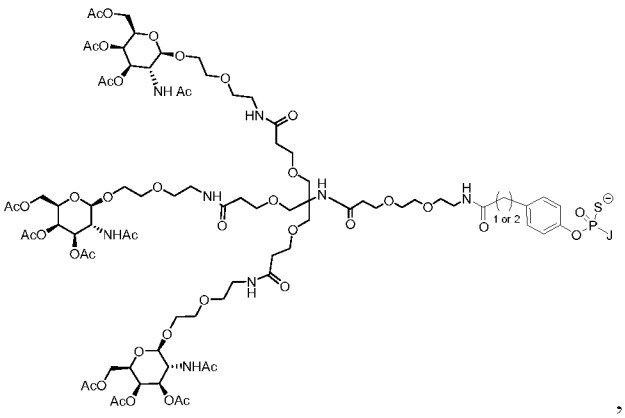
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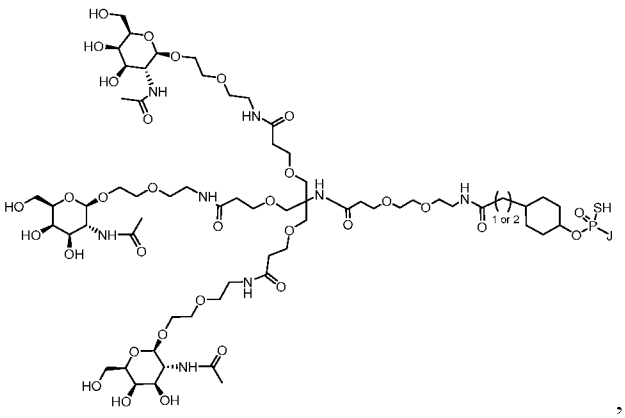
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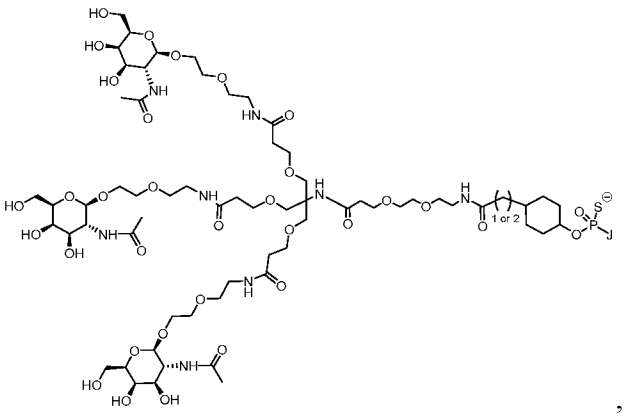
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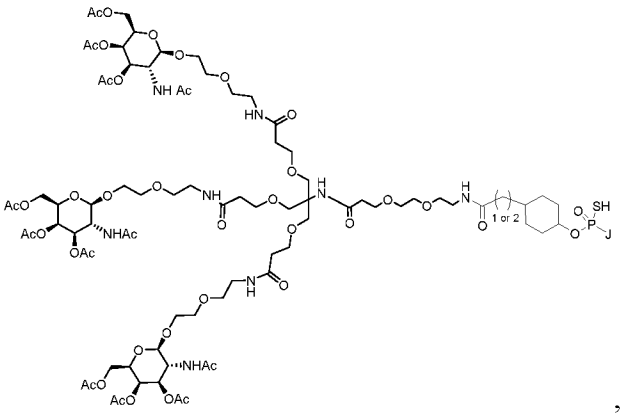
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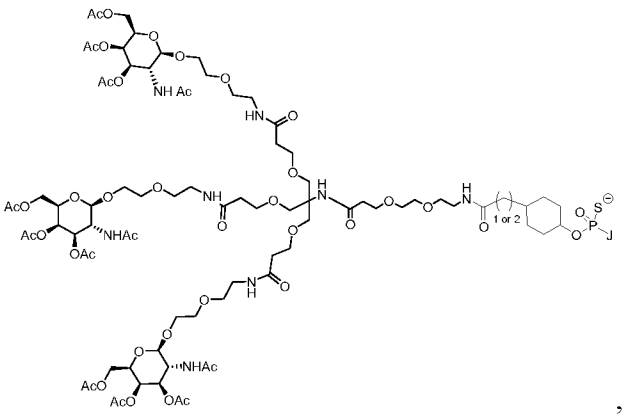
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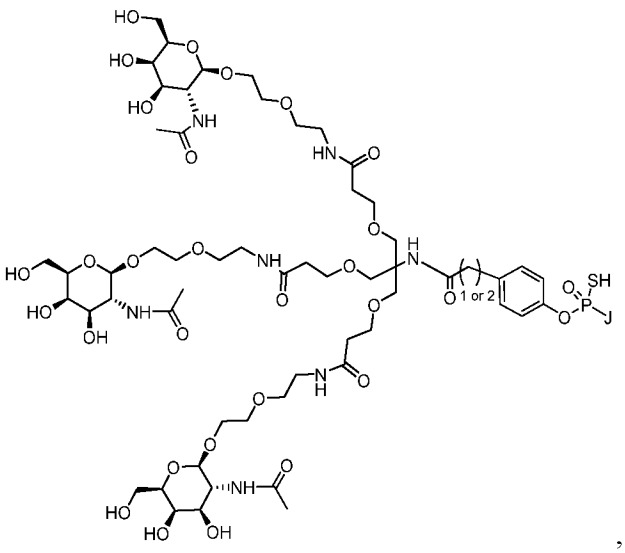
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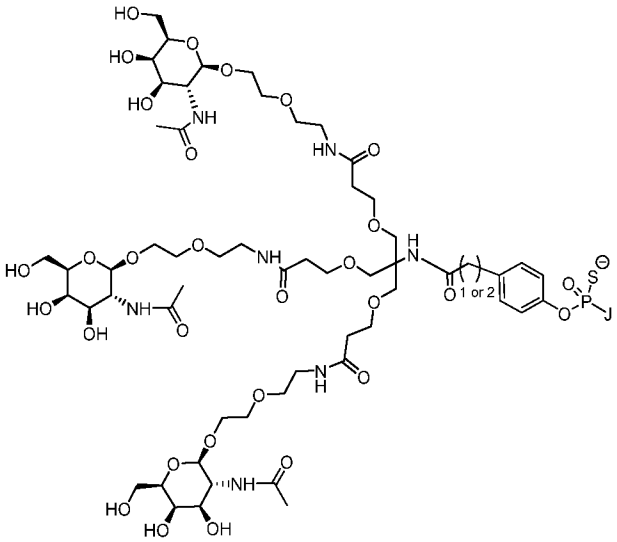
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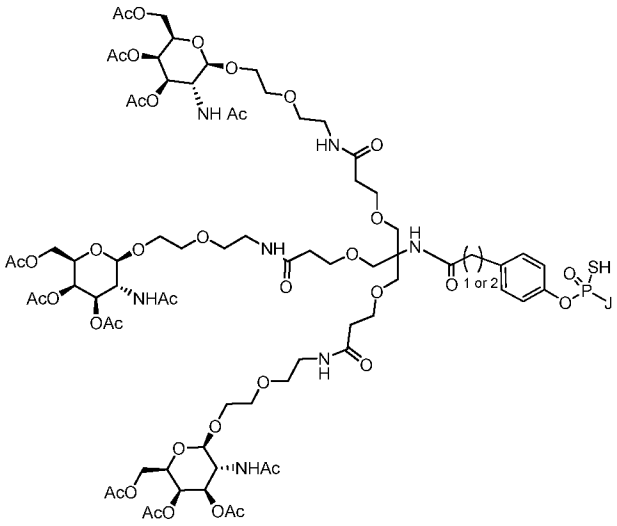
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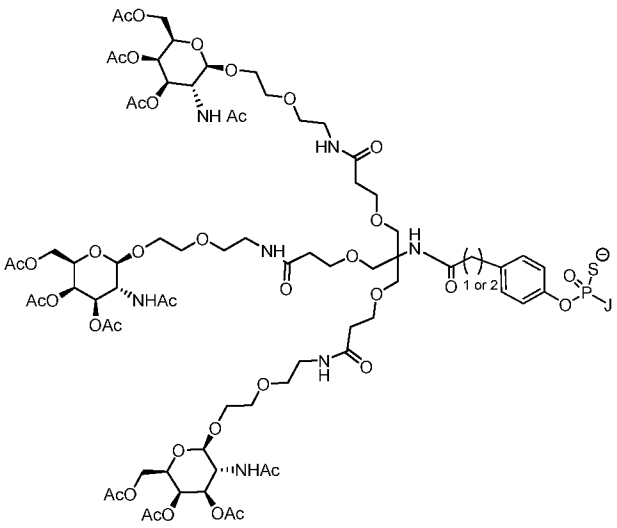
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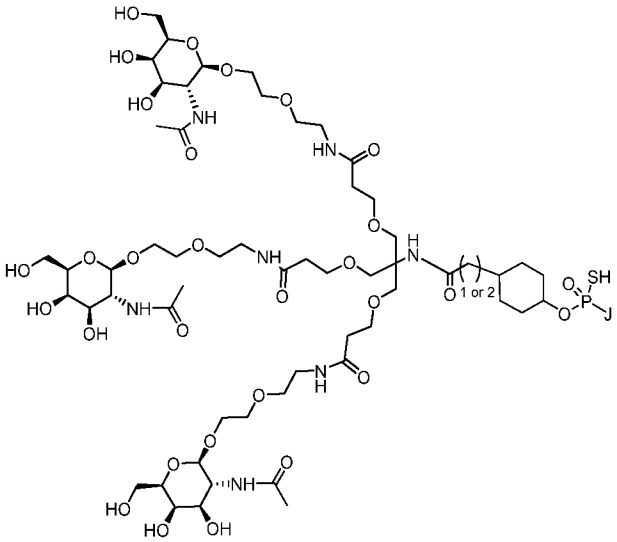
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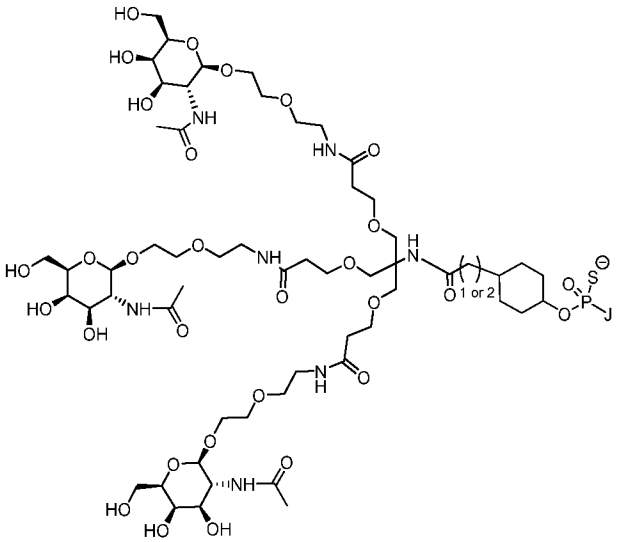
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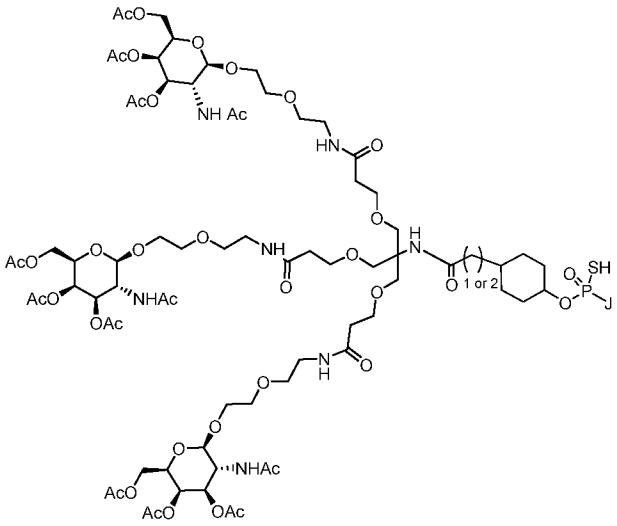
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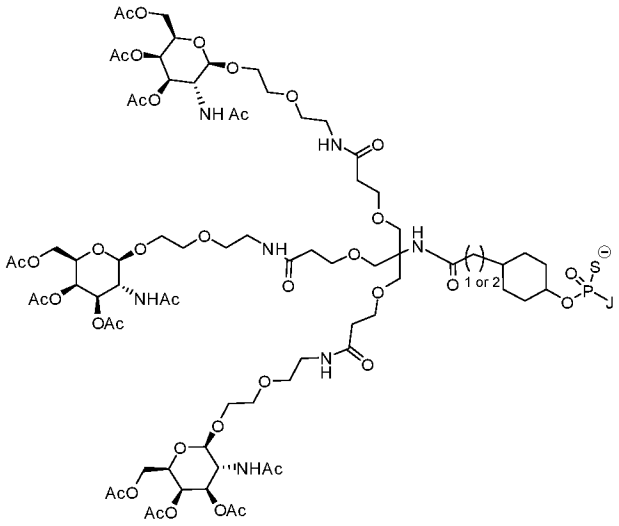
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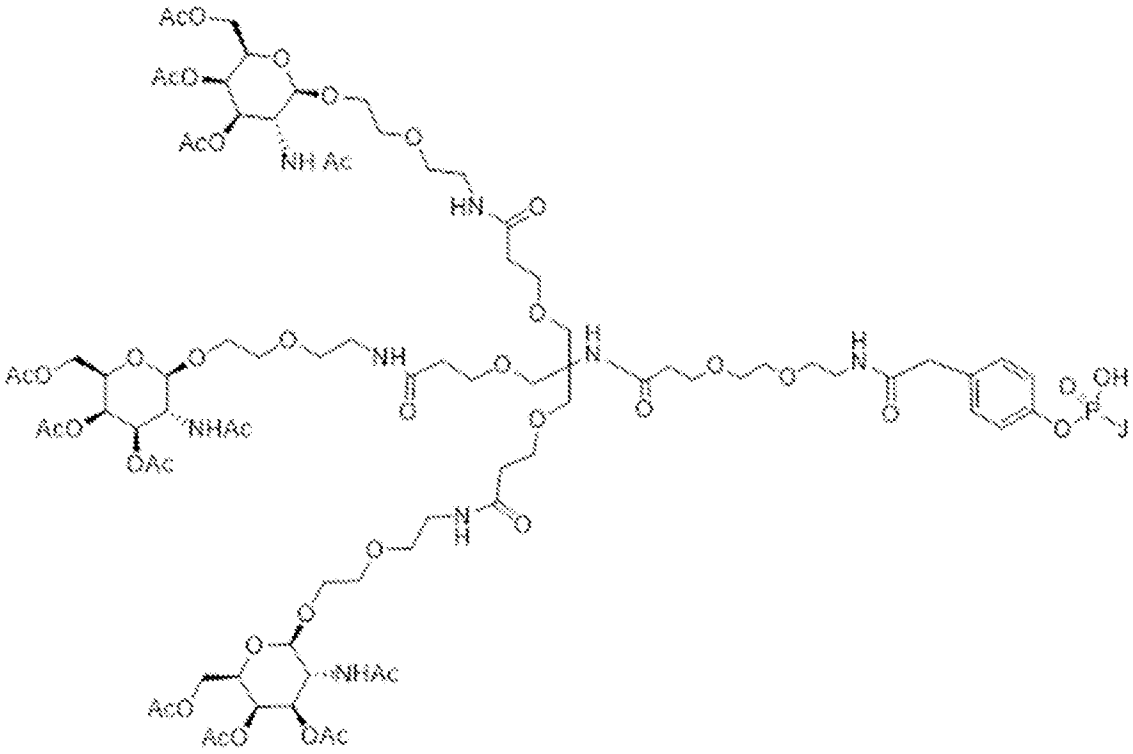


, or



In some embodiments, the oligonucleotide (J) is attached at a 5' end or a 3' end of the oligonucleotide. In some embodiments, the oligonucleotide comprises DNA. In some embodiments, the oligonucleotide comprises RNA. In some embodiments, the oligonucleotide comprises one or more modified internucleoside linkages. In some embodiments, the one or more modified internucleoside linkages comprise alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages. In some embodiments, the compound binds to an asialoglycoprotein receptor. In some embodiments, the compound targets a hepatocyte.

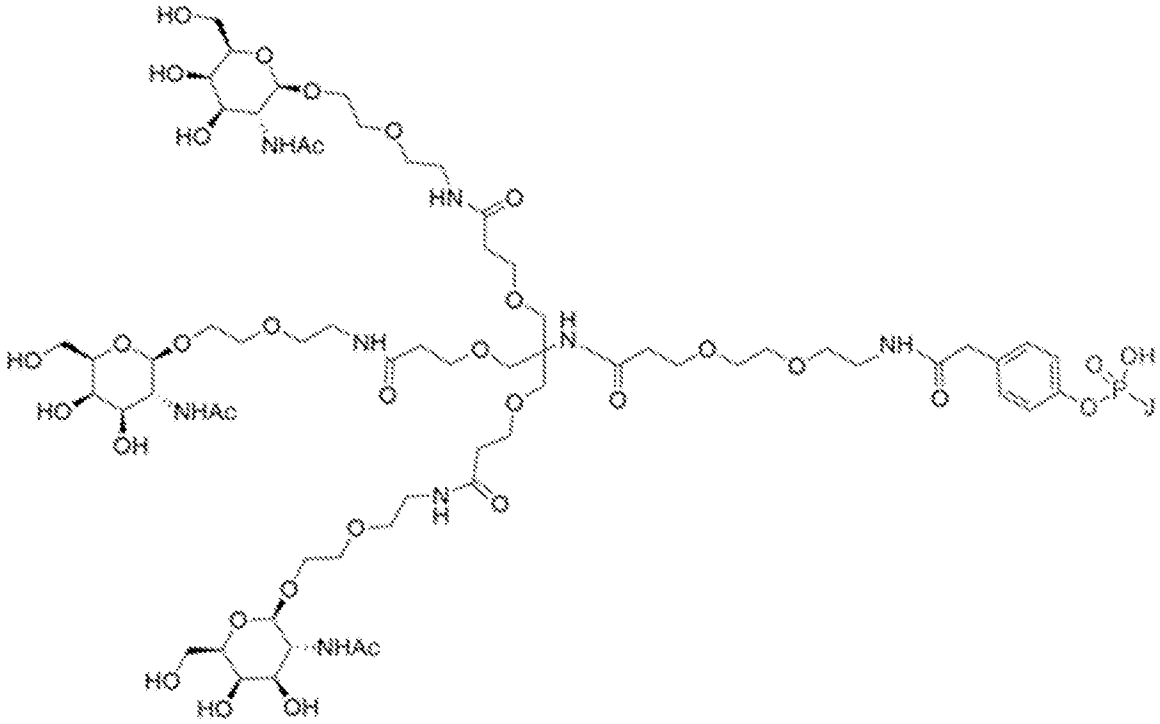
[0153] Some embodiments include the following, where J is the oligonucleotide:



. J may include one or more additional phosphates, or one or more phosphorothioates linking to the

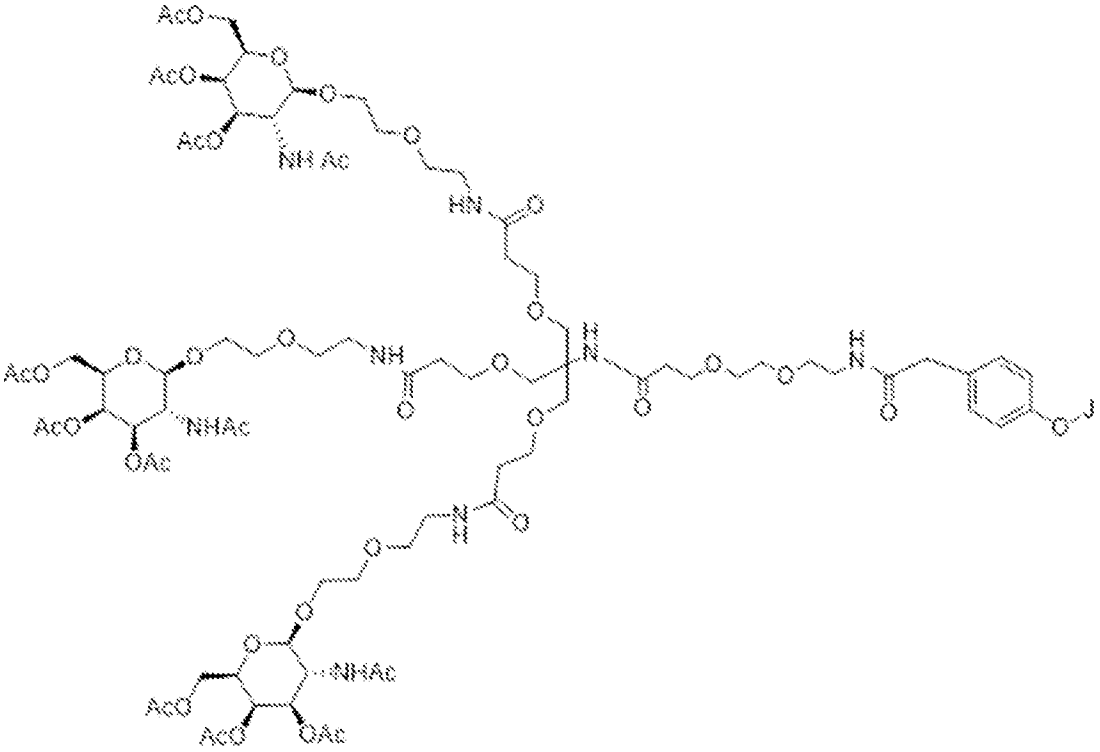
oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

[0154] Some embodiments include the following, where J is the oligonucleotide:



. J may include one or more additional phosphates, or one or more phosphorothioates linking to the oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

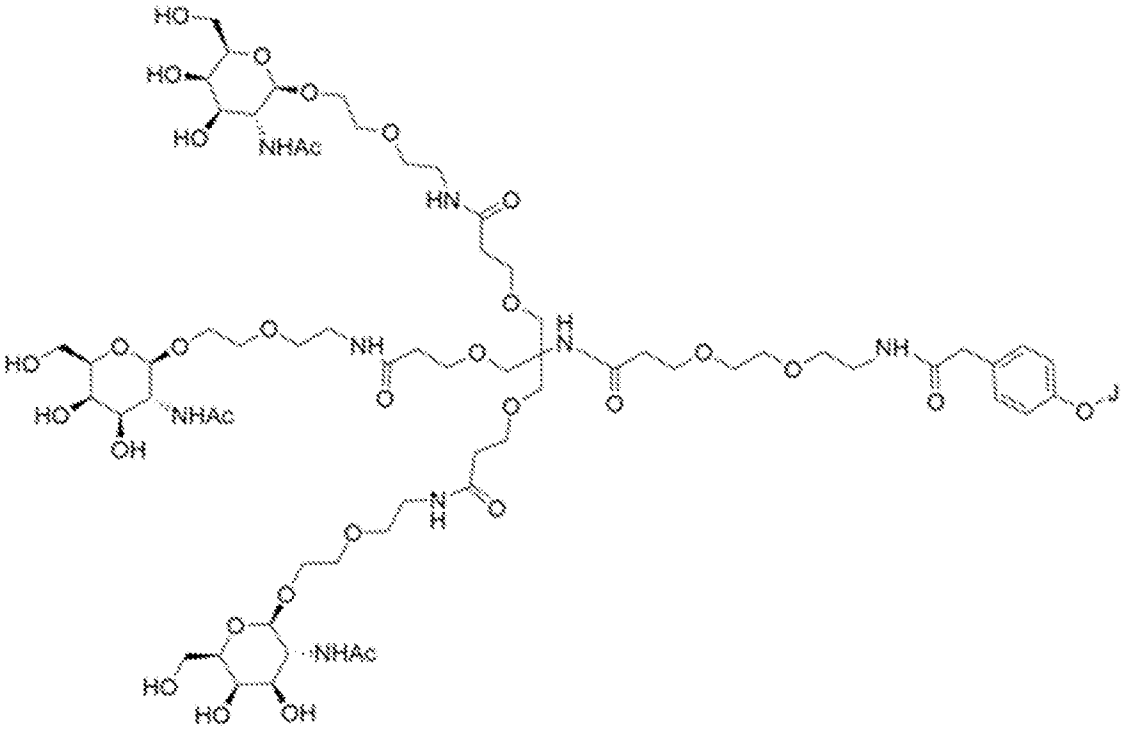
[0155] Some embodiments include the following, where J is the oligonucleotide:



. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or

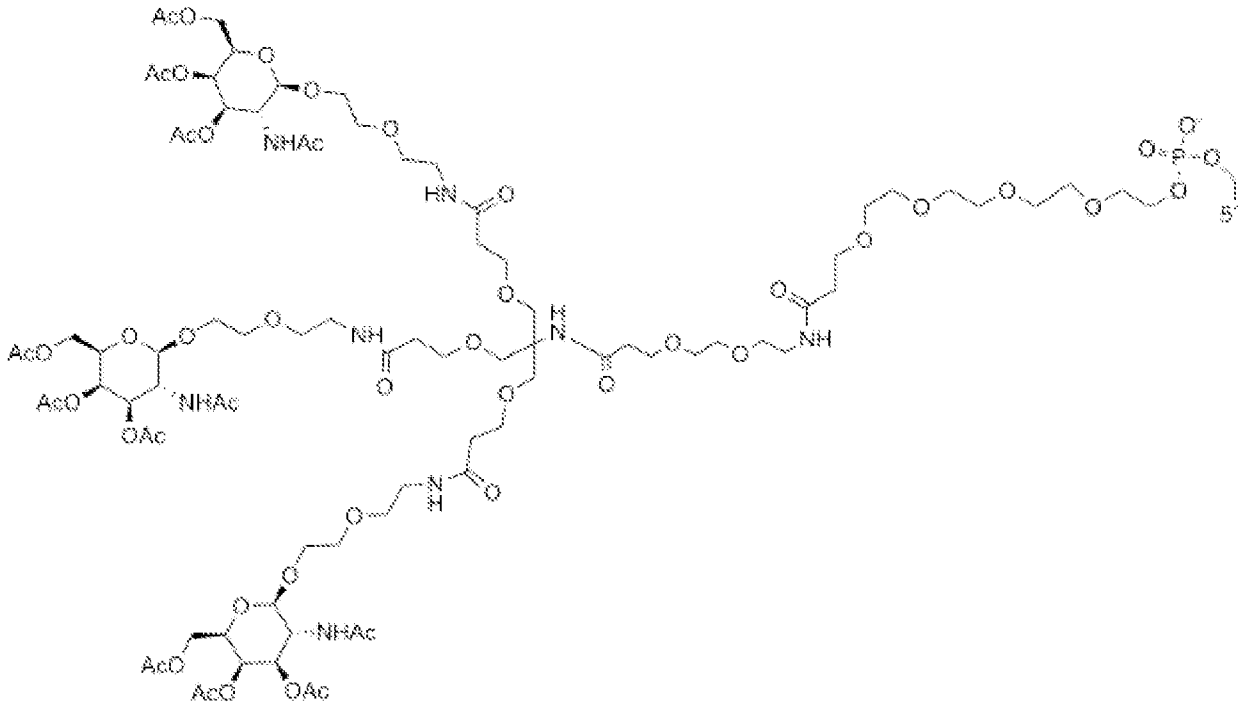
more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

[0156] Some embodiments include the following, where J is the oligonucleotide:

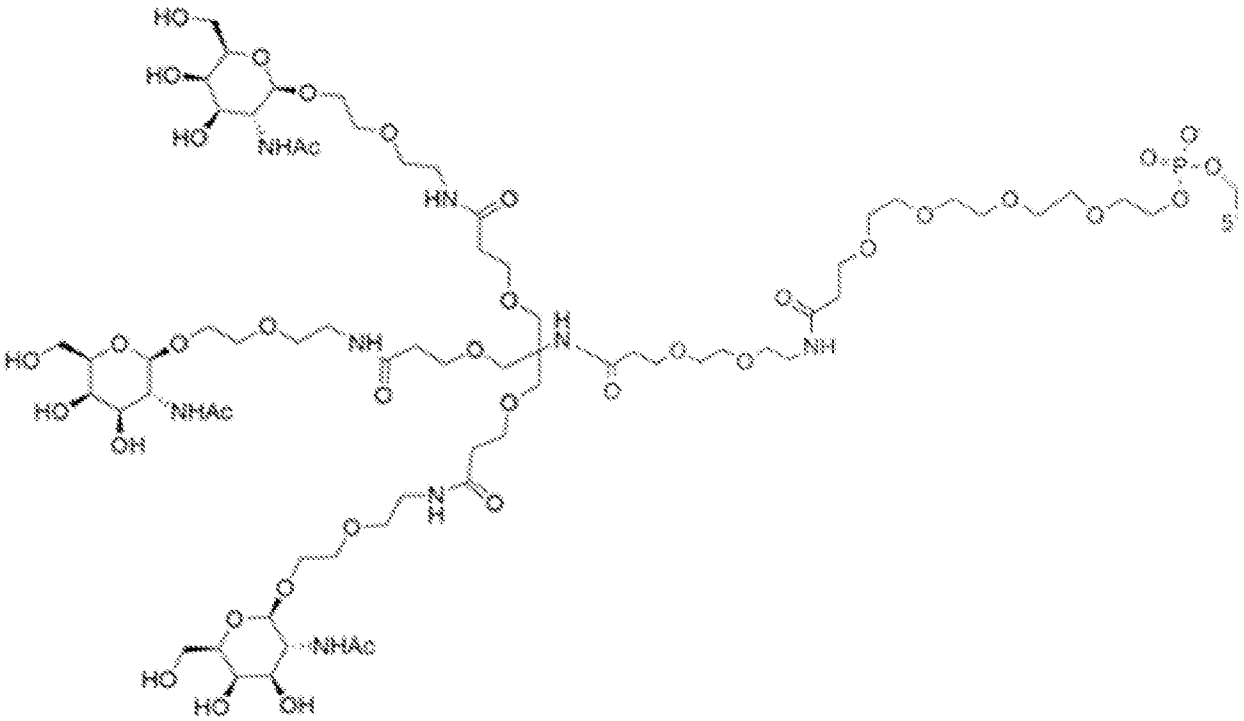


. The structure in this compound attached to the oligonucleotide (J) may be referred to as "ETL17," and is an example of a GalNAc moiety. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

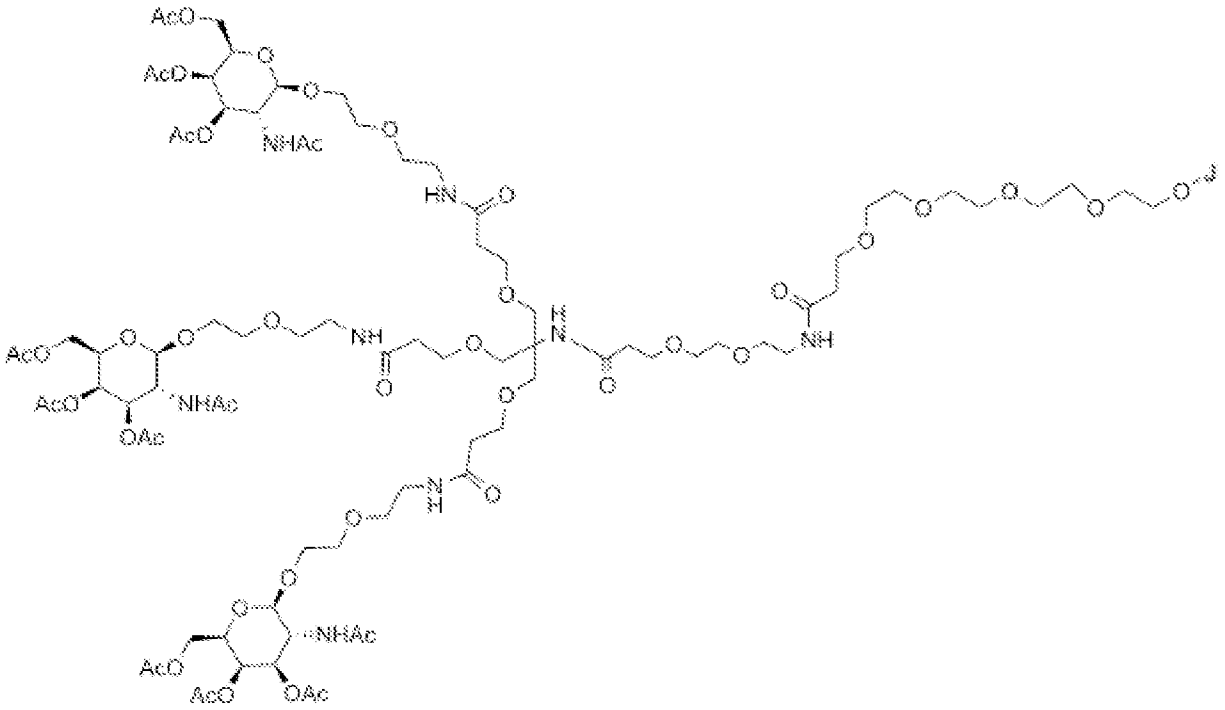
[0157] Some embodiments include the following, where the phosphate or "5'" indicates a connection to the oligonucleotide:



[0158] Some embodiments include the following, where the phosphate or "5'" indicates a connection to the oligonucleotide:

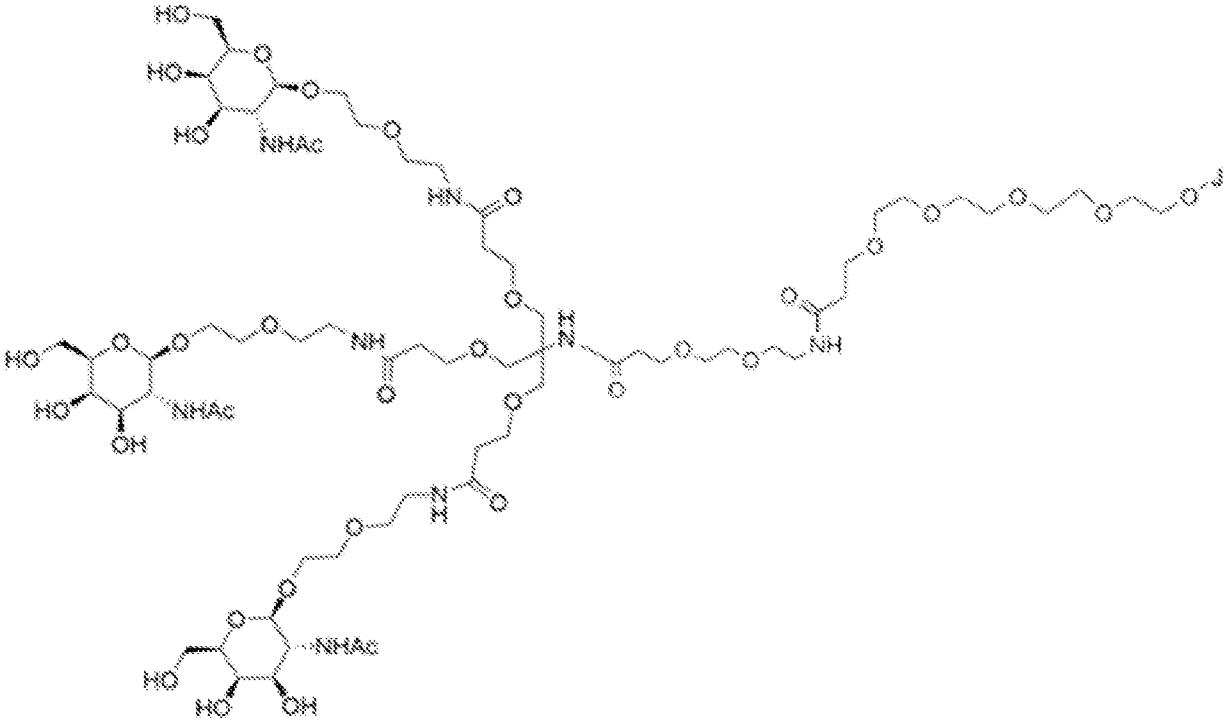


[0159] Some embodiments include the following, where J is the oligonucleotide:



include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

[0160] Some embodiments include the following, where J is the oligonucleotide:



The structure in this compound attached to the oligonucleotide (J) may be referred to as "ETL1," and is an example of a GalNAc moiety. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a

phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

3. siRNA modification patterns

[0161] In some embodiments, the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 modified internucleoside linkages, or a range of modified internucleoside linkages defined by any two of the aforementioned integers. In some embodiments, the sense strand comprises 1-11 modified internucleoside linkages. In some embodiments, the sense strand comprises 2-6 modified internucleoside linkages. In some embodiments, the sense strand comprises 5 modified internucleoside linkages. In some embodiments, the sense strand comprises 4 modified internucleoside linkages.

[0162] In some embodiments, the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 modified internucleoside linkages, or a range of modified internucleoside linkages defined by any two of the aforementioned integers. In some embodiments, the antisense strand comprises 1-11 modified internucleoside linkages. In some embodiments, the antisense strand comprises 2-6 modified internucleoside linkages. In some embodiments, the antisense strand comprises 5 modified internucleoside linkages. In some embodiments, the antisense strand comprises 4 modified internucleoside linkages.

[0163] In some embodiments, the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 modified nucleosides, or a range of modified nucleosides defined by any two of the aforementioned integers. In some embodiments, the sense strand comprises 12-19 modified nucleosides. In some embodiments, the sense strand comprises 12-21 modified nucleosides. In some embodiments, the sense strand comprises 19 modified nucleosides. In some embodiments, the sense strand comprises 21 modified nucleosides.

[0164] In some embodiments, the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 modified nucleosides, or a range of modified nucleosides defined by any two of the aforementioned integers. In some embodiments, the antisense strand comprises 12-19 modified nucleosides. In some embodiments, the antisense strand comprises 12-21 modified nucleosides. In some embodiments, the antisense strand comprises 19 modified nucleosides. In some embodiments, the antisense strand comprises 21 modified nucleosides.

[0165] In some embodiments, the sense strand or the antisense strand further comprises at least 2 additional nucleosides attached to a 3' terminus of the sense strand or the antisense strand. In some embodiments, the sense strand or the antisense strand comprises 2 additional nucleosides attached to a 3' terminus of the sense strand or the antisense strand. As part of the sense strand, the additional nucleosides may or may not be complementary to an ANGPTL4 mRNA. The additional nucleosides of the antisense strand may include a uracil. The 2 additional nucleosides of the antisense strand may both include uracil.

[0166] In some embodiments, the sense strand or the sense strand further comprises at least 2 additional nucleosides attached to a 3' terminus of the sense strand or the sense strand. In some embodiments, the

sense strand or the sense strand comprises 2 additional nucleosides attached to a 3' terminus of the sense strand or the sense strand. The additional nucleosides of the sense strand may include a uracil. The 2 additional nucleosides of the sense strand may both include uracil.

[0167] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises modification pattern 1S: 5'-NfsnsNfnNfnNfNfNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 13954), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 2S: 5'-nsnsnnNfnNfNfNfnnnnnnnnnnsnsn-3' (SEQ ID NO: 13955), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 3S: 5'-nsnsnnNfnNfnNfnnnnnnnnnnsnsn-3' (SEQ ID NO: 13956), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 4S: 5'-NfsnsNfnNfnNfNfNfnNfnNfnNfnNfnNfsnsnN-3' (SEQ ID NO: 13957), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises modification pattern 5S: 5'-nsnsnnNfnNfNfNfnnnnnnnnnnsnsnN-3' (SEQ ID NO: 13958), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, modification pattern 4S or 5S includes a moiety such as a lipid moiety or a sugar moiety. In some embodiments, the sense strand comprises modification pattern 6S: 5'-NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn-3' (SEQ ID NO: 13959), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. Any one of modification patterns 1S-9S may include a GalNAc ligand attached to the 3' end. Any one of modification patterns 1S-9S may include a GalNAc ligand attached to the 5' end. In some embodiments, the sense strand comprises modification pattern 7S: 5'-nsnsnnNfNfNfNfNfnnnnnnnnnnsnsn-3' (SEQ ID NO: 14293), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 8S: 5'-nsnsnnnNfNfNfNfnnnnnnnnnnsnsn-3' (SEQ ID NO: 14294), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 9S: 5'-nsnsnnnnNfNfNfNfnnnnnnnnnnsnsn-3' (SEQ ID NO: 14295), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 10S: 5'-snnnnNfNfnNfNfnnnnnnnnnnsnsn-3' (SEQ ID NO: 14322), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some

embodiments, the sense strand comprises modification pattern 11S: 5'-snnnnNfNfnNfNfnNfnnnnnnnnsnsn-3' (SEQ ID NO: 14323), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 12S: 5'-snnnnnnNfnNfnnnnnnnnnnsnsn-3' (SEQ ID NO: 14324), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 13S: 5'-snnnnnNfNfnNfnNfnnnnnnnnnsnsn-3' (SEQ ID NO: 14325), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 14S: 5'-snnnnnNfNfNfNfnnnnnnnnnnnsnsn-3' (SEQ ID NO: 14326), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 15S: 5'-snnnnnNfNfNfNfndNnnnnnnnnnsnsn-3' (SEQ ID NO: 14327), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 16S: 5'-snnNfnNfnNfndNnnnnnnnnnnsnsn-3' (SEQ ID NO: 14328), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[0168] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises modification pattern 1AS: 5'-nsNfsnNfnNfnNfnNfnnnNfnNfnNfnsnsn-3' (SEQ ID NO: 13960), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 2AS: 5'-nsNfsnnnNfnNfNfnnnnNfnNfnnnsnsn-3' (SEQ ID NO: 13961), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 3AS: 5'-nsNfsnnnNfnnnnnnnNfnNfnnnsnsn-3' (SEQ ID NO: 13962), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 4AS: 5'-nsNfsnNfnNfnnnnnnnNfnNfnnnsnsn-3' (SEQ ID NO: 13963), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 5AS: 5'-nsNfsnnnNfnNfnnnnnNfnNfnnnsnsn-3' (SEQ ID NO: 13964), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 6AS: 5'-nsNfsnNfnNfnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 13965), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 7AS:

5'-nsNfsnNfnNfnNfNfnnnnNfnNfnnnsnsn-3' (SEQ ID NO: 13966), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 8AS: 5'-nsNfsnnnnnnnnnnnNfnnnnnsnsn-3' (SEQ ID NO: 13967), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 9AS: 5'-nsNfsnnnNfnnnnnnnNfnNfnNfnsnsn-3' (SEQ ID NO: 13968), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 10AS: 5'-nsNfsnnnnnnnnnnnNfnNfnnnsnsn-3' (SEQ ID NO: 14296), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 11AS: 5'-nsNfsnnnNfnnNfnnnnNfnNfnnnsnsn-3' (SEQ ID NO: 14297), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 12AS: 5'-nsNfsnnnNfnNfnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 14329), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 13AS: 5'-nsNfsnsNfnNfnNfnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 14330), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 14AS: 5'-nsNfsnNfnNfnnnNfnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 14331), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 15AS: 5'-nsNfsnNfnNfnnnnnNfnNfnNfnNfnsnsn-3' (SEQ ID NO: 14332), wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. Any one of modification patterns 1AS-11AS may include a GalNAc ligand attached to the 3' end. Any one of modification patterns 1AS-11AS may include a GalNAc ligand attached to the 5' end.

[0169] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises modification pattern 1S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 2S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 3S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 4S and the antisense strand comprises modification pattern 1AS, 2AS,

3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 5S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 6S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 7S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 8S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 9S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 10S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 11S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 12S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 13S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 14S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 15S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 16S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS. In some embodiments, the sense strand comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, or 14S. In some embodiments, the antisense strand comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, or 14S. In some embodiments, the sense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, or 11AS. In some embodiments, the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, or 11AS. In some embodiments, the sense strand or the antisense strand comprises modification pattern ASO1.

[0170] Any combination of sense and antisense modification patterns may be used. In some embodiments, the sense strand comprises modification pattern 1S, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 2S, and

the antisense strand comprises modification pattern 2AS. In some embodiments, the sense strand comprises modification pattern 2S, and the antisense strand comprises modification pattern 3AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 4AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 5AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 6AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 7AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 8AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 4AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 5AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 6AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 7AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 8AS. Any combination may include a sense strand having modification pattern 7S, 8S, or 9S. Any combination may include a sense strand having modification pattern 10S, 11S, 12S, 13S, 14S, 15S, or 16S. Any combination may include an antisense strand having modification pattern 10AS or 11AS. Any combination may include an antisense strand having modification pattern 12AS, 13AS, 14AS, or 15AS.

[0171] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 1S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 1S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 1S.

[0172] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 2S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2

nucleoside substitutions, additions, or deletions, and modification pattern 2S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 2S.

[0173] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 3S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 3S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 3S.

[0174] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 4S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 4S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 4S.

[0175] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 5S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 5S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 5S.

[0176] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 6S. In some

embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 6S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 6S.

[0177] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 7S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 7S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 7S.

[0178] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 8S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 8S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 8S.

[0179] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 9S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 9S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 9S.

[0180] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an

antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 1AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 1AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 1AS.

[0181] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 2AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 2AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 2AS.

[0182] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 3AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 3AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 3AS.

[0183] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 4AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 4AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 4AS.

[0184] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 5AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 5AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 5AS.

[0185] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 6AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 6AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 6AS.

[0186] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 7AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 7AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 7AS.

[0187] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 8AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 8AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the

sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 8AS.

[0188] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 9AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 9AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 9AS.

[0189] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 10AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 10AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 10AS.

[0190] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4 wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, and modification pattern 11AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern 11AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern 11AS.

[0191] In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 1S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 2S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of

SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 3S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 4S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 5S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 6S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 7S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 8S. In some embodiments, the sense strand comprises a nucleoside sequence comprising or consisting the sequence of any one of SEQ ID NOs: 1-1854 or 13970-13977, an overhang (such as a 2 base 3' overhang), and modification pattern 9S. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 1AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 2AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 3AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 4AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 5AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 6AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 7AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 8AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 9AS. In some embodiments, the antisense strand

comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 10AS. In some embodiments, the antisense strand comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 1855-3708 or 13978-13985, and an overhang (such as a 2 base 3' overhang), and modification pattern 11AS. In some embodiments, the overhang comprises one or more uracil nucleosides. In some embodiments, the one or more uracil nucleosides of the overhang are connected at the 3' end to another nucleoside via a phosphorothioate linkage. In some embodiments, the overhang comprises one uracil nucleoside. In some embodiments, the overhang comprises two uracil nucleoside.

[0192] Some embodiments include a composition comprising an oligonucleotide that targets Angiopoietin like 4 (ANGPTL4) and when administered to a cell decreases expression of ANGPTL4, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, wherein the sense strand comprises an oligonucleotide sequence of SEQ ID NOs: 759, 1285, 1580, or 1840 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of SEQ ID NOs: 759, 1285, 1580, or 1840 in which at least one internucleoside linkage is modified and at least one base is modified, and wherein the antisense strand comprises an oligonucleotide sequence of SEQ ID NOs: 2613, 3139, 3434, or 3694 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of SEQ ID NOs: 2613, 3139, 3434, or 3694 in which at least one internucleoside linkage is modified and at least one base is modified.

[0193] Some embodiments include a composition comprising an oligonucleotide that targets Angiopoietin like 4 (ANGPTL4) and when administered to a cell decreases expression of ANGPTL4, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, wherein the sense strand comprises an oligonucleotide sequence of any one of SEQ ID NOs: 13970-13973 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of any one of SEQ ID NOs: 13970-13973 in which at least one internucleoside linkage is modified and at least one base is modified, and wherein the antisense strand comprises an oligonucleotide sequence of any one of SEQ ID NOs: 13978-13981 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of any one of SEQ ID NOs: 13978-13981 in which at least one internucleoside linkage is modified and at least one base is modified.

[0194] Some embodiments include a composition comprising an oligonucleotide that targets Angiopoietin like 4 (ANGPTL4) and when administered to a cell decreases expression of ANGPTL4, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, wherein the sense strand comprises an oligonucleotide sequence of any one of SEQ ID NOs: 13974-13977 in which at least one internucleoside linkage is modified and at least one base is

modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of any one of SEQ ID NOs: 13974-13977 in which at least one internucleoside linkage is modified and at least one base is modified, and wherein the antisense strand comprises an oligonucleotide sequence of any one of SEQ ID NOs: 13982-13985 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of any one of SEQ ID NOs: 13982-13985 in which at least one internucleoside linkage is modified and at least one base is modified.

[0195] Some embodiments include a composition comprising an oligonucleotide that targets Angiopoietin like 4 (ANGPTL4) and when administered to a cell decreases expression of ANGPTL4, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, wherein the sense strand comprises an oligonucleotide sequence of any one of SEQ ID NOs: 13990-14005 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of any one of SEQ ID NOs: 13990-14005 in which at least one internucleoside linkage is modified and at least one base is modified, and wherein the antisense strand comprises an oligonucleotide sequence of any one of SEQ ID NOs: 14134-14157 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of any one of SEQ ID NOs: 14134-14157 in which at least one internucleoside linkage is modified and at least one base is modified.

[0196] Some embodiments include a composition comprising an oligonucleotide that targets Angiopoietin like 4 (ANGPTL4) and when administered to a cell decreases expression of ANGPTL4, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, wherein the sense strand comprises an oligonucleotide sequence of any one of SEQ ID NOs: 1-1854 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of any one of SEQ ID NOs: 1-1854 in which at least one internucleoside linkage is modified and at least one base is modified, and wherein the antisense strand comprises an oligonucleotide sequence of any one of SEQ ID NOs: 1855-3708 in which at least one internucleoside linkage is modified and at least one base is modified, or an oligonucleotide sequence comprising 1 or 2 nucleoside, substitutions, additions, or deletions of any one of SEQ ID NOs: 1855-3708 in which at least one internucleoside linkage is modified and at least one base is modified.

[0197] In some embodiments, purines of the sense strand comprise 2' fluoro modified purines. In some embodiments, purines of the sense strand comprise 2' methyl modified purines. In some embodiments, purines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines. In some embodiments, all purines of the sense strand comprise 2' methyl modified purines. In some embodiments, all purines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified purines.

[0198] In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise 2' methyl modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' methyl modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines.

[0199] In some embodiments, purines of the sense strand comprise 2' fluoro modified purines, and pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2' methyl modified purines, and pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2' fluoro modified purines, and pyrimidines of the sense strand comprise 2' methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2' methyl modified purines, and pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and purines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2' methyl modified pyrimidines, and purines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and purines of the sense strand comprise 2' methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2' methyl modified pyrimidines, and purines of the sense strand comprise 2' fluoro modified purines.

[0200] In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines, and all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2' methyl modified purines, and all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines, and all pyrimidines of the sense strand comprise 2' methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2' methyl modified purines, and all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and all purines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2' methyl modified pyrimidines, and all purines of the sense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and all purines of the sense strand comprise 2' methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2' methyl modified pyrimidines, and all purines of the sense strand comprise 2' fluoro modified purines.

[0201] In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines. In some embodiments, purines of the antisense strand comprise 2' methyl modified purines. In some embodiments, purines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines. In some embodiments, all purines of the antisense strand comprise 2' methyl modified purines. In some embodiments, all purines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified purines.

[0202] In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise 2' methyl modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' methyl modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines.

[0203] In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines, and pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2' methyl modified purines, and pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines, and pyrimidines of the antisense strand comprise 2' methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2' methyl modified purines, and pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and purines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2' methyl modified pyrimidines, and purines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and purines of the antisense strand comprise 2' methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2' methyl modified pyrimidines, and purines of the antisense strand comprise 2' fluoro modified purines.

[0204] In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines, and all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2' methyl modified purines, and all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines, and all pyrimidines of the antisense strand comprise 2' methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2' methyl modified purines, and all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and all purines of the

antisense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2' methyl modified pyrimidines, and all purines of the antisense strand comprise a mixture of 2' fluoro and 2' methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and all purines of the antisense strand comprise 2' methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2' methyl modified pyrimidines, and all purines of the antisense strand comprise 2' fluoro modified purines.

[0205] In some cases, the sense strand of any of the siRNAs comprises siRNA with a particular modification pattern. In some embodiments of the modification pattern, position 9 counting from the 5' end of the sense strand may have a 2'F modification. In some embodiments, when position 9 of the sense strand is a pyrimidine, then all purines in the sense strand have a 2'OMe modification. In some embodiments, when position 9 is the only pyrimidine between positions 5 and 11 of the sense stand, then position 9 is the only position with a 2'F modification in the sense strand. In some embodiments, when position 9 and only one other base between positions 5 and 11 of the sense strand are pyrimidines, then both of these pyrimidines are the only two positions with a 2'F modification in the sense strand. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of the sense strand are pyrimidines, and those two other pyrimidines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 pyrimidines between positions 5 and 11 of the sense strand, then all combinations of pyrimidines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that the sense strand does not have three 2'F modifications in a row. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to any or all of these sense strand rules.

[0206] In some embodiments, when position 9 of the sense strand is a purine, then all purines in the sense strand have a 2'OMe modification. In some embodiments, when position 9 is the only purine between positions 5 and 11 of the sense stand, then position 9 is the only position with a 2'F modification in the sense strand. In some embodiments, when position 9 and only one other base between positions 5 and 11 of the sense strand are purines, then both of these purines are the only two positions with a 2'F modification in the sense strand. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of the sense strand are purines, and those two other purines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 purines between positions 5 and 11 of the sense strand, then all combinations of purines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that the sense strand does not have three 2'F modifications in a row. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to any or all of these sense strand rules.

[0207] In some cases, position 9 of the sense strand can be a 2'deoxy. In these cases, 2'F and 2'OMe modifications may occur at the other positions of the sense strand. In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to these sense strand rules.

[0208] In some cases, the sense strand of any of the siRNAs comprises a modification pattern which conforms to these sense strand rules.

4. ASO modification patterns

[0209] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO comprises modification pattern ASO1: 5'-nsnsnsnsnsdNsdNsdNsdNsdNsdNsdNsdNsdNsnsnsnsnsn-3', wherein "dN" is any deoxynucleotide, "n" is a 2'O-methyl or 2'O-methoxyethyl-modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the ASO comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, or 11AS. In some embodiments, the ASO comprises DNA.

[0210] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of ANGPTL4, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3709-13934, and modification pattern ASO1. In some embodiments, the ASO comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3709-13934, or a nucleic acid sequence thereof having 1 or 2 nucleoside substitutions, additions, or deletions, and modification pattern ASO1. In some embodiments, the ASO comprises a nucleoside sequence comprising or consisting of the sequence of any one of SEQ ID NOs: 3709-13934, or a nucleic acid sequence thereof having 3 or 4 nucleoside substitutions, additions, or deletions, and modification pattern ASO1.

[0211] ASO1 modification pattern ASO1 may include a GalNAc ligand attached to the 3' end. ASO1 modification pattern ASO1 may include a GalNAc ligand attached to the 5' end.

D. Formulations

[0212] In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the composition is sterile. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

[0213] In some embodiments, the pharmaceutically acceptable carrier comprises water. In some embodiments, the pharmaceutically acceptable carrier comprises a buffer. In some embodiments, the pharmaceutically acceptable carrier comprises a saline solution. In some embodiments, the pharmaceutically acceptable carrier comprises water, a buffer, or a saline solution. In some embodiments, the composition comprises a liposome. In some embodiments, the pharmaceutically acceptable carrier comprises liposomes, lipids, nanoparticles, proteins, protein-antibody complexes, peptides, cellulose, nanogel, or a combination thereof.

II. METHODS AND USES

[0214] Disclosed herein, in some embodiments, are methods of administering a composition described herein to a subject. Some embodiments relate to use a composition described herein, such as administering the composition to a subject.

[0215] Some embodiments relate to a method of treating a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of treatment. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration treats the disorder in the subject. In some embodiments, the composition treats the disorder in the subject.

[0216] In some embodiments, the treatment comprises prevention, inhibition, or reversion of the disorder in the subject. Some embodiments relate to use of a composition described herein in the method of preventing, inhibiting, or reversing the disorder. Some embodiments relate to a method of preventing, inhibiting, or reversing a disorder a disorder in a subject in need thereof. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration prevents, inhibits, or reverses the disorder in the subject. In some embodiments, the composition prevents, inhibits, or reverses the disorder in the subject.

[0217] Some embodiments relate to a method of preventing a disorder a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of preventing the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration prevents the disorder in the subject. In some embodiments, the composition prevents the disorder in the subject.

[0218] Some embodiments relate to a method of inhibiting a disorder a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of inhibiting the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration inhibits the disorder in the subject. In some embodiments, the composition inhibits the disorder in the subject.

[0219] Some embodiments relate to a method of reversing a disorder a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of reversing the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration reverses the disorder in the subject. In some embodiments, the composition reverses the disorder in the subject.

A. Disorders

[0220] Some embodiments of the methods described herein include treating a disorder in a subject in need thereof. In some embodiments, the disorder is a metabolic disorder. Examples of metabolic disorders include hyperlipidemia (for example, hypertriglyceridemia) and diabetes (for example, type II diabetes). In some embodiments, the metabolic disorder comprises hyperlipidemia. In some embodiments, the metabolic disorder comprises hypertriglyceridemia. In some embodiments, the

metabolic disorder comprises familial chylomicronemia. In some embodiments, the metabolic disorder comprises hypertriglyceridemia in the context of familial chylomicronemia. In some embodiments, the metabolic disorder comprises pancreatitis. In some embodiments, the metabolic disorder comprises acute pancreatitis. In some embodiments, the metabolic disorder comprises hypertriglyceridemia and associated acute pancreatitis. In some embodiments, the metabolic disorder comprises diabetes. In some embodiments, the metabolic disorder comprises type 2 diabetes. In some embodiments, the metabolic disorder comprises a liver disease. An example of liver a disease includes a fatty liver disease. The fatty liver disease may include nonalcoholic fatty liver disease (NAFLD). The fatty liver disease may include non-alcoholic steatohepatitis (NASH). Some embodiments include a method of treating a metabolic disorder in a subject in need thereof, the method comprising administering to the subject a composition comprising an oligonucleotide that targets ANGPTL4.

[0221] In some embodiments, the disorder is a cardiometabolic disorder such as a cardiovascular disorder or a metabolic disorder. In some embodiments, the disorder is a cardiovascular disorder. Examples of cardiovascular disorders include heart disease, myocardial infarction, angina (for example, angina pectoris), and atherosclerosis. In some embodiments, the cardiovascular disorder comprises heart disease. In some embodiments, the cardiovascular disorder comprises myocardial infarction. In some embodiments, the cardiovascular disorder comprises angina pectoris. In some embodiments, the cardiovascular disorder comprises atherosclerosis. Some embodiments include a method of treating a cardiovascular disorder in a subject in need thereof, the method comprising administering to the subject a composition comprising an oligonucleotide that targets ANGPTL4.

B. Subjects

[0222] Some embodiments of the methods described herein include treatment of a subject. Examples of subjects include vertebrates, animals, mammals, dogs, cats, cattle, rodents, mice, rats, primates, monkeys, and humans. In some embodiments, the subject is a vertebrate. In some embodiments, the subject is an animal. In some embodiments, the subject is a mammal. In some embodiments, the subject is a dog. In some embodiments, the subject is a cat. In some embodiments, the subject is a cattle. In some embodiments, the subject is a mouse. In some embodiments, the subject is a rat. In some embodiments, the subject is a primate. In some embodiments, the subject is a monkey. In some embodiments, the subject is an animal, a mammal, a dog, a cat, cattle, a rodent, a mouse, a rat, a primate, or a monkey. In some embodiments, the subject is a human.

[0223] In some embodiments, the subject has a body mass index (BMI) of 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more, or a range defined by any two of the aforementioned integers. In some embodiments, the subject is overweight. In some embodiments, the subject has a BMI of 25 or more. In some embodiments, the subject has a BMI of 25-29. In some embodiments, the subject is obese. In some embodiments, the subject has a BMI of 30 or more. In some embodiments, the subject has a BMI of 30-39. In some embodiments, the subject has a BMI of 40-50. In some embodiments, the subject has a BMI of 25-50.

[0224] In some embodiments, the subject is ≥ 90 years of age. In some embodiments, the subject is ≥ 85 years of age. In some embodiments, the subject is ≥ 80 years of age. In some embodiments, the subject is ≥ 70 years of age. In some embodiments, the subject is ≥ 60 years of age. In some embodiments, the subject is ≥ 50 years of age. In some embodiments, the subject is ≥ 40 years of age. In some embodiments, the subject is ≥ 30 years of age. In some embodiments, the subject is ≥ 20 years of age. In some embodiments, the subject is ≥ 10 years of age. In some embodiments, the subject is ≥ 1 years of age. In some embodiments, the subject is ≥ 0 years of age.

[0225] In some embodiments, the subject is ≤ 100 years of age. In some embodiments, the subject is ≤ 90 years of age. In some embodiments, the subject is ≤ 85 years of age. In some embodiments, the subject is ≤ 80 years of age. In some embodiments, the subject is ≤ 70 years of age. In some embodiments, the subject is ≤ 60 years of age. In some embodiments, the subject is ≤ 50 years of age. In some embodiments, the subject is ≤ 40 years of age. In some embodiments, the subject is ≤ 30 years of age. In some embodiments, the subject is ≤ 20 years of age. In some embodiments, the subject is ≤ 10 years of age. In some embodiments, the subject is ≤ 1 years of age.

[0226] In some embodiments, the subject is between 0 and 100 years of age. In some embodiments, the subject is between 20 and 90 years of age. In some embodiments, the subject is between 30 and 80 years of age. In some embodiments, the subject is between 40 and 75 years of age. In some embodiments, the subject is between 50 and 70 years of age. In some embodiments, the subject is between 40 and 85 years of age.

C. Baseline measurements

[0227] Some embodiments of the methods described herein include obtaining a baseline measurement from a subject. For example, in some embodiments, a baseline measurement is obtained from the subject prior to treating the subject.

[0228] In some embodiments, the baseline measurement is obtained by performing an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay, on the sample obtained from the subject. In some embodiments, the baseline measurement is obtained by an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the baseline measurement is obtained by PCR.

[0229] In some embodiments, the baseline measurement is a baseline triglyceride measurement. In some embodiments, the baseline triglyceride measurement is a baseline triglyceride concentration (for example, mg/dL). In some embodiments, the baseline triglyceride measurement is a baseline circulating triglyceride measurement. In some embodiments, the baseline triglyceride measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[0230] In some embodiments, the baseline measurement is a baseline cholesterol measurement. In some embodiments, the baseline cholesterol measurement is a baseline cholesterol concentration. In some embodiments, the baseline cholesterol concentration is a baseline total cholesterol concentration. In some embodiments, the baseline cholesterol measurement is a baseline circulating cholesterol measurement. In some embodiments, the baseline cholesterol measurement is a baseline low density lipoprotein (LDL)

measurement. In some embodiments, the baseline cholesterol measurement is a baseline very low density lipoprotein (VLDL) measurement. In some embodiments, the baseline cholesterol measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[0231] In some embodiments, the baseline measurement is a baseline HDL measurement. In some embodiments, the baseline HDL measurement is a baseline HDL concentration. In some embodiments, the baseline HDL measurement is indicated relative to a baseline total cholesterol measurement. In some embodiments, the baseline HDL measurement is a baseline circulating HDL measurement. In some embodiments, the baseline HDL measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[0232] In some embodiments, the baseline measurement is a baseline glucose measurement. In some embodiments, the baseline glucose measurement is a baseline glucose concentration (for example, mg/dL). In some embodiments, the baseline glucose measurement comprises a baseline glucose concentration. In some embodiments, the baseline glucose measurement is a baseline circulating glucose measurement. In some embodiments, the baseline glucose measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the baseline glucose measurement is obtained

[0233] In some embodiments, the baseline glucose measurement comprises a baseline glucose tolerance test. In some embodiments, the baseline glucose tolerance test comprises administering glucose to the subject, and then obtaining multiple baseline glucose measurements over time after administering the glucose to the subject. In some embodiments, the glucose is administered orally. In some embodiments, the glucose is administered by injection. In some embodiments, the multiple baseline glucose measurements are integrated into a baseline glucose area under the curve (AUC) measurement. In some embodiments, the baseline glucose tolerance test is performed on the subject in a fasted state such as after an overnight fast. In some embodiments, the baseline glucose measurement comprises a baseline glucose measurement other than a baseline glucose tolerance test.

[0234] In some embodiments, the baseline measurement is a baseline insulin measurement. In some embodiments, the baseline insulin measurement is a baseline insulin sensitivity measurement. In some embodiments, the baseline insulin sensitivity measurement is obtained using a glucose clamp technique such as a hyperinsulinemic euglycemic clamp. In some embodiments, the baseline insulin measurement is a baseline insulin concentration. In some embodiments, the baseline insulin measurement comprises a baseline insulin concentration. In some embodiments, the baseline insulin measurement is a baseline circulating insulin measurement. In some embodiments, the baseline insulin measurement is obtained by an assay such as an immunoassay (for example, an ELISA or an immunoblot), a colorimetric assay, or a fluorescence assay. In some embodiments, the baseline insulin sensitivity measurement comprises a baseline glucose tolerance test. In some embodiments, the baseline insulin sensitivity measurement comprises a baseline insulin sensitivity measurement other than a baseline glucose tolerance test.

[0235] In some embodiments, the baseline insulin measurement comprises a baseline insulin response test. In some embodiments, the baseline insulin response test comprises administering glucose to the

subject and then obtaining multiple baseline insulin measurements over time after administering the glucose to the subject. In some embodiments, the glucose is administered orally. In some embodiments, the glucose is administered by injection. In some embodiments, the multiple baseline insulin measurements are integrated into a baseline insulin AUC measurement. In some embodiments, the baseline insulin response test is performed on the subject in a fasted state such as after an overnight fast.

[0236] In some embodiments, the baseline insulin measurement comprises a baseline glucose response test. In some embodiments, the baseline glucose response test comprises administering insulin to the subject, and then obtaining multiple baseline glucose measurements over time after administering the insulin to the subject. In some embodiments, the insulin is administered by injection. In some embodiments, the multiple baseline glucose measurements are integrated into a baseline glucose AUC measurement. In some embodiments, the multiple baseline glucose measurements are obtained with a glucometer. In some embodiments, the glucose response test is performed on the subject in a fasted state such as after an overnight fast. In some embodiments, the glucose response test is performed on the subject after administering food, drink, or glucose to the subject.

[0237] In some embodiments, the baseline measurement is a baseline liver steatosis measurement. In some embodiments, the baseline liver steatosis measurement is a baseline liver fat percentage (LFP) measurement. In some embodiments, the baseline measurement is a baseline LFP measurement. In some embodiments, the baseline LFP measurement is indicated as a mass/mass percentage of fat/total tissue. In some embodiments, the baseline LFP measurement is indicated as a mass/volume percentage of fat/total tissue. In some embodiments, the baseline LFP measurement is indicated as a volume/mass percentage of fat/total tissue. In some embodiments, the baseline LFP measurement is indicated as a volume/volume percentage of fat/total tissue. In some embodiments, the baseline LFP measurement is indicated as a score. In some embodiments, the baseline LFP measurement is obtained noninvasively. In some embodiments, the baseline LFP measurement is obtained by a medical imaging device. In some embodiments, the baseline LFP measurement is obtained by a device such as a medical resonance imaging (MRI) device, a magnetic resonance spectroscopy device, a computed tomography device, a controlled attenuation parameter (CAP), a transient elastography device, or an ultrasound device. In some embodiments, the baseline LFP measurement is obtained in a liver sample. In some embodiments, the baseline LFP measurement comprises a baseline liver triglyceride measurement. In some embodiments, the baseline LFP measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the baseline LFP measurement or the baseline LFP measurement is obtained using a scoring system upon a visual inspection of a sample such as a histological sample. In some embodiments, the baseline LFP measurement or the baseline LFP measurement is obtained using a stain with an affinity to fats, such as a lysochrome diazo dye.

[0238] In some embodiments, the baseline liver steatosis measurement includes a baseline non-alcoholic fatty liver disease (NAFLD) activity score. In some embodiments, the baseline measurement is a baseline NAFLD activity score. In some embodiments, the baseline NAFLD activity score comprises a numerical value such as a number of points. In some embodiments, the numerical value is 0, 1, 2, 3, 4, 5, 6, 7, or 8,

or a range defined by any two of the aforementioned numerical values. In some embodiments, the numerical value is 0-8. In some embodiments, the baseline NAFLD activity score comprises a steatosis grade such as a baseline liver fat percentage. In some embodiments, a steatosis grade < 5% comprises 0 points in the baseline NAFLD activity score. In some embodiments, a steatosis grade of 5-33% comprises 1 point in the baseline NAFLD activity score. In some embodiments, a steatosis grade of 34-66% comprises 2 points in the baseline NAFLD activity score. In some embodiments, a steatosis grade of > 66% comprises 3 points in the baseline NAFLD activity score. In some embodiments, the baseline NAFLD activity score comprises a lobular inflammation grade. In some embodiments, the lobular inflammation grade comprises an assessment of inflammatory foci. In some embodiments, a lobular inflammation grade comprising 0 foci comprises 0 points in the baseline NAFLD activity score. In some embodiments, a lobular inflammation grade comprising 1 focus per a field (such as a 20x field or a 200x field) comprises 1 point in the baseline NAFLD activity score. In some embodiments, a lobular inflammation grade comprising 2-4 foci per field comprises 2 points in the baseline NAFLD activity score. In some embodiments, a lobular inflammation grade comprising > 4 foci per field comprises 3 points in the baseline NAFLD activity score. In some embodiments, the baseline NAFLD activity score comprises a liver cell injury grade such as an amount of ballooning cells. In some embodiments, a liver cell injury comprising no ballooning cells comprises 0 points in the baseline NAFLD activity score. In some embodiments, a liver cell injury comprising some new balloon cells comprises 1 points in the baseline NAFLD activity score. In some embodiments, a liver cell injury comprising many ballooning cells or prominent ballooning comprises 2 points in the baseline NAFLD activity score. In some embodiments, the baseline NAFLD activity score is obtained invasively, based on histology, and/or in a liver biopsy.

[0239] In some embodiments, the baseline measurement is a baseline ANGPTL4 protein measurement. In some embodiments, the baseline ANGPTL4 protein measurement comprises a baseline ANGPTL4 protein level. In some embodiments, the baseline ANGPTL4 protein level is indicated as a mass or percentage of ANGPTL4 protein per sample weight. In some embodiments, the baseline ANGPTL4 protein level is indicated as a mass or percentage of ANGPTL4 protein per sample volume. In some embodiments, the baseline ANGPTL4 protein level is indicated as a mass or percentage of ANGPTL4 protein per total protein within the sample. In some embodiments, the baseline ANGPTL4 protein measurement is a baseline cell (e.g. hepatocyte) ANGPTL4 protein measurement. In some embodiments, the baseline ANGPTL4 protein measurement is a baseline tissue (e.g. liver tissue) ANGPTL4 protein measurement. In some embodiments, the baseline ANGPTL4 protein measurement is a baseline circulating ANGPTL4 protein measurement. In some embodiments, the baseline ANGPTL4 protein measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[0240] In some embodiments, the baseline measurement is a baseline ANGPTL4 mRNA measurement. In some embodiments, the baseline ANGPTL4 mRNA measurement comprises a baseline ANGPTL4 mRNA level. In some embodiments, the baseline ANGPTL4 mRNA level is indicated as a mass or

percentage of ANGPTL4 mRNA per sample weight. In some embodiments, the baseline ANGPTL4 mRNA level is indicated as a mass or percentage of ANGPTL4 mRNA per sample volume. In some embodiments, the baseline ANGPTL4 mRNA level is indicated as a mass or percentage of ANGPTL4 mRNA per total mRNA within the sample. In some embodiments, the baseline ANGPTL4 mRNA level is indicated as a mass or percentage of ANGPTL4 mRNA per total nucleic acids within the sample. In some embodiments, the baseline ANGPTL4 mRNA level is indicated relative to another mRNA level, such as an mRNA level of a housekeeping gene, within the sample. In some embodiments, the baseline ANGPTL4 mRNA measurement is obtained by an assay such as a polymerase chain reaction (PCR) assay. In some embodiments, the PCR comprises quantitative PCR (qPCR). In some embodiments, the PCR comprises reverse transcription of the ANGPTL4 mRNA.

[0241] Some embodiments of the methods described herein include obtaining a sample from a subject. In some embodiments, the baseline measurement is obtained in a sample obtained from the subject. In some embodiments, the sample is obtained from the subject prior to administration or treatment of the subject with a composition described herein. In some embodiments, a baseline measurement is obtained in a sample obtained from the subject prior to administering the composition to the subject. In some embodiments, the sample is obtained from the subject in a fasted state. In some embodiments, the sample is obtained from the subject after an overnight fasting period. In some embodiments, the sample is obtained from the subject in a fed state.

[0242] In some embodiments, the sample comprises a fluid. In some embodiments, the sample is a fluid sample. In some embodiments, the sample is a blood, plasma, or serum sample. In some embodiments, the sample comprises blood. In some embodiments, the sample is a blood sample. In some embodiments, the sample is a whole-blood sample. In some embodiments, the blood is fractionated or centrifuged. In some embodiments, the sample comprises plasma. In some embodiments, the sample is a plasma sample. In some embodiments, the sample comprises serum. In some embodiments, the sample is a serum sample. For example, the baseline triglyceride 33measurement, the baseline cholesterol measurement, the baseline HDL measurement, the baseline glucose measurement, the baseline insulin measurement, or the baseline ANGPTL4 protein measurement may be obtained in a serum sample from the patient.

[0243] In some embodiments, the sample comprises a tissue. In some embodiments, the sample is a tissue sample. In some embodiments, the sample comprises liver tissue. In some embodiments, the sample is a liver sample. In some embodiments, the sample comprises adipose tissue. In some embodiments, the sample is an adipose sample. In some embodiments, the sample comprises pancreatic tissue. In some embodiments, the sample comprises a pancreas sample. For example, the baseline ANGPTL4 mRNA measurement, or the baseline ANGPTL4 protein measurement, may be obtained in a liver or adipose sample from the patient. In some embodiments, the sample comprises intestinal tissue such as small intestinal tissue. In some embodiments, the sample is a small intestine sample. In some embodiments, the sample comprises lymph node tissue such as mesenteric lymph node tissue. In some embodiments, the sample is a mesenteric lymph node sample. In some embodiments, the sample comprises cardiac tissue such as ventricular or atrial tissue. In some embodiments, the sample is a cardiac

sample. In some embodiments, the tissue sample comprises liver, adipose, small intestine, mesenteric lymph node, or cardiac tissue. In some embodiments, the tissue sample comprises brown adipose tissue, white adipose tissue, kidney tissue, or muscle tissue.

D. Effects

[0244] In some embodiments, the composition or administration of the composition affects a measurement such as a triglyceride measurement, a cholesterol measurement, an HDL measurement, a glucose measurement, an insulin measurement, a liver steatosis measurement, an ANGPTL4 protein measurement (for example, circulating or tissue ANGPTL4 protein levels), or an ANGPTL4 mRNA measurement, relative to the baseline measurement.

[0245] Some embodiments of the methods described herein include obtaining the measurement from a subject. For example, the measurement may be obtained from the subject after treating the subject. In some embodiments, the measurement is obtained in a second sample (such as a fluid or tissue sample described herein) obtained from the subject after the composition is administered to the subject. In some embodiments, the measurement is an indication that the disorder has been treated.

[0246] In some embodiments, the measurement is obtained by an assay as described herein. For example, the assay may comprise an immunoassay, a colorimetric assay, a fluorescence assay, or a PCR assay.

[0247] In some embodiments, the measurement is obtained within 1 week, within 2 weeks, within 3 weeks, within 1 month, within 2 months, within 3 months, within 6 months, within 1 year, within 2 years, within 3 years, within 4 years, or within 5 years after the administration of the composition. In some embodiments, the measurement is obtained after 1 week, after 2 weeks, after 3 weeks, after 1 month, after 2 months, after 3 months, after 6 months, after 1 year, after 2 years, after 3 years, after 4 years, or after 5 years, following the administration of the composition.

[0248] In some embodiments, the measurement is a triglyceride measurement. In some embodiments, the triglyceride measurement is a triglyceride concentration (for example, mg/dL). In some embodiments, the triglyceride measurement is a circulating triglyceride measurement. In some embodiments, the triglyceride measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[0249] In some embodiments, the composition reduces the triglyceride measurement relative to the baseline triglyceride measurement. In some embodiments, the composition reduces circulating triglycerides relative to the baseline triglyceride measurement. In some embodiments, the reduced triglycerides are measured in a second sample obtained from the subject after administering the composition to the subject.

[0250] In some embodiments, the triglyceride measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline triglyceride measurement. In some embodiments, the triglyceride measurement is decreased by about 10% or more, relative to the baseline triglyceride measurement. In some embodiments, the triglyceride measurement is decreased by about

20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline triglyceride measurement. In some embodiments, the triglyceride measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline triglyceride measurement. In some embodiments, the triglyceride measurement is decreased by no more than about 10%, relative to the baseline triglyceride measurement. In some embodiments, the triglyceride measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline triglyceride measurement. In some embodiments, the triglyceride measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or by a range defined by any of the two aforementioned percentages.

[0251] In some embodiments, the measurement is a cholesterol measurement. In some embodiments, the cholesterol measurement is a total cholesterol measurement. In some embodiments, the cholesterol measurement is a cholesterol concentration. In some embodiments, the cholesterol concentration is a total cholesterol concentration. In some embodiments, the cholesterol measurement is a circulating cholesterol measurement. In some embodiments, the cholesterol measurement is a low density lipoprotein (LDL) measurement. In some embodiments, the cholesterol measurement is a very low density lipoprotein (VLDL) measurement. In some embodiments, the cholesterol measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[0252] In some embodiments, the composition reduces the cholesterol measurement relative to the baseline cholesterol measurement. In some embodiments, the composition reduces circulating cholesterol relative to the baseline cholesterol measurement. In some embodiments, the reduced cholesterol is measured in a second sample obtained from the subject after administering the composition to the subject.

[0253] In some embodiments, the cholesterol measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline cholesterol measurement. In some embodiments, the cholesterol measurement is decreased by about 10% or more, relative to the baseline cholesterol measurement. In some embodiments, the cholesterol measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline cholesterol measurement. In some embodiments, the cholesterol is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline cholesterol measurement. In some embodiments, the cholesterol is decreased by no more than about 10%, relative to the baseline cholesterol measurement. In some embodiments, the cholesterol is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline cholesterol measurement. In some embodiments, the cholesterol

measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or by a range defined by any of the two aforementioned percentages.

[0254] In some embodiments, the measurement is an HDL measurement. In some embodiments, the HDL measurement is an HDL concentration. In some embodiments, the HDL measurement is indicated relative to a total cholesterol measurement. In some embodiments, the HDL measurement is a circulating HDL measurement. In some embodiments, the HDL measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[0255] In some embodiments, the composition reduces the HDL measurement relative to the baseline HDL measurement. In some embodiments, the composition increases circulating HDL relative to the baseline HDL measurement. In some embodiments, the increased HDL is measured in a second sample obtained from the subject after administering the composition to the subject.

[0256] In some embodiments, the HDL measurement is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline HDL measurement. In some embodiments, the HDL measurement is increased by about 10% or more, relative to the baseline HDL measurement. In some embodiments, the HDL measurement is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100% or more relative to the baseline HDL measurement. In some embodiments, the HDL measurement is increased by about 200% or more, about 300% or more, about 400% or more, about 500% or more, about 600% or more, about 700% or more, about 800% or more, about 900% or more, or about 1000% or more, relative to the baseline HDL measurement. In some embodiments, the HDL measurement is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline HDL measurement. In some embodiments, the HDL measurement is increased by no more than about 10%, relative to the baseline HDL measurement. In some embodiments, the HDL measurement is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline HDL measurement. In some embodiments, the HDL measurement is increased by no more than about 200%, no more than about 300%, no more than about 400%, no more than about 500%, no more than about 600%, no more than about 700%, no more than about 800%, no more than about 900%, or no more than about 1000%, relative to the baseline HDL measurement. In some embodiments, the HDL measurement is increased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200% 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000%, or by a range defined by any of the two aforementioned percentages.

[0257] In some embodiments, the measurement is a glucose measurement. In some embodiments, the glucose measurement comprises a glucose concentration (for example, mg/dL). In some embodiments, the glucose measurement is a glucose concentration. In some embodiments, the glucose measurement is a circulating glucose measurement. In some embodiments, the glucose measurement is obtained by an

assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the glucose measurement is obtained using a glucometer.

[0258] In some embodiments, the glucose measurement comprises a glucose tolerance test. In some embodiments, the glucose tolerance test comprises administering glucose to the subject, and then obtaining multiple glucose measurements over time after administering the glucose to the subject. In some embodiments, the glucose is administered orally. In some embodiments, the glucose is administered by injection. In some embodiments, the multiple glucose measurements are integrated into a glucose area under the curve (AUC) measurement. In some embodiments, the glucose tolerance test is performed on the subject in a fasted state such as after an overnight fast. In some embodiments, the glucose measurement comprises a glucose measurement other than a glucose tolerance test.

[0259] In some embodiments, the composition reduces the glucose measurement relative to the baseline glucose measurement. In some embodiments, the composition reduces circulating glucose relative to the baseline glucose measurement. In some embodiments, the reduced glucose is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the composition reduces one or more of the multiple glucose measurements of the glucose tolerance test relative to one or more of the multiple glucose measurements of the baseline glucose tolerance test. In some embodiments, the composition reduces the glucose AUC measurement relative to the baseline glucose AUC measurement.

[0260] In some embodiments, the glucose measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline glucose measurement. In some embodiments, the glucose measurement is decreased by about 10% or more, relative to the baseline glucose measurement. In some embodiments, the glucose measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline glucose measurement. In some embodiments, the glucose is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline glucose measurement. In some embodiments, the glucose is decreased by no more than about 10%, relative to the baseline glucose measurement. In some embodiments, the glucose is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline glucose measurement. In some embodiments, the glucose measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or by a range defined by any of the two aforementioned percentages.

[0261] In some embodiments, the measurement is an insulin measurement. In some embodiments, the insulin measurement is an insulin sensitivity measurement. In some embodiments, the insulin sensitivity measurement is obtained using a glucose clamp technique such as a hyperinsulinemic euglycemic clamp. In some embodiments, the insulin measurement comprises an insulin concentration. In some embodiments, the insulin measurement is an insulin concentration. In some embodiments, the insulin measurement is a circulating insulin measurement. In some embodiments, the insulin measurement is

obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the insulin sensitivity measurement comprises a glucose tolerance test. In some embodiments, the insulin sensitivity measurement comprises an insulin sensitivity measurement other than a glucose tolerance test.

[0262] In some embodiments, the insulin measurement comprises an insulin response test. In some embodiments, the insulin response test comprises administering glucose to the subject, and then obtaining multiple insulin measurements over time after administering the glucose to the subject. In some embodiments, the glucose is administered orally. In some embodiments, the glucose is administered by injection. In some embodiments, the multiple insulin measurements are integrated into an insulin AUC measurement. In some embodiments, the insulin response test is performed on the subject in a fasted state such as after an overnight fast.

[0263] In some embodiments, the insulin measurement comprises a glucose response test. In some embodiments, the glucose response test comprises administering insulin to the subject, and then obtaining multiple glucose measurements over time after administering the insulin to the subject. In some embodiments, the insulin is administered by injection. In some embodiments, the multiple glucose measurements are integrated into a glucose AUC measurement. In some embodiments, the multiple glucose measurements are measured with a glucometer. In some embodiments, the glucose response test is performed on the subject in a fasted state such as after an overnight fast. In some embodiments, the glucose response test is performed on the subject after administering food, drink, or glucose to the subject.

[0264] In some embodiments, the composition increases the insulin sensitivity relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by about 10% or more, relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100% or more relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by about 200% or more, about 300% or more, about 400% or more, about 500% or more, about 600% or more, about 700% or more, about 800% or more, about 900% or more, or about 1000% or more, relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by no more than about 10%, relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by no more than about 200%, no

more than about 300%, no more than about 400%, no more than about 500%, no more than about 600%, no more than about 700%, no more than about 800%, no more than about 900%, or no more than about 1000%, relative to the baseline insulin sensitivity measurement. In some embodiments, the insulin sensitivity is increased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200% 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000%, or by a range defined by any of the two aforementioned percentages.

[0265] In some embodiments, the composition reduces the insulin measurement relative to the baseline insulin measurement. In some embodiments, the composition reduces circulating insulin relative to the baseline insulin measurement. In some embodiments, the reduced insulin is measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the composition reduces the insulin AUC measurement relative to the baseline insulin AUC measurement.

[0266] In some embodiments, the insulin measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline insulin measurement. In some embodiments, the insulin measurement is decreased by about 10% or more, relative to the baseline insulin measurement. In some embodiments, the insulin measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline insulin measurement. In some embodiments, the insulin is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline insulin measurement. In some embodiments, the insulin is decreased by no more than about 10%, relative to the baseline insulin measurement. In some embodiments, the insulin is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline insulin measurement. In some embodiments, the insulin measurement is decreased by 2.5%, 5%, 7.5%, 19%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or by a range defined by any of the two aforementioned percentages.

[0267] In some embodiments, the measurement is a liver steatosis measurement. In some embodiments, the liver steatosis measurement is a liver fat percentage (LFP) measurement. In some embodiments, the measurement is a LFP measurement. In some embodiments, the LFP measurement is indicated as a mass/mass percentage of fat/total tissue. In some embodiments, the LFP measurement is indicated as a mass/volume percentage of fat/total tissue. In some embodiments, the LFP measurement is indicated as a volume/mass percentage of fat/total tissue. In some embodiments, the LFP measurement is indicated as a volume/volume percentage of fat/total tissue. In some embodiments, the LFP measurement is indicated as a score. In some embodiments, the LFP measurement is obtained noninvasively. In some embodiments, the LFP measurement is obtained by a medical imaging device. In some embodiments, the LFP measurement is obtained by a device such as a medical resonance imaging (MRI) device, a magnetic resonance spectroscopy device, a computed tomography device, a controlled attenuation parameter (CAP), a transient elastography device, or an ultrasound device. In some embodiments, the LFP measurement is obtained in a second liver sample. In some embodiments, the LFP measurement

comprises a liver triglyceride measurement. In some embodiments, the LFP measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the LFP measurement or the LFP measurement is obtained using a scoring system upon a visual inspection of a sample such as a histological sample. In some embodiments, the LFP measurement or the LFP measurement is obtained using a stain with an affinity to fats, such as a lysochrome diazo dye.

[0268] In some embodiments, the composition reduces the LFP measurement relative to the baseline LFP measurement. In some embodiments, the reduced LFP is measured in a second liver sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduced LFP is measured directly in the subject after administering the composition to the subject. In some embodiments, the LFP measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline LFP measurement. In some embodiments, the LFP measurement is decreased by about 10% or more, relative to the baseline LFP measurement. In some embodiments, the LFP measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline LFP measurement. In some embodiments, the LFP measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline LFP measurement. In some embodiments, the LFP measurement is decreased by no more than about 10%, relative to the baseline LFP measurement. In some embodiments, the LFP measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline LFP measurement. In some embodiments, the LFP measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0269] In some embodiments, the liver steatosis measurement includes a non-alcoholic fatty liver disease (NAFLD) activity score. In some embodiments, the measurement is a NAFLD activity score. In some embodiments, the NAFLD activity score comprises a numerical value such as a number of points. In some embodiments, the numerical value is 0, 1, 2, 3, 4, 5, 6, 7, or 8, or a range defined by any two of the aforementioned numerical values. In some embodiments, the numerical value is 0-8. In some embodiments, the NAFLD activity score comprises a steatosis grade such as a liver fat percentage. In some embodiments, a steatosis grade < 5% comprises 0 points in the NAFLD activity score. In some embodiments, a steatosis grade of 5-33% comprises 1 point in the NAFLD activity score. In some embodiments, a steatosis grade of 34-66% comprises 2 points in the NAFLD activity score. In some embodiments, a steatosis grade of > 66% comprises 3 points in the NAFLD activity score. In some embodiments, the NAFLD activity score comprises a lobular inflammation grade. In some embodiments, the lobular inflammation grade comprises an assessment of inflammatory foci. In some embodiments, a lobular inflammation grade comprising 0 foci comprises 0 points in the NAFLD activity score. In some embodiments, a lobular inflammation grade comprising 1 focus per a field (such as a 20x field or a 200x field) comprises 1 point in the NAFLD activity score. In some embodiments, a lobular inflammation

grade comprising 2-4 foci per field comprises 2 points in the NAFLD activity score. In some embodiments, a lobular inflammation grade comprising > 4 foci per field comprises 3 points in the NAFLD activity score. In some embodiments, the NAFLD activity score comprises a liver cell injury grade such as an amount of ballooning cells. In some embodiments, a liver cell injury comprising no ballooning cells comprises 0 points in the NAFLD activity score. In some embodiments, a liver cell injury comprising some new balloon cells comprises 1 point in the NAFLD activity score. In some embodiments, a liver cell injury comprising many ballooning cells or prominent ballooning comprises 2 points in the NAFLD activity score. In some embodiments, the NAFLD activity score is obtained invasively, based on histology, and/or in a liver biopsy.

[0270] In some embodiments, the composition reduces the NAFLD activity score relative to the baseline NAFLD activity score. In some embodiments, the reduced NAFLD activity score is measured in a second liver sample obtained from the subject after administering the composition to the subject. In some embodiments, the NAFLD activity score is decreased by 1 relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 2 relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 3 relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 4 relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 5 relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 6 relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 7 relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 8 relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 1 or more, relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, or 8 or more, relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by no more than 1, no more than 2, no more than 3, no more than 4, no more than 5, no more than 6, no more than 7, or no more than 8, relative to the baseline NAFLD activity score. In some embodiments, the NAFLD activity score is decreased by 1, 2, 3, 4, 5, 6, 7, or 8, or by a range defined by any of the two aforementioned numbers.

[0271] In some embodiments, the measurement is an ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement comprises an ANGPTL4 protein level. In some embodiments, the ANGPTL4 protein level is indicated as a mass or percentage of ANGPTL4 protein per sample weight. In some embodiments, the ANGPTL4 protein level is indicated as a mass or percentage of ANGPTL4 protein per sample volume. In some embodiments, the ANGPTL4 protein level is indicated as a mass or percentage of ANGPTL4 protein per total protein within the sample. In some embodiments, the ANGPTL4 protein measurement is a cell (e.g. hepatocyte) ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement is a tissue (e.g. liver tissue) ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement is a circulating ANGPTL4

protein measurement. In some embodiments, the baseline ANGPTL4 protein measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[0272] In some embodiments, the composition reduces the ANGPTL4 protein measurement relative to the baseline ANGPTL4 protein measurement. In some embodiments, the composition reduces circulating ANGPTL4 protein levels relative to the baseline ANGPTL4 protein measurement. In some embodiments, the composition reduces tissue ANGPTL4 protein levels (such as liver tissue ANGPTL4 protein levels) relative to the baseline ANGPTL4 protein measurement. In some embodiments, the composition reduces cell ANGPTL4 protein levels (such as hepatocyte ANGPTL4 protein levels) relative to the baseline ANGPTL4 protein measurement. In some embodiments, the reduced ANGPTL4 protein levels are measured in a second sample obtained from the subject after administering the composition to the subject.

[0273] In some embodiments, the ANGPTL4 protein measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement is decreased by about 10% or more, relative to the baseline ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement is decreased by no more than about 10%, relative to the baseline ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline ANGPTL4 protein measurement. In some embodiments, the ANGPTL4 protein measurement is decreased by 2.5%, 5%, 7.5%, 19%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or by a range defined by any of the two aforementioned percentages.

[0274] In some embodiments, the measurement is an ANGPTL4 mRNA measurement. In some embodiments, the ANGPTL4 mRNA measurement comprises an ANGPTL4 mRNA level. In some embodiments, the ANGPTL4 mRNA level is indicated as a mass or percentage of ANGPTL4 mRNA per sample weight. In some embodiments, the ANGPTL4 mRNA level is indicated as a mass or percentage of ANGPTL4 mRNA per sample volume. In some embodiments, the ANGPTL4 mRNA level is indicated as a mass or percentage of ANGPTL4 mRNA per total mRNA within the sample. In some embodiments, the ANGPTL4 mRNA level is indicated as a mass or percentage of ANGPTL4 mRNA per total nucleic acids within the sample. In some embodiments, the ANGPTL4 mRNA level is indicated relative to another mRNA level, such as an mRNA level of a housekeeping gene, within the sample. In some embodiments, the ANGPTL4 mRNA measurement is obtained by an assay such as a PCR assay. In

some embodiments, the PCR comprises qPCR. In some embodiments, the PCR comprises reverse transcription of the ANGPTL4 mRNA.

[0275] In some embodiments, the composition reduces the ANGPTL4 mRNA measurement relative to the baseline ANGPTL4 mRNA measurement. In some embodiments, the ANGPTL4 mRNA measurement is obtained in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the composition reduces ANGPTL4 mRNA levels relative to the baseline ANGPTL4 mRNA levels. In some embodiments, the reduced ANGPTL4 mRNA levels are measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the second sample is a liver sample. In some embodiments, the second sample is an adipose sample.

[0276] In some embodiments, the ANGPTL4 mRNA measurement is reduced by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline ANGPTL4 mRNA measurement. In some embodiments, the ANGPTL4 mRNA measurement is decreased by about 10% or more, relative to the baseline ANGPTL4 mRNA measurement. In some embodiments, the ANGPTL4 mRNA measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, relative to the baseline ANGPTL4 mRNA measurement. In some embodiments, the ANGPTL4 mRNA measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline ANGPTL4 mRNA measurement. In some embodiments, the ANGPTL4 mRNA measurement is decreased by no more than about 10%, relative to the baseline ANGPTL4 mRNA measurement. In some embodiments, the ANGPTL4 mRNA measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline ANGPTL4 mRNA measurement. In some embodiments, the ANGPTL4 mRNA measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or by a range defined by any of the two aforementioned percentages.

III. DEFINITIONS

[0277] Unless defined otherwise, all terms of art, notations and other technical and scientific terms or terminology used herein are intended to have the same meaning as is commonly understood by one of ordinary skill in the art to which the claimed subject matter pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art.

[0278] Throughout this application, various embodiments may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosure. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual

numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[0279] As used in the specification and claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a sample" includes a plurality of samples, including mixtures thereof.

[0280] The terms "determining," "measuring," "evaluating," "assessing," "assaying," and "analyzing" are often used interchangeably herein to refer to forms of measurement. The terms include determining if an element is present or not (for example, detection). These terms can include quantitative, qualitative or quantitative and qualitative determinations. Assessing can be relative or absolute. "Detecting the presence of" can include determining the amount of something present in addition to determining whether it is present or absent depending on the context.

[0281] The terms "subject," and "patient" may be used interchangeably herein. A "subject" can be a biological entity containing expressed genetic materials. The biological entity can be a plant, animal, or microorganism, including, for example, bacteria, viruses, fungi, and protozoa. The subject can be a mammal. The mammal can be a human. The subject may be diagnosed or suspected of being at high risk for a disease. In some cases, the subject is not necessarily diagnosed or suspected of being at high risk for the disease.

[0282] As used herein, the term "about" a number refers to that number plus or minus 10% of that number. The term "about" a range refers to that range minus 10% of its lowest value and plus 10% of its greatest value.

[0283] As used herein, the terms "treatment" or "treating" are used in reference to a pharmaceutical or other intervention regimen for obtaining beneficial or desired results in the recipient. Beneficial or desired results include but are not limited to a therapeutic benefit and/or a prophylactic benefit. A therapeutic benefit may refer to eradication or amelioration of symptoms or of an underlying disorder being treated. Also, a therapeutic benefit can be achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. A prophylactic effect includes delaying, preventing, or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof. For prophylactic benefit, a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease may undergo treatment, even though a diagnosis of this disease may not have been made.

[0284] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

IV. SEQUENCE INFORMATION

[0285] Some embodiments include one or more nucleic acid sequences in the following tables:

Table 1.1 Sequence Information

SEQ ID NO:	Description of Examples
1-1854	ANGPTL4 siRNA oligonucleotide sense strand sequences
1855-3708	ANGPTL4 siRNA oligonucleotide antisense strand sequences
3709-13934	ANGPTL4 ASO sequences
13935	Full-length human ANGPTL4 human mRNA sequence (GenBank Acc.# NM_139314.3)
13936	Full-length ANGPTL4 human pre-mRNA sequence (NC_000019.10: 8364129-8374373)
13937-13944	Sequences for siRNA sense strands targeting mouse ANGPTL4
13945-13952	Sequences for siRNA antisense strands targeting mouse ANGPTL4
13953	Non-targeting control ASO oligonucleotide sequence
13954-13959	Modification pattern 1S to 6S
13960-13968	Modification pattern 1AS to 9AS
13969	Modification pattern ASO1
13970-13977	ANGPTL4 siRNA oligonucleotide sense strand sequences
13978-13985	ANGPTL4 siRNA oligonucleotide antisense strand sequences
13986-14133	Modified ANGPTL4 siRNA oligonucleotide sense strand sequences
14134-14288	Modified ANGPTL4 siRNA oligonucleotide antisense strand sequences
14289-14290	ETD00971 sense and antisense strands
14291-14292	ETD00959 sense and antisense strands
14293-14295	Modification pattern 7S to 9S
14296-14297	Modification pattern 10AS and 11AS
14298	Modified ANGPTL4 siRNA antisense strand sequence example
14299	Modified ANGPTL4 siRNA sense strand sequence example
14300-14303	Modified ANGPTL4 siRNA sense strand sequence examples
14304-14307	Modified ANGPTL4 siRNA antisense strand sequence examples
14308-14314	Modified ANGPTL4 siRNA sense strand sequence examples
14315-14321	Modified ANGPTL4 siRNA antisense strand sequence examples
14322-14328	Modification pattern 10S to 16S
14329-14332	Modification pattern 12AS and 15AS

Table 1.2 Sequences

SEQ ID NO:	Sequence (5' to 3')	SEQ ID NO:	Sequence (5' to 3')
1	AGAAGCCGAGCUGAGCGGA	15	GCGGAUCCUCACACGACUG
2	GAAGCCGAGCUGAGCGGAU	16	CGGAUCCUCACACGACUGU
3	AAGCCGAGCUGAGCGGAUC	17	GGAUCCUCACACGACUGUG
4	AGCCGAGCUGAGCGGAUCC	18	GAUCCUCACACGACUGUGA
5	GCCGAGCUGAGCGGAUCCU	19	AUCCUCACACGACUGUGAU
6	CCGAGCUGAGCGGAUCCUC	20	UCCUCACACGACUGUGAUC
7	CGAGCUGAGCGGAUCCUCA	21	CCUCACACGACUGUGAUCC
8	GAGCUGAGCGGAUCCUCAC	22	CUCACACGACUGUGAUCCG
9	AGCUGAGCGGAUCCUCACA	23	UCACACGACUGUGAUCCGA
10	GCUGAGCGGAUCCUCACAC	24	CACACGACUGUGAUCCGAU
11	CUGAGCGGAUCCUCACACG	25	ACACGACUGUGAUCCGAUU
12	UGAGCGGAUCCUCACACGA	26	CACGACUGUGAUCCGAUUC
13	GAGCGGAUCCUCACACGAC	27	ACGACUGUGAUCCGAUUCU
14	AGCGGAUCCUCACACGACU	28	CGACUGUGAUCCGAUUCUU
		29	GACUGUGAUCCGAUUCUUU
		30	ACUGUGAUCCGAUUCUUUC

31	CUGUGAUCCGAUUCUUUCC	97	CCAGUCCUCGCACCUGGAA
32	UGUGAUCCGAUUCUUUCCA	98	CAGUCCUCGCACCUGGAAC
33	GUGAUCCGAUUCUUUCCAG	99	AGUCCUCGCACCUGGAACC
34	UGAUCCGAUUCUUUCCAGC	100	GUCCUCGCACCUGGAACCC
35	GAUCCGAUUCUUUCCAGCG	101	UCCUCGCACCUGGAACCCC
36	AUCCGAUUCUUUCCAGCGG	102	CCUCGCACCUGGAACCCCA
37	UCCGAUUCUUUCCAGCGGC	103	CUCGCACCUGGAACCCCAA
38	CCGAUUCUUUCCAGCGGCU	104	UCGCACCUGGAACCCCAAC
39	CGAUUCUUUCCAGCGGCUU	105	CGCACCUGGAACCCCAACG
40	GAUUCUUUCCAGCGGCUUC	106	GCACCUGGAACCCCAACGU
41	AUUCUUUCCAGCGGCUUCU	107	CACCUGGAACCCCAACGUC
42	UUCUUUCCAGCGGCUUCUG	108	ACCUGGAACCCCAACGUCC
43	UCUUUCCAGCGGCUUCUGC	109	CCUGGAACCCCAACGUCCC
44	CUUUCCAGCGGCUUCUGCA	110	CUGGAACCCCAACGUCCCC
45	UUUCCAGCGGCUUCUGCAA	111	UGGAACCCCAACGUCCCCG
46	UUCCAGCGGCUUCUGCAAC	112	GGAACCCCAACGUCCCCGA
47	UCCAGCGGCUUCUGCAACC	113	GAACCCCAACGUCCCCGAG
48	CCAGCGGCUUCUGCAACCA	114	AACCCCAACGUCCCCGAGA
49	CAGCGGCUUCUGCAACCAA	115	ACCCCAACGUCCCCGAGAG
50	AGCGGCUUCUGCAACCAAG	116	CCCCAACGUCCCCGAGAGU
51	GCGGCUUCUGCAACCAAGC	117	CCCAACGUCCCCGAGAGUC
52	CGGCUUCUGCAACCAAGCG	118	CCAACGUCCCCGAGAGUCC
53	GGCUUCUGCAACCAAGCGG	119	CAACGUCCCCGAGAGUCCC
54	GCUUCUGCAACCAAGCGGG	120	AACGUCCCCGAGAGUCCCC
55	CUUCUGCAACCAAGCGGGU	121	ACGUCCCCGAGAGUCCCCG
56	UUCUGCAACCAAGCGGGUC	122	CGUCCCCGAGAGUCCCCGA
57	UCUGCAACCAAGCGGGUCU	123	GUCCCCGAGAGUCCCCGAA
58	CUGCAACCAAGCGGGUCUU	124	UCCCCGAGAGUCCCCGAAU
59	UGCAACCAAGCGGGUCUUA	125	CCCCGAGAGUCCCCGAAUC
60	GCAACCAAGCGGGUCUUAC	126	CCCGAGAGUCCCCGAAUCC
61	CAACCAAGCGGGUCUUACC	127	CCGAGAGUCCCCGAAUCCC
62	AACCAAGCGGGUCUUACCC	128	CGAGAGUCCCCGAAUCCCC
63	ACCAAGCGGGUCUUACCCC	129	GAGAGUCCCCGAAUCCCCG
64	CCAAGCGGGUCUUACCCCC	130	AGAGUCCCCGAAUCCCCGC
65	CAAGCGGGUCUUACCCCCG	131	GAGUCCCCGAAUCCCCGCU
66	AAGCGGGUCUUACCCCCGG	132	AGUCCCCGAAUCCCCGCUC
67	AGCGGGUCUUACCCCCGGU	133	GUCCCCGAAUCCCCGCUCC
68	GCGGGUCUUACCCCCGGUC	134	UCCCCGAAUCCCCGCUCCC
69	CGGGUCUUACCCCCGGUCC	135	CCCCGAAUCCCCGCUCCCA
70	GGGUCUUACCCCCGGUCCU	136	CCCGAAUCCCCGCUCCCAG
71	GGUCUUACCCCCGGUCCUC	137	CCGAAUCCCCGCUCCCAGG
72	GUCUUACCCCCGGUCCUCC	138	CGAAUCCCCGCUCCCAGGC
73	UCUUACCCCCGGUCCUCCG	139	GAAUCCCCGCUCCCAGGCU
74	CUUACCCCCGGUCCUCCGC	140	AAUCCCCGCUCCCAGGCUA
75	UUACCCCCGGUCCUCCGCG	141	AUCCCCGCUCCCAGGCUAC
76	UACCCCCGGUCCUCCGCGU	142	UCCCCGCUCCCAGGCUACC
77	ACCCCCGGUCCUCCGCGUC	143	CCCCGCUCCCAGGCUACCU
78	CCCCCGGUCCUCCGCGUCU	144	CCCGCUCCCAGGCUACCUA
79	CCCCGGUCCUCCGCGUCUC	145	CCGCUCCCAGGCUACCUAA
80	CCCGGUCCUCCGCGUCUCC	146	CGCUCCCAGGCUACCUAAG
81	CCGGUCCUCCGCGUCUCCA	147	GCUCCCAGGCUACCUAAGA
82	CGGUCCUCCGCGUCUCCAG	148	CUCCCAGGCUACCUAAGAG
83	GGUCCUCCGCGUCUCCAGU	149	UCCCAGGCUACCUAAGAGG
84	GUCCUCCGCGUCUCCAGUC	150	CCCAGGCUACCUAAGAGGA
85	UCCUCCGCGUCUCCAGUCC	151	CCAGGCUACCUAAGAGGAU
86	CCUCCGCGUCUCCAGUCCU	152	CAGGCUACCUAAGAGGAUG
87	CUCCGCGUCUCCAGUCCUC	153	AGGCUACCUAAGAGGAUGA
88	UCCGCGUCUCCAGUCCUCG	154	GGCUACCUAAGAGGAUGAG
89	CCGCGUCUCCAGUCCUCGC	155	GCUACCUAAGAGGAUGAGC
90	CGCGUCUCCAGUCCUCGCA	156	CUACCUAAGAGGAUGAGCG
91	GCGUCUCCAGUCCUCGCAC	157	UACCUAAGAGGAUGAGCGG
92	CGUCUCCAGUCCUCGCACC	158	ACCUAAGAGGAUGAGCGGU
93	GUCUCCAGUCCUCGCACCU	159	CCUAAGAGGAUGAGCGGUG
94	UCUCCAGUCCUCGCACCUG	160	CUAAGAGGAUGAGCGGUGC
95	CUCCAGUCCUCGCACCUGG	161	UAAGAGGAUGAGCGGUGCU
96	UCCAGUCCUCGCACCUGGA	162	AAGAGGAUGAGCGGUGCUC

163	AGAGGAUGAGCGGUGCUCC	229	UGAGCGCUCAGGGCGGACC
164	GAGGAUGAGCGGUGCUCCG	230	GAGCGCUCAGGGCGGACCC
165	AGGAUGAGCGGUGCUCCGA	231	AGCGCUCAGGGCGGACCCG
166	GGAUGAGCGGUGCUCCGAC	232	GCGCUCAGGGCGGACCCGU
167	GAUGAGCGGUGCUCCGACG	233	CGCUCAGGGCGGACCCGUG
168	AUGAGCGGUGCUCCGACGG	234	GCUCAGGGCGGACCCGUGC
169	UGAGCGGUGCUCCGACGGC	235	CUCAGGGCGGACCCGUGCA
170	GAGCGGUGCUCCGACGGCC	236	UCAGGGCGGACCCGUGCAG
171	AGCGGUGCUCCGACGGCCG	237	CAGGGCGGACCCGUGCAGU
172	GCGGUGCUCCGACGGCCGG	238	AGGGCGGACCCGUGCAGUC
173	CGGUGCUCCGACGGCCGGG	239	GGGCGGACCCGUGCAGUCC
174	GGUGCUCCGACGGCCGGGG	240	GGCGGACCCGUGCAGUCCA
175	GUGCUCCGACGGCCGGGGC	241	GCGGACCCGUGCAGUCCAA
176	UGCUCCGACGGCCGGGGCA	242	CGGACCCGUGCAGUCCAAG
177	GCUCCGACGGCCGGGGCAG	243	GGACCCGUGCAGUCCAAGU
178	CUCCGACGGCCGGGGCAGC	244	GACCCGUGCAGUCCAAGUC
179	UCCGACGGCCGGGGCAGCC	245	ACCCGUGCAGUCCAAGUCG
180	CCGACGGCCGGGGCAGCCC	246	CCCGUGCAGUCCAAGUCGC
181	CGACGGCCGGGGCAGCCCU	247	CCGUGCAGUCCAAGUCGCC
182	GACGGCCGGGGCAGCCCUG	248	CGUGCAGUCCAAGUCGCCG
183	ACGGCCGGGGCAGCCCUGA	249	GUGCAGUCCAAGUCGCCGC
184	CGGCCGGGGCAGCCCUGAU	250	UGCAGUCCAAGUCGCCGCG
185	GGCCGGGGCAGCCCUGAUG	251	GCAGUCCAAGUCGCCGCGC
186	GCCGGGGCAGCCCUGAUGC	252	CAGUCCAAGUCGCCGCGCU
187	CCGGGGCAGCCCUGAUGCU	253	AGUCCAAGUCGCCGCGCUU
188	CGGGGCAGCCCUGAUGCUC	254	GUCCAAGUCGCCGCGCUUU
189	GGGGCAGCCCUGAUGCUCU	255	UCCAAGUCGCCGCGCUUUG
190	GGGCAGCCCUGAUGCUCUG	256	CCAAGUCGCCGCGCUUUGC
191	GGCAGCCCUGAUGCUCUGC	257	CAAGUCGCCGCGCUUUGCG
192	GCAGCCCUGAUGCUCUGCG	258	AAGUCGCCGCGCUUUGCGU
193	CAGCCCUGAUGCUCUGCGC	259	AGUCGCCGCGCUUUGCGUC
194	AGCCCUGAUGCUCUGCGCC	260	GUCGCCGCGCUUUGCGUCC
195	GCCCUGAUGCUCUGCGCCG	261	UCGCCGCGCUUUGCGUCCU
196	CCCUGAUGCUCUGCGCCGC	262	CGCCGCGCUUUGCGUCCUG
197	CCUGAUGCUCUGCGCCGCC	263	GCCGCGCUUUGCGUCCUGG
198	CUGAUGCUCUGCGCCGCCA	264	CCGCGCUUUGCGUCCUGGG
199	UGAUGCUCUGCGCCGCCAC	265	CGCGCUUUGCGUCCUGGGA
200	GAUGCUCUGCGCCGCCACC	266	GCGCUUUGCGUCCUGGGAC
201	AUGCUCUGCGCCGCCACCG	267	CGCUUUGCGUCCUGGGACG
202	UGCUCUGCGCCGCCACCGC	268	GCUUUGCGUCCUGGGACGA
203	GCUCUGCGCCGCCACCGCC	269	CUUUGCGUCCUGGGACGAG
204	CUCUGCGCCGCCACCGCCG	270	UUUGCGUCCUGGGACGAGA
205	UCUGCGCCGCCACCGCCGU	271	UUGCGUCCUGGGACGAGAU
206	CUGCGCCGCCACCGCCGUG	272	UGCGUCCUGGGACGAGAUG
207	UGCGCCGCCACCGCCGUGC	273	GCGUCCUGGGACGAGAUGA
208	GCGCCGCCACCGCCGUGCU	274	CGUCCUGGGACGAGAUGAA
209	CGCCGCCACCGCCGUGCUA	275	GUCCUGGGACGAGAUGAAU
210	GCCGCCACCGCCGUGCUAC	276	UCCUGGGACGAGAUGAAUG
211	CCGCCACCGCCGUGCUACU	277	CCUGGGACGAGAUGAAUGU
212	CGCCACCGCCGUGCUACUG	278	CUGGGACGAGAUGAAUGUC
213	GCCACCGCCGUGCUACUGA	279	UGGGACGAGAUGAAUGUCC
214	CCACCGCCGUGCUACUGAG	280	GGGACGAGAUGAAUGUCCU
215	CACCGCCGUGCUACUGAGC	281	GGACGAGAUGAAUGUCCUG
216	ACCGCCGUGCUACUGAGCG	282	GACGAGAUGAAUGUCCUGG
217	CCGCCGUGCUACUGAGCGC	283	ACGAGAUGAAUGUCCUGGC
218	CGCCGUGCUACUGAGCGCU	284	CGAGAUGAAUGUCCUGGCG
219	GCCGUGCUACUGAGCGCUC	285	GAGAUGAAUGUCCUGGCGC
220	CCGUGCUACUGAGCGCUCA	286	AGAUGAAUGUCCUGGCGCA
221	CGUGCUACUGAGCGCUCAG	287	GAUGAAUGUCCUGGCGCAC
222	GUGCUACUGAGCGCUCAGG	288	AUGAAUGUCCUGGCGCACG
223	UGCUACUGAGCGCUCAGGG	289	UGAAUGUCCUGGCGCACGG
224	GCUACUGAGCGCUCAGGGC	290	GAAUGUCCUGGCGCACGGA
225	CUACUGAGCGCUCAGGGCG	291	AAUGUCCUGGCGCACGGAC
226	UACUGAGCGCUCAGGGCGG	292	AUGUCCUGGCGCACGGACU
227	ACUGAGCGCUCAGGGCGGA	293	UGUCCUGGCGCACGGACUC
228	CUGAGCGCUCAGGGCGGAC	294	GUCCUGGCGCACGGACUCC

295	UCCUGGCGCACGGACUCCU	361	AGCUGAGCGCGCUGGAGCG
296	CCUGGCGCACGGACUCCUG	362	GCUGAGCGCGCUGGAGCGG
297	CUGGCGCACGGACUCCUGC	363	CUGAGCGCGCUGGAGCGGC
298	UGGCGCACGGACUCCUGCA	364	UGAGCGCGCUGGAGCGGCG
299	GGCGCACGGACUCCUGCAG	365	GAGCGCGCUGGAGCGGCGC
300	GCGCACGGACUCCUGCAGC	366	AGCGCGCUGGAGCGGCGCC
301	CGCACGGACUCCUGCAGCU	367	GCGCGCUGGAGCGGCGCCU
302	GCACGGACUCCUGCAGCUC	368	CGCGCUGGAGCGGCGCCUG
303	CACGGACUCCUGCAGCUCG	369	GCGCUGGAGCGGCGCCUGA
304	ACGGACUCCUGCAGCUCGG	370	CGCUGGAGCGGCGCCUGAG
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306	GGACUCCUGCAGCUCGGCC	372	CUGGAGCGGCGCCUGAGCG
307	GACUCCUGCAGCUCGGCCA	373	UGGAGCGGCGCCUGAGCGC
308	ACUCCUGCAGCUCGGCCAG	374	GGAGCGGCGCCUGAGCGCG
309	CUCCUGCAGCUCGGCCAGG	375	GAGCGGCGCCUGAGCGCGU
310	UCCUGCAGCUCGGCCAGGG	376	AGCGGCGCCUGAGCGCGUG
311	CCUGCAGCUCGGCCAGGGG	377	GCGGCGCCUGAGCGCGUGC
312	CUGCAGCUCGGCCAGGGGC	378	CGGCGCCUGAGCGCGUGCG
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314	GCAGCUCGGCCAGGGGCUG	380	GCGCCUGAGCGCGUGCGGG
315	CAGCUCGGCCAGGGGCUGC	381	CGCCUGAGCGCGUGCGGGU
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317	GCUCGGCCAGGGGCUGCGC	383	CCUGAGCGCGUGCGGGUCC
318	CUCGGCCAGGGGCUGCGCG	384	CUGAGCGCGUGCGGGUCCG
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321	GGCCAGGGGCUGCGCGAAC	387	AGCGCGUGCGGGUCCGCCU
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331	UGCGCGAACACGCGGAGCG	397	GGUCCGCCUGUCAGGGAAC
332	GCGCGAACACGCGGAGCGC	398	GUCCGCCUGUCAGGGAACC
333	CGCGAACACGCGGAGCGCA	399	UCCGCCUGUCAGGGAACCG
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335	CGAACACGCGGAGCGCACC	401	CGCCUGUCAGGGAACCGAG
336	GAACACGCGGAGCGCACCC	402	GCCUGUCAGGGAACCGAGG
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349	GCACCCGCAGUCAGCUGAG	415	CCGAGGGGUCCACCGACCU
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352	CCCGCAGUCAGCUGAGCGC	418	AGGGGUCCACCGACCUCCC
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357	AGUCAGCUGAGCGCGCUGG	423	UCCACCGACCUCCCGUUAG
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432	CUCCCGUUAGCCCCUGAGA	498	GCUCAGAACAGCAGGAUCC
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851	GAGGCGCCACGAUGGCUCA	917	UCCCCACGGCGAGUUCUGG
852	AGGCGCCACGAUGGCUCAG	918	CCCCACGGCGAGUUCUGGC
853	GGCGCCACGAUGGCUCAGU	919	CCCACGGCGAGUUCUGGCU
854	GCGCCACGAUGGCUCAGUG	920	CCACGGCGAGUUCUGGCUG
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856	GCCACGAUGGCUCAGUGGA	922	ACGGCGAGUUCUGGCUGGG
857	CCACGAUGGCUCAGUGGAC	923	CGGCGAGUUCUGGCUGGGU
858	CACGAUGGCUCAGUGGACU	924	GGCGAGUUCUGGCUGGGUC
859	ACGAUGGCUCAGUGGACUU	925	GCGAGUUCUGGCUGGGUCU
860	CGAUGGCUCAGUGGACUUC	926	CGAGUUCUGGCUGGGUCUG
861	GAUGGCUCAGUGGACUUCA	927	GAGUUCUGGCUGGGUCUGG
862	AUGGCUCAGUGGACUUCAA	928	AGUUCUGGCUGGGUCUGGA
863	UGGCUCAGUGGACUUCAAC	929	GUUCUGGCUGGGUCUGGAG
864	GGCUCAGUGGACUUCAACC	930	UUCUGGCUGGGUCUGGAGA
865	GCUCAGUGGACUUCAACCG	931	UCUGGCUGGGUCUGGAGAA
866	CUCAGUGGACUUCAACCGG	932	CUGGCUGGGUCUGGAGAAG
867	UCAGUGGACUUCAACCGGC	933	UGGCUGGGUCUGGAGAAGG
868	CAGUGGACUUCAACCGGCC	934	GGCUGGGUCUGGAGAAGGU
869	AGUGGACUUCAACCGGCCC	935	GCUGGGUCUGGAGAAGGUG
870	GUGGACUUCAACCGGCCCU	936	CUGGGUCUGGAGAAGGUGC
871	UGGACUUCAACCGGCCCUG	937	UGGGUCUGGAGAAGGUGCA
872	GGACUUCAACCGGCCCUGG	938	GGGUCUGGAGAAGGUGCAU
873	GACUUCAACCGGCCCUGGG	939	GGUCUGGAGAAGGUGCAUA
874	ACUUCAACCGGCCCUGGGA	940	GUCUGGAGAAGGUGCAUAG
875	CUUCAACCGGCCCUGGGAA	941	UCUGGAGAAGGUGCAUAGC
876	UUCAACCGGCCCUGGGAAG	942	CUGGAGAAGGUGCAUAGCA
877	UCAACCGGCCCUGGGAAGC	943	UGGAGAAGGUGCAUAGCAU
878	CAACCGGCCCUGGGAAGCC	944	GGAGAAGGUGCAUAGCAUC
879	AACCGGCCCUGGGAAGCCU	945	GAGAAGGUGCAUAGCAUCA
880	ACCGGCCCUGGGAAGCCUA	946	AGAAGGUGCAUAGCAUCAC
881	CCGGCCCUGGGAAGCCUAC	947	GAAGGUGCAUAGCAUCACG
882	CGGCCCUGGGAAGCCUACA	948	AAGGUGCAUAGCAUCACGG
883	GGCCCUGGGAAGCCUACAA	949	AGGUGCAUAGCAUCACGGG
884	GCCCUGGGAAGCCUACAAG	950	GGUGCAUAGCAUCACGGGG
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886	CCUGGGAAGCCUACAAGGC	952	UGCAUAGCAUCACGGGGGA
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955	AUAGCAUCACGGGGGACCG	1021	AGUUGCUGCAGUUCUCCGU
956	UAGCAUCACGGGGGACCGC	1022	GUUGCUGCAGUUCUCCGUG
957	AGCAUCACGGGGGACCGCA	1023	UUGCUGCAGUUCUCCGUGC
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959	CAUCACGGGGGACCGCAAC	1025	GCUGCAGUUCUCCGUGCAC
960	AUCACGGGGGACCGCAACA	1026	CUGCAGUUCUCCGUGCACC
961	UCACGGGGGACCGCAACAG	1027	UGCAGUUCUCCGUGCACCU
962	CACGGGGGACCGCAACAGC	1028	GCAGUUCUCCGUGCACCUG
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1002	GACUGGGAUGGCAACGCCG	1068	AGCCUGCAGCUCACUGCAC
1003	ACUGGGAUGGCAACGCCGA	1069	GCCUGCAGCUCACUGCACC
1004	CUGGGAUGGCAACGCCGAG	1070	CCUGCAGCUCACUGCACCC
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1006	GGGAUGGCAACGCCGAGUU	1072	UGCAGCUCACUGCACCCGU
1007	GGAUGGCAACGCCGAGUUG	1073	GCAGCUCACUGCACCCGUG
1008	GAUGGCAACGCCGAGUUGC	1074	CAGCUCACUGCACCCGUGG
1009	AUGGCAACGCCGAGUUGCU	1075	AGCUCACUGCACCCGUGGC
1010	UGGCAACGCCGAGUUGCUG	1076	GCUCACUGCACCCGUGGCC
1011	GGCAACGCCGAGUUGCUGC	1077	CUCACUGCACCCGUGGCCG
1012	GCAACGCCGAGUUGCUGCA	1078	UCACUGCACCCGUGGCCGG
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1014	AACGCCGAGUUGCUGCAGU	1080	ACUGCACCCGUGGCCGGCC
1015	ACGCCGAGUUGCUGCAGUU	1081	CUGCACCCGUGGCCGGCCA
1016	CGCCGAGUUGCUGCAGUUC	1082	UGCACCCGUGGCCGGCCAG
1017	GCCGAGUUGCUGCAGUUCU	1083	GCACCCGUGGCCGGCCAGC
1018	CCGAGUUGCUGCAGUUCUC	1084	CACCCGUGGCCGGCCAGCU
1019	CGAGUUGCUGCAGUUCUCC	1085	ACCCGUGGCCGGCCAGCUG
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1087	CCGUGGCCGGCCAGCUGGG	1153	GGGACCAGGAUCACGACCU
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1090	UGGCCGGCCAGCUGGGCGC	1156	ACCAGGAUCACGACCUCCG
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1092	GCCGGCCAGCUGGGCGCCA	1158	CAGGAUCACGACCUCCGCA
1093	CCGGCCAGCUGGGCGCCAC	1159	AGGAUCACGACCUCCGCAG
1094	CGGCCAGCUGGGCGCCACC	1160	GGAUCACGACCUCCGCAGG
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1106	CGCCACCACCGUCCCACCC	1172	CCGCAGGGACAAGAACUGC
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1398	UGGGCCUGGUCCCAGGCCC	1464	UGCCUGGGCAGGGGCUCCA
1399	GGGCCUGGUCCCAGGCCCA	1465	GCCUGGGCAGGGGCUCCAA
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1401	GCCUGGUCCCAGGCCCACG	1467	CUGGGCAGGGGCUCCAAGG
1402	CCUGGUCCCAGGCCCACGA	1468	UGGGCAGGGGCUCCAAGGA
1403	CUGGUCCCAGGCCCACGAA	1469	GGGCAGGGGCUCCAAGGAG
1404	UGGUCCCAGGCCCACGAAA	1470	GGCAGGGGCUCCAAGGAGG
1405	GGUCCCAGGCCCACGAAAG	1471	GCAGGGGCUCCAAGGAGGG
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1408	CCCAGGCCCACGAAAGACG	1474	GGGGCUCCAAGGAGGGGCC
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1410	CAGGCCCACGAAAGACGGU	1476	GGCUCCAAGGAGGGGCCAU
1411	AGGCCCACGAAAGACGGUG	1477	GCUCCAAGGAGGGGCCAUC
1412	GGCCCACGAAAGACGGUGA	1478	CUCCAAGGAGGGGCCAUCU
1413	GCCCACGAAAGACGGUGAC	1479	UCCAAGGAGGGGCCAUCUG
1414	CCCACGAAAGACGGUGACU	1480	CCAAGGAGGGGCCAUCUGG
1415	CCACGAAAGACGGUGACUC	1481	CAAGGAGGGGCCAUCUGGA
1416	CACGAAAGACGGUGACUCU	1482	AAGGAGGGGCCAUCUGGAA

1483	AGGAGGGGCCAUCUGGAAA	1549	GUGCAGGGGGGCUGCAUGC
1484	GGAGGGGCCAUCUGGAAAC	1550	UGCAGGGGGGCUGCAUGCG
1485	GAGGGGCCAUCUGGAAACU	1551	GCAGGGGGGCUGCAUGCGU
1486	AGGGGCCAUCUGGAAACUU	1552	CAGGGGGGCUGCAUGCGUU
1487	GGGGCCAUCUGGAAACUUG	1553	AGGGGGGCUGCAUGCGUUG
1488	GGGCCAUCUGGAAACUUGU	1554	GGGGGGCUGCAUGCGUUGC
1489	GGCCAUCUGGAAACUUGUG	1555	GGGGGCUGCAUGCGUUGCC
1490	GCCAUCUGGAAACUUGUGG	1556	GGGGCUGCAUGCGUUGCCU
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1492	CAUCUGGAAACUUGUGGAC	1558	GGCUGCAUGCGUUGCCUCC
1493	AUCUGGAAACUUGUGGACA	1559	GCUGCAUGCGUUGCCUCCU
1494	UCUGGAAACUUGUGGACAG	1560	CUGCAUGCGUUGCCUCCUG
1495	CUGGAAACUUGUGGACAGA	1561	UGCAUGCGUUGCCUCCUGA
1496	UGGAAACUUGUGGACAGAG	1562	GCAUGCGUUGCCUCCUGAG
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1943	GCGAGGACUGGAGACGCGG	2009	GCUCAUCCUCUUAGGUAGC
1944	UGCGAGGACUGGAGACGCG	2010	CGCUCAUCCUCUUAGGUAG

2011	CCGCUCAUCCUCUUAGGUA	2077	CCCUGAGCGCUCAGUAGCA
2012	ACCGCUCAUCCUCUUAGGU	2078	GCCCUGAGCGCUCAGUAGC
2013	CACCGCUCAUCCUCUUAGG	2079	CGCCCUGAGCGCUCAGUAG
2014	GCACCGCUCAUCCUCUUAG	2080	CCGCCCUGAGCGCUCAGUA
2015	AGCACCGCUCAUCCUCUUA	2081	UCCGCCCUGAGCGCUCAGU
2016	GAGCACCGCUCAUCCUCUU	2082	GUCCGCCCUGAGCGCUCAG
2017	GGAGCACCGCUCAUCCUCU	2083	GGUCCGCCCUGAGCGCUCA
2018	CGGAGCACCGCUCAUCCUC	2084	GGGUCCGCCCUGAGCGCUC
2019	UCGGAGCACCGCUCAUCCU	2085	CGGGUCCGCCCUGAGCGCU
2020	GUCGGAGCACCGCUCAUCC	2086	ACGGGUCCGCCCUGAGCGC
2021	CGUCGGAGCACCGCUCAUC	2087	CACGGGUCCGCCCUGAGCG
2022	CCGUCGGAGCACCGCUCAU	2088	GCACGGGUCCGCCCUGAGC
2023	GCCGUCGGAGCACCGCUCA	2089	UGCACGGGUCCGCCCUGAG
2024	GGCCGUCGGAGCACCGCUC	2090	CUGCACGGGUCCGCCCUGA
2025	CGGCCGUCGGAGCACCGCU	2091	ACUGCACGGGUCCGCCCUG
2026	CCGGCCGUCGGAGCACCGC	2092	GACUGCACGGGUCCGCCCU
2027	CCCGGCCGUCGGAGCACCG	2093	GGACUGCACGGGUCCGCCC
2028	CCCCGGCCGUCGGAGCACC	2094	UGGACUGCACGGGUCCGCC
2029	GCCCCGGCCGUCGGAGCAC	2095	UUGGACUGCACGGGUCCGC
2030	UGCCCCGGCCGUCGGAGCA	2096	CUUGGACUGCACGGGUCCG
2031	CUGCCCCGGCCGUCGGAGC	2097	ACUUGGACUGCACGGGUCC
2032	GCUGCCCCGGCCGUCGGAG	2098	GACUUGGACUGCACGGGUC
2033	GGCUGCCCCGGCCGUCGGA	2099	CGACUUGGACUGCACGGGU
2034	GGGCUGCCCCGGCCGUCGG	2100	GCGACUUGGACUGCACGGG
2035	AGGGCUGCCCCGGCCGUCG	2101	GGCGACUUGGACUGCACGG
2036	CAGGGCUGCCCCGGCCGUC	2102	CGGCGACUUGGACUGCACG
2037	UCAGGGCUGCCCCGGCCGU	2103	GCGGCGACUUGGACUGCAC
2038	AUCAGGGCUGCCCCGGCCG	2104	CGCGGCGACUUGGACUGCA
2039	CAUCAGGGCUGCCCCGGCC	2105	GCGCGGCGACUUGGACUGC
2040	GCAUCAGGGCUGCCCCGGC	2106	AGCGCGGCGACUUGGACUG
2041	AGCAUCAGGGCUGCCCCGG	2107	AAGCGCGGCGACUUGGACU
2042	GAGCAUCAGGGCUGCCCCG	2108	AAAGCGCGGCGACUUGGAC
2043	AGAGCAUCAGGGCUGCCCC	2109	CAAAGCGCGGCGACUUGGA
2044	CAGAGCAUCAGGGCUGCCC	2110	GCAAAGCGCGGCGACUUGG
2045	GCAGAGCAUCAGGGCUGCC	2111	CGCAAAGCGCGGCGACUUG
2046	CGCAGAGCAUCAGGGCUGC	2112	ACGCAAAGCGCGGCGACUU
2047	GCGCAGAGCAUCAGGGCUG	2113	GACGCAAAGCGCGGCGACU
2048	GGCGCAGAGCAUCAGGGCU	2114	GGACGCAAAGCGCGGCGAC
2049	CGGCGCAGAGCAUCAGGGC	2115	AGGACGCAAAGCGCGGCGA
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2053	GUGGCGGCGCAGAGCAUCA	2119	UCCCAGGACGCAAAGCGCG
2054	GGUGGCGGCGCAGAGCAUC	2120	GUCCCAGGACGCAAAGCGC
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2056	GCGGUGGCGGCGCAGAGCA	2122	UCGUCCCAGGACGCAAAGC
2057	GGCGGUGGCGGCGCAGAGC	2123	CUCGUCCCAGGACGCAAAG
2058	CGGCGGUGGCGGCGCAGAG	2124	UCUCGUCCCAGGACGCAAA
2059	ACGGCGGUGGCGGCGCAGA	2125	AUCUCGUCCCAGGACGCAA
2060	CACGGCGGUGGCGGCGCAG	2126	CAUCUCGUCCCAGGACGCA
2061	GCACGGCGGUGGCGGCGCA	2127	UCAUCUCGUCCCAGGACGC
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2063	UAGCACGGCGGUGGCGGCG	2129	AUUCAUCUCGUCCCAGGAC
2064	GUAGCACGGCGGUGGCGGC	2130	CAUUCAUCUCGUCCCAGGA
2065	AGUAGCACGGCGGUGGCGG	2131	ACAUUCAUCUCGUCCCAGG
2066	CAGUAGCACGGCGGUGGCG	2132	GACAUUCAUCUCGUCCCAG
2067	UCAGUAGCACGGCGGUGGC	2133	GGACAUUCAUCUCGUCCCA
2068	CUCAGUAGCACGGCGGUGG	2134	AGGACAUUCAUCUCGUCCC
2069	GCUCAGUAGCACGGCGGUG	2135	CAGGACAUUCAUCUCGUCC
2070	CGCUCAGUAGCACGGCGGU	2136	CCAGGACAUUCAUCUCGUC
2071	GCGCUCAGUAGCACGGCGG	2137	GCCAGGACAUUCAUCUCGU
2072	AGCGCUCAGUAGCACGGCG	2138	CGCCAGGACAUUCAUCUCG
2073	GAGCGCUCAGUAGCACGGC	2139	GCGCCAGGACAUUCAUCUC
2074	UGAGCGCUCAGUAGCACGG	2140	UGCGCCAGGACAUUCAUCU
2075	CUGAGCGCUCAGUAGCACG	2141	GUGCGCCAGGACAUUCAUC
2076	CCUGAGCGCUCAGUAGCAC	2142	CGUGCGCCAGGACAUUCAU

2143	CCGUGCGCCAGGACAUUCA	2209	AGCGCGCUCAGCUGACUGC
2144	UCCGUGCGCCAGGACAUUC	2210	CAGCGCGCUCAGCUGACUG
2145	GUCCGUGCGCCAGGACAUU	2211	CCAGCGCGCUCAGCUGACU
2146	AGUCCGUGCGCCAGGACAU	2212	UCCAGCGCGCUCAGCUGAC
2147	GAGUCCGUGCGCCAGGACA	2213	CUCCAGCGCGCUCAGCUGA
2148	GGAGUCCGUGCGCCAGGAC	2214	GCUCCAGCGCGCUCAGCUG
2149	AGGAGUCCGUGCGCCAGGA	2215	CGCUCCAGCGCGCUCAGCU
2150	CAGGAGUCCGUGCGCCAGG	2216	CCGCUCCAGCGCGCUCAGC
2151	GCAGGAGUCCGUGCGCCAG	2217	GCCGCUCCAGCGCGCUCAG
2152	UGCAGGAGUCCGUGCGCCA	2218	CGCCGCUCCAGCGCGCUCA
2153	CUGCAGGAGUCCGUGCGCC	2219	GCGCCGCUCCAGCGCGCUC
2154	GCUGCAGGAGUCCGUGCGC	2220	GGCGCCGCUCCAGCGCGCU
2155	AGCUGCAGGAGUCCGUGCG	2221	AGGCGCCGCUCCAGCGCGC
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2157	CGAGCUGCAGGAGUCCGUG	2223	UCAGGCGCCGCUCCAGCGC
2158	CCGAGCUGCAGGAGUCCGU	2224	CUCAGGCGCCGCUCCAGCG
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2160	GGCCGAGCUGCAGGAGUCC	2226	CGCUCAGGCGCCGCUCCAG
2161	UGGCCGAGCUGCAGGAGUC	2227	GCGCUCAGGCGCCGCUCCA
2162	CUGGCCGAGCUGCAGGAGU	2228	CGCGCUCAGGCGCCGCUCC
2163	CCUGGCCGAGCUGCAGGAG	2229	ACGCGCUCAGGCGCCGCUC
2164	CCCUGGCCGAGCUGCAGGA	2230	CACGCGCUCAGGCGCCGCU
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2166	GCCCCUGGCCGAGCUGCAG	2232	CGCACGCGCUCAGGCGCCG
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2168	CAGCCCCUGGCCGAGCUGC	2234	CCCGCACGCGCUCAGGCGC
2169	GCAGCCCCUGGCCGAGCUG	2235	ACCCGCACGCGCUCAGGCG
2170	CGCAGCCCCUGGCCGAGCU	2236	GACCCGCACGCGCUCAGGC
2171	GCGCAGCCCCUGGCCGAGC	2237	GGACCCGCACGCGCUCAGG
2172	CGCGCAGCCCCUGGCCGAG	2238	CGGACCCGCACGCGCUCAG
2173	UCGCGCAGCCCCUGGCCGA	2239	GCGGACCCGCACGCGCUCA
2174	UUCGCGCAGCCCCUGGCCG	2240	GGCGGACCCGCACGCGCUC
2175	GUUCGCGCAGCCCCUGGCC	2241	AGGCGGACCCGCACGCGCU
2176	UGUUCGCGCAGCCCCUGGC	2242	CAGGCGGACCCGCACGCGC
2177	GUGUUCGCGCAGCCCCUGG	2243	ACAGGCGGACCCGCACGCG
2178	CGUGUUCGCGCAGCCCCUG	2244	GACAGGCGGACCCGCACGC
2179	GCGUGUUCGCGCAGCCCCU	2245	UGACAGGCGGACCCGCACG
2180	CGCGUGUUCGCGCAGCCCC	2246	CUGACAGGCGGACCCGCAC
2181	CCGCGUGUUCGCGCAGCCC	2247	CCUGACAGGCGGACCCGCA
2182	UCCGCGUGUUCGCGCAGCC	2248	CCCUGACAGGCGGACCCGC
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2184	GCUCCGCGUGUUCGCGCAG	2250	UUCCCUGACAGGCGGACCC
2185	CGCUCCGCGUGUUCGCGCA	2251	GUUCCCUGACAGGCGGACC
2186	GCGCUCCGCGUGUUCGCGC	2252	GGUUCCCUGACAGGCGGAC
2187	UGCGCUCCGCGUGUUCGCG	2253	CGGUUCCCUGACAGGCGGA
2188	GUGCGCUCCGCGUGUUCGC	2254	UCGGUUCCCUGACAGGCGG
2189	GGUGCGCUCCGCGUGUUCG	2255	CUCGGUUCCCUGACAGGCG
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2191	CGGGUGCGCUCCGCGUGUU	2257	CCCUCGGUUCCCUGACAGG
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2193	UGCGGGUGCGCUCCGCGUG	2259	ACCCCUCGGUUCCCUGACA
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2195	ACUGCGGGUGCGCUCCGCG	2261	GGACCCCUCGGUUCCCUGA
2196	GACUGCGGGUGCGCUCCGC	2262	UGGACCCCUCGGUUCCCUG
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2198	CUGACUGCGGGUGCGCUCC	2264	GGUGGACCCCUCGGUUCCC
2199	GCUGACUGCGGGUGCGCUC	2265	CGGUGGACCCCUCGGUUCC
2200	AGCUGACUGCGGGUGCGCU	2266	UCGGUGGACCCCUCGGUUC
2201	CAGCUGACUGCGGGUGCGC	2267	GUCGGUGGACCCCUCGGUU
2202	UCAGCUGACUGCGGGUGCG	2268	GGUCGGUGGACCCCUCGGU
2203	CUCAGCUGACUGCGGGUGC	2269	AGGUCGGUGGACCCCUCGG
2204	GCUCAGCUGACUGCGGGUG	2270	GAGGUCGGUGGACCCCUCG
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2206	GCGCUCAGCUGACUGCGGG	2272	GGGAGGUCGGUGGACCCCU
2207	CGCGCUCAGCUGACUGCGG	2273	CGGGAGGUCGGUGGACCCC
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2275	AACGGGAGGUCGGUGGACC	2341	UUCUGAGCCUUGAGUUGUG
2276	UAACGGGAGGUCGGUGGAC	2342	GUUCUGAGCCUUGAGUUGU
2277	CUAACGGGAGGUCGGUGGA	2343	UGUUCUGAGCCUUGAGUUG
2278	GCUAACGGGAGGUCGGUGG	2344	CUGUUCUGAGCCUUGAGUU
2279	GGCUAACGGGAGGUCGGUG	2345	GCUGUUCUGAGCCUUGAGU
2280	GGGCUAACGGGAGGUCGGU	2346	UGCUGUUCUGAGCCUUGAG
2281	GGGGCUAACGGGAGGUCGG	2347	CUGCUGUUCUGAGCCUUGA
2282	AGGGGCUAACGGGAGGUCG	2348	CCUGCUGUUCUGAGCCUUG
2283	CAGGGGCUAACGGGAGGUC	2349	UCCUGCUGUUCUGAGCCUU
2284	UCAGGGGCUAACGGGAGGU	2350	AUCCUGCUGUUCUGAGCCU
2285	CUCAGGGGCUAACGGGAGG	2351	GAUCCUGCUGUUCUGAGCC
2286	UCUCAGGGGCUAACGGGAG	2352	GGAUCCUGCUGUUCUGAGC
2287	CUCUCAGGGGCUAACGGGA	2353	UGGAUCCUGCUGUUCUGAG
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2290	CGGCUCUCAGGGGCUAACG	2356	UGCUGGAUCCUGCUGUUCU
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2293	ACCCGGCUCUCAGGGGCUA	2359	AGUUGCUGGAUCCUGCUGU
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2295	CCACCCGGCUCUCAGGGGC	2361	AGAGUUGCUGGAUCCUGCU
2296	UCCACCCGGCUCUCAGGGG	2362	AAGAGUUGCUGGAUCCUGC
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2301	CAGGGUCCACCCGGCUCUC	2367	UGUGGAAGAGUUGCUGGAU
2302	UCAGGGUCCACCCGGCUCU	2368	UUGUGGAAGAGUUGCUGGA
2303	CUCAGGGUCCACCCGGCUC	2369	CUUGUGGAAGAGUUGCUGG
2304	CCUCAGGGUCCACCCGGCU	2370	CCUUGUGGAAGAGUUGCUG
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2307	GGACCUCAGGGUCCACCCG	2373	CCACCUUGUGGAAGAGUUG
2308	AGGACCUCAGGGUCCACCC	2374	GCCACCUUGUGGAAGAGUU
2309	AAGGACCUCAGGGUCCACC	2375	GGCCACCUUGUGGAAGAGU
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2311	UGAAGGACCUCAGGGUCCA	2377	UGGGCCACCUUGUGGAAGA
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2315	GCUGUGAAGGACCUCAGGG	2381	CUGCUGGGCCACCUUGUGG
2316	GGCUGUGAAGGACCUCAGG	2382	GCUGCUGGGCCACCUUGUG
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2319	GCAGGCUGUGAAGGACCUC	2385	GCUGCUGCUGGGCCACCUU
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2321	CUGCAGGCUGUGAAGGACC	2387	CCGCUGCUGCUGGGCCACC
2322	UCUGCAGGCUGUGAAGGAC	2388	GCCGCUGCUGCUGGGCCAC
2323	GUCUGCAGGCUGUGAAGGA	2389	UGCCGCUGCUGCUGGGCCA
2324	UGUCUGCAGGCUGUGAAGG	2390	GUGCCGCUGCUGCUGGGCC
2325	GUGUCUGCAGGCUGUGAAG	2391	GGUGCCGCUGCUGCUGGGC
2326	UGUGUCUGCAGGCUGUGAA	2392	AGGUGCCGCUGCUGCUGGG
2327	UUGUGUCUGCAGGCUGUGA	2393	CAGGUGCCGCUGCUGCUGG
2328	GUUGUGUCUGCAGGCUGUG	2394	CCAGGUGCCGCUGCUGCUG
2329	AGUUGUGUCUGCAGGCUGU	2395	UCCAGGUGCCGCUGCUGCU
2330	GAGUUGUGUCUGCAGGCUG	2396	CUCCAGGUGCCGCUGCUGC
2331	UGAGUUGUGUCUGCAGGCU	2397	UCUCCAGGUGCCGCUGCUG
2332	UUGAGUUGUGUCUGCAGGC	2398	UUCUCCAGGUGCCGCUGCU
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2337	GAGCCUUGAGUUGUGUCUG	2403	GCUGCUUCUCCAGGUGCCG
2338	UGAGCCUUGAGUUGUGUCU	2404	UGCUGCUUCUCCAGGUGCC
2339	CUGAGCCUUGAGUUGUGUC	2405	GUGCUGCUUCUCCAGGUGC
2340	UCUGAGCCUUGAGUUGUGU	2406	GGUGCUGCUUCUCCAGGUG

2407	AGGUGCUGCUUCUCCAGGU	2473	GCCACCUCAUGGUCUAGGU
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2409	GCAGGUGCUGCUUCUCCAG	2475	UGGCCACCUCAUGGUCUAG
2410	CGCAGGUGCUGCUUCUCCA	2476	UUGGCCACCUCAUGGUCUA
2411	UCGCAGGUGCUGCUUCUCC	2477	CUUGGCCACCUCAUGGUCU
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2415	GAAUUCGCAGGUGCUGCUU	2481	CAGGCUUGGCCACCUCAUG
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2431	UGGCUUUGCAGAUGCUGAA	2497	AGCCUCUUUCUUCGGGCAG
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2439	GGCCAAACUGGCUUUGCAG	2505	UCUCGGGCAGCCUCUUUCU
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2441	GAGGCCAAACUGGCUUUGC	2507	CAUCUCGGGCAGCCUCUUU
2442	GGAGGCCAAACUGGCUUUG	2508	CCAUCUCGGGCAGCCUCUU
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2446	UCCAGGAGGCCAAACUGGC	2512	UGGGCCAUCUCGGGCAGCC
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2448	GGUCCAGGAGGCCAAACUG	2514	GCUGGGCCAUCUCGGGCAG
2449	UGGUCCAGGAGGCCAAACU	2515	GGCUGGGCCAUCUCGGGCA
2450	GUGGUCCAGGAGGCCAAAC	2516	UGGCUGGGCCAUCUCGGGC
2451	UGUGGUCCAGGAGGCCAAA	2517	CUGGCUGGGCCAUCUCGGG
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2453	CUUGUGGUCCAGGAGGCCA	2519	AACUGGCUGGGCCAUCUCG
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2455	UGCUUGUGGUCCAGGAGGC	2521	UCAACUGGCUGGGCCAUCU
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2457	GGUGCUUGUGGUCCAGGAG	2523	GGUCAACUGGCUGGGCCAU
2458	AGGUGCUUGUGGUCCAGGA	2524	GGGUCAACUGGCUGGGCCA
2459	UAGGUGCUUGUGGUCCAGG	2525	CGGGUCAACUGGCUGGGCC
2460	CUAGGUGCUUGUGGUCCAG	2526	CCGGGUCAACUGGCUGGGC
2461	UCUAGGUGCUUGUGGUCCA	2527	GCCGGGUCAACUGGCUGGG
2462	GUCUAGGUGCUUGUGGUCC	2528	AGCCGGGUCAACUGGCUGG
2463	GGUCUAGGUGCUUGUGGUC	2529	GAGCCGGGUCAACUGGCUG
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2465	AUGGUCUAGGUGCUUGUGG	2531	GUGAGCCGGGUCAACUGGC
2466	CAUGGUCUAGGUGCUUGUG	2532	UGUGAGCCGGGUCAACUGG
2467	UCAUGGUCUAGGUGCUUGU	2533	UUGUGAGCCGGGUCAACUG
2468	CUCAUGGUCUAGGUGCUUG	2534	AUUGUGAGCCGGGUCAACU
2469	CCUCAUGGUCUAGGUGCUU	2535	CAUUGUGAGCCGGGUCAAC
2470	ACCUCAUGGUCUAGGUGCU	2536	ACAUUGUGAGCCGGGUCAA
2471	CACCUCAUGGUCUAGGUGC	2537	GACAUUGUGAGCCGGGUCA
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2539	CUGACAUUGUGAGCCGGGU	2605	AGUCCACUCUGCCUCUCCC
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2541	GGCUGACAUUGUGAGCCGG	2607	AUAGUCCACUCUGCCUCUC
2542	CGGCUGACAUUGUGAGCCG	2608	AAUAGUCCACUCUGCCUCU
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2546	CAGGCGGCUGACAUUGUGA	2612	UUCAAAUAGUCCACUCUGC
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2548	UGCAGGCGGCUGACAUUGU	2614	AUUUCAAAUAGUCCACUCU
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2550	GGUGCAGGCGGCUGACAUU	2616	GGAUUUCAAAUAGUCCACU
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2552	CCGGUGCAGGCGGCUGACA	2618	CUGGAUUUCAAAUAGUCCA
2553	GCCGGUGCAGGCGGCUGAC	2619	GCUGGAUUUCAAAUAGUCC
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2557	GGCAGCCGGUGCAGGCGGC	2623	UGAGGCUGGAUUUCAAAUA
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2560	CUGGGCAGCCGGUGCAGGC	2626	CCCUGAGGCUGGAUUUCAA
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2569	UGGCAAUCCCUGGGCAGCC	2635	GGCGGAGACCCCUGAGGCU
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2571	CCUGGCAAUCCCUGGGCAG	2637	AUGGCGGAGACCCCUGAGG
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2573	CUCCUGGCAAUCCCUGGGC	2639	AAAUGGCGGAGACCCCUGA
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3117	GCCGCUGCUGUGGGAUGGA	3183	UGGUGGCCUGCAGCGGGUA
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3129	UCUUAAGCUUCUGCCGCUG	3195	GGAUCAACAUGGUGGUGGC
3130	UUCUUAAGCUUCUGCCGCU	3196	UGGAUCAACAUGGUGGUGG
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3647	UGCUUGUGUCCCCAGGGGA	3713	GTTCTGAGGTTGCTTTTATT
3648	CUGCUUGUGUCCCCAGGGG	3714	TTCTGAGGTTGCTTTTATTC
3649	CCUGCUUGUGUCCCCAGGG	3715	TCTGAGGTTGCTTTTATTCC
3650	GCCUGCUUGUGUCCCCAGG	3716	CTGAGGTTGCTTTTATTCCA
3651	CGCCUGCUUGUGUCCCCAG	3717	TGAGGTTGCTTTTATTCCAA
3652	GCGCCUGCUUGUGUCCCCA	3718	GAGGTTGCTTTTATTCCAAG
3653	GGCGCCUGCUUGUGUCCCC	3719	AGGTTGCTTTTATTCCAAGA
3654	UGGCGCCUGCUUGUGUCCC	3720	GGTTGCTTTTATTCCAAGAA
3655	UUGGCGCCUGCUUGUGUCC	3721	GTTGCTTTTATTCCAAGAAC
3656	AUUGGCGCCUGCUUGUGUC	3722	TTGCTTTTATTCCAAGAACT
3657	CAUUGGCGCCUGCUUGUGU	3723	TGCTTTTATTCCAAGAACTC
3658	CCAUUGGCGCCUGCUUGUG	3724	GCTTTTATTCCAAGAACTCT
3659	ACCAUUGGCGCCUGCUUGU	3725	CTTTTATTCCAAGAACTCTG
3660	UACCAUUGGCGCCUGCUUG	3726	TTTTATTCCAAGAACTCTGT

3727	TTTATTCCAAGAACTCTGTG	3793	CTACACACAACAGCACCAGC
3728	TTATTCCAAGAACTCTGTGA	3794	TACACACAACAGCACCAGCA
3729	TATTCCAAGAACTCTGTGAG	3795	ACACACAACAGCACCAGCAC
3730	ATTCCAAGAACTCTGTGAGC	3796	CACACAACAGCACCAGCACC
3731	TTCCAAGAACTCTGTGAGCT	3797	ACACAACAGCACCAGCACCA
3732	TCCAAGAACTCTGTGAGCTC	3798	CACAACAGCACCAGCACCAT
3733	CCAAGAACTCTGTGAGCTCC	3799	ACAACAGCACCAGCACCATG
3734	CAAGAACTCTGTGAGCTCCG	3800	CAACAGCACCAGCACCATGA
3735	AAGAACTCTGTGAGCTCCGC	3801	AACAGCACCAGCACCATGAG
3736	AGAACTCTGTGAGCTCCGCC	3802	ACAGCACCAGCACCATGAGG
3737	GAACTCTGTGAGCTCCGCCC	3803	CAGCACCAGCACCATGAGGG
3738	AACTCTGTGAGCTCCGCCCA	3804	AGCACCAGCACCATGAGGGC
3739	ACTCTGTGAGCTCCGCCCAG	3805	GCACCAGCACCATGAGGGCG
3740	CTCTGTGAGCTCCGCCCAGA	3806	CACCAGCACCATGAGGGCGC
3741	TCTGTGAGCTCCGCCCAGAT	3807	ACCAGCACCATGAGGGCGCT
3742	CTGTGAGCTCCGCCCAGATA	3808	CCAGCACCATGAGGGCGCTC
3743	TGTGAGCTCCGCCCAGATAC	3809	CAGCACCATGAGGGCGCTCT
3744	GTGAGCTCCGCCCAGATACC	3810	AGCACCATGAGGGCGCTCTC
3745	TGAGCTCCGCCCAGATACCA	3811	GCACCATGAGGGCGCTCTCG
3746	GAGCTCCGCCCAGATACCAT	3812	CACCATGAGGGCGCTCTCGA
3747	AGCTCCGCCCAGATACCATT	3813	ACCATGAGGGCGCTCTCGAC
3748	GCTCCGCCCAGATACCATTG	3814	CCATGAGGGCGCTCTCGACC
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3750	TCCGCCCAGATACCATTGGC	3816	ATGAGGGCGCTCTCGACCCA
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4274	CTTCCAGAAGATTCCCTTCT	4340	GAGGTTGGAATGGCTGCAGG
4275	TTCCAGAAGATTCCCTTCTT	4341	AGGTTGGAATGGCTGCAGGT
4276	TCCAGAAGATTCCCTTCTTA	4342	GGTTGGAATGGCTGCAGGTG
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4278	CAGAAGATTCCCTTCTTAAG	4344	TTGGAATGGCTGCAGGTGCC
4279	AGAAGATTCCCTTCTTAAGC	4345	TGGAATGGCTGCAGGTGCCA
4280	GAAGATTCCCTTCTTAAGCT	4346	GGAATGGCTGCAGGTGCCAA
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4283	GATTCCCTTCTTAAGCTTCT	4349	ATGGCTGCAGGTGCCAAACC
4284	ATTCCCTTCTTAAGCTTCTG	4350	TGGCTGCAGGTGCCAAACCA
4285	TTCCCTTCTTAAGCTTCTGC	4351	GGCTGCAGGTGCCAAACCAC
4286	TCCCTTCTTAAGCTTCTGCC	4352	GCTGCAGGTGCCAAACCACC
4287	CCCTTCTTAAGCTTCTGCCG	4353	CTGCAGGTGCCAAACCACCA
4288	CCTTCTTAAGCTTCTGCCGC	4354	TGCAGGTGCCAAACCACCAG
4289	CTTCTTAAGCTTCTGCCGCT	4355	GCAGGTGCCAAACCACCAGC
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4292	CTTAAGCTTCTGCCGCTGCT	4358	GGTGCCAAACCACCAGCCTC
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4294	TAAGCTTCTGCCGCTGCTGT	4360	TGCCAAACCACCAGCCTCCT
4295	AAGCTTCTGCCGCTGCTGTG	4361	GCCAAACCACCAGCCTCCTG
4296	AGCTTCTGCCGCTGCTGTGG	4362	CCAAACCACCAGCCTCCTGC
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4298	CTTCTGCCGCTGCTGTGGGA	4364	AAACCACCAGCCTCCTGCCG
4299	TTCTGCCGCTGCTGTGGGAT	4365	AACCACCAGCCTCCTGCCGG
4300	TCTGCCGCTGCTGTGGGATG	4366	ACCACCAGCCTCCTGCCGGG
4301	CTGCCGCTGCTGTGGGATGG	4367	CCACCAGCCTCCTGCCGGGG
4302	TGCCGCTGCTGTGGGATGGA	4368	CACCAGCCTCCTGCCGGGGT
4303	GCCGCTGCTGTGGGATGGAG	4369	ACCAGCCTCCTGCCGGGGTC
4304	CCGCTGCTGTGGGATGGAGC	4370	CCAGCCTCCTGCCGGGGTCA
4305	CGCTGCTGTGGGATGGAGCG	4371	CAGCCTCCTGCCGGGGTCAG
4306	GCTGCTGTGGGATGGAGCGG	4372	AGCCTCCTGCCGGGGTCAGG
4307	CTGCTGTGGGATGGAGCGGA	4373	GCCTCCTGCCGGGGTCAGGG
4308	TGCTGTGGGATGGAGCGGAA	4374	CCTCCTGCCGGGGTCAGGGG
4309	GCTGTGGGATGGAGCGGAAG	4375	CTCCTGCCGGGGTCAGGGGA
4310	CTGTGGGATGGAGCGGAAGT	4376	TCCTGCCGGGGTCAGGGGAG
4311	TGTGGGATGGAGCGGAAGTA	4377	CCTGCCGGGGTCAGGGGAGA
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4315	GGATGGAGCGGAAGTACTGG	4381	CCGGGGTCAGGGGAGAGGGA
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4318	TGGAGCGGAAGTACTGGCCG	4384	GGGTCAGGGGAGAGGGAACA
4319	GGAGCGGAAGTACTGGCCGT	4385	GGTCAGGGGAGAGGGAACAT
4320	GAGCGGAAGTACTGGCCGTT	4386	GTCAGGGGAGAGGGAACATG

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4390	GGGGAGAGGGAACATGGTCA	4456	GAGGATGAGGCAGGTTGGGG
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4393	GAGAGGGAACATGGTCAGGT	4459	GATGAGGCAGGTTGGGGACC
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4395	GAGGGAACATGGTCAGGTCT	4461	TGAGGCAGGTTGGGGACCAG
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4422	ACCGATGGGGCTGAAAGGAG	4488	TTTGGACTTGACTTTTTTTT
4423	CCGATGGGGCTGAAAGGAGA	4489	TTGGACTTGACTTTTTTTTT
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4430	GGCTGAAAGGAGATAGGGAT	4496	TGACTTTTTTTTTTTTGAGA
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4432	CTGAAAGGAGATAGGGATAG	4498	ACTTTTTTTTTTTTGAGATT
4433	TGAAAGGAGATAGGGATAGG	4499	CTTTTTTTTTTTTGAGATTG
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4438	GGAGATAGGGATAGGGTTGA	4504	TTTTTTTTGAGATTGAGTCT
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4452	GGTTGAGGATGAGGCAGGTT	4518	GAGTCTTACTCTGTCACCCA

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4847	AGGGGGTTTCACCATGTTGG	4913	GCCTCCCAAAGTGCTGGGAT
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4918	CCAAAGTGCTGGGATTACAG	4984	CAGGGTTTCACCATGTTGGC
4919	CAAAGTGCTGGGATTACAGG	4985	AGGGTTTCACCATGTTGGCC
4920	AAAGTGCTGGGATTACAGGT	4986	GGGTTTCACCATGTTGGCCA
4921	AAGTGCTGGGATTACAGGTA	4987	GGTTTCACCATGTTGGCCAG
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4925	GCTGGGATTACAGGTATGAC	4991	TCACCATGTTGGCCAGGCTA
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4929	GGATTACAGGTATGACCCAC	4995	CATGTTGGCCAGGCTAGTTT
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4931	ATTACAGGTATGACCCACTG	4997	TGTTGGCCAGGCTAGTTTTG
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4933	TACAGGTATGACCCACTGCG	4999	TTGGCCAGGCTAGTTTTGAA
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4935	CAGGTATGACCCACTGCGCC	5001	GGCCAGGCTAGTTTTGAACT
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5464	ATTTCGCCCTGTTGCTCAGA	5530	TGCTGGGATTGCAAGTGTGA
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5466	TTCGCCCTGTTGCTCAGATT	5532	CTGGGATTGCAAGTGTGAGC
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5468	CGCCCTGTTGCTCAGATTGG	5534	GGGATTGCAAGTGTGAGCCA
5469	GCCCTGTTGCTCAGATTGGT	5535	GGATTGCAAGTGTGAGCCAC
5470	CCCTGTTGCTCAGATTGGTC	5536	GATTGCAAGTGTGAGCCACC
5471	CCTGTTGCTCAGATTGGTCT	5537	ATTGCAAGTGTGAGCCACCG
5472	CTGTTGCTCAGATTGGTCTC	5538	TTGCAAGTGTGAGCCACCGT
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5474	GTTGCTCAGATTGGTCTCCT	5540	GCAAGTGTGAGCCACCGTGC
5475	TTGCTCAGATTGGTCTCCTG	5541	CAAGTGTGAGCCACCGTGCC
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5494	GGGCTCAAGTGATCCACTCG	5560	CTAATTTTTTTTTTTTTTTG
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6650	CGGTGGTGGCGCCCAGCTGG	6716	CACCCAGGTGCACGGAGAAC
6651	GGTGGTGGCGCCCAGCTGGC	6717	ACCCAGGTGCACGGAGAACT
6652	GTGGTGGCGCCCAGCTGGCC	6718	CCCAGGTGCACGGAGAACTG
6653	TGGTGGCGCCCAGCTGGCCG	6719	CCAGGTGCACGGAGAACTGC
6654	GGTGGCGCCCAGCTGGCCGG	6720	CAGGTGCACGGAGAACTGCA
6655	GTGGCGCCCAGCTGGCCGGC	6721	AGGTGCACGGAGAACTGCAG
6656	TGGCGCCCAGCTGGCCGGCC	6722	GGTGCACGGAGAACTGCAGC
6657	GGCGCCCAGCTGGCCGGCCA	6723	GTGCACGGAGAACTGCAGCA
6658	GCGCCCAGCTGGCCGGCCAC	6724	TGCACGGAGAACTGCAGCAA
6659	CGCCCAGCTGGCCGGCCACG	6725	GCACGGAGAACTGCAGCAAC
6660	GCCCAGCTGGCCGGCCACGG	6726	CACGGAGAACTGCAGCAACT
6661	CCCAGCTGGCCGGCCACGGG	6727	ACGGAGAACTGCAGCAACTC
6662	CCAGCTGGCCGGCCACGGGT	6728	CGGAGAACTGCAGCAACTCG
6663	CAGCTGGCCGGCCACGGGTG	6729	GGAGAACTGCAGCAACTCGG
6664	AGCTGGCCGGCCACGGGTGC	6730	GAGAACTGCAGCAACTCGGC
6665	GCTGGCCGGCCACGGGTGCA	6731	AGAACTGCAGCAACTCGGCG
6666	CTGGCCGGCCACGGGTGCAG	6732	GAACTGCAGCAACTCGGCGT
6667	TGGCCGGCCACGGGTGCAGT	6733	AACTGCAGCAACTCGGCGTT
6668	GGCCGGCCACGGGTGCAGTG	6734	ACTGCAGCAACTCGGCGTTG
6669	GCCGGCCACGGGTGCAGTGA	6735	CTGCAGCAACTCGGCGTTGC
6670	CCGGCCACGGGTGCAGTGAG	6736	TGCAGCAACTCGGCGTTGCC
6671	CGGCCACGGGTGCAGTGAGC	6737	GCAGCAACTCGGCGTTGCCA
6672	GGCCACGGGTGCAGTGAGCT	6738	CAGCAACTCGGCGTTGCCAT
6673	GCCACGGGTGCAGTGAGCTG	6739	AGCAACTCGGCGTTGCCATC
6674	CCACGGGTGCAGTGAGCTGC	6740	GCAACTCGGCGTTGCCATCC
6675	CACGGGTGCAGTGAGCTGCA	6741	CAACTCGGCGTTGCCATCCC
6676	ACGGGTGCAGTGAGCTGCAG	6742	AACTCGGCGTTGCCATCCCA
6677	CGGGTGCAGTGAGCTGCAGG	6743	ACTCGGCGTTGCCATCCCAG
6678	GGGTGCAGTGAGCTGCAGGC	6744	CTCGGCGTTGCCATCCCAGT
6679	GGTGCAGTGAGCTGCAGGCT	6745	TCGGCGTTGCCATCCCAGTC
6680	GTGCAGTGAGCTGCAGGCTA	6746	CGGCGTTGCCATCCCAGTCC
6681	TGCAGTGAGCTGCAGGCTAT	6747	GGCGTTGCCATCCCAGTCCC
6682	GCAGTGAGCTGCAGGCTATA	6748	GCGTTGCCATCCCAGTCCCG
6683	CAGTGAGCTGCAGGCTATAG	6749	CGTTGCCATCCCAGTCCCGC
6684	AGTGAGCTGCAGGCTATAGG	6750	GTTGCCATCCCAGTCCCGCA
6685	GTGAGCTGCAGGCTATAGGC	6751	TTGCCATCCCAGTCCCGCAG
6686	TGAGCTGCAGGCTATAGGCC	6752	TGCCATCCCAGTCCCGCAGC
6687	GAGCTGCAGGCTATAGGCCG	6753	GCCATCCCAGTCCCGCAGCT
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6689	GCTGCAGGCTATAGGCCGTG	6755	CATCCCAGTCCCGCAGCTGC
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6694	AGGCTATAGGCCGTGTCCTC	6760	CAGTCCCGCAGCTGCACGGC
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6696	GCTATAGGCCGTGTCCTCGC	6762	GTCCCGCAGCTGCACGGCCA

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6766	CGCAGCTGCACGGCCAGGCG	6832	CAGAACTCGCCTGGAGTGGG
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6768	CAGCTGCACGGCCAGGCGGC	6834	GAACTCGCCTGGAGTGGGAG
6769	AGCTGCACGGCCAGGCGGCT	6835	AACTCGCCTGGAGTGGGAGA
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6779	CCAGGCGGCTGTTGCGGTCC	6845	GAGTGGGAGAGGCCACTCCA
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6783	GCGGCTGTTGCGGTCCCCCG	6849	GGGAGAGGCCACTCCATGAG
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6787	CTGTTGCGGTCCCCCGTGAT	6853	GAGGCCACTCCATGAGGCAG
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6795	GTCCCCCGTGATGCTATGCA	6861	TCCATGAGGCAGGGCCACTT
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6797	CCCCCGTGATGCTATGCACC	6863	CATGAGGCAGGGCCACTTCT
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6799	CCCGTGATGCTATGCACCTT	6865	TGAGGCAGGGCCACTTCTGA
6800	CCGTGATGCTATGCACCTTC	6866	GAGGCAGGGCCACTTCTGAG
6801	CGTGATGCTATGCACCTTCT	6867	AGGCAGGGCCACTTCTGAGG
6802	GTGATGCTATGCACCTTCTC	6868	GGCAGGGCCACTTCTGAGGG
6803	TGATGCTATGCACCTTCTCC	6869	GCAGGGCCACTTCTGAGGGT
6804	GATGCTATGCACCTTCTCCA	6870	CAGGGCCACTTCTGAGGGTC
6805	ATGCTATGCACCTTCTCCAG	6871	AGGGCCACTTCTGAGGGTCC
6806	TGCTATGCACCTTCTCCAGA	6872	GGGCCACTTCTGAGGGTCCC
6807	GCTATGCACCTTCTCCAGAC	6873	GGCCACTTCTGAGGGTCCCT
6808	CTATGCACCTTCTCCAGACC	6874	GCCACTTCTGAGGGTCCCTC
6809	TATGCACCTTCTCCAGACCC	6875	CCACTTCTGAGGGTCCCTCT
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6811	TGCACCTTCTCCAGACCCAG	6877	ACTTCTGAGGGTCCCTCTTC
6812	GCACCTTCTCCAGACCCAGC	6878	CTTCTGAGGGTCCCTCTTCC
6813	CACCTTCTCCAGACCCAGCC	6879	TTCTGAGGGTCCCTCTTCCT
6814	ACCTTCTCCAGACCCAGCCA	6880	TCTGAGGGTCCCTCTTCCTC
6815	CCTTCTCCAGACCCAGCCAG	6881	CTGAGGGTCCCTCTTCCTCC
6816	CTTCTCCAGACCCAGCCAGA	6882	TGAGGGTCCCTCTTCCTCCC
6817	TTCTCCAGACCCAGCCAGAA	6883	GAGGGTCCCTCTTCCTCCCC
6818	TCTCCAGACCCAGCCAGAAC	6884	AGGGTCCCTCTTCCTCCCCT
6819	CTCCAGACCCAGCCAGAACT	6885	GGGTCCCTCTTCCTCCCCTG
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6825	ACCCAGCCAGAACTCGCCTG	6891	CTCTTCCTCCCCTGCCTCTG
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6896	CCTCCCCTGCCTCTGTCCCC	6962	TTCCCAGGGCCGGTTGAAGT
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6902	CTGCCTCTGTCCCCACTAGA	6968	GGGCCGGTTGAAGTCCACTG
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6907	TCTGTCCCCACTAGAAACAC	6973	GGTTGAAGTCCACTGAGCCA
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7211	CTTTGTCCCAAGAACCCAGC	7277	TCTCTGGGCCAGCTGAACTG
7212	TTTGTCCCAAGAACCCAGCA	7278	CTCTGGGCCAGCTGAACTGG
7213	TTGTCCCAAGAACCCAGCAG	7279	TCTGGGCCAGCTGAACTGGG
7214	TGTCCCAAGAACCCAGCAGG	7280	CTGGGCCAGCTGAACTGGGT
7215	GTCCCAAGAACCCAGCAGGG	7281	TGGGCCAGCTGAACTGGGTA
7216	TCCCAAGAACCCAGCAGGGA	7282	GGGCCAGCTGAACTGGGTAA
7217	CCCAAGAACCCAGCAGGGAC	7283	GGCCAGCTGAACTGGGTAAA
7218	CCAAGAACCCAGCAGGGACT	7284	GCCAGCTGAACTGGGTAAAA
7219	CAAGAACCCAGCAGGGACTG	7285	CCAGCTGAACTGGGTAAAAC
7220	AAGAACCCAGCAGGGACTGA	7286	CAGCTGAACTGGGTAAAACC
7221	AGAACCCAGCAGGGACTGAG	7287	AGCTGAACTGGGTAAAACCC
7222	GAACCCAGCAGGGACTGAGT	7288	GCTGAACTGGGTAAAACCCC
7223	AACCCAGCAGGGACTGAGTG	7289	CTGAACTGGGTAAAACCCCG
7224	ACCCAGCAGGGACTGAGTGT	7290	TGAACTGGGTAAAACCCCGT

7291	GAACTGGGTAAAACCCCGTG	7357	TTTCTTTTTTTTTTTTTTTT
7292	AACTGGGTAAAACCCCGTGT	7358	TTCTTTTTTTTTTTTTTTTT
7293	ACTGGGTAAAACCCCGTGTT	7359	TCTTTTTTTTTTTTTTTTTT
7294	CTGGGTAAAACCCCGTGTTG	7360	CTTTTTTTTTTTTTTTTTTT
7295	TGGGTAAAACCCCGTGTTGT	7361	TTTTTTTTTTTTTTTTTTTT
7296	GGGTAAAACCCCGTGTTGTA	7362	TTTTTTTTTTTTTTTTTTTT
7297	GGTAAAACCCCGTGTTGTAA	7363	TTTTTTTTTTTTTTTTTTTA
7298	GTAAAACCCCGTGTTGTAAC	7364	TTTTTTTTTTTTTTTTTTAG
7299	TAAAACCCCGTGTTGTAACC	7365	TTTTTTTTTTTTTTTTTAGA
7300	AAAACCCCGTGTTGTAACCT	7366	TTTTTTTTTTTTTTTTAGAG
7301	AAACCCCGTGTTGTAACCTC	7367	TTTTTTTTTTTTTTTAGAGA
7302	AACCCCGTGTTGTAACCTCT	7368	TTTTTTTTTTTTTTAGAGAT
7303	ACCCCGTGTTGTAACCTCTT	7369	TTTTTTTTTTTTTAGAGATG
7304	CCCCGTGTTGTAACCTCTTG	7370	TTTTTTTTTTTTAGAGATGG
7305	CCCGTGTTGTAACCTCTTGT	7371	TTTTTTTTTTTAGAGATGGA
7306	CCGTGTTGTAACCTCTTGTA	7372	TTTTTTTTTTAGAGATGGAG
7307	CGTGTTGTAACCTCTTGTAA	7373	TTTTTTTTTAGAGATGGAGT
7308	GTGTTGTAACCTCTTGTAAT	7374	TTTTTTTTAGAGATGGAGTC
7309	TGTTGTAACCTCTTGTAATG	7375	TTTTTTTAGAGATGGAGTCT
7310	GTTGTAACCTCTTGTAATGG	7376	TTTTTTAGAGATGGAGTCTC
7311	TTGTAACCTCTTGTAATGGA	7377	TTTTTAGAGATGGAGTCTCA
7312	TGTAACCTCTTGTAATGGAA	7378	TTTTAGAGATGGAGTCTCAC
7313	GTAACCTCTTGTAATGGAAA	7379	TTTAGAGATGGAGTCTCACT
7314	TAACCTCTTGTAATGGAAAG	7380	TTAGAGATGGAGTCTCACTC
7315	AACCTCTTGTAATGGAAAGG	7381	TAGAGATGGAGTCTCACTCT
7316	ACCTCTTGTAATGGAAAGGA	7382	AGAGATGGAGTCTCACTCTG
7317	CCTCTTGTAATGGAAAGGAC	7383	GAGATGGAGTCTCACTCTGT
7318	CTCTTGTAATGGAAAGGACT	7384	AGATGGAGTCTCACTCTGTT
7319	TCTTGTAATGGAAAGGACTT	7385	GATGGAGTCTCACTCTGTTG
7320	CTTGTAATGGAAAGGACTTC	7386	ATGGAGTCTCACTCTGTTGC
7321	TTGTAATGGAAAGGACTTCT	7387	TGGAGTCTCACTCTGTTGCC
7322	TGTAATGGAAAGGACTTCTC	7388	GGAGTCTCACTCTGTTGCCC
7323	GTAATGGAAAGGACTTCTCA	7389	GAGTCTCACTCTGTTGCCCA
7324	TAATGGAAAGGACTTCTCAG	7390	AGTCTCACTCTGTTGCCCAG
7325	AATGGAAAGGACTTCTCAGT	7391	GTCTCACTCTGTTGCCCAGG
7326	ATGGAAAGGACTTCTCAGTG	7392	TCTCACTCTGTTGCCCAGGC
7327	TGGAAAGGACTTCTCAGTGG	7393	CTCACTCTGTTGCCCAGGCT
7328	GGAAAGGACTTCTCAGTGGA	7394	TCACTCTGTTGCCCAGGCTG
7329	GAAAGGACTTCTCAGTGGAA	7395	CACTCTGTTGCCCAGGCTGG
7330	AAAGGACTTCTCAGTGGAAA	7396	ACTCTGTTGCCCAGGCTGGA
7331	AAGGACTTCTCAGTGGAAAA	7397	CTCTGTTGCCCAGGCTGGAT
7332	AGGACTTCTCAGTGGAAAAA	7398	TCTGTTGCCCAGGCTGGATC
7333	GGACTTCTCAGTGGAAAAAA	7399	CTGTTGCCCAGGCTGGATCG
7334	GACTTCTCAGTGGAAAAAAA	7400	TGTTGCCCAGGCTGGATCGC
7335	ACTTCTCAGTGGAAAAAAAA	7401	GTTGCCCAGGCTGGATCGCA
7336	CTTCTCAGTGGAAAAAAAAG	7402	TTGCCCAGGCTGGATCGCAG
7337	TTCTCAGTGGAAAAAAAAGC	7403	TGCCCAGGCTGGATCGCAGT
7338	TCTCAGTGGAAAAAAAAGCT	7404	GCCCAGGCTGGATCGCAGTG
7339	CTCAGTGGAAAAAAAAGCTT	7405	CCCAGGCTGGATCGCAGTGC
7340	TCAGTGGAAAAAAAAGCTTT	7406	CCAGGCTGGATCGCAGTGCC
7341	CAGTGGAAAAAAAAGCTTTC	7407	CAGGCTGGATCGCAGTGCCG
7342	AGTGGAAAAAAAAGCTTTCT	7408	AGGCTGGATCGCAGTGCCGC
7343	GTGGAAAAAAAAGCTTTCTT	7409	GGCTGGATCGCAGTGCCGCA
7344	TGGAAAAAAAAGCTTTCTTT	7410	GCTGGATCGCAGTGCCGCAA
7345	GGAAAAAAAAGCTTTCTTTT	7411	CTGGATCGCAGTGCCGCAAT
7346	GAAAAAAAAGCTTTCTTTTT	7412	TGGATCGCAGTGCCGCAATC
7347	AAAAAAAAGCTTTCTTTTTT	7413	GGATCGCAGTGCCGCAATCT
7348	AAAAAAAGCTTTCTTTTTTT	7414	GATCGCAGTGCCGCAATCTC
7349	AAAAAAGCTTTCTTTTTTTT	7415	ATCGCAGTGCCGCAATCTCA
7350	AAAAAGCTTTCTTTTTTTTT	7416	TCGCAGTGCCGCAATCTCAG
7351	AAAAGCTTTCTTTTTTTTTT	7417	CGCAGTGCCGCAATCTCAGC
7352	AAAGCTTTCTTTTTTTTTTT	7418	GCAGTGCCGCAATCTCAGCT
7353	AAGCTTTCTTTTTTTTTTTT	7419	CAGTGCCGCAATCTCAGCTC
7354	AGCTTTCTTTTTTTTTTTTT	7420	AGTGCCGCAATCTCAGCTCA
7355	GCTTTCTTTTTTTTTTTTTT	7421	GTGCCGCAATCTCAGCTCAC
7356	CTTTCTTTTTTTTTTTTTTT	7422	TGCCGCAATCTCAGCTCACT

7423	GCCGCAATCTCAGCTCACTG	7489	CAAGCAGCTGGAATCACAGG
7424	CCGCAATCTCAGCTCACTGC	7490	AAGCAGCTGGAATCACAGGC
7425	CGCAATCTCAGCTCACTGCA	7491	AGCAGCTGGAATCACAGGCA
7426	GCAATCTCAGCTCACTGCAA	7492	GCAGCTGGAATCACAGGCAC
7427	CAATCTCAGCTCACTGCAAC	7493	CAGCTGGAATCACAGGCACG
7428	AATCTCAGCTCACTGCAACC	7494	AGCTGGAATCACAGGCACGC
7429	ATCTCAGCTCACTGCAACCT	7495	GCTGGAATCACAGGCACGCC
7430	TCTCAGCTCACTGCAACCTC	7496	CTGGAATCACAGGCACGCCC
7431	CTCAGCTCACTGCAACCTCT	7497	TGGAATCACAGGCACGCCCG
7432	TCAGCTCACTGCAACCTCTG	7498	GGAATCACAGGCACGCCCGG
7433	CAGCTCACTGCAACCTCTGC	7499	GAATCACAGGCACGCCCGGC
7434	AGCTCACTGCAACCTCTGCC	7500	AATCACAGGCACGCCCGGCT
7435	GCTCACTGCAACCTCTGCCT	7501	ATCACAGGCACGCCCGGCTA
7436	CTCACTGCAACCTCTGCCTT	7502	TCACAGGCACGCCCGGCTAA
7437	TCACTGCAACCTCTGCCTTC	7503	CACAGGCACGCCCGGCTAAT
7438	CACTGCAACCTCTGCCTTCG	7504	ACAGGCACGCCCGGCTAATG
7439	ACTGCAACCTCTGCCTTCGG	7505	CAGGCACGCCCGGCTAATGT
7440	CTGCAACCTCTGCCTTCGGG	7506	AGGCACGCCCGGCTAATGTT
7441	TGCAACCTCTGCCTTCGGGG	7507	GGCACGCCCGGCTAATGTTT
7442	GCAACCTCTGCCTTCGGGGC	7508	GCACGCCCGGCTAATGTTTA
7443	CAACCTCTGCCTTCGGGGCT	7509	CACGCCCGGCTAATGTTTAT
7444	AACCTCTGCCTTCGGGGCTC	7510	ACGCCCGGCTAATGTTTATG
7445	ACCTCTGCCTTCGGGGCTCA	7511	CGCCCGGCTAATGTTTATGT
7446	CCTCTGCCTTCGGGGCTCAA	7512	GCCCGGCTAATGTTTATGTT
7447	CTCTGCCTTCGGGGCTCAAG	7513	CCCGGCTAATGTTTATGTTG
7448	TCTGCCTTCGGGGCTCAAGC	7514	CCGGCTAATGTTTATGTTGG
7449	CTGCCTTCGGGGCTCAAGCG	7515	CGGCTAATGTTTATGTTGGT
7450	TGCCTTCGGGGCTCAAGCGA	7516	GGCTAATGTTTATGTTGGTA
7451	GCCTTCGGGGCTCAAGCGAT	7517	GCTAATGTTTATGTTGGTAG
7452	CCTTCGGGGCTCAAGCGATT	7518	CTAATGTTTATGTTGGTAGA
7453	CTTCGGGGCTCAAGCGATTC	7519	TAATGTTTATGTTGGTAGAG
7454	TTCGGGGCTCAAGCGATTCT	7520	AATGTTTATGTTGGTAGAGA
7455	TCGGGGCTCAAGCGATTCTT	7521	ATGTTTATGTTGGTAGAGAT
7456	CGGGGCTCAAGCGATTCTTG	7522	TGTTTATGTTGGTAGAGATA
7457	GGGGCTCAAGCGATTCTTGT	7523	GTTTATGTTGGTAGAGATAG
7458	GGGCTCAAGCGATTCTTGTG	7524	TTTATGTTGGTAGAGATAGG
7459	GGCTCAAGCGATTCTTGTGC	7525	TTATGTTGGTAGAGATAGGG
7460	GCTCAAGCGATTCTTGTGCT	7526	TATGTTGGTAGAGATAGGGT
7461	CTCAAGCGATTCTTGTGCTT	7527	ATGTTGGTAGAGATAGGGTT
7462	TCAAGCGATTCTTGTGCTTC	7528	TGTTGGTAGAGATAGGGTTT
7463	CAAGCGATTCTTGTGCTTCA	7529	GTTGGTAGAGATAGGGTTTC
7464	AAGCGATTCTTGTGCTTCAG	7530	TTGGTAGAGATAGGGTTTCA
7465	AGCGATTCTTGTGCTTCAGC	7531	TGGTAGAGATAGGGTTTCAC
7466	GCGATTCTTGTGCTTCAGCC	7532	GGTAGAGATAGGGTTTCACC
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7468	GATTCTTGTGCTTCAGCCCC	7534	TAGAGATAGGGTTTCACCAT
7469	ATTCTTGTGCTTCAGCCCCA	7535	AGAGATAGGGTTTCACCATG
7470	TTCTTGTGCTTCAGCCCCAC	7536	GAGATAGGGTTTCACCATGT
7471	TCTTGTGCTTCAGCCCCACA	7537	AGATAGGGTTTCACCATGTT
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7474	TGTGCTTCAGCCCCACAAGC	7540	TAGGGTTTCACCATGTTGGC
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7476	TGCTTCAGCCCCACAAGCAG	7542	GGGTTTCACCATGTTGGCCA
7477	GCTTCAGCCCCACAAGCAGC	7543	GGTTTCACCATGTTGGCCAG
7478	CTTCAGCCCCACAAGCAGCT	7544	GTTTCACCATGTTGGCCAGG
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7480	TCAGCCCCACAAGCAGCTGG	7546	TTCACCATGTTGGCCAGGCT
7481	CAGCCCCACAAGCAGCTGGA	7547	TCACCATGTTGGCCAGGCTG
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7483	GCCCCACAAGCAGCTGGAAT	7549	ACCATGTTGGCCAGGCTGGT
7484	CCCCACAAGCAGCTGGAATC	7550	CCATGTTGGCCAGGCTGGTC
7485	CCCACAAGCAGCTGGAATCA	7551	CATGTTGGCCAGGCTGGTCT
7486	CCACAAGCAGCTGGAATCAC	7552	ATGTTGGCCAGGCTGGTCTT
7487	CACAAGCAGCTGGAATCACA	7553	TGTTGGCCAGGCTGGTCTTG
7488	ACAAGCAGCTGGAATCACAG	7554	GTTGGCCAGGCTGGTCTTGA

7555	TTGGCCAGGCTGGTCTTGAA	7621	GCATTTCAGGTGTAAGCCAC
7556	TGGCCAGGCTGGTCTTGAAC	7622	CATTTCAGGTGTAAGCCACC
7557	GGCCAGGCTGGTCTTGAACT	7623	ATTTCAGGTGTAAGCCACCG
7558	GCCAGGCTGGTCTTGAACTT	7624	TTTCAGGTGTAAGCCACCGT
7559	CCAGGCTGGTCTTGAACTTC	7625	TTCAGGTGTAAGCCACCGTG
7560	CAGGCTGGTCTTGAACTTCT	7626	TCAGGTGTAAGCCACCGTGC
7561	AGGCTGGTCTTGAACTTCTG	7627	CAGGTGTAAGCCACCGTGCT
7562	GGCTGGTCTTGAACTTCTGA	7628	AGGTGTAAGCCACCGTGCTC
7563	GCTGGTCTTGAACTTCTGAC	7629	GGTGTAAGCCACCGTGCTCA
7564	CTGGTCTTGAACTTCTGACC	7630	GTGTAAGCCACCGTGCTCAG
7565	TGGTCTTGAACTTCTGACCT	7631	TGTAAGCCACCGTGCTCAGC
7566	GGTCTTGAACTTCTGACCTC	7632	GTAAGCCACCGTGCTCAGCC
7567	GTCTTGAACTTCTGACCTCA	7633	TAAGCCACCGTGCTCAGCCT
7568	TCTTGAACTTCTGACCTCAA	7634	AAGCCACCGTGCTCAGCCTT
7569	CTTGAACTTCTGACCTCAAG	7635	AGCCACCGTGCTCAGCCTTT
7570	TTGAACTTCTGACCTCAAGT	7636	GCCACCGTGCTCAGCCTTTG
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7572	GAACTTCTGACCTCAAGTGA	7638	CACCGTGCTCAGCCTTTGTT
7573	AACTTCTGACCTCAAGTGAT	7639	ACCGTGCTCAGCCTTTGTTT
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7584	TCAAGTGATTTGCCCGCCTC	7650	CCTTTGTTTTTTTTTAGAAA
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7586	AAGTGATTTGCCCGCCTCAG	7652	TTTGTTTTTTTTTAGAAACG
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7591	ATTTGCCCGCCTCAGCCTCC	7657	TTTTTTTTAGAAACGAGGTT
7592	TTTGCCCGCCTCAGCCTCCC	7658	TTTTTTTAGAAACGAGGTTT
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7594	TGCCCGCCTCAGCCTCCCAA	7660	TTTTTAGAAACGAGGTTTTG
7595	GCCCGCCTCAGCCTCCCAAA	7661	TTTTAGAAACGAGGTTTTGT
7596	CCCGCCTCAGCCTCCCAAAG	7662	TTTAGAAACGAGGTTTTGTT
7597	CCGCCTCAGCCTCCCAAAGT	7663	TTAGAAACGAGGTTTTGTTG
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7599	GCCTCAGCCTCCCAAAGTGC	7665	AGAAACGAGGTTTTGTTGTG
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7601	CTCAGCCTCCCAAAGTGCTG	7667	AAACGAGGTTTTGTTGTGTT
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7604	AGCCTCCCAAAGTGCTGGCA	7670	CGAGGTTTTGTTGTGTTGCC
7605	GCCTCCCAAAGTGCTGGCAT	7671	GAGGTTTTGTTGTGTTGCCC
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7607	CTCCCAAAGTGCTGGCATTT	7673	GGTTTTGTTGTGTTGCCCAG
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7610	CCAAAGTGCTGGCATTTCAG	7676	TTTGTTGTGTTGCCCAGGTT
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7614	AGTGCTGGCATTTCAGGTGT	7680	TTGTGTTGCCCAGGTTGGAG
7615	GTGCTGGCATTTCAGGTGTA	7681	TGTGTTGCCCAGGTTGGAGT
7616	TGCTGGCATTTCAGGTGTAA	7682	GTGTTGCCCAGGTTGGAGTG
7617	GCTGGCATTTCAGGTGTAAG	7683	TGTTGCCCAGGTTGGAGTGC
7618	CTGGCATTTCAGGTGTAAGC	7684	GTTGCCCAGGTTGGAGTGCG
7619	TGGCATTTCAGGTGTAAGCC	7685	TTGCCCAGGTTGGAGTGCGG
7620	GGCATTTCAGGTGTAAGCCA	7686	TGCCCAGGTTGGAGTGCGGT

7687	GCCCAGGTTGGAGTGCGGTG	7753	GGCTGAAGTGACCCTCCTGC
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7690	CAGGTTGGAGTGCGGTGGCT	7756	TGAAGTGACCCTCCTGCCTT
7691	AGGTTGGAGTGCGGTGGCTA	7757	GAAGTGACCCTCCTGCCTTG
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7693	GTTGGAGTGCGGTGGCTATT	7759	AGTGACCCTCCTGCCTTGGC
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7707	GCTATTCACAGGTGTGATCA	7773	CTTGGCCTCCCGAGTAGCTG
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7721	TGATCACGGCTCACGGCAGC	7787	TAGCTGGGACTACAGGCATG
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7723	ATCACGGCTCACGGCAGCCT	7789	GCTGGGACTACAGGCATGTG
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7741	CTTTAACTCCTGGGCTGAAG	7807	TGCCACCATGCCCAGCAAGG
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7743	TTAACTCCTGGGCTGAAGTG	7809	CCACCATGCCCAGCAAGGGC
7744	TAACTCCTGGGCTGAAGTGA	7810	CACCATGCCCAGCAAGGGCT
7745	AACTCCTGGGCTGAAGTGAC	7811	ACCATGCCCAGCAAGGGCTG
7746	ACTCCTGGGCTGAAGTGACC	7812	CCATGCCCAGCAAGGGCTGA
7747	CTCCTGGGCTGAAGTGACCC	7813	CATGCCCAGCAAGGGCTGAA
7748	TCCTGGGCTGAAGTGACCCT	7814	ATGCCCAGCAAGGGCTGAAT
7749	CCTGGGCTGAAGTGACCCTC	7815	TGCCCAGCAAGGGCTGAATT
7750	CTGGGCTGAAGTGACCCTCC	7816	GCCCAGCAAGGGCTGAATTT
7751	TGGGCTGAAGTGACCCTCCT	7817	CCCAGCAAGGGCTGAATTTT
7752	GGGCTGAAGTGACCCTCCTG	7818	CCAGCAAGGGCTGAATTTTA

7819	CAGCAAGGGCTGAATTTTAT	7885	GGAGTCTCGCTCTGTCGCCC
7820	AGCAAGGGCTGAATTTTATT	7886	GAGTCTCGCTCTGTCGCCCA
7821	GCAAGGGCTGAATTTTATTT	7887	AGTCTCGCTCTGTCGCCCAG
7822	CAAGGGCTGAATTTTATTTT	7888	GTCTCGCTCTGTCGCCCAGG
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7824	AGGGCTGAATTTTATTTTAT	7890	CTCGCTCTGTCGCCCAGGCT
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7827	GCTGAATTTTATTTTATTTT	7893	GCTCTGTCGCCCAGGCTGGA
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7829	TGAATTTTATTTTATTTTAT	7895	TCTGTCGCCCAGGCTGGAGT
7830	GAATTTTATTTTATTTTATT	7896	CTGTCGCCCAGGCTGGAGTG
7831	AATTTTATTTTATTTTATTT	7897	TGTCGCCCAGGCTGGAGTGC
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7835	TTATTTTATTTTATTTTATT	7901	GCCCAGGCTGGAGTGCGGTG
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7839	TTTATTTTATTTTATTTTCT	7905	AGGCTGGAGTGCGGTGGCGT
7840	TTATTTTATTTTATTTTCTC	7906	GGCTGGAGTGCGGTGGCGTC
7841	TATTTTATTTTATTTTCTCT	7907	GCTGGAGTGCGGTGGCGTCA
7842	ATTTTATTTTATTTTCTCTT	7908	CTGGAGTGCGGTGGCGTCAT
7843	TTTTATTTTATTTTCTCTTT	7909	TGGAGTGCGGTGGCGTCATC
7844	TTTATTTTATTTTCTCTTTT	7910	GGAGTGCGGTGGCGTCATCT
7845	TTATTTTATTTTCTCTTTTT	7911	GAGTGCGGTGGCGTCATCTC
7846	TATTTTATTTTCTCTTTTTT	7912	AGTGCGGTGGCGTCATCTCA
7847	ATTTTATTTTCTCTTTTTTA	7913	GTGCGGTGGCGTCATCTCAG
7848	TTTTATTTTCTCTTTTTTAT	7914	TGCGGTGGCGTCATCTCAGC
7849	TTTATTTTCTCTTTTTTATT	7915	GCGGTGGCGTCATCTCAGCT
7850	TTATTTTCTCTTTTTTATTT	7916	CGGTGGCGTCATCTCAGCTC
7851	TATTTTCTCTTTTTTATTTT	7917	GGTGGCGTCATCTCAGCTCA
7852	ATTTTCTCTTTTTTATTTTT	7918	GTGGCGTCATCTCAGCTCAC
7853	TTTTCTCTTTTTTATTTTTT	7919	TGGCGTCATCTCAGCTCACT
7854	TTTCTCTTTTTTATTTTTTT	7920	GGCGTCATCTCAGCTCACTG
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7856	TCTCTTTTTTATTTTTTTGA	7922	CGTCATCTCAGCTCACTGCA
7857	CTCTTTTTTATTTTTTTGAT	7923	GTCATCTCAGCTCACTGCAA
7858	TCTTTTTTATTTTTTTGATG	7924	TCATCTCAGCTCACTGCAAC
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7860	TTTTTTATTTTTTTGATGGG	7926	ATCTCAGCTCACTGCAACCT
7861	TTTTTATTTTTTTGATGGGG	7927	TCTCAGCTCACTGCAACCTC
7862	TTTTATTTTTTTGATGGGGG	7928	CTCAGCTCACTGCAACCTCT
7863	TTTATTTTTTTGATGGGGGG	7929	TCAGCTCACTGCAACCTCTG
7864	TTATTTTTTTGATGGGGGGA	7930	CAGCTCACTGCAACCTCTGC
7865	TATTTTTTTGATGGGGGGAC	7931	AGCTCACTGCAACCTCTGCC
7866	ATTTTTTTGATGGGGGGACG	7932	GCTCACTGCAACCTCTGCCT
7867	TTTTTTTGATGGGGGGACGG	7933	CTCACTGCAACCTCTGCCTC
7868	TTTTTTGATGGGGGGACGGA	7934	TCACTGCAACCTCTGCCTCC
7869	TTTTTGATGGGGGGACGGAG	7935	CACTGCAACCTCTGCCTCCC
7870	TTTTGATGGGGGGACGGAGT	7936	ACTGCAACCTCTGCCTCCCA
7871	TTTGATGGGGGGACGGAGTC	7937	CTGCAACCTCTGCCTCCCAG
7872	TTGATGGGGGGACGGAGTCT	7938	TGCAACCTCTGCCTCCCAGG
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8398	GTCAGGAGTTTGAGACCAGC	8464	AGCTGGGTGTGGTTGCTCGC
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8401	AGGAGTTTGAGACCAGCCAG	8467	TGGGTGTGGTTGCTCGCACC
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8406	TTTGAGACCAGCCAGACCAA	8472	GTGGTTGCTCGCACCTGTAG
8407	TTGAGACCAGCCAGACCAAC	8473	TGGTTGCTCGCACCTGTAGT
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8411	GACCAGCCAGACCAACATGG	8477	TGCTCGCACCTGTAGTCTCA
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9049	GGTCCACAAGGCACCTGGAG	9115	CCTCTCTGGCACACAGGCTT
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9058	GGCACCTGGAGGACCAGCCC	9124	CACACAGGCTTTCTTCCCAC
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9588	AACACCCCAAATGGGAATTG	9654	TCCTCTGACTCAATGGAGGC
9589	ACACCCCAAATGGGAATTGA	9655	CCTCTGACTCAATGGAGGCT
9590	CACCCCAAATGGGAATTGAG	9656	CTCTGACTCAATGGAGGCTC
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9593	CCCAAATGGGAATTGAGCAA	9659	TGACTCAATGGAGGCTCCAT
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9599	TGGGAATTGAGCAAGGACTT	9665	AATGGAGGCTCCATGAGGCT
9600	GGGAATTGAGCAAGGACTTC	9666	ATGGAGGCTCCATGAGGCTG

9667	TGGAGGCTCCATGAGGCTGG	9733	GGCCCCAGCGCATAGCAGCT
9668	GGAGGCTCCATGAGGCTGGG	9734	GCCCCAGCGCATAGCAGCTG
9669	GAGGCTCCATGAGGCTGGGG	9735	CCCCAGCGCATAGCAGCTGC
9670	AGGCTCCATGAGGCTGGGGA	9736	CCCAGCGCATAGCAGCTGCT
9671	GGCTCCATGAGGCTGGGGAC	9737	CCAGCGCATAGCAGCTGCTC
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9673	CTCCATGAGGCTGGGGACAA	9739	AGCGCATAGCAGCTGCTCAA
9674	TCCATGAGGCTGGGGACAAG	9740	GCGCATAGCAGCTGCTCAAT
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9676	CATGAGGCTGGGGACAAGGA	9742	GCATAGCAGCTGCTCAATAA
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9679	GAGGCTGGGGACAAGGAGCA	9745	TAGCAGCTGCTCAATAAAGA
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9681	GGCTGGGGACAAGGAGCAGC	9747	GCAGCTGCTCAATAAAGACT
9682	GCTGGGGACAAGGAGCAGCT	9748	CAGCTGCTCAATAAAGACTT
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9684	TGGGGACAAGGAGCAGCTCT	9750	GCTGCTCAATAAAGACTTGA
9685	GGGGACAAGGAGCAGCTCTG	9751	CTGCTCAATAAAGACTTGAG
9686	GGGACAAGGAGCAGCTCTGC	9752	TGCTCAATAAAGACTTGAGG
9687	GGACAAGGAGCAGCTCTGCC	9753	GCTCAATAAAGACTTGAGGA
9688	GACAAGGAGCAGCTCTGCCC	9754	CTCAATAAAGACTTGAGGAA
9689	ACAAGGAGCAGCTCTGCCCA	9755	TCAATAAAGACTTGAGGAAT
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9727	CACGCAGGCCCCAGCGCATA	9793	CATGCCTGTAATCCAGCACT
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10217	GAGCGAGACTCCGTCTCAAA	10283	GAGGCAGCAGGTCCAGAACG
10218	AGCGAGACTCCGTCTCAAAA	10284	AGGCAGCAGGTCCAGAACGG
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10221	GAGACTCCGTCTCAAAAAGC	10287	CAGCAGGTCCAGAACGGGAA
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10224	ACTCCGTCTCAAAAAGCAAA	10290	CAGGTCCAGAACGGGAAGAA
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10230	TCTCAAAAAGCAAACAAAAC	10296	CAGAACGGGAAGAACTGTGC
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10232	TCAAAAAGCAAACAAAACAG	10298	GAACGGGAAGAACTGTGCTG
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10235	AAAAGCAAACAAAACAGTCT	10301	CGGGAAGAACTGTGCTGAGC
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10237	AAGCAAACAAAACAGTCTTG	10303	GGAAGAACTGTGCTGAGCAG
10238	AGCAAACAAAACAGTCTTGA	10304	GAAGAACTGTGCTGAGCAGG
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10245	AAAACAGTCTTGACAAATGA	10311	TGTGCTGAGCAGGAGCATCT
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10251	GTCTTGACAAATGAATGAAT	10317	GAGCAGGAGCATCTCAGAGG
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10254	TTGACAAATGAATGAATGAA	10320	CAGGAGCATCTCAGAGGCTC
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10330	TCAGAGGCTCTGCCTGGGGT	10396	GAGGGAGGAGGGGAGGATGG
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10364	GGAGAGGAGGCAGGGTTGAG	10430	GGAGGCTCAGACGCTCCAGA
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10862	TGGCGGGGTTGGGGGCGGGC	10928	CAGGTCTACAGTGCTGGAAG
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11409	AAGGTTCTAACCTTCAGGAT	11475	AAGTCCCTCAAGACCTCTTT
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11413	TTCTAACCTTCAGGATGGCA	11479	CCCTCAAGACCTCTTTCTCC
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11419	CCTTCAGGATGGCACCCCGA	11485	AGACCTCTTTCTCCACCTCT
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11970	GGGGTCCAGCTATCAGAGGG	12036	AATTCGCAGGTGCTGCTTCT
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11972	GGTCCAGCTATCAGAGGGAC	12038	TTCGCAGGTGCTGCTTCTCC
11973	GTCCAGCTATCAGAGGGACC	12039	TCGCAGGTGCTGCTTCTCCA
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12046	TGCTGCTTCTCCAGGTGCCG	12112	TGAGCCTTGAGTTGTGTCTG
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12602	TTTGAGATGGAGTCGAGCTC	12668	CCTCCGCCTCCCGGGTTCAA
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12611	GAGTCGAGCTCTGTCGCCCA	12677	CCCGGGTTCAAGAGGTTCTC
12612	AGTCGAGCTCTGTCGCCCAG	12678	CCGGGTTCAAGAGGTTCTCC
12613	GTCGAGCTCTGTCGCCCAGG	12679	CGGGTTCAAGAGGTTCTCCT
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13149	CCGGTCGTTTTTTAATTTTA	13215	TGTGTAGAAGAGACGGGGGT
13150	CGGTCGTTTTTTAATTTTAT	13216	GTGTAGAAGAGACGGGGGTC
13151	GGTCGTTTTTTAATTTTATA	13217	TGTAGAAGAGACGGGGGTCT
13152	GTCGTTTTTTAATTTTATAT	13218	GTAGAAGAGACGGGGGTCTC
13153	TCGTTTTTTAATTTTATATT	13219	TAGAAGAGACGGGGGTCTCG
13154	CGTTTTTTAATTTTATATTT	13220	AGAAGAGACGGGGGTCTCGC
13155	GTTTTTTAATTTTATATTTA	13221	GAAGAGACGGGGGTCTCGCT
13156	TTTTTTAATTTTATATTTAT	13222	AAGAGACGGGGGTCTCGCTA
13157	TTTTTAATTTTATATTTATT	13223	AGAGACGGGGGTCTCGCTAT
13158	TTTTAATTTTATATTTATTT	13224	GAGACGGGGGTCTCGCTATT
13159	TTTAATTTTATATTTATTTT	13225	AGACGGGGGTCTCGCTATTT
13160	TTAATTTTATATTTATTTTA	13226	GACGGGGGTCTCGCTATTTT
13161	TAATTTTATATTTATTTTAT	13227	ACGGGGGTCTCGCTATTTTG
13162	AATTTTATATTTATTTTATT	13228	CGGGGGTCTCGCTATTTTGC
13163	ATTTTATATTTATTTTATTT	13229	GGGGGTCTCGCTATTTTGCT
13164	TTTTATATTTATTTTATTTT	13230	GGGGTCTCGCTATTTTGCTT

13231	GGGTCTCGCTATTTTGCTTT	13297	TCCTAAGGGGGGAGCCCATC
13232	GGTCTCGCTATTTTGCTTTA	13298	CCTAAGGGGGGAGCCCATCC
13233	GTCTCGCTATTTTGCTTTAG	13299	CTAAGGGGGGAGCCCATCCC
13234	TCTCGCTATTTTGCTTTAGG	13300	TAAGGGGGGAGCCCATCCCT
13235	CTCGCTATTTTGCTTTAGGT	13301	AAGGGGGGAGCCCATCCCTT
13236	TCGCTATTTTGCTTTAGGTG	13302	AGGGGGGAGCCCATCCCTTG
13237	CGCTATTTTGCTTTAGGTGG	13303	GGGGGGAGCCCATCCCTTGA
13238	GCTATTTTGCTTTAGGTGGT	13304	GGGGGAGCCCATCCCTTGAC
13239	CTATTTTGCTTTAGGTGGTC	13305	GGGGAGCCCATCCCTTGACG
13240	TATTTTGCTTTAGGTGGTCT	13306	GGGAGCCCATCCCTTGACGC
13241	ATTTTGCTTTAGGTGGTCTT	13307	GGAGCCCATCCCTTGACGCA
13242	TTTTGCTTTAGGTGGTCTTG	13308	GAGCCCATCCCTTGACGCAG
13243	TTTGCTTTAGGTGGTCTTGA	13309	AGCCCATCCCTTGACGCAGG
13244	TTGCTTTAGGTGGTCTTGAA	13310	GCCCATCCCTTGACGCAGGG
13245	TGCTTTAGGTGGTCTTGAAT	13311	CCCATCCCTTGACGCAGGGA
13246	GCTTTAGGTGGTCTTGAATT	13312	CCATCCCTTGACGCAGGGAA
13247	CTTTAGGTGGTCTTGAATTC	13313	CATCCCTTGACGCAGGGAAG
13248	TTTAGGTGGTCTTGAATTCC	13314	ATCCCTTGACGCAGGGAAGC
13249	TTAGGTGGTCTTGAATTCCT	13315	TCCCTTGACGCAGGGAAGCC
13250	TAGGTGGTCTTGAATTCCTG	13316	CCCTTGACGCAGGGAAGCCC
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13252	GGTGGTCTTGAATTCCTGGC	13318	CTTGACGCAGGGAAGCCCAG
13253	GTGGTCTTGAATTCCTGGCC	13319	TTGACGCAGGGAAGCCCAGG
13254	TGGTCTTGAATTCCTGGCCT	13320	TGACGCAGGGAAGCCCAGGG
13255	GGTCTTGAATTCCTGGCCTT	13321	GACGCAGGGAAGCCCAGGGA
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13257	TCTTGAATTCCTGGCCTTGA	13323	CGCAGGGAAGCCCAGGGAGC
13258	CTTGAATTCCTGGCCTTGAG	13324	GCAGGGAAGCCCAGGGAGCC
13259	TTGAATTCCTGGCCTTGAGC	13325	CAGGGAAGCCCAGGGAGCCA
13260	TGAATTCCTGGCCTTGAGCG	13326	AGGGAAGCCCAGGGAGCCAC
13261	GAATTCCTGGCCTTGAGCGA	13327	GGGAAGCCCAGGGAGCCACA
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13263	ATTCCTGGCCTTGAGCGAAC	13329	GAAGCCCAGGGAGCCACAGT
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13265	TCCTGGCCTTGAGCGAACCT	13331	AGCCCAGGGAGCCACAGTTG
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13268	TGGCCTTGAGCGAACCTCCC	13334	CCAGGGAGCCACAGTTGCGC
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13270	GCCTTGAGCGAACCTCCCTC	13336	AGGGAGCCACAGTTGCGCAC
13271	CCTTGAGCGAACCTCCCTCC	13337	GGGAGCCACAGTTGCGCACC
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13279	GAACCTCCCTCCTCGGCTTC	13345	CAGTTGCGCACCCCGCCCCC
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13285	CCCTCCTCGGCTTCCTAAGG	13351	CGCACCCCGCCCCCACGCCC
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13289	CCTCGGCTTCCTAAGGGGGG	13355	CCCCGCCCCCACGCCCCACT
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13292	CGGCTTCCTAAGGGGGGAGC	13358	CGCCCCCACGCCCCACTCCT
13293	GGCTTCCTAAGGGGGGAGCC	13359	GCCCCCACGCCCCACTCCTG
13294	GCTTCCTAAGGGGGGAGCCC	13360	CCCCCACGCCCCACTCCTGT
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13366	CGCCCCACTCCTGTCCATAC	13432	GGGACACGTACCTGCAGGCT
13367	GCCCCACTCCTGTCCATACC	13433	GGACACGTACCTGCAGGCTG
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13369	CCCACTCCTGTCCATACCCT	13435	ACACGTACCTGCAGGCTGTG
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13373	CTCCTGTCCATACCCTTCCA	13439	GTACCTGCAGGCTGTGAAGG
13374	TCCTGTCCATACCCTTCCAA	13440	TACCTGCAGGCTGTGAAGGA
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13376	CTGTCCATACCCTTCCAAGC	13442	CCTGCAGGCTGTGAAGGACC
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13378	GTCCATACCCTTCCAAGCCA	13444	TGCAGGCTGTGAAGGACCTC
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13409	AGGGGCGCGGAGAACCAGCC	13475	GGCTCTCAGGGGCTAACGGG
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13412	GGCGCGGAGAACCAGCCCTG	13478	TCTCAGGGGCTAACGGGAGG
13413	GCGCGGAGAACCAGCCCTGG	13479	CTCAGGGGCTAACGGGAGGT
13414	CGCGGAGAACCAGCCCTGGG	13480	TCAGGGGCTAACGGGAGGTC
13415	GCGGAGAACCAGCCCTGGGG	13481	CAGGGGCTAACGGGAGGTCG
13416	CGGAGAACCAGCCCTGGGGA	13482	AGGGGCTAACGGGAGGTCGG
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13419	AGAACCAGCCCTGGGGACAC	13485	GGCTAACGGGAGGTCGGTGG
13420	GAACCAGCCCTGGGGACACG	13486	GCTAACGGGAGGTCGGTGGA
13421	AACCAGCCCTGGGGACACGT	13487	CTAACGGGAGGTCGGTGGAC
13422	ACCAGCCCTGGGGACACGTA	13488	TAACGGGAGGTCGGTGGACC
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13773	CCTGGGAGCGGGGATTCGGG	13839	GAGGACCGGGGGTAAGACCC
13774	CTGGGAGCGGGGATTCGGGG	13840	AGGACCGGGGGTAAGACCCG
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13777	GGAGCGGGGATTCGGGGACT	13843	ACCGGGGGTAAGACCCGCTT
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13779	AGCGGGGATTCGGGGACTCT	13845	CGGGGGTAAGACCCGCTTGG
13780	GCGGGGATTCGGGGACTCTC	13846	GGGGGTAAGACCCGCTTGGT
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13782	GGGGATTCGGGGACTCTCGG	13848	GGGTAAGACCCGCTTGGTTG
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13791	GGGACTCTCGGGGACGTTGG	13857	CCGCTTGGTTGCAGAAGCCG
13792	GGACTCTCGGGGACGTTGGG	13858	CGCTTGGTTGCAGAAGCCGC
13793	GACTCTCGGGGACGTTGGGG	13859	GCTTGGTTGCAGAAGCCGCT
13794	ACTCTCGGGGACGTTGGGGT	13860	CTTGGTTGCAGAAGCCGCTG
13795	CTCTCGGGGACGTTGGGGTT	13861	TTGGTTGCAGAAGCCGCTGG
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13798	TCGGGGACGTTGGGGTTCCA	13864	GTTGCAGAAGCCGCTGGAAA
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13804	ACGTTGGGGTTCCAGGTGCG	13870	GAAGCCGCTGGAAAGAATCG
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13824	AGGACTGGAGACGCGGAGGA	13890	GATCACAGTCGTGTGAGGAT

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13900	GTGTGAGGATCCGCTCAGCT
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	GGCTCACTGCAGCCTCCGCCTCCTGGGTTCAAGT	13938	AfsusAfgAfgUfGfGfaAfgUfaUfuGfuAfsusu
	GATTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGA	13939	AfsusUfgAfgAfUfUfgGfaAfuGfgCfuAfsusu
	TTACAGGTTCCCGCCACCATGCACAGATAATTGT	13940	UfscsAfgAfuGfGfAfgGfcUfgGfaCfaAfsusu

13941	asgsagCfaAfCfAfggaaacaaaususu
13942	asusagAfgUfGfGfaaguauuguasusu
13943	asusugAfgAfUfUfggaauggcuasusu
13944	uscsagAfuGfGfAfggcuggacaasusu
13945	asUfsuUfgUfuUfcCfuguUfgCfuCfususu
13946	usAfscAfaUfaCfuUfccaCfuCfuAfususu
13947	usAfsgCfcAfuUfcCfaauCfuCfaAfususu
13948	usUfsgUfcCfaGfcCfuccAfuCfuGfasusu
13949	asUfsuugUfuuccuguUfgCfucususu
13950	usAfscaaUfacuuccaCfuCfuaususu
13951	usAfsgccAfuuccaauCfuCfaaususu
13952	usUfsgucCfagccuccAfuCfugasusu
13953	tscstsasasdCsdCsdGsdAsdGsdCsdTsdGsdAsdTsgsgsascst
13954	NfsnsNfnNfnNfNfnNfnNfnNfnNfnNfsnsn
13955	nsnsnnNfnNfNfNfnnnnnnnnnnsnsn
13956	nsnsnnNfnNfnNfnnnnnnnnnnsnsn
13957	NfsnsNfnNfnNfNfnNfnNfnNfnNfnNfsnsnN
13958	nsnsnnNfnNfNfNfnnnnnnnnnnsnsnN
13959	NfsnsNfnNfnNfnNfnNfnNfnNfnNfsnsn
13960	nsNfsnNfnNfnNfnNfnnnNfnNfnNfnsnsn
13961	nsNfsnnnNfnNfNfnnnnNfnNfnnnsnsn
13962	nsNfsnnnNfnnnnnnnNfnNfnnnsnsn
13963	nsNfsnNfnNfnnnnnnnNfnNfnnnsnsn
13964	nsNfsnnnNfnNfnnnnnNfnNfnnnsnsn
13965	nsNfsnNfnNfnNfnNfnNfnNfnNfnNfnsnsn
13966	nsNfsnNfnNfnNfNfnnnnNfnNfnnnsnsn
13967	nsNfsnnnnnnnnnnnNfnnnnnsnsn
13968	nsNfsnnnNfnnnnnnnNfnNfnNfnsnsn
13969	nsnsnsnsnsdNsdNsdNsdNsdNsdNsdNsdNsdNsdNsnsnsnsnsn
13970	CAGAGUGGACUAUUUGAAA
13971	AGCUUAAGAAGGGAAUCUA
13972	GAUCGAGGCUGCAGGAUAA
13973	CAGAGUUCUUGGAAUAAAA
13974	CAGAGUGGACUAUUUGAAAUU
13975	AGCUUAAGAAGGGAAUCUAUU
13976	GAUCGAGGCUGCAGGAUAAUU
13977	CAGAGUUCUUGGAAUAAAAUU
13978	UUUCAAAUAGUCCACUCUG
13979	UAGAUUCCCUUCUUAAGCU
13980	UUAUCCUGCAGCCUCGAUC
13981	UUUUAUUCCAAGAACUCUG
13982	UUUCAAAUAGUCCACUCUGUU
13983	UAGAUUCCCUUCUUAAGCUUU
13984	UUAUCCUGCAGCCUCGAUCUU
13985	UUUUAUUCCAAGAACUCUGUU
13986	csasgaGfuGfgAfcuauuugaaasusu
13987	asgscuUfaAfgAfagggaaucuasusu
13988	gsasucGfaGfgCfugcaggauaasusu
13989	**csasgaGfuUfcUfuggaauaaaasusu**
13990	csasgaGfuGfGfAfcuauuugaaasusu
13991	asgscuUfaAfGfAfagggaaucuasusu
13992	gsasucGfaGfGfCfugcaggauaasusu
13993	**csasgaGfuUfCfUfuggaauaaaasusu**
13994	cagaGfuGfGfAfcuauuugaaasusu
13995	agcuUfaAfGfAfagggaaucuasusu
13996	gaucGfaGfGfCfugcaggauaasusu
13997	**cagaGfuUfCfUfuggaauaaaasusu**
13998	cagaGfuGfgAfcuauuugaaasusu
13999	agcuUfaAfgAfagggaaucuasusu
14000	gaucGfaGfgCfugcaggauaasusu
14001	**cagaGfuUfcUfuggaauaaaasusu**
14002	CfsasGfaGfuGfgAfcUfaUfuUfgAfaAfsusu
14003	AfsgsCfuUfaAfgAfaGfgGfaAfuCfuAfsusu
14004	GfsasUfcGfaGfgCfuGfcAfgGfaUfaAfsusu
14005	**CfsasGfaGfuUfcUfuGfgAfaUfaAfaAfsusu**
14006	**CAGAGUUCUUGGAAUAAAAUU, with modification pattern 1S**
14007	**CAGAGUUCUUGGAAUAAAAUU, with modification pattern 2S**
14008	**CAGAGUUCUUGGAAUAAAAUU, with modification pattern 3S**
14009	**CAGAGUUCUUGGAAUAAAAUU, with modification pattern 4S**
14010	**CAGAGUUCUUGGAAUAAAAUU, with modification pattern 5S**
14011	**CAGAGUUCUUGGAAUAAAAUU, with modification pattern 6S**
14012	GfsusGfaUfcCfGfAfuUfcUfuUfcCfaAfsusu
14013	UfsgsAfuCfcGfAfUfuCfuUfuCfcAfgAfsusu
14014	GfsasUfcCfgAfUfUfcUfuUfcCfaGfcAfsusu
14015	AfsusCfcGfaUfUfCfuUfuCfcAfgCfgAfsusu
14016	UfsusCfuGfcAfAfCfcAfaGfcGfgGfuAfsusu
14017	AfscsGfuCfcCfCfGfaGfaGfuCfcCfcAfsusu
14018	UfsgsCfgUfcCfUfGfgGfaCfgAfgAfuAfsusu
14019	GfsgsGfaCfgAfGfAfuGfaAfuGfuCfcAfsusu
14020	GfsasCfgAfgAfUfGfaAfuGfuCfcUfgAfsusu
14021	UfsgsAfaUfgUfCfCfuGfgCfgCfaCfgAfsusu
14022	GfsasAfuGfuCfCfUfgGfcGfcAfcGfgAfsusu
14023	AfsasUfgUfcCfUfGfgCfgCfaCfgGfaAfsusu
14024	AfsusGfuCfcUfGfGfcGfcAfcGfgAfcAfsusu
14025	UfsgsUfcCfuGfGfCfgCfaCfgGfaCfuAfsusu
14026	GfsgsCfcAfgGfGfGfcUfgCfgCfgAfaAfsusu
14027	CfscsAfgGfgGfCfUfgCfgCfgAfaCfaAfsusu
14028	GfsgsGfgCfuGfCfGfcGfaAfcAfcGfcAfsusu
14029	GfsgsCfuGfcGfCfGfaAfcAfcGfcGfgAfsusu
14030	GfscsUfgCfgCfGfAfaCfaCfgCfgGfaAfsusu
14031	CfsusGfcGfcGfAfAfcAfcGfcGfgAfgAfsusu
14032	UfsgsCfgCfgAfAfCfaCfgCfgGfaGfcAfsusu
14033	GfscsGfcGfaAfCfAfcGfcGfgAfgCfgAfsusu
14034	CfsgsCfgAfaCfAfCfgCfgGfaGfcGfcAfsusu
14035	GfscsGfaAfcAfCfGfcGfgAfgCfgCfaAfsusu
14036	CfsgsAfaCfaCfGfCfgGfaGfcGfcAfcAfsusu
14037	AfsasCfaCfgCfGfGfaGfcGfcAfcCfcAfsusu
14038	AfscsAfcGfcGfGfAfgCfgCfaCfcCfgAfsusu
14039	CfsasCfgCfgGfAfGfcGfcAfcCfcGfcAfsusu
14040	GfscsGfgAfgCfGfCfaCfcCfgCfaGfuAfsusu
14041	GfscsGfcAfcCfCfGfcAfgUfcAfgCfuAfsusu
14042	GfscsAfcCfcGfCfAfgUfcAfgCfuGfaAfsusu
14043	GfsgsAfaCfcGfAfGfgGfgUfcCfaCfcAfsusu
14044	GfsasAfcCfgAfGfGfgGfuCfcAfcCfgAfsusu
14045	AfscsCfuCfcCfGfUfuAfgCfcCfcUfgAfsusu
14046	CfscsUfcCfcGfUfUfaGfcCfcCfuGfaAfsusu
14047	CfscsGfuUfaGfCfCfcCfuGfaGfaGfcAfsusu
14048	UfsgsCfaGfaCfAfCfaAfcUfcAfaGfgAfsusu
14049	AfsgsAfcAfcAfAfCfuCfaAfgGfcUfcAfsusu
14050	CfsasGfgAfuCfCfAfgCfaAfcUfcUfuAfsusu
14051	AfsgsCfaAfcUfCfUfuCfcAfcAfaGfgAfsusu
14052	CfsasAfcUfcUfUfCfcAfcAfaGfgUfgAfsusu
14053	AfsasCfuCfuUfCfCfaCfaAfgGfuGfgAfsusu
14054	AfsgsCfaCfcUfGfCfgAfaUfuCfaGfcAfsusu
14055	CfscsUfaGfaCfCfAfuGfaGfgUfgGfcAfsusu
14056	GfsgsCfcAfaGfCfCfuGfcCfcGfaAfgAfsusu
14057	CfscsAfaGfcCfUfGfcCfcGfaAfgAfaAfsusu
14058	AfsgsCfcUfgCfCfCfgAfaGfaAfaGfaAfsusu
14059	UfsgsGfaGfgCfUfGfgAfcAfgUfaAfuAfsusu
14060	GfsgsCfuGfgAfCfAfgUfaAfuUfcAfgAfsusu
14061	CfsasGfuAfaUfUfCfaGfaGfgCfgCfcAfsusu
14062	AfsgsUfaAfuUfCfAfgAfgGfcGfcCfaAfsusu
14063	GfsusAfaUfuCfAfGfaGfgCfgCfcAfcAfsusu
14064	UfsasAfuUfcAfGfAfgGfcGfcCfaCfgAfsusu

14065	AfsgsAfgGfcGfCfCfaCfgAfuGfgCfuAfsusu
14066	UfsgsGfaCfuUfCfAfaCfcGfgCfcCfuAfsusu
14067	GfsgsAfcUfuCfAfAfcCfgGfcCfcUfgAfsusu
14068	UfsusCfaAfcCfGfGfcCfcUfgGfgAfaAfsusu
14069	CfsusGfgGfaAfGfCfcUfaCfaAfgGfcAfsusu
14070	UfsgsGfgAfaGfCfCfuAfcAfaGfgCfgAfsusu
14071	GfscsCfuAfcAfAfGfgCfgGfgGfuUfuAfsusu
14072	UfsasCfaAfgGfCfGfgGfgUfuUfgGfgAfsusu
14073	GfsgsCfgGfgGfUfUfuGfgGfgAfuCfcAfsusu
14074	GfsasGfaAfgGfUfGfcAfuAfgCfaUfcAfsusu
14075	GfsgsAfcUfgGfGfAfuGfgCfaAfcGfcAfsusu
14076	GfsasCfuGfgGfAfUfgGfcAfaCfgCfcAfsusu
14077	UfsgsGfgAfuGfGfCfaAfcGfcCfgAfgAfsusu
14078	CfsgsUfgCfaCfCfUfgGfgUfgGfcGfaAfsusu
14079	CfsusCfcGfuAfCfCfcUfuCfuCfcAfcAfsusu
14080	UfscsCfgUfaCfCfCfuUfcUfcCfaCfuAfsusu
14081	GfsusAfcCfcUfUfCfuCfcAfcUfuGfgAfsusu
14082	AfscsUfuGfgGfAfCfcAfgGfaUfcAfcAfsusu
14083	UfsusGfgGfaCfCfAfgGfaUfcAfcGfaAfsusu
14084	GfsgsGfaCfcAfGfGfaUfcAfcGfaCfcAfsusu
14085	GfsgsAfcCfaGfGfAfuCfaCfgAfcCfuAfsusu
14086	GfsasCfcAfgGfAfUfcAfcGfaCfcUfcAfsusu
14087	CfscsAfgGfaUfCfAfcGfaCfcUfcCfgAfsusu
14088	CfsasGfgAfuCfAfCfgAfcCfuCfcGfcAfsusu
14089	GfsasUfcAfcGfAfCfcUfcCfgCfaGfgAfsusu
14090	AfsusCfaCfgAfCfCfuCfcGfcAfgGfgAfsusu
14091	CfsasCfgAfcCfUfCfcGfcAfgGfgAfcAfsusu
14092	AfscsGfaCfcUfCfCfgCfaGfgGfaCfaAfsusu
14093	CfsgsAfcCfuCfCfGfcAfgGfgAfcAfaAfsusu
14094	UfscsCfgCfaGfGfGfaCfaAfgAfaCfuAfsusu
14095	CfscsGfcAfgGfGfAfcAfaGfaAfcUfgAfsusu
14096	GfsgsCfcAfgUfAfCfuUfcCfgCfuCfcAfsusu
14097	GfscsCfaGfuAfCfUfuCfcGfcUfcCfaAfsusu
14098	GfsgsCfgGfgGfCfCfgCfuAfcUfaCfcAfsusu
14099	CfsasGfgCfcAfCfCfaCfcAfuGfuUfgAfsusu
14100	CfsasCfcAfcCfAfUfgUfuGfaUfcCfaAfsusu
14101	AfscsCfaUfgUfUfGfaUfcCfaGfcCfcAfsusu
14102	CfscsAfuGfuUfGfAfuCfcAfgCfcCfaAfsusu
14103	GfsasCfuCfuUfGfGfcUfcUfgCfcCfgAfsusu
14104	AfscsUfcUfuGfGfCfuCfuGfcCfcGfaAfsusu
14105	UfsgsCfcUfcCfUfGfaGfaUfcGfaGfgAfsusu
14106	GfscsCfuCfcUfGfAfgAfuCfgAfgGfcAfsusu
14107	CfscsUfcCfuGfAfGfaUfcGfaGfgCfuAfsusu
14108	AfsgsAfgGfcGfUfGfgAfcCfaAfgGfgAfsusu
14109	GfsasGfgCfgUfGfGfaCfcAfaGfgGfgAfsusu
14110	UfsgsGfaCfcAfAfGfgGfgCfaUfgGfaAfsusu
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14112	GfsusGfuGfuAfGfGfuCfcCfcUfgGfgAfsusu
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14114	usgsugAfuCfCfGfauucuuuccasusu
14115	csusgcGfaAfUfUfcagcaucugasusu
14116	usgscgAfaUfUfCfagcaucugcasusu
14117	gscsgaAfuUfCfAfgcaucugcaasusu
14118	asasagCfcAfGfUfuuggccuccasusu
14119	usgsgaCfcAfCfAfagcaccuagasusu
14120	csasgaGfuGfGfAfcuauuugaaasusu
14121	ususuuUfgGfUfGfaacugcaagasusu
14122	asgscgGfcAfGfAfagcuuaagaasusu
14123	asgscuUfaAfGfAfagggaaucuasusu
14124	gsgsccAfuCfUfGfgaaacuuguasusu
14125	gscscaUfcUfGfGfaaacuugugasusu
14126	asusgcGfuUfGfCfcuccugagaasusu
14127	gsasucGfaGfGfCfugcaggauaasusu
14128	asuscgAfgGfCfUfgcaggauauasusu
14129	usgscaGfgAfUfAfugcucagacasusu
14130	asusgcUfcAfGfAfcucuagaggasusu
14131	uscsaaUfgGfCfGfgacucagucasusu
14132	csasgaGfuUfCfUfuggaauaaaasusu
14133	gsasguUfcUfUfGfgaauaaaagasusu
14134	usUfsucaAfauaguccAfcUfcugsusu
14135	usAfsgauUfcccuucuUfaAfgcususu
14136	usUfsaucCfugcagccUfcGfaucsusu
14137	**usUfsuuaUfuccaagaAfcUfcugsusu**
14138	usUfsuCfaAfaUfAfguccAfcUfcugsusu
14139	usAfsgAfuUfcCfCfuucuUfaAfgcususu
14140	usUfsaUfcCfuGfCfagccUfcGfaucsusu
14141	**usUfsuUfaUfuCfCfaagaAfcUfcugsusu**
14142	usUfsuCfaAfauaguccAfcUfcugsusu
14143	usAfsgAfuUfcccuucuUfaAfgcususu
14144	usUfsaUfcCfugcagccUfcGfaucsusu
14145	**usUfsuUfaUfuccaagaAfcUfcugsusu**
14146	usUfsucaAfaUfaguccAfcUfcugsusu
14147	usAfsgauUfcCfcuucuUfaAfgcususu
14148	usUfsaucCfuGfcagccUfcGfaucsusu
14149	**usUfsuuaUfuCfcaagaAfcUfcugsusu**
14150	usUfsucaaauaguccAfcucugsusu
14151	usAfsgauucccuucuUfaagcususu
14152	usUfsauccugcagccUfcgaucsusu
14153	**usUfsuuauuccaagaAfcucugsusu**
14154	usUfsuCfaAfaUfaGfuccAfcUfcUfgsusu
14155	usAfsgAfuUfcCfcUfucuUfaAfgCfususu
14156	usUfsaUfcCfuGfcAfgccUfcGfaUfcsusu
14157	**usUfsuUfaUfuCfcAfagaAfcUfcUfgsusu**
14158	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 1AS**
14159	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 2AS**
14160	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 3AS**
14161	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 4AS**
14162	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 5AS**
14163	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 6AS**
14164	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 7AS**
14165	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 8AS**
14166	**UUUUAUUCCAAGAACUCUGUU, with modification pattern 9AS**
14167	usUfsgGfaAfaGfaAfucgGfaUfcAfcsusu
14168	usCfsuGfgAfaAfgAfaucGfgAfuCfasusu
14169	usGfscUfgGfaAfaGfaauCfgGfaUfcsusu
14170	usCfsgCfuGfgAfaAfgaaUfcGfgAfususu
14171	usAfscCfcGfcUfuGfguuGfcAfgAfasusu
14172	usGfsgGfgAfcUfcUfcggGfgAfcGfususu
14173	usAfsuCfuCfgUfcCfcagGfaCfgCfasusu
14174	usGfsgAfcAfuUfcAfucuCfgUfcCfcsusu
14175	usCfsaGfgAfcAfuUfcauCfuCfgUfcsusu
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14177	usCfscGfuGfcGfcCfaggAfcAfuUfcsusu
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14185	usUfscCfgCfgUfgUfucgCfgCfaGfcsusu
14186	usCfsuCfcGfcGfuGfuucGfcGfcAfgsusu
14187	usGfscUfcCfgCfgUfguuCfgCfgCfasusu

14188	usCfsgCfuCfcGfcGfuguUfcGfcGfcsusu	14254	usCfsaAfcAfuGfgUfgguGfgCfcUfgsusu
14189	usGfscGfcUfcCfgCfgugUfuCfgCfgsusu	14255	usUfsgGfaUfcAfaCfaugGfuGfgUfgsusu
14190	usUfsgCfgCfuCfcGfcguGfuUfcGfcsusu	14256	usGfsgGfcUfgGfaUfcaaCfaUfgGfususu
14191	usGfsuGfcGfcUfcCfgcgUfgUfuCfgsusu	14257	usUfsgGfgCfuGfgAfucaAfcAfuGfgsusu
14192	usGfsgGfuGfcGfcUfccgCfgUfgUfususu	14258	usCfsgGfgCfaGfaGfccaAfgAfgUfcsusu
14193	usCfsgGfgUfgCfgCfuccGfcGfuGfususu	14259	usUfscGfgGfcAfgAfgccAfaGfaGfususu
14194	usGfscGfgGfuGfcGfcucCfgCfgUfgsusu	14260	usCfscUfcGfaUfcUfcagGfaGfgCfasusu
14195	usAfscUfgCfgGfgUfgcgCfuCfcGfcsusu	14261	usGfscCfuCfgAfuCfucaGfgAfgGfcsusu
14196	usAfsgCfuGfaCfuGfcggGfuGfcGfcsusu	14262	usAfsgCfcUfcGfaUfcucAfgGfaGfgsusu
14197	usUfscAfgCfuGfaCfugcGfgGfuGfcsusu	14263	usCfscCfuUfgGfuCfcacGfcCfuCfususu
14198	usGfsgUfgGfaCfcCfcucGfgUfuCfcsusu	14264	usCfscCfcUfuGfgUfccaCfgCfcUfcsusu
14199	usCfsgGfuGfgAfcCfccuCfgGfuUfcsusu	14265	usUfscCfaUfgCfcCfcuuGfgUfcCfasusu
14200	usCfsaGfgGfgCfuAfacgGfgAfgGfususu	14266	usGfsgGfgAfcCfuAfcacAfcAfaCfasusu
14201	usUfscAfgGfgGfcUfaacGfgGfaGfgsusu	14267	usCfscCfaGfgGfgAfccuAfcAfcAfcsusu
14202	usGfscUfcUfcAfgGfggcUfaAfcGfgsusu	14268	usGfsuCfcCfcAfgGfggaCfcUfaCfasusu
14203	usCfscUfuGfaGfuUfgugUfcUfgCfasusu	14269	usGfsgaaAfgaaucggAfuCfacasusu
14204	usGfsaGfcCfuUfgAfguuGfuGfuCfususu	14270	usCfsagaUfgcugaauUfcGfcagsusu
14205	usAfsaGfaGfuUfgCfuggAfuCfcUfgsusu	14271	usGfscagAfugcugaaUfuCfgcasusu
14206	usCfscUfuGfuGfgAfagaGfuUfgCfususu	14272	usUfsgcaGfaugcugaAfuUfcgcsusu
14207	usCfsaCfcUfuGfuGfgaaGfaGfuUfgsusu	14273	usGfsgagGfccaaacuGfgCfuuususu
14208	usCfscAfcCfuUfgUfggaAfgAfgUfususu	14274	usCfsuagGfugcuuguGfgUfccasusu
14209	usGfscUfgAfaUfuCfgcaGfgUfgCfususu	14275	usUfsucaAfauaguccAfcUfcugsusu
14210	usGfscCfaCfcUfcAfuggUfcUfaGfgsusu	14276	usCfsuugCfaguucacCfaAfaaasusu
14211	usCfsuUfcGfgGfcAfggcUfuGfgCfcsusu	14277	usUfscuuAfagcuucuGfcCfgcususu
14212	usUfsuCfuUfcGfgGfcagGfcUfuGfgsusu	14278	usAfsgauUfcccuucuUfaAfgcususu
14213	usUfscUfuUfcUfuCfgggCfaGfgCfususu	14279	usAfscaaGfuuuccagAfuGfgccsusu
14214	usAfsuUfaCfuGfuCfcagCfcUfcCfasusu	14280	usCfsacaAfguuuccaGfaUfggcsusu
14215	usCfsuGfaAfuUfaCfuguCfcAfgCfcsusu	14281	usUfscucAfggaggcaAfcGfcausususu
14216	usGfsgCfgCfcUfcUfgaaUfuAfcUfgsusu	14282	usUfsaucCfugcagccUfcGfaucsusu
14217	usUfsgGfcGfcCfuCfugaAfuUfaCfususu	14283	usAfsuauCfcugcagcCfuCfgausususu
14218	usGfsuGfgCfgCfcUfcugAfaUfuAfcsusu	14284	usGfsucuGfagcauauCfcUfgcasusu
14219	usCfsgUfgGfcGfcCfucuGfaAfuUfasusu	14285	usCfscucUfagagucuGfaGfcausususu
14220	usAfsgCfcAfuCfgUfggcGfcCfuCfususu	14286	usGfsacuGfaguccgcCfaUfugasusu
14221	usAfsgGfgCfcGfgUfugaAfgUfcCfasusu	14287	usUfsuuaUfuccaagaAfcUfcugsusu
14222	usCfsaGfgGfcCfgGfuugAfaGfuCfcsusu	14288	usCfsuuuUfauuccaaGfaAfcucsusu
14223	usUfsuCfcCfaGfgGfccgGfuUfgAfasusu	14289	gsgsacAfaUfAfCfuuccacucuasusu
14224	usGfscCfuUfgUfaGfgcuUfcCfcAfgsusu	14290	usAfsgagUfggaaguaUfuGfuccsusu
14225	usCfsgCfcUfuGfuAfggcUfuCfcCfasusu	14291	asgscaGfaAfUfCfugagaauacasusu
14226	usAfsaAfcCfcCfgCfcuuGfuAfgGfcsusu	14292	usGfsuauUfcucagauUfcUfgcususu
14227	usCfscCfaAfaCfcCfcgcCfuUfgUfasusu	14293	nsnsnnNfNfNfNfNfnnnnnnnnnnsnsn
14228	usGfsgAfuCfcCfcAfaacCfcCfgCfcsusu	14294	nsnsnnnNfNfNfNfnnnnnnnnnnsnsn
14229	usGfsaUfgCfuAfuGfcacCfuUfcUfcsusu	14295	nsnsnnnnNfNfNfNfnnnnnnnnnsnsn
14230	usGfscGfuUfgCfcAfuccCfaGfuCfcsusu	14296	nsNfsnnnnnnnnnnnNfnNfnnnsnsn
14231	usGfsgCfgUfuGfcCfaucCfcAfgUfcsusu	14297	nsNfsnnnNfnnNfnnnnNfnNfnnnsnsn
14232	usCfsuCfgGfcGfuUfgccAfuCfcCfasusu	14298	usUfsuUfaUfuCfcAfaGfaAfcUfcUfgsusu
14233	usUfscGfcCfaCfcCfaggUfgCfaCfgsusu	14299	csasgagUfUfCfUfuggaauaaaasusu
14234	usGfsuGfgAfgAfaGfgguAfcGfgAfgsusu	14300	sggacAfGfuAfAfuucagaggcasusu
14235	usAfsgUfgGfaGfaAfgggUfaCfgGfasusu	14301	suggaGfAfaGfGfuGfcauagcaasusu
14236	usCfscAfaGfuGfgAfgaaGfgGfuAfcsusu	14302	saccaccAfuGfuugauccagasusu
14237	usGfsuGfaUfcCfuGfgucCfcAfaGfususu	14303	sugcugUfUfgUfgUfguaggucasusu
14238	usUfscGfuGfaUfcCfuggUfcCfcAfasusu	14304	usGfscCfuCfuGfaAfuUfaCfuGfuCfcsusu
14239	usGfsgUfcGfuGfaUfccuGfgUfcCfcsusu	14305	usUfsgCfuAfuGfcAfcCfuUfcUfcCfasusu
14240	usAfsgGfuCfgUfgAfuccUfgGfuCfcsusu	14306	usCfsuGfgAfuCfaAfcAfuGfgUfgGfususu
14241	usGfsaGfgUfcGfuGfaucCfuGfgUfcsusu	14307	usGfsaCfcUfaCfaCfaCfaAfcAfgCfasusu
14242	usCfsgGfaGfgUfcGfugaUfcCfuGfgsusu	14308	scagagUfUfCfUfuggaauaaaasusu
14243	usGfscGfgAfgGfuCfgugAfuCfcUfgsusu	14309	scagagUfUfCfUfuggaauaaaasusu
14244	usCfscUfgCfgGfaGfgucGfuGfaUfcsusu	14310	scagagUfUfCfUfuggaauaaaasusu
14245	usCfscCfuGfcGfgAfgguCfgUfgAfususu	14311	scagagUfUfCfUfuggaauaaaasusu
14246	usGfsuCfcCfuGfcGfgagGfuCfgUfgsusu	14312	scagagUfUfCfUfuggaauaaaasusu
14247	usUfsgUfcCfcUfgCfggaGfgUfcGfususu	14313	scagagUfUfCfUfudGgaauaaaasusu
14248	usUfsuGfuCfcCfuGfcggAfgGfuCfgsusu	14314	suaUfgCfuCfadGacucuagagasusu
14249	usAfsgUfuCfuUfgUfcccUfgCfgGfasusu	14315	usUfsuUfaUfuCfcAfaGfaAfcUfcUfgsusu
14250	usCfsaGfuUfcUfuGfuccCfuGfcGfgsusu	14316	usUfsuuaUfuCfcAfaGfaAfcUfcUfgsusu
14251	usGfsgAfgCfgGfaAfguaCfuGfgCfcsusu	14317	usUfsusUfaUfuCfcAfaGfaAfcUfcUfgsusu
14252	usUfsgGfaGfcGfgAfaguAfcUfgGfcsusu	14318	usUfsuUfaUfuccAfaGfaAfcUfcUfgsusu
14253	usGfsgUfaGfuAfgCfggcCfcCfgCfcsusu	14319	usUfsuUfaUfuccaaGfaAfcUfcUfgsusu

14320	usUfsuUfaUfuCfcAfaGfaAfcUfcUfgsusu	14328	snnNfnNfnNfndNnnnnnnnnnnsnsn
14321	usCfsuCfuAfgAfgUfcUfgAfgCfaUfasusu	14329	nsNfsnnnNfnNfnNfnNfnNfnNfnNfnsnsn
14322	snnnnNfNfnNfNfnnnnnnnnnnsnsn	14330	nsNfsnsNfnNfnNfnNfnNfnNfnNfnNfnsnsn
14323	snnnnNfNfnNfNfnNfnnnnnnnnsnsn	14331	nsNfsnNfnNfnnnNfnNfnNfnNfnNfnsnsn
14324	snnnnnnNfnNfnnnnnnnnnnsnsn	14332	nsNfsnNfnNfnnnnnNfnNfnNfnNfnsnsn
14325	snnnnnNfNfnNfnNfnnnnnnnnnsnsn		
14326	snnnnnNfNfNfNfnnnnnnnnnnsnsn		
14327	snnnnnNfNfNfNfndNnnnnnnnnsnsn		

[0286] In **Table 1.2**, Nf (e.g. Af, Cf, Gf, Tf or Uf) indicates a 2' fluoro-modified nucleoside, n (e.g. a, c, g, t or u) indicates a 2' O-methyl modified nucleoside, and "s" indicates a phosphorothioate linkage.

V. EXAMPLES

[0287] The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

Example 1: Loss of Function Variants in ANGPTL4 Are Associated with Decreased Risk of Cardiovascular and Metabolic Disease

[0288] Approximately 30,000,000 imputed variants were analyzed in ~375,000 individuals from the UK Biobank cohort for associations with cardiometabolic traits including circulating triglyceride levels, hyperlipidemia, chronic ischemic heart disease, myocardial infarction, Type 2 diabetes, and lipid-lowering and diabetes medication use. Additionally, rare loss of function variants were evaluated in a gene burden test in a subset of ~45,000 individuals from the UK Biobank cohort with available exome sequencing data. Case counts in the full and exome-sequenced cohorts are shown in **Table 2**.

Table 2. Case and Value Counts for Tested Cardiometabolic Traits

Trait	Imputed Genotypes Cases/Counts	Exome Sequencing Cases/Counts
Hyperlipidemia	80,196	10,112
Chronic ischemic heart disease	26,771	3,135
Angina pectoris	22,200	2,685
Myocardial Infarction	15,250	1,616
Type 2 diabetes mellitus	20,663	2,512
Medication - simvastatin	42,197	5,404
Medication - metformin	9,262	1,184
Family history of heart disease	162,657	20,211
Family history of diabetes	76,202	9,845
Blood Triglycerides	356,875	43,055
Blood HDL	327,461	40,600

[0289] Protective associations were observed between a low-frequency and a rare missense variant (rs116843064; MAF=0.02 and rs140744493; MAF=0.003) within ANGPTL4 and cardiometabolic traits (see **Table 3**). The major allele (chr19-8429323-G, hg19) of the rs116843064 variant encodes for a glutamic acid residue and the minor allele (chr19-8429323-A, hg19) a lysine at amino acid position 40 of the full length ANGPTL4 protein (Glu40Lys; E40K). A lysine at position 40 reduces the inhibition of

LPL by ANGPTL4; rs116843064 is thus a loss of function variant. The major allele (chr19-8436373-C, hg19) of the rs140744493 variant encodes for an arginine residue and the minor allele (chr19-8436373-T, hg19) a cysteine at amino acid position 336 of the full length ANGPTL4 protein (Arg336Cys; R336C). A cysteine at position 336 impairs cellular secretion of ANGPTL4; rs140744493 is thus also a loss of function variant. Carriers of the minor allele of both of these variants had a reduced risk of a range of cardiometabolic diseases, as well as reduced circulating triglycerides (p=2.35x10^-145; beta=-0.048 and p=2.64x10^-4; beta=-0.018 for rs116843064 and rs140744493, respectively) and increased high density lipoprotein levels (p=2.35x10^-145; beta=-0.048 and p=2.64x10^-4; beta=-0.018 for rs116843064 and rs140744493, respectively). Accordingly, in some cases therapeutic inhibition or modulation of ANGPTL4 may be an effective genetically-informed method of treatment for cardiovascular and metabolic disease.

Table 3. Association of ANGPTL4 Missense Variants with Cardiometabolic Traits

	rs116843064 (E40K)		rs140744493 (R336C)	
Trait	**Effect Size**	**P**	**Effect Size**	**P**
Hyperlipidemia	0.87 (OR)	2.04E-10	NS	NS
Chronic ischemic heart disease	0.84 (OR)	1.03E-06	NS	NS
Angina pectoris	0.85 (OR)	1.59E-05	0.81 (OR)	0.04
Myocardial Infarction	0.85 (OR)	4.53E-04	NS	NS
Type 2 diabetes mellitus	0.88 (OR)	7.31E-04	NS	NS
Medication - simvastatin	0.91 (OR)	1.13E-03	0.83 (OR)	0.01
Medication - metformin	0.79 (OR)	9.11E-05	NS	NS
Family history of heart disease	0.95 (OR)	5.55E-03	0.91 (OR)	0.04
Family history of diabetes	0.94 (OR)	2.20E-03	NS	NS
Blood Triglycerides	-0.048 (beta)	2.35E-145	-0.018 (beta)	2.13E-04
Blood HDL	0.023 (beta)	3.15E-115	0.011 (beta)	9.70E-06

NS = Not Significant, OR = Odds Ratio

[0290] Using the subset of individuals with available exome sequencing data (approximately 45,000 of the 375,000 individuals), a gene burden test was applied to assess the association of ANGPTL4 loss of function variants on cardiometabolic traits. Gene burden tests are used to aggregate rare variants in a gene by functional class that are too rare to be tested individually. In total, 17 rare predicted loss of function variants (frameshift, stop gained and splice donor/acceptor variants) in 72 total carriers were tested. Individuals carrying predicted ANGPTL4 loss of function variants had significantly lower triglyceride levels when compared to non-carriers (p=2.64E-4; beta=-0.097). These results are directionally consistent with the results obtained in the larger cohort for the rs116843064 and rs140744493 inactivating missense variants, and further confirm that ANGPTL4 loss of function results in lower circulating triglyceride levels.

Example 2: Bioinformatic selection of sequences in order to identify therapeutic siRNAs to downmodulate expression of the ANGPTL4 mRNA

[0291] Screening sets were defined based on bioinformatic analysis. Therapeutic siRNAs were designed to target human ANGPTL4, and the ANGPTL4 sequence of at least one toxicology-relevant species, in this case, the non-human primates (NHP) rhesus and cynomolgus monkeys. Drivers for the design of the screening set were predicted specificity of the siRNAs against the transcriptome of the relevant species as well as cross-reactivity between species. Predicted specificity in human, rhesus monkey, cynomolgus monkey, mouse and rat was determined for sense (S) and antisense (AS) strands. These were assigned a "specificity score" which considers the likelihood of unintended downregulation of any other transcript by full or partial complementarity of an siRNA strand (up to 4 mismatches within positions 2-18) as well as the number and positions of mismatches. Thus, off-target(s) for antisense and sense strands of each siRNA were identified. In addition, the number of potential off-targets was used as an additional specificity factor in the specificity score. As identified, siRNAs with high specificity and a low number of predicted off-targets provide a benefit of increased targeting specificity.

[0292] In addition to selecting siRNA sequences with high sequence specificity to ANGPTL4 mRNA, siRNA sequences within the seed region were analyzed for similarity to seed regions of known miRNAs. siRNAs can function in a miRNA like manner via base-pairing with complementary sequences within the 3'-UTR of mRNA molecules. The complementarity typically encompasses the 5'-bases at positions 2-7 of the miRNA (seed region). To circumvent siRNAs to act via functional miRNA binding sites, siRNA strands containing natural miRNA seed regions were avoided. Seed regions identified in miRNAs from human, mouse, rat, rhesus monkey, dog, rabbit and pig are referred to as "conserved". Combining the "specificity score" with miRNA seed analysis yielded a "specificity category". This is divided into categories 1-4, with 1 having the highest specificity and 4 having the lowest specificity. Each strand of the siRNA is assigned to a specificity category.

[0293] Species cross-reactivity was assessed for human, cynomolgus monkey, rhesus monkey, mouse and rat. The analysis was based on a canonical siRNA design using 19 bases and 17 bases (without considering positions 1 and 19) for cross-reactivity. Full match as well as single mismatch analyses were included.

[0294] Analysis of the human Single Nucleotide Polymorphism (SNP) database (NCBI-DB-SNP) to identify siRNAs targeting regions with known SNPs was also carried out to identify siRNAs that may be non-functional in individuals containing the SNP. Information regarding the positions of SNPs within the target sequence as well as minor allele frequency (MAF) in case data was obtained in this analysis.

[0295] Initial analysis of the relevant ANGPTL4 mRNA sequence revealed few sequences that fulfil the specificity parameters and at the same time target ANGPTL4 mRNA in all of the analyzed relevant species. Therefore, it was decided to design independent screening subsets for the therapeutic siRNAs.

[0296] The siRNAs in these subsets recognize the human ANGPTL4 sequence, as a human cell culture system is selected for determination of *in vitro* activity. Therefore, the siRNAs in these subsets can be used to target human ANGPTL4 in a therapeutic setting.

[0297] The number of siRNAs that were derived from human ANGPTL4 mRNA (NM_139314.3) without consideration of specificity or species cross-reactivity was 1,854 (antisense and sense strand sequences included in SEQ ID NOS: 1-3708).

[0298] Prioritizing sequences for target specificity, species cross-reactivity, miRNA seed region sequences and SNPs as described above yields subset A. The siRNAs in subset A are included in **Table 4**.

Table 4. Subset A

siRNA Name	Sense Strand Sequence SEQ ID NO:	Antisense Strand Sequence SEQ ID NO:
siRNA 32	32	1886
siRNA 33	33	1887
siRNA 34	34	1888
siRNA 35	35	1889
siRNA 36	36	1890
siRNA 56	56	1910
siRNA 57	57	1911
siRNA 58	58	1912
siRNA 59	59	1913
siRNA 61	61	1915
siRNA 62	62	1916
siRNA 63	63	1917
siRNA 64	64	1918
siRNA 79	79	1933
siRNA 80	80	1934
siRNA 84	84	1938
siRNA 111	111	1965
siRNA 112	112	1966
siRNA 116	116	1970
siRNA 117	117	1971
siRNA 118	118	1972
siRNA 119	119	1973
siRNA 120	120	1974
siRNA 121	121	1975
siRNA 125	125	1979
siRNA 126	126	1980
siRNA 127	127	1981
siRNA 128	128	1982
siRNA 129	129	1983
siRNA 149	149	2003
siRNA 150	150	2004
siRNA 152	152	2006
siRNA 153	153	2007
siRNA 154	154	2008
siRNA 157	157	2011
siRNA 158	158	2012
siRNA 159	159	2013
siRNA 161	161	2015
siRNA 164	164	2018
siRNA 165	165	2019
siRNA 166	166	2020
siRNA 167	167	2021
siRNA 168	168	2022
siRNA 169	169	2023
siRNA 172	172	2026
siRNA 174	174	2028
siRNA 175	175	2029
siRNA 177	177	2031
siRNA 196	196	2050
siRNA 198	198	2052
siRNA 199	199	2053
siRNA 210	210	2064
siRNA 211	211	2065
siRNA 212	212	2066
siRNA 214	214	2068
siRNA 215	215	2069
siRNA 216	216	2070
siRNA 217	217	2071
siRNA 218	218	2072
siRNA 219	219	2073
siRNA 221	221	2075
siRNA 222	222	2076
siRNA 223	223	2077
siRNA 228	228	2082
siRNA 230	230	2084
siRNA 231	231	2085
siRNA 240	240	2094
siRNA 241	241	2095
siRNA 245	245	2099
siRNA 246	246	2100

siRNA 250	250	2104
siRNA 252	252	2106
siRNA 253	253	2107
siRNA 254	254	2108
siRNA 255	255	2109
siRNA 260	260	2114
siRNA 261	261	2115
siRNA 262	262	2116
siRNA 263	263	2117
siRNA 265	265	2119
siRNA 266	266	2120
siRNA 271	271	2125
siRNA 272	272	2126
siRNA 274	274	2128
siRNA 280	280	2134
siRNA 282	282	2136
siRNA 289	289	2143
siRNA 290	290	2144
siRNA 291	291	2145
siRNA 292	292	2146
siRNA 293	293	2147
siRNA 299	299	2153
siRNA 304	304	2158
siRNA 321	321	2175
siRNA 323	323	2177
siRNA 325	325	2179
siRNA 326	326	2180
siRNA 328	328	2182
siRNA 329	329	2183
siRNA 330	330	2184
siRNA 331	331	2185
siRNA 332	332	2186
siRNA 333	333	2187
siRNA 334	334	2188
siRNA 335	335	2189
siRNA 337	337	2191
siRNA 338	338	2192
siRNA 339	339	2193
siRNA 342	342	2196
siRNA 347	347	2201
siRNA 349	349	2203
siRNA 350	350	2204
siRNA 352	352	2206
siRNA 353	353	2207
siRNA 356	356	2210
siRNA 377	377	2231

siRNA 380	380	2234
siRNA 382	382	2236
siRNA 386	386	2240
siRNA 388	388	2242
siRNA 391	391	2245
siRNA 392	392	2246
siRNA 393	393	2247
siRNA 394	394	2248
siRNA 397	397	2251
siRNA 398	398	2252
siRNA 399	399	2253
siRNA 402	402	2256
siRNA 404	404	2258
siRNA 405	405	2259
siRNA 411	411	2265
siRNA 412	412	2266
siRNA 413	413	2267
siRNA 414	414	2268
siRNA 415	415	2269
siRNA 417	417	2271
siRNA 419	419	2273
siRNA 420	420	2274
siRNA 421	421	2275
siRNA 422	422	2276
siRNA 423	423	2277
siRNA 424	424	2278
siRNA 425	425	2279
siRNA 426	426	2280
siRNA 427	427	2281
siRNA 428	428	2282
siRNA 429	429	2283
siRNA 430	430	2284
siRNA 431	431	2285
siRNA 435	435	2289
siRNA 481	481	2335
siRNA 484	484	2338
siRNA 506	506	2360
siRNA 509	509	2363
siRNA 517	517	2371
siRNA 519	519	2373
siRNA 520	520	2374
siRNA 565	565	2419
siRNA 570	570	2424
siRNA 571	571	2425
siRNA 572	572	2426
siRNA 589	589	2443

siRNA 607	607	2461
siRNA 608	608	2462
siRNA 610	610	2464
siRNA 611	611	2465
siRNA 612	612	2466
siRNA 616	616	2470
siRNA 617	617	2471
siRNA 620	620	2474
siRNA 623	623	2477
siRNA 635	635	2489
siRNA 637	637	2491
siRNA 640	640	2494
siRNA 643	643	2497
siRNA 653	653	2507
siRNA 672	672	2526
siRNA 673	673	2527
siRNA 674	674	2528
siRNA 675	675	2529
siRNA 676	676	2530
siRNA 677	677	2531
siRNA 678	678	2532
siRNA 679	679	2533
siRNA 681	681	2535
siRNA 682	682	2536
siRNA 683	683	2537
siRNA 684	684	2538
siRNA 686	686	2540
siRNA 687	687	2541
siRNA 689	689	2543
siRNA 692	692	2546
siRNA 695	695	2549
siRNA 830	830	2684
siRNA 834	834	2688
siRNA 841	841	2695
siRNA 842	842	2696
siRNA 843	843	2697
siRNA 844	844	2698
siRNA 850	850	2704
siRNA 851	851	2705
siRNA 852	852	2706
siRNA 853	853	2707
siRNA 854	854	2708
siRNA 856	856	2710
siRNA 857	857	2711
siRNA 859	859	2713
siRNA 866	866	2720

siRNA 868	868	2722
siRNA 871	871	2725
siRNA 872	872	2726
siRNA 876	876	2730
siRNA 887	887	2741
siRNA 888	888	2742
siRNA 890	890	2744
siRNA 892	892	2746
siRNA 893	893	2747
siRNA 894	894	2748
siRNA 897	897	2751
siRNA 900	900	2754
siRNA 902	902	2756
siRNA 907	907	2761
siRNA 911	911	2765
siRNA 912	912	2766
siRNA 913	913	2767
siRNA 914	914	2768
siRNA 915	915	2769
siRNA 916	916	2770
siRNA 917	917	2771
siRNA 918	918	2772
siRNA 919	919	2773
siRNA 920	920	2774
siRNA 921	921	2775
siRNA 922	922	2776
siRNA 925	925	2779
siRNA 945	945	2799
siRNA 968	968	2822
siRNA 1001	1001	2855
siRNA 1002	1002	2856
siRNA 1005	1005	2859
siRNA 1006	1006	2860
siRNA 1009	1009	2863
siRNA 1010	1010	2864
siRNA 1011	1011	2865
siRNA 1013	1013	2867
siRNA 1028	1028	2882
siRNA 1032	1032	2886
siRNA 1037	1037	2891
siRNA 1052	1052	2906
siRNA 1053	1053	2907
siRNA 1054	1054	2908
siRNA 1055	1055	2909
siRNA 1057	1057	2911
siRNA 1058	1058	2912

siRNA 1064	1064	2918
siRNA 1112	1112	2966
siRNA 1122	1122	2976
siRNA 1124	1124	2978
siRNA 1126	1126	2980
siRNA 1127	1127	2981
siRNA 1133	1133	2987
siRNA 1134	1134	2988
siRNA 1136	1136	2990
siRNA 1137	1137	2991
siRNA 1147	1147	3001
siRNA 1148	1148	3002
siRNA 1149	1149	3003
siRNA 1151	1151	3005
siRNA 1153	1153	3007
siRNA 1154	1154	3008
siRNA 1155	1155	3009
siRNA 1157	1157	3011
siRNA 1158	1158	3012
siRNA 1161	1161	3015
siRNA 1162	1162	3016
siRNA 1163	1163	3017
siRNA 1164	1164	3018
siRNA 1165	1165	3019
siRNA 1166	1166	3020
siRNA 1171	1171	3025
siRNA 1172	1172	3026
siRNA 1175	1175	3029
siRNA 1181	1181	3035
siRNA 1182	1182	3036
siRNA 1184	1184	3038
siRNA 1248	1248	3102
siRNA 1249	1249	3103
siRNA 1252	1252	3106
siRNA 1253	1253	3107
siRNA 1259	1259	3113
siRNA 1276	1276	3130
siRNA 1285	1285	3139
siRNA 1310	1310	3164
siRNA 1315	1315	3169
siRNA 1338	1338	3192
siRNA 1343	1343	3197
siRNA 1347	1347	3201
siRNA 1348	1348	3202
siRNA 1349	1349	3203
siRNA 1350	1350	3204

siRNA 1351	1351	3205
siRNA 1352	1352	3206
siRNA 1378	1378	3232
siRNA 1405	1405	3259
siRNA 1407	1407	3261
siRNA 1413	1413	3267
siRNA 1414	1414	3268
siRNA 1415	1415	3269
siRNA 1416	1416	3270
siRNA 1417	1417	3271
siRNA 1418	1418	3272
siRNA 1429	1429	3283
siRNA 1430	1430	3284
siRNA 1448	1448	3302
siRNA 1477	1477	3331
siRNA 1487	1487	3341
siRNA 1488	1488	3342
siRNA 1489	1489	3343
siRNA 1493	1493	3347
siRNA 1494	1494	3348
siRNA 1519	1519	3373
siRNA 1523	1523	3377
siRNA 1538	1538	3392
siRNA 1556	1556	3410
siRNA 1561	1561	3415
siRNA 1563	1563	3417
siRNA 1564	1564	3418
siRNA 1565	1565	3419
siRNA 1570	1570	3424
siRNA 1571	1571	3425
siRNA 1572	1572	3426
siRNA 1580	1580	3434
siRNA 1581	1581	3435
siRNA 1589	1589	3443
siRNA 1597	1597	3451
siRNA 1598	1598	3452
siRNA 1601	1601	3455
siRNA 1602	1602	3456
siRNA 1603	1603	3457
siRNA 1604	1604	3458
siRNA 1605	1605	3459
siRNA 1606	1606	3460
siRNA 1610	1610	3464
siRNA 1611	1611	3465
siRNA 1613	1613	3467
siRNA 1614	1614	3468

siRNA 1617	1617	3471
siRNA 1693	1693	3547
siRNA 1699	1699	3553
siRNA 1701	1701	3555
siRNA 1702	1702	3556
siRNA 1703	1703	3557
siRNA 1722	1722	3576
siRNA 1740	1740	3594
siRNA 1741	1741	3595
siRNA 1742	1742	3596
siRNA 1745	1745	3599
siRNA 1747	1747	3601
siRNA 1748	1748	3602
siRNA 1749	1749	3603

siRNA 1751	1751	3605
siRNA 1754	1754	3608
siRNA 1755	1755	3609
siRNA 1779	1779	3633
siRNA 1780	1780	3634
siRNA 1784	1784	3638
siRNA 1787	1787	3641
siRNA 1788	1788	3642
siRNA 1798	1798	3652
siRNA 1799	1799	3653
siRNA 1800	1800	3654
siRNA 1801	1801	3655
siRNA 1802	1802	3656
siRNA 1803	1803	3657

[0299] Subset A includes 102 siRNA sequences that are cross-reactive with NHP ANGPTL4 mRNA (siRNAs 33, 34, 35, 36, 56, 121, 272, 280, 282, 289, 290, 291, 292, 293, 321, 323, 326, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 342, 347, 349, 411, 412, 430, 431, 435, 481, 484, 509, 517, 519, 520, 565, 620, 635, 637, 640, 830, 834, 841, 842, 843, 844, 850, 871, 872, 876, 887, 888, 894, 897, 902, 945, 1001, 1002, 1005, 1037, 1133, 1134, 1137, 1149, 1151, 1153, 1154, 1155, 1157, 1158, 1161, 1162, 1164, 1165, 1166, 1171, 1172, 1248, 1249, 1315, 1338, 1343, 1347, 1348, 1429, 1430, 1570, 1571, 1572, 1610, 1611, 1617, 1780, 1784, and 1787). The siRNAs in subset A that may be cross-reactive with NHP ANGPTL4 mRNA were tested *in vitro* (see, e.g., **Table 5**). The sense strand of any of these siRNAs may include any one of modification patterns 1S-9S. The antisense strand of any of these siRNAs may include any one of modification patterns 1AS-11AS.

[0300] The siRNAs in subset A have the following characteristics:

- Cross-reactivity: With 19mer in human ANGPTL4 mRNA, with 17mer/19mer in NHP ANGPTL4
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species
- Off-target frequency: ≤20 human off-targets matched with 2 mismatches in antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[0301] The siRNA sequences in subset A were selected for more stringent specificity to yield subset B. Subset B includes 323 siRNAs (siRNAs 32, 33, 34, 35, 36, 56, 57, 58, 59, 61, 62, 63, 64, 79, 80, 112, 116, 117, 118, 119, 120, 125, 126, 127, 128, 129, 149, 150, 152, 153, 157, 158, 159, 161, 164, 165, 166, 167, 168, 169, 172, 174, 175, 196, 199, 211, 212, 214, 215, 216, 217, 218, 219, 221, 222, 223, 228, 230, 231, 240, 241, 245, 246, 250, 252, 253, 254, 255, 260, 261, 262, 263, 265, 266, 271, 272, 274, 280, 289, 290, 291, 292, 293, 299, 304, 321, 323, 325, 326, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339,

342, 347, 349, 350, 352, 353, 356, 380, 382, 386, 388, 391, 392, 393, 394, 397, 398, 399, 402, 404, 405, 411, 412, 413, 414, 415, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 435, 484, 517, 519, 520, 565, 570, 571, 572, 607, 608, 610, 611, 612, 616, 617, 620, 635, 637, 640, 672, 673, 674, 675, 676, 677, 678, 679, 681, 682, 683, 684, 686, 687, 689, 692, 695, 830, 841, 842, 843, 844, 850, 851, 852, 853, 854, 856, 857, 866, 868, 871, 872, 876, 887, 888, 890, 892, 893, 894, 902, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 945, 1001, 1002, 1005, 1006, 1009, 1010, 1011, 1013, 1028, 1032, 1052, 1053, 1054, 1055, 1057, 1058, 1112, 1122, 1124, 1126, 1127, 1133, 1134, 1147, 1148, 1149, 1151, 1153, 1154, 1155, 1157, 1158, 1161, 1162, 1164, 1165, 1166, 1175, 1182, 1184, 1252, 1253, 1259, 1276, 1285, 1310, 1315, 1343, 1347, 1348, 1349, 1350, 1351, 1405, 1407, 1413, 1414, 1415, 1416, 1417, 1418, 1429, 1430, 1448, 1519, 1523, 1556, 1561, 1563, 1564, 1565, 1571, 1572, 1580, 1581, 1589, 1597, 1601, 1602, 1603, 1604, 1605, 1606, 1611, 1613, 1614, 1693, 1699, 1701, 1702, 1703, 1722, 1740, 1741, 1742, 1745, 1747, 1748, 1749, 1751, 1754, 1755, 1779, 1780, 1784, 1788, 1798, 1799, 1801, 1802, and 1803). This subset includes 85 siRNA sequences that are cross-reactive with NHP ANGPTL4 mRNA (siRNAs 33, 34, 35, 36, 56, 272, 280, 289, 290, 291, 292, 293, 321, 323, 326, 328, 329, 330, 331, 332, 333, 334, 335, 337, 338, 339, 342, 347, 349, 411, 412, 430, 431, 435, 484, 517, 519, 520, 565, 620, 635, 637, 640, 830, 841, 842, 843, 844, 850, 871, 872, 876, 887, 888, 894, 902, 945, 1001, 1002, 1005, 1133, 1134, 1149, 1151, 1153, 1154, 1155, 1157, 1158, 1161, 1162, 1164, 1165, 1166, 1315, 1343, 1347, 1348, 1429, 1430, 1571, 1572, 1611, 1780, and 1784).

[0302] The siRNAs in subset B have the following characteristics:

- Cross-reactivity: With 19mer in human ANGPTL4 mRNA, with 17mer/19mer in NHP ANGPTL4
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species
- Off-target frequency: ≤15 human off-targets matched with 2 mismatches in antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[0303] The siRNA sequences in subset B were further selected for absence of seed regions in the AS strand that are identical to a seed region of known human miRNA to yield subset C. Subset C includes 183 siRNAs (siRNAs 32, 36, 56, 57, 58, 61, 62, 79, 80, 117, 119, 125, 126, 128, 149, 152, 157, 158, 159, 161, 165, 166, 167, 168, 169, 174, 196, 211, 212, 217, 218, 219, 230, 231, 245, 246, 253, 260, 261, 262, 271, 272, 280, 289, 291, 292, 293, 304, 321, 323, 325, 326, 328, 330, 331, 332, 333, 334, 337, 338, 342, 347, 349, 352, 353, 356, 380, 382, 386, 388, 391, 392, 394, 399, 413, 414, 415, 422, 423, 424, 425, 426, 435, 517, 519, 520, 565, 571, 607, 608, 612, 617, 620, 635, 640, 672, 673, 674, 675, 678, 679, 681, 683, 684, 687, 692, 842, 843, 850, 851, 854, 866, 868, 876, 892, 893, 902, 911, 912, 913, 914, 916, 919, 945, 1001, 1002, 1006, 1010, 1028, 1052, 1053, 1054, 1055, 1057, 1112, 1124, 1127, 1147, 1149, 1151, 1153, 1155, 1157, 1164, 1175, 1182, 1184, 1259, 1276, 1285, 1315, 1343, 1349, 1350, 1351, 1405, 1407, 1413, 1415, 1418, 1564, 1571, 1581, 1589, 1597, 1601, 1602, 1603, 1604, 1605, 1606, 1613, 1614, 1693, 1701,

1722, 1740, 1745, 1751, 1755, 1801, 1802, and 1803). This subset includes 47 siRNA sequences that are cross-reactive with NHP ANGPTL4 mRNA (siRNAs 36, 56, 272, 280, 289, 291, 292, 293, 321, 323, 326, 328, 330, 331, 332, 333, 334, 337, 338, 342, 347, 349, 435, 517, 519, 520, 565, 620, 635, 640, 842, 843, 850, 876, 902, 945, 1001, 1002, 1149, 1151, 1153, 1155, 1157, 1164, 1315, 1343, and 1571).

[0304] The siRNAs in subset C have the following characteristics:

- Cross-reactivity: With 19mer in human ANGPTL4 mRNA, with 17mer/19mer in NHP ANGPTL4
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species. AS strand: seed region not identical to seed region of known human miRNA
- Off-target frequency: ≤15 human off-targets matched with 2 mismatches by antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[0305] The siRNA sequences in subset C were also selected for absence of seed regions in the AS or S strands that are identical to a seed region of known human miRNA to yield subset D. Subset D includes 114 siRNAs (siRNAs 32, 36, 56, 58, 61, 62, 80, 117, 119, 126, 152, 154, 157, 158, 159, 161, 166, 169, 174, 177, 196, 211, 212, 217, 218, 230, 231, 245, 253, 260, 261, 271, 272, 280, 289, 293, 304, 328, 330, 331, 332, 333, 334, 337, 342, 347, 349, 353, 356, 386, 388, 391, 392, 394, 414, 415, 422, 423, 424, 426, 435, 520, 571, 608, 612, 617, 653, 672, 678, 679, 681, 683, 692, 842, 843, 851, 854, 859, 876, 892, 900, 913, 914, 919, 968, 1001, 1002, 1054, 1057, 1064, 1112, 1124, 1157, 1164, 1182, 1184, 1248, 1259, 1343, 1351, 1352, 1415, 1418, 1564, 1581, 1602, 1614, 1693, 1701, 1722, 1740, 1751, 1755, and 1787). This subset includes 26 siRNA sequences that are cross-reactive with NHP ANGPTL4 mRNA (siRNAs 36, 56, 272, 280, 289, 293, 328, 330, 331, 332, 333, 334, 337, 342, 347, 349, 435, 520, 842, 843, 876, 1001, 1002, 1157, 1164, and 1343).

[0306] The siRNAs in subset D have the following characteristics:

- Cross-reactivity: With 19mer in human ANGPTL4 mRNA, with 17mer/19mer in NHP ANGPTL4
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species. AS+SS strand: seed region not identical to seed region of known human miRNA
- Off-target frequency: ≤20 human off-targets matched with 2 mismatches by antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[0307] The siRNA sequences in subset D were further selected for more stringent specificity to yield subset E. Subset E includes 104 siRNAs (siRNAs 32, 36, 56, 58, 61, 62, 80, 117, 119, 126, 152, 157, 158, 159, 161, 166, 169, 174, 196, 211, 212, 217, 218, 230, 231, 245, 253, 260, 261, 271, 272, 280, 289, 293, 304, 328, 330, 331, 332, 333, 334, 337, 342, 347, 349, 353, 356, 386, 388, 391, 392, 394, 414, 415,

422, 423, 424, 426, 435, 520, 571, 608, 612, 617, 672, 678, 679, 681, 683, 692, 842, 843, 851, 854, 876, 892, 913, 914, 919, 1001, 1002, 1054, 1057, 1112, 1124, 1157, 1164, 1182, 1184, 1259, 1343, 1351, 1415, 1418, 1564, 1581, 1602, 1614, 1693, 1701, 1722, 1740, 1751, and 1755). This set includes 26 siRNA sequences that are cross-reactive with NHP ANGPTL4 mRNA (siRNAs 36, 56, 272, 280, 289, 293, 328, 330, 331, 332, 333, 334, 337, 342, 347, 349, 435, 520, 842, 843, 876, 1001, 1002, 1157, 1164, and 1343).

[0308] The siRNAs in subset E have the following characteristics:

- Cross-reactivity: With 19mer in human ANGPTL4 mRNA, with 17mer/19mer in NHP ANGPTL4
- Specificity category: For human and NHP: AS2 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region not conserved in human, mouse, and rat and not present in >4 species. AS+SS strand: seed region not identical to seed region of known human miRNA
- Off-target frequency: ≤15 human off-targets matched with 2 mismatches by antisense strand
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[0309] The siRNA sequences targeting ANGPTL4 can also be selected using other criteria. Subset F includes 115 siRNAs (siRNAs 32, 57, 119, 120, 125, 126, 127, 128, 164, 165, 166, 167, 168, 169, 174, 175, 176, 177, 199, 250, 252, 255, 260, 261, 262, 263, 353, 356, 363, 372, 403, 404, 412, 413, 417, 423, 424, 425, 426, 427, 428, 429, 565, 570, 571, 572, 589, 607, 608, 610, 611, 612, 672, 673, 674, 675, 676, 677, 678, 679, 689, 695, 759, 801, 851, 852, 853, 854, 857, 859, 866, 868, 907, 911, 912, 913, 914, 915, 918, 919, 972, 1006, 1009, 1010, 1011, 1013, 1028, 1034, 1037, 1048, 1126, 1276, 1285, 1349, 1489, 1490, 1564, 1565, 1580, 1581, 1589, 1597, 1598, 1601, 1602, 1603, 1604, 1605, 1606, 1610, 1701, 1702, 1789, 1840, and 1842).

[0310] The siRNAs in subset F met the following criteria:

- Cross-reactivity: With 19mer in human ANGPTL4 mRNA. One or fewer mismatches with 19mer in either rhesus or cynomolgus monkey.
- Specificity category: For human: AS2 or better, SS3 or better. For NHP: AS3 or better, SS3 or better
- miRNA seeds: AS+SS strand: seed region conserved in <4 species (out of 7). AS and SS strand: seed region not conserved between human, mouse and rat
- Off-target frequency: For human: no perfect match or single mismatches. For NHP: no perfect match
- SNPs: siRNA target sites do not harbor SNPs with a MAF ≥ 1% (pos. 2-18)

[0311] Subset G includes 20 siRNAs (siRNAs 32, 570, 571, 572, 589, 607, 759, 801, 1276, 1285, 1489, 1490, 1564, 1580, 1581, 1589, 1597, 1702, 1840, and 1842). The siRNAs in subset G include siRNAs from subset F that were tested *in vitro* (see, e.g., **Table 6**). In some cases, the sense strand of any of the siRNAs of subset G comprises modification pattern 2S. In some cases, the antisense strand of any of the

siRNAs of subset G comprises modification pattern 3AS. The siRNAs in subset G may comprise any other modification pattern(s) (e.g. any of modification patterns 1S-9S, or 1AS-11AS).

[0312] Any siRNA among any of subsets A-G may comprise any modification pattern described herein. If a sequence is a different number of nucleotides in length than a modification pattern, the modification pattern may still be used with the appropriate number of additional nucleotides added 5' or 3' to match the number of nucleotides in the modification pattern. For example, if a sense or antisense strand of the siRNA among any of subsets A-G comprises 19 nucleotides, and a modification pattern comprises 21 nucleotides, UU may be added onto the 5' end of the sense or antisense strand.

Example 3: Chemically modified ANGPTL4 siRNAs

[0313] The siRNAs targeting ANGPTL4 can be synthesized with chemical modifications with the sense strand having modification pattern 1S (SEQ ID NO: 13954) and the antisense strand having modification pattern 1AS (SEQ ID NO: 13960). In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand. The sense strand or antisense strand may have a GalNAc moiety attached to it.

[0314] The siRNAs targeting ANGPTL4 can also be synthesized with chemical modifications with the sense strand having modification pattern 2S (SEQ ID NO: 13955) and the antisense strand having modification pattern 3AS (SEQ ID NO: 13962). In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand. The sense strand or antisense strand may have a GalNAc moiety attached to it.

[0315] The siRNAs targeting ANGPTL4 can also be synthesized with chemical modifications with the sense strand having modification pattern 2S (SEQ ID NO: 13955) and the antisense strand having modification pattern 9AS (SEQ ID NO: 13968). In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand. The sense strand or antisense strand may have a GalNAc moiety attached to it.

[0316] The siRNAs targeting ANGPTL4 can also be synthesized with chemical modifications with the sense strand having modification pattern 3S (SEQ ID NO: 13954) and the antisense strand having modification pattern 3AS (SEQ ID NO: 13962). In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand. The sense strand or antisense strand may have a GalNAc moiety attached to it.

[0317] The siRNAs targeting ANGPTL4 can also be synthesized with chemical modifications with the sense strand having modification pattern 6S (SEQ ID NO: 13959) and the antisense strand having modification pattern 6AS (SEQ ID NO: 13965). In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand. The sense strand or antisense strand may have a GalNAc moiety attached to it.

[0318] The siRNAs targeting ANGPTL4 can also be synthesized with chemical modifications with the sense strand having modification pattern 6S (SEQ ID NO: 13959) and the antisense strand having modification pattern 8AS (SEQ ID NO: 13967). In addition, adenosine can be placed at position 19 in the

sense strand and uridine at position 1 in the antisense strand. The sense strand or antisense strand may have a GalNAc moiety attached to it.

[0319] Some examples include modification pattern 7S, 8S, or 9S. Some examples include modification pattern 10AS or 11AS). The sense strand or antisense strand that includes any of these modification patterns may have a GalNAc moiety attached to it.

Example 4: Screening ANGPTL4 siRNAs for activity in cells in culture

[0320] Chemically modified ANGPTL4 siRNAs cross reactive for human and non-human primate were assayed for ANGPTL4 mRNA knockdown activity in cells in culture. U-138 MG (ATCC® HTB-16) cells were seeded in 96-well tissue culture plates at a cell density of 7,500 cells per well in EMEM (BD Biosciences Catalog No. 670086) supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere composed of air plus 5% carbon dioxide. The ANGPTL4 siRNAs were individually transfected into U-138 MG cells in duplicate wells at 10 nM final concentration using 0.3 μL Lipofectamine RNAiMax (Fisher) per well. Silencer Select Negative Control #1 (ThermoFisher, Catalog# 4390843) was transfected at 10 nM final concentration as a control. After incubation for 48 hours at 37°C, total RNA was harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, Catalog# A35374) according to the manufacturer's instructions. The level of ANGPTL4 mRNA from each well was measured in triplicate by real-time qPCR on an Applied Biosystems 7500 Fast Real-Time PCR machine using TaqMan Gene Expression Assay for human ANGPTL4 (ThermoFisher, assay# Hs01101127_m1). The level of PPIA mRNA was measured using TaqMan Gene Expression Assay (ThermoFisher, assay# Hs99999904_m1) and used to determine relative ANGPTL4 mRNA levels in each well using the delta-delta Ct method. All data were normalized to relative ANGPTL4 mRNA levels in untreated U-138 MG cells. A subset of the siRNAs were also tested at 1 nM concentration. Results are shown in **Table 5** and **Table 6**. The siRNAs in **Table 5** (ETD00646-ETD00747) each comprised a sense strand having modification pattern 1S, and an sense strand having modification pattern 1AS. The siRNAs in **Table 6** (ETD00915-ETD00934) each comprised a sense strand having modification pattern 2S, and an sense strand having modification pattern 3AS. These siRNAs may include any modification pattern(s) (e.g. any of modification patterns 1S-9S, or 1AS-11AS).

Table 5. Knockdown Activity of ANGPTL4-Specific siRNAs at 1 nM and 10 nM in Human U-138 MG cells

siRNA name	Sense Strand SEQ ID NO:	Antisense Strand SEQ ID NO:	Relative ANGPTL4 mRNA Level	
			1 nM siRNA	10 nM siRNA
Untreated Cells	-	-	1.00	1.00
Negative Control siRNA	-	-	1.15	1.14
ETD00646	14012	14167	ND	0.72
ETD00647	14013	14168	ND	0.97
ETD00648	14014	14169	ND	0.84
ETD00649	14015	14170	0.94	0.69

ETD00650	14016	14171	ND	2.08
ETD00651	14017	14172	0.99	0.71
ETD00652	14018	14173	ND	1.06
ETD00653	14019	14174	1.03	0.63
ETD00654	14020	14175	1.18	0.68
ETD00655	14021	14176	1.05	0.65
ETD00656	14022	14177	ND	0.86
ETD00657	14023	14178	ND	0.96
ETD00658	14024	14179	ND	0.87
ETD00659	14025	14180	ND	1.02
ETD00660	14026	14181	ND	0.84
ETD00661	14027	14182	ND	0.84
ETD00662	14028	14183	ND	0.82
ETD00663	14029	14184	ND	0.94
ETD00664	14030	14185	ND	0.97
ETD00665	14031	14186	ND	1.22
ETD00666	14032	14187	ND	1.24
ETD00667	14033	14188	ND	0.88
ETD00668	14034	14189	ND	1.00
ETD00669	14035	14190	1.05	0.68
ETD00670	14036	14191	ND	0.93
ETD00671	14037	14192	ND	1.59
ETD00672	14038	14193	ND	1.41
ETD00673	14039	14194	ND	1.80
ETD00674	14040	14195	ND	1.87
ETD00675	14041	14196	ND	1.04
ETD00676	14042	14197	ND	1.28
ETD00677	14043	14198	ND	1.39
ETD00678	14044	14199	ND	1.49
ETD00679	14045	14200	ND	1.28
ETD00680	14046	14201	ND	1.52
ETD00681	14047	14202	ND	2.12
ETD00682	14048	14203	ND	0.91
ETD00683	14049	14204	1.06	0.47
ETD00684	14050	14205	0.88	0.63
ETD00685	14051	14206	ND	1.02
ETD00686	14052	14207	0.79	0.66
ETD00687	14053	14208	ND	0.91
ETD00688	14054	14209	ND	0.84
ETD00689	14055	14210	1.01	0.51
ETD00690	14056	14211	ND	1.29
ETD00691	14057	14212	ND	0.80
ETD00692	14058	14213	ND	0.78

ETD00693	14059	14214	ND	1.09
ETD00694	14060	14215	1.16	0.58
ETD00695	14061	14216	ND	1.79
ETD00696	14062	14217	ND	1.55
ETD00697	14063	14218	ND	1.42
ETD00698	14064	14219	ND	1.83
ETD00699	14065	14220	ND	1.10
ETD00700	14066	14221	ND	1.33
ETD00701	14067	14222	ND	1.13
ETD00702	14068	14223	ND	0.85
ETD00703	14069	14224	ND	1.26
ETD00704	14070	14225	ND	1.14
ETD00705	14071	14226	ND	1.72
ETD00706	14072	14227	ND	1.63
ETD00707	14073	14228	ND	0.92
ETD00708	14074	14229	ND	1.69
ETD00709	14075	14230	1.24	0.69
ETD00710	14076	14231	ND	2.23
ETD00711	14077	14232	ND	1.02
ETD00712	14078	14233	ND	1.21
ETD00713	14079	14234	1.09	0.48
ETD00714	14080	14235	0.94	0.50
ETD00715	14081	14236	0.98	0.65
ETD00716	14082	14237	0.91	0.59
ETD00717	14083	14238	ND	0.82
ETD00718	14084	14239	ND	1.09
ETD00719	14085	14240	ND	0.84
ETD00720	14086	14241	ND	1.82
ETD00721	14087	14242	0.64	0.47
ETD00722	14088	14243	ND	1.52
ETD00723	14089	14244	ND	1.08
ETD00724	14090	14245	ND	0.91
ETD00725	14091	14246	ND	0.93
ETD00726	14092	14247	ND	0.90
ETD00727	14093	14248	ND	0.76
ETD00728	14094	14249	0.94	0.43
ETD00729	14095	14250	1.08	0.71
ETD00730	14096	14251	ND	0.80
ETD00731	14097	14252	1.25	0.56
ETD00732	14098	14253	ND	1.25
ETD00733	14099	14254	ND	0.88
ETD00734	14100	14255	ND	1.15
ETD00735	14101	14256	ND	1.11

ETD00736	14102	14257	0.90	0.48
ETD00737	14103	14258	ND	1.10
ETD00738	14104	14259	ND	0.83
ETD00739	14105	14260	ND	1.33
ETD00740	14106	14261	ND	1.40
ETD00741	14107	14262	ND	0.96
ETD00742	14108	14263	ND	1.30
ETD00743	14109	14264	1.04	0.63
ETD00744	14110	14265	ND	1.24
ETD00745	14111	14266	ND	1.42
ETD00746	14112	14267	ND	1.20
ETD00747	14113	14268	ND	1.21

"-" untreated U-138MG cells; Negative Control siRNA, Silencer Select Negative Control #1; ND, Not Determined

Table 6. Knockdown Activity of ANGPTL4-Specific siRNAs at 1 nM and 10 nM in Human U-138 MG Cells

siRNA name	Sense Strand SEQ ID NO:	Antisense Strand SEQ ID NO:	Relative ANGPTL4 mRNA Level	
			1 nM siRNA	10 nM siRNA
Untreated Cells	-	-	1.00	1.00
Negative Control siRNA	-	-	1.23	1.10
ETD00915	14114	14269	1.05	0.85
ETD00916	14115	14270	0.62	0.39
ETD00917	14116	14271	0.84	0.86
ETD00918	14117	14272	1.02	1.03
ETD00919	14118	14273	1.01	1.02
ETD00920	14119	14274	0.91	1.15
ETD00921	14120	14275	0.78	0.48
ETD00922	14121	14276	1.18	1.10
ETD00923	14122	14277	0.91	0.93
ETD00924	14123	14278	0.82	0.57
ETD00925	14124	14279	0.79	0.57
ETD00926	14125	14280	0.77	0.47
ETD00927	14126	14281	0.98	0.73
ETD00928	14127	14282	0.87	0.50
ETD00929	14128	14283	0.91	0.54
ETD00930	14129	14284	0.85	0.58
ETD00931	14130	14285	0.85	0.46
ETD00932	14131	14286	1.01	0.72
ETD00933	14132	14287	0.38	0.33
ETD00934	14133	14288	0.65	0.37

"-" untreated U-138MG cells; Negative Control siRNA, Silencer Select Negative Control #1; ND, Not Determined

Example 5: Determining the IC50 of ANGPTL4 siRNAs

[0321] The IC50 values for knockdown of ANGPTL4 mRNA by select ANGPTL4 siRNAs were determined in U-138 MG cells. The siRNAs were assayed individually at 30 nM, 10 nM, 3 nM, 1 nM and 0.3 nM, or 3 nM, 1 nM, 0.3 nM, 0.1 nM and 0.03 nM, or 30 nM, 10 nM, 3 nM, 1 nM, 0.3 nM, 0.1 nM and 0.03 nM. The U-138 MG (ATCC® HTB-16) cells were seeded in 96-well tissue culture plates at a cell density of 7,500 cells per well in EMEM (BD Biosciences Catalog No. 670086) supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere composed of air plus 5% carbon dioxide. The ANGPTL4 siRNAs were individually transfected into U-138 MG cells in triplicate wells using 0.3 µL Lipofectamine RNAiMax (Fisher) per well. After incubation for 48 hours at 37°C, total RNA was harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, Catalog# A35374) according to the manufacturer's instructions. The level of ANGPTL4 mRNA from each well was measured in triplicate by real-time qPCR on an Applied Biosystems 7500 Fast Real-Time PCR machine using TaqMan Gene Expression Assay for human ANGPTL4 (ThermoFisher, assay# Hs01101127_m1). The level of PPIA mRNA was measured using TaqMan Gene Expression Assay (ThermoFisher, assay# Hs99999904_m1) and used to determine relative ANGPTL4 mRNA levels in each well using the delta-delta Ct method. All data were normalized to relative ANGPTL4 mRNA levels in untreated U-138 MG cells. Curve fit was accomplish using the [inhibitor] vs. response (three parameters) function in GraphPad Prism software. Results are shown in **Table 7**.

Table 7. IC50 Values of ANGPTL4 siRNAs in Human U-138 MG Cells

siRNA	[siRNA]	Relative ANGPTL4 mRNA Levels	IC50 (nM)
-	-	1	ND
ETD00714	30 nM	0.27	4.27
	10 nM	0.43	
	3 nM	0.52	
	1 nM	0.69	
	0.3 nM	0.75	
ETD00721	30 nM	0.54	2.69
	10 nM	0.61	
	3 nM	0.86	
	1 nM	1.09	
	0.3 nM	1.21	
ETD00728	30 nM	0.57	5.10
	10 nM	0.79	
	3 nM	0.95	
	1 nM	1.29	
	0.3 nM	1.27	
ETD00736	30 nM	0.35	8.06
	10 nM	0.36	
	3 nM	0.76	
	1 nM	0.71	
	0.3 nM	0.78	
ETD00916	3 nM	0.20	0.42

	1 nM	0.45	
	0.3 nM	0.68	
	0.1 nM	0.89	
	0.03 nM	1.07	
ETD00921	30 nM	0.43	0.16
	10 nM	0.43	
	3 nM	0.49	
	1 nM	0.55	
	0.3 nM	0.86	
	0.1 nM	0.93	
	0.03 nM	1.30	
ETD00924	30 nM	0.44	0.54
	10 nM	0.47	
	3 nM	0.52	
	1 nM	0.63	
	0.3 nM	0.82	
	0.1 nM	0.91	
	0.03 nM	0.99	
ETD00925	3 nM	0.21	ND
	1 nM	0.69	
	0.3 nM	0.99	
	0.1 nM	0.87	
	0.03 nM	0.88	
ETD00926	3 nM	0.46	0.91
	1 nM	0.84	
	0.3 nM	1.09	
	0.1 nM	1.21	
	0.03 nM	1.46	
ETD00928	30 nM	0.56	0.13
	10 nM	0.47	
	3 nM	0.49	
	1 nM	0.55	
	0.3 nM	0.76	
	0.1 nM	1.45	
	0.03 nM	1.55	
ETD00930	3 nM	0.70	ND
	1 nM	0.76	
	0.3 nM	0.95	
	0.1 nM	0.90	
	0.03 nM	1.07	
ETD00931	3 nM	0.29	ND
	1 nM	0.77	
	0.3 nM	0.88	
	0.1 nM	0.97	
	0.03 nM	0.92	
ETD00933	30 nM	0.26	0.13
	10 nM	0.26	
	3 nM	0.28	
	1 nM	0.29	
	0.3 nM	0.37	
	0.1 nM	0.67	
	0.03 nM	0.71	
ETD00934	3 nM	0.53	ND
	1 nM	0.66	

	0.3 nM	0.65	
	0.1 nM	0.97	
	0.03 nM	0.98	

"-" untreated U-138 MG cells; ND, Not Determined

[0322] Some siRNAs having sense strands in accordance with SEQ ID NOs: 13974-13977, and having antisense strands in accordance with SEQ ID NOs: 13982-13985, were synthesized with an alternative modification pattern and are included in **Table 8**. The siRNAs in **Table 8** were based, at least partially, on siRNAs having sense strand sequences comprising the sequences of SEQ ID NOs: 759, 1285, 1580, and 1840, and having antisense strand sequences comprising the sequences of SEQ ID NOs: 2613, 3139, 3434, and 3694.

Table 8. Alternative Modification Patterns of Select siRNAs

ETD#	**Sense strand sequence (5'-3')**	**Antisense strand sequence (5'-3')**
ETD01062	csasgaGfuGfgAfcuauuugaaasusu	usUfsucaAfauaguccAfcUfcugsusu
ETD01063	asgscuUfaAfgAfagggaaucuasusu	usAfsgauUfcccuucuUfaAfgcususu
ETD01064	gsasucGfaGfgCfugcaggauaasusu	usUfsaucCfugcagccUfcGfaucsusu
ETD01065	csasgaGfuUfcUfuggaauaaaasusu	usUfsuuaUfuccaagaAfcUfcugsusu
ETD#	**Sense strand – SEQ ID NO:**	**Antisense strand – SEQ ID NO:**
ETD01062	13986	14134
ETD01063	13987	14135
ETD01064	13988	14136
ETD01065	13989	14137

[0323] IC50 values for knockdown of ANGPTL4 mRNA for ETD01062, ETD01063, ETD01064 and ETD01065 ANGPTL4 siRNAs were determined in U-138 MG cells. The siRNAs were assayed individually at 30 nM, 10 nM, 3 nM, 1 nM, 0.3 nM, 0.1 nM and 0.03 nM. The U-138 MG (ATCC® HTB-16) cells were seeded in 96-well tissue culture plates at a cell density of 7,500 cells per well in EMEM (BD Biosciences Catalog No. 670086) supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere composed of air plus 5% carbon dioxide. The ANGPTL4 siRNAs were individually transfected into U-138 MG cells in triplicate wells using 0.3 µL Lipofectamine RNAiMax (Fisher) per well. After incubation for 48 hours at 37°C, total RNA was harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, Catalog# A35374) according to the manufacturer's instructions. The level of ANGPTL4 mRNA from each well was measured in triplicate by real-time qPCR on an Applied Biosystems 7500 Fast Real-Time PCR machine using TaqMan Gene Expression Assay for human ANGPTL4 (ThermoFisher, assay# Hs01101127_m1). The level of PPIA mRNA was measured using TaqMan Gene Expression Assay (ThermoFisher, assay# Hs99999904_m1) and used to determine relative ANGPTL4 mRNA levels in each well using the delta-delta Ct method. All data were normalized to relative ANGPTL4 mRNA levels in untreated U-138 MG cells. Curve fit was accomplished using the [inhibitor] vs. response (three parameters) function in GraphPad Prism software. Results are shown in

Table 9.

Table 9. IC50 Values of ETD01062, ETD01063, ETD01064 and ETD01065 ANGPTL4 siRNAs in Human U-138 MG Cells

siRNA	[siRNA]	Relative ANGPTL4 mRNA Levels	IC50 (nM)
-	-	1	ND
ETD01062	30 nM	0.41	0.22
	10 nM	0.39	
	3 nM	0.36	
	1 nM	0.42	
	0.3 nM	0.63	
	0.1 nM	0.70	
	0.03 nM	0.82	
ETD01063	30 nM	0.68	1.24
	10 nM	0.62	
	3 nM	0.62	
	1 nM	0.71	
	0.3 nM	1.54	
	0.1 nM	1.15	
	0.03 nM	0.89	
ETD01064	30 nM	0.83	0.25
	10 nM	0.41	
	3 nM	0.57	
	1 nM	0.57	
	0.3 nM	0.71	
	0.1 nM	1.27	
	0.03 nM	0.89	
ETD01065	30 nM	0.24	0.07
	10 nM	0.23	
	3 nM	0.20	
	1 nM	0.27	
	0.3 nM	0.31	
	0.1 nM	0.42	
	0.03 nM	0.56	

"-" untreated U-138 MG cells; ND, Not Determined

Example 6: Assessing the extent of nuclease resistance of ANGPTL4 siRNAs

[0324] Resistance of select ANGPTL4 siRNAs to nuclease digestion was assessed by incubating the siRNAs in rat liver tritosomes. Each siRNA (7 ng/μL final concentration) was placed into a PCR tube containing a cocktail prepared on ice containing 1x catabolic buffer (Xenotech, Catalog# K5200, Lot# 18-1-0698), 0.5x rat tritosomes (Xenotech, Catalog# R0610.LT, Lot# 1610405), 0.1U/μL porcine intestinal heparin (Zageno, Catalog# H3149-10KU). An aliquot was removed, an equal volume of 50 mM EDTA was added, and the sample placed at -80°C. This sample was designated as the 0 hr timepoint. The remainder of the reaction was placed in an Eppendorf Mastercycler Gradient and incubated at 37°C. After incubation for 4 and 24 hours, an aliquot was removed from the reaction and stopped by addition of an equal volume of 50 mM EDTA and placed at -80°C until analysis by gel electrophoresis. All samples were then thawed on ice and 6x DNA Gel Loading Dye (ThermoFisher Catalog# R0611) was added to 1x final concentration. 20 μL of each sample was loaded onto a 20%

polyacrylamide TBE gel (ThermoFisher, Catalog# EC63155BOX). Electrophoresis was carried out at a constant 100V for 75 minutes in an XCell SureLock Mini-Cell Electrophoresis System (ThermoFisher) using 1x TBE (Tris/boric/EDTA) (Fisher, Catalog# FERB52) as the tank buffer. The siRNA was visualized by staining the gel with a 1:10,000 dilution of SYBR Gold (ThermoFisher, Catalog# S-11494) in TBE for 15 minutes at room temperature with rocking. The gel was washed with 1x TBE for 15 minutes and then placed on a FotoPrep1 UV transilluminator (Fotodyne). The gel was imaged using the camera app set on MONO on an iPhone 6s with a yellow gel filter (Neewer) placed over the lens. Band intensity was measured using NIH ImageJ using the "Analyze: Gels" function. The remaining siRNA percent was normalized to the value obtained at the 0 hr timepoint for that siRNA. Results are shown in **Table 10**. By using this assay, we were able to determine that some siRNAs are more resistant to nuclease digestion with more remaining intact over time compared with other siRNAs with the same modification pattern.

Table 10. Resistance of ANGPTL4 siRNAs to Nucleases Present in Rat Liver Tritosomes

siRNA	Timepoint (hr)	% remaining
ETD00686	0	100%
	4	79%
	24	27%
ETD00714	0	100%
	4	66%
	24	33%
ETD00721	0	100%
	4	77%
	24	47%
ETD00728	0	100%
	4	74%
	24	32%
ETD00736	0	100%
	4	81%
	24	39%
ETD00916	0	100%
	4	85%
	24	59%
ETD00924	0	100%
	4	68%
	24	24%
ETD00926	0	100%
	4	74%
	24	47%

ETD00928	0	100%
	4	73%
	24	25%
ETD00933	0	100%
	4	73%
	24	28%

Example 7: Screening ANGPTL4 ASOs for activity in cells in culture

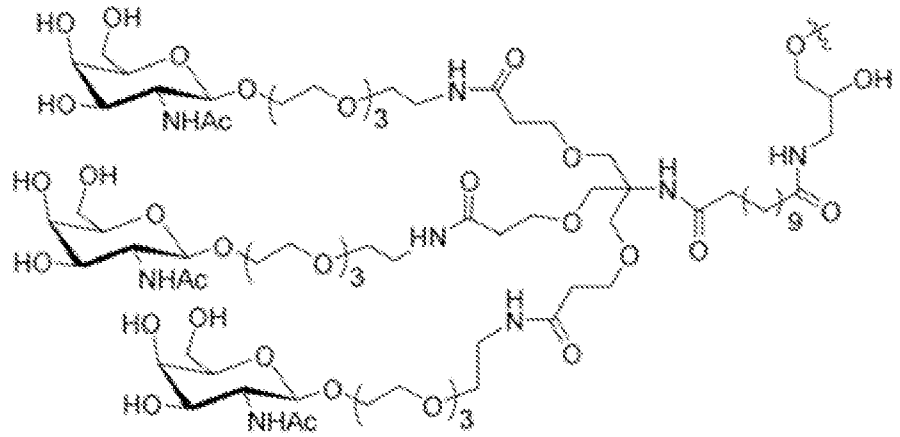
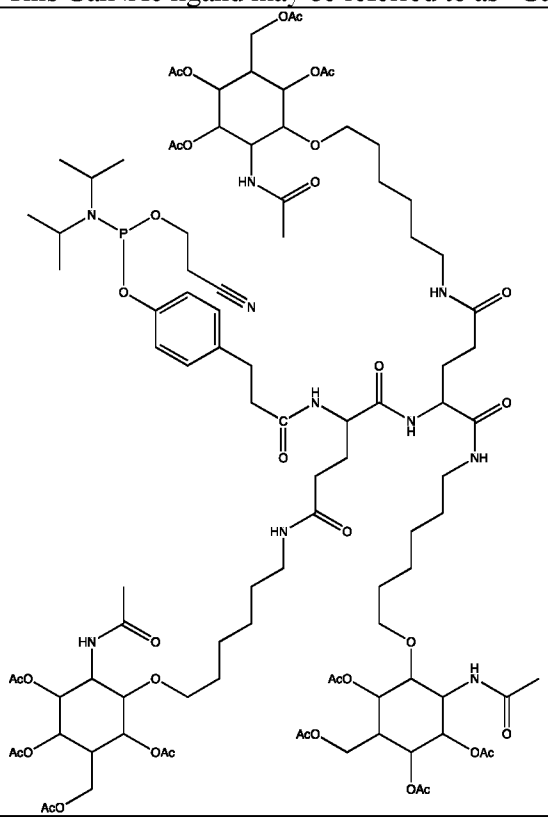
[0325] ANGPTL4 ASOs with sequences provided in SEQ ID NOs: 3709-13934 and those possessing modification pattern ASO1 (SEQ ID NO: 13969) are to be assayed for ANGPTL4 mRNA reduction activity in cells in culture. A cell line such as ARPE-19 that expresses ANGPTL4 (ATCC® CRL-2302) will be seeded in 96-well tissue culture plates at a cell density of 10,000 cells per well in DMEM supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere of air plus 5% carbon dioxide. The ANGPTL4 ASOs are individually transfected into cells in duplicate wells at 1 uM final concentration using 0.3 uL Lipofectamine RNAiMax (Fisher) per well. A negative control ASO (SEQ ID NO: 13953) is also transfected at 1 uM final concentration. After incubation for 48 hours at 37°C, total RNA is harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, Catalog# A35374) according to the manufacturer's instructions. The level of ANGPTL4 mRNA from each well will be measured in triplicate by real-time qPCR on an Applied Biosystems 7500 Fast Real-Time PCR machine using TaqMan Gene Expression Assay for human ANGPTL4 (ThermoFisher, assay# Hs01101127_m1). The level of PPIA mRNA is measured using TaqMan Gene Expression Assay (ThermoFisher, assay# Hs99999904_m1) and used to determine relative ANGPTL4 mRNA levels in each well using the delta-delta Ct method. Data are normalized to relative ANGPTL4 mRNA levels in untreated ARPE-19 cells.

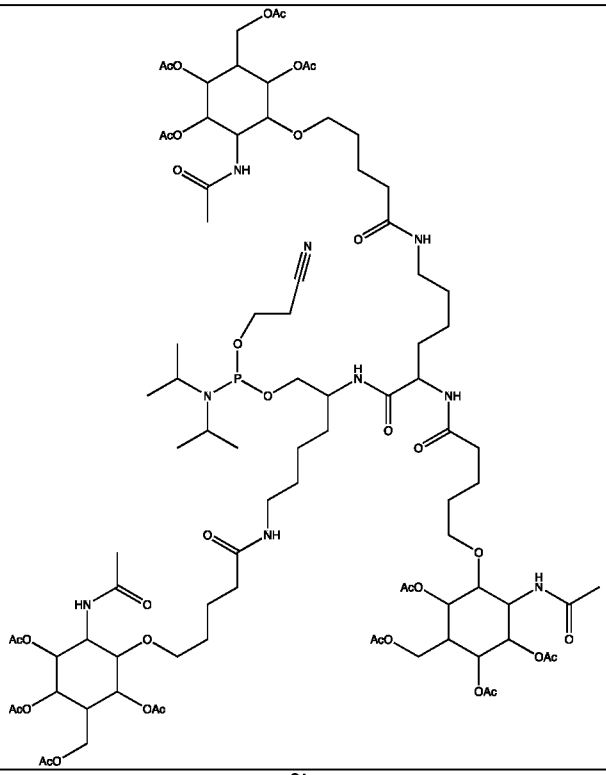
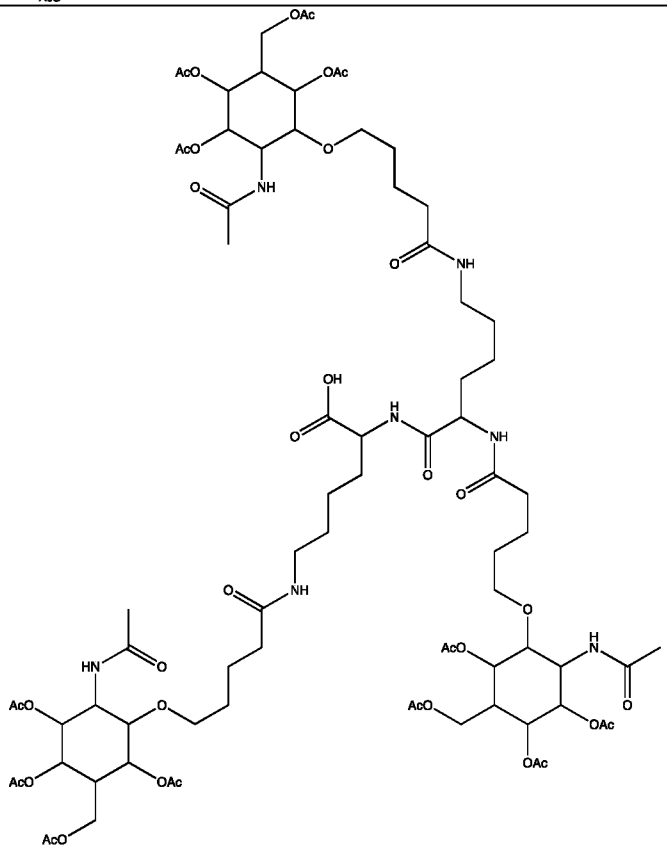
[0326] The ANGPTL4 ASOs showing the greatest degree of reduction of ANGPTL4 mRNA at 1 uM are to be tested in a second screen for activity at 100 nM concentration using the transfection procedures as described above.

Example 8: GalNAc ligand for hepatocyte targeting of oligonucleotides

[0327] Without limiting the disclosure to these individual methods, there are at least two general methods for attachment of multivalent N-acetylgalactosamine (GalNAc) ligands to oligonucleotides: solid or solution-phase conjugations. GalNAc ligands may be attached to solid phase resin for 3' conjugation or at the 5' terminus using GalNAc phosphoramidite reagents. GalNAc phosphoramidites may be coupled on solid phase as for other nucleosides in the oligonucleotide sequence at any position in the sequence. Reagents for GalNAc conjugation to oligonucleotides are shown in **Table 11**.

Table 11. GalNAc Conjugation Reagents

Type of conjugation	Structure
Solid phase 3' attachment where squiggly line is rest of oligonucleotide chain and right-most OH is where attachment` to solid phase is.	 This GalNAc ligand may be referred to as "GalNAc23" or "GalNAc#23."
Solid phase 5' attachment phosphoramidite	

Solid phase 5' attachment Phosphoramidite	
Solution phase Carboxylic acid for amide coupling anywhere on oligonucleotide	 Where Ac is an acetyl group or other hydroxyl protecting group that can be removed under basic, acid or reducing conditions.

[0328] In solution phase conjugation, the oligonucleotide sequence—including a reactive conjugation site—is formed on the resin. The oligonucleotide is then removed from the resin and GalNAc is conjugated to the reactive site.

[0329] The carboxy GalNAc derivatives may be coupled to amino-modified oligonucleotides. The peptide coupling conditions are known to the skilled in the art using a carbodiimide coupling agent like DCC (N,N′-Dicyclohexylcarbodiimide), EDC (N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide) or EDC.HCl (N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride and an additive like HOBt (1-hydroxybenztriazole), HOSu (N-hydroxysuccinimide), TBTU (N,N,N′,N′-Tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate, HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) or HOAt (1-Hydroxy-7-azabenzotriazole and common combinations thereof such as TBTU/HOBt or HBTU/HOAt to form activated amine-reactive esters.

[0330] Amine groups may be incorporated into oligonucleotides using a number of known, commercially available reagents at the 5’ terminus, 3’ terminus or anywhere in between.

[0331] Non-limiting examples of reagents for oligonucleotide synthesis to incorporate an amino group include:

- 5’ attachment:
- 6-(4-Monomethoxytritylamino)hexyl-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite CAS Number: 114616-27-2
- 5'-Amino-Modifier TEG CE-Phosphoramidite
- 10-(O-trifluoroacetamido-N-ethyl)-triethyleneglycol-1-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite
- 3’ attachment:
- 3'-Amino-Modifier Serinol CPG
- 3-Dimethoxytrityloxy-2-(3-(fluorenylmethoxycarbonylamino)propanamido)propyl-1-O-succinyl-long chain alkylamino-CPG (where CPG stands for controlled-pore glass and is the solid support)
- Amino-Modifier Serinol Phosphoramidite
- 3-Dimethoxytrityloxy-2-(3-(fluorenylmethoxycarbonylamino)propanamido)propyl-1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite

[0332] Internal (base modified):

- Amino-Modifier C6 dT
- 5'-Dimethoxytrityl-5-[N-(trifluoroacetylaminohexyl)-3-acrylimido]-2'-deoxyUridine,3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite. CAS Number: 178925-21-8

[0333] Solution phase conjugations may occur after oligonucleotide synthesis via reactions between non-nucleosidic nucleophilic functional groups that are attached to the oligonucleotide and electrophilic GalNAc reagents. Examples of nucleophilic groups include amines and thiols, and examples of electrophilic reagents include activated esters (e.g. N-hydroxysuccinimide, pentafluorophenyl) and maleimides.

Example 9: Inhibition of ANGPTL4 in a mouse model of hypertriglyceridemia

[0334] In this experiment, a murine model of hypertriglyceridemia is to be used to evaluate the effect of siRNA or ASO inhibition of ANGPTL4 expressed in the liver compared to an anti-mouse ANGPTL4 antibody. The mouse strain C57Bl/6 Apoetm1Unc mice (Jackson Labs) will be maintained on a high fat Western diet (Research Diets, D12492; 60% fat by calories).

[0335] Four groups of mice (n=12/group) will be utilized in this study. Animals will be maintained on a high fat diet during the study. On Day -4 before the first injection, chow will be removed for an overnight fast. On Day -3 before the first injection, all animals will be anesthetized and 300 uL of blood collected in serum separator tubes via the submandibular vein to assess baseline triglyceride, serum glucose, insulin sensitivity, total cholesterol levels, HDL Cholesterol levels, liver function and serum levels of ANGPTL4 protein. On Study Day 0, Group 1 mice will be injected intraperitoneally with 600 uL normal saline, Group 2 mice will be injected intraperitoneally with 600 ug of anti-mouse ANGPTL4 antibody in 600 uL, Group 3 mice will be injected subcutaneously with 100 ug of GalNAc-ANGPTL4 siRNA targeting mouse ANGPTL4 with sense strand selected from sequences provided in SEQ ID NO: 13937-13944, 14289, or 14291, and antisense strands selected from sequences provided in SEQ ID NO: 13945-13952, 14290, or 14292, in 200 uL of normal saline, and Group 4 mice will be injected subcutaneously with 150 ug of GalNAc-ANGPTL4 ASO targeting mouse ANGPTL4 in 200 uL of normal saline. The sense strands selected from sequences provided in SEQ ID NO: 13937-13944, 14289, or 14291 will comprise a GalNAc ligand attached to the 3' end of the sense strands. On the afternoon of Day 3, the chow will be removed from all Groups for an overnight fast. On Day 4, the animals from all Groups will be anesthetized and 150 uL of blood collected in serum separator tubes via the submandibular vein to assess serum triglycerides, glucose, total cholesterol, HDL cholesterol and levels of ANGPTL4 protein. Animals from all groups will then undergo an oral glucose tolerance test and insulin tolerance test to evaluate insulin sensitivity. Chow will be supplied again as normal after blood has been collected and insulin sensitivity tests conducted. Weekly thereafter starting on Day 7 the animals from Group 2 will be dosed as on Day 0 for a total of 15 injections. Every other week thereafter starting on Day 14 the animals from Group 3 and Group 4 will be dosed as on Day 0 for a total of 8 injections. Every other week starting on Day 10, the mice from all Groups will be fasted (overnight) and bled (150 uL into serum separator tubes) to assess serum triglyceride, glucose, total cholesterol, HDL cholesterol and levels of ANGPTL4 protein, and undergo insulin sensitivity tests. On the third day after the final injection, the chow will be removed from all Groups for an overnight fast. On the fourth day after the final injection, the animals from all Groups will be anesthetized, euthanized and bled via cardiac puncture to collect 500 uL of blood into serum separator tubes to assess triglyceride, serum glucose, insulin sensitivity, total cholesterol levels, HDL cholesterol levels, liver function and serum levels of ANGPTL4 protein. Tissue from the liver, small intestine and mesenteric lymph nodes will be collected from all animals and immersed in 10% neutral buffered formalin for histopathological analysis. A liver sample will also be collected from all animals and placed in RNAlater. The levels of ANGPTL4 mRNA will be assessed by RT-qPCR using

TaqMan assays for mouse ANGPTL4 (ThermoFisher, assay# Mm00480431_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1).

[0336] Animals treated with the anti-mouse ANGPTL4 antibody (Group 2), mice treated with GalNAc-ANGPTL4 siRNA (Group 3), and mice treated with GalNAc-ANGPTL4 ASO (Group 4) are expected to have decreased triglycerides, total serum cholesterol, serum glucose as well as decreased serum ANGPTL4 protein levels, and increased HDL cholesterol and insulin sensitivity, compared with mice from Group 1 (saline). Animals in Group 2 and Group 3 are also expected to have decreased ANGPTL4 mRNA in liver samples.

Example 10: Inhibition of ANGPTL4 in non-human primates using GalNAc-ANGPTL4 siRNA and GalNAc-ANGPTL4 ASO

[0337] In this experiment, a NHP model of hypertriglyceridemia is used to evaluate the effect of siRNA or ASO inhibition of ANGPTL4 expressed in the liver. Three groups of cynomolgus monkeys will be used (n=5/group) that are placed on a high-fat diet (Western Primate Diet, 5S2T) before the initiation of the study. Alternatively, three groups of rhesus monkeys will be used (n=5/group) that are placed on a high fructose diet before the initiation of the study. Animals are to be given 7 biweekly subcutaneous injections of saline (Group 1), GalNAc-ANGPTL4 siRNA (Group 2), or GalNAc-ANGPTL4 ASO (Group 3). The modified GalNAc-ANGPTL4 siRNA sequences are chosen from subset A that are cross-reactive between human and NHP, and include any one of modification patterns 1S-9S and 1AS-11AS, or another pattern of modification described herein. Other GalNAc-ANGPTL4 siRNA sequences may be chosen from subset F that are cross-reactive between human and NHP, or modifications thereof. Blood samples for lipid and glycemic measurements will be collected at baseline and at 4, 8, and 14 weeks of the study and analyzed for lipid content, serum glucose, insulin sensitivity and ANGPTL4 protein. All animals from each group are necropsied 2 weeks after the last blood collection. Tissue from the liver, small intestine and mesenteric lymph nodes will be collected from all animals and immersed in 10% neutral buffered formalin for histopathological analysis. A liver sample will also be collected from all animals and placed in RNAlater. The levels of ANGPTL4 mRNA will be assessed by RT-qPCR using TaqMan assays for cynomolgus ANGPTL4 (ThermoFisher, assay# Mf01101127_m1) or rhesus ANGPTL4, and the cynomolgus housekeeping gene PPIA (ThermoFisher, assay# Mf04932064_gH) or rhesus PPIA.

[0338] It is expected that animals treated with the GalNAc ANGPTL4 siRNA (Group 2) and animals treated with GalNAc-ANGPTL4 ASO (Group 3) will show decreased triglycerides, total serum cholesterol and serum glucose as well as decreased serum ANGPTL4 protein levels, and increased HDL cholesterol and insulin sensitivity, compared with animals from Group 1 (saline). It is also expected that animals in Group 1 and Group 3 will show decreased ANGPTL4 mRNA in liver samples.

Example 11: Inhibition of ANGPTL4 in a clinical trial using GalNAc-ANGPTL4 siRNA and GalNAc-ANGPTL4 ASO

[0339] In this study, human subjects with hypertriglyceridemia are used to evaluate the effect of siRNA or ASO inhibition of ANGPTL4 expressed in the liver. Selection criteria for inclusion in the study are ages 40-90, BMI ≥ 30, and serum triglycerides ≥ 250 mg/dL. Three groups of subjects will be included (n=15/group) in the study. Subjects are to be given 5 weekly subcutaneous injections of saline (Group 1), GalNAc-ANGPTL4 siRNA (Group 2), or GalNAc-ANGPTL4 ASO (Group 3). The modified GalNAc-ANGPTL4 siRNA sequences are chosen from subset A that show high activity in cells in culture in the experiments of Example 4. Blood samples for lipid and glycemic measurements will be collected at baseline and at 3, 6, and 12 weeks of the study and analyzed for lipid content, serum glucose, insulin sensitivity, ANGPTL4 protein, and liver and kidney function.

[0340] It is expected that subjects treated with the GalNAc ANGPTL4 siRNA (Group 2) and subjects treated with GalNAc-ANGPTL4 ASO (Group 3) will show decreased triglycerides, total serum cholesterol and serum glucose as well as decreased serum ANGPTL4 protein levels, and increased HDL cholesterol and insulin sensitivity, compared with subjects from Group 1 (saline).

Example 12: siRNA-mediated knockdown of ANGPTL4 in a mouse model of hypertriglyceridemia

[0341] The effects of siRNA-mediated knockdown of ANGPTL4 in the liver was investigated in a murine model of hypertriglyceridemia. Eight- to ten-week-old C57Bl/6 Apoetm1Unc mice (Jackson Labs) were placed on a high fat Western diet (Research Diets, D12492; 60% fat by calories) for two weeks prior to the start of the study on Day 0. On Day 0 and Day 7, mice in Group 1 (n=4) were given 200 uL of phosphate buffered saline (PBS) and mice in Group 2 (n=4) were given 200 ug of the siRNA targeting mouse ANGPTL4 (ETD00642: sense strand having the sequence of SEQ ID NO: 13941 and a 3' conjugated GalNAc ligand, and antisense strand having the sequence of SEQ ID NO: 13949) in 200 uL PBS by subcutaneous injection. Serum samples were collected from all mice fed ad libidum on Day 13. On Day 14, serum samples were collected from all mice after a 24 hour fast. Clinical chemistry assays including those for triglyceride and glucose were performed at IDEXX Laboratories, Incorporated. All mice were then euthanized and a liver sample from each was collected and placed in RNAlater (ThermoFisher Cat#AM7020). Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. The levels of liver ANGPTL4 mRNA were assessed by RT-qPCR using TaqMan assays for mouse ANGPTL4 (ThermoFisher, assay# Mm00480431_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1). Data were normalized to the level in animals receiving PBS (Group 1). Results are shown in **Table 12**. Mice receiving ETD00642 (Group2) had reduced levels of liver ANGPTL4 mRNA compared to mice receiving PBS (Group 1).

Table 12. Day 14 ANGPTL4 mRNA Levels in Mice Treated with ETD00642

Group #	Animal #	Relative Liver ANGPTL4 mRNA Level	Mean Relative Liver ANGPTL4 mRNA level
1	1	1.30	1.00
	2	0.95	
	3	1.11	
	4	0.73	
2	5	0.48	0.47
	6	0.55	
	7	0.51	
	8	0.36	

[0342] The levels of triglycerides and glucose are shown in **Table 13**. The serum triglyceride levels in fed mice on Day 13 and fasted mice on Day 14 were lower in mice receiving ETD00642 (Group 2) than in control mice receiving PBS (Group1). The serum glucose levels in fed mice on Day 13 were lower in mice receiving ETD00642 (Group 2) than in control mice receiving PBS (Group1). The serum glucose levels in fasted mice on Day 14 were also lower in mice receiving ETD00642 (Group 2) than in control mice receiving PBS (Group1), but the difference between Groups was less than that in the fasted mice.

Table 13. Triglyceride and Glucose Levels in Mice Treated with ETD00642

		Triglycerides (mg/dL)				Glucose (mg/dL)			
		Fed (Day 13)		Fasted (Day 14)		Fed (Day 13)		Fasted (Day 14)	
Group #	Animal #	individual	Mean	individual	Mean	individual	Mean	individual	Mean
1	1	180	201	119	117	297	296	129	103
	2	213		135		300		110	
	3	193		99		305		91	
	4	217		113		280		80	
2	5	148	140	65	69	210	202	97	89
	6	158		66		218		100	
	7	66		61		221		76	
	8	186		85		158		83	

Example 13: Activity of siRNAs targeting ANGPTL4 in Non-Human Primates

[0343] The activity of four siRNAs targeting ANGPTL4 were tested individually in cynomolgus monkeys. The siRNAs utilized in this study included ETD01117, ETD01118, ETD01119, and ETD01120 (see **Table 16** for siRNA details).

[0344] Female cynomolgus monkeys (*Macaca fascicularis*, Cambodian origin, Orient BioResource Center, Alice, TX) were at least 18 months of age and weighed 2.5-3 kg at study start. After arrival, the animals were pair housed in stainless steel cages suspended over flush pans. Fluorescent lighting on a 12 hour on/off cycle was used and the temperature maintained at 18-29□C at a target relative humidity of 30-70% with at least 10-15 air exchanges per hour. Animals were acclimated for a period of at least

twenty-eight days, during which time they were examined for overall general health and observed daily. Animals were limit fed daily with certified primate diet (5048). Tap water was provided *ad libitum*.

[0345] Monkeys (3/group) were administered the siRNA test article once on Day 0 by subcutaneous injection as described in **Table 14**. In-life, animals were evaluated for clinical signs of toxicity, body weights, and food consumption. Prior to and during the study evaluations for clinical chemistry parameters were performed.

Table 14. siRNA Dosing Information

Group	siRNA	Dosage (mg/kg)	Conc. (mg/mL)	Animal No.
1	ETD01117	5	50	1-3
2	ETD01118	5	50	4-6
3	ETD01119	5	50	7-9
4	ETD01120	5	50	10-12

[0346] Whole blood (approximately 2-3 mL) was collected from fasted animals twice prior to first dose (Day -7 and -2), and from surviving animals on Days 7, 14. Whole blood (approximately 2-3 mL) was collected from non-fasted animals once prior to dosing (Day -8). Blood samples were analyzed for clinical chemistry parameters, processed to serum for measurement of ANGPTL4 levels, and processed to plasma for lipoprotein profile assay.

[0347] An AlphaLISA immunoassay (PerkinElmer AL3017) was used to measure serum ANGPTL4 levels according to the recommended protocols provided by the manufacturer. Briefly, standard analyte (recombinant human ANGPTL4 encoding residues Gly26-Ser406) and serum samples were prepared in 1X AlphaLISA Assay Buffer (PerkinElmer AL000C). For each assay, 5 µL of prepared standard analyte or diluted sample were added to a 96-well white ½ Area OptiPlate (PerkinElmer 6002290) followed by the addition of 10 µL of Acceptor bead mix. Then the plate was sealed with TopSeal A-PLUS (PerkinElmer 6050185) and incubated for 30 minutes at room temperature. Next, 10 µL of biotinylated antibody was added to each well of the plate. The plate was sealed and incubated for 60 minutes at room temperature. Afterwards, 25 µL of streptavidin Donor beads were added in the dark to prevent photobleaching. The plate was sealed, covered with foil, and incubated at room temperature for 30 minutes prior to measuring AlphaLISA signal. All Alpha assays were measured on the Alpha-enabled EnVision multilabel plate reader using the 640as mirror module (#444) and the M570w emission filter (#244). Standard Alpha measurement settings were used: excitation wavelength at 680 nm was used to excite Donor beads and emission wavelength at 615 nm measured as Alpha signal; total measurement time 550 ms and excitation time 180 ms were used. A standard curve was generated by plotting the Alpha signal counts versus the concentration of analyte using GraphPad Prism version 9 for macOS (GraphPad Software). The curve was fit according to a nonlinear regression using the 4-parameter logistic equation (sigmoidal dose-response curve with variable slope) and a 1/Y2 data weighting. Signal for samples was converted to pg/mL from interpolation of the standard curve from each plate and corrected for dilution of sample prior to assay. The results are shown in **Table 15**. Results indicate that

after treatment with siRNAs targeting ANGPTL4 the mean levels of ANGPTL4 protein in serum were reduced. In addition, mean levels of serum ANGPTL4 protein levels were lower in fed animals than in fasted animals.

Table 15. Serum ANGPTL4 Protein Levels in Non-Human Primates Treated with ANGPTL4 siRNAs

Group # (n=3)	siRNA	Day	Group Means*
1	ETD01117	-8 (fed)	0.66
		-7	0.97
		-2	1.03
		7	0.66
		14	0.38
2	ETD01118	-8 (fed)	0.68
		-7	1.10
		-2	0.90
		7	0.61
		14	0.68
3	ETD01119	-8 (fed)	0.73
		-7	1.07
		-2	0.93
		7	0.50
		14	0.65
4	ETD01120	-8 (fed)	0.49
		-7	0.94
		-2	1.06
		7	0.52
		14	0.52

*relative to the mean of Day -7 and Day -2 values in each group

Example 14: siRNAs targeting ANGPTL4

[0348] Some non-limiting examples of siRNAs have one or more characteristics of the siRNAs in **Table 16**.

Table 16. Exemplary modified siRNAs

siRNA Name	Sense Strand Sequence - SEQ ID NO:	Additional Characteristic of Sense Strand	Antisense Strand Sequence - SEQ ID NO:
ETD01062	13986	-	14134
ETD01063	13987	-	14135
ETD01064	13988	-	14136
ETD01065	13989	-	14137
ETD01117	13990	GalNAc#23 conjugated at 3' end	14134
ETD01118	13991	GalNAc#23 conjugated at 3' end	14135
ETD01119	13992	GalNAc#23 conjugated at 3' end	14136

ETD01120	13993	GalNAc#23 conjugated at 3' end	14137
ETD01117.1	13994	GalNAc ligand conjugated at 5' end	14134
ETD01118.1	13995	GalNAc ligand conjugated at 5' end	14135
ETD01119.1	13996	GalNAc ligand conjugated at 5' end	14136
ETD01120.1	13997	GalNAc ligand conjugated at 5' end	14137
ETD01117.2	13998	GalNAc ligand conjugated at 5' end	14134
ETD01118.2	13999	GalNAc ligand conjugated at 5' end	14135
ETD01119.2	14000	GalNAc ligand conjugated at 5' end	14136
ETD01120.2	14001	GalNAc ligand conjugated at 5' end	14137
ETD01117.3	14006	GalNAc ligand conjugated at 5' end	14138
ETD01118.3	14007	GalNAc ligand conjugated at 5' end	14139
ETD01119.3	14008	GalNAc ligand conjugated at 5' end	14140
ETD01120.3	14009	GalNAc ligand conjugated at 5' end	14141
ETD01117.4	14006	GalNAc ligand conjugated at 5' end	14142
ETD01118.4	14007	GalNAc ligand conjugated at 5' end	14143
ETD01119.4	14008	GalNAc ligand conjugated at 5' end	14144
ETD01120.4	14009	GalNAc ligand conjugated at 5' end	14145
ETD01117.5	14006	GalNAc ligand conjugated at 5' end	14146
ETD01118.5	14007	GalNAc ligand conjugated at 5' end	14147
ETD01119.5	14008	GalNAc ligand conjugated at 5' end	14148
ETD01120.5	14009	GalNAc ligand conjugated at 5' end	14149
ETD01117.6	14006	GalNAc ligand conjugated at 5' end	14150
ETD01118.6	14007	GalNAc ligand conjugated at 5' end	14151
ETD01119.6	14008	GalNAc ligand conjugated at 5' end	14152
ETD01120.6	14009	GalNAc ligand conjugated at 5' end	14153
ETD01117.7	14002	GalNAc ligand conjugated at 5' end	14154
ETD01118.7	14003	GalNAc ligand conjugated at 5' end	14155

ETD01119.7	14004	GalNAc ligand conjugated at 5' end	14156
ETD01120.7	14005	GalNAc ligand conjugated at 5' end	14157
ETD01162 GalNAc#23	14005	GalNAc#23 conjugated at 3' end	14298
ETD00164 GalNAc#23	14005	GalNAc#23 conjugated at 3' end	14153
ETD01178	14005	GalNAc ligand conjugated at 5' end	14298
ETD01179	14299	GalNAc ligand conjugated at 5' end	14298

Example 15: Effects of chronic dosing of an ANGPTL4 siRNA versus an anti-ANGPTL4 antibody in a mouse model of hypertriglyceridemia

[0349] A comparison of the effects of chronic exposure of anti-ANGPTL4 antibody and ANGPTL4 siRNA was investigated in a murine model of hypertriglyceridemia. Eight- to ten-week-old C57Bl/6 Apoetm1Unc mice (Jackson Labs) were placed on a high fat Western diet (Research Diets, D12492; 60% fat by calories) for approximately 6 weeks prior to the start of the study on Day 0. On Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91 and 98 mice in Group 1 (n=12) were administered 200 uL of phosphate buffered saline (PBS) by subcutaneous injection, mice in Group 2 (n=12) were administered 800 ug of 14D12 anti-ANGPTL4 monoclonal antibody (Creative Biosciences) in 160 uL PBS by intraperitoneal injection, and mice in Group 3 (n=12) were given 50 ug of the siRNA targeting mouse ANGPTL4 in 100 uL PBS by subcutaneous injection. The siRNA targeting mouse ANGPTL4 included ETD00971 conjugated to GalNAc#23, and was designated "ETD00971 GalNAc#23." Animals were maintained on a high fat diet during the study. Sequence information for ETD00971 is indicated in **Table 1**.

[0350] On Days -8, 6, 13, 20, 34, 48, 78 and 90, all animals were subjected to a 24 hr fast and 300 uL of blood was collected in serum separator tubes via the submandibular vein to assess serum triglyceride levels. Clinical chemistry assays were performed at IDEXX Laboratories, Incorporated. On Day 104, all surviving mice were euthanized, livers were weighed, and livers, small intestines, mesenteric lymph nodes and epididymal adipose tissues were harvested and placed in 10% formalin prior to histopathological analysis. A separate liver sample from each mouse was collected and placed in RNAlater (ThermoFisher Cat#AM7020). Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. The levels of liver ANGPTL4 mRNA were assessed by RT-qPCR using TaqMan assays for mouse ANGPTL4 (ThermoFisher, assay# Mm00480431_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1). Data were normalized to the level in animals receiving PBS (Group 1). Results are shown in **Table 17**. Mice receiving ETD00971 GalNAc#23 (Group

3) had highly reduced levels of liver ANGPTL4 mRNA compared to mice receiving PBS (Group 1) or 14D12 antibody (Group 3).

Table 17. Liver ANGPTL4 mRNA Levels in Mice After Chronic Dosing with 14D12 Antibody or ANGPTL4 siRNA

Group #	Treatment	Animal #	Relative Liver ANGPTL4 mRNA Level	Mean Relative Liver ANGPTL4 mRNA level
1	PBS	1	0.75	1.00
		2	1.04	
		3	0.70	
		4	0.76	
		5	0.78	
		6	1.23	
		7	0.89	
		8	1.28	
		9	1.68	
		10	1.02	
		11	1.04	
		12	1.25	
2	14D12	13	0.76	0.70
		14	0.90	
		15	0.84	
		16	0.58	
		17	0.86	
		18	0.28	
		19	0.63	
		20	0.94	
		21	0.64	
		22	0.67	
		23	ND*	
		24	0.93	
3	ETD00971 GalNAc#23	25	0.17	0.17
		26	0.22	
		27	0.19	
		28	0.17	
		29	ND*	
		30	0.16	
		31	0.10	
		32	0.11	
		33	0.19	
		34	0.25	
		35	0.19	
		36	0.24	

ND*: found moribund prior to study termination

[0351] The levels of serum triglycerides are shown in **Table 18**. The serum triglyceride levels were lower in both the fasted and fed states in mice treated with ETD00971 GalNAc#23 (Group 3) or 14D12 (Group 2) than in control mice receiving PBS (Group 1). Thus, compositions comprising oligonucleotides such as siRNAs targeting ANGPTL4 may be useful for decreasing circulating triglycerides in a subject.

Table 18. Mean Serum Triglyceride Levels in Mice After Chronic Dosing with 14D12 Antibody or ANGPTL4 siRNA

	Mean Serum Triglyceride (mg/dL)		
Day	**Group 1 - PBS**	**Group 2 – 14D12**	**Group 3 – ETD00971 GalNAc#23**
-8	100	121	110
6	121	63	84
13	112	50	78
20	103	47	71
34	107	54	71
48	131	52	66
76	139	66	72
90	139	54	65

[0352] Tissues listed above from all mice were trimmed, processed in a routine manner, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically.

[0353] In control Group 1, mesenteric lymph nodes had small, cleft-like subcapsular sinuses and few cortical macrophages with small amounts of phagocytosed cells/debris. The mesentery associated with the control lymph nodes was unremarkable. In these animals, the small intestine had slender villi and smooth serosal surfaces.

[0354] By contrast, extensive morphological changes were present in animals that received the 14D12 mAb (Group 2). Granulomatous inflammation in the lymph nodes of these animals was characterized by the dilated subcapsular sinuses containing basophilic extracellular material; macrophages as well as multinucleated giant cells were present multifocally in cortex as well as medulla. The granulomatous inflammation multifocally extended into the mesentery and was also present on seral surfaces of the small intestine. However, the small intestinal mucosa was essentially normal in these animals, and their villi were slender. The epididymal adipose tissue was also essentially normal in animals that received the 14D12 mAb. However, minimal infiltrate (mononuclear cell and/or mixed cell type) was observed occurring at a higher frequency in Group 2 (10/11 animals examined) compared to Groups 1 (5/11 animals examined) and Group 3 (2/12 animals examined). In general, hepatocellular vacuolation was less severe in Group 2 animals administered the 14D12 mAb than those of control Group 1 mice.

[0355] Most of the lymph nodes of animals that received ETD00971 GalNAc#23 (Group 3) were relatively normal, without evidence of a granulomatous inflammatory reaction. A few lymph nodes had increased infiltrates of macrophages with cellular debris (similar to the control Group 1 animals). The mesentery and small intestine of these animals were also essentially normal, except for one animal that had a minimal mesenteric granulomatous inflammation. As in other groups, the epididymal adipose tissue was unremarkable. Hepatocytes in Group 3 had vacuolation but it was less severe and less frequent than in animals receiving 14D12 mAb (Group 2) or PBS (Group 1), indicating reduced hepatic steatosis in animals that received ETD00971 GalNAc#23 (Group 3) than in animals that received 14D12 mAb (Group 2) or PBS (Group 1). These data indicate that targeting ANGPTL4 may be useful for treating a subject with obesity or a liver disease such as NAFLD or NASH, and for decreasing a liver steatosis measurement. Some examples of liver steatosis measurements include a liver fat percentage

measurement or a NAFLD activity score. These data further indicate that oligonucleotides such as siRNAs targeting ANGPTL4 may be useful for treating a subject with obesity or a liver disease such as NAFLD or NASH, and for decreasing a triglyceride measurement or a liver steatosis measurement in a subject with surprising efficacy, or with decreased toxicity, when compared to another treatment.

Example 16: Reduction of liver mRNA expression by siRNAs targeting ANGPTL4 in non-human primates

[0356] The activity of three siRNAs targeting human and non-human primate ANGPTL4 were tested individually in cynomolgus monkeys. The siRNAs utilized in this study included ETD01120, ETD01162 GalNAc#23 and ETD01164 GalNAc#23. Each of these siRNAs includes a modified version of a sense strand comprising the sequence of SEQ ID NO: 13977 (derived from SEQ ID NO: 13973), and a modified version of an antisense strand comprising the sequence of SEQ ID NO: 13985 (derived from SEQ ID NO: 13981). ETD01120 includes modification patterns 2S and 3AS. ETD01162 GalNAc#23 includes modification patterns 6S and 6AS. ETD01164 GalNAc#23 includes modification patterns 6S and 8AS. Some additional details of these siRNAs are provided in **Table 16**.

[0357] Female cynomolgus monkeys (*Macaca fascicularis*, Cambodian origin, Bioculture Group, Glenmoor, PA, Orient BioResource Center, Alice, TX) were at least 18 months of age and weighed 2.5-4 kg at study start. After arrival, the animals were pair housed in stainless steel cages suspended over flush pans. Fluorescent lighting on a 12 hour on/off cycle was used and the temperature was maintained at 18-29°C at a target relative humidity of 30-70% with at least 10-15 air exchanges per hour. Animals were acclimated for a period of at least twenty-eight days, during which time they were examined for overall general health and observed daily. All animals were fed a high fat diet (LabDiet 5LOP) starting at least 5 weeks prior to dose administration and were provided with ~100 grams per day. Starting at least 5 weeks prior to dose administration and continuing until necropsy, each animal received a high fructose treat at least twice daily (Narvon beverage concentrate, 20 mL twice per day, diluted or undiluted, offered by oral syringe, as a frozen treat, and/or as a hand-held gelatin block. Tap water was provided *ad libitum*.

[0358] Monkeys (3/group) were administered the vehicle (normal saline) or the siRNA test article once on Day 1 by subcutaneous injection as described in **Table 19**. In-life, animals were evaluated for clinical signs of toxicity, body weights, and food consumption. Prior to and during the study evaluations for clinical chemistry parameters were performed.

Table 19. siRNA Dosing Information

Group	Treatment	Day of Dose	Dosage (mg/kg)	Conc. (mg/mL)	Animal No.
1	vehicle	1	0 (vehicle)	0	1, 3
2	ETD01162 GalNAc#23	1	10	100	4-6
3	ETD01164 GalNAc#23	1	10	100	7-9

4	ETD01162 GalNAc#23	36	4	40	10, 11
5	ETD01120	1	10	100	12-15
6	vehicle	36	0 (vehicle)	0	2, 12

[0359] All animals from each group were necropsied 21 days following test article administration. A ~2x2x2 mm piece from each liver lobe was collected, placed separately in RNAlater solution, and stored in a 4ºC refrigerator overnight then in a -20ºC freezer until analysis. The levels of ANGPTL4 mRNA in the liver were assessed by RT-qPCR using TaqMan assays for cynomolgus ANGPTL4 (ThermoFisher, assay# Mf01101127_m1) and the cynomolgus housekeeping gene GAPDH (ThermoFisher, assay# Mf04392546_g1). The results are shown in **Table 20**, **Table 21**, **Table 22** and **Table 23**. Results indicate that after treatment with siRNAs targeting ANGPTL4 the mean levels of ANGPTL4 mRNA in all liver lobes analyzed were reduced.

Table 20. Relative Liver ANGPTL4 mRNA Levels in the Left Lateral Lobe in Cynomolgus Monkeys After a Single Dose of ANGPTL4 siRNA

Group	Treatment	Dosage (mg/kg)	Animal #	Relative ANGPTL4 mRNA level	Mean Relative ANGPTL4 mRNA level
1	vehicle	-	1	1.75	1.000
6	vehicle		2	1.11	
1	vehicle	-	3	0.50	
6	vehicle		12	1.03	
2	ETD01162 GalNAc#23	10	4	0.18	0.33
			5	0.49	
			6	0.43	
3	ETD01164 GalNAc#23	10	7	0.65	0.41
			8	0.34	
			9	0.30	
5	ETD01120	10	13	0.27	0.42
			14	0.27	
			15	1.02	
4	ETD01162 GalNAc#23	4	10	0.60	0.76
			11	0.95	

Table 21. Relative Liver ANGPTL4 mRNA Levels in the Left Medial Lobe in Cynomolgus Monkeys After a Single Dose of ANGPTL4 siRNA

Group	Treatment	Dosage (mg/kg)	Animal #	Relative ANGPTL4 mRNA level	Mean Relative ANGPTL4 mRNA level
1	vehicle	-	1	1.52	1.00
6	vehicle		2	1.02	
1	vehicle	-	3	0.45	
6	vehicle		12	1.42	
2	ETD01162 GalNAc#23	10	4	0.23	0.38
			5	0.52	
			6	0.44	
3		10	7	0.75	0.44

	ETD01164 GalNAc#23		8	0.36	
			9	0.32	
5	ETD01120	10	13	0.31	0.44
			14	0.25	
			15	1.12	
4	ETD01162 GalNAc#23	4	10	0.62	0.76
			11	0.93	

Table 22. Relative Liver ANGPTL4 mRNA Levels in the Right Lateral Lobe in Cynomolgus Monkeys After a Single Dose of ANGPTL4 siRNA

Group	Treatment	Dosage (mg/kg)	Animal #	Relative ANGPTL4 mRNA level	Mean Relative ANGPTL4 mRNA level
1	vehicle	-	1	1.35	1.00
6	vehicle		2	0.80	
1	vehicle	-	3	ND	
6	vehicle		12	0.92	
2	ETD01162 GalNAc#23	10	4	0.23	0.30
			5	0.37	
			6	0.32	
3	ETD01164 GalNAc#23	10	7	0.64	0.43
			8	0.34	
			9	0.38	
5	ETD01120	10	13	0.22	0.38
			14	0.31	
			15	0.80	
4	ETD01162 GalNAc#23	4	10	0.35	0.64
			11	1.16	

Table 23. Relative Liver ANGPTL4 mRNA Levels in the Right Medial Lobe in Cynomolgus Monkeys After a Single Dose of ANGPTL4 siRNA

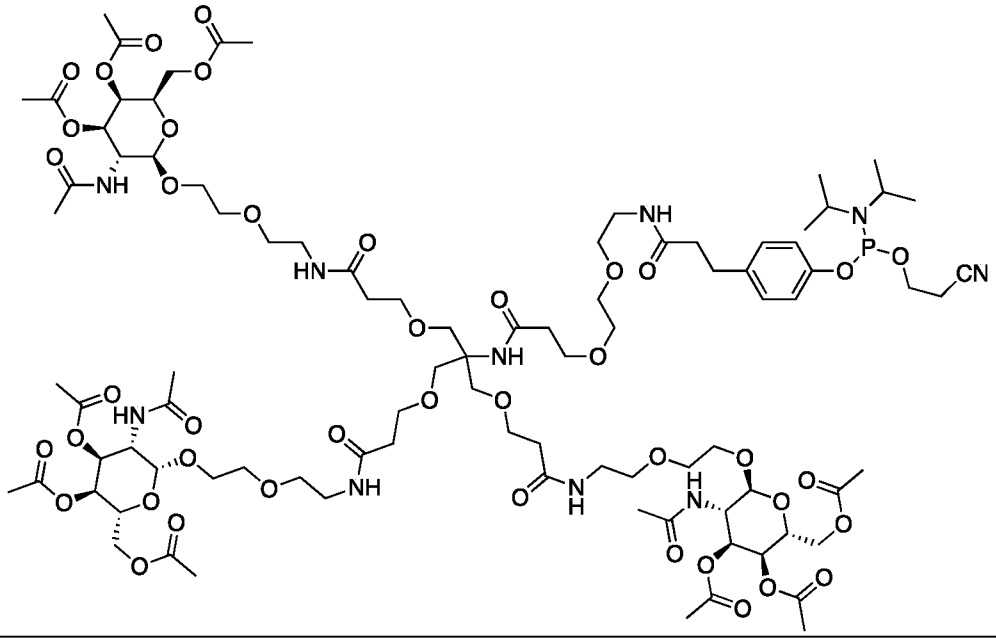
Group	Treatment	Dosage (mg/kg)	Animal #	Relative ANGPTL4 mRNA level	Mean Relative ANGPTL4 mRNA level
1	vehicle	-	1	1.07	1.00
6	vehicle		2	0.65	
1	vehicle	-	3	2.29	
6	vehicle		12	0.63	
2	ETD01162 GalNAc#23	10	4	0.16	0.20
			5	0.22	
			6	0.22	
3	ETD01164 GalNAc#23	10	7	0.41	0.27
			8	0.23	
			9	0.21	
5	ETD01120	10	13	0.14	0.25
			14	0.20	
			15	0.55	
4	ETD01162 GalNAc#23	4	10	0.44	0.57
			11	0.74	

[0360] Additional experiments are performed in nonhuman primates to determine the efficacy of ETD01178 and ETD01179 to decrease liver ANGPTL4 mRNA levels. Each of these siRNAs also includes a modified version of a sense strand comprising the sequence of SEQ ID NO: 13977 (derived from SEQ ID NO: 13973), and a modified version of an antisense strand comprising the sequence of SEQ ID NO: 13985 (derived from SEQ ID NO: 13981). ETD01178 includes modification patterns 6S and 6AS. ETD01179 includes modification patterns 8S and 6AS. Administration of these siRNAs is expected to also reduce ANGPTL4 mRNA measurements in liver samples, relative to baseline ANGPTL4 mRNA measurements.

Example 17: GalNAc ligands for hepatocyte targeting of oligonucleotides

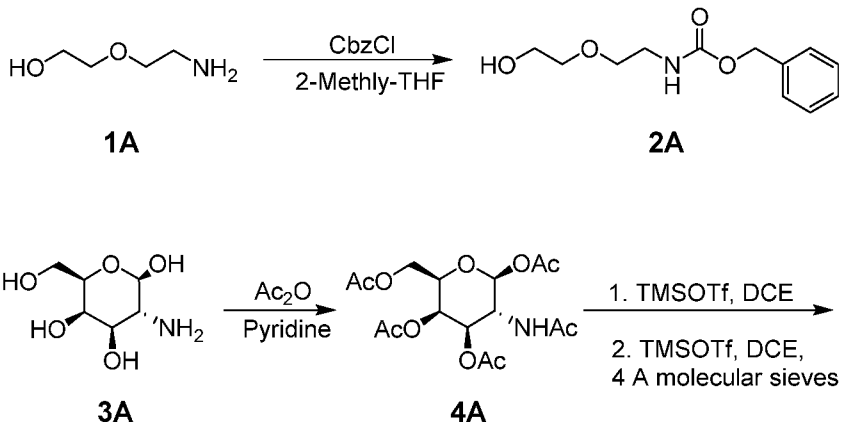
[0361] Without limiting the disclosure to these individual methods, there are at least two general methods for attachment of multivalent N-acetylgalactosamine (GalNAc) ligands to oligonucleotides: solid or solution-phase conjugations. GalNAc ligands may be attached to solid phase resin for 3' conjugation or at the 5' terminus using GalNAc phosphoramidite reagents. GalNAc phosphoramidites may be coupled on solid phase as for other nucleosides in the oligonucleotide sequence at any position in the sequence. A non-limiting example of a phosphoramidite reagent for GalNAc conjugation to a 5' end oligonucleotide is shown in **Table 24**.

Table 24. GalNAc Conjugation Reagent

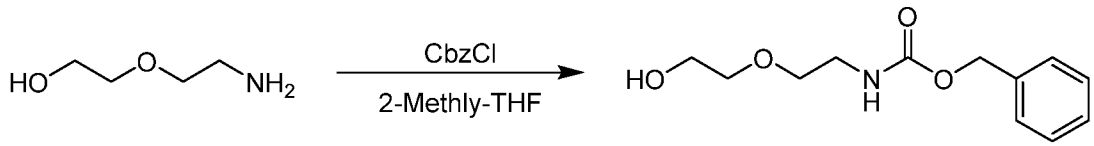
Type of conjugation	Structure
Solid phase 5' attachment phosphoramidite	

[0362] The following includes examples of synthesis reactions used to create a GalNAc moiety:

Scheme for the preparation of NAcegal-Linker-TMSOTf

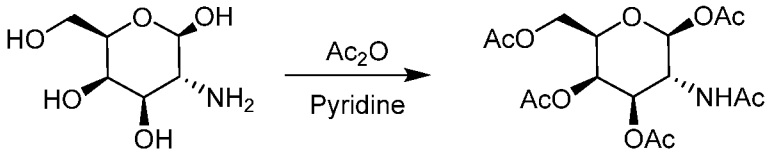


General procedure for preparation of Compound 2A



[0363] To a solution of Compound 1A (500 g, 4.76 mol, 476 mL) in 2-Methly-THF (2.00 L) is added CbzCl (406 g, 2.38 mol, 338 mL) in 2-Methyl-THF (750 mL) dropwise at 0 °C. The mixture is stirred at 25 °C for 2 hrs under N2 atmosphere. TLC (DCM: MeOH = 20:1, PMA) may indicate CbzCl is consumed completely and one new spot (Rf = 0.43) formed. The reaction mixture is added HCl/EtOAc (1 N, 180 mL) and stirred for 30 mins, white solid is removed by filtration through celite, the filtrate is concentrated under vacuum to give Compound 2A (540 g, 2.26 mol, 47.5% yield) as a pale yellow oil and used into the next step without further purification. 1H NMR: δ 7.28 - 7.41 (m, 5 H), 5.55 (br s, 1 H), 5.01 - 5.22 (m, 2 H), 3.63 - 3.80 (m, 2 H), 3.46 - 3.59 (m, 4 H), 3.29 - 3.44 (m, 2 H), 2.83 - 3.02 (m, 1 H).

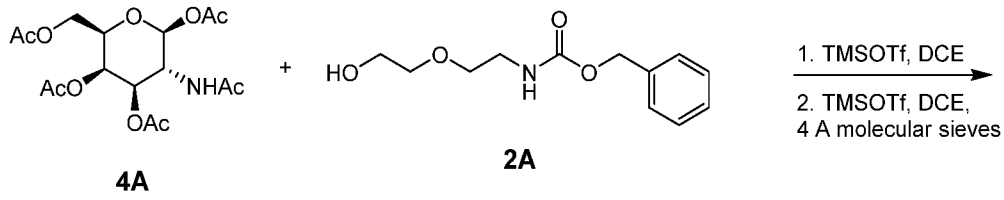
General procedure for preparation of Compound 4A



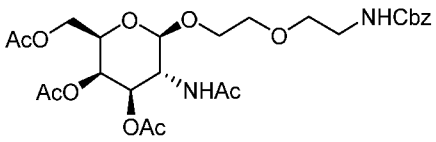
[0364] To a solution of Compound 3A (1.00 kg, 4.64 mol, HCl) in pyridine (5.00 L) is added acetyl acetate (4.73 kg, 46.4 mol, 4.34 L) dropwise at 0 °C under N_2 atmosphere. The mixture is stirred at 25 °C for 16 hrs under N_2 atmosphere. TLC (DCM: MeOH = 20:1, PMA) indicated Compound 3A is

consumed completely and two new spots (R_f = 0.35) formed. The reaction mixture is added to cold water (30.0 L) and stirred at 0 °C for 0.5 hr, white solid formed, filtered and dried to give Compound 4A (1.55 kg, 3.98 mol, 85.8% yield) as a white solid and used in the next step without further purification. ^{1}H NMR: δ 7.90 (d, *J* = 9.29 Hz, 1 H), 5.64 (d, *J* = 8.78 Hz, 1 H), 5.26 (d, *J* = 3.01 Hz, 1 H), 5.06 (dd, *J* = 11.29, 3.26 Hz, 1 H), 4.22 (t, *J* = 6.15 Hz, 1 H), 3.95 - 4.16 (m, 3 H), 2.12 (s, 3 H), 2.03 (s, 3 H), 1.99 (s, 3 H), 1.90 (s, 3 H), 1.78 (s, 3 H).

General procedure for preparation of Compound 5A



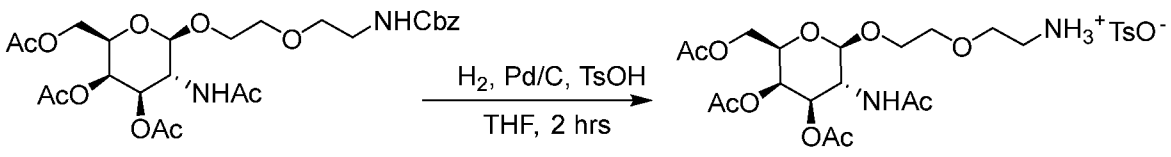
4A **2A**



5A

[0365] To a solution of Compound 4A (300 g, 771 mmol) in DCE (1.50 L) is added TMSOTf (257 g, 1.16 mol, 209 mL) and stirred for 2 hrs at 60 °C, and then stirred for 1 hr at 25 °C. Compound 2A (203 g, 848 mmol) is dissolved in DCE (1.50 L) and added 4 Å powder molecular sieves (150 g) stirring for 30 mins under N_2 atmosphere. Then the solution of Compound 4A in DCE is added dropwise to the mixture at 0 °C. The mixture is stirred at 25 °C for 16 hrs under N_2 atmosphere. TLC (DCM: MeOH = 25:1, PMA) indicated Compound 4A is consumed completely and new spot (R_f = 0.24) formed. The reaction mixture is filtered and washed with sat. $NaHCO_3$ (2.00 L), water (2.00 L) and sat. brine (2.00 L). The organic layer is dried over anhydrous Na_2SO4, filtered and concentrated under reduced pressure to give a residue. The residue is triturated with 2-Me-THE/heptane (5/3, v/v, 1.80 L) for 2 hrs, filtered and dried to give Compound 5A (225 g, 389 mmol, 50.3% yield, 98.4% purity) as a white solid. ^{1}H NMR: δ 7.81 (d, *J* = 9.29 Hz, 1 H), 7.20 - 7.42 (m, 6 H), 5.21 (d, *J* = 3.26 Hz, 1 H), 4.92 - 5.05 (m, 3 H), 4.55 (d, *J* = 8.28 Hz, 1 H), 3.98 - 4.07 (m, 3 H), 3.82 - 3.93 (m, 1 H),3.71 - 3.81 (m, 1 H), 3.55 - 3.62 (m, 1 H), 3.43 - 3.53 (m, 2 H), 3.37 - 3.43 (m, 2 H), 3.14 (q, *J* = 5.77 Hz, 2 H), 2.10 (s, 3 H), 1.99 (s, 3 H), 1.89 (s, 3 H), 1.77 (s, 3 H).

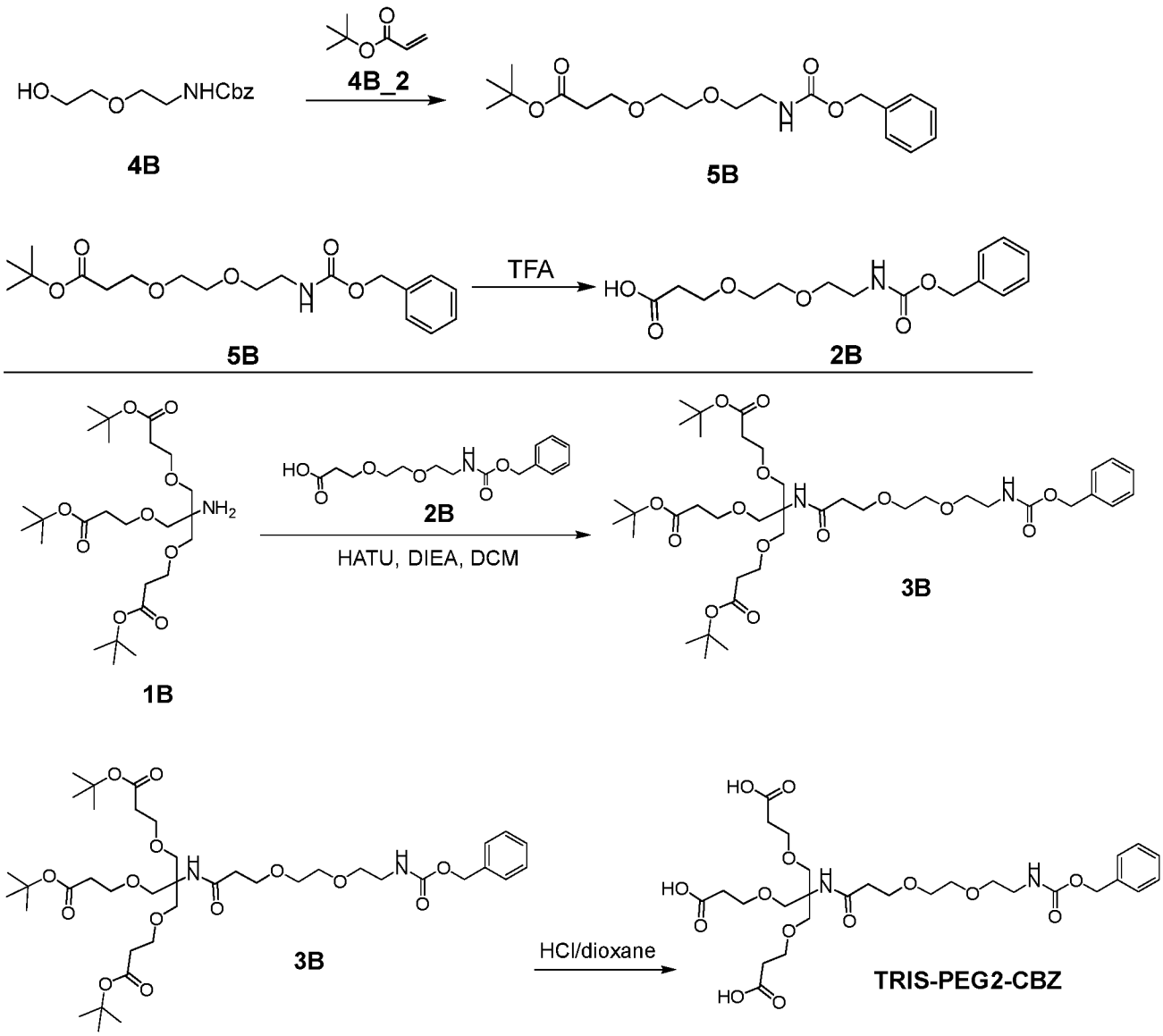
General procedure for preparation of NAcegal-Linker-Tosylate salt



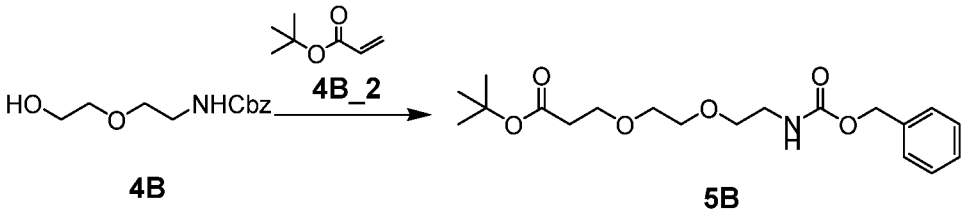
5A **NAcegal-Linker-TMSOTf**

[0366] To a solution of Compound 5A (200 g, 352 mmol) in THF (1.0 L) is added dry Pd/C (15.0 g, 10% purity) and TsOH (60.6 g, 352 mmol) under N_2 atmosphere. The suspension is degassed under vacuum and purged with H_2 several times. The mixture is stirred at 25 °C for 3 hrs under H_2 (45 psi) atmosphere. TLC (DCM: MeOH = 10:1, PMA) indicated Compound 5A is consumed completely and one new spot (R_f = 0.04) is formed. The reaction mixture is filtered and concentrated (≤ 40 ° C) under reduced pressure to give a residue. Diluted with anhydrous DCM (500 mL, dried overnight with 4 Å molecular sieves (dried at 300 ° C for 12 hrs)) and concentrate to give a residue and run Karl Fisher (KF) to check for water content. This is repeated 3 times with anhydrous DCM (500 mL) dilutions and concentration to give NAcegal-Linker-TMSOTf (205 g, 95.8% yield, TsOH salt) as a foamy white solid. ^{1}H NMR: δ 7.91 (d, *J* = 9.03 Hz, 1 H), 7.53 - 7.86 (m, 2 H), 7.49 (d, *J* = 8.03 Hz, 2 H), 7.13 (d, *J* = 8.03 Hz, 2 H), 5.22 (d, *J* = 3.26 Hz, 1 H), 4.98 (dd, *J* = 11.29, 3.26 Hz, 1 H), 4.57 (d, *J* = 8.53 Hz, 1 H), 3.99 - 4.05 (m, 3 H), 3.87 - 3.94 (m, 1 H), 3.79 - 3.85 (m, 1 H), 3.51 - 3.62 (m, 5 H), 2.96 (br t, *J* = 5.14 Hz, 2 H), 2.29 (s, 3 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.89 (s, 3 H), 1.78 (s, 3 H).

Scheme for the preparation of TRIS-PEG2-CBZ



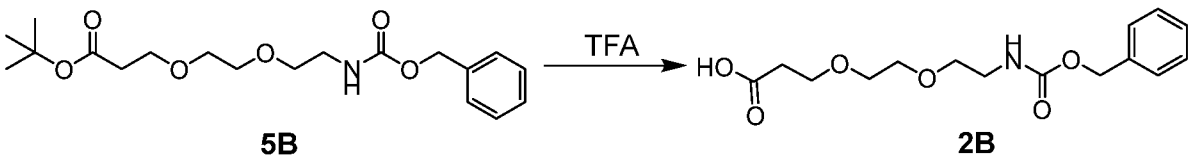
General procedure for preparation of Compound 5B



4B 5B

[0367] To a solution of Compound 4B (400 g, 1.67 mol, 1.00 *eq*) and NaOH (10 M, 16.7 mL, 0.10 *eq*) in THF (2.00 L) is added Compound 4B_2 (1.07 kg, 8.36 mol, 1.20 L, 5.00 *eq*), the mixture is stirred at 30 °C for 2 hrs. LCMS showed the desired MS is given. Five batches of solution are combined to one batch, then the mixture is diluted with water (6.00 L), extracted with ethyl acetate (3.00 L*3), the combined organic layer is washed with brine (3.00 L), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude is purified by column chromatography (SiO_2, petroleum ether : ethyl acetate=100:1-10:1, R_f=0.5) to give Compound 5B (2.36 kg, 6.43 mol, 76.9% yield) as light yellow oil. HNMR: δ 7.31-7.36 (m, 5 H), 5.38 (s, 1 H), 5.11-5.16 (m, 2 H), 3.75 (t, J=6.4 Hz), 3.54-3.62 (m, 6 H), 3.39 (d, *J*=5.2 Hz), 2.61 (t, *J*=6.0 Hz).

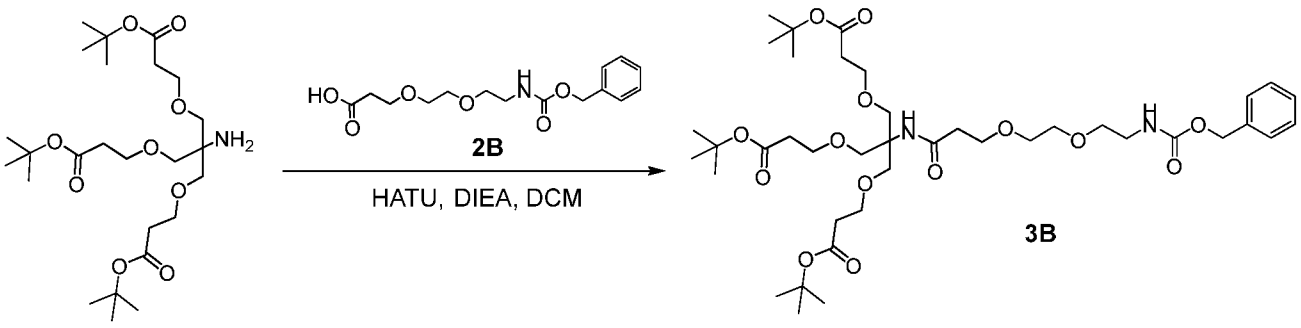
General procedure for preparation of 3-oxo-1-phenyl-2,7,10-trioxa-4-azatridecan-13-oic acid (Compound 2B below)



5B 2B

[0368] To a solution of Compound 5B (741 g, 2.02 mol, 1.00 *eq*) in DCM (2.80 L) is added TFA (1.43 kg, 12.5 mol, 928 mL, 6.22 *eq*), the mixture is stirred at 25 °C for 3 hrs. LCMS showed the desired MS is given. The mixture is diluted with DCM (5.00 L), washed with water (3.00 L*3), brine (2.00 L), the combined organic layer is dried over Na_2SO_4, filtered and concentrated under vacuum to give Compound 2B (1800 g, crude) as light yellow oil. HNMR: δ 9.46 (s, 5 H), 7.27-7.34 (m, 5 H), 6.50-6.65 (m, 1 H), 5.71 (s, 1 H), 5.10-5.15 (m, 2 H), 3.68-3.70 (m, 14 H), 3.58-3.61 (m, 6 H), 3.39 (s, 2 H), 2.55 (s, 6 H), 2.44 (s, 2 H).

General procedure for preparation of Compound 3B

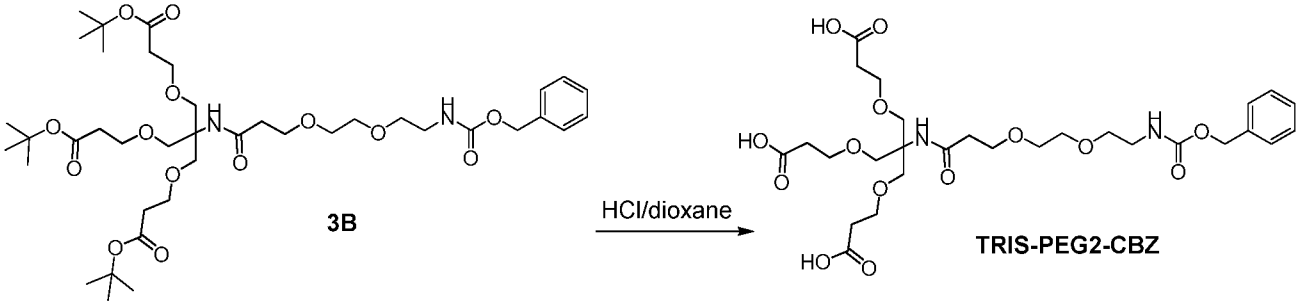


1B 3B

[0369] To a solution of Compound 2B (375 g, 999 mmol, 83.0% purity, 1.00 *eq*) in DCM (1.80 L) is added HATU (570 g, 1.50 mol, 1.50 *eq*) and DIEA (258 g, 2.00 mol, 348 mL, 2.00 *eq*) at 0 °C, the mixture is stirred at 0 °C for 30 min, then Compound 1B (606 g, 1.20 mol, 1.20 *eq*) is added, the mixture

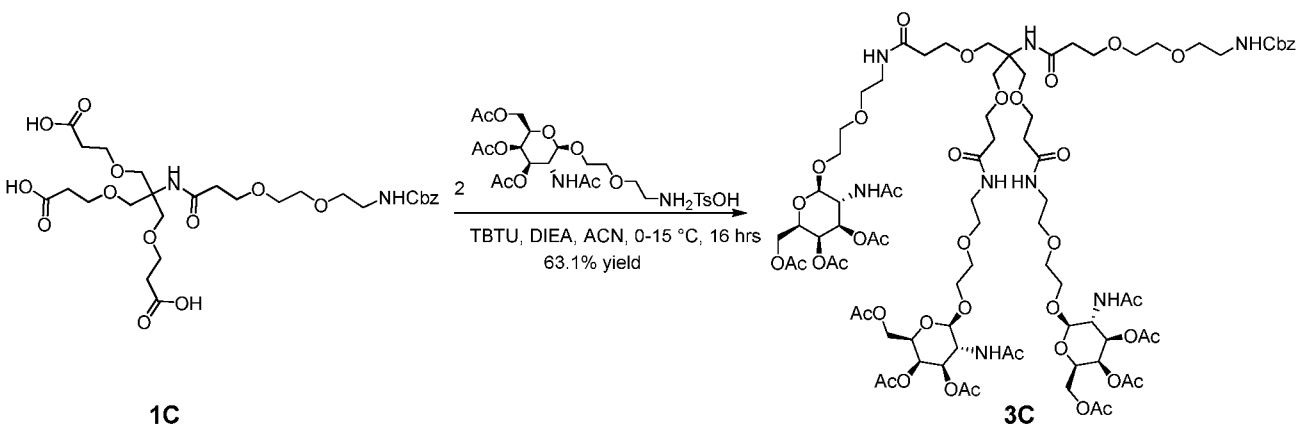
is stirred at 25 °C for 1 hr. LCMS showed desired MS is given. The mixture is combined to one batch, then the mixture is diluted with DCM (5.00 L), washed with 1 N HCl aqueous solution (2.00 L*2), then the organic layer is washed with saturated Na_2CO_3 aqueous solution (2.00 L *2) and brine (2.00 L), the organic layer is dried over Na_2SO_4, filtered and concentrated under vacuum to give Compound 3B (3.88 kg, crude) as yellow oil.

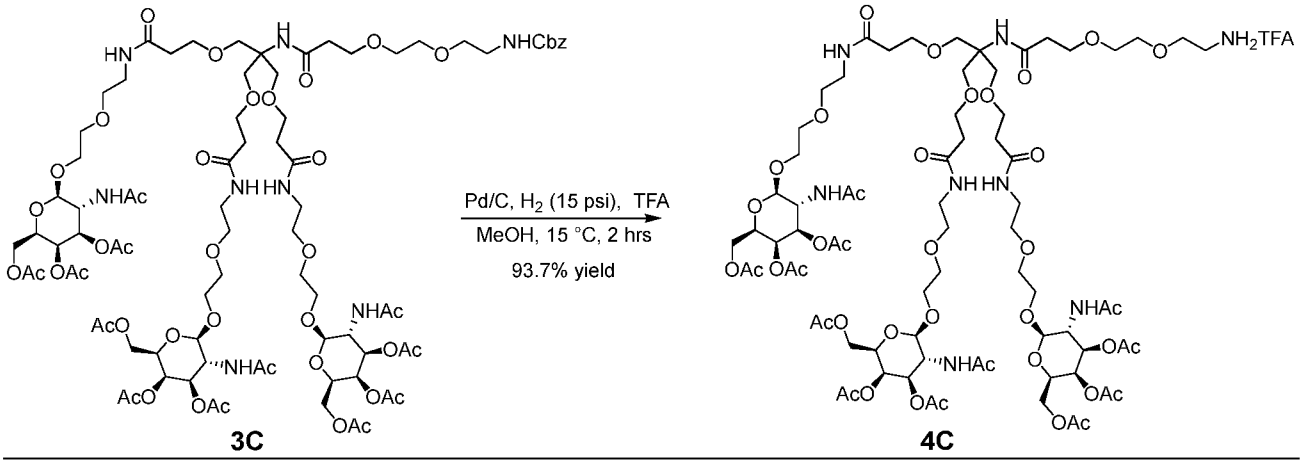
General procedure for preparation of TRIS-PEG2-CBZ.



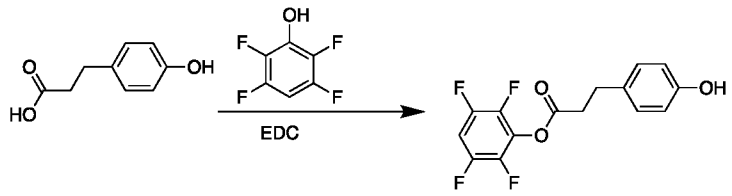
[0370] A solution of Compound 3B (775 g, 487 mmol, 50.3% purity, 1.00 *eq*) in HCl/dioxane (4 M, 2.91 L, 23.8 *eq*) is stirred at 25 °C for 2 hrs. LCMS showed the desired MS is given. The mixture is concentrated under vacuum to give a residue. Then the combined residue is diluted with DCM (5.00 L), adjusted to pH=8 with 2.5 M NaOH aqueous solution, and separated. The aqueous phase is extracted with DCM (3.00 L) again, then the aqueous solution is adjusted to pH=3 with 1 N HCl aqueous solution, then extracted with DCM (5.00 L*2), the combined organic layer is washed with brine (3.00 L), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude is purified by column chromatography (SiO_2, DCM:MeOH=0:1-12:1, 0.1% HOAc, R_f=0.4). The residue is diluted with DCM (5.00 L), adjusted to pH=8 with 2.5 M NaOH aqueous solution, separated, the aqueous solution is extracted with DCM (3.00 L) again, then the aqueous solution is adjusted to pH=3 with 6 N HCl aqueous solution, extracted with DCM:MeOH=10:1 (5.00 L*2), the combined organic layer is washed with brine (2.00 L), dried over Na_2SO_4, filtered and concentrated under vacuum to give a residue. Then the residue is diluted with MeCN (5.00 L), concentrated under vacuum, repeat this procedure twice to remove water to give TRIS-PEG2-CBZ (1.25 kg, 1.91 mol, 78.1% yield, 95.8% purity) as light yellow oil. ^{1}HNMR: 400 MHz, MeOD, δ 7.30-7.35 (5 H), 5.07 (s, 2 H), 3.65-3.70 (m, 16 H), 3.59 (s, 4 H), 3.45 (t, *J*=5.6 Hz), 2.51 (t, *J*=6.0 Hz), 2.43 (t, 6.4 Hz).

Scheme for the preparation of TriNGal-TRIS-Peg2-Phosph 8c

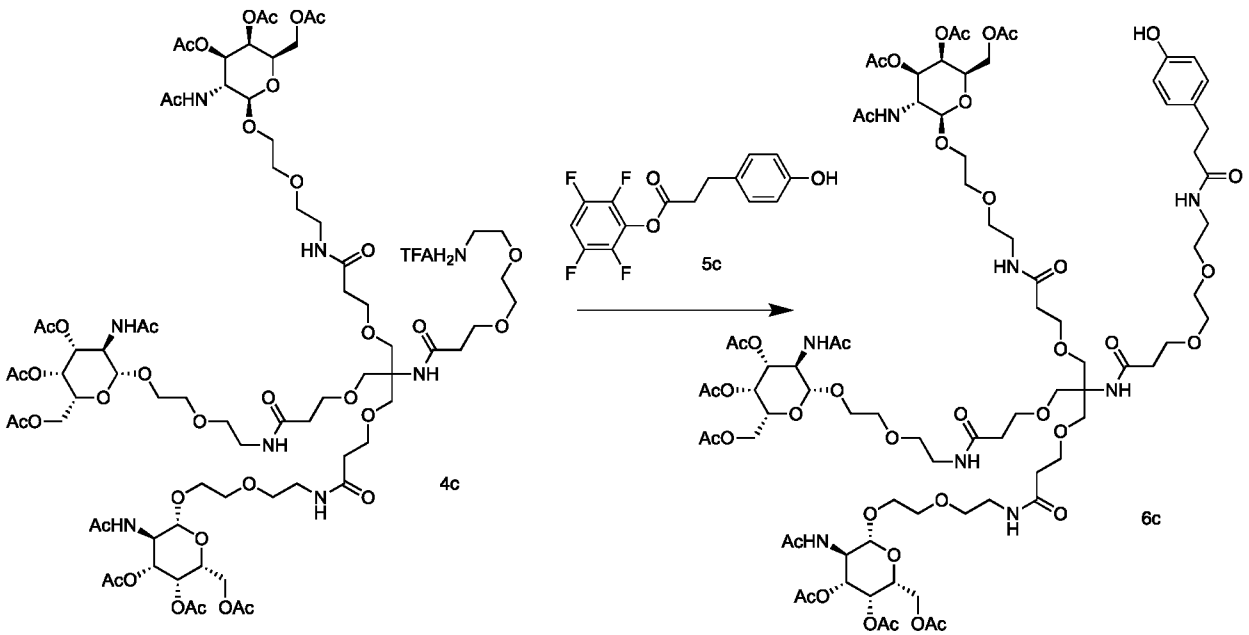




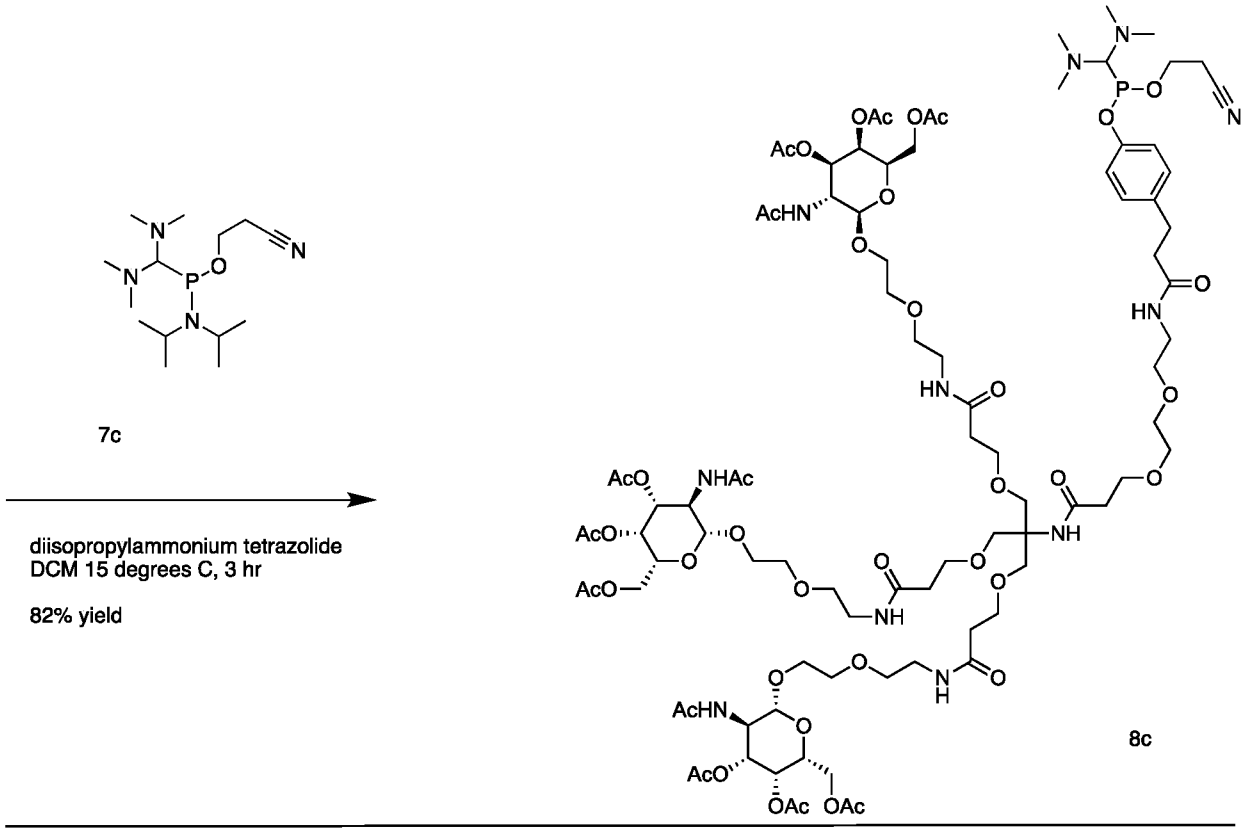
3C 4C



5c

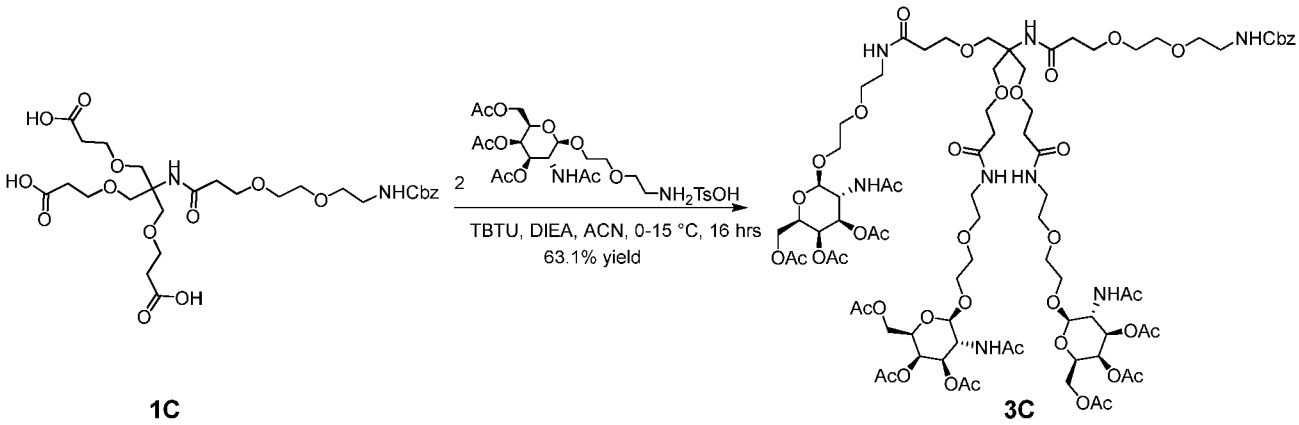


4c 6c



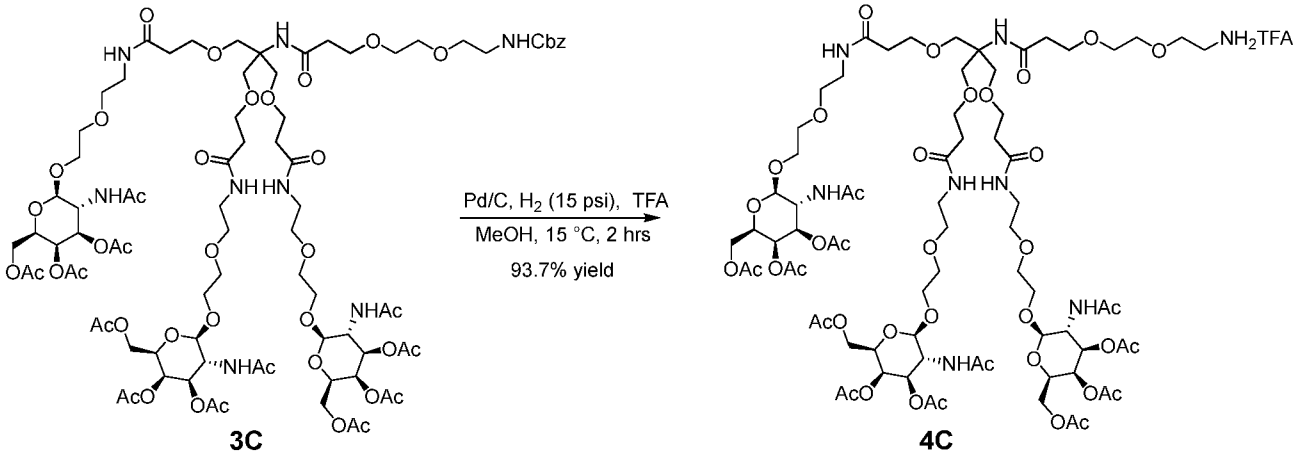
TriGNal-TRIS-Peg2-Phosph 8c

General procedure for preparation of Compound 3C



[0371] To a solution of Compound 1C (155 g, 245 mmol, 1.00 *eq*) in ACN (1500 mL) is added TBTU (260 g, 811 mmol, 3.30 *eq*), DIEA (209 g, 1.62 mol, 282 mL, 6.60 *eq*) and Compound 2C (492 g, 811 mmol, 3.30 *eq*, TsOH) at 0 °C, the mixture is stirred at 15 °C for 16 hrs. LCMS showed the desired MS is given. The mixture is concentrated under vacuum to give a residue, then the mixture is diluted with DCM (2000 mL), washed with 1 N HCl aqueous solution (700 mL * 2), then saturated $NaHCO_3$ aqueous solution (700 mL *2) and concentrated under vacuum. The crude is purified by column chromatography to give Compound 3C (304 g, 155 mmol, 63.1% yield, 96.0% purity) as a yellow solid.

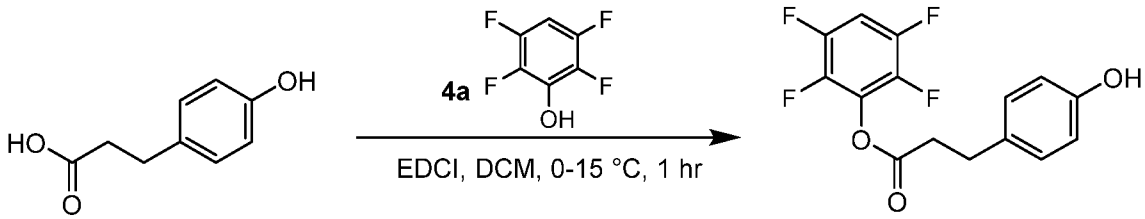
General procedure for preparation of Compound 4C



3C 4C

[0372] Two batches solution of Compound 3C (55.0 g, 29.2 mmol, 1.00 *eq*) in MeOH (1600 mL) is added Pd/C (6.60 g, 19.1 mmol, 10.0 % purity) and TFA (3.34 g, 29.2 mmol, 2.17 mL, 1.00 *eq*), the mixture is degassed under vacuum and purged with H_2. The mixture is stirred under H_2 (15 psi) at 15 °C for 2 hours. LCMS showed the desired MS is given. The mixture is filtered and the filtrate is concentrated under vacuum to give Compound 4C (106 g, 54.8 mmol, 93.7% yield, 96.2% purity, TFA) as a white solid.

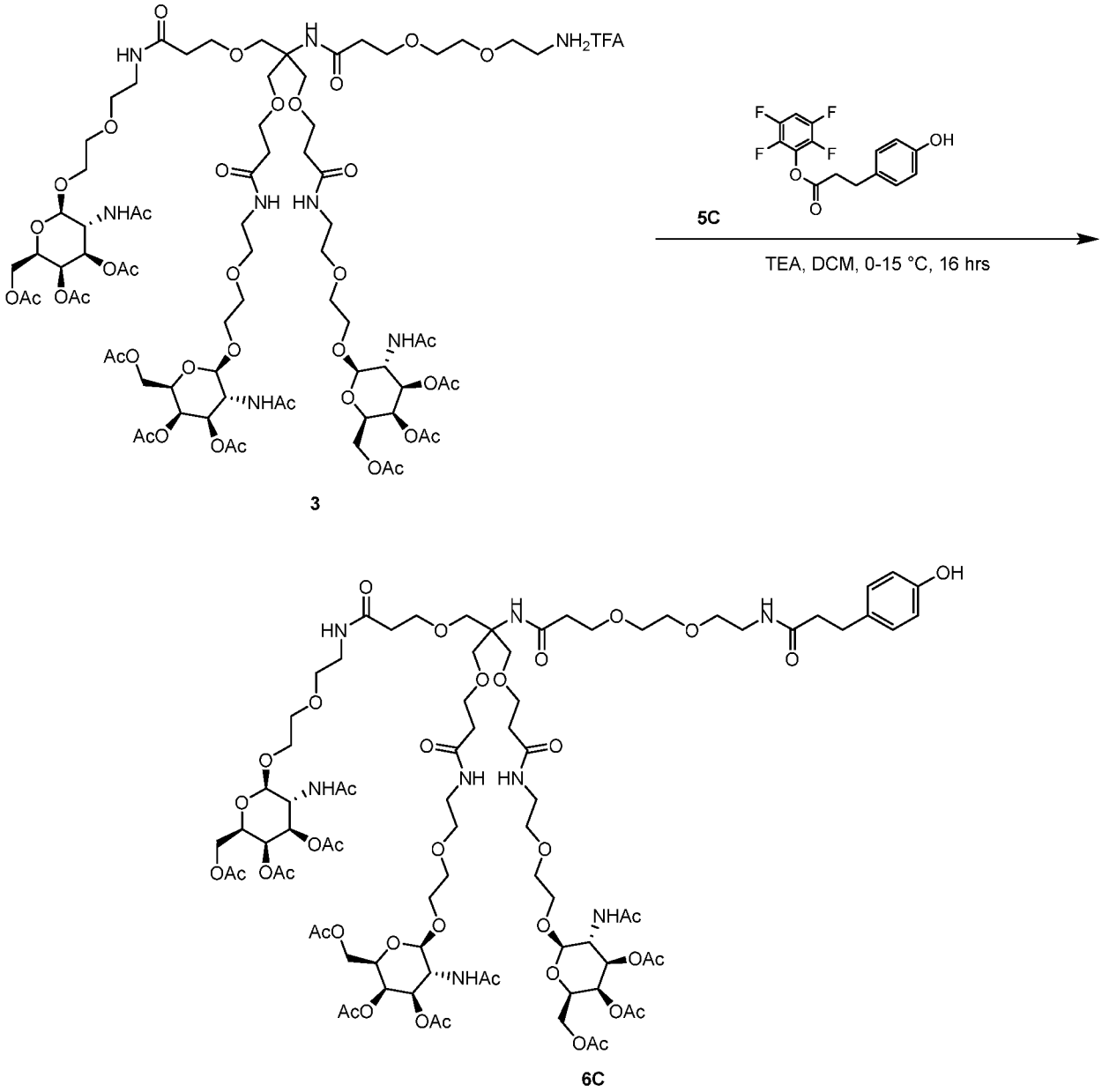
General procedure for preparation of compound 5C



4 5C

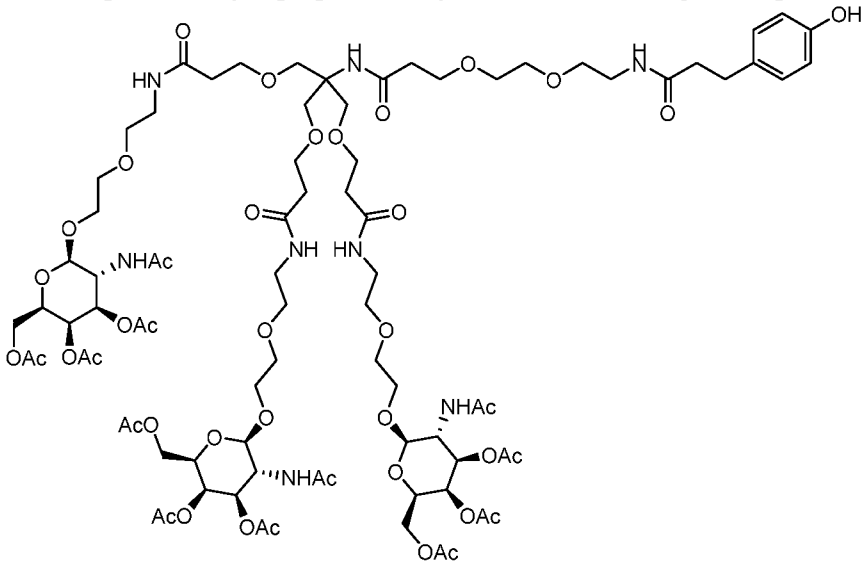
[0373] Two batches in parallel. To a solution of EDCI (28.8 g, 150 mmol, 1.00 eq) in DCM (125 mL) is added compound **4a** (25.0 g, 150 mmol, 1.00 eq) dropwise at 0 °C, then the mixture is added to compound 4 (25.0 g, 150 mmol, 1.00 eq) in DCM (125 mL) at 0 °C, then the mixture is stirred at 25 °C for 1 hr. TLC (Petroleum ether : Ethyl acetate = 3 : 1, R_f = 0.45) showed the reactant is consumed and one new spot is formed. The reaction mixture is diluted with DCM (100 mL) then washed with aq.$NaHCO_3$ (250 mL * 1) and brine (250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue is purified by column chromatography (SiO_2, Petroleum ether : Ethyl acetate = 100 : 1 to 3 : 1), TLC (SiO_2, Petroleum ether : Ethyl acetate = 3:1), R_f = 0.45 , then concentrated under reduced pressure to give a residue. Compound **5C** (57.0 g, 176 mmol, 58.4% yield, 96.9% purity) is obtained as colorless oil and confirmed **^{1}HNMR:** EW33072-2-P1A, 400 MHz, DMSO δ 9.21 (s, 1 H), 7.07-7.09 (m, 2 H), 6.67-6.70 (m, 2 H), 3.02-3.04 (m, 2 H), 2.86-2.90 (m, 2 H)

General procedure for preparation of compound 6

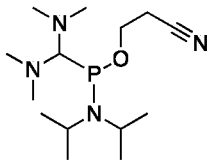


[0374] To a mixture of compound **3** (79.0 g, 41.0 mmol, 96.4% purity, 1.00 eq, TFA) and compound **6C** (14.2 g, 43.8 mmol, 96.9% purity, 1.07 eq) in DCM (800 mL) is added TEA (16.6 g, 164 mmol, 22.8 mL, 4.00 eq) dropwise at 0 °C, the mixture is stirred at 15 °C for 16 hrs. LCMS (EW33072-12-P1B, Rt = 0.844 min) showed the desired mass is detected. The reaction mixture is diluted with DCM (400 mL) and washed with aq.$NaHCO_3$ (400 mL * 1) and brine(400 mL * 1), then the mixture is diluted with DCM (2.00 L) and washed with 0.7 M Na_2CO_3 (1000 mL * 3) and brine(800 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue is used to next step directly without purification. Compound **6** (80.0 g, crude) is obtained as white solid and confirmed via **^{1}HNMR:** EW33072-12-P1A, 400 MHz, MeOD δ 7.02 - 7.04 (m, 2 H), 6.68 - 6.70 (m, 2 H), 5.34 - 5.35 (s, 3 H), 5.07 - 5.08 (d, J = 4.00 Hz, 3 H), 4.62 - 4.64 (d, J = 8.00 Hz, 3 H), 3.71 - 4.16 (m, 16 H), 3.31 - 3.70 (m, 44 H), 2.80 - 2.83 (m, 2 H), 2.68 (m, 2 H), 2.46 - 2.47 (m, 10 H), 2.14 (s, 9 H), 2.03 (s, 9 H), 1.94 - 1.95 (d, J = 4.00 Hz, 18 H).

General procedure for preparation of TriGNal-TRIS-Peg2-Phosph 8c



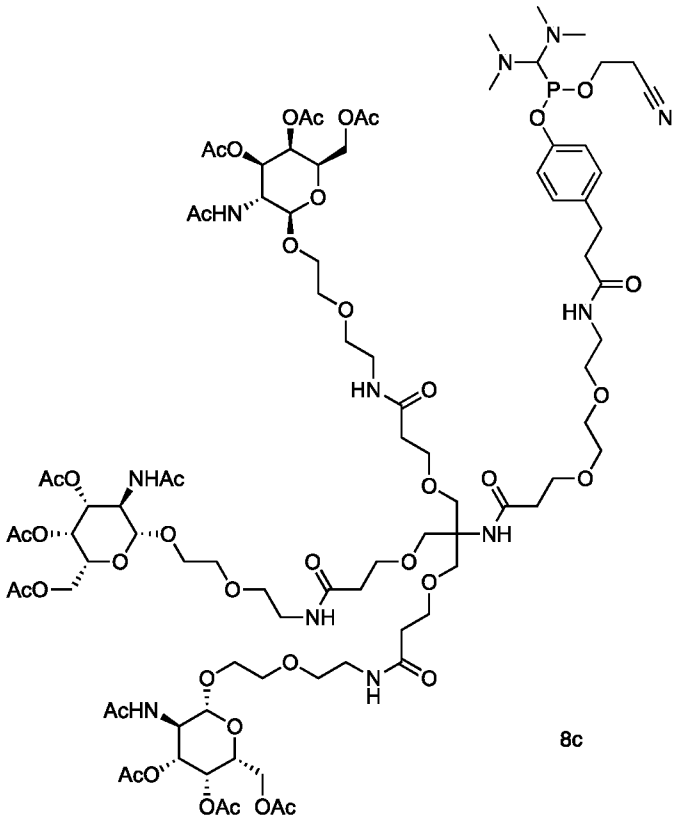
6C



7c

diisopropylammonium tetrazolide
DCM 15 degrees C, 3 hr

82% yield



8c

[0375] Two batches are synthesized in parallel. To a solution of compound **6C** (40.0 g, 21.1 mmol, 1.00 eq in DCM (600 mL) is added diisopropylammonium tetrazolide (3.62 g, 21.1 mmol, 1.00 eq) and compound **7c** (6.37 g, 21.1 mmol, 6.71 mL, 1.00 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 1 hr, then added compound **7c** (3.18 g, 10.6 mmol, 3.35 mL, 0.50 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 30 mins, then added compound **7c** (3.18 g, 10.6 mmol, 3.35 mL, 0.50 eq) in DCM (8.00 mL) drop-wise, the mixture is stirred at 30 °C for 1.5 hrs. LCMS (EW33072-17-P1C1, Rt = 0.921 min) showed the desired MS+1 is detected. LCMS (EW33072-17-P1C2, Rt = 0.919 min) showed the desired MS+1 is detected. Two batches are combined for work-up.

The mixture is diluted with DCM (1.20 L), washed with saturated $NaHCO_3$ aqueous solution (1.60 L * 2), 3% DMF in H_2O (1.60 L * 2), H_2O (1.60 L * 3), brine (1.60 L), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue is purified by column chromatography (SiO_2, DCM : MeOH : TEA = 100 : 3 : 2) TLC (SiO_2, DCM: MeOH = 10:1, R_f = 0.45), then concentrated under reduced pressure to give a residue. **Compound 8C** (76.0 g, 34.8 mmol, 82.5% yield, 96.0% purity) is obtained as white solid and confirmed via **^{1}HNMR:** EW33072-19-P1C, 400 MHz, MeOD

δ 7.13-7.15 (d, *J* = 8.50 Hz, 2 H), 6.95-6.97 (dd, *J* =8.38, 1.13 Hz, 2 H), 5.34 (d, *J* =2.88 Hz, 3 H), .09 (dd, *J* =11.26, 3.38 Hz, 3 H), 4.64 (d, *J* =8.50 Hz, 3 H), 3.99 - 4.20 (m, 12 H), 3.88 - 3.98 (m, 5 H), 3.66 - 3.83 (m, 20 H), 3.51 - 3.65 (m, 17 H), 3.33 - 3.50 (m, 9 H), 2.87 (t, *J* =7.63 Hz, 2 H), 2.76 (t, *J* =5.94 Hz, 2 H), 2.42 - 2.50 (m, 10 H), 2.14 (s, 9 H), 2.03 (s, 9 H), 1.94 - 1.95 (d, *J* =6.13 Hz, 18 H), 1.24-1.26 (d, *J* =6.75 Hz, 6 H), 1.18-1.20 (d, *J* =6.75 Hz, 6 H)

Example 18: Modification motif 1

[0376] An example ANGPTL4 siRNA includes a combination of the following modifications:

- Position 9 (from 5' to 3') of the sense strand is 2' F.
- If position 9 is a pyrimidine then all purines in the Sense Strand are 2'OMe, and 1-5 pyrimidines between positions 5 and 11 are 2' F provided that there are never three 2'F modifications in a row.
- If position 9 is a purine then all pyrimidines in the Sense Strand are 2'OMe, and 1-5 purines between positions 5 and 11 are 2' F provided that there are never three 2'F modifications in a row.
- Antisense strand odd-numbered positions are 2'OMe and even-numbered positions are a mixture of 2' F and 2' deoxy.

Example 19: Modification motif 2

[0377] An example ANGPTL4 siRNA includes a combination of the following modifications:

- Position 9 (from 5' to 3') of the sense strand is 2' deoxy.
- Sense strand positions 5, 7 and 8 are 2' F.
- All pyrimidines in positions 10-21 are 2' OMe, and purines are a mixture of 2' OMe and 2' F. Alternatively, all purines in positions 10-21 are 2' OMe and all pyrimidines in positions 10-21 are a mixture of 2' OMe and 2' F.
- Antisense strand odd-numbered positions are 2'OMe and even-numbered positions are a mixture of 2' F and 2' deoxy.

Example 20: Screening siRNAs targeting human ANGPTL4 in mice transfected with AAV8-TBG-h-ANGPTL4

[0378] Several siRNAs targeting human ANGPTL4, namely ETD01179, ETD01656, ETD01657, ETD01658 and ETD01659 were tested for activity in mice following transfection with an adeno-associated viral vector. The siRNAs were attached to the GalNAc ligand ETL1. The siRNA sequences are shown in **Table 25A-25B**, where Nf is a 2' fluoro-modified nucleoside, n is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

Table 25A. Example siRNA Sequences

ETD#	Sense Strand Sequence (5′-3′) with GalNAc moiety	Antisense Strand Sequence (5′-3′)
ETD01179	[ETL1]csasgagUfUfCfUfuggaauaaaasusu	usUfsuUfaUfuCfcAfaGfaAfcUfcUfgsusu
ETD01656	[ETL1]sggacAfGfuAfAfuucagaggcasusu	usGfscCfuCfuGfaAfuUfaCfuGfuCfcsusu
ETD01657	[ETL1]suggaGfAfaGfGfuGfcauagcaasusu	usUfsgCfuAfuGfcAfcCfuUfcUfcCfasusu
ETD01658	[ETL1]saccaccAfuGfuugauccagasusu	usCfsuGfgAfuCfaAfcAfuGfgUfgGfususu
ETD01659	[ETL1]sugcugUfUfgUfgUfguaggucasusu	usGfsaCfcUfaCfaCfaCfaAfcAfgCfasusu

Table 25B. Example siRNA Sequences

ETD#	Sense Strand SEQ ID NO:	Antisense Strand SEQ ID NO:
ETD01179	14299	14298
ETD01656	14300	14304
ETD01657	14301	14305
ETD01658	14302	14306
ETD01659	14303	14307

[0379] Six to eight week old female mice (C57Bl/6) were injected with 10 uL of a recombinant adeno-associated virus 8 (AAV8) vector (1.8 x 10E13 genome copies/mL) by the retroorbital route. The recombinant AAV8 contained positions 29-1870 of the human ANGPTL4 sequence (NM_139314) under the control of the human thyroxine binding globulin promoter in an AAV2 backbone packaged in AAV8 capsid (AAV8-TBG-h-ANGPTL4). On Day 14 after infection, serum was collected and the level of human ANGPTL4 protein in each mouse was measured using an AlphaLISA immunoassay (PerkinElmer AL3017) according to the recommended protocols provided by the manufacturer. Briefly, standard analyte (recombinant human ANGPTL4 encoding residues Gly26-Ser406) and serum samples were prepared in 1X AlphaLISA Assay Buffer (PerkinElmer AL000C). For each assay, 5 µL of prepared standard analyte or diluted sample were added to a 96-well white ½ Area OptiPlate (PerkinElmer 6002290) followed by the addition of 10 µL of Acceptor bead mix. Then the plate was sealed with TopSeal A-PLUS (PerkinElmer 6050185) and incubated for 30 minutes at room temperature. Next, 10 µL of biotinylated antibody was added to each well of the plate. The plate was sealed and incubated for 60 minutes at room temperature. Afterwards, 25 µL of streptavidin Donor beads were added in the dark to prevent photobleaching. The plate was sealed, covered with foil, and incubated at room temperature for 30 minutes prior to measuring AlphaLISA signal. All Alpha assays were measured on the Alpha-enabled EnVision multilabel plate reader using the 640as mirror module (#444) and the M570w emission filter (#244). Standard Alpha measurement settings were used: excitation wavelength at 680 nm was used to excite Donor beads and emission wavelength at 615 nm measured as Alpha signal; total measurement

time 550 ms and excitation time 180 ms were used. A standard curve was generated by plotting the Alpha signal counts versus the concentration of analyte using GraphPad Prism version 9 for macOS (GraphPad Software). The curve was fit according to a nonlinear regression using the 4-parameter logistic equation (sigmoidal dose-response curve with variable slope) and a 1/Y2 data weighting (Prism version 9, Software MacKiev).

[0380] Mice were allocated into groups (n=4) such that the groups had similar serum levels of ANGPTL4 protein and then given a subcutaneous injection of a single 100 μg dose of a GalNAc-conjugated siRNA or PBS as vehicle control. On Days 0, 3, 7 and 14 after injection, serum was collected to assess serum ANGPTL4 protein concentrations by AlphaLISA using the methods described above. The ANGPTL4 serum concentration at each timepoint was made relative to the level of ANGPTL4 protein in the Day 0 sample for each individual mouse. The results are shown in **Table 26**. Mice injected with ETD01179 had the greatest reduction in serum ANGPTL4 of the siRNAs tested, with lower levels on Day 14 and Day 14 than on Day 3 relative to Day 0. Mice injected ETD01656, ETD01657, EETD01658 and ETD01659 did not as large of a reduction in ANGPTL4 protein.

Table 26. Relative Mean Serum Human ANGPTL4 Levels in AAV8-TBG-h- ANGPTL4 Mice

Group	n	Treatment	Dose (μg)	Mean serum human ANGPTL4 protein (Relative to Day 0)			
				Day 0	Day 3	Day 7	Day 14
1	4	PBS	0	1.00	0.85	0.67	0.60
2	4	ETD01179	100	1.00	0.20	0.04	0.06
3	4	ETD01656	100	1.00	0.72	0.68	0.88
4	4	ETD01657	100	1.00	1.00	1.30	0.96
5	4	ETD01658	100	1.00	0.88	0.74	0.92
6	4	ETD01659	100	1.00	0.94	0.60	0.52

[0381] Mice were sacrificed on Day 14 and a liver sample from each was collected and placed in RNAlater (ThermoFisher Catalog# AM7020) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The relative levels of liver ANGPTL4 mRNA were assessed by RT-qPCR using TaqMan assays for human ANGPTL4 (ThermoFisher, assay# Hs01101127_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the level in animals receiving PBS. Results are shown in **Table 27**. Mice injected with ETD01179 was the most active, having substantially lower levels in mean liver human ANGPTL4 mRNA on Day 14 relative to mice receiving PBS.

Table 27. Relative Human ANGPTL4 mRNA Levels in Livers of AAV8-TBG-h- ANGPTL4 Mice

Group	n	Treatment	Dose (µg)	Mean human ANGPTL4 mRNA (Relative to Group 1, Day 14)
1	4	PBS	0	1.00
2	4	ETD01179	100	0.26
3	4	ETD01656	100	0.63
4	4	ETD01657	100	1.21
5	4	ETD01658	100	0.86
6	4	ETD01659	100	0.86

Example 21. Screening additional siRNAs targeting human ANGPTL4 and alternatively modified versions of ETD01179 in mice transfected with AAV8-TBG-h-ANGPTL4

[0382] Several siRNAs targeting human ANGPTL4 were tested for activity in mice following transfection with an adeno-associated viral vector. These were siRNAs with alternative modifications to siRNA ETD01179 as well as an siRNA with a different target sequence, ETD01782. The siRNAs were attached to the GalNAc ligand ETL1 at the 5' end of the sense strand. The siRNA sequences are shown in **Table 28A-28B**, where Nf is a 2' fluoro-modified nucleoside, n is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

Table 28A. siRNA Sequences

ETD#	Sense Strand Sequence (5'-3') with GalNAc moiety	Antisense Strand Sequence (5'-3')
ETD01179	[ETL1]csasgagUfUfCfUfuggaauaaaasusu	usUfsuUfaUfuCfcAfaGfaAfcUfcUfgsusu
ETD01776	[ETL1]scagagUfUfCfUfuggaauaaaasusu	usUfsuUfaUfuCfcAfaGfaAfcUfcUfgsusu
ETD01768	[ETL1]scagagUfUfCfUfuggaauaaaasusu	usUfsuuaUfuCfcAfaGfaAfcUfcUfgsusu
ETD01769	[ETL1]scagagUfUfCfUfuggaauaaaasusu	usUfsusUfaUfuCfcAfaGfaAfcUfcUfgsusu
ETD01770	[ETL1]scagagUfUfCfUfuggaauaaaasusu	usUfsuUfaUfuccAfaGfaAfcUfcUfgsusu
ETD01771	[ETL1]scagagUfUfCfUfuggaauaaaasusu	usUfsuUfaUfuccaaGfaAfcUfcUfgsusu
ETD01772	[ETL1]scagagUfUfCfUfudGgaauaaaasusu	usUfsuUfaUfuCfcAfaGfaAfcUfcUfgsusu
ETD01782	[ETL1]suaUfgCfuCfadGacucuagagasusu	usCfsuCfuAfgAfgUfcUfgAfgCfaUfasusu

Table 28B. Example siRNA Sequences

ETD#	Sense Strand SEQ ID NO:	Antisense Strand SEQ ID NO:
ETD01179	14299	14298
ETD01776	14308	14315
ETD01768	14309	14316
ETD01769	14310	14317
ETD01770	14311	14318
ETD01771	14312	14319
ETD01772	14313	14320
ETD01782	14314	14321

[0383] Six to eight week old female mice (C57Bl/6) were injected with 10 uL of a recombinant adeno-associated virus 8 (AAV8) vector (1.8 x 10E13 genome copies/mL) by the retroorbital route. The recombinant AAV8 contained positions 29-1870 of the human ANGPTL4 sequence (NM_139314) under the control of the human thyroxine binding globulin promoter in an AAV2 backbone packaged in AAV8 capsid (AAV8-TBG-h-ANGPTL4). On Day 14 after infection, serum was collected and the level of human ANGPTL4 protein in each mouse was measured using an AlphaLISA immunoassay (PerkinElmer AL3017) according to the recommended protocols provided by the manufacturer. Briefly, standard analyte (recombinant human ANGPTL4 encoding residues Gly26-Ser406) and serum samples were

prepared in 1X AlphaLISA Assay Buffer (PerkinElmer AL000C). For each assay, 5 µL of prepared standard analyte or diluted sample were added to a 96-well white ½ Area OptiPlate (PerkinElmer 6002290) followed by the addition of 10 µL of Acceptor bead mix. Then the plate was sealed with TopSeal A-PLUS (PerkinElmer 6050185) and incubated for 30 minutes at room temperature. Next, 10 µL of biotinylated antibody was added to each well of the plate. The plate was sealed and incubated for 60 minutes at room temperature. Afterwards, 25 µL of streptavidin Donor beads were added in the dark to prevent photobleaching. The plate was sealed, covered with foil, and incubated at room temperature for 30 minutes prior to measuring AlphaLISA signal. All Alpha assays were measured on the Alpha-enabled EnVision multilabel plate reader using the 640as mirror module (#444) and the M570w emission filter (#244). Standard Alpha measurement settings were used: excitation wavelength at 680 nm was used to excite Donor beads and emission wavelength at 615 nm measured as Alpha signal; total measurement time 550 ms and excitation time 180 ms were used. A standard curve was generated by plotting the Alpha signal counts versus the concentration of analyte using GraphPad Prism version 9 for macOS (GraphPad Software). The curve was fit according to a nonlinear regression using the 4-parameter logistic equation (sigmoidal dose-response curve with variable slope) and a 1/Y2 data weighting (Prism version 9, Software MacKiev).

[0384] Mice were allocated into groups (n=4) such that the groups had similar serum levels of ANGPTL4 protein and then given a subcutaneous injection of a single 60 µg dose of a GalNAc-conjugated siRNA or PBS as vehicle control. On Days 0, 4 and 10 after injection, serum was collected to assess serum ANGPTL4 protein concentrations by AlphaLISA using the methods described above. The ANGPTL4 serum concentration at each timepoint was made relative to the level of ANGPTL4 protein in the Day 0 sample for each individual mouse. The results are shown in **Table 29**. Mice injected with an alternatively modified versions of ETD01179, namely ETD01776, ETD01768, ETD01769, ETD01770, ETD01771 and ETD01772, had greater reductions in serum ANGPTL4 protein on Days 3 and 10 relative to Day 0 than mice injected with ETD01179. Mice injected with the new siRNA sequence, ETD01782, had reduced ANGPTL4 protein compared to the mice receiving the PBS control.

Table 29. Relative Mean Serum Human ANGPTL4 Levels in AAV8-TBG-h-ANGPTL4 Mice

Group	n	Treatment	Dose (µg)	Mean serum human ANGPTL4 protein (Relative to Day 0)		
				Day 0	Day 4	Day 10
1	4	PBS	0	1.00	0.89	0.78
2	4	ETD01179	40	1.00	0.78	0.51
3	4	ETD01776	40	1.00	0.54	0.29
4	4	ETD01768	40	1.00	0.68	0.35
5	4	ETD01769	40	1.00	0.69	0.30
6	4	ETD01770	40	1.00	0.51	0.27
7	4	ETD01771	40	1.00	0.35	0.29
8	4	ETD01772	40	1.00	0.65	0.33
9	4	ETD01782	40	1.00	0.70	0.54

[0385] Mice were sacrificed on Day 10 and a liver sample from each was collected and placed in RNAlater (ThermoFisher Catalog# AM7020) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The relative levels of liver ANGPTL4 mRNA were assessed by RT-qPCR using TaqMan assays for human ANGPTL4 (ThermoFisher, assay# Hs01101127_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the level in animals receiving PBS. Results are shown in **Table 30.** Mice injected with an alternatively modified versions of ETD01179, namely ETD01776, ETD01768, ETD01769, ETD01770, and ETD01771, had substantially lower levels in mean liver human ANGPTL4 mRNA on Day 10 relative to mice receiving ETD01179. Mice injected with the new siRNA sequence, ETD01782, had substantially lower levels in mean liver human ANGPTL4 mRNA on Day 10 relative to mice receiving the PBS control.

Table 30. Relative Human ANGPTL4 mRNA Levels in Livers of AAV8-TBG-h-ANGPTL4 Mice

Group	n	Treatment	Dose (µg)	Mean human ANGPTL4 mRNA (Relative to Group 1, Day 10)
1	4	PBS	0	1.00
2	4	ETD01179	40	0.47
3	4	ETD01776	40	0.17
4	4	ETD01768	40	0.15
5	4	ETD01769	40	0.28
6	4	ETD01770	40	0.46
7	4	ETD01771	40	0.30
8	4	ETD01772	40	1.00
9	4	ETD01782	40	0.88

[0386] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WE CLAIM:

1. A composition comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity; wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand; and

wherein the sense strand comprises modification pattern 8S, 7S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, or 16S; or wherein or the antisense strand comprises modification pattern 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS.

2. A composition comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity; wherein any one of the following is true with regard to a strand of the oligonucleotide:

all purines comprise 2' fluoro modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines,

all purines comprise 2' methyl modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines,

all purines comprise 2' fluoro modified purines, and all pyrimidines comprise 2' methyl modified pyrimidines,

all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines,

all pyrimidines comprise 2' methyl modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines, or

all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise 2' methyl modified purines.

3. The composition of claim 2, wherein the increase or decrease is by about 10% or more, as compared to prior to administration.

4. A composition comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases a liver steatosis measurement in the subject.

5. The composition of claim 4, wherein the decrease is by about 10% or more, as compared to prior to administration.

6. The composition of claim 4, wherein the oligonucleotide comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 7S, 8S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, 16S, 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, 9AS, 10AS, 11AS, 12AS, 13AS, 14AS, or 15AS.

7. The composition of claim 4 or 5, wherein any one of the following is true with regard to a strand of the oligonucleotide:

all purines comprise 2' fluoro modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines,

all purines comprise 2' methyl modified purines, and all pyrimidines comprise a mixture of 2' fluoro and 2' methyl modified pyrimidines,

all purines comprise 2' fluoro modified purines, and all pyrimidines comprise 2' methyl modified pyrimidines,

all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines,

all pyrimidines comprise 2' methyl modified pyrimidines, and all purines comprise a mixture of 2' fluoro and 2' methyl modified purines, or

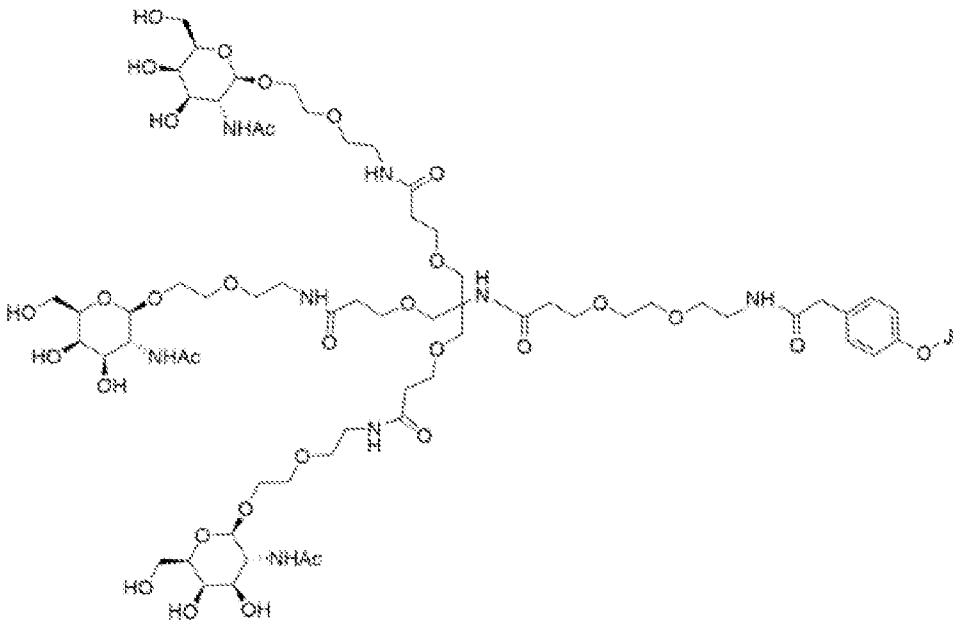
all pyrimidines comprise 2' fluoro modified pyrimidines, and all purines comprise 2' methyl modified purines.

8. The composition of any one of claims 1, 2 or 4, wherein the composition comprises an siRNA.

9. The composition of any one of claims 1, 2 or 4, wherein the composition comprises an antisense oligonucleotide (ASO).

10. The composition of any one of claims 1, 2 or 4, wherein the oligonucleotide comprises a N-acetylgalactosamine (GalNAc) moiety attached to a 5' or 3' end of the oligonucleotide.

11. The composition of claim 10, comprising:



, wherein J comprises the oligonucleotide, and wherein J comprises an optional phosphate or phosphorothioate linking to the oligonucleotide.

12. A composition comprising an siRNA comprising a sense strand comprising a GalNAc moiety attached at a 5' or 3' end and the nucleotide sequence of SEQ ID NO: 14005 or 14299, and an antisense strand having the nucleotide sequence of SEQ ID NO: 14298 or 14153.

13. A method of reducing an ANGPTL4 protein or mRNA measurement in the liver of a subject, comprising administering an effective amount of the composition of any one of claims 1, 2, 4 or 12 to the subject.

14. The method of claim 13, wherein the subject is a primate.

15. A method of treating a subject having a liver disease, comprising administering an effective amount of the composition of any one of claims 1, 2, 4 or 12 to the subject.

16. The method of claim 15, wherein the liver disease comprises nonalcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/032358

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C12N 15/113; A61K 31/713 (2022.01)
ADD.

CPC - INV. - C12N 15/113; A61K 31/713 (2022.08)

ADD. - C12N 2310/11; C12N 2320/32 (2022.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2019/0038768 A1 (ALNYLAM PHARMACEUTICALS INC.) 07 February 2019 (07.02.2019) entire document	1-9, 12-16
A	US 7,250,496 B2 (BENTWICH) 31 July 2007 (31.07.2007) entire document	1-9, 12-16
A	US 2018/0177847 A1 (THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM et al) 28 June 2018 (28.06.2018) entire document	1-9, 12-16
P, X	WO 2021/119019 A1 (EMPIRICO INC.) 17 June 2021 (17.06.2021) entire document	1-9, 12-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 October 2022	NOV 03 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/032358

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NOs: 14005, 14153, 14298, and 14299 were searched.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/032358

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-9, 12-16

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/032358

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-16 are drawn to compositions comprising siRNA polynucleotides targeting ANGPTL4.

The first invention of Group I+ is restricted to an siRNA comprising a sense strand selected to be SEQ ID NO: 14005 and an antisense strand selected to be SEQ ID NO: 14298, and compositions comprising the same. It is believed that claims 1-9 and 12-16 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs 14005 and 14298.

Applicant is invited to elect additional sense and antisense strands, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an siRNA comprising a sense strand selected to be SEQ ID NO: 14299 and an antisense strand selected to be SEQ ID NO: 14153, and compositions comprising the same. Additional sense and antisense strands, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element responsible for targeting ANGPTL4, requiring the selection of alternative siRNAs where "A composition comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity; wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand; and wherein the sense strand comprises modification pattern 8S, 7S, 9S, 10S, 11S, 12S, 13S, 14S, 15S, or 16S; or wherein or the antisense strand comprises modification pattern 10AS, 11 AS, 12AS, 13AS, 14AS, or 15AS."

Additionally, even if Groups I+ were considered to share the technical features of a composition comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity; wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand; and wherein the sense strand comprises modification pattern; or wherein or the antisense strand comprises modification pattern; a composition comprising an oligonucleotide that targets ANGPTL4 and when administered to a subject in an effective amount decreases a liver steatosis measurement in the subject; a composition comprising an siRNA comprising a sense strand comprising a GalNAc moiety attached at a 5' or 3' end. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2019/0038768 to Alnylam Pharmaceuticals Inc. discloses a composition (siRNA composition, Para. [0256]) comprising an oligonucleotide that targets ANGPTL4 (a double-stranded RNAi (dsRNA) agent capable of inhibiting the expression of a target gene, Para. [0020]) and when administered to a subject in an effective amount decreases circulating triglycerides, decreases circulating glucose, decreases a liver steatosis measurement, increases circulating high-density lipoproteins (HDL), or increases insulin sensitivity (a method for delivering the dsRNA to a specific target in a subject by subcutaneous or intravenenuous administration, Para. [0017]; a double-stranded RNAi (dsRNA) agent capable of inhibiting the expression of a target gene, Para. [0020]); wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand (dsRNA agent comprises a sense strand and an antisense strand, Para. [0016]); and wherein the sense strand comprises modification pattern; or wherein or the antisense strand comprises modification pattern (The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end, Para. [0016]); a composition (siRNA composition, Para. [0256]) comprising an oligonucleotide that targets ANGPTL4 (a double-stranded RNAi (dsRNA) agent capable of inhibiting the expression of a target gene, Para. [0020]) and when administered to a subject in an effective amount decreases a liver steatosis measurement in the subject (a method for delivering the dsRNA to a specific target in a subject by subcutaneous or intravenenuous administration, Para. [0017]; a double-stranded RNAi (dsRNA) agent capable of inhibiting the expression of a target gene, Para. [0020]); a composition (siRNA composition, Para. [0256]) comprising an siRNA comprising a sense strand comprising a GalNAc moiety attached at a 5' or 3' end (these motifs interrupts the modification pattern, if present, of the sense and/or antisense strand. The dsRNA agent optionally conjugates with a GalNAc derivative ligand, for instance on the sense strand, Para. [0018]; modifications on three consecutive nucleotides at positions 9, 10, 11 from the 5' end, Para. [0016]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.