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(54) Title: COMPOSITIONS AND METHODS FOR MODULATING APOA1 AND ABCA1 EXPRESSION

(57) **Abrégé/Abstract:**

Aspects of the invention provide single stranded oligonucleotides for activating or enhancing expression of APOA1 or ABCA1. Further aspects provide compositions and kits comprising single stranded oligonucleotides for activating or enhancing expression of APOA1 or ABCA1. Methods for modulating expression of APOA1 or ABCA1 using the single stranded oligonucleotides are also provided. Further aspects of the invention provide methods for selecting a candidate oligonucleotide for activating or enhancing expression of APOA1 or ABCA1.

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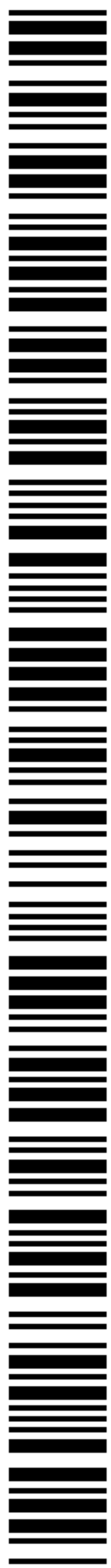
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COMPOSITIONS AND METHODS FOR MODULATING APOA1 AND ABCA1 EXPRESSION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 61/785,778, entitled “COMPOSITIONS AND METHODS FOR MODULATING APOA1 AND ABCA1 EXPRESSION”, filed March 14, 2013 and U.S. Provisional Application No. 61/647,949, entitled “COMPOSITIONS AND METHODS FOR MODULATING APOA1 AND ABCA1 EXPRESSION”, filed May 16, 2012, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to oligonucleotide based compositions, as well as methods of using oligonucleotide based compositions for treating disease.

BACKGROUND OF THE INVENTION

Accumulation of lipids in the blood can cause a variety of conditions and diseases, *e.g.*, dyslipidemia and atherosclerosis. Atherosclerosis in particular is the leading cause of death in industrialized societies, making prevention and treatment a high public health concern. Low-density lipoprotein (LDL) is a major transporter of fat molecules, *e.g.*, cholesterol, in the blood stream that delivers fat molecules to cells. High-density lipoprotein (HDL) is another transporter of fat molecules that moves lipids, *e.g.* cholesterol, from cells to the liver. High levels of LDL are associated with health problems such as dyslipidemia and atherosclerosis, while HDL is protective against atherosclerosis and is involved in maintenance of cholesterol homeostasis.

Dyslipidemia generally describes a condition when an abnormal amount of lipids is present in the blood. Hyperlipidemia, which accounts for the majority of dyslipidemias, refers to an abnormally high amount of lipids in the blood. Hyperlipidemia is often associated with hormonal diseases such as diabetes, hypothyroidism, metabolic syndrome, and Cushing syndrome. Examples of common lipids in dyslipidemias include triglycerides like cholesterol and fat. Abnormal amounts lipids or lipoproteins in the blood can lead to atherosclerosis, heart disease, and stroke.

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Atherosclerotic diseases, *e.g.* coronary artery disease (CAD) and myocardial infarction (MI), involve a thickening of artery walls caused by accumulation of fat in the blood, most commonly cholesterol. This thickening is thought to be the result of chronic inflammation of arteriole walls due to accumulation of LDLs in the vessel walls. LDL molecules can become oxidized once inside vessel walls, resulting in cell damage and recruitment of immune cells like macrophages to absorb the oxidized LDL. Once macrophages internalize oxidized LDL, they become saturated with cholesterol and are referred to as foam cells. Smooth muscle cells are then recruited and form a fibrous region. These processes eventually lead to formation of plaques block arteries and can cause heart attack and stroke. HDL is capable of transporting cholesterol from foam cells to the liver, which aids in inhibition of inflammation and plaque formation.

APOA1 (apolipoprotein A-I) is the major protein component of high density lipoprotein (HDL) in the blood. HDLs pick up cholesterol from cells by interaction with the cholesterol efflux regulatory protein ABCA1 (ATP-binding cassette transporter A1). The interaction of APOA1 and ABCA1 is important for cholesterol homeostasis and protection against diseases like atherosclerosis through transport of cholesterol from atherosclerotic lesions. Mouse models of atherosclerosis have demonstrated that ApoA1 reduces free cholesterol accumulation in vivo in atherosclerotic lesions.

SUMMARY OF THE INVENTION

Aspects of the invention disclosed herein provide methods and compositions that are useful for upregulating APOA1 and/or ABCA1 in cells. In some embodiments, single stranded oligonucleotides are provided that target a PRC2-associated region of an APOA1 gene or an ABCA1 gene (*e.g.*, human APOA1, human ABCA1) and thereby cause upregulation of the gene. In some embodiments, single stranded oligonucleotides are provided that target a PRC2-associated region of the gene encoding APOA1 or ABCA1. In some embodiments, these single stranded oligonucleotides activate or enhance expression of APOA1 or ABCA1 by relieving or preventing PRC2 mediated repression of APOA1 or ABCA1.

Some aspects of the invention disclosed herein provide methods and compositions that are useful for upregulating APOA1, ABCA1, or both for the treatment and/or prevention of dyslipidemia. Other aspects of the invention disclosed herein provide methods and

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compositions that are useful for upregulating APOA1, ABCA1, or both for the treatment and/or prevention of atherosclerosis.

Further aspects of the invention provide methods for selecting oligonucleotides for activating or enhancing expression of APOA1 and/or ABCA1. In some embodiments, methods are provided for selecting a set of oligonucleotides that is enriched in candidates (e.g., compared with a random selection of oligonucleotides) for activating or enhancing expression of APOA1 and/or ABCA1. Accordingly, the methods may be used to establish sets of clinical candidates that are enriched in oligonucleotides that activate or enhance expression of APOA1 and/or ABCA1. Such libraries may be utilized, for example, to identify lead oligonucleotides for developing therapeutics to treat APOA1 and/or ABCA1. Furthermore, in some embodiments, oligonucleotide chemistries are provided that are useful for controlling the pharmacokinetics, biodistribution, bioavailability and/or efficacy of the single stranded oligonucleotides for activating expression of APOA1 and/or ABCA1.

According to some aspects of the invention single stranded oligonucleotides are provided that have a region of complementarity that is complementary with (e.g., at least 8 consecutive nucleotides of) a PRC2-associated region of an APOA1 or an ABCA1 gene, e.g., a PRC2-associated region of the nucleotide sequence set forth as SEQ ID NO: 1, 2, 5 or 6. In some embodiments, the oligonucleotide has at least one of the following features: a) a sequence that is 5'X-Y-Z, in which X is any nucleotide and in which X is at the 5' end of the oligonucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a human seed sequence of a microRNA, and Z is a nucleotide sequence of 1 to 23 nucleotides in length; b) a sequence that does not comprise three or more consecutive guanosine nucleotides; c) a sequence that has less than a threshold level of sequence identity with every sequence of nucleotides, of equivalent length to the second nucleotide sequence, that are between 50 kilobases upstream of a 5'-end of an off-target gene and 50 kilobases downstream of a 3'-end of the off-target gene; d) a sequence that is complementary to a PRC2-associated region that encodes an RNA that forms a secondary structure comprising at least two single stranded loops; and e) a sequence that has greater than 60% G-C content. In some embodiments, the single stranded oligonucleotide has at least two of features a), b), c), d), and e), each independently selected. In some embodiments, the single stranded oligonucleotide has at least three of features a), b), c), d), and e), each independently selected. In some embodiments, the single stranded oligonucleotide has at least four of features a), b),

c), d), and e), each independently selected. In some embodiments, the single stranded oligonucleotide has each of features a), b), c), d), and e). In certain embodiments, the oligonucleotide has the sequence 5'-X-Y-Z, in which the oligonucleotide is 8-50 nucleotides in length.

5 According to some aspects of the invention, single stranded oligonucleotides are provided that have a sequence X-Y-Z, in which X is any nucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a seed sequence of a human microRNA, and Z is a nucleotide sequence of 1 to 23 nucleotides in length, in which the single stranded oligonucleotide is complementary with a PRC2-associated region of an APOA1 gene or an
10 ABCA1 gene, e.g., a PRC2-associated region of the nucleotide sequence set forth as SEQ ID NO: 1, 2, 5 or 6. In some aspects of the invention, single stranded oligonucleotides are provided that have a sequence 5'-X-Y-Z, in which X is any nucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a seed sequence of a human microRNA, and Z is a nucleotide sequence of 1 to 23 nucleotides in length, in which the single stranded
15 oligonucleotide is complementary with at least 8 consecutive nucleotides of a PRC2-associated region of an APOA1 gene or an ABCA1 gene, e.g., a PRC2-associated region of the nucleotide sequence set forth as SEQ ID NO: 1, 2, 5 or 6. In some embodiments, Y is a sequence selected from Table 1. In some embodiments, the PRC2-associated region is a sequence listed in any one of SEQ ID NOS: 9 to 194.

20 In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 195 to 187501, or a fragment thereof that is at least 8 nucleotides. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 195 to 187501, in which the 5' end of the nucleotide sequence provided is the 5' end of the oligonucleotide. In
25 some embodiments, the region of complementarity (*e.g.*, the at least 8 consecutive nucleotides) is also present within the nucleotide sequence set forth as SEQ ID NO: 3, 4, 7 or 8.

 In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 195 to 187501. In some embodiments, the
30 single stranded oligonucleotide comprises a fragment of at least 8 nucleotides of a nucleotide sequence as set forth in any one of SEQ ID NOS: 195 to 187501.

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In some embodiments, the PRC2-associated region is a sequence listed in any one of SEQ ID NOS: 9 to 150. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 195 to 120357 or a fragment thereof that is at least 8 nucleotides. In some embodiments, the single stranded
5 oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 195 to 120357, wherein the 5' end of the nucleotide sequence provided in any one of SEQ ID NOS: 195 to 120357 is the 5' end of the oligonucleotide. In some embodiments, the at least 8 consecutive nucleotides are also present within the nucleotide sequence set forth as SEQ ID NO: 3 or 7.

10 In some embodiments, the PRC2-associated region is a sequence listed in any one of SEQ ID NOS: 151 to 194. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 119697 to 187501 or a fragment thereof that is at least 8 nucleotides. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS:
15 119697 to 187501, wherein the 5' end of the nucleotide sequence provided in any one of SEQ ID NOS: 119697 to 187501 is the 5' end of the oligonucleotide. In some embodiments, the at least 8 consecutive nucleotides are present within the nucleotide sequence set forth as SEQ ID NO: 4 or 8.

In some embodiments, a single stranded oligonucleotide comprises a nucleotide
20 sequence as set forth in Table 4. In some embodiments, the single stranded oligonucleotide comprises a fragment of at least 8 nucleotides of a nucleotide sequence as set forth in Table 4. In some embodiments, a single stranded oligonucleotide consists of a nucleotide sequence as set forth in Table 4.

In some embodiments, the single stranded oligonucleotide does not comprise three or
25 more consecutive guanosine nucleotides. In some embodiments, the single stranded oligonucleotide does not comprise four or more consecutive guanosine nucleotides.

In some embodiments, the single stranded oligonucleotide is 8 to 30 nucleotides in length. In some embodiments, the single stranded oligonucleotide is up to 50 nucleotides in length. In some embodiments, the single stranded oligonucleotide is 8 to 10 nucleotides in
30 length and all but 1, 2, or 3 of the nucleotides of the complementary sequence of the PRC2-associated region are cytosine or guanosine nucleotides.

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In some embodiments, the single stranded oligonucleotide is complementary with at least 8 consecutive nucleotides of a PRC2-associated region of an APOA1 gene or an ABCA1 gene, e.g., a PRC2-associated region of a nucleotide sequence set forth as SEQ ID NO: 1, 2, 5 or 6, in which the nucleotide sequence of the single stranded oligonucleotide

comprises one or more of a nucleotide sequence selected from the group consisting of

(a) (X)XXXXXX, (X)xXXXX, (X)xxXXX, (X)xxxXX, (X)xxxxX and (X)xxxxX,

(b) (X)XXxxxx, (X)XxXxxx, (X)XxxXX, (X)XxxxX, (X)XxxxxX, (X)xXXxxx, (X)xXxXX, (X)xXxxX, (X)xXxxxX, (X)xxXXx, (X)xxXxx, (X)xxxXXx, (X)xxxXx and (X)xxxxXX,

(c) (X)XXXxxx, (X)xXXXxx, (X)xxXXXx, (X)xxxXXX, (X)XXxXX, (X)XXxxX, (X)XXxxxX, (X)xXXxX, (X)xXXxxX, (X)xxXXxX, (X)XxXXxx, (X)XxxXXx, (X)XxxxXX, (X)xXxXXx, (X)xXxxXX, (X)xxXxXX, (X)xXxXx and (X)XxXxX,

(d) (X)xxXXX, (X)xXxXXX, (X)xXXxXX, (X)xXXXxX, (X)xXXXXx, (X)XxxXXXX, (X)XxXxXX, (X)XxXXxX, (X)XxXXx, (X)XXxxXX, (X)XXxXxX,

(X)XXxXXx, (X)XXXxxX, (X)XXXxXx, and (X)XXXXxx,

(e) (X)xXXXXX, (X)XxXXXX, (X)XXxXXX, (X)XXXxXX, (X)XXXXxX and (X)XXXXXx, and

(f) XXXXXX, XxXXXXX, XXxXXXX, XXXxXXX, XXXXxXX, XXXXXxX and XXXXXXx, wherein "X" denotes a nucleotide analogue, (X) denotes an optional nucleotide analogue, and "x" denotes a DNA or RNA nucleotide unit.

In some embodiments, at least one nucleotide of the oligonucleotide is a nucleotide analogue. In some embodiments, the at least one nucleotide analogue results in an increase in T_m of the oligonucleotide in a range of 1 to 5 °C compared with an oligonucleotide that does not have the at least one nucleotide analogue.

In some embodiments, at least one nucleotide of the oligonucleotide comprises a 2' O-methyl. In some embodiments, each nucleotide of the oligonucleotide comprises a 2' O-methyl. In some embodiments, the oligonucleotide comprises at least one ribonucleotide, at least one deoxyribonucleotide, or at least one bridged nucleotide. In some embodiments, the bridged nucleotide is a LNA nucleotide, a cEt nucleotide or a ENA modified nucleotide. In some embodiments, each nucleotide of the oligonucleotide is a LNA nucleotide.

In some embodiments, the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides. In some embodiments, the

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nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-O-methyl nucleotides. In some embodiments, the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and ENA nucleotide analogues. In some embodiments, the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and LNA nucleotides. In some embodiments, the 5' nucleotide of the oligonucleotide is a deoxyribonucleotide. In some embodiments, the nucleotides of the oligonucleotide comprise alternating LNA nucleotides and 2'-O-methyl nucleotides. In some embodiments, the 5' nucleotide of the oligonucleotide is a LNA nucleotide. In some embodiments, the nucleotides of the oligonucleotide comprise deoxyribonucleotides flanked by at least one LNA nucleotide on each of the 5' and 3' ends of the deoxyribonucleotides.

In some embodiments, the single stranded oligonucleotide comprises modified internucleotide linkages (*e.g.*, phosphorothioate internucleotide linkages or other linkages) between at least two, at least three, at least four, at least five or more nucleotides. In some embodiments, the single stranded oligonucleotide comprises modified internucleotide linkages (*e.g.*, phosphorothioate internucleotide linkages or other linkages) between all nucleotides.

In some embodiments, the nucleotide at the 3' position of the oligonucleotide has a 3' hydroxyl group. In some embodiments, the nucleotide at the 3' position of the oligonucleotide has a 3' thiophosphate. In some embodiments, the single stranded oligonucleotide has a biotin moiety or other moiety conjugated to its 5' or 3' nucleotide. In some embodiments, the single stranded oligonucleotide has cholesterol, Vitamin A, folate, sigma receptor ligands, aptamers, peptides, such as CPP, hydrophobic molecules, such as lipids, ASGPR or dynamic polyconjugates and variants thereof at its 5' or 3' end.

According to some aspects of the invention compositions are provided that comprise any of the oligonucleotides disclosed herein, and a carrier. In some embodiments, compositions are provided that comprise any of the oligonucleotides in a buffered solution. In some embodiments, the oligonucleotide is conjugated to the carrier. In some embodiments, the carrier is a peptide. In some embodiments, the carrier is a steroid. According to some aspects of the invention pharmaceutical compositions are provided that comprise any of the oligonucleotides disclosed herein, and a pharmaceutically acceptable carrier.

According to other aspects of the invention, kits are provided that comprise a container housing any of the compositions disclosed herein.

According to some aspects of the invention, methods of increasing expression of APOA1 or ABCA1 in a cell are provided. In some embodiments, the methods involve delivering any one or more of the single stranded oligonucleotides disclosed herein into the cell. In some embodiments, delivery of the single stranded oligonucleotide into the cell results in a level of expression of APOA1 or ABCA1 that is greater (*e.g.*, at least 50% greater) than a level of expression of APOA1 or ABCA1 in a control cell that does not comprise the single stranded oligonucleotide.

According to some aspects of the invention, methods of increasing levels of APOA1 or ABCA1 in a subject are provided. According to some aspects of the invention, methods of treating a condition (*e.g.*, dyslipidemia, atherosclerosis) associated with decreased levels of APOA1 or ABCA1 in a subject are provided. In some embodiments, the methods involve administering any one or more of the single stranded oligonucleotides disclosed herein to the subject.

BRIEF DESCRIPTION OF TABLES

Table 1: Hexamers that are not seed sequences of human miRNAs.

Table 2: Oligonucleotides made for testing in the lab. RQ (column 3) and RQ SE (column 4) shows the activity of the oligo relative to a control well (usually carrier alone) and the standard error for the triplicate replicates of the experiment. [oligo] is shown in nanomolar for in vitro experiments and in milligrams per kilogram of body weight for in vivo experiments. The sequence of each oligonucleotide, including any modified nucleotides, is shown in Table 4.

Table 3: A listing of oligonucleotide modifications.

Table 4: Formatted oligonucleotide sequences made for testing showing nucleotide modifications. The table shows the sequence of the modified nucleotides, where lnaX represents an LNA nucleotide with 3' phosphorothioate linkage, omeX is a 2'-O-methyl nucleotide, dX is a deoxy nucleotide. An s at the end of a nucleotide code indicates that the nucleotide had a 3' phosphorothioate linkage. The "-Sup" at the end of the sequence marks the fact that the 3' end lacks either a phosphate or thiophosphate on the 3' linkage. The Formatted Sequence column shows the sequence of the oligonucleotide, including modified nucleotides, for the oligonucleotides tested in Table 2.

Table 5: Cell lines

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

Aspects of the invention provided herein relate to the discovery of polycomb repressive complex 2 (PRC2)-interacting RNAs. Polycomb repressive complex 2 (PRC2) is a histone methyltransferase and a known epigenetic regulator involved in silencing of genomic regions through methylation of histone H3. Among other functions, PRC2 interacts with long noncoding RNAs (lncRNAs), such as RepA, Xist, and Tsix, to catalyze trimethylation of histone H3-lysine27. PRC2 contains four subunits, Eed, Suz12, RbAp48, and Ezh2. Aspects of the invention relate to the recognition that single stranded oligonucleotides that bind to PRC2-associated regions of RNAs (*e.g.*, lncRNAs) that are expressed from within a genomic region that encompasses or that is in functional proximity to the APOA1 or ABCA1 gene can induce or enhance expression of APOA1 or ABCA1. In some embodiments, this upregulation is believed to result from inhibition of PRC2 mediated repression of APOA1 or ABCA1.

As used herein, the term “PRC2-associated region” refers to a region of a nucleic acid that comprises or encodes a sequence of nucleotides that interact directly or indirectly with a component of PRC2. A PRC2-associated region may be present in a RNA (*e.g.*, a long non-coding RNA (lncRNA)) that that interacts with a PRC2. A PRC2-associated region may be present in a DNA that encodes an RNA that interacts with PRC2. In some cases, the PRC2-associated region is equivalently referred to as a PRC2-interacting region.

In some embodiments, a PRC2-associated region is a region of an RNA that crosslinks to a component of PRC2 in response to *in situ* ultraviolet irradiation of a cell that expresses the RNA, or a region of genomic DNA that encodes that RNA region. In some embodiments, a PRC2-associated region is a region of an RNA that immunoprecipitates with an antibody that targets a component of PRC2, or a region of genomic DNA that encodes that RNA region. In some embodiments, a PRC2-associated region is a region of an RNA that immunoprecipitates with an antibody that binds specifically to SUZ12, EED, EZH2 or RBBP4 (which as noted above are components of PRC2), or a region of genomic DNA that encodes that RNA region.

In some embodiments, a PRC2-associated region is a region of an RNA that is protected from nucleases (*e.g.*, RNases) in an RNA-immunoprecipitation assay that employs an antibody that targets a component of PRC2, or a region of genomic DNA that encodes that

protected RNA region. In some embodiments, a PRC2-associated region is a region of an RNA that is protected from nucleases (*e.g.*, RNases) in an RNA-immunoprecipitation assay that employs an antibody that targets SUZ12, EED, EZH2 or RBBP4, or a region of genomic DNA that encodes that protected RNA region.

5 In some embodiments, a PRC2-associated region is a region of an RNA within which occur a relatively high frequency of sequence reads in a sequencing reaction of products of an RNA-immunoprecipitation assay that employs an antibody that targets a component of PRC2, or a region of genomic DNA that encodes that RNA region. In some embodiments, a PRC2-associated region is a region of an RNA within which occur a relatively high frequency of
10 sequence reads in a sequencing reaction of products of an RNA-immunoprecipitation assay that employs an antibody that binds specifically to SUZ12, EED, EZH2 or RBBP4, or a region of genomic DNA that encodes that protected RNA region. In such embodiments, the PRC2-associated region may be referred to as a “peak.”

In some embodiments, a PRC2-associated region comprises a sequence of 40 to 60
15 nucleotides that interact with PRC2 complex. In some embodiments, a PRC2-associated region comprises a sequence of 40 to 60 nucleotides that encode an RNA that interacts with PRC2. In some embodiments, a PRC2-associated region comprises a sequence of up to 5kb in length that comprises a sequence (*e.g.*, of 40 to 60 nucleotides) that interacts with PRC2. In some embodiments, a PRC2-associated region comprises a sequence of up to 5kb
20 in length within which an RNA is encoded that has a sequence (*e.g.*, of 40 to 60 nucleotides) that is known to interact with PRC2. In some embodiments, a PRC2-associated region comprises a sequence of about 4kb in length that comprise a sequence (*e.g.*, of 40 to 60 nucleotides) that interacts with PRC2. In some embodiments, a PRC2-associated region comprises a sequence of about 4kb in length within which an RNA is encoded that includes a
25 sequence (*e.g.*, of 40 to 60 nucleotides) that is known to interact with PRC2. In some embodiments, a PRC2-associated region has a sequence as set forth in any one of SEQ ID NOS: 9 to 194.

In some embodiments, single stranded oligonucleotides are provided that specifically bind to, or are complementary to, a PRC2-associated region in a genomic region that
30 encompasses or that is in proximity to the APOA1 or ABCA1 gene. In some embodiments, single stranded oligonucleotides are provided that specifically bind to, or are complementary to, a PRC2-associated region that has a sequence as set forth in any one of SEQ ID NOS: 9 to

194. In some embodiments, single stranded oligonucleotides are provided that specifically bind to, or are complementary to, a PRC2-associated region that has a sequence as set forth in any one of SEQ ID NOS: 9 to 194 combined with up to 2kb, up to 5kb, or up to 10kb of flanking sequences from a corresponding genomic region to which these SEQ IDs map (e.g.,
5 in a human genome). In some embodiments, single stranded oligonucleotides have a sequence as set forth in any one of SEQ ID NOS: 195 to 187501. In some embodiments, a single stranded oligonucleotide has a sequence as set forth in Table 4.

Without being bound by a theory of invention, these oligonucleotides are able to interfere with the binding of and function of PRC2, by preventing recruitment of PRC2 to a
10 specific chromosomal locus. For example, a single administration of single stranded oligonucleotides designed to specifically bind a PRC2-associated region lncRNA can stably displace not only the lncRNA, but also the PRC2 that binds to the lncRNA, from binding chromatin. After displacement, the full complement of PRC2 is not recovered for up to 24 hours. Further, lncRNA can recruit PRC2 in a cis fashion, repressing gene expression at or
15 near the specific chromosomal locus from which the lncRNA was transcribed.

Methods of modulating gene expression are provided, in some embodiments, that may be carried out *in vitro*, *ex vivo*, or *in vivo*. It is understood that any reference to uses of compounds throughout the description contemplates use of the compound in preparation of a pharmaceutical composition or medicament for use in the treatment of condition (e.g.,
20 dyslipidemia, atherosclerosis) associated with decreased levels or activity of APOA1 or ABCA1. Thus, as one nonlimiting example, this aspect of the invention includes use of such single stranded oligonucleotides in the preparation of a medicament for use in the treatment of disease, wherein the treatment involves upregulating expression of APOA1 or ABCA1.

In further aspects of the invention, methods are provided for selecting a candidate
25 oligonucleotide for activating expression of APOA1 or ABCA1. The methods generally involve selecting as a candidate oligonucleotide, a single stranded oligonucleotide comprising a nucleotide sequence that is complementary to a PRC2-associated region (e.g., a nucleotide sequence as set forth in any one of SEQ ID NOS: 9 to 194). In some embodiments, sets of oligonucleotides may be selected that are enriched (e.g., compared with a random selection of
30 oligonucleotides) in oligonucleotides that activate expression of APOA1 or ABCA1.

Single Stranded Oligonucleotides for Modulating Expression of APOA1 or ABCA1

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In one aspect of the invention, single stranded oligonucleotides complementary to the PRC2-associated regions are provided for modulating expression of APOA1 or ABCA1 in a cell. In some embodiments, expression of APOA1 or ABCA1 is upregulated or increased. In some embodiments, single stranded oligonucleotides complementary to these PRC2-associated regions inhibit the interaction of PRC2 with long RNA transcripts such that gene expression is upregulated or increased. In some embodiments, single stranded oligonucleotides complementary to these PRC2-associated regions inhibit the interaction of PRC2 with long RNA transcripts, resulting in reduced methylation of histone H3 and reduced gene inactivation, such that gene expression is upregulated or increased. In some
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10
embodiments, this interaction may be disrupted or inhibited due to a change in the structure of the long RNA that prevents or reduces binding to PRC2. The oligonucleotide may be selected using any of the methods disclosed herein for selecting a candidate oligonucleotide for activating expression of APOA1 or ABCA1.

The single stranded oligonucleotide may comprise a region of complementarity that is
15
complementary with a PRC2-associated region of a nucleotide sequence set forth in any one of SEQ ID NOs: 9-194. The region of complementarity of the single stranded oligonucleotide may be complementary with at least 6, *e.g.*, at least 7, at least 8, at least 9, at least 10, at least 15 or more consecutive nucleotides of the PRC2-associated region.

The PRC2-associated region may map to a position in a chromosome between 50
20
kilobases upstream of a 5'-end of the APOA1 or ABCA1 gene and 50 kilobases downstream of a 3'-end of the APOA1 or ABCA1 gene. The PRC2-associated region may map to a position in a chromosome between 25 kilobases upstream of a 5'-end of the APOA1 or ABCA1 gene and 25 kilobases downstream of a 3'-end of the APOA1 or ABCA1 gene. The PRC2-associated region may map to a position in a chromosome between 12 kilobases
25
upstream of a 5'-end of the APOA1 or ABCA1 gene and 12 kilobases downstream of a 3'-end of the APOA1 or ABCA1 gene. The PRC2-associated region may map to a position in a chromosome between 5 kilobases upstream of a 5'-end of the APOA1 or ABCA1 gene and 12 kilobases downstream of a 3'-end of the APOA1 or ABCA1 gene.

The genomic position of the selected PRC2-associated region relative to the APOA1
30
or ABCA1 gene may vary. For example, the PRC2-associated region may be upstream of the 5' end of the APOA1 or ABCA1 gene. The PRC2-associated region may be downstream of the 3' end of the APOA1 or ABCA1 gene. The PRC2-associated region may be within an

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intron of the APOA1 or ABCA1 gene. The PRC2-associated region may be within an exon of the APOA1 or ABCA1 gene. The PRC2-associated region may traverse an intron-exon junction, a 5'-UTR-exon junction or a 3'-UTR-exon junction of the APOA1 or ABCA1 gene.

The single stranded oligonucleotide may comprise a sequence having the formula X-
5 Y-Z, in which X is any nucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a human seed sequence of a microRNA, and Z is a nucleotide sequence of varying length. In some embodiments X is the 5' nucleotide of the oligonucleotide. In some
embodiments, when X is anchored at the 5' end of the oligonucleotide, the oligonucleotide does not have any nucleotides or nucleotide analogs linked 5' to X. In some embodiments,
10 other compounds such as peptides or sterols may be linked at the 5' end in this embodiment as long as they are not nucleotides or nucleotide analogs. In some embodiments, the single stranded oligonucleotide has a sequence 5'X-Y-Z and is 8-50 nucleotides in length. Oligonucleotides that have these sequence characteristics are predicted to avoid the miRNA pathway. Therefore, in some embodiments, oligonucleotides having these sequence
15 characteristics are unlikely to have an unintended consequence of functioning in a cell as a miRNA molecule. The Y sequence may be a nucleotide sequence of 6 nucleotides in length set forth in Table 1.

The single stranded oligonucleotide may have a sequence that does not contain
guanosine nucleotide stretches (*e.g.*, 3 or more, 4 or more, 5 or more, 6 or more consecutive
20 guanosine nucleotides). In some embodiments, oligonucleotides having guanosine nucleotide stretches have increased non-specific binding and/or off-target effects, compared with oligonucleotides that do not have guanosine nucleotide stretches.

The single stranded oligonucleotide may have a sequence that has less than a
threshold level of sequence identity with every sequence of nucleotides, of equivalent length,
25 that map to a genomic position encompassing or in proximity to an off-target gene. For example, an oligonucleotide may be designed to ensure that it does not have a sequence that maps to genomic positions encompassing or in proximity with all known genes (*e.g.*, all known protein coding genes) other than APOA1 or ABCA1. In a similar embodiment, an oligonucleotide may be designed to ensure that it does not have a sequence that maps to any
30 other known PRC2-associated region, particularly PRC2-associated regions that are functionally related to any other known gene (*e.g.*, any other known protein coding gene). In either case, the oligonucleotide is expected to have a reduced likelihood of having off-target

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effects. The threshold level of sequence identity may be 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99% or 100% sequence identity.

The single stranded oligonucleotide may have a sequence that is complementary to a PRC2-associated region that encodes an RNA that forms a secondary structure comprising at least two single stranded loops. It has been discovered that, in some embodiments, oligonucleotides that are complementary to a PRC2-associated region that encodes an RNA that forms a secondary structure comprising one or more single stranded loops (*e.g.*, at least two single stranded loops) have a greater likelihood of being active (*e.g.*, of being capable of activating or enhancing expression of a target gene) than a randomly selected oligonucleotide. In some cases, the secondary structure may comprise a double stranded stem between the at least two single stranded loops. Accordingly, the region of complementarity between the oligonucleotide and the PRC2-associated region may be at a location of the PRC2 associated region that encodes at least a portion of at least one of the loops. In some cases, the region of complementarity between the oligonucleotide and the PRC2-associated region may be at a location of the PRC2-associated region that encodes at least a portion of at least two of the loops. In some cases, the region of complementarity between the oligonucleotide and the PRC2 associated region that encodes at least a portion of the double stranded stem. In some embodiments, a PRC2-associated region (*e.g.*, of an lncRNA) is identified (*e.g.*, using RIP-Seq methodology or information derived therefrom). In some embodiments, the predicted secondary structure RNA (*e.g.*, lncRNA) containing the PRC2-associated region is determined using RNA secondary structure prediction algorithms, *e.g.*, RNAfold, mfold. In some embodiments, oligonucleotides are designed to target a region of the RNA that forms a secondary structure comprising one or more single stranded loop (*e.g.*, at least two single stranded loops) structures which may comprise a double stranded stem between the at least two single stranded loops.

The single stranded oligonucleotide may have a sequence that has greater than 30% G-C content, greater than 40% G-C content, greater than 50% G-C content, greater than 60% G-C content, greater than 70% G-C content, or greater than 80% G-C content. The single stranded oligonucleotide may have a sequence that has up to 100% G-C content, up to 95% G-C content, up to 90% G-C content, or up to 80% G-C content. In some embodiments in which the oligonucleotide is 8 to 10 nucleotides in length, all but 1, 2, 3, 4, or 5 of the

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nucleotides of the complementary sequence of the PRC2-associated region are cytosine or guanosine nucleotides. In some embodiments, the sequence of the PRC2-associated region to which the single stranded oligonucleotide is complementary comprises no more than 3 nucleotides selected from adenine and uracil.

5 The single stranded oligonucleotide may be complementary to a chromosome of a different species (*e.g.*, a mouse, rat, rabbit, goat, monkey, *etc.*) at a position that encompasses or that is in proximity to that species' homolog of APOA1 or ABCA1. The single stranded oligonucleotide may be complementary to a human genomic region encompassing or in proximity to the APOA1 or ABCA1 gene and also be complementary to a mouse genomic
10 region encompassing or in proximity to the mouse homolog of APOA1 or ABCA1. For example, the single stranded oligonucleotide may be complementary to a sequence as set forth in SEQ ID NO: 1, 2, 5 or 6, which is a human genomic region encompassing or in proximity to the APOA1 or ABCA1 gene, and also be complementary to a sequence as set forth in SEQ ID NO: 3 or 4, which is a mouse genomic region encompassing or in proximity
15 to the mouse homolog of the APOA1 or ABCA1 gene. Oligonucleotides having these characteristics may be tested *in vivo* or *in vitro* for efficacy in multiple species (*e.g.*, human and mouse). This approach also facilitates development of clinical candidates for treating human disease by selecting a species in which an appropriate animal exists for the disease.

 In some embodiments, the region of complementarity of the single stranded
20 oligonucleotide is complementary with at least 8 to 15, 8 to 30, 8 to 40, or 10 to 50, or 5 to 50, or 5 to 40 bases, *e.g.*, 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, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 consecutive nucleotides of a PRC2-associated region. In some embodiments, the region of complementarity is complementary with at least 8 consecutive nucleotides of a
25 PRC2-associated region. In some embodiments the sequence of the single stranded oligonucleotide is based on an RNA sequence that binds to PRC2, or a portion thereof, said portion having a length of from 5 to 40 contiguous base pairs, or about 8 to 40 bases, or about 5 to 15, or about 5 to 30, or about 5 to 40 bases, or about 5 to 50 bases.

 Complementary, as the term is used in the art, refers to the capacity for precise pairing
30 between two nucleotides. For example, if a nucleotide at a certain position of an oligonucleotide is capable of hydrogen bonding with a nucleotide at the same position of PRC2-associated region, then the single stranded nucleotide and PRC2-associated region are

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considered to be complementary to each other at that position. The single stranded nucleotide and PRC2-associated region are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides that can hydrogen bond with each other through their bases. Thus, “complementary” is a term which is used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the single stranded nucleotide and PRC2-associated region. For example, if a base at one position of a single stranded nucleotide is capable of hydrogen bonding with a base at the corresponding position of a PRC2-associated region, then the bases are considered to be complementary to each other at that position. 100% complementarity is not required.

The single stranded oligonucleotide may be at least 80% complementary to (optionally one of at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% complementary to) the consecutive nucleotides of a PRC2-associated region. In some embodiments the single stranded oligonucleotide may contain 1, 2 or 3 base mismatches compared to the portion of the consecutive nucleotides of a PRC2-associated region. In some embodiments the single stranded oligonucleotide may have up to 3 mismatches over 15 bases, or up to 2 mismatches over 10 bases.

It is understood in the art that a complementary nucleotide sequence need not be 100% complementary to that of its target to be specifically hybridizable. In some embodiments, a complementary nucleic acid sequence for purposes of the present disclosure is specifically hybridizable when binding of the sequence to the target molecule (*e.g.*, lncRNA) interferes with the normal function of the target (*e.g.*, lncRNA) to cause a loss of activity (*e.g.*, inhibiting PRC2-associated repression with consequent up-regulation of gene expression) and there is a sufficient degree of complementarity to avoid non-specific binding of the sequence to non-target sequences under conditions in which avoidance of non-specific binding is desired, *e.g.*, under physiological conditions in the case of *in vivo* assays or therapeutic treatment, and in the case of *in vitro* assays, under conditions in which the assays are performed under suitable conditions of stringency.

In some embodiments, the single stranded oligonucleotide is 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 or more nucleotides in length. In a preferred embodiment, the oligonucleotide is 8 to 30 nucleotides in length.

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In some embodiments, the PRC2-associated region occurs on the same DNA strand as a gene sequence (sense). In some embodiments, the PRC2-associated region occurs on the opposite DNA strand as a gene sequence (anti-sense). Oligonucleotides complementary to a PRC2-associated region can bind either sense or anti-sense sequences. Base pairings may include both canonical Watson-Crick base pairing and non-Watson-Crick base pairing (e.g., Wobble base pairing and Hoogsteen base pairing). It is understood that for complementary base pairings, adenosine-type bases (A) are complementary to thymidine-type bases (T) or uracil-type bases (U), that cytosine-type bases (C) are complementary to guanosine-type bases (G), and that universal bases such as 3-nitropyrrole or 5-nitroindole can hybridize to and are considered complementary to any A, C, U, or T. Inosine (I) has also been considered in the art to be a universal base and is considered complementary to any A, C, U or T.

In some embodiments, any one or more thymidine (T) nucleotides (or modified nucleotide thereof) or uridine (U) nucleotides (or a modified nucleotide thereof) in a sequence provided herein, including a sequence provided in the sequence listing, may be replaced with any other nucleotide suitable for base pairing (e.g., via a Watson-Crick base pair) with an adenosine nucleotide. In some embodiments, any one or more thymidine (T) nucleotides (or modified nucleotide thereof) or uridine (U) nucleotides (or a modified nucleotide thereof) in a sequence provided herein, including a sequence provided in the sequence listing, may be suitably replaced with a different pyrimidine nucleotide or vice versa. In some embodiments, any one or more thymidine (T) nucleotides (or modified nucleotide thereof) in a sequence provided herein, including a sequence provided in the sequence listing, may be suitably replaced with a uridine (U) nucleotide (or a modified nucleotide thereof) or vice versa.

In some embodiments, GC content of the single stranded oligonucleotide is preferably between about 30-60 %. Contiguous runs of three or more Gs or Cs may not be preferable in some embodiments. Accordingly, in some embodiments, the oligonucleotide does not comprise a stretch of three or more guanosine nucleotides.

In some embodiments, the single stranded oligonucleotide specifically binds to, or is complementary to an RNA that is encoded in a genome (e.g., a human genome) as a single contiguous transcript (e.g., a non-spliced RNA). In some embodiments, the single stranded oligonucleotide specifically binds to, or is complementary to an RNA that is encoded in a genome (e.g., a human genome), in which the distance in the genome between the 5' end of

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the coding region of the RNA and the 3' end of the coding region of the RNA is less than 1 kb, less than 2 kb, less than 3 kb, less than 4 kb, less than 5 kb, less than 7 kb, less than 8 kb, less than 9 kb, less than 10 kb, or less than 20 kb.

It is to be understood that any oligonucleotide provided herein can be excluded. In some embodiments, a single stranded oligonucleotide is not complementary to SEQ ID NO: 187522. In some embodiments, a single stranded oligonucleotide is not complementary to SEQ ID NO: 187523.

In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 36 to 3115 or 3159 to 4038 of SEQ ID NO: 80. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 160 or 197 to 4056 of SEQ ID NO: 83. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 4008 or 4045 to 4046 of SEQ ID NO: 84. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 76 or 114 to 4045 of SEQ ID NO: 91. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 743 or 781 to 4045 of SEQ ID NO: 92. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 253 or 295 to 2316 or 2354 to 4046 of SEQ ID NO: 93. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 413 or 455 to 2476 or 2514 to 4047 of SEQ ID NO: 94. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 1421 or 1463 to 3484 or 3522 to 4024 of SEQ ID NO: 95. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 2821 or 2863 to 4042 of SEQ ID NO: 96. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 3646 or 3688 to 4023 of SEQ ID NO: 97. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 67 or 111 to 3141 or 3198 to 3428 or 3519 to 4050 of SEQ ID NO: 183. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 1199 or 1256 to 1486 or 1577 to 4044 of SEQ ID NO: 184. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 419, or 494 to 2471 or 2508 to 4074 of SEQ ID NO: 191. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 787 or 824 to 4058 of

SEQ ID NO: 192. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 3029 or 3067 to 4041 of SEQ ID NO: 193. In some embodiments, a single-stranded oligonucleotide is complementary to a sequence within nucleotides 1 to 2546 or 2584 to 4040 of SEQ ID NO: 194.

5 In some embodiments, it has been found that single stranded oligonucleotides disclosed herein may increase expression of mRNA corresponding to the gene by at least about 50% (i.e. 150% of normal or 1.5 fold), or by about 2 fold to about 5 fold. In some embodiments it is contemplated that expression may be increased by at least about 15 fold, 20 fold, 30 fold, 40 fold, 50 fold or 100 fold, or any range between any of the foregoing
10 numbers. It has also been found that increased mRNA expression has been shown to correlate to increased protein expression.

In some or any of the embodiments of the oligonucleotides described herein, or processes for designing or synthesizing them, the oligonucleotides will upregulate gene expression and may specifically bind or specifically hybridize or be complementary to the
15 PRC2 binding RNA that is transcribed from the same strand as a protein coding reference gene. The oligonucleotide may bind to a region of the PRC2 binding RNA that originates within or overlaps an intron, exon, intron exon junction, 5' UTR, 3' UTR, a translation initiation region, or a translation termination region of a protein coding sense strand of a reference gene (refGene).

20 In some or any of the embodiments of oligonucleotides described herein, or processes for designing or synthesizing them, the oligonucleotides will upregulate gene expression and may specifically bind or specifically hybridize or be complementary to a PRC2 binding RNA that transcribed from the opposite strand (the antisense strand) of a protein coding reference gene. The oligonucleotide may bind to a region of the PRC2 binding RNA that originates
25 within or overlaps an intron, exon, intron exon junction, 5' UTR, 3' UTR, a translation initiation region, or a translation termination region of a protein coding antisense strand of a reference gene

The oligonucleotides described herein may be modified, *e.g.*, comprise a modified sugar moiety, a modified internucleoside linkage, a modified nucleotide and/or combinations
30 thereof. In addition, the oligonucleotides can exhibit one or more of the following properties: do not induce substantial cleavage or degradation of the target RNA; do not cause substantially complete cleavage or degradation of the target RNA; do not activate the RNase

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H pathway; do not activate RISC; do not recruit any Argonaute family protein; are not cleaved by Dicer; do not mediate alternative splicing; are not immune stimulatory; are nuclease resistant; have improved cell uptake compared to unmodified oligonucleotides; are not toxic to cells or mammals; may have improved endosomal exit; do interfere with
 5 interaction of lncRNA with PRC2, preferably the Ezh2 subunit but optionally the Suz12, Eed, RbAp46/48 subunits or accessory factors such as Jarid2; do decrease histone H3 lysine27 methylation and/or do upregulate gene expression.

Oligonucleotides that are designed to interact with RNA to modulate gene expression are a distinct subset of base sequences from those that are designed to bind a DNA target
 10 (*e.g.*, are complementary to the underlying genomic DNA sequence from which the RNA is transcribed).

Any of the oligonucleotides disclosed herein may be linked to one or more other oligonucleotides disclosed herein by a linker, *e.g.*, a cleavable linker.

15 *Method for Selecting Candidate Oligonucleotides for Activating Expression of APOA1 or ABCA1*

Methods are provided herein for selecting a candidate oligonucleotide for activating or enhancing expression of APOA1 or ABCA1. The target selection methods may generally involve steps for selecting single stranded oligonucleotides having any of the structural and
 20 functional characteristics disclosed herein. Typically, the methods involve one or more steps aimed at identifying oligonucleotides that target a PRC2-associated region that is functionally related to APOA1 or ABCA1, for example a PRC2-associated region of a lncRNA that regulates expression of APOA1 or ABCA1 by facilitating (*e.g.*, in a *cis*-regulatory manner) the recruitment of PRC2 to the APOA1 or ABCA1 gene. Such oligonucleotides are expected
 25 to be candidates for activating expression of APOA1 or ABCA1 because of their ability to hybridize with the PRC2-associated region of a nucleic acid (*e.g.*, a lncRNA). In some embodiments, this hybridization event is understood to disrupt interaction of PRC2 with the nucleic acid (*e.g.*, a lncRNA) and as a result disrupt recruitment of PRC2 and its associated co-repressors (*e.g.*, chromatin remodeling factors) to the APOA1 or ABCA1 gene locus.

30 Methods of selecting a candidate oligonucleotide may involve selecting a PRC2-associated region (*e.g.*, a nucleotide sequence as set forth in any one of SEQ ID NOS: 9 to 194) that maps to a chromosomal position encompassing or in proximity to the APOA1 or

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ABCA1 gene (*e.g.*, a chromosomal position having a sequence as set forth in SEQ ID NOs: 9-194). The PRC2-associated region may map to the strand of the chromosome comprising the sense strand of the APOA1 or ABCA1 gene, in which case the candidate oligonucleotide is complementary to the sense strand of the APOA1 or ABCA1 gene (*i.e.*, is antisense to the APOA1 or ABCA1 gene). Alternatively, the PRC2-associated region may map to the strand of the first chromosome comprising the antisense strand of the APOA1 or ABCA1 gene, in which case the oligonucleotide is complementary to the antisense strand (the template strand) of the APOA1 or ABCA1 gene (*i.e.*, is sense to the APOA1 or ABCA1 gene).

Methods for selecting a set of candidate oligonucleotides that is enriched in oligonucleotides that activate expression of APOA1 or ABCA1 may involve selecting one or more PRC2-associated regions that map to a chromosomal position that encompasses or that is in proximity to the APOA1 or ABCA1 gene and selecting a set of oligonucleotides, in which each oligonucleotide in the set comprises a nucleotide sequence that is complementary with the one or more PRC2-associated regions. As used herein, the phrase, “a set of oligonucleotides that is enriched in oligonucleotides that activate expression of” refers to a set of oligonucleotides that has a greater number of oligonucleotides that activate expression of a target gene (*e.g.*, APOA1 or ABCA1) compared with a random selection of oligonucleotides of the same physicochemical properties (*e.g.*, the same GC content, T_m , length *etc.*) as the enriched set.

Where the design and/or synthesis of a single stranded oligonucleotide involves design and/or synthesis of a sequence that is complementary to a nucleic acid or PRC2-associated region described by such sequence information, the skilled person is readily able to determine the complementary sequence, *e.g.*, through understanding of Watson Crick base pairing rules which form part of the common general knowledge in the field.

In some embodiments design and/or synthesis of a single stranded oligonucleotide involves manufacture of an oligonucleotide from starting materials by techniques known to those of skill in the art, where the synthesis may be based on a sequence of a PRC2-associated region, or portion thereof.

Methods of design and/or synthesis of a single stranded oligonucleotide may involve one or more of the steps of:

Identifying and/or selecting PRC2-associated region;

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Designing a nucleic acid sequence having a desired degree of sequence identity or complementarity to a PRC2-associated region or a portion thereof;

Synthesizing a single stranded oligonucleotide to the designed sequence;

Purifying the synthesized single stranded oligonucleotide; and

5 Optionally mixing the synthesized single stranded oligonucleotide with at least one pharmaceutically acceptable diluent, carrier or excipient to form a pharmaceutical composition or medicament.

Single stranded oligonucleotides so designed and/or synthesized may be useful in method of modulating gene expression as described herein.

10 Preferably, single stranded oligonucleotides of the invention are synthesized chemically. Oligonucleotides used to practice this invention can be synthesized *in vitro* by well-known chemical synthesis techniques.

Oligonucleotides of the invention can be stabilized against nucleolytic degradation such as by the incorporation of a modification, *e.g.*, a nucleotide modification. For example,
15 nucleic acid sequences of the invention include a phosphorothioate at least the first, second, or third internucleotide linkage at the 5' or 3' end of the nucleotide sequence. As another example, the nucleic acid sequence can include a 2'-modified nucleotide, *e.g.*, a 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-
20 dimethylaminoethyloxyethyl (2'-O-DMAEOE), or 2'-O--N-methylacetamido (2'-O--NMA). As another example, the nucleic acid sequence can include at least one 2'-O-methyl-modified nucleotide, and in some embodiments, all of the nucleotides include a 2'-O-methyl modification. In some embodiments, the nucleic acids are "locked," *i.e.*, comprise nucleic acid analogues in which the ribose ring is "locked" by a methylene bridge connecting the 2'-
25 O atom and the 4'-C atom.

It is understood that any of the modified chemistries or formats of single stranded oligonucleotides described herein can be combined with each other, and that one, two, three, four, five, or more different types of modifications can be included within the same molecule.

In some embodiments, the method may further comprise the steps of amplifying the
30 synthesized single stranded oligonucleotide, and/or purifying the single stranded oligonucleotide (or amplified single stranded oligonucleotide), and/or sequencing the single stranded oligonucleotide so obtained.

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As such, the process of preparing a single stranded oligonucleotide may be a process that is for use in the manufacture of a pharmaceutical composition or medicament for use in the treatment of disease, optionally wherein the treatment involves modulating expression of a gene associated with a PRC2-associated region.

5 In the methods described above a PRC2-associated region may be, or have been, identified, or obtained, by a method that involves identifying RNA that binds to PRC2.

Such methods may involve the following steps: providing a sample containing nuclear ribonucleic acids, contacting the sample with an agent that binds specifically to PRC2 or a subunit thereof, allowing complexes to form between the agent and protein in the sample,
10 partitioning the complexes, synthesizing nucleic acid that is complementary to nucleic acid present in the complexes.

Where the single stranded oligonucleotide is based on a PRC2-associated region, or a portion of such a sequence, it may be based on information about that sequence, *e.g.*, sequence information available in written or electronic form, which may include sequence
15 information contained in publicly available scientific publications or sequence databases.

Nucleotide Analogues

In some embodiments, the oligonucleotide may comprise at least one ribonucleotide, at least one deoxyribonucleotide, and/or at least one bridged nucleotide. In some
20 embodiments, the oligonucleotide may comprise a bridged nucleotide, such as a locked nucleic acid (LNA) nucleotide, a constrained ethyl (cEt) nucleotide, or an ethylene bridged nucleic acid (ENA) nucleotide. Examples of such nucleotides are disclosed herein and known in the art. In some embodiments, the oligonucleotide comprises a nucleotide analog disclosed in one of the following United States Patent or Patent Application Publications: US
25 7,399,845, US 7,741,457, US 8,022,193, US 7,569,686, US 7,335,765, US 7,314,923, US 7,335,765, and US 7,816,333, US 20110009471, the entire contents of each of which are incorporated herein by reference for all purposes. The oligonucleotide may have one or more 2' O-methyl nucleotides. The oligonucleotide may consist entirely of 2' O-methyl nucleotides.

30 Often the single stranded oligonucleotide has one or more nucleotide analogues. For example, the single stranded oligonucleotide may have at least one nucleotide analogue that results in an increase in T_m of the oligonucleotide in a range of 1°C, 2 °C, 3°C, 4 °C, or 5°C

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compared with an oligonucleotide that does not have the at least one nucleotide analogue. The single stranded oligonucleotide may have a plurality of nucleotide analogues that results in a total increase in T_m of the oligonucleotide in a range of 2 °C, 3 °C, 4 °C, 5 °C, 6 °C, 7 °C, 8 °C, 9 °C, 10 °C, 15 °C, 20 °C, 25 °C, 30 °C, 35 °C, 40 °C, 45 °C or more compared
5 with an oligonucleotide that does not have the nucleotide analogue.

The oligonucleotide may be of up to 50 nucleotides in length in which 2 to 10, 2 to 15, 2 to 16, 2 to 17, 2 to 18, 2 to 19, 2 to 20, 2 to 25, 2 to 30, 2 to 40, 2 to 45, or more nucleotides of the oligonucleotide are nucleotide analogues. The oligonucleotide may be of 8 to 30 nucleotides in length in which 2 to 10, 2 to 15, 2 to 16, 2 to 17, 2 to 18, 2 to 19, 2 to 20,
10 2 to 25, 2 to 30 nucleotides of the oligonucleotide are nucleotide analogues.

The oligonucleotide may be of 8 to 15 nucleotides in length in which 2 to 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9, 2 to 10, 2 to 11, 2 to 12, 2 to 13, 2 to 14 nucleotides of the oligonucleotide are nucleotide analogues. Optionally, the oligonucleotides may have every nucleotide except 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides modified.

15 The oligonucleotide may consist entirely of bridged nucleotides (*e.g.*, LNA nucleotides, cEt nucleotides, ENA nucleotides). The oligonucleotide may comprise alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides. The oligonucleotide may comprise alternating deoxyribonucleotides and 2'-O-methyl nucleotides. The oligonucleotide may comprise alternating deoxyribonucleotides and ENA nucleotide
20 analogues. The oligonucleotide may comprise alternating deoxyribonucleotides and LNA nucleotides. The oligonucleotide may comprise alternating LNA nucleotides and 2'-O-methyl nucleotides. The oligonucleotide may have a 5' nucleotide that is a bridged nucleotide (*e.g.*, a LNA nucleotide, cEt nucleotide, ENA nucleotide). The oligonucleotide may have a 5' nucleotide that is a deoxyribonucleotide.

25 The oligonucleotide may comprise deoxyribonucleotides flanked by at least one bridged nucleotide (*e.g.*, a LNA nucleotide, cEt nucleotide, ENA nucleotide) on each of the 5' and 3' ends of the deoxyribonucleotides. The oligonucleotide may comprise deoxyribonucleotides flanked by 1, 2, 3, 4, 5, 6, 7, 8 or more bridged nucleotides (*e.g.*, LNA nucleotides, cEt nucleotides, ENA nucleotides) on each of the 5' and 3' ends of the
30 deoxyribonucleotides. The 3' position of the oligonucleotide may have a 3' hydroxyl group. The 3' position of the oligonucleotide may have a 3' thiophosphate.

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The oligonucleotide may be conjugated with a label. For example, the oligonucleotide may be conjugated with a biotin moiety, cholesterol, Vitamin A, folate, sigma receptor ligands, aptamers, peptides, such as CPP, hydrophobic molecules, such as lipids, ASGPR or dynamic polyconjugates and variants thereof at its 5' or 3' end.

5 Preferably the single stranded oligonucleotide comprises one or more modifications comprising: a modified sugar moiety, and/or a modified internucleoside linkage, and/or a modified nucleotide and/or combinations thereof. It is not necessary for all positions in a given oligonucleotide to be uniformly modified, and in fact more than one of the modifications described herein may be incorporated in a single oligonucleotide or even at
10 within a single nucleoside within an oligonucleotide.

In some embodiments, the single stranded oligonucleotides are chimeric oligonucleotides that contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified
15 nucleotides that confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the target) and a region that is a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. Chimeric single stranded oligonucleotides of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides,
oligonucleosides and/or oligonucleotide mimetics as described above. Such compounds have
20 also been referred to in the art as hybrids or gapmers. Representative United States patents that teach the preparation of such hybrid structures comprise, but are not limited to, US patent nos. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, each of which is herein incorporated by reference.

25 In some embodiments, the single stranded oligonucleotide comprises at least one nucleotide modified at the 2' position of the sugar, most preferably a 2'-O-alkyl, 2'-O-alkyl-O-alkyl or 2'-fluoro-modified nucleotide. In other preferred embodiments, RNA modifications include 2'-fluoro, 2'-amino and 2' O-methyl modifications on the ribose of pyrimidines, abasic residues or an inverted base at the 3' end of the RNA. Such modifications are
30 routinely incorporated into oligonucleotides and these oligonucleotides have been shown to have a higher T_m (i.e., higher target binding affinity) than 2'-deoxyoligonucleotides against a given target.

A number of nucleotide and nucleoside modifications have been shown to make the oligonucleotide into which they are incorporated more resistant to nuclease digestion than the native oligodeoxynucleotide; these modified oligos survive intact for a longer time than unmodified oligonucleotides. Specific examples of modified oligonucleotides include those comprising modified backbones, for example, phosphorothioates, phosphotriesters, methyl phosphonates, short chain alkyl or cycloalkyl intersugar linkages or short chain heteroatomic or heterocyclic intersugar linkages. Most preferred are oligonucleotides with phosphorothioate backbones and those with heteroatom backbones, particularly $\text{CH}_2\text{-NH-O-CH}_2$, $\text{CH}_2\text{-N(CH}_3\text{)-O-CH}_2$ (known as a methylene(methylimino) or MMI backbone, $\text{CH}_2\text{-O-N(CH}_3\text{)-CH}_2$, $\text{CH}_2\text{-N(CH}_3\text{)-N(CH}_3\text{)-CH}_2$ and $\text{O-N(CH}_3\text{)-CH}_2\text{-CH}_2$ backbones, wherein the native phosphodiester backbone is represented as O-P-O-CH_2); amide backbones (see De Mesmaeker et al. *Acc. Chem. Res.* 1995, 28:366-374); morpholino backbone structures (see Summerton and Weller, U.S. Pat. No. 5,034,506); peptide nucleic acid (PNA) backbone (wherein the phosphodiester backbone of the oligonucleotide is replaced with a polyamide backbone, the nucleotides being bound directly or indirectly to the aza nitrogen atoms of the polyamide backbone, see Nielsen et al., *Science* 1991, 254, 1497). Phosphorus-containing linkages include, but are not limited to, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates comprising 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates comprising 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'; see US patent nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050.

Morpholino-based oligomeric compounds are described in Dwaine A. Braasch and David R. Corey, *Biochemistry*, 2002, 41(14), 4503-4510; *Genesis*, volume 30, issue 3, 2001; Heasman, J., *Dev. Biol.*, 2002, 243, 209-214; Nasevicius et al., *Nat. Genet.*, 2000, 26, 216-220; Lacerra et al., *Proc. Natl. Acad. Sci.*, 2000, 97, 9591-9596; and U.S. Pat. No. 5,034,506, issued Jul. 23, 1991. In some embodiments, the morpholino-based oligomeric compound is a

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phosphorodiamidate morpholino oligomer (PMO) (*e.g.*, as described in Iverson, *Curr. Opin. Mol. Ther.*, 3:235-238, 2001; and Wang et al., *J. Gene Med.*, 12:354-364, 2010; the disclosures of which are incorporated herein by reference in their entireties).

Cyclohexenyl nucleic acid oligonucleotide mimetics are described in Wang et al., *J. Am. Chem. Soc.*, 2000, 122, 8595-8602.

Modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These comprise those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts; see US patent nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264, 562; 5, 264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596, 086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623, 070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference.

Modified oligonucleotides are also known that include oligonucleotides that are based on or constructed from arabinonucleotide or modified arabinonucleotide residues.

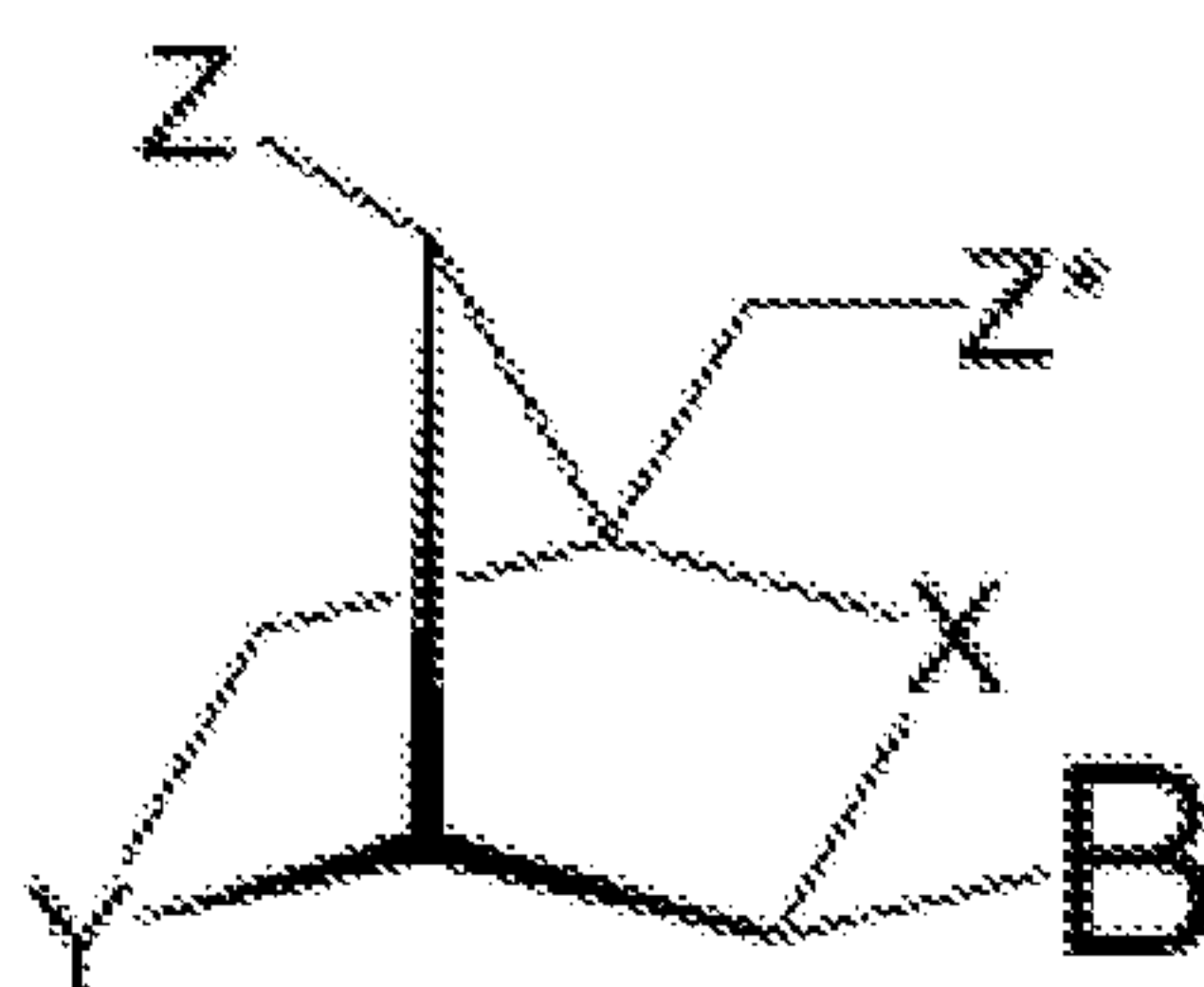
Arabinonucleosides are stereoisomers of ribonucleosides, differing only in the configuration at the 2'-position of the sugar ring. In some embodiments, a 2'-arabino modification is 2'-F arabino. In some embodiments, the modified oligonucleotide is 2'-fluoro-D-arabinonucleic acid (FANA) (as described in, for example, Lon et al., *Biochem.*, 41:3457-3467, 2002 and Min et al., *Bioorg. Med. Chem. Lett.*, 12:2651-2654, 2002; the disclosures of which are incorporated herein by reference in their entireties). Similar modifications can also be made at other positions on the sugar, particularly the 3' position of the sugar on a 3' terminal nucleoside or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide.

PCT Publication No. WO 99/67378 discloses arabinonucleic acids (ANA) oligomers and their analogues for improved sequence specific inhibition of gene expression via association to complementary messenger RNA.

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Other preferred modifications include ethylene-bridged nucleic acids (ENAs) (*e.g.*, International Patent Publication No. WO 2005/042777, Morita et al., Nucleic Acid Res., Suppl 1:241-242, 2001; Surono et al., Hum. Gene Ther., 15:749-757, 2004; Koizumi, Curr. Opin. Mol. Ther., 8:144-149, 2006 and Horie et al., Nucleic Acids Symp. Ser (Oxf), 49:171-
 5 172, 2005; the disclosures of which are incorporated herein by reference in their entireties). Preferred ENAs include, but are not limited to, 2'-O,4'-C-ethylene-bridged nucleic acids.

Examples of LNAs are described in WO/2008/043753 and include compounds of the following general formula.



10

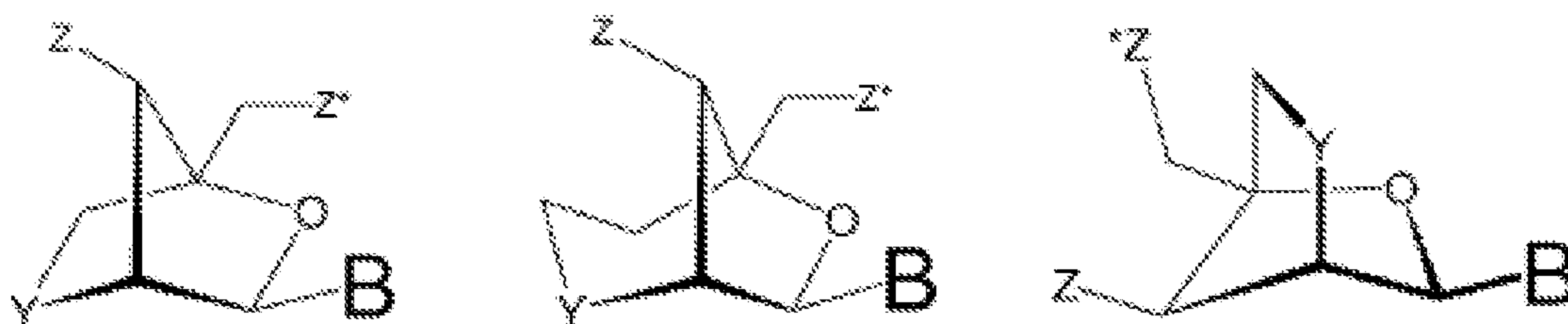
where X and Y are independently selected among the groups -O-,

-S-, -N(H)-, N(R)-, -CH₂- or -CH- (if part of a double bond),

-CH₂-O-, -CH₂-S-, -CH₂-N(H)-, -CH₂-N(R)-, -CH₂-CH₂- or -CH₂-CH- (if part of a
 15 double bond),

-CH=CH-, where R is selected from hydrogen and C₁₋₄-alkyl; Z and Z* are independently selected among an internucleoside linkage, a terminal group or a protecting group; B constitutes a natural or non-natural nucleotide base moiety; and the asymmetric groups may be found in either orientation.

20 Preferably, the LNA used in the oligonucleotides described herein comprises at least one LNA unit according any of the formulas



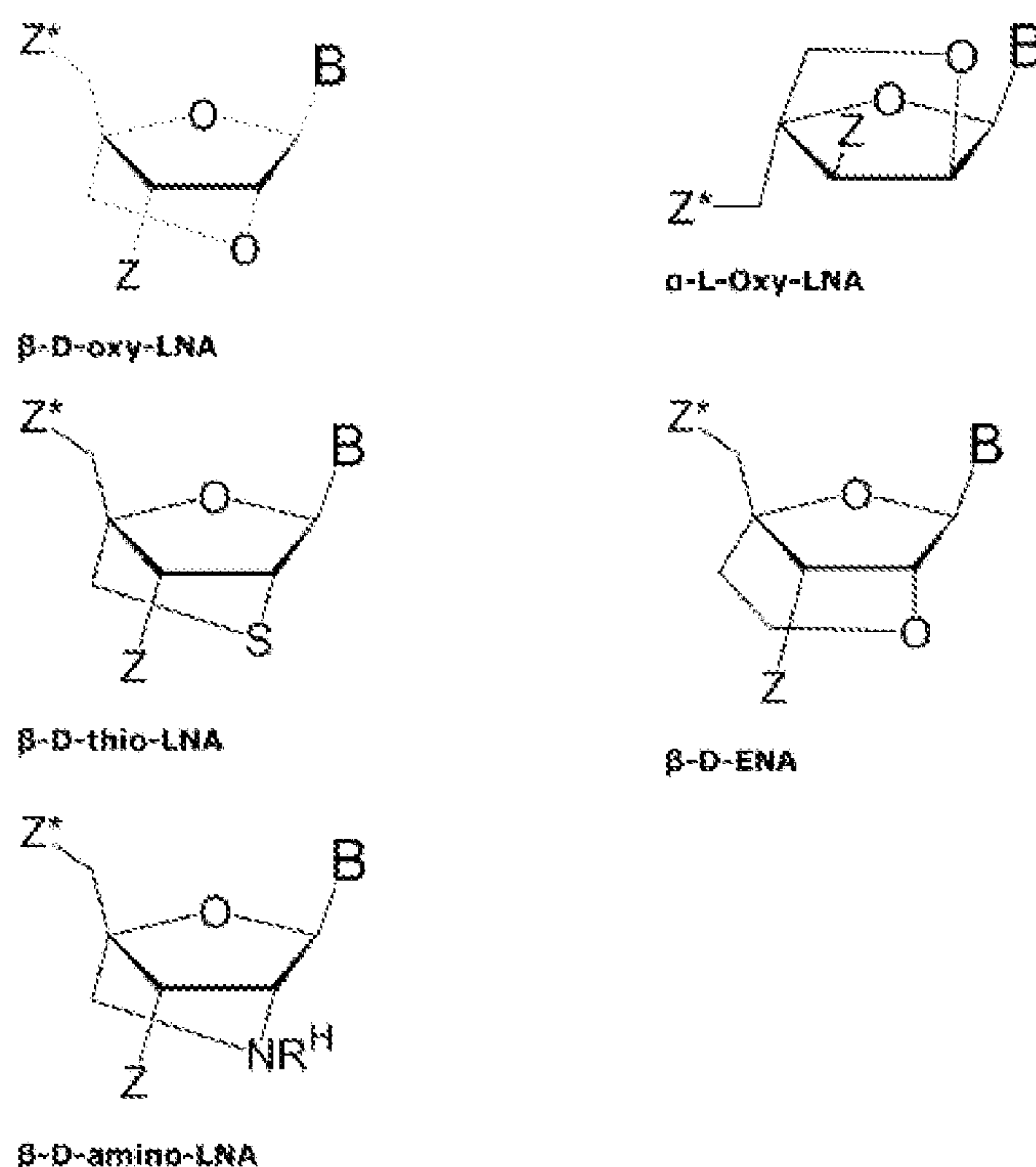
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wherein Y is -O-, -S-, -NH-, or N(R^H); Z and Z* are independently selected among an internucleoside linkage, a terminal group or a protecting group; B constitutes a natural or non-natural nucleotide base moiety, and RH is selected from hydrogen and C₁₋₄-alkyl.

5 In some embodiments, the Locked Nucleic Acid (LNA) used in the oligonucleotides described herein comprises at least one Locked Nucleic Acid (LNA) unit according any of the formulas shown in Scheme 2 of PCT/DK2006/000512.

In some embodiments, the LNA used in the oligomer of the invention comprises internucleoside linkages selected from -O-P(O)₂-O-, -O-P(O,S)-O-, -O-P(S)₂-O-, -S-P(O)₂-O-,
 10 -S-P(O,S)-O-, -S-P(S)₂-O-, -O-P(O)₂-S-, -O-P(O,S)-S-, -S-P(O)₂-S-, -O-PO(R^H)-O-, O-PO(OCH₃)-O-, -O-PO(NR^H)-O-, -O-PO(OCH₂CH₂S-R)-O-, -O-PO(BH₃)-O-, -O-PO(NHR^H)-O-, -O-P(O)₂-NR^H-, -NR^H-P(O)₂-O-, -NR^H-CO-O-, where R^H is selected from hydrogen and C₁₋₄-alkyl.

Specifically preferred LNA units are shown in scheme 2:



Scheme 2

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The term "thio-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above is selected from S or -CH₂-S-. Thio-LNA can be in both beta-D and alpha-L-configuration.

The term "amino-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above is selected from -N(H)-, N(R)-, CH₂-N(H)-, and -CH₂-N(R)- where R is selected from hydrogen and C₁₋₄-alkyl. Amino-LNA can be in both beta-D and alpha-L-configuration.

The term "oxy-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above represents -O- or -CH₂-O-. Oxy-LNA can be in both beta-D and alpha-L-configuration.

The term "ena-LNA" comprises a locked nucleotide in which Y in the general formula above is -CH₂-O- (where the oxygen atom of -CH₂-O- is attached to the 2'-position relative to the base B).

LNAs are described in additional detail herein.

One or more substituted sugar moieties can also be included, *e.g.*, one of the following at the 2' position: OH, SH, SCH₃, F, OCN, OCH₃, OCH₃, OCH₃ O(CH₂)_n CH₃, O(CH₂)_n NH₂ or O(CH₂)_n CH₃ where n is from 1 to about 10; Ci to C10 lower alkyl, alkoxyalkoxy, substituted lower alkyl, alkaryl or aralkyl; Cl; Br; CN; CF₃; OCF₃; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; SOCH₃; SO₂ CH₃; ONO₂; NO₂; N₃; NH₂; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy [2'-O-CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl)] (Martin et al, *Helv. Chim. Acta*, 1995, 78, 486). Other preferred modifications include 2'-methoxy (2'-O-CH₃), 2'-propoxy (2'-OCH₂ CH₂CH₃) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyls in place of the pentofuranosyl group.

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Single stranded oligonucleotides can also include, additionally or alternatively, nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U). Modified nucleobases include nucleobases found only infrequently or transiently in natural nucleic acids, *e.g.*, hypoxanthine, 6-methyladenine, 5-Me pyrimidines, particularly 5-methylcytosine (also referred to as 5-methyl-2' deoxycytosine and often referred to in the art as 5-Me-C), 5-hydroxymethylcytosine (HMC), glycosyl HMC and gentobiosyl HMC, isocytosine, pseudoisocytosine, as well as synthetic nucleobases, *e.g.*, 2-aminoadenine, 2- (methylamino)adenine, 2-(imidazolylalkyl)adenine, 2- (aminoalkylamino)adenine or other heterosubstituted alkyladenines, 2-thiouracil, 2-thiothymine, 5-bromouracil, 5-hydroxymethyluracil, 5-propynyluracil, 8-azaguanine, 7-deazaguanine, N6 (6-aminohexyl)adenine, 6-aminopurine, 2-aminopurine, 2-chloro-6-aminopurine and 2,6-diaminopurine or other diaminopurines. See, *e.g.*, Kornberg, "DNA Replication," W. H. Freeman & Co., San Francisco, 1980, pp75-77; and Gebeyehu, G., et al. Nucl. Acids Res., 15:4513 (1987)). A "universal" base known in the art, *e.g.*, inosine, can also be included. 5-Me-C substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C. (Sanghvi, in Crooke, and Lebleu, eds., Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and may be used as base substitutions.

It is not necessary for all positions in a given oligonucleotide to be uniformly modified, and in fact more than one of the modifications described herein may be incorporated in a single oligonucleotide or even at within a single nucleoside within an oligonucleotide.

In some embodiments, both a sugar and an internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, for example, an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to,

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US patent nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al, Science, 1991, 254, 1497-1500.

Single stranded oligonucleotides can also include one or more nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases comprise the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases comprise other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudo-uracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8- thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5- bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylquanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3- deazaguanine and 3-deazaadenine.

Further, nucleobases comprise those disclosed in United States Patent No. 3,687,808, those disclosed in "The Concise Encyclopedia of Polymer Science And Engineering", pages 858-859, Kroschwitz, ed. John Wiley & Sons, 1990; those disclosed by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, page 613, and those disclosed by Sanghvi, Chapter 15, Antisense Research and Applications," pages 289- 302, Crooke, and Lebleu, eds., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, comprising 2-aminopropyladenine, 5-propynyluracil and 5- propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, et al., eds, "Antisense Research and Applications," CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications. Modified nucleobases are described in US patent nos. 3,687,808, as well as 4,845,205; 5,130,302; 5,134,066; 5,175, 273; 5, 367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177;

5,525,711; 5,552,540; 5,587,469; 5,596,091; 5,614,617; 5,750,692, and 5,681,941, each of which is herein incorporated by reference.

In some embodiments, the single stranded oligonucleotides are chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the oligonucleotide. For example, one or more single stranded oligonucleotides, of the same or different types, can be conjugated to each other; or single stranded oligonucleotides can be conjugated to targeting moieties with enhanced specificity for a cell type or tissue type. Such moieties include, but are not limited to, lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, *e.g.*, hexyl-S- tritylthiol (Manoharan et al, Ann. N. Y. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49- 54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl- rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Mancharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-t oxysterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937). See also US patent nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552, 538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486, 603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762, 779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082, 830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5, 245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391, 723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5, 565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599, 928 and 5,688,941, each of which is herein incorporated by reference.

These moieties or conjugates can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the

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invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugate groups include cholesterol, lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve uptake, enhance resistance to degradation, and/or strengthen sequence-specific hybridization with the target nucleic acid. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve uptake, distribution, metabolism or excretion of the compounds of the present invention. Representative conjugate groups are disclosed in International Patent Application No. PCT/US92/09196, filed Oct. 23, 1992, and U.S. Pat. No. 6,287,860, which are incorporated herein by reference. Conjugate moieties include, but are not limited to, lipid moieties such as a cholesterol moiety, cholic acid, a thioether, *e.g.*, hexyl-5-tritylthiol, a thiocholesterol, an aliphatic chain, *e.g.*, dodecandiol or undecyl residues, a phospholipid, *e.g.*, di-hexadecyl-rac- glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxy cholesterol moiety. See, *e.g.*, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941.

In some embodiments, single stranded oligonucleotide modification include modification of the 5' or 3' end of the oligonucleotide. In some embodiments, the 3' end of the oligonucleotide comprises a hydroxyl group or a thiophosphate. It should be appreciated that additional molecules (*e.g.* a biotin moiety or a fluorophor) can be conjugated to the 5' or 3' end of the single stranded oligonucleotide. In some embodiments, the single stranded oligonucleotide comprises a biotin moiety conjugated to the 5' nucleotide.

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In some embodiments, the single stranded oligonucleotide comprises locked nucleic acids (LNA), ENA modified nucleotides, 2'-O-methyl nucleotides, or 2'-fluoro-deoxyribonucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating deoxyribonucleotides and 2'-O-methyl nucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating deoxyribonucleotides and ENA modified nucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating deoxyribonucleotides and locked nucleic acid nucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating locked nucleic acid nucleotides and 2'-O-methyl nucleotides.

In some embodiments, the 5' nucleotide of the oligonucleotide is a deoxyribonucleotide. In some embodiments, the 5' nucleotide of the oligonucleotide is a locked nucleic acid nucleotide. In some embodiments, the nucleotides of the oligonucleotide comprise deoxyribonucleotides flanked by at least one locked nucleic acid nucleotide on each of the 5' and 3' ends of the deoxyribonucleotides. In some embodiments, the nucleotide at the 3' position of the oligonucleotide has a 3' hydroxyl group or a 3' thiophosphate.

In some embodiments, the single stranded oligonucleotide comprises phosphorothioate internucleotide linkages. In some embodiments, the single stranded oligonucleotide comprises phosphorothioate internucleotide linkages between at least two nucleotides. In some embodiments, the single stranded oligonucleotide comprises phosphorothioate internucleotide linkages between all nucleotides.

It should be appreciated that the single stranded oligonucleotide can have any combination of modifications as described herein.

The oligonucleotide may comprise a nucleotide sequence having one or more of the following modification patterns.

(a) (X)XXXXXX, (X)xXXXXX, (X)xxXXXX, (X)xxxXXX, (X)xxxxXx and (X)xxxxxX,
 (b) (X)XXxxxx, (X)XxXXXX, (X)XxxXXX, (X)XxxxXx, (X)XxxxxX, (X)xXXxxx,
 (X)xXxXxx, (X)xXxxXx, (X)xXxxxX, (X)xxXXxx, (X)xxXxXx, (X)xxXxxX, (X)xxxXXx,
 (X)xxxXxX and (X)xxxxXX,

(c) (X)XXXxxx, (X)xXXXxx, (X)xxXXXx, (X)xxxXXX, (X)XXxXxx, (X)XXxxXx,
 (X)XXxxxX, (X)xXXxXx, (X)xXXxxX, (X)xxXXxX, (X)XxXXxx, (X)XxxXXx
 (X)XxxxXX, (X)xXxXXx, (X)xXxxXX, (X)xxXxXX, (X)xXxXxX and (X)XxXxXx,

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(d) (X)_{xx}XXX, (X)_xX_xXXX, (X)_xXX_xXX, (X)_xXXX_xX, (X)_xXXXX_x,
 (X)X_{xx}XXXX, (X)X_xX_xXX, (X)X_xXX_xX, (X)X_xXX_x, (X)XX_{xx}XX, (X)XX_xX_xX,
 (X)XX_xXX_x, (X)XXX_{xx}X, (X)XXX_xX_x, and (X)XXXX_{xx},

(e) (X)_xXXXXXX, (X)X_xXXXX, (X)XX_xXXX, (X)XXX_xXX, (X)XXXX_xX and
 5 (X)XXXX_{xx}, and

(f) XXXXXXX, X_xXXXXX, XX_xXXXX, XXX_xXXX, XXXX_xXX, XXXXX_xX and
 XXXXXXX_x, in which “X” denotes a nucleotide analogue, (X) denotes an optional nucleotide
 analogue, and “x” denotes a DNA or RNA nucleotide unit. Each of the above listed patterns
 may appear one or more times within an oligonucleotide, alone or in combination with any of
 10 the other disclosed modification patterns.

Methods for Modulating Gene Expression

In one aspect, the invention relates to methods for modulating gene expression in a
 cell (*e.g.*, a cell for which APOA1 or ABCA1 levels are reduced) for research purposes (*e.g.*,
 15 to study the function of the gene in the cell). In another aspect, the invention relates to
 methods for modulating gene expression in a cell (*e.g.*, a cell for which APOA1 or ABCA1
 levels are reduced) for gene or epigenetic therapy. The cells can be *in vitro*, *ex vivo*, or *in*
vivo (*e.g.*, in a subject who has a disease resulting from reduced expression or activity of
 APOA1 or ABCA1. In some embodiments, methods for modulating gene expression in a cell
 20 comprise delivering a single stranded oligonucleotide as described herein. In some
 embodiments, delivery of the single stranded oligonucleotide to the cell results in a level of
 expression of gene that is at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%,
 100%, 200% or more greater than a level of expression of gene in a control cell to which the
 single stranded oligonucleotide has not been delivered. In certain embodiments, delivery of
 25 the single stranded oligonucleotide to the cell results in a level of expression of gene that is at
 least 50% greater than a level of expression of gene in a control cell to which the single
 stranded oligonucleotide has not been delivered.

In another aspect of the invention, methods comprise administering to a subject (*e.g.* a
 human) a composition comprising a single stranded oligonucleotide as described herein to
 30 increase protein levels in the subject. In some embodiments, the increase in protein levels is
 at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, or more,
 higher than the amount of a protein in the subject before administering.

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As another example, to increase expression of APOA1 or ABCA1 in a cell, the methods include introducing into the cell a single stranded oligonucleotide that is sufficiently complementary to a PRC2-associated region (*e.g.*, of a long non-coding RNA) that maps to a genomic position encompassing or in proximity to the APOA1 or ABCA1 gene.

5 In another aspect of the invention provides methods of treating a condition (*e.g.*, dyslipidemia, atherosclerosis) associated with decreased levels of expression of APOA1 or ABCA1 in a subject, the method comprising administering a single stranded oligonucleotide as described herein.

10 A subject can include a non-human mammal, *e.g.* mouse, rat, guinea pig, rabbit, cat, dog, goat, cow, or horse. In preferred embodiments, a subject is a human. Single stranded oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals, including humans. Single stranded oligonucleotides can be useful therapeutic modalities that can be configured to be useful in treatment regimes for the treatment of cells, tissues and animals, especially humans.

15 For therapeutics, an animal, preferably a human, suspected of having dyslipidemia or atherosclerosis is treated by administering single stranded oligonucleotide in accordance with this invention. For example, in one non-limiting embodiment, the methods comprise the step of administering to the animal in need of treatment, a therapeutically effective amount of a single stranded oligonucleotide as described herein.

20 *Formulation, Delivery, And Dosing*

The oligonucleotides described herein can be formulated for administration to a subject for treating a condition (*e.g.*, dyslipidemia, atherosclerosis) associated with decreased levels of APOA1 or ABCA1. It should be understood that the formulations, compositions and methods can be practiced with any of the oligonucleotides disclosed herein.

25 The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient (*e.g.*, an oligonucleotide or compound of the invention) which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration, *e.g.*, intradermal or inhalation. The amount of active ingredient which can be combined with a carrier material to produce a

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single dosage form will generally be that amount of the compound which produces a therapeutic effect, *e.g.* tumor regression.

Pharmaceutical formulations of this invention can be prepared according to any method known to the art for the manufacture of pharmaceuticals. Such formulations can contain sweetening agents, flavoring agents, coloring agents and preserving agents. A formulation can be admixed with nontoxic pharmaceutically acceptable excipients which are suitable for manufacture. Formulations may comprise one or more diluents, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, lyophilized powders, sprays, creams, lotions, controlled release formulations, tablets, pills, gels, on patches, in implants, etc.

A formulated single stranded oligonucleotide composition can assume a variety of states. In some examples, the composition is at least partially crystalline, uniformly crystalline, and/or anhydrous (*e.g.*, less than 80, 50, 30, 20, or 10% water). In another example, the single stranded oligonucleotide is in an aqueous phase, *e.g.*, in a solution that includes water. The aqueous phase or the crystalline compositions can, *e.g.*, be incorporated into a delivery vehicle, *e.g.*, a liposome (particularly for the aqueous phase) or a particle (*e.g.*, a microparticle as can be appropriate for a crystalline composition). Generally, the single stranded oligonucleotide composition is formulated in a manner that is compatible with the intended method of administration.

In some embodiments, the composition is prepared by at least one of the following methods: spray drying, lyophilization, vacuum drying, evaporation, fluid bed drying, or a combination of these techniques; or sonication with a lipid, freeze-drying, condensation and other self-assembly.

A single stranded oligonucleotide preparation can be formulated or administered (together or separately) in combination with another agent, *e.g.*, another therapeutic agent or an agent that stabilizes a single stranded oligonucleotide, *e.g.*, a protein that complexes with single stranded oligonucleotide. Still other agents include chelators, *e.g.*, EDTA (*e.g.*, to remove divalent cations such as Mg^{2+}), salts, RNase inhibitors (*e.g.*, a broad specificity RNase inhibitor such as RNasin) and so forth.

In one embodiment, the single stranded oligonucleotide preparation includes another single stranded oligonucleotide, *e.g.*, a second single stranded oligonucleotide that modulates expression of a second gene or a second single stranded oligonucleotide that modulates

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expression of the first gene. Still other preparation can include at least 3, 5, ten, twenty, fifty, or a hundred or more different single stranded oligonucleotide species. Such single stranded oligonucleotides can mediated gene expression with respect to a similar number of different genes. In one embodiment, the single stranded oligonucleotide preparation includes at least a
5 second therapeutic agent (*e.g.*, an agent other than an oligonucleotide).

Route of Delivery

A composition that includes a single stranded oligonucleotide can be delivered to a subject by a variety of routes. Exemplary routes include: intravenous, intradermal, topical,
10 rectal, parenteral, anal, intravaginal, intranasal, pulmonary, ocular. The term "therapeutically effective amount" is the amount of oligonucleotide present in the composition that is needed to provide the desired level of APOA1 or ABCA1 expression in the subject to be treated to give the anticipated physiological response. The term "physiologically effective amount" is that amount delivered to a subject to give the desired palliative or curative effect. The term
15 "pharmaceutically acceptable carrier" means that the carrier can be administered to a subject with no significant adverse toxicological effects to the subject.

The single stranded oligonucleotide molecules of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically include one or more species of single stranded oligonucleotide and a pharmaceutically
20 acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is
25 incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic, vaginal, rectal,
30 intranasal, transdermal), oral or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, or intrathecal or intraventricular administration.

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The route and site of administration may be chosen to enhance targeting. For example, to target muscle cells, intramuscular injection into the muscles of interest would be a logical choice. Lung cells might be targeted by administering the single stranded oligonucleotide in aerosol form. The vascular endothelial cells could be targeted by coating a balloon catheter with the single stranded oligonucleotide and mechanically introducing the oligonucleotide.

Topical administration refers to the delivery to a subject by contacting the formulation directly to a surface of the subject. The most common form of topical delivery is to the skin, but a composition disclosed herein can also be directly applied to other surfaces of the body, *e.g.*, to the eye, a mucous membrane, to surfaces of a body cavity or to an internal surface. As mentioned above, the most common topical delivery is to the skin. The term encompasses several routes of administration including, but not limited to, topical and transdermal. These modes of administration typically include penetration of the skin's permeability barrier and efficient delivery to the target tissue or stratum. Topical administration can be used as a means to penetrate the epidermis and dermis and ultimately achieve systemic delivery of the composition. Topical administration can also be used as a means to selectively deliver oligonucleotides to the epidermis or dermis of a subject, or to specific strata thereof, or to an underlying tissue.

Formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

Transdermal delivery is a valuable route for the administration of lipid soluble therapeutics. The dermis is more permeable than the epidermis and therefore absorption is much more rapid through abraded, burned or denuded skin. Inflammation and other physiologic conditions that increase blood flow to the skin also enhance transdermal adsorption. Absorption via this route may be enhanced by the use of an oily vehicle (inunction) or through the use of one or more penetration enhancers. Other effective ways to deliver a composition disclosed herein via the transdermal route include hydration of the skin and the use of controlled release topical patches. The transdermal route provides a potentially effective means to deliver a composition disclosed herein for systemic and/or local therapy. In addition, iontophoresis (transfer of ionic solutes through biological

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membranes under the influence of an electric field), phonophoresis or sonophoresis (use of ultrasound to enhance the absorption of various therapeutic agents across biological membranes, notably the skin and the cornea), and optimization of vehicle characteristics relative to dose position and retention at the site of administration may be useful methods for enhancing the transport of topically applied compositions across skin and mucosal sites.

Both the oral and nasal membranes offer advantages over other routes of administration. For example, oligonucleotides administered through these membranes may have a rapid onset of action, provide therapeutic plasma levels, avoid first pass effect of hepatic metabolism, and avoid exposure of the oligonucleotides to the hostile gastrointestinal (GI) environment. Additional advantages include easy access to the membrane sites so that the oligonucleotide can be applied, localized and removed easily.

In oral delivery, compositions can be targeted to a surface of the oral cavity, *e.g.*, to sublingual mucosa which includes the membrane of ventral surface of the tongue and the floor of the mouth or the buccal mucosa which constitutes the lining of the cheek. The sublingual mucosa is relatively permeable thus giving rapid absorption and acceptable bioavailability of many agents. Further, the sublingual mucosa is convenient, acceptable and easily accessible.

A pharmaceutical composition of single stranded oligonucleotide may also be administered to the buccal cavity of a human being by spraying into the cavity, without inhalation, from a metered dose spray dispenser, a mixed micellar pharmaceutical formulation as described above and a propellant. In one embodiment, the dispenser is first shaken prior to spraying the pharmaceutical formulation and propellant into the buccal cavity.

Compositions for oral administration include powders or granules, suspensions or solutions in water, syrups, slurries, emulsions, elixirs or non-aqueous media, tablets, capsules, lozenges, or troches. In the case of tablets, carriers that can be used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the nucleic acid compositions can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added.

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Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, intrathecal or intraventricular administration. In some embodiments, parental administration involves administration directly to the site of disease (*e.g.* injection into a tumor).

5 Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

10 Any of the single stranded oligonucleotides described herein can be administered to ocular tissue. For example, the compositions can be applied to the surface of the eye or nearby tissue, *e.g.*, the inside of the eyelid. For ocular administration, ointments or droppable liquids may be delivered by ocular delivery systems known to the art such as applicators or eye droppers. Such compositions can include mucomimetics such as hyaluronic acid,
15 chondroitin sulfate, hydroxypropyl methylcellulose or poly(vinyl alcohol), preservatives such as sorbic acid, EDTA or benzylchromium chloride, and the usual quantities of diluents and/or carriers. The single stranded oligonucleotide can also be administered to the interior of the eye, and can be introduced by a needle or other delivery device which can introduce it to a selected area or structure.

20 Pulmonary delivery compositions can be delivered by inhalation by the patient of a dispersion so that the composition, preferably single stranded oligonucleotides, within the dispersion can reach the lung where it can be readily absorbed through the alveolar region directly into blood circulation. Pulmonary delivery can be effective both for systemic delivery and for localized delivery to treat diseases of the lungs.

25 Pulmonary delivery can be achieved by different approaches, including the use of nebulized, aerosolized, micellular and dry powder-based formulations. Delivery can be achieved with liquid nebulizers, aerosol-based inhalers, and dry powder dispersion devices. Metered-dose devices are preferred. One of the benefits of using an atomizer or inhaler is that the potential for contamination is minimized because the devices are self-contained. Dry
30 powder dispersion devices, for example, deliver agents that may be readily formulated as dry powders. A single stranded oligonucleotide composition may be stably stored as lyophilized or spray-dried powders by itself or in combination with suitable powder carriers. The

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delivery of a composition for inhalation can be mediated by a dosing timing element which can include a timer, a dose counter, time measuring device, or a time indicator which when incorporated into the device enables dose tracking, compliance monitoring, and/or dose triggering to a patient during administration of the aerosol medicament.

5 The term "powder" means a composition that consists of finely dispersed solid particles that are free flowing and capable of being readily dispersed in an inhalation device and subsequently inhaled by a subject so that the particles reach the lungs to permit penetration into the alveoli. Thus, the powder is said to be "respirable." Preferably the average particle size is less than about 10 μm in diameter preferably with a relatively uniform
10 spheroidal shape distribution. More preferably the diameter is less than about 7.5 μm and most preferably less than about 5.0 μm . Usually the particle size distribution is between about 0.1 μm and about 5 μm in diameter, particularly about 0.3 μm to about 5 μm .

 The term "dry" means that the composition has a moisture content below about 10% by weight (% w) water, usually below about 5% w and preferably less than about 3% w. A
15 dry composition can be such that the particles are readily dispersible in an inhalation device to form an aerosol.

 The types of pharmaceutical excipients that are useful as carrier include stabilizers such as human serum albumin (HSA), bulking agents such as carbohydrates, amino acids and polypeptides; pH adjusters or buffers; salts such as sodium chloride; and the like. These
20 carriers may be in a crystalline or amorphous form or may be a mixture of the two.

 Suitable pH adjusters or buffers include organic salts prepared from organic acids and bases, such as sodium citrate, sodium ascorbate, and the like; sodium citrate is preferred. Pulmonary administration of a micellar single stranded oligonucleotide formulation may be achieved through metered dose spray devices with propellants such as tetrafluoroethane,
25 heptafluoroethane, dimethylfluoropropane, tetrafluoropropane, butane, isobutane, dimethyl ether and other non-CFC and CFC propellants.

 Exemplary devices include devices which are introduced into the vasculature, *e.g.*, devices inserted into the lumen of a vascular tissue, or which devices themselves form a part of the vasculature, including stents, catheters, heart valves, and other vascular devices. These
30 devices, *e.g.*, catheters or stents, can be placed in the vasculature of the lung, heart, or leg.

 Other devices include non-vascular devices, *e.g.*, devices implanted in the peritoneum, or in organ or glandular tissue, *e.g.*, artificial organs. The device can release a

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therapeutic substance in addition to a single stranded oligonucleotide, *e.g.*, a device can release insulin.

In one embodiment, unit doses or measured doses of a composition that includes single stranded oligonucleotide are dispensed by an implanted device. The device can
5 include a sensor that monitors a parameter within a subject. For example, the device can include pump, *e.g.*, and, optionally, associated electronics.

Tissue, *e.g.*, cells or organs can be treated with a single stranded oligonucleotide, *ex vivo* and then administered or implanted in a subject. The tissue can be autologous, allogeneic, or xenogeneic tissue. *E.g.*, tissue can be treated to reduce graft v. host disease . In
10 other embodiments, the tissue is allogeneic and the tissue is treated to treat a disorder characterized by unwanted gene expression in that tissue. *E.g.*, tissue, *e.g.*, hematopoietic cells, *e.g.*, bone marrow hematopoietic cells, can be treated to inhibit unwanted cell proliferation. Introduction of treated tissue, whether autologous or transplant, can be combined with other therapies. In some implementations, the single stranded oligonucleotide
15 treated cells are insulated from other cells, *e.g.*, by a semi-permeable porous barrier that prevents the cells from leaving the implant, but enables molecules from the body to reach the cells and molecules produced by the cells to enter the body. In one embodiment, the porous barrier is formed from alginate.

In one embodiment, a contraceptive device is coated with or contains a single
20 stranded oligonucleotide. Exemplary devices include condoms, diaphragms, IUD (implantable uterine devices, sponges, vaginal sheaths, and birth control devices.

Dosage

In one aspect, the invention features a method of administering a single stranded
25 oligonucleotide (*e.g.*, as a compound or as a component of a composition) to a subject (*e.g.*, a human subject). In one embodiment, the unit dose is between about 10 mg and 25 mg per kg of bodyweight. In one embodiment, the unit dose is between about 1 mg and 100 mg per kg of bodyweight. In one embodiment, the unit dose is between about 0.1 mg and 500 mg per kg of bodyweight. In some embodiments, the unit dose is more than 0.001, 0.005, 0.01, 0.05,
30 0.1, 0.5, 1, 2, 5, 10, 25, 50 or 100 mg per kg of bodyweight.

The defined amount can be an amount effective to treat or prevent a disease or disorder, *e.g.*, a disease or disorder associated with the APOA1 or ABCA1. The unit dose, for

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example, can be administered by injection (*e.g.*, intravenous or intramuscular), an inhaled dose, or a topical application.

In some embodiments, the unit dose is administered daily. In some embodiments, less frequently than once a day, *e.g.*, less than every 2, 4, 8 or 30 days. In another embodiment, the unit dose is not administered with a frequency (*e.g.*, not a regular frequency). For example, the unit dose may be administered a single time. In some embodiments, the unit dose is administered more than once a day, *e.g.*, once an hour, two hours, four hours, eight hours, twelve hours, etc.

In one embodiment, a subject is administered an initial dose and one or more maintenance doses of a single stranded oligonucleotide. The maintenance dose or doses are generally lower than the initial dose, *e.g.*, one-half less of the initial dose. A maintenance regimen can include treating the subject with a dose or doses ranging from 0.0001 to 100 mg/kg of body weight per day, *e.g.*, 100, 10, 1, 0.1, 0.01, 0.001, or 0.0001 mg per kg of bodyweight per day. The maintenance doses may be administered no more than once every 1, 5, 10, or 30 days. Further, the treatment regimen may last for a period of time which will vary depending upon the nature of the particular disease, its severity and the overall condition of the patient. In some embodiments the dosage may be delivered no more than once per day, *e.g.*, no more than once per 24, 36, 48, or more hours, *e.g.*, no more than once for every 5 or 8 days. Following treatment, the patient can be monitored for changes in his condition and for alleviation of the symptoms of the disease state. The dosage of the oligonucleotide may either be increased in the event the patient does not respond significantly to current dosage levels, or the dose may be decreased if an alleviation of the symptoms of the disease state is observed, if the disease state has been ablated, or if undesired side-effects are observed.

The effective dose can be administered in a single dose or in two or more doses, as desired or considered appropriate under the specific circumstances. If desired to facilitate repeated or frequent infusions, implantation of a delivery device, *e.g.*, a pump, semi-permanent stent (*e.g.*, intravenous, intraperitoneal, intracisternal or intracapsular), or reservoir may be advisable.

In some embodiments, the oligonucleotide pharmaceutical composition includes a plurality of single stranded oligonucleotide species. In another embodiment, the single stranded oligonucleotide species has sequences that are non-overlapping and non-adjacent to

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another species with respect to a naturally occurring target sequence (*e.g.*, a PRC2-associated region). In another embodiment, the plurality of single stranded oligonucleotide species is specific for different PRC2-associated regions. In another embodiment, the single stranded oligonucleotide is allele specific. In some cases, a patient is treated with a single stranded
5 oligonucleotide in conjunction with other therapeutic modalities.

Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein the compound of the invention is administered in maintenance doses, ranging from 0.0001 mg to 100 mg per kg of body weight.

10 The concentration of the single stranded oligonucleotide composition is an amount sufficient to be effective in treating or preventing a disorder or to regulate a physiological condition in humans. The concentration or amount of single stranded oligonucleotide administered will depend on the parameters determined for the agent and the method of administration, *e.g.* nasal, buccal, pulmonary. For example, nasal formulations may tend to
15 require much lower concentrations of some ingredients in order to avoid irritation or burning of the nasal passages. It is sometimes desirable to dilute an oral formulation up to 10-100 times in order to provide a suitable nasal formulation.

Certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the
20 general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a single stranded oligonucleotide can include a single treatment or, preferably, can include a series of treatments. It will also be appreciated that the effective dosage of a single stranded oligonucleotide used for treatment may increase or decrease over the course of a particular treatment. For example, the subject
25 can be monitored after administering a single stranded oligonucleotide composition. Based on information from the monitoring, an additional amount of the single stranded oligonucleotide composition can be administered.

Dosing is dependent on severity and responsiveness of the disease condition to be treated, with the course of treatment lasting from several days to several months, or until a
30 cure is effected or a diminution of disease state is achieved. Optimal dosing schedules can be calculated from measurements of APOA1 or ABCA1 expression levels in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing

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methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual compounds, and can generally be estimated based on EC50s found to be effective in in vitro and in vivo animal models. In some embodiments, the animal models include transgenic animals that express a human APOA1 or ABCA1. In another
5 embodiment, the composition for testing includes a single stranded oligonucleotide that is complementary, at least in an internal region, to a sequence that is conserved between APOA1 or ABCA1 in the animal model and the APOA1 or ABCA1 in a human.

In one embodiment, the administration of the single stranded oligonucleotide composition is parenteral, *e.g.* intravenous (*e.g.*, as a bolus or as a diffusible infusion),
10 intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular, intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral or ocular. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The composition can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are
15 discussed in more detail below.

Kits

In certain aspects of the invention, kits are provided, comprising a container housing a composition comprising a single stranded oligonucleotide. In some embodiments, the
20 composition is a pharmaceutical composition comprising a single stranded oligonucleotide and a pharmaceutically acceptable carrier. In some embodiments, the individual components of the pharmaceutical composition may be provided in one container. Alternatively, it may be desirable to provide the components of the pharmaceutical composition separately in two or more containers, *e.g.*, one container for single stranded oligonucleotides, and at least
25 another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

30 The present invention is further illustrated by the following Examples, which in no way should be construed as further limiting. The entire contents of all of the references

(including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated by reference.

5

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

MATERIALS AND METHODS:

10

Real Time PCR

RNA was harvested from the cells using Promega SV 96 Total RNA Isolation system or Trizol omitting the DNase step. RNA harvested from cells is normalized so that equal RNA was input to each reverse transcription reaction. Reverse transcriptase reactions were performed using the Superscript II kit and real time PCR performed on cDNA samples using
 15 icycler SYBR green chemistry (Biorad). A baseline level of mRNA expression for APOA1 was determined through quantitative PCR as outlined above. A baseline level of mRNA expression for ABCA1 is determined through quantitative PCR as outlined above. Baseline levels were also determined for mRNA of various housekeeping genes which are constitutively expressed. A “control” housekeeping gene with approximately the same level
 20 of baseline expression as the target gene was chosen for comparison purposes.

Cell Culture

Human hepatocyte Hep3B, human hepatocyte HepG2 cells, mouse hepatoma Hepa1-6 cells, and human renal proximal tubule epithelial cells (RPTEC) were cultured using
 25 conditions known in the art (see, *e.g.* Current Protocols in Cell Biology). Details of the cell lines used in the experiments described herein are provided in Table 5.

Table 5. Cell lines

Cell Line	Source	Species	Gender	Cell Type	Tissue	Status	Culture Conditions
hHEP primary	Celsis	human	F	hepatocytes	liver	primary	DMEM hiGlucose +
Rhesus	Celsis	rhesus	M	hepatocytes	liver	primary	DMEM hiGlucose +

HEP primary							
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Oligonucleotide design

Oligonucleotides were designed within PRC2-interacting regions in order to upregulate APOA1. The sequence and structure of each oligonucleotide is shown in Table 4. A description of the nucleotide analogs, modifications and intranucleotide linkages used for certain oligonucleotides tested and described is provided in Table 3. SEQ ID NOs: 187502 to 187521 were gapmer control oligos targeting APOA1.

***In vitro* transfection of cells with oligonucleotides**

Oligonucleotides were designed within PRC2-interacting regions in order to upregulate APOA1. Cells were seeded into each well of 24-well plates at a density of 25,000 cells per 500uL and transfections are performed with Lipofectamine and the single stranded oligonucleotides. Control wells contained Lipofectamine alone. At 48 hours post-transfection, approximately 200 uL of cell culture supernatants were stored at -80 C for ELISA. At 48 hours post-transfection, RNA was harvested from the cells and quantitative PCR was carried out as outlined above. The percent induction of target mRNA expression by each oligonucleotide was determined by normalizing mRNA levels in the presence of the oligonucleotide to the mRNA levels in the presence of control (Lipofectamine alone). This was compared side-by-side with the increase in mRNA expression of the “control” housekeeping gene.

Oligonucleotides are designed within PRC2-interacting regions in order to upregulate ABCA1. Cells are seeded into each well of 24-well plates at a density of 25,000 cells per 500uL and transfections are performed with Lipofectamine and the single stranded oligonucleotides. Control wells contain Lipofectamine alone. At 48 hours post-transfection, approximately 200 uL of cell culture supernatants are stored at -80 C for ELISA. At 48 hours post-transfection, RNA is harvested from the cells and quantitative PCR is carried out as outlined above. The percent induction of target mRNA expression by each oligonucleotide is determined by normalizing mRNA levels in the presence of the oligonucleotide to the mRNA

levels in the presence of control (Lipofectamine alone). This is compared side-by-side with the increase in mRNA expression of the “control” housekeeping gene.

***In vitro* delivery of single stranded oligonucleotides**

5 Oligonucleotides are designed as candidates for upregulating ABCA1 expression. The single stranded oligonucleotides are designed to be complementary to a PRC2-interacting region within a sequence as set forth in SEQ ID NO: 5 or 6. The oligonucleotides are tested in at least duplicate. Briefly, cells are transfected *in vitro* with each of the oligonucleotides as described above. ABCA1 expression in cells following treatment is
10 evaluated by qRT-PCR. Oligonucleotides that upregulate ABCA1 expression are identified.

RESULTS:

***In vitro* delivery of single stranded oligonucleotides upregulate APOA1**

Oligonucleotides were designed as candidates for upregulating APOA1 expression. A
15 total of 70 single stranded oligonucleotides were designed to be complementary to a PRC2-interacting region within a sequence as set forth in SEQ ID NO: 1 or 2. Oligonucleotides were tested in at least duplicate. The sequence and structural features of the oligonucleotides are set forth in Table 4. Briefly, cells were transfected *in vitro* with the oligonucleotides as described above. APOA1 expression in cells following treatment was evaluated by qRT-
20 PCR. Oligonucleotides that upregulated APOA1 expression were identified. Further details are outlined in Table 2.

Tables

Table 1: Hexamers that are not seed sequences of human miRNAs

AAAAAA, AAAAAG, AAAACA, AAAAGA, AAAAGC, AAAAGG, AAAAUA, AAACAA, AAACAC, AAACAG,
25 AAACAU, AAACCC, AAACCU, AAACGA, AAACGC, AAACGU, AAACUA, AAACUC, AAACUU, AAAGAU,
AAAGCC, AAAGGA, AAAGGG, AAAGUC, AAUAC, AAUAU, AAUUCG, AAUUCU, AAUUGC, AAUUGU,
AAUUA, AAUUG, AACAAC, AACAAG, AACAAU, AACACA, AACACG, AACAGA, AACAGC, AACAGG,
AACAUC, AACAUG, AACCAA, AACCAC, AACCAG, AACCAU, AACCCC, AACCCG, AACCGA, AACCGC,
AACCGG, AACCUA, AACCUU, AACGAA, AACGAC, AACGAG, AACGAU, AACGCU, AACGGG, AACGGU,

AACGUA, AACGUC, AACGUG, AACGUU, AACUAU, AACUCA, AACUCC, AACUCG, AACUGA, AACUGC,
AACUGU, AACUUA, AACUUC, AACUUG, AACUUU, AAGAAA, AAGAAG, AAGAAU, AAGACG, AAGAGA,
AAGAGC, AAGAGG, AAGAGU, AAGAUU, AAGCAA, AAGCAC, AAGCAG, AAGCAU, AAGCCA, AAGCCC,
AAGCCG, AAGCCU, AAGCGA, AAGCGG, AAGCGU, AAGCUA, AAGGAA, AAGGAC, AAGGCU, AAGGGC,
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GGUUAA, GGUUAG, GGUUAU, GGUUCA, GGUUCC, GGUUCG, GGUUGC, GGUUUC, GGUUUU,
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GUAAUA, GUAUAC, GUAUAG, GUAAUU, GUACAA, GUACAC, GUACAG, GUACAU, GUACCA, GUACCC,
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25 GUAGAA, GUAGAC, GUAGCA, GUAGCC, GUAGCG, GUAGCU, GUAGGA, GUAGGC, GUAGGG,
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 UGAUAU, UGAUCA, UGAUCG, UGAUCU, UGAUGA, UGAUGC, UGAUGG, UGAUGU, UGAUUA,

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-01	1.72953309	0.38593508	APOA1	30	hHEP primary	qRTPCR	
APOA1-02	1.65297164	0.26240546	APOA1	30	hHEP primary	qRTPCR	

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Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-03	1.74397325	0.06536137	APOA1	30	hHEP primary	qRTPCR	
APOA1-04	2.0996343	0.2876618	APOA1	30	hHEP primary	qRTPCR	
APOA1-05	1.71754382	0.15037132	APOA1	30	hHEP primary	qRTPCR	
APOA1-06	2.09435192	0.50263098	APOA1	30	hHEP primary	qRTPCR	
APOA1-07	2.35121919	0.39782252	APOA1	30	hHEP primary	qRTPCR	
APOA1-08	2.25583899	0.45353672	APOA1	30	hHEP primary	qRTPCR	
APOA1-09	1.87408722	0.56362016	APOA1	30	hHEP primary	qRTPCR	
APOA1-10	1.88351159	1.07415213	APOA1	30	hHEP primary	qRTPCR	
APOA1-11	1.87452852	1.15292269	APOA1	30	hHEP primary	qRTPCR	
APOA1-12	1.68704027	0.70914192	APOA1	30	hHEP primary	qRTPCR	
APOA1-13	1.16271652	0.15392998	APOA1	30	hHEP primary	qRTPCR	
APOA1-14	1.42852588	0.27620042	APOA1	30	hHEP primary	qRTPCR	
APOA1-15	1.54852506	0.23393251	APOA1	30	hHEP primary	qRTPCR	
APOA1-16	1.69392154	0.19855031	APOA1	30	hHEP primary	qRTPCR	
APOA1-17	1.73362922	0.06508272	APOA1	30	hHEP primary	qRTPCR	
APOA1-18	1.75581561	0.28839206	APOA1	30	hHEP primary	qRTPCR	
APOA1-19	1.75387129	0.12968574	APOA1	30	hHEP primary	qRTPCR	
APOA1-20	2.14124283	0.26096495	APOA1	30	hHEP primary	qRTPCR	
APOA1-21	2.11610962	0.3854349	APOA1	30	hHEP primary	qRTPCR	
APOA1-22	1.90687309	0.46088318	APOA1	30	hHEP primary	qRTPCR	
APOA1-23	1.46156108	0.50872343	APOA1	30	hHEP primary	qRTPCR	
APOA1-24	1.2343356	0.30560655	APOA1	30	hHEP primary	qRTPCR	
APOA1-25	1.21966092	0.09432521	APOA1	30	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-26	1.28479929	0.26687871	APOA1	30	hHEP primary	qRTPCR	
APOA1-27	1.24643066	0.13561291	APOA1	30	hHEP primary	qRTPCR	
APOA1-28	1.47336789	0.17895867	APOA1	30	hHEP primary	qRTPCR	
APOA1-29	1.27656602	0.14525187	APOA1	30	hHEP primary	qRTPCR	
APOA1-30	1.50764756	0.18334138	APOA1	30	hHEP primary	qRTPCR	
APOA1-31	1.65674419	0.34639842	APOA1	30	hHEP primary	qRTPCR	
APOA1-32	1.83196248	0.20756384	APOA1	30	hHEP primary	qRTPCR	
APOA1-33	1.72607346	0.36095721	APOA1	30	hHEP primary	qRTPCR	
APOA1-34	1.58186221	0.62302249	APOA1	30	hHEP primary	qRTPCR	
APOA1-35	1.44464989	0.58844576	APOA1	30	hHEP primary	qRTPCR	
APOA1-36	1.24362343	0.38366142	APOA1	30	hHEP primary	qRTPCR	
APOA1-37	1.15659228	0.23594549	APOA1	30	hHEP primary	qRTPCR	
APOA1-38	1.20089332	0.08299166	APOA1	30	hHEP primary	qRTPCR	
APOA1-39	1.19682637	0.06003989	APOA1	30	hHEP primary	qRTPCR	
APOA1-40	1.43549146	0.13903918	APOA1	30	hHEP primary	qRTPCR	
APOA1-41	1.34668295	0.12179207	APOA1	30	hHEP primary	qRTPCR	
APOA1-42	1.52166423	0.38408035	APOA1	30	hHEP primary	qRTPCR	
APOA1-43	1.33787399	0.34543502	APOA1	30	hHEP primary	qRTPCR	
APOA1-44	1.52824997	0.19034374	APOA1	30	hHEP primary	qRTPCR	
APOA1-45	1.43901401	0.28673717	APOA1	30	hHEP primary	qRTPCR	
APOA1-46	1.5495	0.35875889	APOA1	30	hHEP primary	qRTPCR	
APOA1-47	1.43714933	0.68563121	APOA1	30	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-48	1.10920683	0.37030472	APOA1	30	hHEP primary	qRTPCR	
APOA1-49	0.75144318	0.08113415	APOA1	30	hHEP primary	qRTPCR	
APOA1-50	0.70723551	0.16220968	APOA1	30	hHEP primary	qRTPCR	
Untreated	0.66633377	0.0114874	APOA1	0	hHEP primary	qRTPCR	
RNAiMax	1	0	APOA1	0	hHEP primary	qRTPCR	
Untreated	1	0	APOA1	0	hHEP primary	qRTPCR	
RNAiMax	1.50119142	0.02564126	APOA1	0	hHEP primary	qRTPCR	
APOA1-01	2.59595768	0.58454517	APOA1	30	hHEP primary	qRTPCR	
APOA1-02	2.47836992	0.37666392	APOA1	30	hHEP primary	qRTPCR	
APOA1-03	2.61967067	0.14150997	APOA1	30	hHEP primary	qRTPCR	
APOA1-04	3.15904416	0.48215112	APOA1	30	hHEP primary	qRTPCR	
APOA1-05	2.57463247	0.18077739	APOA1	30	hHEP primary	qRTPCR	
APOA1-06	3.14580653	0.77234823	APOA1	30	hHEP primary	qRTPCR	
APOA1-07	3.53790063	0.64947983	APOA1	30	hHEP primary	qRTPCR	
APOA1-08	3.39573936	0.73102183	APOA1	30	hHEP primary	qRTPCR	
APOA1-09	2.82342809	0.88688923	APOA1	30	hHEP primary	qRTPCR	
APOA1-10	2.84806778	1.65960442	APOA1	30	hHEP primary	qRTPCR	
APOA1-11	2.83446639	1.77845013	APOA1	30	hHEP primary	qRTPCR	
APOA1-12	2.54332893	1.10144966	APOA1	30	hHEP primary	qRTPCR	
APOA1-13	1.74174066	0.20043824	APOA1	30	hHEP primary	qRTPCR	
APOA1-14	2.14172941	0.40249982	APOA1	30	hHEP primary	qRTPCR	
APOA1-15	2.32262333	0.34115951	APOA1	30	hHEP primary	qRTPCR	
APOA1-16	2.54524123	0.32372985	APOA1	30	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-17	2.60379662	0.13535426	APOA1	30	hHEP primary	qRTPCR	
APOA1-18	2.63145824	0.40644961	APOA1	30	hHEP primary	qRTPCR	
APOA1-19	2.63501621	0.22762625	APOA1	30	hHEP primary	qRTPCR	
APOA1-20	3.21881652	0.43310927	APOA1	30	hHEP primary	qRTPCR	
APOA1-21	3.17992747	0.60559106	APOA1	30	hHEP primary	qRTPCR	
APOA1-22	2.86753905	0.72193248	APOA1	30	hHEP primary	qRTPCR	
APOA1-23	2.20339037	0.79656635	APOA1	30	hHEP primary	qRTPCR	
APOA1-24	1.85776896	0.4831969	APOA1	30	hHEP primary	qRTPCR	
APOA1-25	1.82919045	0.11991616	APOA1	30	hHEP primary	qRTPCR	
APOA1-26	1.92498763	0.38255281	APOA1	30	hHEP primary	qRTPCR	
APOA1-27	1.872221	0.21819787	APOA1	30	hHEP primary	qRTPCR	
APOA1-28	2.20894694	0.24572723	APOA1	30	hHEP primary	qRTPCR	
APOA1-29	1.91504651	0.20941403	APOA1	30	hHEP primary	qRTPCR	
APOA1-30	2.26166637	0.26557529	APOA1	30	hHEP primary	qRTPCR	
APOA1-31	2.48597106	0.52038611	APOA1	30	hHEP primary	qRTPCR	
APOA1-32	2.74827717	0.29965983	APOA1	30	hHEP primary	qRTPCR	
APOA1-33	2.5916897	0.55185035	APOA1	30	hHEP primary	qRTPCR	
APOA1-34	2.37945254	0.95946153	APOA1	30	hHEP primary	qRTPCR	
APOA1-35	2.17400395	0.90772983	APOA1	30	hHEP primary	qRTPCR	
APOA1-36	1.86809218	0.58698475	APOA1	30	hHEP primary	qRTPCR	
APOA1-37	1.73031334	0.32102823	APOA1	30	hHEP primary	qRTPCR	
APOA1-38	1.80411848	0.14707304	APOA1	30	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-39	1.79600638	0.08218318	APOA1	30	hHEP primary	qRTPCR	
APOA1-40	2.15252385	0.18449913	APOA1	30	hHEP primary	qRTPCR	
APOA1-41	2.01851463	0.1465385	APOA1	30	hHEP primary	qRTPCR	
APOA1-42	2.27706516	0.5438083	APOA1	30	hHEP primary	qRTPCR	
APOA1-43	2.00775529	0.52159254	APOA1	30	hHEP primary	qRTPCR	
APOA1-44	2.29182403	0.2688113	APOA1	30	hHEP primary	qRTPCR	
APOA1-45	2.15520256	0.403239	APOA1	30	hHEP primary	qRTPCR	
APOA1-46	2.32745816	0.55199343	APOA1	30	hHEP primary	qRTPCR	
APOA1-47	2.16493754	1.05770319	APOA1	30	hHEP primary	qRTPCR	
APOA1-48	1.66582169	0.56453292	APOA1	30	hHEP primary	qRTPCR	
APOA1-49	1.12820592	0.12598572	APOA1	30	hHEP primary	qRTPCR	
APOA1-50	1.0653361	0.25668883	APOA1	30	hHEP primary	qRTPCR	
RNAiMax	1	0	APOA1	0	hHEP primary	qRTPCR	
Untreated	0.68289266	0.00979906	APOA1	0	hHEP primary	qRTPCR	
APOA1-01	2.2916217	1.04866742	APOA1	30	hHEP primary	qRTPCR	
APOA1-02	1.72987491	0.2225552	APOA1	30	hHEP primary	qRTPCR	
APOA1-03	2.07532502	0.51531192	APOA1	30	hHEP primary	qRTPCR	
APOA1-04	2.20493747	0.62729492	APOA1	30	hHEP primary	qRTPCR	
APOA1-05	2.23394203	0.77019317	APOA1	30	hHEP primary	qRTPCR	
APOA1-06	2.00431747	0.6758265	APOA1	30	hHEP primary	qRTPCR	
APOA1-07	2.34353775	0.728281	APOA1	30	hHEP primary	qRTPCR	
APOA1-08	2.50906043	0.83967306	APOA1	30	hHEP primary	qRTPCR	
APOA1-09	2.22312576	0.56435323	APOA1	30	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-10	2.22212001	0.66321686	APOA1	30	hHEP primary	qRTPCR	
APOA1-11	2.55103454	0.72862128	APOA1	30	hHEP primary	qRTPCR	
APOA1-12	2.11781341	0.51816795	APOA1	30	hHEP primary	qRTPCR	
APOA1-13	1.98247361	0.49365327	APOA1	30	hHEP primary	qRTPCR	
APOA1-14	2.13525177	0.72448804	APOA1	30	hHEP primary	qRTPCR	
APOA1-15	2.16024977	0.63259782	APOA1	30	hHEP primary	qRTPCR	
APOA1-16	2.45613053	0.97134737	APOA1	30	hHEP primary	qRTPCR	
APOA1-17	1.97374054	0.6591072	APOA1	30	hHEP primary	qRTPCR	
APOA1-18	1.99859048	0.78501085	APOA1	30	hHEP primary	qRTPCR	
APOA1-19	2.19914061	0.73852861	APOA1	30	hHEP primary	qRTPCR	
APOA1-20	2.27391127	0.74207028	APOA1	30	hHEP primary	qRTPCR	
APOA1-21	2.60875069	0.7439227	APOA1	30	hHEP primary	qRTPCR	
APOA1-22	2.31838416	1.05386751	APOA1	30	hHEP primary	qRTPCR	
APOA1-23	2.05907172	0.83091903	APOA1	30	hHEP primary	qRTPCR	
APOA1-24	2.07785479	0.65297826	APOA1	30	hHEP primary	qRTPCR	
APOA1-25	1.87523823	0.68172973	APOA1	30	hHEP primary	qRTPCR	
APOA1-26	1.94493143	0.71515253	APOA1	30	hHEP primary	qRTPCR	
APOA1-27	1.7604053	0.54898253	APOA1	30	hHEP primary	qRTPCR	
APOA1-28	2.02256966	0.57674342	APOA1	30	hHEP primary	qRTPCR	
APOA1-29	1.77026775	0.59656828	APOA1	30	hHEP primary	qRTPCR	
APOA1-30	2.17762038	0.60526676	APOA1	30	hHEP primary	qRTPCR	
APOA1-31	2.06704273	0.67575768	APOA1	30	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-32	2.09477161	0.65526344	APOA1	30	hHEP primary	qRTPCR	
APOA1-33	2.15990714	0.79290909	APOA1	30	hHEP primary	qRTPCR	
APOA1-34	2.00319175	0.58818945	APOA1	30	hHEP primary	qRTPCR	
APOA1-35	1.85395321	0.67677642	APOA1	30	hHEP primary	qRTPCR	
APOA1-36	1.76089152	0.70945074	APOA1	30	hHEP primary	qRTPCR	
APOA1-37	1.71562585	0.78114807	APOA1	30	hHEP primary	qRTPCR	
APOA1-38	1.80641212	0.8331741	APOA1	30	hHEP primary	qRTPCR	
APOA1-39	1.76542166	0.53374263	APOA1	30	hHEP primary	qRTPCR	
APOA1-40	2.15329824	0.50965092	APOA1	30	hHEP primary	qRTPCR	
APOA1-41	1.5939654	0.54044002	APOA1	30	hHEP primary	qRTPCR	
APOA1-42	1.94378262	0.50702954	APOA1	30	hHEP primary	qRTPCR	
APOA1-43	1.79963282	0.44705064	APOA1	30	hHEP primary	qRTPCR	
APOA1-44	1.9575475	0.7189088	APOA1	30	hHEP primary	qRTPCR	
APOA1-45	1.98531492	0.68656113	APOA1	30	hHEP primary	qRTPCR	
APOA1-46	2.03417331	0.71255862	APOA1	30	hHEP primary	qRTPCR	
APOA1-47	1.79039551	0.71423975	APOA1	30	hHEP primary	qRTPCR	
APOA1-48	1.86791984	0.48531732	APOA1	30	hHEP primary	qRTPCR	
APOA1-49	1.40729249	0.5376716	APOA1	30	hHEP primary	qRTPCR	
APOA1-50	1.28785038	0.72066311	APOA1	30	hHEP primary	qRTPCR	
RNAiMAX	1	0	APOA1	0	hHEP primary	qRTPCR	
Untreated	0.6819422	0.0118879	APOA1	0	hHEP primary	qRTPCR	
APOA1-01	2.71830639	1.05041684	APOA1	30	hHEP primary	qRTPCR	
APOA1-02	1.88112279	0.07528921	APOA1	30	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-03	2.39266721	0.31016346	APOA1	30	hHEP primary	qRTPCR	
APOA1-04	2.60733815	0.32321736	APOA1	30	hHEP primary	qRTPCR	
APOA1-05	2.70219145	0.48168842	APOA1	30	hHEP primary	qRTPCR	
APOA1-06	2.31011895	0.63605704	APOA1	30	hHEP primary	qRTPCR	
APOA1-07	2.76702681	0.50750456	APOA1	30	hHEP primary	qRTPCR	
APOA1-08	2.92047341	0.7414812	APOA1	30	hHEP primary	qRTPCR	
APOA1-09	2.58380646	0.29575356	APOA1	30	hHEP primary	qRTPCR	
APOA1-10	2.63329611	0.39062455	APOA1	30	hHEP primary	qRTPCR	
APOA1-11	3.02299013	0.35792068	APOA1	30	hHEP primary	qRTPCR	
APOA1-12	2.45594349	0.24444055	APOA1	30	hHEP primary	qRTPCR	
APOA1-13	2.33019523	0.05300335	APOA1	30	hHEP primary	qRTPCR	
APOA1-14	2.63746736	0.17510821	APOA1	30	hHEP primary	qRTPCR	
APOA1-15	2.60414983	0.09554169	APOA1	30	hHEP primary	qRTPCR	
APOA1-16	3.14275776	0.03004565	APOA1	30	hHEP primary	qRTPCR	
APOA1-17	2.40257112	0.31614309	APOA1	30	hHEP primary	qRTPCR	
APOA1-18	2.5078604	0.38248593	APOA1	30	hHEP primary	qRTPCR	
APOA1-19	2.69342601	0.29186053	APOA1	30	hHEP primary	qRTPCR	
APOA1-20	2.74946689	0.38411325	APOA1	30	hHEP primary	qRTPCR	
APOA1-21	3.12584682	0.16723109	APOA1	30	hHEP primary	qRTPCR	
APOA1-22	2.89075721	0.82651217	APOA1	30	hHEP primary	qRTPCR	
APOA1-23	2.62409939	0.27905348	APOA1	30	hHEP primary	qRTPCR	
APOA1-24	2.52878662	0.17190803	APOA1	30	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-25	2.35726538	0.00908916	APOA1	30	hHEP primary	qRTPCR	
APOA1-26	2.44870406	0.07618463	APOA1	30	hHEP primary	qRTPCR	
APOA1-27	2.142703	0.11669677	APOA1	30	hHEP primary	qRTPCR	
APOA1-28	2.42914069	0.0552219	APOA1	30	hHEP primary	qRTPCR	
APOA1-29	2.18753629	0.10724495	APOA1	30	hHEP primary	qRTPCR	
APOA1-30	2.57935625	0.25562987	APOA1	30	hHEP primary	qRTPCR	
APOA1-31	2.44368853	0.5093	APOA1	30	hHEP primary	qRTPCR	
APOA1-32	2.52042432	0.31704036	APOA1	30	hHEP primary	qRTPCR	
APOA1-33	2.71709733	0.10804851	APOA1	30	hHEP primary	qRTPCR	
APOA1-34	2.38912947	0.26852646	APOA1	30	hHEP primary	qRTPCR	
APOA1-35	2.30584024	0.2728256	APOA1	30	hHEP primary	qRTPCR	
APOA1-36	2.21806753	0.35770213	APOA1	30	hHEP primary	qRTPCR	
APOA1-37	2.2676807	0.03154035	APOA1	30	hHEP primary	qRTPCR	
APOA1-38	2.36348973	0.33205758	APOA1	30	hHEP primary	qRTPCR	
APOA1-39	2.14209344	0.04095004	APOA1	30	hHEP primary	qRTPCR	
APOA1-40	2.49645464	0.19064923	APOA1	30	hHEP primary	qRTPCR	
APOA1-41	1.97318223	0.08183464	APOA1	30	hHEP primary	qRTPCR	
APOA1-42	2.28402767	0.19575069	APOA1	30	hHEP primary	qRTPCR	
APOA1-43	2.11567127	0.01185387	APOA1	30	hHEP primary	qRTPCR	
APOA1-44	2.45435172	0.18655161	APOA1	30	hHEP primary	qRTPCR	
APOA1-45	2.4596595	0.17899977	APOA1	30	hHEP primary	qRTPCR	
APOA1-46	2.53777058	0.02791179	APOA1	30	hHEP primary	qRTPCR	
APOA1-47	2.28337183	0.19008065	APOA1	30	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-48	2.20236802	0.13316374	APOA1	30	hHEP primary	qRTPCR	
APOA1-49	1.67934139	0.46000468	APOA1	30	hHEP primary	qRTPCR	
APOA1-50	1.58596593	0.71583121	APOA1	30	hHEP primary	qRTPCR	
RNAiMAX	1	0	APOA1	0	hHEP primary	qRTPCR	
Untreated	0.95011044	0.12569078	APOA1	0	hHEP primary	qRTPCR	
APOA1-01	1.32009381	0.38354504	APOA1	30	hHEP primary	qRTPCR	
APOA1-02	2.25037605	0.54340273	APOA1	30	hHEP primary	qRTPCR	
APOA1-03	3.39934478	0.78662326	APOA1	30	hHEP primary	qRTPCR	
APOA1-04	3.62748969	0.95472458	APOA1	30	hHEP primary	qRTPCR	
APOA1-05	2.1724992	0.15444594	APOA1	30	hHEP primary	qRTPCR	
APOA1-06	2.53583922	0.93191254	APOA1	30	hHEP primary	qRTPCR	
APOA1-07	1.17214844	0.15053091	APOA1	30	hHEP primary	qRTPCR	
APOA1-08	1.08019567	0.18819106	APOA1	30	hHEP primary	qRTPCR	
APOA1-09	1.16192946	0.40624907	APOA1	30	hHEP primary	qRTPCR	
APOA1-10	2.57620777	0.04887442	APOA1	30	hHEP primary	qRTPCR	
APOA1-11	0.98228447	0.42158841	APOA1	30	hHEP primary	qRTPCR	
APOA1-12	0.43200047	0.01451453	APOA1	30	hHEP primary	qRTPCR	
APOA1-13	1.16861619	0.07900628	APOA1	30	hHEP primary	qRTPCR	
APOA1-14	2.70713998	0	APOA1	30	hHEP primary	qRTPCR	
APOA1-15	2.20661641	0.3310359	APOA1	30	hHEP primary	qRTPCR	
APOA1-16	1.86032992	0.06809628	APOA1	30	hHEP primary	qRTPCR	
APOA1-17	1.62199017	0.16569278	APOA1	30	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-18	1.52707036	0.24816296	APOA1	30	hHEP primary	qRTPCR	
APOA1-19	1.54519288	0.50481203	APOA1	30	hHEP primary	qRTPCR	
APOA1-20	1.16494654	0.04848346	APOA1	30	hHEP primary	qRTPCR	
APOA1-21	1.34354967	0.40059626	APOA1	30	hHEP primary	qRTPCR	
APOA1-22	1.48819118	0.57268075	APOA1	30	hHEP primary	qRTPCR	
APOA1-23	1.17727428	0.45488447	APOA1	30	hHEP primary	qRTPCR	
APOA1-24	0.62736747	0.14589916	APOA1	30	hHEP primary	qRTPCR	
APOA1-25	0.83327169	0.15432419	APOA1	30	hHEP primary	qRTPCR	
APOA1-26	1.63793583	0.33477148	APOA1	30	hHEP primary	qRTPCR	
APOA1-27	1.02743913	0.03348776	APOA1	30	hHEP primary	qRTPCR	
APOA1-28	2.45089415	0.12051014	APOA1	30	hHEP primary	qRTPCR	
APOA1-29	1.27616578	0.08079063	APOA1	30	hHEP primary	qRTPCR	
APOA1-30	1.80673776	0.27965441	APOA1	30	hHEP primary	qRTPCR	
APOA1-31	1.61304315	0.46990116	APOA1	30	hHEP primary	qRTPCR	
APOA1-32	1.34512926	0.1592741	APOA1	30	hHEP primary	qRTPCR	
APOA1-33	0.91122355	0.07179223	APOA1	30	hHEP primary	qRTPCR	
APOA1-34	0.60325839	0.19685483	APOA1	30	hHEP primary	qRTPCR	
APOA1-35	0.8561943	0.16877563	APOA1	30	hHEP primary	qRTPCR	
APOA1-36	1.04658238	0.24588398	APOA1	30	hHEP primary	qRTPCR	
APOA1-37	1.47883856	0.63951155	APOA1	30	hHEP primary	qRTPCR	
APOA1-38	2.33897913	0.87539932	APOA1	30	hHEP primary	qRTPCR	
APOA1-39	1.81201696	0.0349262	APOA1	30	hHEP primary	qRTPCR	
APOA1-40	2.03481861	0.36005052	APOA1	30	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-41	1.63450747	0.00660703	APOA1	30	hHEP primary	qRTPCR	
APOA1-42	1.25005328	0.10406799	APOA1	30	hHEP primary	qRTPCR	
APOA1-43	0.85533162	0.23242445	APOA1	30	hHEP primary	qRTPCR	
APOA1-44	1.02476895	0.47160076	APOA1	30	hHEP primary	qRTPCR	
APOA1-45	1.23408832	0.32581499	APOA1	30	hHEP primary	qRTPCR	
APOA1-46	0.87817882	0.37249556	APOA1	30	hHEP primary	qRTPCR	
APOA1-47	0.32501979	0.08790894	APOA1	30	hHEP primary	qRTPCR	
APOA1-48	0.70597756	0.25663068	APOA1	30	hHEP primary	qRTPCR	
APOA1-49	1.51915549	0.61339915	APOA1	30	hHEP primary	qRTPCR	
APOA1-50	1.53949535	0.33628602	APOA1	30	hHEP primary	qRTPCR	
RNAiMAX	1	0	APOA1	0	hHEP primary	qRTPCR	
Untreated	1.33575817	0.29931193	APOA1	0	hHEP primary	qRTPCR	
APOA1-01	1.68587911	0.0162356	APOA1	30	hHEP primary	qRTPCR	
APOA1-02	0.43827897	0.02769865	APOA1	30	hHEP primary	qRTPCR	
APOA1-03	1.49739324	0.18754426	APOA1	30	hHEP primary	qRTPCR	
APOA1-04	0.25773075	0.00376984	APOA1	30	hHEP primary	qRTPCR	
APOA1-05	1.60136848	0.11721219	APOA1	30	hHEP primary	qRTPCR	
APOA1-06	1.83378456	0.12750393	APOA1	30	hHEP primary	qRTPCR	
APOA1-07	1.86028683	0.77173521	APOA1	30	hHEP primary	qRTPCR	
APOA1-08	0.10222146	0.00357709	APOA1	30	hHEP primary	qRTPCR	
APOA1-09	1.0334552	0.12820525	APOA1	30	hHEP primary	qRTPCR	
APOA1-10	1.66757857	0.13398654	APOA1	30	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-11	1.41965478	0.00083991	APOA1	30	hHEP primary	qRTPCR	
APOA1-12	1.02497094	0.05691061	APOA1	30	hHEP primary	qRTPCR	
APOA1-13	1.97803809	0.12451971	APOA1	30	hHEP primary	qRTPCR	
APOA1-14	3.14793112	0.39142821	APOA1	30	hHEP primary	qRTPCR	
APOA1-15	0.36604515	0.05762825	APOA1	30	hHEP primary	qRTPCR	
APOA1-16	0.71630357	0.01972257	APOA1	30	hHEP primary	qRTPCR	
APOA1-17	1.08355437	0.46768049	APOA1	30	hHEP primary	qRTPCR	
APOA1-18	0.11935219	0.01268216	APOA1	30	hHEP primary	qRTPCR	
APOA1-19	2.97143948	0.88668789	APOA1	30	hHEP primary	qRTPCR	
APOA1-20	2.59074612	0.99251769	APOA1	30	hHEP primary	qRTPCR	
APOA1-21	3.28621376	0.25305198	APOA1	30	hHEP primary	qRTPCR	
APOA1-22	2.16273456	0.42130976	APOA1	30	hHEP primary	qRTPCR	
APOA1-23	1.1882136	0.14110988	APOA1	30	hHEP primary	qRTPCR	
APOA1-24	1.84047301	0.74183983	APOA1	30	hHEP primary	qRTPCR	
APOA1-25	3.98826067	2.3920974	APOA1	30	hHEP primary	qRTPCR	
APOA1-26	1.79088474	0.11769682	APOA1	30	hHEP primary	qRTPCR	
APOA1-27	3.9325658	0.39378198	APOA1	30	hHEP primary	qRTPCR	
APOA1-28	3.99859626	2.0037457	APOA1	30	hHEP primary	qRTPCR	
APOA1-29	3.56306045	2.28083477	APOA1	30	hHEP primary	qRTPCR	
APOA1-30	3.51956175	2.13807035	APOA1	30	hHEP primary	qRTPCR	
APOA1-31	3.04527758	0.92972903	APOA1	30	hHEP primary	qRTPCR	
APOA1-32	1.79384301	0.55000028	APOA1	30	hHEP primary	qRTPCR	
APOA1-33	1.67003563	0.18466426	APOA1	30	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-34	1.41786641	0.26654324	APOA1	30	hHEP primary	qRTPCR	
APOA1-35	1.25025304	0.04899078	APOA1	30	hHEP primary	qRTPCR	
APOA1-36	2.67168189	0.99552937	APOA1	30	hHEP primary	qRTPCR	
APOA1-37	1.23042435	0.20690604	APOA1	30	hHEP primary	qRTPCR	
APOA1-38	2.44673273	0.10567045	APOA1	30	hHEP primary	qRTPCR	
APOA1-39	2.1161272	0.70735331	APOA1	30	hHEP primary	qRTPCR	
APOA1-40	1.66034823	0.45438378	APOA1	30	hHEP primary	qRTPCR	
APOA1-41	1.80174664	0.34233653	APOA1	30	hHEP primary	qRTPCR	
APOA1-42	1.51766756	0.01923899	APOA1	30	hHEP primary	qRTPCR	
APOA1-43	0.66436901	0.05026191	APOA1	30	hHEP primary	qRTPCR	
APOA1-44	1.44569277	0.20449644	APOA1	30	hHEP primary	qRTPCR	
APOA1-45	0.78009657	0.17750165	APOA1	30	hHEP primary	qRTPCR	
APOA1-46	1.41394441	0.04735972	APOA1	30	hHEP primary	qRTPCR	
APOA1-47	3.72598276	0.76672547	APOA1	30	hHEP primary	qRTPCR	
APOA1-48	1.73746444	0.43254675	APOA1	30	hHEP primary	qRTPCR	
APOA1-49	1.75356323	0.33192439	APOA1	30	hHEP primary	qRTPCR	
APOA1-50	0.24216743	0	APOA1	30	hHEP primary	qRTPCR	
Untreated	1	0	APOA1	0	hHEP primary	qRTPCR	
Water	1.01537814	0.10896869	APOA1	0	hHEP primary	qRTPCR	
APOA1-01	1.02026099	0.23770184	APOA1	30	hHEP primary	qRTPCR	
APOA1-02	1.23479224	0.27193123	APOA1	30	hHEP primary	qRTPCR	
APOA1-03	1.31786233	0.32700841	APOA1	30	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-04	1.46771507	0.36638066	APOA1	30	hHEP primary	qRTPCR	
APOA1-05	0.85500459	0.22458949	APOA1	30	hHEP primary	qRTPCR	
APOA1-06	1.14333129	0.27527342	APOA1	30	hHEP primary	qRTPCR	
APOA1-07	0.87181049	0.19548773	APOA1	30	hHEP primary	qRTPCR	
APOA1-08	1.11457956	0.33005572	APOA1	30	hHEP primary	qRTPCR	
APOA1-09	0.98453165	0.27444462	APOA1	30	hHEP primary	qRTPCR	
APOA1-10	1.54890506	0.41959256	APOA1	30	hHEP primary	qRTPCR	
APOA1-11	1.09366409	0.29936315	APOA1	30	hHEP primary	qRTPCR	
APOA1-12	0.84812918	0.26568593	APOA1	30	hHEP primary	qRTPCR	
APOA1-13	0.96763485	0.09196502	APOA1	30	hHEP primary	qRTPCR	
APOA1-14	0.91534813	0.14234054	APOA1	30	hHEP primary	qRTPCR	
APOA1-15	0.98981044	0.14781698	APOA1	30	hHEP primary	qRTPCR	
APOA1-16	1.18031224	0.19166608	APOA1	30	hHEP primary	qRTPCR	
APOA1-17	1.2011975	0.23687242	APOA1	30	hHEP primary	qRTPCR	
APOA1-18	0.95763778	0.17954214	APOA1	30	hHEP primary	qRTPCR	
APOA1-19	1.15415372	0.13108297	APOA1	30	hHEP primary	qRTPCR	
APOA1-20	1.19128334	0.16094358	APOA1	30	hHEP primary	qRTPCR	
APOA1-21	1.2112898	0.17657456	APOA1	30	hHEP primary	qRTPCR	
APOA1-22	1.22266851	0.28065423	APOA1	30	hHEP primary	qRTPCR	
APOA1-23	0.98012118	0.23036807	APOA1	30	hHEP primary	qRTPCR	
APOA1-24	0.83736437	0.20521604	APOA1	30	hHEP primary	qRTPCR	
APOA1-25	0.95809816	0.10584968	APOA1	30	hHEP primary	qRTPCR	
APOA1-26	1.18941969	0.20322595	APOA1	30	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-27	1.10072235	0.16197046	APOA1	30	hHEP primary	qRTPCR	
APOA1-28	1.3894071	0.19951892	APOA1	30	hHEP primary	qRTPCR	
APOA1-29	1.0868702	0.22594987	APOA1	30	hHEP primary	qRTPCR	
APOA1-30	1.11534776	0.07815254	APOA1	30	hHEP primary	qRTPCR	
APOA1-31	1.16043705	0.13909264	APOA1	30	hHEP primary	qRTPCR	
APOA1-32	1.01065182	0.1572921	APOA1	30	hHEP primary	qRTPCR	
APOA1-33	0.97380861	0.17378755	APOA1	30	hHEP primary	qRTPCR	
APOA1-34	1.04250323	0.22699154	APOA1	30	hHEP primary	qRTPCR	
APOA1-35	0.84653635	0.19125732	APOA1	30	hHEP primary	qRTPCR	
APOA1-36	0.63308695	0.18390914	APOA1	30	hHEP primary	qRTPCR	
APOA1-37	0.92051978	0.10891757	APOA1	30	hHEP primary	qRTPCR	
APOA1-38	1.50689993	0.08644879	APOA1	30	hHEP primary	qRTPCR	
APOA1-39	1.11546265	0.07173467	APOA1	30	hHEP primary	qRTPCR	
APOA1-40	1.4013078	0.14015501	APOA1	30	hHEP primary	qRTPCR	
APOA1-41	0.95779085	0.14727817	APOA1	30	hHEP primary	qRTPCR	
APOA1-42	0.75605983	0.1397345	APOA1	30	hHEP primary	qRTPCR	
APOA1-43	0.88158439	0.16552727	APOA1	30	hHEP primary	qRTPCR	
APOA1-44	1.0500748	0.16534592	APOA1	30	hHEP primary	qRTPCR	
APOA1-45	0.92568934	0.15286822	APOA1	30	hHEP primary	qRTPCR	
APOA1-46	0.95304119	0.18905573	APOA1	30	hHEP primary	qRTPCR	
APOA1-47	0.72388363	0.20625725	APOA1	30	hHEP primary	qRTPCR	
APOA1-48	0.63452037	0.15982252	APOA1	30	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-49	0.78381416	0.06757521	APOA1	30	hHEP primary	qRTPCR	
APOA1-50	0.71597656	0.01591082	APOA1	30	hHEP primary	qRTPCR	
Untreated	1	0	APOA1	0	hHEP primary	qRTPCR	
Water	0.93924665	0.02969757	APOA1	0	hHEP primary	qRTPCR	
APOA1-01	0.83095626	0.21631389	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-02	0.8876824	0.19200961	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-03	0.91613228	0.11709133	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-04	0.92907695	0.02626855	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-05	0.80985489	0.05353296	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-06	0.95266787	0.08972678	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-07	1.08043172	0.12871318	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-08	0.78747003	0.0458151	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-09	0.85571323	0.07321611	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-10	1.60088464	0.09043729	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-11	1.00761106	0.09039756	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-12	0.83920121	0.08573001	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-13	0.91072071	0.0871394	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic

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Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
							delivery
APOA1-14	0.70265895	0.07333552	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-15	0.71547311	0.03462638	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-16	0.70817229	0.03289699	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-17	0.78238905	0.06940852	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-18	0.79371617	0.08022504	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-19	0.79141392	0.04477798	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-20	0.85801084	0.05366667	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-21	0.80035091	0.06097814	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-22	0.82658823	0.0497681	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-23	0.77149221	0.01602221	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-24	0.98566569	0.00632856	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-25	1.13280614	0.08705471	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-26	0.84009533	0.01101489	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-27	0.79598115	0.04425806	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-28	0.85431105	0.07635182	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-29	0.700423	0.05309015	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-30	0.77954825	0.08851127	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-31	0.68788289	0.04658558	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-32	0.74574816	0.06803198	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-33	0.77162977	0.05999265	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-34	0.78443584	0.05205294	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-35	0.73862198	0.02006332	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-36	1.00634215	0.06979684	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-37	0.96135879	0.07009048	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-38	1.22422459	0.04612546	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-39	0.81062907	0.02064826	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-40	0.85154085	0.04822399	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-41	0.72197439	0.0022181	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-42	0.77123213	0.00817725	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-43	0.79344641	0.02951852	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-44	0.8838882	0.07558371	APOA1	5000	hHEP	qRTPCR	7 day

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Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		gymnotic delivery
APOA1-45	0.81294197	0.05062538	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-46	1.00219897	0.0824217	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-47	0.9232121	0.05757279	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-48	1.08114015	0.10432756	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-49	0.64402362	0.07770435	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
APOA1-50	0.95078973	0.06535035	APOA1	5000	hHEP primary	qRTPCR	7 day gymnotic delivery
Untreated	1	0	APOA1	0	Rhesus HEP primary	qRTPCR	
RNAiMax	0.99884413	0.04600691	APOA1	0	Rhesus HEP primary	qRTPCR	
APOA1-01	1.35610346	0.07501137	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-02	1.29448143	0.02309117	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-03	1.18558583	0.00763564	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-04	1.06642893	0.04670327	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-05	1.64350984	0.08563658	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-06	1.46357903	0.04770982	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-07	1.66732753	0.12044051	APOA1	20000	Rhesus HEP	qRTPCR	2 day gymnotic

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		delivery
APOA1-08	1.42957342	0.01249259	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-09	1.2998451	0.08328923	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-10	1.52501725	0.00838624	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-11	1.20742902	0.06257191	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-12	0.98351911	0.05570561	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-13	1.06420926	0.01352089	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.47269591	0.04762093	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-15	1.01593181	0.0466318	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-16	1.19895758	0.02763229	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-17	0.88105172	0.00782852	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-18	1.31136627	0.0064572	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-19	1.2056567	0.04737777	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-20	1.26930682	0.02753274	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-21	1.11367534	0.03503577	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-22	1.27338661	0.02154267	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-23	1.19049743	0.02027885	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-24	1.04698621	0.03232239	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-25	1.58660914	0.14080533	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.86213835	0.00018833	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	2.10581693	0.15111387	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.98055399	0.10307062	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-29	1.40437381	0.01257963	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-30	1.27168734	0.02961935	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-31	1.15992463	0.01936407	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-32	1.16456331	0.0570679	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-33	1.29820188	0.04361753	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-34	1.17343818	0.04474002	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-35	1.68720878	0.02672721	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-36	1.40406933	0.05201243	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-37	1.14577369	0.09075636	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	2.12806048	0.19015489	APOA1	20000	Rhesus	qRTPCR	2 day

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					HEP primary		gymnotic delivery
APOA1-39	1.16915349	0.00094597	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-40	1.19907058	0.0025586	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-41	1.24321488	0.08979382	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.62663135	0.05063175	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-43	1.22838499	0.06225601	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-44	1.18458924	0.05844139	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-45	1.17520364	0.04230154	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-46	0.96264402	0.05088288	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-47	1.1900275	0.06951272	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-48	2.00874599	0.07954203	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-49	1.11355371	0.0039948	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-50	1.08414991	0.01243284	APOA1	20000	Rhesus HEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1	0	APOA1	0	hHEP primary	qRTPCR	
APOA1-14	1.08694838	0.18251335	APOA1	0.0003	hHEP primary	qRTPCR	
APOA1-14	1.05194003	0.15181404	APOA1	0.0016	hHEP primary	qRTPCR	
APOA1-14	1.53925884	0.18553087	APOA1	0.008	hHEP primary	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-14	1.52047547	0.35804358	APOA1	0.04	hHEP primary	qRTPCR	
APOA1-14	1.53104358	0.1930136	APOA1	0.2	hHEP primary	qRTPCR	
APOA1-14	2.12099067	0.29931038	APOA1	1	hHEP primary	qRTPCR	
APOA1-14	2.25928913	0.51423765	APOA1	5	hHEP primary	qRTPCR	
APOA1-26	1	0	APOA1	0	hHEP primary	qRTPCR	
APOA1-26	1.08553363	0.0767314	APOA1	0.0003	hHEP primary	qRTPCR	
APOA1-26	1.15868135	0.08227044	APOA1	0.0016	hHEP primary	qRTPCR	
APOA1-26	1.52412576	0.20682262	APOA1	0.008	hHEP primary	qRTPCR	
APOA1-26	1.31825093	0.24922943	APOA1	0.04	hHEP primary	qRTPCR	
APOA1-26	1.57248749	0.28024257	APOA1	0.2	hHEP primary	qRTPCR	
APOA1-26	1.58728753	0.26666262	APOA1	1	hHEP primary	qRTPCR	
APOA1-26	2.55476113	0.40031901	APOA1	5	hHEP primary	qRTPCR	
APOA1-27	1	0	APOA1	0	hHEP primary	qRTPCR	
APOA1-27	0.98316863	0.08604414	APOA1	0.0003	hHEP primary	qRTPCR	
APOA1-27	1.05752462	0.08617287	APOA1	0.0016	hHEP primary	qRTPCR	
APOA1-27	1.52615535	0.26226753	APOA1	0.008	hHEP primary	qRTPCR	
APOA1-27	1.26027422	0.23746766	APOA1	0.04	hHEP primary	qRTPCR	
APOA1-27	1.43678902	0.088956	APOA1	0.2	hHEP primary	qRTPCR	
APOA1-27	1.78583681	0.23233442	APOA1	1	hHEP primary	qRTPCR	
APOA1-27	2.33077582	0.34733247	APOA1	5	hHEP primary	qRTPCR	
APOA1-28	1	0	APOA1	0	hHEP primary	qRTPCR	
APOA1-28	0.99808283	0.08754604	APOA1	0.0003	hHEP primary	qRTPCR	
APOA1-28	1.09627964	0.10546149	APOA1	0.0016	hHEP	qRTPCR	

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		
APOA1-28	1.74635808	0.2128014	APOA1	0.008	hHEP primary	qRTPCR	
APOA1-28	1.32686535	0.30053538	APOA1	0.04	hHEP primary	qRTPCR	
APOA1-28	1.55116686	0.2545156	APOA1	0.2	hHEP primary	qRTPCR	
APOA1-28	1.75193166	0.29635319	APOA1	1	hHEP primary	qRTPCR	
APOA1-28	2.26556635	0.30759034	APOA1	5	hHEP primary	qRTPCR	
APOA1-38	1	0	APOA1	0	hHEP primary	qRTPCR	
APOA1-38	0.88492503	0.06629437	APOA1	0.0003	hHEP primary	qRTPCR	
APOA1-38	1.05734891	0.11363534	APOA1	0.0016	hHEP primary	qRTPCR	
APOA1-38	1.57897899	0.28185073	APOA1	0.008	hHEP primary	qRTPCR	
APOA1-38	1.22436431	0.28448495	APOA1	0.04	hHEP primary	qRTPCR	
APOA1-38	1.59431372	0.28418325	APOA1	0.2	hHEP primary	qRTPCR	
APOA1-38	1.72576685	0.24330581	APOA1	1	hHEP primary	qRTPCR	
APOA1-38	1.88788569	0.20070977	APOA1	5	hHEP primary	qRTPCR	
APOA1-42	1	0	APOA1	0	hHEP primary	qRTPCR	
APOA1-42	1.08101142	0.25215396	APOA1	0.0003	hHEP primary	qRTPCR	
APOA1-42	1.04455528	0.09799083	APOA1	0.0016	hHEP primary	qRTPCR	
APOA1-42	1.41948528	0.12776744	APOA1	0.008	hHEP primary	qRTPCR	
APOA1-42	1.15260293	0.20470935	APOA1	0.04	hHEP primary	qRTPCR	
APOA1-42	1.79896507	0.27164046	APOA1	0.2	hHEP primary	qRTPCR	
APOA1-42	1.714465	0.2708664	APOA1	1	hHEP primary	qRTPCR	
APOA1-42	2.65590093	0.665345	APOA1	5	hHEP primary	qRTPCR	
APOA1-14	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
							delivery
APOA1-14	1.22664385	0.08136829	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.20001603	0.16149277	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.34241832	0.166079	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.250667	0.13525874	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.50787957	0.26834293	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.62349636	0.20814037	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	3.10508875	0.32974659	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.03057865	0.1099187	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.15081722	0.16409535	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.13969479	0.1419007	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.12042625	0.18319122	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.1241745	0.1969907	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.32298492	0.18004037	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.79781279	0.34218058	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-27	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.1402176	0.19965713	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.26675707	0.18370679	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.26012213	0.1129072	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.18290313	0.15673768	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.3771192	0.24095227	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.54307506	0.27285199	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.98758533	0.57279042	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.11908946	0.10118137	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.31622532	0.24397655	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.29780578	0.17961127	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.32246936	0.18646197	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.31539138	0.15026478	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.38882146	0.13582825	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.71414157	0.36521339	APOA1	20	hHEP	qRTPCR	2 day

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		gymnotic delivery
APOA1-38	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.09493393	0.16440193	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.21259515	0.1811953	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.18730143	0.1815182	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.20937799	0.16112497	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.31738897	0.17408158	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.30481928	0.17998918	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.48167673	0.22830116	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.07180406	0.15995264	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.20060918	0.17805838	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.19564064	0.19452738	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.25800421	0.16546956	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.37990276	0.1382772	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.58449876	0.27634275	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
							delivery
APOA1-42	2.47049804	0.5427229	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.28982321	0.05728385	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.34549175	0.04239393	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.23831059	0.1267953	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.32069205	0.09056565	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.53271184	0.1290343	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1.62601823	0.08363984	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	2.48171181	0.28713262	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.03431614	0.05662417	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.19463505	0.09180064	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.12434637	0.05894831	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.19037386	0.07353796	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.19090382	0.06103311	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-26	1.54145359	0.14448417	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-26	1.98830673	0.15677505	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.08446817	0.09323671	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.17896543	0.08221723	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.18835793	0.09092287	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.22087528	0.15488819	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.29480261	0.17391472	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	1.81439782	0.17194589	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-27	2.13089066	0.38625974	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.11273557	0.04341545	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.23336596	0.11761839	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.31691986	0.08728456	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.29161178	0.11762106	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	1.41606478	0.21530244	APOA1	0.8	hHEP	qRTPCR	2 day

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
					primary		gymnotic delivery
APOA1-28	1.96931875	0.16623081	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-28	2.30778783	0.16497488	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.05735	0.19977389	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.17022731	0.15556619	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.26481706	0.18783056	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.27521361	0.09730602	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.36058844	0.30876272	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.57888871	0.20587799	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-38	1.80614809	0.36361908	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1	0	APOA1	0	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.11366546	0.17789828	APOA1	0.0013	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.22215537	0.11647732	APOA1	0.0064	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.24401865	0.14212687	APOA1	0.032	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	1.40406236	0.12126081	APOA1	0.16	hHEP primary	qRTPCR	2 day gymnotic

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
							delivery
APOA1-42	1.74777513	0.17270537	APOA1	0.8	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	2.23756758	0.31858478	APOA1	4	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-42	3.09552924	0.53473194	APOA1	20	hHEP primary	qRTPCR	2 day gymnotic delivery
APOA1-14	1	0.09626066	APOA1	0	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-14	1.34858968	0.05721875	APOA1	4	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-14	1.72994754	0.10753775	APOA1	20	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-26	1	0.07416862	APOA1	0	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-26	1.5241653	0.11911112	APOA1	4	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-26	1.48229434	0.09405181	APOA1	20	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-27	1	0.08432072	APOA1	0	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-27	1.65637371	0.07032466	APOA1	4	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-27	2.23268013	0.21512241	APOA1	20	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-28	1	0.04689792	APOA1	0	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-28	1.90877233	0.13653732	APOA1	4	hHEP primary	ELISA	Apoa1 protein in supernatant
APOA1-28	2.24666516	0.05232185	APOA1	20	hHEP primary	ELISA	Apoa1 protein in supernatant

Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Assay Type	Note
APOA1-38	1	0.04662436	APOA1	0	hHEP primary	ELISA	Apoa1 protein in supernatent
APOA1-38	1.79639412	0.1346576	APOA1	4	hHEP primary	ELISA	Apoa1 protein in supernatent
APOA1-38	1.98484153	0.07789635	APOA1	20	hHEP primary	ELISA	Apoa1 protein in supernatent
APOA1-42	1	0.0789846	APOA1	0	hHEP primary	ELISA	Apoa1 protein in supernatent
APOA1-42	1.55336049	0.0775668	APOA1	4	hHEP primary	ELISA	Apoa1 protein in supernatent
APOA1-42	2.32240326	0.16792097	APOA1	20	hHEP primary	ELISA	Apoa1 protein in supernatent

Table 3: A listing of oligonucleotide modifications.

Symbol	Feature Description
bio	5' biotin
dAs	DNA w/3' thiophosphate
dCs	DNA w/3' thiophosphate
dGs	DNA w/3' thiophosphate
dTs	DNA w/3' thiophosphate
dG	DNA
d5mCs	deoxy-5-methylcytidine w/3' thiophosphate
enaAs	ENA w/3' thiophosphate
enaCs	ENA w/3' thiophosphate
enaGs	ENA w/3' thiophosphate
enaTs	ENA w/3' thiophosphate
fluAs	2'-fluoro w/3' thiophosphate
fluCs	2'-fluoro w/3' thiophosphate
fluGs	2'-fluoro w/3' thiophosphate
fluUs	2'-fluoro w/3' thiophosphate
lnaAs	LNA w/3' thiophosphate
lnaCs	LNA w/3' thiophosphate
lnaGs	LNA w/3' thiophosphate
lnaTs	LNA w/3' thiophosphate

Symbol	Feature Description
omeAs	2'-OMe w/3' thiophosphate
omeCs	2'-OMe w/3' thiophosphate
omeGs	2'-OMe w/3' thiophosphate
omeTs	2'-OMe w/3' thiophosphate
lnaAs-Sup	LNA w/3' thiophosphate at 3' terminus
lnaCs-Sup	LNA w/3' thiophosphate at 3' terminus
lnaGs-Sup	LNA w/3' thiophosphate at 3' terminus
lnaTs-Sup	LNA w/3' thiophosphate at 3' terminus
lnaA-Sup	LNA w/3' OH at 3' terminus
lnaC-Sup	LNA w/3' OH at 3' terminus
lnaG-Sup	LNA w/3' OH at 3' terminus
lnaT-Sup	LNA w/3' OH at 3' terminus
omeA-Sup	2'-OMe w/3' OH at 3' terminus
omeC-Sup	2'-OMe w/3' OH at 3' terminus
omeG-Sup	2'-OMe w/3' OH at 3' terminus
omeU-Sup	2'-OMe w/3' OH at 3' terminus
dAs-Sup	DNA w/3' thiophosphate at 3' terminus
dCs-Sup	DNA w/3' thiophosphate at 3' terminus
dGs-Sup	DNA w/3' thiophosphate at 3' terminus
dTs-Sup	DNA w/3' thiophosphate at 3' terminus
dA-Sup	DNA w/3' OH at 3' terminus
dC-Sup	DNA w/3' OH at 3' terminus
dG-Sup	DNA w/3' OH at 3' terminus
dT-Sup	DNA w/3' OH at 3' terminus

Table 4: Formatted oligonucleotide sequences made for testing in the lab showing nucleotide modifications.

Oligo Name	Base Sequence	Formatted Sequence	SeqID
APOA1-01 m01	CTAAGAGACAG GTGG	lnaCs;omeUs;lnaAs;omeAs;lnaGs;omeAs;lnaGs;omeA s;lnaCs;omeAs;lnaGs;omeGs;lnaTs;omeGs;lnaG-Sup	182805
APOA1-02 m01	ACTGAAGCTGG AAAG	lnaAs;omeCs;lnaTs;omeGs;lnaAs;omeAs;lnaGs;omeCs ;lnaTs;omeGs;lnaGs;omeAs;lnaAs;omeAs;lnaG-Sup	182846
APOA1-03 m01	GGATTGGAACC TGCC	lnaGs;omeGs;lnaAs;omeUs;lnaTs;omeUs;lnaGs;omeA s;lnaAs;omeCs;lnaCs;omeUs;lnaGs;omeCs;lnaC-Sup	183562
APOA1-04 m01	GCAGATAGAA AACCG	lnaGs;omeCs;lnaAs;omeGs;lnaAs;omeUs;lnaAs;omeG s;lnaAs;omeAs;lnaAs;omeAs;lnaCs;omeCs;lnaG-Sup	184065
APOA1-05 m01	TTTGAAGTGAT GGTC	lnaTs;omeUs;lnaTs;omeGs;lnaAs;omeAs;lnaGs;omeUs ;lnaGs;omeAs;lnaTs;omeGs;lnaGs;omeUs;lnaC-Sup	184347

APOA1-06 m01	CTCTATTTGCC AGC	lnaCs;omeUs;lnaCs;omeUs;lnaAs;omeUs;lnaTs;omeUs;lnaGs;omeCs;lnaCs;omeCs;lnaAs;omeGs;lnaC-Sup	184876
APOA1-07 m01	GGATGAAAGCT GCGG	lnaGs;omeGs;lnaAs;omeUs;lnaGs;omeAs;lnaAs;omeAs;lnaGs;omeCs;lnaTs;omeGs;lnaCs;omeGs;lnaG-Sup	185269
APOA1-08 m01	GATGAAAGCTG CGGT	lnaGs;omeAs;lnaTs;omeGs;lnaAs;omeAs;lnaAs;omeGs;lnaCs;omeUs;lnaGs;omeCs;lnaGs;omeGs;lnaT-Sup	185270
APOA1-09 m01	TGAAAGCTGCG GTGC	lnaTs;omeGs;lnaAs;omeAs;lnaAs;omeGs;lnaCs;omeUs;lnaGs;omeCs;lnaGs;omeGs;lnaTs;omeGs;lnaC-Sup	185272
APOA1-10 m01	CGTGCTCTTCCT GAC	lnaCs;omeGs;lnaTs;omeGs;lnaCs;omeUs;lnaCs;omeUs;lnaTs;omeCs;lnaCs;omeUs;lnaGs;omeAs;lnaC-Sup	185297
APOA1-11 m01	CTCAAAGACAG CGGC	lnaCs;omeUs;lnaCs;omeAs;lnaAs;omeAs;lnaGs;omeAs;lnaCs;omeAs;lnaGs;omeCs;lnaGs;omeGs;lnaC-Sup	185593
APOA1-12 m01	CAGCGGCAGA GACTA	lnaCs;omeAs;lnaGs;omeCs;lnaGs;omeGs;lnaCs;omeAs;lnaGs;omeAs;lnaGs;omeAs;lnaCs;omeUs;lnaA-Sup	185601
APOA1-13 m01	AGCGGCAGAG ACTAT	lnaAs;omeGs;lnaCs;omeGs;lnaGs;omeCs;lnaAs;omeGs;lnaAs;omeGs;lnaAs;omeCs;lnaTs;omeAs;lnaT-Sup	185602
APOA1-14 m01	GCGGCAGAGA CTATG	lnaGs;omeCs;lnaGs;omeGs;lnaCs;omeAs;lnaGs;omeAs;lnaGs;omeAs;lnaCs;omeUs;lnaAs;omeUs;lnaG-Sup	185603
APOA1-15 m01	GTGTCCCAGTT TGAA	lnaGs;omeUs;lnaGs;omeUs;lnaCs;omeCs;lnaCs;omeAs;lnaGs;omeUs;lnaTs;omeUs;lnaGs;omeAs;lnaA-Sup	185617
APOA1-16 m01	CAGCTAAAGTA AGGA	lnaCs;omeAs;lnaGs;omeCs;lnaTs;omeAs;lnaAs;omeAs;lnaGs;omeUs;lnaAs;omeAs;lnaGs;omeGs;lnaA-Sup	185650
APOA1-17 m01	CCCTCCAGCCT AAAG	lnaCs;omeCs;lnaCs;omeUs;lnaCs;omeCs;lnaAs;omeGs;lnaCs;omeCs;lnaTs;omeAs;lnaAs;omeAs;lnaG-Sup	186239
APOA1-18 m01	ATGAGCAAGG ATCTG	lnaAs;omeUs;lnaGs;omeAs;lnaGs;omeCs;lnaAs;omeAs;lnaGs;omeGs;lnaAs;omeUs;lnaCs;omeUs;lnaG-Sup	186374
APOA1-19 m01	AAGGTGCAGCC CTAC	lnaAs;omeAs;lnaGs;omeGs;lnaTs;omeGs;lnaCs;omeAs;lnaGs;omeCs;lnaCs;omeCs;lnaTs;omeAs;lnaC-Sup	186404
APOA1-20 m01	AGGTGCAGCCC TACC	lnaAs;omeGs;lnaGs;omeUs;lnaGs;omeCs;lnaAs;omeGs;lnaCs;omeCs;lnaCs;omeUs;lnaAs;omeCs;lnaC-Sup	186405
APOA1-21 m01	CCCTACCTGGA CGAC	lnaCs;omeCs;lnaCs;omeUs;lnaAs;omeCs;lnaCs;omeUs;lnaGs;omeGs;lnaAs;omeCs;lnaGs;omeAs;lnaC-Sup	186413
APOA1-22 m01	CCTACCTGGAC GACT	lnaCs;omeCs;lnaTs;omeAs;lnaCs;omeCs;lnaTs;omeGs;lnaGs;omeAs;lnaCs;omeGs;lnaAs;omeCs;lnaT-Sup	186414
APOA1-23 m01	CTACCTGGACG ACTT	lnaCs;omeUs;lnaAs;omeCs;lnaCs;omeUs;lnaGs;omeGs;lnaAs;omeCs;lnaGs;omeAs;lnaCs;omeUs;lnaT-Sup	186415
APOA1-24 m01	ATGGAGCTCTA CCGC	lnaAs;omeUs;lnaGs;omeGs;lnaAs;omeGs;lnaCs;omeUs;lnaCs;omeUs;lnaAs;omeCs;lnaCs;omeGs;lnaC-Sup	186452
APOA1-25 m01	GAGCTCTACCG CCAG	lnaGs;omeAs;lnaGs;omeCs;lnaTs;omeCs;lnaTs;omeAs;lnaCs;omeCs;lnaGs;omeCs;lnaCs;omeAs;lnaG-Sup	186455
APOA1-26 m01	AGCTCTACCGC CAGA	lnaAs;omeGs;lnaCs;omeUs;lnaCs;omeUs;lnaAs;omeCs;lnaCs;omeGs;lnaCs;omeCs;lnaAs;omeGs;lnaA-Sup	186456
APOA1-27 m01	GCTCTACCGCC AGAA	lnaGs;omeCs;lnaTs;omeCs;lnaTs;omeAs;lnaCs;omeCs;lnaGs;omeCs;lnaCs;omeAs;lnaGs;omeAs;lnaA-Sup	186457
APOA1-28 m01	CTCTACCGCCA GAAG	lnaCs;omeUs;lnaCs;omeUs;lnaAs;omeCs;lnaCs;omeGs;lnaCs;omeCs;lnaAs;omeGs;lnaAs;omeAs;lnaG-Sup	186458
APOA1-	TCTACCGCCAG	lnaTs;omeCs;lnaTs;omeAs;lnaCs;omeCs;lnaGs;omeCs;	186459

29 m01	AAGG	lNaCs;omeAs;lNaGs;omeAs;lNaAs;omeGs;lNaG-Sup	
APOA1-30 m01	CTACCGCCAGA AGGT	lNaCs;omeUs;lNaAs;omeCs;lNaCs;omeGs;lNaCs;omeCs;lNaAs;omeGs;lNaAs;omeAs;lNaGs;omeGs;lNaT-Sup	186460
APOA1-31 m01	TACCGCCAGAA GGTG	lNaTs;omeAs;lNaCs;omeCs;lNaGs;omeCs;lNaCs;omeAs;lNaGs;omeAs;lNaAs;omeGs;lNaGs;omeUs;lNaG-Sup	186461
APOA1-32 m01	ACCGCCAGAAG GTGG	lNaAs;omeCs;lNaCs;omeGs;lNaCs;omeCs;lNaAs;omeGs;lNaAs;omeAs;lNaGs;omeGs;lNaTs;omeGs;lNaG-Sup	186462
APOA1-33 m01	CCGCCAGAAG GTGGA	lNaCs;omeCs;lNaGs;omeCs;lNaCs;omeAs;lNaGs;omeAs;lNaAs;omeGs;lNaGs;omeUs;lNaGs;omeGs;lNaA-Sup	186463
APOA1-34 m01	GCGCGGCCA GAAGC	lNaGs;omeCs;lNaGs;omeCs;lNaGs;omeCs;lNaGs;omeCs;lNaCs;omeAs;lNaGs;omeAs;lNaAs;omeGs;lNaC-Sup	186504
APOA1-35 m01	GCGCGCCAGA AGCTG	lNaGs;omeCs;lNaGs;omeCs;lNaGs;omeCs;lNaCs;omeAs;lNaGs;omeAs;lNaAs;omeGs;lNaCs;omeUs;lNaG-Sup	186506
APOA1-36 m01	CGCGCCAGAA GCTGC	lNaCs;omeGs;lNaCs;omeGs;lNaCs;omeCs;lNaAs;omeGs;lNaAs;omeAs;lNaGs;omeCs;lNaTs;omeGs;lNaC-Sup	186507
APOA1-37 m01	GCGCCAGAAG CTGCA	lNaGs;omeCs;lNaGs;omeCs;lNaCs;omeAs;lNaGs;omeAs;lNaAs;omeGs;lNaCs;omeUs;lNaGs;omeCs;lNaA-Sup	186508
APOA1-38 m01	CCAGAAGCTGC ACGA	lNaCs;omeCs;lNaAs;omeGs;lNaAs;omeAs;lNaGs;omeCs;lNaTs;omeGs;lNaCs;omeAs;lNaCs;omeGs;lNaA-Sup	186511
APOA1-39 m01	AGCTGCACGAG CTGC	lNaAs;omeGs;lNaCs;omeUs;lNaGs;omeCs;lNaAs;omeCs;lNaGs;omeAs;lNaGs;omeCs;lNaTs;omeGs;lNaC-Sup	186516
APOA1-40 m01	CTGCACGAGCT GCAA	lNaCs;omeUs;lNaGs;omeCs;lNaAs;omeCs;lNaGs;omeAs;lNaGs;omeCs;lNaTs;omeGs;lNaCs;omeAs;lNaA-Sup	186518
APOA1-41 m01	TGCACGAGCTG CAAG	lNaTs;omeGs;lNaCs;omeAs;lNaCs;omeGs;lNaAs;omeGs;lNaCs;omeUs;lNaGs;omeCs;lNaAs;omeAs;lNaG-Sup	186519
APOA1-42 m01	GAGGAGATGC GCGAC	lNaGs;omeAs;lNaGs;omeGs;lNaAs;omeGs;lNaAs;omeU s;lNaGs;omeCs;lNaGs;omeCs;lNaGs;omeAs;lNaC-Sup	186554
APOA1-43 m01	CTGTTGTAGCT CTGG	lNaCs;omeUs;lNaGs;omeUs;lNaTs;omeGs;lNaTs;omeAs;lNaGs;omeCs;lNaTs;omeCs;lNaTs;omeGs;lNaG-Sup	115212
APOA1-44 m01	AAGGTCTCCCA ATAG	lNaAs;omeAs;lNaGs;omeGs;lNaTs;omeCs;lNaTs;omeCs;lNaCs;omeCs;lNaAs;omeAs;lNaTs;omeAs;lNaG-Sup	115624
APOA1-45 m01	CAAGAAGCTGC TATG	lNaCs;omeAs;lNaAs;omeGs;lNaAs;omeAs;lNaGs;omeCs;lNaTs;omeGs;lNaCs;omeUs;lNaAs;omeUs;lNaG-Sup	116345
APOA1-46 m01	CTCCCTCTGTCC TAC	lNaCs;omeUs;lNaCs;omeCs;lNaCs;omeUs;lNaCs;omeUs;lNaGs;omeUs;lNaCs;omeCs;lNaTs;omeAs;lNaC-Sup	117021
APOA1-47 m01	TCCCCAGAACC GGCT	lNaTs;omeCs;lNaCs;omeCs;lNaCs;omeAs;lNaGs;omeAs;lNaAs;omeCs;lNaCs;omeGs;lNaGs;omeCs;lNaT-Sup	117158
APOA1-48 m01	AGCGTGCAGG AGTCC	lNaAs;omeGs;lNaCs;omeGs;lNaTs;omeGs;lNaCs;omeAs;lNaGs;omeGs;lNaAs;omeGs;lNaTs;omeCs;lNaC-Sup	118348
APOA1-49 m01	CAGCGTGCAG GAGTC	lNaCs;omeAs;lNaGs;omeCs;lNaGs;omeUs;lNaGs;omeC s;lNaAs;omeGs;lNaGs;omeAs;lNaGs;omeUs;lNaC-Sup	118349
APOA1-50 m01	AGCAGCGTGCA GGAG	lNaAs;omeGs;lNaCs;omeAs;lNaGs;omeCs;lNaGs;omeU s;lNaGs;omeCs;lNaAs;omeGs;lNaGs;omeAs;lNaG-Sup	118351
APOA1-51 m01	CTTCTCGCAGT CTCT	lNaCs;lNaTs;lNaTs;d5mCs;dTs;d5mCs;dGs;d5mCs;dAs;dGs;dTs;d5mCs;lNaTs;lNaCs;lNaT-Sup	187502
APOA1-52 m01	CCGCAGCTTTC ATCC	lNaCs;lNaCs;lNaGs;d5mCs;dAs;dGs;d5mCs;dTs;dTs;dTs;d5mCs;dAs;lNaTs;lNaCs;lNaC-Sup	187503

APOA1-53 m01	ACCGCAGCTTT CATC	lnaAs;lnaCs;lnaCs;dGs;d5mCs;dAs;dGs;d5mCs;dTs;dTs;dTs;d5mCs;lnaAs;lnaTs;lnaC-Sup	187504
APOA1-54 m01	CACCGCAGCTT TCAT	lnaCs;lnaAs;lnaCs;d5mCs;dGs;d5mCs;dAs;dGs;d5mCs;dTs;dTs;dTs;lnaCs;lnaAs;lnaT-Sup	187505
APOA1-55 m01	GAAATGCCGA GCCTG	lnaGs;lnaAs;lnaAs;dAs;dTs;dGs;d5mCs;d5mCs;dGs;dAs;dGs;d5mCs;lnaCs;lnaTs;lnaG-Sup	187506
APOA1-56 m01	CTTCACTCGAT CCCA	lnaCs;lnaTs;lnaTs;d5mCs;dAs;d5mCs;dTs;d5mCs;dGs;dAs;dTs;d5mCs;lnaCs;lnaCs;lnaA-Sup	187507
APOA1-57 m01	GTCCTTCACTC GATC	lnaGs;lnaTs;lnaCs;d5mCs;dTs;dTs;d5mCs;dAs;d5mCs;dTs;d5mCs;dGs;lnaAs;lnaTs;lnaC-Sup	187508
APOA1-58 m01	GGTCCTTCACT CGAT	lnaGs;lnaGs;lnaTs;d5mCs;d5mCs;dTs;dTs;d5mCs;dAs;d5mCs;dTs;d5mCs;lnaGs;lnaAs;lnaT-Sup	187509
APOA1-59 m01	GCCGCTGTCTT TGAG	lnaGs;lnaCs;lnaCs;dGs;d5mCs;dTs;dGs;dTs;d5mCs;dTs;dTs;dTs;lnaGs;lnaAs;lnaG-Sup	187510
APOA1-60 m01	CATAGTCTCTG CCGC	lnaCs;lnaAs;lnaTs;dAs;dGs;dTs;d5mCs;dTs;d5mCs;dTs;dGs;d5mCs;lnaCs;lnaGs;lnaC-Sup	187511
APOA1-61 m01	GCGGAGCCTTC AAAC	lnaGs;lnaCs;lnaGs;dGs;dAs;dGs;d5mCs;d5mCs;dTs;dTs;d5mCs;dAs;lnaAs;lnaAs;lnaC-Sup	187512
APOA1-62 m01	AAGTCGTCCAG GTAG	lnaAs;lnaAs;lnaGs;dTs;d5mCs;dGs;dTs;d5mCs;d5mCs;dAs;dGs;dGs;lnaTs;lnaAs;lnaG-Sup	187513
APOA1-63 m01	CTCTTGACAGCT CGTG	lnaCs;lnaTs;lnaCs;dTs;dTs;dGs;d5mCs;dAs;dGs;d5mCs;dTs;d5mCs;lnaGs;lnaTs;lnaG-Sup	187514
APOA1-64 m01	GTCGCGCATCT CCTC	lnaGs;lnaTs;lnaCs;dGs;d5mCs;dGs;d5mCs;dAs;dTs;d5mCs;dTs;d5mCs;lnaCs;lnaTs;lnaC-Sup	187515
APOA1-65 m01	CAGCGCGTCCA CATG	lnaCs;lnaAs;lnaGs;d5mCs;dGs;d5mCs;dGs;dTs;d5mCs;d5mCs;dAs;d5mCs;lnaAs;lnaTs;lnaG-Sup	187516
APOA1-66 m01	GCTCGTCGCTG TAGG	lnaGs;lnaCs;lnaTs;d5mCs;dGs;dTs;d5mCs;dGs;d5mCs;dTs;dGs;dTs;lnaAs;lnaGs;lnaG-Sup	187517
APOA1-67 m01	CCGCCGTTCTC CTTG	lnaCs;lnaCs;lnaGs;d5mCs;d5mCs;dGs;dTs;dTs;d5mCs;dTs;d5mCs;d5mCs;lnaTs;lnaTs;lnaG-Sup	187518
APOA1-68 m01	CTTGGCGTGGT ACTC	lnaCs;lnaTs;lnaTs;dGs;dGs;d5mCs;dGs;dTs;dGs;dGs;dTs;dAs;lnaCs;lnaTs;lnaC-Sup	187519
APOA1-69 m01	CAGATGCTCGG TGGC	lnaCs;lnaAs;lnaGs;dAs;dTs;dGs;d5mCs;dTs;d5mCs;dGs;dGs;dTs;lnaGs;lnaGs;lnaC-Sup	187520
APOA1-70 m01	GTGTACTCCTC GAGA	lnaGs;lnaTs;lnaGs;dTs;dAs;d5mCs;dTs;d5mCs;d5mCs;dTs;d5mCs;dGs;lnaAs;lnaGs;lnaA-Sup	187521

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

SEQ ID	Chrom	Gene	Chr. Start	Chr. End	Strand
1	chr11	APOA1	116694468	116720338	-
2	chr11	APOA1	116694468	116720338	+
3	chr4	Abca1	53031660	53184767	-
4	chr4	Abca1	53031660	53184767	+
5	chr9	ABCA1	107531283	107702527	-

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SEQ ID	Chrom	Gene	Chr. Start	Chr. End	Strand
6	chr9	ABCA1	107531283	107702527	+
7	chr9	Apoa1	46024712	46050549	+
8	chr9	Apoa1	46024712	46050549	-
9	chr11	APOA1	116703452	116703490	-
10	chr11	APOA1	116716006	116716043	-
11	chr9	ABCA1	107544853	107544898	-
12	chr9	ABCA1	107545317	107545373	-
13	chr9	ABCA1	107549175	107549221	-
14	chr9	ABCA1	107550274	107550320	-
15	chr9	ABCA1	107550704	107550746	-
16	chr9	ABCA1	107550769	107550815	-
17	chr9	ABCA1	107553424	107553449	-
18	chr9	ABCA1	107555135	107555180	-
19	chr9	ABCA1	107559478	107559514	-
20	chr9	ABCA1	107562144	107562189	-
21	chr9	ABCA1	107562811	107562856	-
22	chr9	ABCA1	107564383	107564429	-
23	chr9	ABCA1	107564542	107564589	-
24	chr9	ABCA1	107565573	107565597	-
25	chr9	ABCA1	107566955	107566997	-
26	chr9	ABCA1	107567799	107567822	-
27	chr9	ABCA1	107568594	107568642	-
28	chr9	ABCA1	107570966	107571012	-
29	chr9	ABCA1	107571761	107571807	-
30	chr9	ABCA1	107572492	107572538	-
31	chr9	ABCA1	107573100	107573151	-
32	chr9	ABCA1	107574024	107574054	-
33	chr9	ABCA1	107574852	107574906	-
34	chr9	ABCA1	107574906	107574968	-
35	chr9	ABCA1	107576399	107576466	-
36	chr9	ABCA1	107576708	107576754	-
37	chr9	ABCA1	107578270	107578349	-
38	chr9	ABCA1	107578369	107578447	-
39	chr9	ABCA1	107582257	107582303	-
40	chr9	ABCA1	107583704	107583756	-
41	chr9	ABCA1	107584821	107584867	-
42	chr9	ABCA1	107590239	107590277	-
43	chr9	ABCA1	107590789	107590834	-
44	chr9	ABCA1	107591342	107591392	-

SEQ ID	Chrom	Gene	Chr. Start	Chr. End	Strand
45	chr9	ABCA1	107593256	107593298	-
46	chr9	ABCA1	107593396	107593433	-
47	chr9	ABCA1	107593922	107593967	-
48	chr9	ABCA1	107594977	107595047	-
49	chr9	ABCA1	107596375	107596423	-
50	chr9	ABCA1	107597784	107597829	-
51	chr9	ABCA1	107597907	107597985	-
52	chr9	ABCA1	107602215	107602260	-
53	chr9	ABCA1	107602653	107602701	-
54	chr9	ABCA1	107613685	107613749	-
55	chr9	ABCA1	107615130	107615165	-
56	chr9	ABCA1	107620268	107620352	-
57	chr9	ABCA1	107620400	107620445	-
58	chr9	ABCA1	107624149	107624175	-
59	chr9	ABCA1	107625349	107625393	-
60	chr9	ABCA1	107632152	107632259	-
61	chr9	ABCA1	107640145	107640188	-
62	chr9	ABCA1	107648733	107648779	-
63	chr9	ABCA1	107651606	107651651	-
64	chr9	ABCA1	107651838	107651884	-
65	chr9	ABCA1	107654768	107654818	-
66	chr9	ABCA1	107656823	107656846	-
67	chr9	ABCA1	107663411	107663449	-
68	chr9	ABCA1	107664297	107664344	-
69	chr9	ABCA1	107666346	107666399	-
70	chr9	ABCA1	107666418	107666515	-
71	chr9	ABCA1	107669296	107669353	-
72	chr9	ABCA1	107669453	107669501	-
73	chr9	ABCA1	107669654	107669754	-
74	chr9	ABCA1	107669789	107669837	-
75	chr9	ABCA1	107688863	107688904	-
76	chr9	ABCA1	107689641	107689696	-
77	chr9	ABCA1	107689892	107689938	-
78	chr9	ABCA1	107690078	107690126	-
79	chr9	ABCA1	107690345	107690386	-
80	chr11	APOA1	116701452	116705490	-
81	chr11	ABCA1	116714006	116718043	-
82	chr9	ABCA1	107542853	107546898	-
83	chr9	ABCA1	107543317	107547373	-

SEQ ID	Chrom	Gene	Chr. Start	Chr. End	Strand
84	chr9	ABCA1	107547175	107551221	-
85	chr9	ABCA1	107548274	107552320	-
86	chr9	ABCA1	107548704	107552746	-
87	chr9	ABCA1	107548769	107552815	-
88	chr9	ABCA1	107551424	107555449	-
89	chr9	ABCA1	107553135	107557180	-
90	chr9	ABCA1	107557478	107561514	-
91	chr9	ABCA1	107560144	107564189	-
92	chr9	ABCA1	107560811	107564856	-
93	chr9	ABCA1	107562383	107566429	-
94	chr9	ABCA1	107562542	107566589	-
95	chr9	ABCA1	107563573	107567597	-
96	chr9	ABCA1	107564955	107568997	-
97	chr9	ABCA1	107565799	107569822	-
98	chr9	ABCA1	107566594	107570642	-
99	chr9	ABCA1	107568966	107573012	-
100	chr9	ABCA1	107569761	107573807	-
101	chr9	ABCA1	107570492	107574538	-
102	chr9	ABCA1	107571100	107575151	-
103	chr9	ABCA1	107572024	107576054	-
104	chr9	ABCA1	107572852	107576906	-
105	chr9	ABCA1	107572906	107576968	-
106	chr9	ABCA1	107574399	107578466	-
107	chr9	ABCA1	107574708	107578754	-
108	chr9	ABCA1	107576270	107580349	-
109	chr9	ABCA1	107576369	107580447	-
110	chr9	ABCA1	107580257	107584303	-
111	chr9	ABCA1	107581704	107585756	-
112	chr9	ABCA1	107582821	107586867	-
113	chr9	ABCA1	107588239	107592277	-
114	chr9	ABCA1	107588789	107592834	-
115	chr9	ABCA1	107589342	107593392	-
116	chr9	ABCA1	107591256	107595298	-
117	chr9	ABCA1	107591396	107595433	-
118	chr9	ABCA1	107591922	107595967	-
119	chr9	ABCA1	107592977	107597047	-
120	chr9	ABCA1	107594375	107598423	-
121	chr9	ABCA1	107595784	107599829	-
122	chr9	ABCA1	107595907	107599985	-

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SEQ ID	Chrom	Gene	Chr. Start	Chr. End	Strand
123	chr9	ABCA1	107600215	107604260	-
124	chr9	ABCA1	107600653	107604701	-
125	chr9	ABCA1	107611685	107615749	-
126	chr9	ABCA1	107613130	107617165	-
127	chr9	ABCA1	107618268	107622352	-
128	chr9	ABCA1	107618400	107622445	-
129	chr9	ABCA1	107622149	107626175	-
130	chr9	ABCA1	107623349	107627393	-
131	chr9	ABCA1	107630152	107634259	-
132	chr9	ABCA1	107638145	107642188	-
133	chr9	ABCA1	107646733	107650779	-
134	chr9	ABCA1	107649606	107653651	-
135	chr9	ABCA1	107649838	107653884	-
136	chr9	ABCA1	107652768	107656818	-
137	chr9	ABCA1	107654823	107658846	-
138	chr9	ABCA1	107661411	107665449	-
139	chr9	ABCA1	107662297	107666344	-
140	chr9	ABCA1	107664346	107668399	-
141	chr9	ABCA1	107664418	107668515	-
142	chr9	ABCA1	107667296	107671353	-
143	chr9	ABCA1	107667453	107671501	-
144	chr9	ABCA1	107667654	107671754	-
145	chr9	ABCA1	107667789	107671837	-
146	chr9	ABCA1	107686863	107690904	-
147	chr9	ABCA1	107687641	107691696	-
148	chr9	ABCA1	107687892	107691938	-
149	chr9	ABCA1	107688078	107692126	-
150	chr9	ABCA1	107688345	107692386	-
151	chr11	APOA1	116707870	116707947	+
152	chr11	APOA1	116714416	116714458	+
153	chr11	APOA1	116714536	116714578	+
154	chr11	APOA1	116714762	116714821	+
155	chr9	ABCA1	107535234	107535273	+
156	chr9	ABCA1	107544880	107544926	+
157	chr9	ABCA1	107547830	107547871	+
158	chr9	ABCA1	107555512	107555554	+
159	chr9	ABCA1	107565561	107565603	+
160	chr9	ABCA1	107573103	107573142	+
161	chr9	ABCA1	107599184	107599234	+

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SEQ ID	Chrom	Gene	Chr. Start	Chr. End	Strand
162	chr9	ABCA1	107601126	107601170	+
163	chr9	ABCA1	107607774	107607819	+
164	chr9	ABCA1	107613720	107613783	+
165	chr9	ABCA1	107623957	107624003	+
166	chr9	ABCA1	107630025	107630076	+
167	chr9	ABCA1	107631197	107631265	+
168	chr9	ABCA1	107633948	107633996	+
169	chr9	ABCA1	107648816	107648890	+
170	chr9	ABCA1	107650500	107650558	+
171	chr9	ABCA1	107665550	107665591	+
172	chr9	ABCA1	107666033	107666073	+
173	chr11	APOA1	116705870	116709947	+
174	chr11	APOA1	116712416	116716458	+
175	chr11	APOA1	116712536	116716578	+
176	chr11	APOA1	116712762	116716821	+
177	chr9	ABCA1	107533234	107537273	+
178	chr9	ABCA1	107542880	107546926	+
179	chr9	ABCA1	107545830	107549871	+
180	chr9	ABCA1	107553512	107557554	+
181	chr9	ABCA1	107563561	107567603	+
182	chr9	ABCA1	107571103	107575142	+
183	chr9	ABCA1	107597184	107601234	+
184	chr9	ABCA1	107599126	107603170	+
185	chr9	ABCA1	107605774	107609819	+
186	chr9	ABCA1	107611720	107615783	+
187	chr9	ABCA1	107621957	107626003	+
188	chr9	ABCA1	107628025	107632076	+
189	chr9	ABCA1	107629197	107633265	+
190	chr9	ABCA1	107631948	107635996	+
191	chr9	ABCA1	107646816	107650890	+
192	chr9	ABCA1	107648500	107652558	+
193	chr9	ABCA1	107663550	107667591	+
194	chr9	ABCA1	107664033	107668073	+

Single Strand Oligonucleotides (Antisense Strand of Target Gene)

SeqID range: 195-120357

5 SeqIDs w/o G Runs:

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195-211, 225-291, 304-393, 410-413, 426-428, 440-471, 485-805, 819-907, 920-1059, 1074-1087, 1102-1457, 1478-1484, 1506-1575, 1601-1664, 1678-1707, 1738-1747, 1761-1779, 1793-1798, 1847-1864, 1878-1881, 1896-2022, 2048-2069, 2083-2087, 2110-2176, 2191-2193, 2208-2356, 2379-2441, 2456-2475, 2489-2515, 2543-2554, 2568-2631, 2645-2649, 2663-2759, 2774-2782, 2796-2819, 2833-2928, 2942-2999, 3005-3032, 3034-3079, 3093-3111, 3126-3191, 3205-3206, 3252-3340, 3355-3434, 3462-3582, 3596-3638, 3652-3951, 3965-3967, 3989-4002, 4018-4066, 4080-4126, 4141-4341, 4355-4535, 4549-4597, 4612-4626, 4640-4661, 4675-4702, 4715-4832, 4838-4847, 4867-4979, 4993-5124, 5138-5410, 5424-5430, 5445-5508, 5523-5524, 5539-5569, 5583-5585, 5599-5606, 5625-5628, 5643-5960, 5975-6043, 6065-6087, 6102-6245, 6259-6322, 6331-6340, 6363-6407, 6430-6433, 6452-6648, 6662-6898, 6912-6979, 6993-7038, 7052-7060, 7074-7128, 7142-7204, 7218-7224, 7238-7282, 7296-7298, 7312-7340, 7355-7366, 7380-7447, 7461-7490, 7504-7626, 7640-8113, 8127-8184, 8198-8292, 8306-8401, 8415-8450, 8464-8599, 8614-8620, 8634-8972, 8987-9619, 9657-9753, 9767-9775, 9796-9877, 9891-9903, 9917-9945, 9959-10050, 10064-10388, 10390-10449, 10463-10662, 10676-10738, 10759-10762, 10776-10904, 10919-10946, 10960-10982, 10996-11315, 11329-11334, 11348-11357, 11382-11391, 11405-11419, 11445-11471, 11486-11594, 11608-11701, 11715-11746, 11760-11761, 11775-11854, 11869-12122, 12136-12317, 12331-12564, 12578-12829, 12844-13071, 13105-13168, 13183-13193, 13207-13382, 13396-13419, 13434-13449, 13463-13470, 13484-13762, 13776-13973, 13987-14023, 14037-14038, 14052-14213, 14232-14336, 14350-14353, 14367-14407, 14421-14436, 14450-14533, 14558-14607, 14622-14624, 14640-14871, 14886-15023, 15033-15055, 15065-15083, 15096-15166, 15174-15195, 15209-15322, 15337-15354, 15368-15399, 15413-15537, 15552-15577, 15591-15813, 15828-15900, 15914-16035, 16051-16144, 16158-16186, 16211-16535, 16572-16703, 16718-16765, 16780-16868, 16895-17140, 17155-17301, 17315-17404, 17418-17578, 17592-17702, 17716-17777, 17791-18138, 18152-18255, 18269-18320, 18335-18348, 18362-18470, 18484-18583, 18598-18637, 18642-18656, 18671-18696, 18706-18708, 18730-18747, 18761-18775, 18792-18805, 18814-19044, 19058-19229, 19243-19346, 19360-19378, 19392-19516, 19539-19667, 19681-19733, 19748-19971, 19983-20019, 20033-20059, 20071-20191, 20205-20310, 20317-20322, 20344-20521, 20535-20649, 20663-20945, 20954-20956, 20970-20980, 20994-21046, 21051-21097, 21112-21149, 21157-21167, 21189-21231, 21246-21345, 21359-21739, 21766-22118, 22132-22260, 22281-22323, 22337-22403, 22421-23228, 23242-23268, 23293-23358, 23372-23450, 23465-23600, 23603-23733, 23748-23955, 23969-24132, 24143-24179, 24193-24208, 24218-24291, 24307-24310, 24324-24359, 24373-24425, 24439-24467, 24482-24506, 24520-24522, 24536-24554, 24568-24629, 24644-24670, 24684-24781, 24795-24890, 24904-24983, 24997-25037, 25051-25077, 25091-25163, 25177-25483, 25497-25554, 25569-25651, 25676-25778, 25794-25806, 25821-25832, 25846-25990, 26004-26085, 26093-26111, 26119-26156, 26170-26213, 26220-26231, 26244-26288, 26311-26368, 26383-26404, 26419-26585, 26599-26640, 26654-26693, 26708, 26722-26727, 26741-26762, 26777-26871, 26885-27097, 27111-27116, 27130-27277, 27301-27454, 27468-27638, 27652-27717, 27732-27758, 27772-27780, 27794-27833, 27850-27912, 27926-28007, 28021-28201, 28215-28337, 28351-28551, 28565-

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DEMANDE OU BREVET VOLUMINEUX

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CLAIMS

What is claimed is:

1. A single stranded oligonucleotide having a sequence 5'-X-Y-Z, wherein X is any nucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a seed
5 sequence of a human microRNA, and Z is a nucleotide sequence of 1-23 nucleotides in length, wherein the single stranded oligonucleotide is complementary with at least 8 consecutive nucleotides of a PRC2-associated region of an APOA1 gene or an ABCA1 gene.
2. The single stranded oligonucleotide of claim 1, wherein the oligonucleotide does not comprise three or more consecutive guanosine nucleotides.
- 10 3. The single stranded oligonucleotide of any one of claim claim 1 or 2, wherein the oligonucleotide does not comprise four or more consecutive guanosine nucleotides.
4. The single stranded oligonucleotide of any one of claims 1 to 3, wherein the oligonucleotide is 8 to 30 nucleotides in length.
5. The single stranded oligonucleotide of any one of claims 1 to 3, wherein the
15 oligonucleotide is 8 to 10 nucleotides in length and all but 1, 2, or 3 of the nucleotides of the complementary sequence of the PRC2-associated region are cytosine or guanosine nucleotides.
6. The single stranded oligonucleotide of any one of claims 1 to 5, wherein at least one nucleotide of the oligonucleotide is a nucleotide analogue.
- 20 7. The single stranded oligonucleotide of claim 6, wherein the at least one nucleotide analogue results in an increase in T_m of the oligonucleotide in a range of 1 to 5 °C compared with an oligonucleotide that does not have the at least one nucleotide analogue.
8. The single stranded oligonucleotide of any one of claims 1 to 7, wherein at least one nucleotide of the oligonucleotide comprises a 2' O-methyl.
- 25 9. The single stranded oligonucleotide of any one of claims 1 to 8, wherein each nucleotide of the oligonucleotide comprises a 2' O-methyl.

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10. The single stranded oligonucleotide of any one of claims 1 to 8, wherein the oligonucleotide comprises at least one ribonucleotide, at least one deoxyribonucleotide, or at least one bridged nucleotide.

11. The single strand oligonucleotide of claim 10, wherein the bridged nucleotide
5 is a LNA nucleotide, a cEt nucleotide or a ENA modified nucleotide.

12. The single stranded oligonucleotide of any one of claims 1 to 6, wherein each nucleotide of the oligonucleotide is a LNA nucleotide.

13. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-fluoro-
10 deoxyribonucleotides.

14. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-O-methyl nucleotides.

15. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the
15 nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and ENA nucleotide analogues.

16. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and LNA nucleotides.

17. The single stranded oligonucleotide of any one of claims 13 to 16, wherein the
20 5' nucleotide of the oligonucleotide is a deoxyribonucleotide.

18. The single stranded oligonucleotide of any one of claims 1 to 7, wherein the nucleotides of the oligonucleotide comprise alternating LNA nucleotides and 2'-O-methyl nucleotides.

19. The single stranded oligonucleotide of claim 18, wherein the 5' nucleotide of
25 the oligonucleotide is a LNA nucleotide.

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20. The single stranded oligonucleotide of any one of claims 1 to 8, wherein the nucleotides of the oligonucleotide comprise deoxyribonucleotides flanked by at least one LNA nucleotide on each of the 5' and 3' ends of the deoxyribonucleotides.

21. The single stranded oligonucleotide of any one of claims 1 to 20, further comprising phosphorothioate internucleotide linkages between at least two nucleotides.

22. The single stranded oligonucleotide of claim 21, further comprising phosphorothioate internucleotide linkages between all nucleotides.

23. The single stranded oligonucleotide of any one of claims 1 to 22, wherein the nucleotide at the 3' position of the oligonucleotide has a 3' hydroxyl group.

24. The single stranded oligonucleotide of any one of claims 1 to 22, wherein the nucleotide at the 3' position of the oligonucleotide has a 3' thiophosphate.

25. The single stranded oligonucleotide of any one of claims 1 to 24, further comprising a biotin moiety conjugated to the 5' nucleotide.

26. A single stranded oligonucleotide comprising a region of complementarity that is complementary with at least 8 consecutive nucleotides of a PRC2-associated region of an APOA1 gene or an ABCA1 gene, wherein the oligonucleotide has at least one of:

a) a sequence that is 5'X-Y-Z, wherein X is any nucleotide and wherein X is anchored at the 5' end of the oligonucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a human seed sequence of a microRNA, and Z is a nucleotide sequence of 1 to 23 nucleotides in length;

b) a sequence that does not comprise three or more consecutive guanosine nucleotides;

c) a sequence that has less than a threshold level of sequence identity with every sequence of nucleotides, of equivalent length to the second nucleotide sequence, that are between 50 kilobases upstream of a 5'-end of an off-target gene and 50 kilobases downstream of a 3'-end of the off-target gene;

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d) a sequence that is complementary to a PRC2-associated region that encodes an RNA that forms a secondary structure comprising at least two single stranded loops; and/or

e) a sequence that has greater than 60% G-C content.

27. The single stranded oligonucleotide of claim 26, wherein the oligonucleotide
5 has the sequence 5'X-Y-Z and wherein the oligonucleotide is 8-50 nucleotides in length.

28. A composition comprising a single stranded oligonucleotide of any one of claims 1 to 27 and a carrier.

29. A composition comprising a single stranded oligonucleotide of any one of claims 1 to 27 in a buffered solution.

10 30. A composition of claim 28, wherein the oligonucleotide is conjugated to the carrier.

31. The composition of claim 30, wherein the carrier is a peptide.

32. The composition of claim 30, wherein the carrier is a steroid.

15 33. A pharmaceutical composition comprising a composition of any one of claims 28 to 32 and a pharmaceutically acceptable carrier.

34. A kit comprising a container housing the composition of any one of claims 28 to 33.

20 35. A method of increasing expression of an APOA1 gene or an ABCA1 gene in a cell, the method comprising delivering the single stranded oligonucleotide of any one of claims 1 to 25 into the cell.

36. The method of claim 35, wherein delivery of the single stranded oligonucleotide into the cell results in a level of expression of the APOA1 gene or the ABCA1 gene that is at least 50% greater than a level of expression of APOA1 or ABCA1 in a control cell that does not comprise the single stranded oligonucleotide.

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37. A method increasing levels of an APOA1 gene or an ABCA1 gene in a subject, the method comprising administering the single stranded oligonucleotide of any one of claims 1 to 27 to the subject.

38. A method of treating a condition associated with decreased levels of an
5 APOA1 gene or an ABCA1 gene in a subject, the method comprising administering the single stranded oligonucleotide of any one of claims A1 to A36to the subject.

39. The method of claim 38, wherein the condition is dyslipidemia or atherosclerosis.