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(57) Abstract: Nucleic acid products and compositions and their uses are provided. In particular, nucleic acid products are provided that modulate, interfere with, or inhibit APOC3 gene expression. The products can be oligomeric compounds that comprise at least a first region of linked nucleosides having at least a first nucleobase sequence that is at least partially complementary to at least a portion of RNA transcribed from a APOC3 gene, wherein said first nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs 1 to 39.

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Products and compositions

Cross Reference to Related Patent Applications

This application claims the benefit of and priority to two U.S. Provisional Patent Applications, Nos. 63/214,608, filed June 24, 2021, and 63/318,287, filed March 9, 2022, the contents of which are incorporated herein by reference in their entirety.

Field

Nucleic acid products and compositions, and their uses, that modulate, in particular interfere with, or inhibit, apolipoprotein C3 (APOC3) gene expression are provided. Specific embodiments provide methods, compounds, and compositions for reducing expression of APOC3 mRNA and protein in an animal. Such methods, compounds, and compositions are useful to treat, prevent, or ameliorate APOC3-associated disorders such as dyslipidemia, hypertriglyceridemia, hyperchylomicronemia, and atherosclerotic cardiovascular disease (ASCVD).

Background

Triglycerides are esters of glycerol with three fatty acids. They serve as storage of fat and energy and are transported via the bloodstream. Excess level of blood triglycerides have been recognized early on as causative agents or bystanders of a range of disorders. More recent evidence suggests a causative role, partly in conjunction with elevated levels of cholesterol (in particular LDL cholesterol) in ASCVD and disorders subsumed under this term or associated therewith. A more comprehensive list of disorders associated with elevated levels of triglycerides is given in the embodiments disclosed further below.

Apolipoprotein C3 is secreted by the liver and the small intestine. It can be found on triglyceride-rich lipoproteins including very low density lipoproteins (VLDL) and chylomicrons. It is involved in the negative regulation of lipid catabolism, especially triglyceride catabolism, and of the clearance of VLDL, LDL and HDL lipoproteins. A molecular function of APOC3 is the inhibition of lipoprotein lipase and of hepatic lipase.

Disease

Abnormal amounts of circulating triglycerides, also referred to as hypertriglyceridemia, is a recognized disorder in itself which is inter alia owed to the fact that such abnormal amounts, in particular if they persist over extended periods of time, may entail disorders of the cardiovascular system and/or inflammation.

Treatment

Established treatments include the administration of statins such as Rosuvastatin and Simvastatin as well as of fibrates such as fenofibrate. However, statins may cause side effects, and certain patients are statin-intolerant.

There therefore remains a need for therapies to treat APOC3-associated diseases. We, therefore, aim to provide compounds, methods, and pharmaceutical compositions for the treatment of such diseases.

Double-stranded RNA (dsRNA) able to complementarily bind expressed mRNA has been shown to be able to block gene expression (Fire et al., 1998, Nature. 1998 Feb 19;391 (6669):806-1 1 and Elbashir et at., 2001 , Nature. 2001 May 24;41 1 (6836):494-8) by a mechanism that has been termed RNA interference (RNAi). Short dsRNAs direct gene-specific, post-transcriptional silencing in many organisms, including vertebrates, and have become a useful tool for studying gene function. RNAi is

mediated by the RNA-induced silencing complex (RISC), a sequence-specific, multi-component nuclease that destroys messenger RNAs homologous to the silencing trigger loaded into the RISC complex. Interfering RNA (iRNA) such as siRNAs, antisense RNA, and micro-RNA are oligonucleotides that prevent the formation of proteins by gene-silencing i.e. inhibiting gene translation of the protein through degradation of mRNA molecules. Gene-silencing agents are becoming increasingly important for therapeutic applications in medicine.

According to Watts and Corey in the Journal of Pathology (2012; Vol 226, p 365-379) there are algorithms that can be used to design nucleic acid silencing triggers, but all of these have severe limitations. It may take various experimental methods to identify potent siRNAs, as algorithms do not take into account factors such as tertiary structure of the target mRNA or the involvement of RNA binding proteins. Therefore the discovery of a potent nucleic acid silencing trigger with minimal off-target effects is a complex process. For the pharmaceutical development of these highly charged molecules it is necessary that they can be synthesised economically, distributed to target tissues, enter cells and function within acceptable limits of toxicity. An aim is to, therefore, provide compounds, methods, and pharmaceutical compositions for the treatment of thromboembolic diseases as described herein, which comprise oligomeric compounds that modulate, in particular inhibit, gene expression by RNAi.

Summary

Nucleic acid products are provided that modulate, in particular, interfere with or inhibit, apolipoprotein C3 (APOC3) gene expression, and associated therapeutic uses. Specific oligomeric compounds and sequences are described herein. This summary provides a simplified form that is further described below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to determine the scope of the claimed subject matter.

Brief description of the drawings

Figure 1a shows dose curves of APOC3 leads for candidates in primary human hepatocytes;

Figure 1b shows dose curves of APOC3 leads for Humanized mouse study in primary human hepatocytes;

Figure 2 shows a timeline including the time point of applying the dose to the mice and time points for taking samples;

Figure 3 shows remaining liver APOC3 mRNA and plasma APOC3 protein levels for the animals treated with APOC3-targeting mxRNA constructs as compared to the control animals;

Figure 4 shows serum triglycerides and total cholesterol in the serum of the animals treated with APOC3-targeting mxRNA constructs as compared to the control (PBS);

Figure 5a shows a Mean Percent of remaining APOC3 mRNA in liver tissues in plasma measured using ELISA for the animals treated with APOC3-targeting mxRNA constructs (10mg/kg) as compared to the control animals;

Figure 5b shows APOC3 protein levels in plasma measured using ELISA for the animals treated with APOC3-targeting mxRNA constructs (10mg/kg) as compared to the control animals;

Figure 6a shows the mean percent of triglycerides (TG) in the serum of the animals treated with APOC3 targeting mxRNA constructs as compared to the control animals at weeks 2 and 6;

Figure 6b shows the total cholesterol (TC) level in serum of animals treated with APOC3 targeting mxRNA constructs as compared to the control animals at weeks 2 and 6;

Figure 7 prevents a schematic overview of the duration study performed with compound A28(14-4)mF (also designated STP125G) in mice with a humanized liver;

Figure 8a shows APOC3 mRNA as a function of time as observed in the duration study between control and treatment groups;

Figure 8b shows APOC3 protein knockdown as a function of time as observed in the duration study between control and treatment groups;

Figure 9a show serum triglyceride levels as a function of time between control and treatment groups;

Figure 9b show serum total cholesterol levels as a function of time between control and treatment groups; and

Figure 10 illustrates the humanized liver of the mice used for the duration study.

Detailed Description and Embodiments

The following are non-limiting aspects:

Aspect 1. An oligomeric compound capable of inhibiting expression of APOC3, wherein said compound comprises at least a first region of linked nucleosides having at least a first nucleobase sequence that is at least partially complementary to at least a portion of RNA transcribed from a APOC3 gene, wherein said first nucleobase sequence is selected from the following sequences, or a portion thereof: sequences of SEQ ID NOs 1 to 391, wherein said portion preferably has a length of at least 18 nucleotides.

Particularly preferred embodiments relate to mxRNAs: for further details see the embodiments and their discussion further below.

In addition, the antisense and sense regions disclosed herein may serve as building blocks for compounds which are directed to multiple targets. The general architecture of such compound ds is described in WO2020/065602.

Furthermore, and as disclosed further below, the disclosed embodiments also relate to double-stranded RNAs (dsRNAs). In contrast to an mxRNA, which has a hairpin-like structure connecting the sense and antisense RNA strands, a dsRNA lacks the hairpin loop and, therefore, dsRNA comprises two strands.

Aspect 2. A composition comprising an oligomeric compound according to aspect 1, and a physiologically acceptable excipient.

Aspect 3. A pharmaceutical composition comprising an oligomeric compound according to aspect 1.

Aspect 4. An oligomeric compound according to aspect 1, for use in human or veterinary medicine or therapy.

Aspect 5. An oligomeric compound according to aspect 1, for use in a method of treating a disease or disorder.

Aspect 6. A method of treating a disease or disorder comprising administration of an oligomeric compound according to aspect 1, to an individual in need of treatment.

Aspect 7. Use of an oligomeric compound according to aspect 1, for use in research as a gene function analysis tool.

Aspect 8. Use of an oligomeric compound according to aspect 1 in the manufacture of a medicament for a treatment of a disease or disorder.

Further embodiments are described below by way of example only. These examples represent the best ways of putting the disclosed embodiments into practice that are currently known to the applicant, although they are not the only ways in which this could be achieved.

It will be understood that the benefits and advantages described herein may relate to one embodiment or may relate to several embodiments. The embodiments are not limited to those that solve any or all of the stated problems or those that have any or all of the stated benefits and advantages.

Features of different aspects and embodiments as described herein may be combined as appropriate, as would be apparent to a skilled person, and may be combined with any other aspects.

Definitions

The following definitions pertain to the disclosed embodiments throughout. In many instances, the definitions, in addition to the respective definition as such, provide non-exhaustive listings of possible implementations, which amount to preferred embodiments.

Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical synthesis, and chemical analysis. Certain such techniques and procedures may be found for example in "Carbohydrate Modifications in Antisense Research" Edited by Sangvi and Cook, American Chemical Society , Washington D.C., 1994; "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., 21st edition, 2005; and "Antisense Drug Technology, Principles, Strategies, and Applications" Edited by Stanley T. Crooke, CRC Press, Boca Raton, Florida; and Sambrook et al., "Molecular Cloning, A laboratory Manual," 2nd Edition, Cold Spring Harbor Laboratory Press, 1989, which are hereby incorporated by reference for any purpose. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

Unless otherwise indicated, the following terms have the following meanings:

As used herein, "excipient" means any compound or mixture of compounds that is added to a composition as provided herein that is suitable for delivery of an oligomeric compound.

As used herein, "nucleoside" means a compound comprising a nucleobase moiety and a sugar moiety. Nucleosides include, but are not limited to, naturally occurring nucleosides (as found in DNA and RNA) and modified nucleosides. Nucleosides may be linked to a phosphate moiety, phosphate-linked nucleosides also being referred to as "nucleotides".

As used herein, "chemical modification" or "chemically modified" means a chemical difference in a compound when compared to a naturally occurring counterpart. Chemical modifications of oligonucleotides include nucleoside modifications (including sugar moiety modifications and nucleobase modifications) and internucleoside linkage modifications. In reference to an oligonucleotide, chemical modification does not include differences only in nucleobase sequence.

As used herein, "furanosyl" means a structure comprising a 5-membered ring comprising four carbon atoms and one oxygen atom.

As used herein, "naturally occurring sugar moiety" means a ribofuranosyl as found in naturally occurring RNA or a deoxyribofuranosyl as found in naturally occurring DNA. A "naturally occurring sugar moiety" as referred to herein is also termed as an "unmodified sugar moiety". In particular, such a "naturally occurring sugar moiety" or an "unmodified sugar moiety" as referred to herein has a -H (DNA sugar moiety) or –OH (RNA sugar moiety) at the 2'-position of the sugar moiety, especially a -H (DNA sugar moiety) at the 2'-position of the sugar moiety.

As used herein, "sugar moiety" means a naturally occurring sugar moiety or a modified sugar moiety of a nucleoside. As used herein, "modified sugar moiety" means a substituted sugar moiety or a sugar surrogate.

As used herein, "substituted sugar moiety" means a furanosyl that has been substituted. Substituted sugar moieties include, but are not limited to furanosyls comprising substituents at the 2'-position, the 3'-position, the 5'-position and / or the 4'-position. Certain substituted sugar moieties are bicyclic sugar moieties.

As used herein, "2'-substituted sugar moiety" means a furanosyl comprising a substituent at the 2'-position other than H or OH. Unless otherwise indicated, a 2'-substituted sugar moiety is not a bicyclic sugar moiety (i.e., the 2' -substituent of a 2'-substituted sugar moiety does not form a bridge to another atom of the furanosyl ring).

As used herein, "MOE" means $-OCH_2CH_2OCH_3$.

As used herein, "2'-F nucleoside" refers to a nucleoside comprising a sugar comprising fluorine at the 2' position. Unless otherwise indicated, the fluorine in a 2'-F nucleoside is in the ribo position (replacing the OH of a natural ribose). Duplexes of uniformly modified 2'-fluorinated (ribo) oligonucleotides hybridized to RNA strands are not RNase H substrates while the ara analogs retain RNase H activity.

As used herein the term "sugar surrogate" means a structure that does not comprise a furanosyl and that is capable of replacing the naturally occurring sugar moiety of a nucleoside, such that the resulting nucleoside sub-units are capable of linking together and / or linking to other nucleosides to form an oligomeric compound which is capable of hybridizing to a complementary oligomeric compound. Such structures include rings comprising a different number of atoms than furanosyl (*e.g.*, 4, 6, or 7-membered rings); replacement of the oxygen of a furanosyl with a non-oxygen atom (*e.g.*, carbon, sulfur, or nitrogen); or both a change in the number of atoms and a replacement of the oxygen. Such structures may also comprise substitutions corresponding to those described for substituted sugar moieties (*e.g.*, 6-membered carbocyclic bicyclic sugar surrogates optionally comprising additional substituents). Sugar surrogates also include more complex sugar replacements (*e.g.*, the non-ring systems of peptide nucleic acid). Sugar surrogates include without limitation morpholinos, cyclohexenyls and cyclohexitols.

As used herein, "bicyclic sugar moiety" means a modified sugar moiety comprising a 4 to 7 membered ring (including but not limited to a furanosyl) comprising a bridge connecting two atoms of the 4 to 7 membered ring to form a second ring, resulting in a bicyclic structure. In certain embodiments, the 4 to 7 membered ring is a sugar ring. In certain embodiments the 4 to 7 membered ring is a furanosyl. In certain such embodiments, the bridge connects the 2 '-carbon and the 4 '-carbon of the furanosyl.

As used herein, "nucleotide" means a nucleoside further comprising a phosphate linking group. As used herein, "linked nucleosides" may or may not be linked by phosphate linkages and thus includes, but is

not limited to "linked nucleotides." As used herein, "linked nucleosides" are nucleosides that are connected in a continuous sequence (*i.e.* no additional nucleosides are present between those that are linked).

As used herein, "nucleobase" means a group of atoms that can be linked to a sugar moiety to create a nucleoside that is capable of incorporation into an oligonucleotide, and wherein the group of atoms is capable of bonding, more specifically hydrogen bonding, with a complementary naturally occurring nucleobase of another oligonucleotide or nucleic acid. Nucleobases may be naturally occurring or may be modified.

As used herein the terms, "unmodified nucleobase" or "naturally occurring nucleobase" means the naturally occurring heterocyclic nucleobases of RNA or DNA: the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) (including 5-methyl C), and uracil (U).

As used herein, "modified nucleobase" means any nucleobase that is not a naturally occurring nucleobase.

As used herein, "modified nucleoside" means a nucleoside comprising at least one chemical modification compared to naturally occurring RNA or DNA nucleosides. Modified nucleosides can comprise a modified sugar moiety and / or a modified nucleobase.

As used herein, "bicyclic nucleoside" or "BNA" means a nucleoside comprising a bicyclic sugar moiety.

As used herein, "locked nucleic acid nucleoside" or "LNA" means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH_2-O-2'bridge.

As used herein, "2 '-substituted nucleoside" means a nucleoside comprising a substituent at the 2'-position of the sugar moiety other than H or OH. Unless otherwise indicated, a 2 '-substituted nucleoside is not a bicyclic nucleoside.

As used herein, "deoxynucleoside" means a nucleoside comprising 2'-H furanosyl sugar moiety, as found in naturally occurring deoxyribonucleosides (DNA). In certain embodiments, a 2'-deoxynucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (*e.g.*, uracil).

As used herein, "oligonucleotide" means a compound comprising a plurality of linked nucleosides. In certain embodiments, an oligonucleotide comprises one or more unmodified ribonucleosides (RNA) and / or unmodified deoxyribonucleosides (DNA) and / or one or more modified nucleosides.

As used herein, "modified oligonucleotide" means an oligonucleotide comprising at least one modified nucleoside and / or at least one modified internucleoside linkage.

Preferred modified internucleoside linkages are those which confer increased stability as compared to the naturally occurring phosphodiesters. "Stability" means, in particular, the stability against hydrolysis including enzyme-catalyzed hydrolysis, enzymes including exonucleases and endonucleases.

Preferred positions for such modified internucleoside linkages include the termini and the hairpin loop of single-stranded oligomeric compounds. For example, the internucleoside linkages connecting first and second nucleoside and second and third nucleoside counting from the 5' terminus, and/or the internucleoside linkages connecting first and second nucleoside and second and third nucleoside counting from the 3' terminus are modified. In addition, a linkage connecting the terminal nucleoside of the 3' terminus with a ligand, such as GalNAc, may be modified.

As discussed above, preferred positions are in the hairpin loop of said single-stranded oligomeric compounds. In particular, all linkages, all but one linkages or the majority of linkages in the hairpin loop are modified. As used herein, "linkages in the hairpin loop" designates the linkages between nucleosides which are not engaged in base pairing. For example, in a hairpin loop consisting of five nucleosides, there are four linkages between nucleosides which are not engaged in base pairing. Preferably, the term "linkages in the hairpin loop" also extends to the linkages connecting the stem to the loop, *i.e.*, those linkages which connect a base-paired nucleoside to a non-based paired nucleoside. Generally, there are two such positions in hairpins and mxRNAs as described herein.

Most preferred is that modified internucleoside linkages are at both termini and in the hairpin loop. As used herein, "linkage" or "linking group" means a group of atoms that link together two or more other groups of atoms.

As used herein "internucleoside linkage" means a covalent linkage between adjacent nucleosides in an oligonucleotide.

As used herein "naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage. As used herein, "modified internucleoside linkage" means any internucleoside linkage other than a naturally occurring internucleoside linkage. In particular, a "modified internucleoside linkage" as referred to herein can include a modified phosphorous linking group such as a phosphorothioate or phosphorodithioate internucleoside linkage.

As used herein, "terminal internucleoside linkage" means the linkage between the last two nucleosides of an oligonucleotide or defined region thereof.

As used herein, "phosphorus linking group" means a linking group comprising a phosphorus atom and can include naturally occurring phosphorous linking groups as present in naturally occurring RNA or DNA, such as phosphodiester linking groups, or modified phosphorous linking groups that are not generally present in naturally occurring RNA or DNA, such as phosphorothioate or phosphorodithioate linking groups. Phosphorus linking groups can therefore include without limitation, phosphodiester, phosphorothioate, phosphorodithioate, phosphonate, methylphosphonate, phosphoramidate, phosphorothioamidate, thionoalkylphosphonate, phosphotriesters, thionoalkylphosphotriester and boranophosphate.

As used herein, "internucleoside phosphorus linking group" means a phosphorus linking group that directly links two nucleosides.

As used herein, "oligomeric compound" means a polymeric structure comprising two or more substructures. In certain embodiments, an oligomeric compound comprises an oligonucleotide, such as a modified oligonucletide. In certain embodiments, an oligomeric compound further comprises one or more conjugate groups and / or terminal groups and / or ligands. In certain embodiments, an oligomeric compound consists of an oligonucleotide. In certain embodiments, an oligomeric compound comprises a backbone of one or more linked monomeric sugar moieties, where each linked monomeric sugar moiety is directly or indirectly attached to a heterocyclic base moiety. In certain embodiments, oligomeric compounds may also include monomeric sugar moieties that are not linked to a heterocyclic base moiety, thereby providing abasic sites. Oligomeric compounds may be defined in terms of a nucleobase sequence only, *i.e.*, by specifying the sequence of A, G, C, U (or T). In such a case, the

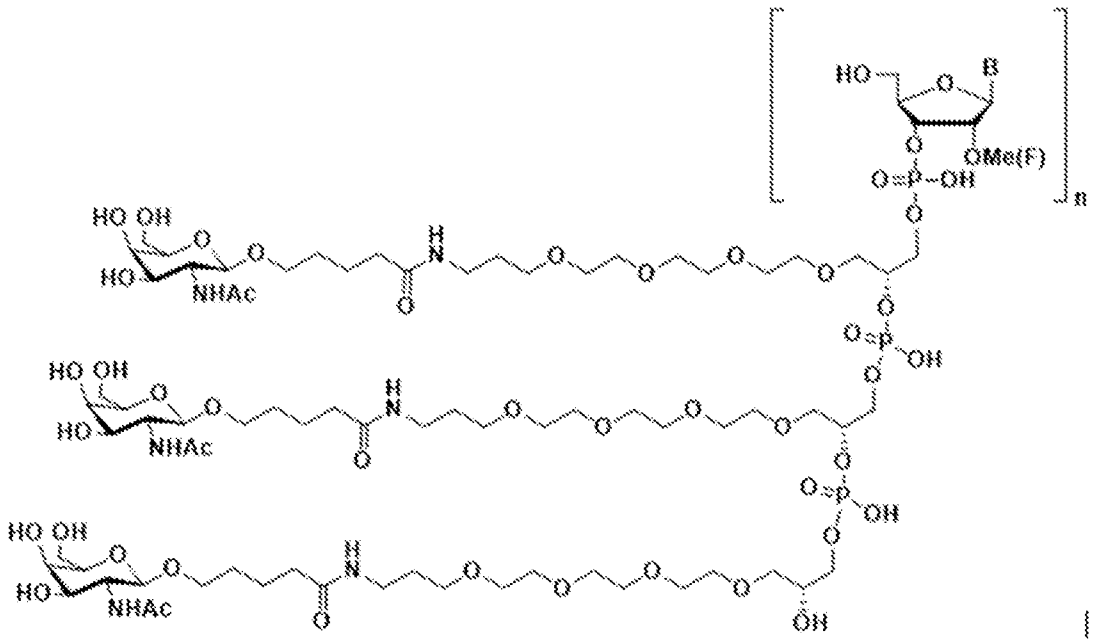
structure of the sugar-phosphate backbone is not particularly limited and may or may not comprise modified sugars and/or modified phosphates. On the other hand, oligomeric compounds may be more comprehensively defined, i.e, by specifying not only the nucleobase sequence, but also the structure of the backbone, in particular the modification status of the sugars (unmodified, 2'-OMe modified, 2'-F modified etc.) and/or of the phosphates.

As used herein, "terminal group" means one or more atom attached to either, or both, the 3 ' end or the 5' end of an oligonucleotide. In certain embodiments, a terminal group comprises one or more terminal group nucleosides.

As used herein, "conjugate" or "conjugate group" means an atom or group of atoms bound to an oligonucleotide or oligomeric compound. In certain embodiments, a conjugate group links a ligand to a modified oligonucleotide or oligomeric compound. In general, conjugate groups can modify one or more properties of the compound to which they are attached, including, but not limited to pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and / or clearance properties.

As used herein, "conjugate linker" or "linker" in the context of a conjugate group means a portion of a conjugate group comprising any atom or group of atoms and which covalently link an oligonucleotide to another portion of the conjugate group. In certain embodiments, the point of attachment on the oligomeric compound is the 3 '-oxygen atom of the 3'-hydroxyl group of the 3' terminal nucleoside of the oligonucleotide. In certain embodiments the point of attachment on the oligomeric compound is the 5'-oxygen atom of the 5'-hydroxyl group of the 5' terminal nucleoside of the oligonucleotide. In certain embodiments, the bond for forming attachment to the oligomeric compound is a cleavable bond. In certain such embodiments, such cleavable bond constitutes all or part of a cleavable moiety.

In certain embodiments, conjugate groups comprise a cleavable moiety (*e.g.*, a cleavable bond or cleavable nucleoside) and ligand portion that can comprise one or more ligands, such as a carbohydrate cluster portion, such as an N-Acetyl-Galactosamine, also referred to as “GalNAc”, cluster portion. In certain embodiments, the carbohydrate cluster portion is identified by the number and identity of the ligand. For example, in certain embodiments, the carbohydrate cluster portion comprises 2 GalNAc groups. For example, in certain embodiments, the carbohydrate cluster portion comprises 3 GalNAc groups and this is particularly preferred. In certain embodiments, the carbohydrate cluster portion comprises 4 GalNAc groups. Such ligand portions are attached to an oligomeric compound via a cleavable moiety, such as a cleavable bond or cleavable nucleoside. The ligands can be arranged in a linear or branched configuration, such as a biantennary or triantennary configurations. A preferred carbohydrate cluster, also referred to as “toothbrush,” has the following formula:



wherein in said structural formula one, two, or three phosphodiester linkages can also be substituted by phosphothionate linkages.

As used herein, "cleavable moiety" means a bond or group that is capable of being cleaved under physiological conditions. In certain embodiments, a cleavable moiety is cleaved inside a cell or sub-cellular compartments, such as an endosome or lysosome. In certain embodiments, a cleavable moiety is cleaved by endogenous enzymes, such as nucleases. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is a phosphodiester linkage.

As used herein, "cleavable bond" means any chemical bond capable of being broken.

As used herein, "carbohydrate cluster" means a compound having one or more carbohydrate residues attached to a linker group.

As used herein, "modified carbohydrate" means any carbohydrate having one or more chemical modifications relative to naturally occurring carbohydrates.

As used herein, "carbohydrate derivative" means any compound which may be synthesized using a carbohydrate as a starting material or intermediate.

As used herein, "carbohydrate" means a naturally occurring carbohydrate, a modified carbohydrate, or a carbohydrate derivative. A carbohydrate is a biomolecule including carbon (C), hydrogen (H) and oxygen (O) atoms. Carbohydrates can include monosaccharide, disaccharides, trisaccharides, tetrasaccharides, oligosaccharides or polysaccharides, such as one or more galactose moieties, one or more lactose moieties, one or more N-Acetyl-Galactosamine moieties, and / or one or more mannose moieties. A particularly preferred carbohydrate is N-Acetyl-Galactosamine.

As used herein, "strand" means an oligomeric compound comprising linked nucleosides.

As used herein, "single strand" or "single-stranded" means an oligomeric compound comprising linked nucleosides that are connected in a continuous sequence without a break therebetween. Such single

strands may include regions of sufficient self-complementarity so as to be capable of forming a stable self-duplex in a hairpin structure.

As used herein, "hairpin" means a single stranded oligomeric compound that includes a duplex formed by base pairing between sequences in the strand that are self-complementary and opposite in directionality.

As used herein, "hairpin loop" means an unpaired loop of linked nucleosides in a hairpin that is created as a result of hybridization of the self-complementary sequences. The resulting structure looks like a loop or a U-shape.

In particular, short hairpin RNA, also denoted as shRNA, comprises a duplex region and a loop connecting the regions forming the duplex. The end of the duplex region which does not carry the loop may be blunt-ended or carry (a) 3' and/or (a) 5' overhang(s). Preference is given to blunt-ended constructs.

As used herein, "directionality" means the end-to-end chemical orientation of an oligonucleotide based on the chemical convention of numbering of carbon atoms in the sugar moiety meaning that there will be a 5′-end defined by the 5′ carbon of the sugar moiety, and a 3′-end defined by the 3' carbon of the sugar moiety. In a duplex or double stranded oligonucleotide, the respective strands run in opposite 5' to 3' directions to permit base pairing between them.

As used herein, "duplex" or also abbreviated as "dup" means two or more complementary strand regions, or strands, of an oligonucleotide or oligonucleotides, hybridized together by way of non-covalent, sequence-specific interaction therebetween. Most commonly, the hybridization in the duplex will be between nucleobases adenine (A) and thymine (T), and / or (A) adenine and uracil (U), and / or guanine (G) and cytosine (C). The duplex may be part of a single stranded structure, wherein self-complementarity leads to hybridization, or as a result of hybridization between respective strands in a double stranded construct.

As used herein, "double strand" or "double stranded" means a pair of oligomeric compounds that are hybridized to one another. In certain embodiments, a double-stranded oligomeric compound comprises a first and a second oligomeric compound.

As used herein, "expression" means the process by which a gene ultimately results in a protein. Expression includes, but is not limited to, transcription, post-transcriptional modification (*e.g.*, splicing, polyadenlyation, addition of 5 '-cap), and translation.

As used herein, "transcription" or "transcribed" means the first of several steps of DNA based gene expression in which a target sequence of DNA is copied into RNA (especially mRNA) by the enzyme RNA polymerase. During transcription, a DNA sequence is read by an RNA polymerase, which produces a complementary, antiparallel RNA sequence called a primary transcript.

As used herein, "target sequence" means a sequence to which an oligomeric compound is intended to hybridize to result in a desired activity with respect to APOC3 expression. Oligonucleotides have sufficient complementarity to their target sequences to allow hybridization under physiological conditions.

As used herein, "nucleobase complementarity" or "complementarity" when in reference to nucleobases means a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to

uracil (U). In both DNA and RNA, guanine (G) is complementary to cytosine (C). In certain embodiments, complementary nucleobase means a nucleobase of an oligomeric compound that is capable of base pairing with a nucleobase of its target sequence. For example, if a nucleobase at a certain position of an oligomeric compound is capable of hydrogen bonding with a nucleobase at a certain position of a target sequence, then the position of hydrogen bonding between the oligomeric compound and the target sequence is considered to be complementary at that nucleobase pair. Nucleobases comprising certain modifications may maintain the ability to pair with a counterpart nucleobase and thus, are still capable of nucleobase complementarity.

As used herein, "non-complementary" in reference to nucleobases means a pair of nucleobases that do not form hydrogen bonds with one another.

As used herein, "complementary" in reference to oligomeric compounds (*e.g.*, linked nucleosides, oligonucleotides) means the capacity of such oligomeric compounds or regions thereof to hybridize to a target sequence, or to a region of the oligomeric compound itself, through nucleobase complementarity. Complementary oligomeric compounds need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. In certain embodiments, complementary oligomeric compounds or regions are complementary at 70% of the nucleobases (70% complementary). In certain embodiments, complementary oligomeric compounds or regions are 80%> complementary. In certain embodiments, complementary oligomeric compounds or regions are 90%> complementary. In certain embodiments, complementary oligomeric compounds or regions are at least 95% complementary. In certain embodiments, complementary oligomeric compounds or regions are 100% complementary.

As used herein, "self-complementarity" in reference to oligomeric compounds means a compound that may fold back on itself, creating a duplex as a result of nucleobase hybridization of internal complementary strand regions. Depending on how close together and / or how long the strand regions are, then the compound may form hairpin loops, junctions, bulges or internal loops.

As used herein, "mismatch" means a nucleobase of an oligomeric compound that is not capable of pairing with a nucleobase at a corresponding position of a target sequence, or at a corresponding position of the oligomeric compound itself when the oligomeric compound hybridizes as a result of self-complementarity, when the oligomeric compound and the target sequence and / or self-complementary regions of the oligomeric compound, are aligned.

As used herein, "hybridization" means the pairing of complementary oligomeric compounds (*e.g.*, an oligomeric compound and its target sequence). While not limited to a particular mechanism, the most common mechanism of pairing involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases.

As used herein, "specifically hybridizes" means the ability of an oligomeric compound to hybridize to one nucleic acid site with greater affinity than it hybridizes to another nucleic acid site.

As used herein, "fully complementary" in reference to an oligomeric compound or region thereof means that each nucleobase of the oligomeric compound or region thereof is capable of pairing with a nucleobase of a complementary nucleic acid target sequence or a self-complementary region of the oligomeric compound. Thus, a fully complementary oligomeric compound or region thereof comprises

no mismatches or unhybridized nucleobases with respect to its target sequence or a self-complementary region of the oligomeric compound.

As used herein, "percent complementarity" means the percentage of nucleobases of an oligomeric compound that are complementary to an equal-length portion of a target nucleic acid. Percent complementarity is calculated by dividing the number of nucleobases of the oligomeric compound that are complementary to nucleobases at corresponding positions in the target nucleic acid by the total length of the oligomeric compound.

As used herein, "percent identity" means the number of nucleobases in a first nucleic acid that are the same type (independent of chemical modification) as nucleobases at corresponding positions in a second nucleic acid, divided by the total number of nucleobases in the first nucleic acid.

As used herein, "modulation" means a change of amount or quality of a molecule, function, or activity when compared to the amount or quality of a molecule, function, or activity prior to modulation. For example, modulation includes the change, either an increase (stimulation or induction) or a decrease (inhibition or reduction) in gene expression.

As used herein, "type of modification" in reference to a nucleoside or a nucleoside of a "type" means the chemical modification of a nucleoside and includes modified and unmodified nucleosides. Accordingly, unless otherwise indicated, a "nucleoside having a modification of a first type" may be an unmodified nucleoside.

As used herein, "differently modified" means chemical modifications or chemical substituents that are different from one another, including absence of modifications. Thus, for example, a MOE nucleoside and an unmodified naturally occurring RNA nucleoside are "differently modified," even though the naturally occurring nucleoside is unmodified. Likewise, DNA and RNA oligonucleotides are "differently modified," even though both are naturally-occurring unmodified nucleosides. Nucleosides that are the same but for comprising different nucleobases are not differently modified. For example, a nucleoside comprising a 2'-OMe modified sugar moiety and an unmodified adenine nucleobase and a nucleoside comprising a 2'-OMe modified sugar moiety and an unmodified thymine nucleobase are not differently modified.

As used herein, "the same type of modifications" refers to modifications that are the same as one another, including absence of modifications. Thus, for example, two unmodified RNA nucleosides have "the same type of modification," even though the RNA nucleosides are unmodified. Such nucleosides having the same type modification may comprise different nucleobases.

As used herein, "region" or "regions", or "portion" or "portions", mean a plurality of linked nucleosides that have a function or character as defined herein, in particular with reference to the claims and definitions as provided herein. Typically such regions or portions comprise at least 10, at least 11, at least 12 or at least 13 linked nucleosides. For example, such regions can comprise 13 to 20 linked nucleosides, such as 13 to 16 or 18 to 20 linked nucleosides. Typically a first region as defined herein consists essentially of 18 to 20 nucleosides and a second region as defined herein consists essentially of 13 to 16 linked nucleosides.

As used herein, "pharmaceutically acceptable carrier or diluent" means any substance suitable for use in administering to an animal. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile saline. In certain embodiments, such sterile saline is pharmaceutical grade saline.

As used herein, "substituent" and "substituent group," means an atom or group that replaces the atom or group of a named parent compound. For example a substituent of a modified nucleoside is any atom or group that differs from the atom or group found in a naturally occurring nucleoside (*e.g.*, a modified 2'-substituent is any atom or group at the 2 '-position of a nucleoside other than H or OH). Substituent groups can be protected or unprotected. In certain embodiments, compounds of the present disclosure have substituents at one or at more than one position of the parent compound. Substituents may also be further substituted with other substituent groups and may be attached directly or via a linking group such as oxygen or an alkyl or hydrocarbyl group to a parent compound.

Such substituents can be present as the modification on the sugar moiety, in particular a substituent present at the 2'-position of the sugar moiety. Unless otherwise indicated, groups amenable for use as substituents include without limitation, one or more of halo, hydroxyl, alkyl, alkenyl, alkynyl, acyl, carboxyl, alkoxy, alkoxyalkylene and amino substituents. Certain substituents as described herein can represent modifications directly attached to a ring of a sugar moiety (such as a halo, such as fluoro, directly attached to a sugar ring), or a modification indirectly linked to a ring of a sugar moiety by way of an oxygen linking atom that itself is directly linked to the sugar moiety (such as an alkoxyalkylene, such as methoxyethylene, linked to an oxygen atom, overall providing an MOE substituent as described herein attached to the 2'-position of the sugar moiety).

As used herein, "alkyl," as used herein, means a saturated straight or branched monovalent C_{1-6} hydrocarbon radical, with methyl being a most preferred alkyl as a substituent at the 2'-position of the sugar moiety. The alkyl group typically attaches to an oxygen linking atom at the 2'poisition of the sugar, therefore, overall providing a –Oalkyl substituent, such as an -OCH_3 substituent, on a sugar moiety of an oligomeric compound as described herein. This will be well understood be a person skilled in the art.

As used herein, "alkylene" means a saturated straight or branched divalent hydrocarbon radical of the general formula -C_nH_{2n}- where n is 1-6. Methylene or ethylene are preferred alkylenes.

As used herein, "alkenyl" means a straight or branched unsaturated monovalent C_{2-6} hydrocarbon radical, with ethenyl or propenyl being most preferred alkenyls as a substituent at the 2'-position of the sugar moiety. As will be well understood in the art, the degree of unsaturation that is present in an alkenyl radical is the presence of at least one carbon to carbon double bond. The alkenyl group typically attaches to an oxygen linking atom at the 2'-position of the sugar, therefore, overall providing a –Oalkenyl substituent, such as an –$OCH_2CH=CH_2$ substituent, on a sugar moiety of an oligomeric compound as described herein. This will be well understood be a person skilled in the art.

As used herein, "alkynyl" means a straight or branched unsaturated C_{2-6} hydrocarbon radical, with ethynyl being a most preferred alkynyl as a substituent at the 2'-position of the sugar moiety. As will be well understood in the art, the degree of unsaturation that is present in an alkynyl radical is the presence of at least one carbon to carbon triple bond. The alkynyl group typically attaches to an oxygen linking atom at the 2'-position of the sugar, therefore, overall providing a –Oalkynyl substituent on a sugar

moiety of an oligomeric compound as described herein. This will be well understood be a person skilled in the art.

As used herein, "carboxyl" is a radical having a general formula $–CO_2H$.

As used herein, "acyl" means a radical formed by removal of a hydroxyl group from a carboxyl radical as defined herein and has the general Formula -C(O)-X where X is typically C_{1-6} alkyl.

As used herein, "alkoxy" means a radical formed between an alkyl group, such as a C_{1-6} alkyl group, and an oxygen atom wherein the oxygen atom is used to attach the alkoxy group either to a parent molecule (such as at the 2'-position of a sugar moiety), or to another group such as an alkylene group as defined herein. Examples of alkoxy groups include without limitation, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy and tert-butoxy. Alkoxy groups as used herein may optionally include further substituent groups.

As used herein, alkoxyalkylene means an alkoxy group as defined herein that is attached to an alkylene group also as defined herein, and wherein the oxygen atom of the alkoxy group attaches to the alkylene group and the alkylene attaches to a parent molecule. The alkylene group typically attaches to an oxygen linking atom at the 2'-position of the sugar, therefore, overall providing a –Oalkylenealkoxy substituent, such as an $–OCH_2CH_2OCH_3$ substituent, on a sugar moiety of an oligomeric compound as described herein. This will be well understood by a person skilled in the art and is generally referred to as an MOE substituent as defined herein and as known in the art.

As used herein, "amino" includes primary, secondary and tertiary amino groups.

As used herein, "halo" and "halogen," mean an atom selected from fluorine, chlorine, bromine and iodine.

As used herein, the term "mxRNA" is in particular understood as defined in WO 2020/044186 A2 which is incorporated by reference herein in its entirety.

It will also be understood that oligomeric compounds as described herein may have one or more non-hybridizing nucleosides at one or both ends of one or both strands (overhangs) and / or one or more internal non-hybridizing nucleosides (mismatches) provided there is sufficient complementarity to maintain hybridization under physiologically relevant conditions. Alternatively, oligomeric compounds as described herein may be blunt ended at at least one end.

The term "comprising" is used herein to mean including the method steps or elements identified, but that such steps or elements do not comprise an exclusive list and as such there may be present additional steps or elements.

Further, to the extent that the term "includes" is used in either the detailed description or the claims, such term is intended to be inclusive in a manner similar to the term "comprising" as "comprising" is interpreted when employed as a transitional word in a claim.

The following exemplary embodiments (items) are provided:

1. An oligomeric compound capable of inhibiting expression of APOC3, wherein the compound comprises at least a first region of linked nucleosides having at least a first nucleobase sequence that is at least partially complementary to at least a portion of RNA transcribed from an APOC3 gene, wherein the first nucleobase sequence is selected from the following sequences, or a portion thereof: sequences

of Tables 1a and 2a (SEQ ID NOs: 1 to 391), wherein the portion preferably has a length of at least 18 nucleotides.

Said first region is also referred to as the antisense region, and said second region is also referred to as the sense region. As disclosed in preferred embodiments below, said two regions may be located on the same strand, preferably in an adjacent manner. This gives rise to hairpin molecules, also referred to as mxRNAs. On the other hand, said two regions may be located on separate strands which gives rise to double-stranded RNAs (dsRNAs), wherein preferably each strand consists of the respective region. Moreover, said regions may serve as building blocks for muRNAs (see above at Aspect 1). In other words, said first and said second region as defined herein may be used, in accordance with the following definition of muRNAs as first and third regions, respectively:

A nucleic acid construct (muRNA) comprising at least:

(a) a first nucleic acid portion that is at least partially complementary to at least a first portion of an RNA which is transcribed from a APOC3 gene;

(b) a second nucleic acid portion that is at least partially complementary to at least a second portion of an RNA which is transcribed from another gene;

(c) a third nucleic acid portion that is at least partially complementary to said first nucleic acid portion of (a), so as to form a first nucleic acid duplex region therewith; and

(d) a fourth nucleic acid portion that is at least partially complementary to said second nucleic acid portion of (b), so as to form a second nucleic acid duplex region therewith.

Preferred embodiments of and further aspects relating to muRNAs are disclosed in WO2020/065602.

2. The oligomeric compound according to item 1, which further comprises at least a second region of linked nucleosides having at least a second nucleobase sequence that is at least partially complementary to the first nucleobase sequence and is selected from the following sequences, or a portion thereof: sequences of Tables 1c and 2c (SEQ ID NOs: 401 to 791), wherein the portion preferably has a length of at least 11 nucleotides, or wherein the portion preferably has a length of at least 8, 9, 10 or 11 nucleotides, more preferably at least 10 nucleotides.

3. The oligomeric compound according to item 1 or 2, wherein the first nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 175, 293, 262, 297, 277, 366, 337, 254, 274, 286, 137, 149, 280, 343, 225, 221, 185, 373, 121, 281, 331, 367, 296, 28, 345, 328, 339, 278, 271, 212, 223, 369, 276, 332, 300, 341, 334, 138, 193, 340, 31, 167, 275, 191, 336, 90, 346, 219, 283, 213, 23, 24, 285, 347, 370, 206, 282, 342, 272, 303, 220, 209, 29, 89, 291, 117, 372, 218, 368, 148, 217, 128, 338, 171, 94, 324, and 299.

4. The oligomeric compound according to item 3, wherein the second nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 575, 693, 662, 697, 677, 766, 737, 654, 674, 686, 537, 549, 680, 743, 625, 621, 585, 773, 521, 681, 731, 767, 696, 428, 745, 728, 739, 678, 671, 612, 623, 769, 676, 732, 700, 741, 734, 538, 593, 740, 431, 567, 675, 591, 736, 490, 746, 619, 683, 613, 423, 424, 685, 747, 770, 606, 682, 742, 672, 703, 620, 609, 429, 489, 691, 517, 772, 618, 768, 548, 617, 528, 738, 571, 494, 724, and 699.

5. The oligomeric compound according to any of items 1 to 4, wherein the first nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 277, 337, 28,

343, 369, 366, 274, 367, 336, 332, 293, 373, 280, 221, 334, 286, 149, 193, 328, 175, 262, 254, 185, 328, 271, 137, 225, 167, 297, and 191.

6. The oligomeric compound according to item 5, wherein the second nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 677, 737, 428, 743, 769, 766, 674, 767, 736, 732, 693, 773, 680, 621, 734, 686, 549, 593, 728, 575, 662, 654, 585, 728, 671, 537, 625, 567, 697, and 591.

7. The oligomeric compound according to any of items 1 to 6, wherein the first nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 28, 277, 336, 337, 366, 367, and 369, preferably SEQ ID NO: 28 or 277, more preferably SEQ ID NO: 28. These embodiments define antisense nucleobase sequences which provide for surprisingly outstanding performance. For evidence, reference is made to the Examples.

8. The oligomeric compound according to item 7, wherein the second nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 428, 677, 736, 737, 766, 767, and 769, preferably SEQ ID NO: 428 or 677, more preferably SEQ ID NO: 428.

9. The oligomeric compound according to any of items 1 to 8, wherein the first region of linked nucleosides consists essentially of 18 to 35, preferably 18 to 20, more preferably 18 or 19, and yet more preferably 19 linked nucleosides.

10. The oligomeric compound according to any of items 2 to 9, wherein the second region of linked nucleosides consists essentially of 11 to 35, preferably 11 to 20, more preferably 13 to 16, and yet more preferably 14 or 15, most preferably 14 linked nucleosides; or wherein the second region of linked nucleosides consists essentially of 10 to 35, preferably 10 to 20, more preferably 10 to 16, and yet more preferably 10 to 15 linked nucleosides.

11. The oligomeric compound according to any of items 2 to 10, which comprises at least one complementary duplex region that comprises at least a portion of the first nucleoside region directly or indirectly linked to at least a portion of the second nucleoside region, wherein preferably the duplex region has a length of 11 to 19, more preferably 14 to 19, and yet more preferably 14 or 15 base pairs, most preferably 14 base pairs, wherein optionally there is one mismatch within the duplex region; or which comprises at least one complementary duplex region that comprises at least a portion of the first nucleoside region directly or indirectly linked to at least a portion of the second nucleoside region, wherein preferably the duplex region has a length of 10 to 19, more preferably 12 to 19, and yet more preferably 12 to 15 base pairs, wherein optionally there is one mismatch within the duplex region.

12. The oligomeric compound according to item 11, wherein each of the first and second nucleoside regions has a 5’ to 3’ directionality thereby defining 5’ and 3’ regions respectively thereof.

13. The oligomeric compound according to item 12, wherein the 5’ region of the first nucleoside region is directly or indirectly linked to the 3’ region of the second nucleoside region, for example by complementary base pairing, and / or wherein the 3’ region of the first nucleoside region is directly or indirectly linked to the 5’ region of the second nucleoside region, wherein preferably the 5' terminal nucleoside of the first nucleoside region base pairs with the 3' terminal nucleoside of the second nucleoside region; or wherein the 5’ region of the first nucleoside region is directly or indirectly linked to the 3’ region of the second nucleoside region, for example by complementary base pairing, wherein

preferably the 5' terminal nucleoside of the first nucleoside region base pairs with the 3' terminal nucleoside of the second nucleoside region.

14. The oligomeric compound according to item 12 or 13, wherein the 3' region of the first nucleoside region is directly or indirectly linked to the 5' region of the second nucleoside region, wherein preferably the first nucleoside region is directly and covalently linked to the second nucleoside region such as by a phosphate, a phosphorothioate, or a phosphorodithoate.

15. The oligomeric compound according to any of items 1 to 14, which further comprises one or more ligands.

16. The oligomeric compound according to item 15, wherein the one or more ligands are conjugated to the second nucleoside region and/or the first nucleoside region.

17. The oligomeric compound according to item 16, as dependent on claim 12, wherein the one or more ligands are conjugated at the 3' region, preferably to the 3' end of the second nucleoside region and/or of the first nucleoside region, and/or to the 5' end of the second nucleoside region.

18. The oligomeric compound according to any of item 15 to 17, wherein the one or more ligands are any cell directing moiety, such as lipids, carbohydrates, aptamers, vitamins and / or peptides that bind cellular membrane or a specific target on cellular surface.

19. The oligomeric compound according to item 18, wherein the one or more ligands comprise one or more carbohydrates.

20. The oligomeric compound according to item 19, wherein the one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide or polysaccharide.

21. The oligomeric compound according to item 20, wherein the one or more carbohydrates comprise or consist of one or more hexose moieties.

22. The oligomeric compound according to item 21, wherein the one or more hexose moieties are one or more galactose moieties, one or more lactose moieties, one or more N-Acetyl-Galactosamine moieties, and / or one or more mannose moieties.

23. The oligomeric compound according to item 22, wherein the one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

24. The oligomeric compound according to item 23, which comprises two or three N-Acetyl-Galactosamine moieties, preferably three.

25. The oligomeric compound according to any of items 15 to 24, wherein the one or more ligands are attached to the oligomeric compound, preferably to the second nucleoside region thereof, in a linear configuration, or in a branched configuration.

26. The oligomeric compound according to item 25, wherein the one or more ligands are attached to the oligomeric compound as a biantennary or triantennary configuration.

27. The oligomeric compound according to any one of items 1 to 26, wherein the compound consists of the first region of linked nucleosides and the second region of linked nucleosides.

Each of said regions may constitute a separate strand, thereby giving rise to a double-stranded RNA (dsRNA). Particularly preferred dsRNAs are those with a length of the first strand of 19 nucleosides and a length of the second region of 14 or 15, preferably 14 nucleosides. When used for defining the length

of a region or strand, the terms “nucleoside” and “nucleotide” (sometimes abbreviated “nt”) are used equivalently.

28. The oligomeric compound according to item 12, wherein the oligomeric compound comprises a single strand comprising the first and second nucleoside regions, wherein the single strand dimerises whereby at least a portion of the first nucleoside region is directly or indirectly linked to at least a portion of the second nucleoside region so as to form the at least partially complementary duplex region. In other words, the oligomeric compound comprises a single strand comprising the first and second nucleoside regions, wherein at least a portion of the first nucleoside region is directly or indirectly linked to at least a portion of the second nucleoside region so as to form the at least partially complementary duplex region.

29. The oligomeric compound according to item 28, wherein the first nucleoside region has a greater number of linked nucleosides compared to the second nucleoside region, whereby the additional number of linked nucleosides of the first nucleoside region form a hairpin loop linking the first and second nucleoside regions.

Such compounds are also referred to as hairpins or mxRNAs herein.

30. The oligomeric compound according to item 29, as dependent on claim 12, whereby the hairpin loop is present at the 3' region of the first nucleoside region.

31. The oligomeric compound according to item 29 or 30, wherein the hairpin loop comprises 4 or 5 linked nucleosides.

Particularly advantageous is a length of the first region of 19 nucleosides, of the second region of 14 nucleotides, and of the hairpin loop of five nucleotides, wherein the five nucleotides in the hairpin are the five 3’-terminal nucleosides of the first region. Such molecular architecture of a hairpin or mxRNA is also designated “14-5-14” herein.

32. The oligomeric compound according to any one of items 28 to 31, wherein the single strand has a nucleobase sequence selected from SEQ ID NOs: 792 to 803, preferably from SEQ ID NOs: 792, 793, 796, 800 and 803, most preferably from SEQ ID NOs: 796 and 803 particularly SEQ ID NO: 803.

33. The oligomeric compound according to item 32, wherein the single strand is selected from Table 3b, in particular from constructs A28(14-4)mF and A277(12-5_, A28(14-4)mF being especially advantageous.

34. The oligomeric compound according to any of items 1 to 33, which comprises internucleoside linkages and wherein at least one internucleoside linkage is a modified internucleoside linkage. Specific modified internucleoside linkages are the subject of the embodiments which follow. Certain modified internucleoside linkages are known in the art and described in, for example, Hu et al., *Signal Transduction and Targeted Therapy* (2020)5:101.

35. The oligomeric compound according to item 34, wherein the modified internucleoside linkage is a phosphorothioate or phosphorodithioate internucleoside linkage.

36. The oligomeric compound according to item 35, which comprises 1 to 15 phosphorothioate or phosphorodithioate internucleoside linkages.

37. The oligomeric compound according to item 36, which comprises 7, 8, 9 or 10 phosphorothioate or phosphorodithioate internucleoside linkages.

38. The oligomeric compound according to any of items 35 to 37, as dependent on item 12, which comprises one or more phosphorothioate or phosphorodithioate internucleoside linkages at the 5' region of the first nucleoside region.

39. The oligomeric compound according to any of items 35 to 38, as dependent on item 12, which comprises one or more phosphorothioate or phosphorodithioate internucleoside linkages at the 5' region of the second nucleoside region.

40. The oligomeric compound according to any of items 35 to 39, as dependent on item 28, which comprises phosphorothioate or phosphorodithioate internucleoside linkages between at least two, preferably at least three, preferably at least four, preferably at least five, adjacent nucleosides of the hairpin loop, dependent on the number of nucleotides present in the hairpin loop.

41. The oligomeric compound according to item 40, which comprises a phosphorothioate or phosphorodithioate internucleoside linkage between each adjacent nucleoside that is present in the hairpin loop.

42. The oligomeric compound according to any of items 1 to 41, wherein at least one nucleoside comprises a modified sugar.

Preferred modified sugars are subject of the embodiments which follow. Certain modified sugars are known in the art and described in, for example, Hu et al., *Signal Transduction and Targeted Therapy* (2020)5:101.

43. The oligomeric compound according to item 42, wherein the modified sugar is selected from 2' modified sugars, locked nucleic acid (LNA) sugar, (S)-constrained ethyl bicyclic nucleic acid sugar, tricyclo-DNA sugar, morpholino, unlocked nucleic acid (UNA) sugar, and glycol nucleic acid (GNA) sugar.

44. The oligomeric compound according to item 43, wherein the 2' modified sugar is selected from 2'-O-methyl modified sugar, 2'-O-methoxyethyl modified sugar, 2'-F modified sugar, 2'-arabino-fluoro modified sugar, 2'-O-benzyl modified sugar, and 2'-O-methyl-4-pyridine modified sugar.

45. The oligomeric compound according to item 44, wherein at least one modified sugar is a 2'-O-methyl modified sugar.

46. The oligomeric compound according to item 44 or 45, wherein at least one modified sugar is a 2'-F modified sugar.

47. The oligomeric compound of item 45 or 46, wherein the sugar is ribose.

48. The oligomeric compound according to any of items 45 to 48, as dependent on item 12, wherein sugars of the nucleosides at any of positions 2 and 14 downstream from the first nucleoside of the 5' region of the first nucleoside region, do not contain 2'-O-methyl modifications.

49. The oligomeric compound according to any of items 45 to 48, as dependent on item 12, wherein sugars of the nucleosides of the second nucleoside region, that correspond in position to any of the nucleosides of the first nucleoside region at any of positions 9 to 11 downstream from the first nucleotide of the 5' region of the first nucleoside region, in particular from sequence A277(12-5) and A28(14-4)mF do not contain 2'-O-methyl modifications.

50. The oligomeric compound of any one of items 45 to 49, wherein the 3' terminal position of the second nucleoside region does not contain a 2'-O-methyl modification.

51. The oligomeric compound according to item 49 or 50, wherein sugars of the nucleosides at any of positions 2 and 14 downstream from the first nucleoside of the 5' region of the first nucleoside region, contain 2'-F modifications.

52. The oligomeric compound according to any of items 49 to 51, wherein sugars of the nucleosides of the second nucleoside region, that correspond in position to any of the nucleosides of the first nucleoside region at any of positions 9 to 11 downstream from the first nucleoside of the 5' region of the first nucleoside region, contain 2'-F modifications.

53. The oligomeric compound of item 51 or 52, wherein the 3' terminal position of the second nucleoside region contains a 2'-F modification.

54. The oligomeric compound according to any of items 47 to 53, as dependent on item 12, wherein one or more of the odd numbered nucleosides starting from the 5' region of the first nucleoside region are modified, and / or wherein one or more of the even numbered nucleotides starting from the 5' region of the first nucleoside region are modified, wherein typically the modification of the even numbered nucleotides is a second modification that is different from the modification of odd numbered nucleotides.

55. The oligomeric compound according to item 54, wherein one or more of the odd numbered nucleosides starting from the 3' region of the second nucleoside region are modified by a modification that is different from the modification of odd numbered nucleosides of the first nucleoside region.

56. The oligomeric compound according to item 54 or 55, wherein one or more of the even numbered nucleosides starting from the 3' region of the second nucleoside region are modified by a modification that is different from the modification of even numbered nucleosides of the first nucleoside region according to item 55.

57. The oligomeric compound according to any of items 54 to 56, wherein at least one or more of the modified even numbered nucleosides of the first nucleoside region is adjacent to at least one or more of the differently modified odd numbered nucleosides of the first nucleoside region.

58. The oligomeric compound according to any of items 54 to 57, wherein at least one or more of the modified even numbered nucleosides of the second nucleoside region is adjacent to at least one or more of the differently modified odd numbered nucleosides of the second nucleoside region.

59. The oligomeric compound according to any of items 54 to 58, wherein sugars of one or more of the odd numbered nucleosides starting from the 5' region of the first nucleoside region are 2'-O-methyl modified sugars.

60. The oligomeric compound according to any of items 54 to 59, wherein one or more of the even numbered nucleosides starting from the 5' region of the first nucleoside region are 2'-F modified sugars.

61. The oligomeric compound according to any of items 54 to 60, wherein sugars of one or more of the odd numbered nucleosides starting from the 3' region of the second nucleoside region are 2'-F modified sugars.

62. The oligomeric compound according to any of items 54 to 61, wherein one or more of the even numbered nucleosides starting from the 3' region of the second nucleoside region are 2'-O-methyl modified sugars.

63. The oligomeric compound according to any of items 42 to 62, wherein sugars of a plurality of adjacent nucleosides of the first nucleoside region are modified by a common modification.

64. The oligomeric compound according to any of items 42 to 63, wherein sugars of a plurality of adjacent nucleosides of the second nucleoside region are modified by a common modification.

65. The oligomeric compound according to any of items 54 to 64, as dependent on item 31, wherein sugars of a plurality of adjacent nucleosides of the hairpin loop are modified by a common modification.

66. The oligomeric compound according to any of items 63 to 65, wherein the common modification is a 2'-F modified sugar.

67. The oligomeric compound according to any of items 63 to 65, wherein the common modification is a 2'-O-methyl modified sugar.

68. The oligomeric compound according to item 67, wherein the plurality of adjacent 2'-O-methyl modified sugars are present in at least eight adjacent nucleosides of the first and / or second nucleoside regions.

69. The oligomeric compound according to item 67, wherein the plurality of adjacent 2'-O-methyl modified sugars are present in three or four adjacent nucleosides of the hairpin loop.

70. The oligomeric compound according to item 42, as dependent on item 29, wherein the hairpin loop comprises at least one nucleoside having a modified sugar.

71. The oligomeric compound according to item 70, wherein the at least one nucleoside is adjacent a nucleoside with a differently modified sugar.

72. The oligomeric compound according to item 71, wherein the modified sugar is a 2'-O-methyl modified sugar, and the differently modifies sugar is a 2'-F modified sugar.

73. The oligomeric compound according to any of items 1 to 72, which comprises one or more nucleosides having an un-modified sugar moiety.

74. The oligomeric compound according to item 73, wherein the unmodified sugar is present in the 5' region of the second nucleoside region.

75. The oligomeric compound according to item 73 or 74, as dependent on item 29, wherein the unmodified sugar is present in the hairpin loop.

76. The oligomeric compound according to any of items 1 to 75, wherein one or more nucleosides of the first nucleoside region and / or the second nucleoside region is an inverted nucleoside and is attached to an adjacent nucleoside via the 3' carbon of its sugar and the 3' carbon of the sugar of the adjacent nucleoside, and / or one or more nucleosides of the first nucleoside region and / or the second nucleoside region is an inverted nucleoside and is attached to an adjacent nucleoside via the 5' carbon of its sugar and the 5' carbon of the sugar of the adjacent nucleoside.

77. The oligomeric compound according to any of items 1 to 76, which is blunt ended.

78. The oligomeric compound according to any of items 1 to 76, wherein either the first or second nucleoside region has an overhang.

79. The oligomeric compound according to any one of the preceding items, wherein the first region of linked nucleotides is selected from Table 1b or Table 2b, preferably from the entries in Table 1b which have a nucleobase sequence as defined in any one of item 3, 5 or 7.

80. The oligomeric compound according to any one of the preceding items, wherein the second region of linked nucleotides is selected from Table 1d or Table 2d, preferably from the entries in Table 1b which have a nucleobase sequence as defined in any one of items 4, 6 or 8.

81. A composition comprising an oligomeric compound according to any of items 1 to 80, and a physiologically acceptable excipient.

82. A pharmaceutical composition comprising an oligomeric compound according to any of items 1 to 80.

83. The pharmaceutical composition of item 82, further comprising a pharmaceutically acceptable excipient, diluent, antioxidant, and/or preservative.

84. The pharmaceutical composition of item 82 or 83, wherein the oligomeric compound is the only pharmaceutically active agent.

85. The pharmaceutical composition of item 84, wherein the pharmaceutical composition is to be administered to patients or individuals which are statin-intolerant and/or for whom statins are contraindicated.

86. The pharmaceutical composition of item 82 or 83, wherein the pharmaceutical composition furthermore comprises one or more further pharmaceutically active agents.

87. The pharmaceutical composition of item 86, wherein the further pharmaceutically active agent(s) is/are a further oligomeric compound which is directed to a target different from APOC3, preferably PCSK9; Vascepa; Vupanorsen; statins such as Rosuvastatin and Simvastatin; fibrates such fenofibrate; and/or LDL-cholesterol lowering compounds such as statins and ezetimib.

88. The pharmaceutical composition of item 86 or 87, wherein the oligomeric compound and the further pharmaceutically active agent(s) are to be administered concomitantly or in any order.

89. An oligomeric compound according to any of item 1 to 80, for use in human or veterinary medicine or therapy.

90. An oligomeric compound according to any of items 1 to 80, for use in a method of treating, ameliorating and/or preventing a disease or disorder.

91. The compound for use of item 90, wherein the disease or disorder is an APOC3-associated disease or disorder, or a disease or disorder requiring reduction of APOC3 expression levels, the disease or disorder preferably being selected from dyslipidemia including mixed dyslipidemia; hyperchylomicronemia including familial hyperchylomicronemia; hypertriglyceridemia, preferably severe hypertriglyceridemia and/or hypertriglyceridemia with blood triglyceride levels above 500 mg/dl; inflammation including low-grade inflammation; atherosclerosis; atherosclerotic cardiovascular diseases (ASCVD) including major adverse cardiovascular events (MACE) such as myocardial infarction, stroke and peripheral arterial disease; and pancreatitis including acute pancreatitis.

92. A method of treating a disease or disorder comprising administration of an oligomeric compound according to any of item 1 to 80, to an individual in need of treatment.

93. The method according to item 92, wherein the oligomeric compound is administered subcutaneously or intravenously to the individual.

93. Use of an oligomeric compound according to any of item 1 to 80, for use in research as a gene function analysis tool.

94. Use of an oligomeric compound according to any of items 1 to 80 in the manufacture of a medicament for a treatment of a disease or disorder. The diseases and disorders are preferably the same as set forth under item 91 above.

Effects achieved by the oligomeric compounds

Due to the use of the oligomeric compounds as described herein, a significant reduction of APOC3 mRNA, especially in vitro or in liver tissues consisting essentially of human hepatocytes, can be achieved as *e.g.* shown in the examples disclosed herein. In addition, a significant reduction of APCO3 proteins in the plasma level, *e.g.* of mice having a liver consisting essentially of human hepatocytes, can be achieved by using the oligomeric constructs as described herein. In particular these effects can last over an extended time period such as six weeks, *e.g.* in mice having a liver consisting essentially of human hepatocytes.

In addition, by using oligomeric compounds as described herein, significant degrees of reduction of triglyceride levels in the serum, in particular of mice having a liver essentially consisting of human hepatocytes, can be achieved, also over an extended period of time, such as six weeks. An unexpected and surprising finding is that, in addition to the reduction of triglycerides in the serum, in particular of the same mice, a significant reduction in the level of cholesterol in the serum is achieved at the same time over an extended time period, such as six weeks.

It has also been surprisingly found that, in certain embodiments, the aforementioned beneficial effects can be achieved by using oligomeric compounds as described herein in the form of shRNA constructs having a reduced number of fluorine substitutions, such as five fluorine substitutions in total, on the respective 2' positions of their ribose units compared to conventional shRNA molecules having an alternating series of 2'-fluoro and 2'-O-methyl modifications.

Furthermore, it was surprisingly found that, in certain embodiments, the mentioned effects are achieved by using oligomeric compounds as described herein in the form of shRNA constructs as described herein having a reduced length of *e.g.* 29 linked nucleosides compared to conventional shRNA molecules. The same effects can also surprisingly be achieved for such constructs having a length of the sense strand of about 10 nucleosides.

The aforementioned effects can be achieved by using a dosage of about 10 mg/kg body weight to 30 mg/kg body weight, in particular with respect to mice.

Constructs of the oligomeric compounds

The following Tables show nucleobase sequences of antisense and sense strands of oligomeric compounds as described herein, and definitions of antisense and sense strands of modified oligomeric compounds (the notation including nucleobase sequence, sugar modifications, and, where applicable, modified phosphates).

The notation used is common in the art and as the following meaning:
A represents adenine;
U represents uracil;
C represents cytosine;
G represents guanine.
P represents a terminal phosphate group which is preferred but not indispensable;
m represents a methyl modification at the 2' position of the sugar of the underlying nucleoside;
f represents a fluoro modification at the 2' position of the sugar of the underlying nucleoside.
r indicates an unmodified (2'-OH) ribonucleotide;
(ps) or # represents a phosphorothioate inter-nucleoside linkage;
i represents an inverted inter-nucleoside linkage, which can be either 3'-3', or 5'-5';
vp represents vinyl phosphonate;

mvp represents methyl vinyl phosphonate;
3xGalNAc represents a trivalent GalNAc.
Sometimes, nucleosides are shown in square brackets for ease of reading. This notation does not indicate structural elements or modifications.

To the extent displayed, the presence of a 5'-terminal phosphate ("P") is optional. Conversely, to the extent a 5'-terminal phosphate is not displayed, its presence is optional as well. Generally, there is no requirement for a 5'-terminal phosphate in compounds to be administered to mammalian cells, since a mammalian kinase adds a 5'-terminal phosphate in the case of its absence.

Furthermore when a notation like "A277(12-5)mF" is used, the term "A277" designates the sequence suitable for RNAi with APOC3, wherein the first number in the round brackets, *i.e.* 12 in the present case, designates the number of base pairs within a duplex region within a shRNA, and the second number in the round brackets, in this case 5, designates the number of nucleotides present in the hairpin loop of the shRNA. If there is no designation after the hyphen in the round brackets, it means that the loop consists of 5 nucleotides.

Tables 1a to 1d below show nucleobase sequences and sugar-phosphate backbone modifications of antisense and sense strands of the 376 constructs selected in accordance with the Examples. The above disclosed 30 preferred oligomeric compounds have been selected from these 376 constructs. The numbering in Table 1a coincides with the number of the corresponding entry in the sequence listing. For Table 1c the following applies: entry number in the sequence listing = entry number in the Table + 400.

Table 1a: Nucleobase sequences of the antisense strands of 376 exemplary constructs:

#	Nucleobase sequence
1	UUCUAGGGAUGAACUGAGC
2	UCUCUAGGGAUGAACUGAG
3	UCCUCUAGGGAUGAACUGA
4	UGCCUCUAGGGAUGAACUG
5	UUGCCUCUAGGGAUGAACU
6	UCUGCCUCUAGGGAUGAAC
7	UGCUGCCUCUAGGGAUGAA
8	UAGCUGCCUCUAGGGAUGA
9	UGCAGCUGCCUCUAGGGAU
10	UAGCAGCUGCCUCUAGGGA
11	UGAGCAGCUGCCUCUAGGG
12	UGGAGCAGCUGCCUCUAGG
13	UUGUUCCUGGAGCAGCUGC
14	UCUGUUCCUGGAGCAGCUG
15	UCCUCUGUUCCUGGAGCAG
16	UACCUCUGUUCCUGGAGCA
17	UCACCUCUGUUCCUGGAGC
18	UGCACCUCUGUUCCUGGAG
19	UGGCACCUCUGUUCCUGGA
20	UUGGCACCUCUGUUCCUGG
21	UAUGGCACCUCUGUUCCUG
22	UCAUGGCACCUCUGUUCCU
23	UUGCAUGGCACCUCUGUUC
24	UCUGCAUGGCACCUCUGUU
25	UGCUGCAUGGCACCUCUGU
26	UGGCUGCAUGGCACCUCUG
27	UGGGCUGCAUGGCACCUCU

28	UCAACAAGGAGUACCCGGG
29	UACAACAAGGAGUACCCGG
30	UAACAACAAGGAGUACCCG
31	UCAACAACAAGGAGUACCC
32	UGCAACAACAAGGAGUACC
33	UGGCAACAACAAGGAGUAC
34	UGGGCAACAACAAGGAGUA
35	UAGGGCAACAACAAGGAGU
36	UGAGGGCAACAACAAGGAG
37	UGGAGGGCAACAACAAGGA
38	UAGGAGGGCAACAACAAGG
39	UCAGGAGGGCAACAACAAG
40	UCCAGGAGGGCAACAACAA
41	UGCCAGGAGGGCAACAACA
42	UCGCCAGGAGGGCAACAAC
43	UGCGCCAGGAGGGCAACAA
44	UAGCGCCAGGAGGGCAACA
45	UGAGCGCCAGGAGGGCAAC
46	UGGAGCGCCAGGAGGGCAA
47	UAGGAGCGCCAGGAGGGCA
48	UGCCAGGAGCGCCAGGAGG
49	UAGAGGCCAGGAGCGCCAG
50	UCAGAGGCCAGGAGCGCCA
51	UGCAGAGGCCAGGAGCGCC
52	UGGCAGAGGCCAGGAGCGC
53	UGGGCAGAGGCCAGGAGCG
54	UUCGGGCAGAGGCCAGGAG
55	UCUCGGGCAGAGGCCAGGA
56	UGCUCGGGCAGAGGCCAGG
57	UAGCUCGGGCAGAGGCCAG
58	UAAGCUCGGGCAGAGGCCA
59	UGAAGCUCGGGCAGAGGCC
60	UUGAAGCUCGGGCAGAGGC
61	UCUGAAGCUCGGGCAGAGG
62	UUCUGAAGCUCGGGCAGAG
63	UCUCUGAAGCUCGGGCAGA
64	UCCUCUGAAGCUCGGGCAG
65	UGCCUCUGAAGCUCGGGCA
66	UGGCCUCUGAAGCUCGGGC
67	UCGGCCUCUGAAGCUCGGG
68	UUCGGCCUCUGAAGCUCGG
69	UCUCGGCCUCUGAAGCUCG
70	UCCUCGGCCUCUGAAGCUC
71	UUCCUCGGCCUCUGAAGCU
72	UAUCCUCGGCCUCUGAAGC
73	UCAUCCUCGGCCUCUGAAG
74	UGCAUCCUCGGCCUCUGAA
75	UGGCAUCCUCGGCCUCUGA
76	UAGGCAUCCUCGGCCUCUG
77	UGAGGCAUCCUCGGCCUCU
78	UGGAGGCAUCCUCGGCCUC
79	UGGGAGGCAUCCUCGGCCU
80	UAGGGAGGCAUCCUCGGCC
81	UAAGGGAGGCAUCCUCGGC
82	UGAAGGGAGGCAUCCUCGG
83	UAGAAGGGAGGCAUCCUCG
84	UGAGAAGGGAGGCAUCCUC

85	UUGAGAAGGGAGGCAUCCU
86	UCUGAGAAGGGAGGCAUCC
87	UGCUGAGAAGGGAGGCAUC
88	UAGCUGAGAAGGGAGGCAU
89	UUGAAGCUGAGAAGGGAGG
90	UAUGAAGCUGAGAAGGGAG
91	UCAUGAAGCUGAGAAGGGA
92	UGCAUGAAGCUGAGAAGGG
93	UUGCAUGAAGCUGAGAAGG
94	UCUGCAUGAAGCUGAGAAG
95	UCCUGCAUGAAGCUGAGAA
96	UCCCUGCAUGAAGCUGAGA
97	UACCCUGCAUGAAGCUGAG
98	UAACCCUGCAUGAAGCUGA
99	UUAACCCUGCAUGAAGCUG
100	UGUAACCCUGCAUGAAGCU
101	UUGUAACCCUGCAUGAAGC
102	UAUGUAACCCUGCAUGAAG
103	UCAUGUAACCCUGCAUGAA
104	UUCAUGUAACCCUGCAUGA
105	UUUCAUGUAACCCUGCAUG
106	UCUUCAUGUAACCCUGCAU
107	UGCUUCAUGUAACCCUGCA
108	UUGCUUCAUGUAACCCUGC
109	UGUGCUUCAUGUAACCCUG
110	UCGUGCUUCAUGUAACCCU
111	UGCGUGCUUCAUGUAACCC
112	UGGCGUGCUUCAUGUAACC
113	UUGGCGUGCUUCAUGUAAC
114	UGUGGCGUGCUUCAUGUAA
115	UGGUGGCGUGCUUCAUGUA
116	UUGGUGGCGUGCUUCAUGU
117	UUUGGUGGCGUGCUUCAUG
118	UCUUGGUGGCGUGCUUCAU
119	UUCUUGGUGGCGUGCUUCA
120	UGUCUUGGUGGCGUGCUUC
121	UGGUCUUGGUGGCGUGCUU
122	UCGGUCUUGGUGGCGUGCU
123	UGCGGUCUUGGUGGCGUGC
124	UGGCGGUCUUGGUGGCGUG
125	UUGGCGGUCUUGGUGGCGU
126	UUUGGCGGUCUUGGUGGCG
127	UCUUGGCGGUCUUGGUGGC
128	UCCUUGGCGGUCUUGGUGG
129	UUCCUUGGCGGUCUUGGUG
130	UAUCCUUGGCGGUCUUGGU
131	UCAUCCUUGGCGGUCUUGG
132	UGCAUCCUUGGCGGUCUUG
133	UUGCAUCCUUGGCGGUCUU
134	UGUGCAUCCUUGGCGGUCU
135	UAGUGCAUCCUUGGCGGUC
136	UCAGUGCAUCCUUGGCGGU
137	UUCAGUGCAUCCUUGGCGG
138	UCUCAGUGCAUCCUUGGCG
139	UGCUCAGUGCAUCCUUGGC
140	UUGCUCAGUGCAUCCUUGG
141	UCUGCUCAGUGCAUCCUUG

142	UGCUGCUCAGUGCAUCCUU
143	UCGCUGCUCAGUGCAUCCU
144	UACGCUGCUCAGUGCAUCC
145	UCACGCUGCUCAGUGCAUC
146	UGCACGCUGCUCAGUGCAU
147	UUGCACGCUGCUCAGUGCA
148	UCUGCACGCUGCUCAGUGC
149	UCCUGCACGCUGCUCAGUG
150	UUCCUGCACGCUGCUCAGU
151	UACUCCUGCACGCUGCUCA
152	UGGGACUCCUGCACGCUGC
153	UUGGGACUCCUGCACGCUG
154	UCUGGGACUCCUGCACGCU
155	UCCUGGGACUCCUGCACGC
156	UACCUGGGACUCCUGCACG
157	UCACCUGGGACUCCUGCAC
158	UCCACCUGGGACUCCUGCA
159	UGGGCCACCUGGGACUCCU
160	UUGGGCCACCUGGGACUCC
161	UUGCUGGGCCACCUGGGAC
162	UCUGCUGGGCCACCUGGGA
163	UGGCCUGCUGGGCCACCUG
164	UCCUGGCCUGCUGGGCCAC
165	UCCAUCGGUCACCCAGCCC
166	UGCCAUCGGUCACCCAGCC
167	UAGCCAUCGGUCACCCAGC
168	UAAGCCAUCGGUCACCCAG
169	UGAAGCCAUCGGUCACCCA
170	UUGAAGCCAUCGGUCACCC
171	UCUGAAGCCAUCGGUCACC
172	UACUGAAGCCAUCGGUCAC
173	UAACUGAAGCCAUCGGUCA
174	UGAACUGAAGCCAUCGGUC
175	UGGAACUGAAGCCAUCGGU
176	UGGGAACUGAAGCCAUCGG
177	UAGGGAACUGAAGCCAUCG
178	UCAGGGAACUGAAGCCAUC
179	UUCAGGGAACUGAAGCCAU
180	UUUCAGGGAACUGAAGCCA
181	UUUUCAGGGAACUGAAGCC
182	UCUUUCAGGGAACUGAAGC
183	UUCUUUCAGGGAACUGAAG
184	UGUCUUUCAGGGAACUGAA
185	UAGUCUUUCAGGGAACUGA
186	UUAGUCUUUCAGGGAACUG
187	UGUAGUCUUUCAGGGAACU
188	UAGUAGUCUUUCAGGGAAC
189	UCAGUAGUCUUUCAGGGAA
190	UCCAGUAGUCUUUCAGGGA
191	UUCCAGUAGUCUUUCAGGG
192	UCUCCAGUAGUCUUUCAGG
193	UGCUCCAGUAGUCUUUCAG
194	UUGCUCCAGUAGUCUUUCA
195	UGUGCUCCAGUAGUCUUUC
196	UGGUGCUCCAGUAGUCUUU
197	UCGGUGCUCCAGUAGUCUU
198	UACGGUGCUCCAGUAGUCU

199	UAACGGUGCUCCAGUAGUC
200	UUAACGGUGCUCCAGUAGU
201	UUUAACGGUGCUCCAGUAG
202	UCUUAACGGUGCUCCAGUA
203	UCCUUAACGGUGCUCCAGU
204	UUCCUUAACGGUGCUCCAG
205	UGUCCUUAACGGUGCUCCA
206	UUGUCCUUAACGGUGCUCC
207	UUUGUCCUUAACGGUGCUC
208	UCUUGUCCUUAACGGUGCU
209	UACUUGUCCUUAACGGUGC
210	UAACUUGUCCUUAACGGUG
211	UGAACUUGUCCUUAACGGU
212	UAGAACUUGUCCUUAACGG
213	UGAGAACUUGUCCUUAACG
214	UAGAGAACUUGUCCUUAAC
215	UCAGAGAACUUGUCCUUAA
216	UUCAGAGAACUUGUCCUUA
217	UCUCAGAGAACUUGUCCUU
218	UACUCAGAGAACUUGUCCU
219	UAACUCAGAGAACUUGUCC
220	UGAACUCAGAGAACUUGUC
221	UCAGAACUCAGAGAACUUG
222	UCCAGAACUCAGAGAACUU
223	UCCCAGAACUCAGAGAACU
224	UUCCCAGAACUCAGAGAAC
225	UAUCCCAGAACUCAGAGAA
226	UAAUCCCAGAACUCAGAGA
227	UAAAUCCCAGAACUCAGAG
228	UCAAAUCCCAGAACUCAGA
229	UCCAAAUCCCAGAACUCAG
230	UUCCAAAUCCCAGAACUCA
231	UGUCCAAAUCCCAGAACUC
232	UGGUCCAAAUCCCAGAACU
233	UGGGUCCAAAUCCCAGAAC
234	UAGGGUCCAAAUCCCAGAA
235	UCAGGGUCCAAAUCCCAGA
236	UUCAGGGUCCAAAUCCCAG
237	UGACCUCAGGGUCCAAAUC
238	UUGACCUCAGGGUCCAAAU
239	UCUGACCUCAGGGUCCAAA
240	UUCUGACCUCAGGGUCCAA
241	UGUCUGACCUCAGGGUCCA
242	UGGUCUGACCUCAGGGUCC
243	UUGGUCUGACCUCAGGGUC
244	UUUGGUCUGACCUCAGGGU
245	UGUUGGUCUGACCUCAGGG
246	UAGUUGGUCUGACCUCAGG
247	UAAGUUGGUCUGACCUCAG
248	UGAAGUUGGUCUGACCUCA
249	UUGAAGUUGGUCUGACCUC
250	UCUGAAGUUGGUCUGACCU
251	UGGCUGAAGUUGGUCUGAC
252	UCGGCUGAAGUUGGUCUGA
253	UACGGCUGAAGUUGGUCUG
254	UCACGGCUGAAGUUGGUCU
255	UCCACGGCUGAAGUUGGUC

256	UGCCACGGCUGAAGUUGGU
257	UCAGCCACGGCUGAAGUUG
258	UGCAGCCACGGCUGAAGUU
259	UGGCAGCCACGGCUGAAGU
260	UAGGCAGCCACGGCUGAAG
261	UCAGGCAGCCACGGCUGAA
262	UUCUCAGGCAGCCACGGCU
263	UGUCUCAGGCAGCCACGGC
264	UGGUCUCAGGCAGCCACGG
265	UAGGUCUCAGGCAGCCACG
266	UUGAGGUCUCAGGCAGCCA
267	UUUGAGGUCUCAGGCAGCC
268	UAUUGAGGUCUCAGGCAGC
269	UUAUUGAGGUCUCAGGCAG
270	UGUAUUGAGGUCUCAGGCA
271	UGGUAUUGAGGUCUCAGGC
272	UGGGUAUUGAGGUCUCAGG
273	UUAGGCAGGUGGACUUGGG
274	UAUAGGCAGGUGGACUUGG
275	UGAUAGGCAGGUGGACUUG
276	UGGAUAGGCAGGUGGACUU
277	UUGGAUAGGCAGGUGGACU
278	UAUGGAUAGGCAGGUGGAC
279	UGAUGGAUAGGCAGGUGGA
280	UGGAUGGAUAGGCAGGUGG
281	UAGGAUGGAUAGGCAGGUG
282	UCAGGAUGGAUAGGCAGGU
283	UGCAGGAUGGAUAGGCAGG
284	UCGCAGGAUGGAUAGGCAG
285	UUCGCAGGAUGGAUAGGCA
286	UCUCGCAGGAUGGAUAGGC
287	UGCUCGCAGGAUGGAUAGG
288	UAGCUCGCAGGAUGGAUAG
289	UGAGCUCGCAGGAUGGAUA
290	UGGAGCUCGCAGGAUGGAU
291	UAGGAGCUCGCAGGAUGGA
292	UAAGGAGCUCGCAGGAUGG
293	UCAAGGAGCUCGCAGGAUG
294	UCCAAGGAGCUCGCAGGAU
295	UCCCAAGGAGCUCGCAGGA
296	UACCCAAGGAGCUCGCAGG
297	UGACCCAAGGAGCUCGCAG
298	UGGACCCAAGGAGCUCGCA
299	UAGGACCCAAGGAGCUCGC
300	UCAGGACCCAAGGAGCUCG
301	UGCAGGACCCAAGGAGCUC
302	UUGCAGGACCCAAGGAGCU
303	UUUGCAGGACCCAAGGAGC
304	UAUUGCAGGACCCAAGGAG
305	UGAUUGCAGGACCCAAGGA
306	UAGAUUGCAGGACCCAAGG
307	UGAGAUUGCAGGACCCAAG
308	UGGAGAUUGCAGGACCCAA
309	UUGGAGAUUGCAGGACCCA
310	UCUGGAGAUUGCAGGACCC
311	UCCUGGAGAUUGCAGGACC
312	UCCCUGGAGAUUGCAGGAC

313	UGCCCUGGAGAUUGCAGGA
314	UAGCCCUGGAGAUUGCAGG
315	UCAGCCCUGGAGAUUGCAG
316	UGCAGCCCUGGAGAUUGCA
317	UGGCAGCCCUGGAGAUUGC
318	UGGGCAGCCCUGGAGAUUG
319	UUUUAAGCAACCUACAGGG
320	UUUUUAAGCAACCUACAGG
321	UCUUUUAAGCAACCUACAG
322	UCCUUUUAAGCAACCUACA
323	UCCCUUUUAAGCAACCUAC
324	UUCCCUUUUAAGCAACCUA
325	UGUCCCUUUUAAGCAACCU
326	UACUGUCCCUUUUAAGCAA
327	UUACUGUCCCUUUUAAGCA
328	UAUACUGUCCCUUUUAAGC
329	UAAUACUGUCCCUUUUAAG
330	UGAAUACUGUCCCUUUUAA
331	UAGAAUACUGUCCCUUUUA
332	UGAGAAUACUGUCCCUUUU
333	UUGAGAAUACUGUCCCUUU
334	UCUGAGAAUACUGUCCCUU
335	UACUGAGAAUACUGUCCCU
336	UCACUGAGAAUACUGUCCC
337	UGCACUGAGAAUACUGUCC
338	UAGCACUGAGAAUACUGUC
339	UGAGCACUGAGAAUACUGU
340	UAGAGCACUGAGAAUACUG
341	UGAGAGCACUGAGAAUACU
342	UGGAGAGCACUGAGAAUAC
343	UAGGAGAGCACUGAGAAUA
344	UUAGGAGAGCACUGAGAAU
345	UGUAGGAGAGCACUGAGAA
346	UGGUAGGAGAGCACUGAGA
347	UGGGUAGGAGAGCACUGAG
348	UGGCCAGGCAUGAGGUGGG
349	UGGGCCAGGCAUGAGGUGG
350	UGCCAGCAUGCCUGGAGGG
351	UGGCCAGCAUGCCUGGAGG
352	UAGGCCAGCAUGCCUGGAG
353	UGAGGCCAGCAUGCCUGGA
354	UGGAGGCCAGCAUGCCUGG
355	UGGGAGGCCAGCAUGCCUG
356	UUGGGAGGCCAGCAUGCCU
357	UAUUGGGAGGCCAGCAUGC
358	UUAUUGGGAGGCCAGCAUG
359	UUUAUUGGGAGGCCAGCAU
360	UUUUAUUGGGAGGCCAGCA
361	UCUUUAUUGGGAGGCCAGC
362	UGCUUUAUUGGGAGGCCAG
363	UAGCUUUAUUGGGAGGCCA
364	UCAGCUUUAUUGGGAGGCC
365	UCCAGCUUUAUUGGGAGGC
366	UUCCAGCUUUAUUGGGAGG
367	UGUCCAGCUUUAUUGGGAG
368	UUUGUCCAGCUUUAUUGGG
369	UCUUGUCCAGCUUUAUUGG

370	UUCUUGUCCAGCUUUAUUG
371	UUUCUUGUCCAGCUUUAUU
372	UCUUCUUGUCCAGCUUUAU
373	UGCUUCUUGUCCAGCUUUA
374	UGCAGCUUCUUGUCCAGCU
375	UUAGCAGCUUCUUGUCCAG
376	UAUAGCAGCUUCUUGUCCA

Table 1b: Nucleobase sequences and sugar-phosphate backbone modifications of the antisense strands of 376 exemplary constructs:

#	Oligo Sequence (5' to 3') and backbone modifications
1	PmU.fU.mC.fU.mA.fG.mG.fG.mA.fU.mG.fA.mA.fC.mU.fG.mA.fG.mC
2	PmU.fC.mU.fC.mU.fA.mG.fG.mG.fA.mU.fG.mA.fA.mC.fU.mG.fA.mG
3	PmU.fC.mC.fU.mC.fU.mA.fG.mG.fG.mA.fU.mG.fA.mA.fC.mU.fG.mA
4	PmU.fG.mC.fC.mU.fC.mU.fA.mG.fG.mG.fA.mU.fG.mA.fA.mC.fU.mG
5	PmU.fU.mG.fC.mC.fU.mC.fU.mA.fG.mG.fG.mA.fU.mG.fA.mA.fC.mU
6	PmU.fC.mU.fG.mC.fC.mU.fC.mU.fA.mG.fG.mG.fA.mU.fG.mA.fA.mC
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135	PmU.fA.mG.fU.mG.fC.mA.fU.mC.fC.mU.fU.mG.fG.mC.fG.mG.fU.mC
136	PmU.fC.mA.fG.mU.fG.mC.fA.mU.fC.mC.fU.mU.fG.mG.fC.mG.fG.mU
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150	PmU.fU.mC.fC.mU.fG.mC.fA.mC.fG.mC.fU.mG.fC.mU.fC.mA.fG.mU
151	PmU.fA.mC.fU.mC.fC.mU.fG.mC.fA.mC.fG.mC.fU.mG.fC.mU.fC.mA
152	PmU.fG.mG.fG.mA.fC.mU.fC.mC.fU.mG.fC.mA.fC.mG.fC.mU.fG.mC
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157	PmU.fC.mA.fC.mC.fU.mG.fG.mG.fA.mC.fU.mC.fC.mU.fG.mC.fA.mC
158	PmU.fC.mC.fA.mC.fC.mU.fG.mG.fG.mA.fC.mU.fC.mC.fU.mG.fC.mA

159	PmU.fG.mG.fG.mC.fC.mA.fC.mC.fU.mG.fG.mG.fA.mC.fU.mC.fC.mU
160	PmU.fU.mG.fG.mG.fC.mC.fA.mC.fC.mU.fG.mG.fG.mA.fC.mU.fC.mC
161	PmU.fU.mG.fC.mU.fG.mG.fG.mC.fC.mA.fC.mC.fU.mG.fG.mG.fA.mC
162	PmU.fC.mU.fG.mC.fU.mG.fG.mG.fC.mC.fA.mC.fC.mU.fG.mG.fG.mA
163	PmU.fG.mG.fC.mC.fU.mG.fC.mU.fG.mG.fG.mC.fC.mA.fC.mC.fU.mG
164	PmU.fC.mC.fU.mG.fG.mC.fC.mU.fG.mC.fU.mG.fG.mG.fC.mC.fA.mC
165	PmU.fC.mC.fA.mU.fC.mG.fG.mU.fC.mA.fC.mC.fC.mA.fG.mC.fC.mC
166	PmU.fG.mC.fC.mA.fU.mC.fG.mG.fU.mC.fA.mC.fC.mC.fA.mG.fC.mC
167	PmU.fA.mG.fC.mC.fA.mU.fC.mG.fG.mU.fC.mA.fC.mC.fC.mA.fG.mC
168	PmU.fA.mA.fG.mC.fC.mA.fU.mC.fG.mG.fU.mC.fA.mC.fC.mC.fA.mG
169	PmU.fG.mA.fA.mG.fC.mC.fA.mU.fC.mG.fG.mU.fC.mA.fC.mC.fC.mA
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171	PmU.fC.mU.fG.mA.fA.mG.fC.mC.fA.mU.fC.mG.fG.mU.fC.mA.fC.mC
172	PmU.fA.mC.fU.mG.fA.mA.fG.mC.fC.mA.fU.mC.fG.mG.fU.mC.fA.mC
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175	PmU.fG.mG.fA.mA.fC.mU.fG.mA.fA.mG.fC.mC.fA.mU.fC.mG.fG.mU
176	PmU.fG.mG.fG.mA.fA.mC.fU.mG.fA.mA.fG.mC.fC.mA.fU.mC.fG.mG
177	PmU.fA.mG.fG.mG.fA.mA.fC.mU.fG.mA.fA.mG.fC.mC.fA.mU.fC.mG
178	PmU.fC.mA.fG.mG.fG.mA.fA.mC.fU.mG.fA.mA.fG.mC.fC.mA.fU.mC
179	PmU.fU.mC.fA.mG.fG.mG.fA.mA.fC.mU.fG.mA.fA.mG.fC.mC.fA.mU
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190	PmU.fC.mC.fA.mG.fU.mA.fG.mU.fC.mU.fU.mU.fC.mA.fG.mG.fG.mA
191	PmU.fU.mC.fC.mA.fG.mU.fA.mG.fU.mC.fU.mU.fU.mC.fA.mG.fG.mG
192	PmU.fC.mU.fC.mC.fA.mG.fU.mA.fG.mU.fC.mU.fU.mU.fC.mA.fG.mG
193	PmU.fG.mC.fU.mC.fC.mA.fG.mU.fA.mG.fU.mC.fU.mU.fU.mC.fA.mG
194	PmU.fU.mG.fC.mU.fC.mC.fA.mG.fU.mA.fG.mU.fC.mU.fU.mU.fC.mA
195	PmU.fG.mU.fG.mC.fU.mC.fC.mA.fG.mU.fA.mG.fU.mC.fU.mU.fU.mC
196	PmU.fG.mG.fU.mG.fC.mU.fC.mC.fA.mG.fU.mA.fG.mU.fC.mU.fU.mU
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199	PmU.fA.mA.fC.mG.fG.mU.fG.mC.fU.mC.fC.mA.fG.mU.fA.mG.fU.mC
200	PmU.fU.mA.fA.mC.fG.mG.fU.mG.fC.mU.fC.mC.fA.mG.fU.mA.fG.mU
201	PmU.fU.mU.fA.mA.fC.mG.fG.mU.fG.mC.fU.mC.fC.mA.fG.mU.fA.mG
202	PmU.fC.mU.fU.mA.fA.mC.fG.mG.fU.mG.fC.mU.fC.mC.fA.mG.fU.mA
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207	PmU.fU.mU.fG.mU.fC.mC.fU.mU.fA.mA.fC.mG.fG.mU.fG.mC.fU.mC
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214	PmU.fA.mG.fA.mG.fA.mA.fC.mU.fU.mG.fU.mC.fC.mU.fU.mA.fA.mC
215	PmU.fC.mA.fG.mA.fG.mA.fA.mC.fU.mU.fG.mU.fC.mC.fU.mU.fA.mA

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217	PmU.fC.mU.fC.mA.fG.mA.fG.mA.fA.mC.fU.mU.fG.mU.fC.mC.fU.mU
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219	PmU.fA.mA.fC.mU.fC.mA.fG.mA.fG.mA.fA.mC.fU.mU.fG.mU.fC.mC
220	PmU.fG.mA.fA.mC.fU.mC.fA.mG.fA.mG.fA.mA.fC.mU.fU.mG.fU.mC
221	PmU.fC.mA.fG.mA.fA.mC.fU.mC.fA.mG.fA.mG.fA.mA.fC.mU.fU.mG
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224	PmU.fU.mC.fC.mC.fA.mG.fA.mA.fC.mU.fC.mA.fG.mA.fG.mA.fA.mC
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227	PmU.fA.mA.fA.mU.fC.mC.fC.mA.fG.mA.fA.mC.fU.mC.fA.mG.fA.mG
228	PmU.fC.mA.fA.mA.fU.mC.fC.mC.fA.mG.fA.mA.fC.mU.fC.mA.fG.mA
229	PmU.fC.mC.fA.mA.fA.mU.fC.mC.fC.mA.fG.mA.fA.mC.fU.mC.fA.mG
230	PmU.fU.mC.fC.mA.fA.mA.fU.mC.fC.mC.fA.mG.fA.mA.fC.mU.fC.mA
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232	PmU.fG.mG.fU.mC.fC.mA.fA.mA.fU.mC.fC.mC.fA.mG.fA.mA.fC.mU
233	PmU.fG.mG.fG.mU.fC.mC.fA.mA.fA.mU.fC.mC.fC.mA.fG.mA.fA.mC
234	PmU.fA.mG.fG.mG.fU.mC.fC.mA.fA.mA.fU.mC.fC.mC.fA.mG.fA.mA
235	PmU.fC.mA.fG.mG.fG.mU.fC.mC.fA.mA.fA.mU.fC.mC.fC.mA.fG.mA
236	PmU.fU.mC.fA.mG.fG.mG.fU.mC.fC.mA.fA.mA.fU.mC.fC.mC.fA.mG
237	PmU.fG.mA.fC.mC.fU.mC.fA.mG.fG.mG.fU.mC.fC.mA.fA.mA.fU.mC
238	PmU.fU.mG.fA.mC.fC.mU.fC.mA.fG.mG.fG.mU.fC.mC.fA.mA.fA.mU
239	PmU.fC.mU.fG.mA.fC.mC.fU.mC.fA.mG.fG.mG.fU.mC.fC.mA.fA.mA
240	PmU.fU.mC.fU.mG.fA.mC.fC.mU.fC.mA.fG.mG.fG.mU.fC.mC.fA.mA
241	PmU.fG.mU.fC.mU.fG.mA.fC.mC.fU.mC.fA.mG.fG.mG.fU.mC.fC.mA
242	PmU.fG.mG.fU.mC.fU.mG.fA.mC.fC.mU.fC.mA.fG.mG.fG.mU.fC.mC
243	PmU.fU.mG.fG.mU.fC.mU.fG.mA.fC.mC.fU.mC.fA.mG.fG.mG.fU.mC
244	PmU.fU.mU.fG.mG.fU.mC.fU.mG.fA.mC.fC.mU.fC.mA.fG.mG.fG.mU
245	PmU.fG.mU.fU.mG.fG.mU.fC.mU.fG.mA.fC.mC.fU.mC.fA.mG.fG.mG
246	PmU.fA.mG.fU.mU.fG.mG.fU.mC.fU.mG.fA.mC.fC.mU.fC.mA.fG.mG
247	PmU.fA.mA.fG.mU.fU.mG.fG.mU.fC.mU.fG.mA.fC.mC.fU.mC.fA.mG
248	PmU.fG.mA.fA.mG.fU.mU.fG.mG.fU.mC.fU.mG.fA.mC.fC.mU.fC.mA
249	PmU.fU.mG.fA.mA.fG.mU.fU.mG.fG.mU.fC.mU.fG.mA.fC.mC.fU.mC
250	PmU.fC.mU.fG.mA.fA.mG.fU.mU.fG.mG.fU.mC.fU.mG.fA.mC.fC.mU
251	PmU.fG.mG.fC.mU.fG.mA.fA.mG.fU.mU.fG.mG.fU.mC.fU.mG.fA.mC
252	PmU.fC.mG.fG.mC.fU.mG.fA.mA.fG.mU.fU.mG.fG.mU.fC.mU.fG.mA
253	PmU.fA.mC.fG.mG.fC.mU.fG.mA.fA.mG.fU.mU.fG.mG.fU.mC.fU.mG
254	PmU.fC.mA.fC.mG.fG.mC.fU.mG.fA.mA.fG.mU.fU.mG.fG.mU.fC.mU
255	PmU.fC.mC.fA.mC.fG.mG.fC.mU.fG.mA.fA.mG.fU.mU.fG.mG.fU.mC
256	PmU.fG.mC.fC.mA.fC.mG.fG.mC.fU.mG.fA.mA.fG.mU.fU.mG.fG.mU
257	PmU.fC.mA.fG.mC.fC.mA.fC.mG.fG.mC.fU.mG.fA.mA.fG.mU.fU.mG
258	PmU.fG.mC.fA.mG.fC.mC.fA.mC.fG.mG.fC.mU.fG.mA.fA.mG.fU.mU
259	PmU.fG.mG.fC.mA.fG.mC.fC.mA.fC.mG.fG.mC.fU.mG.fA.mA.fG.mU
260	PmU.fA.mG.fG.mC.fA.mG.fC.mC.fA.mC.fG.mG.fC.mU.fG.mA.fA.mG
261	PmU.fC.mA.fG.mG.fC.mA.fG.mC.fC.mA.fC.mG.fG.mC.fU.mG.fA.mA
262	PmU.fU.mC.fU.mC.fA.mG.fG.mC.fA.mG.fC.mC.fA.mC.fG.mG.fC.mU
263	PmU.fG.mU.fC.mU.fC.mA.fG.mG.fC.mA.fG.mC.fC.mA.fC.mG.fG.mC
264	PmU.fG.mG.fU.mC.fU.mC.fA.mG.fG.mC.fA.mG.fC.mC.fA.mC.fG.mG
265	PmU.fA.mG.fG.mU.fC.mU.fC.mA.fG.mG.fC.mA.fG.mC.fC.mA.fC.mG
266	PmU.fU.mG.fA.mG.fG.mU.fC.mU.fC.mA.fG.mG.fC.mA.fG.mC.fC.mA
267	PmU.fU.mU.fG.mA.fG.mG.fU.mC.fU.mC.fA.mG.fG.mC.fA.mG.fC.mC
268	PmU.fA.mU.fU.mG.fA.mG.fG.mU.fC.mU.fC.mA.fG.mG.fC.mA.fG.mC
269	PmU.fU.mA.fU.mU.fG.mA.fG.mG.fU.mC.fU.mC.fA.mG.fG.mC.fA.mG
270	PmU.fG.mU.fA.mU.fU.mG.fA.mG.fG.mU.fC.mU.fC.mA.fG.mG.fC.mA
271	PmU.fG.mG.fU.mA.fU.mU.fG.mA.fG.mG.fU.mC.fU.mC.fA.mG.fG.mC
272	PmU.fG.mG.fG.mU.fA.mU.fU.mG.fA.mG.fG.mU.fC.mU.fC.mA.fG.mG

273	PmU.fU.mA.fG.mG.fC.mA.fG.mG.fU.mG.fG.mA.fC.mU.fU.mG.fG.mG
274	PmU.fA.mU.fA.mG.fG.mC.fA.mG.fG.mU.fG.mG.fA.mC.fU.mU.fG.mG
275	PmU.fG.mA.fU.mA.fG.mG.fC.mA.fG.mG.fU.mG.fG.mA.fC.mU.fU.mG
276	PmU.fG.mG.fA.mU.fA.mG.fG.mC.fA.mG.fG.mU.fG.mG.fA.mC.fU.mU
277	PmU.fU.mG.fG.mA.fU.mA.fG.mG.fC.mA.fG.mG.fU.mG.fG.mA.fC.mU
278	PmU.fA.mU.fG.mG.fA.mU.fA.mG.fG.mC.fA.mG.fG.mU.fG.mG.fA.mC
279	PmU.fG.mA.fU.mG.fG.mA.fU.mA.fG.mG.fC.mA.fG.mG.fU.mG.fG.mA
280	PmU.fG.mG.fA.mU.fG.mG.fA.mU.fA.mG.fG.mC.fA.mG.fG.mU.fG.mG
281	PmU.fA.mG.fG.mA.fU.mG.fG.mA.fU.mA.fG.mG.fC.mA.fG.mG.fU.mG
282	PmU.fC.mA.fG.mG.fA.mU.fG.mG.fA.mU.fA.mG.fG.mC.fA.mG.fG.mU
283	PmU.fG.mC.fA.mG.fG.mA.fU.mG.fG.mA.fU.mA.fG.mG.fC.mA.fG.mG
284	PmU.fC.mG.fC.mA.fG.mG.fA.mU.fG.mG.fA.mU.fA.mG.fG.mC.fA.mG
285	PmU.fU.mC.fG.mC.fA.mG.fG.mA.fU.mG.fG.mA.fU.mA.fG.mG.fC.mA
286	PmU.fC.mU.fC.mG.fC.mA.fG.mG.fA.mU.fG.mG.fA.mU.fA.mG.fG.mC
287	PmU.fG.mC.fU.mC.fG.mC.fA.mG.fG.mA.fU.mG.fG.mA.fU.mA.fG.mG
288	PmU.fA.mG.fC.mU.fC.mG.fC.mA.fG.mG.fA.mU.fG.mG.fA.mU.fA.mG
289	PmU.fG.mA.fG.mC.fU.mC.fG.mC.fA.mG.fG.mA.fU.mG.fG.mA.fU.mA
290	PmU.fG.mG.fA.mG.fC.mU.fC.mG.fC.mA.fG.mG.fA.mU.fG.mG.fA.mU
291	PmU.fA.mG.fG.mA.fG.mC.fU.mC.fG.mC.fA.mG.fG.mA.fU.mG.fG.mA
292	PmU.fA.mA.fG.mG.fA.mG.fC.mU.fC.mG.fC.mA.fG.mG.fA.mU.fG.mG
293	PmU.fC.mA.fA.mG.fG.mA.fG.mC.fU.mC.fG.mC.fA.mG.fG.mA.fU.mG
294	PmU.fC.mC.fA.mA.fG.mG.fA.mG.fC.mU.fC.mG.fC.mA.fG.mG.fA.mU
295	PmU.fC.mC.fC.mA.fA.mG.fG.mA.fG.mC.fU.mC.fG.mC.fA.mG.fG.mA
296	PmU.fA.mC.fC.mC.fA.mA.fG.mG.fA.mG.fC.mU.fC.mG.fC.mA.fG.mG
297	PmU.fG.mA.fC.mC.fC.mA.fA.mG.fG.mA.fG.mC.fU.mC.fG.mC.fA.mG
298	PmU.fG.mG.fA.mC.fC.mC.fA.mA.fG.mG.fA.mG.fC.mU.fC.mG.fC.mA
299	PmU.fA.mG.fG.mA.fC.mC.fC.mA.fA.mG.fG.mA.fG.mC.fU.mC.fG.mC
300	PmU.fC.mA.fG.mG.fA.mC.fC.mC.fA.mA.fG.mG.fA.mG.fC.mU.fC.mG
301	PmU.fG.mC.fA.mG.fG.mA.fC.mC.fC.mA.fA.mG.fG.mA.fG.mC.fU.mC
302	PmU.fU.mG.fC.mA.fG.mG.fA.mC.fC.mC.fA.mA.fG.mG.fA.mG.fC.mU
303	PmU.fU.mU.fG.mC.fA.mG.fG.mA.fC.mC.fC.mA.fA.mG.fG.mA.fG.mC
304	PmU.fA.mU.fU.mG.fC.mA.fG.mG.fA.mC.fC.mC.fA.mA.fG.mG.fA.mG
305	PmU.fG.mA.fU.mU.fG.mC.fA.mG.fG.mA.fC.mC.fC.mA.fA.mG.fG.mA
306	PmU.fA.mG.fA.mU.fU.mG.fC.mA.fG.mG.fA.mC.fC.mC.fA.mA.fG.mG
307	PmU.fG.mA.fG.mA.fU.mU.fG.mC.fA.mG.fG.mA.fC.mC.fC.mA.fA.mG
308	PmU.fG.mG.fA.mG.fA.mU.fU.mG.fC.mA.fG.mG.fA.mC.fC.mC.fA.mA
309	PmU.fU.mG.fG.mA.fG.mA.fU.mU.fG.mC.fA.mG.fG.mA.fC.mC.fC.mA
310	PmU.fC.mU.fG.mG.fA.mG.fA.mU.fU.mG.fC.mA.fG.mG.fA.mC.fC.mC
311	PmU.fC.mC.fU.mG.fG.mA.fG.mA.fU.mU.fG.mC.fA.mG.fG.mA.fC.mC
312	PmU.fC.mC.fC.mU.fG.mG.fA.mG.fA.mU.fU.mG.fC.mA.fG.mG.fA.mC
313	PmU.fG.mC.fC.mC.fU.mG.fG.mA.fG.mA.fU.mU.fG.mC.fA.mG.fG.mA
314	PmU.fA.mG.fC.mC.fC.mU.fG.mG.fA.mG.fA.mU.fU.mG.fC.mA.fG.mG
315	PmU.fC.mA.fG.mC.fC.mC.fU.mG.fG.mA.fG.mA.fU.mU.fG.mC.fA.mG
316	PmU.fG.mC.fA.mG.fC.mC.fC.mU.fG.mG.fA.mG.fA.mU.fU.mG.fC.mA
317	PmU.fG.mG.fC.mA.fG.mC.fC.mC.fU.mG.fG.mA.fG.mA.fU.mU.fG.mC
318	PmU.fG.mG.fG.mC.fA.mG.fC.mC.fC.mU.fG.mG.fA.mG.fA.mU.fU.mG
319	PmU.fU.mU.fU.mA.fA.mG.fC.mA.fA.mC.fC.mU.fA.mC.fA.mG.fG.mG
320	PmU.fU.mU.fU.mU.fA.mA.fG.mC.fA.mA.fC.mC.fU.mA.fC.mA.fG.mG
321	PmU.fC.mU.fU.mU.fU.mA.fA.mG.fC.mA.fA.mC.fC.mU.fA.mC.fA.mG
322	PmU.fC.mC.fU.mU.fU.mU.fA.mA.fG.mC.fA.mA.fC.mC.fU.mA.fC.mA
323	PmU.fC.mC.fC.mU.fU.mU.fU.mA.fA.mG.fC.mA.fA.mC.fC.mU.fA.mC
324	PmU.fU.mC.fC.mC.fU.mU.fU.mU.fA.mA.fG.mC.fA.mA.fC.mC.fU.mA
325	PmU.fG.mU.fC.mC.fC.mU.fU.mU.fU.mA.fA.mG.fC.mA.fA.mC.fC.mU
326	PmU.fA.mC.fU.mG.fU.mC.fC.mC.fU.mU.fU.mU.fA.mA.fG.mC.fA.mA
327	PmU.fU.mA.fC.mU.fG.mU.fC.mC.fC.mU.fU.mU.fU.mA.fA.mG.fC.mA
328	PmU.fA.mU.fA.mC.fU.mG.fU.mC.fC.mC.fU.mU.fU.mU.fA.mA.fG.mC
329	PmU.fA.mA.fU.mA.fC.mU.fG.mU.fC.mC.fC.mU.fU.mU.fU.mA.fA.mG

330	PmU.fG.mA.fA.mU.fA.mC.fU.mG.fU.mC.fC.mC.fU.mU.fU.mU.fA.mA
331	PmU.fA.mG.fA.mA.fU.mA.fC.mU.fG.mU.fC.mC.fC.mU.fU.mU.fU.mA
332	PmU.fG.mA.fG.mA.fA.mU.fA.mC.fU.mG.fU.mC.fC.mC.fU.mU.fU.mU
333	PmU.fU.mG.fA.mG.fA.mA.fU.mA.fC.mU.fG.mU.fC.mC.fC.mU.fU.mU
334	PmU.fC.mU.fG.mA.fG.mA.fA.mU.fA.mC.fU.mG.fU.mC.fC.mC.fU.mU
335	PmU.fA.mC.fU.mG.fA.mG.fA.mA.fU.mA.fC.mU.fG.mU.fC.mC.fC.mU
336	PmU.fC.mA.fC.mU.fG.mA.fG.mA.fA.mU.fA.mC.fU.mG.fU.mC.fC.mC
337	PmU.fG.mC.fA.mC.fU.mG.fA.mG.fA.mA.fU.mA.fC.mU.fG.mU.fC.mC
338	PmU.fA.mG.fC.mA.fC.mU.fG.mA.fG.mA.fA.mU.fA.mC.fU.mG.fU.mC
339	PmU.fG.mA.fG.mC.fA.mC.fU.mG.fA.mG.fA.mA.fU.mA.fC.mU.fG.mU
340	PmU.fA.mG.fA.mG.fC.mA.fC.mU.fG.mA.fG.mA.fA.mU.fA.mC.fU.mG
341	PmU.fG.mA.fG.mA.fG.mC.fA.mC.fU.mG.fA.mG.fA.mA.fU.mA.fC.mU
342	PmU.fG.mG.fA.mG.fA.mG.fC.mA.fC.mU.fG.mA.fG.mA.fA.mU.fA.mC
343	PmU.fA.mG.fG.mA.fG.mA.fG.mC.fA.mC.fU.mG.fA.mG.fA.mA.fU.mA
344	PmU.fU.mA.fG.mG.fA.mG.fA.mG.fC.mA.fC.mU.fG.mA.fG.mA.fA.mU
345	PmU.fG.mU.fA.mG.fG.mA.fG.mA.fG.mC.fA.mC.fU.mG.fA.mG.fA.mA
346	PmU.fG.mG.fU.mA.fG.mG.fA.mG.fA.mG.fC.mA.fC.mU.fG.mA.fG.mA
347	PmU.fG.mG.fG.mU.fA.mG.fG.mA.fG.mA.fG.mC.fA.mC.fU.mG.fA.mG
348	PmU.fG.mG.fC.mC.fA.mG.fG.mC.fA.mU.fG.mA.fG.mG.fU.mG.fG.mG
349	PmU.fG.mG.fG.mC.fC.mA.fG.mG.fC.mA.fU.mG.fA.mG.fG.mU.fG.mG
350	PmU.fG.mC.fC.mA.fG.mC.fA.mU.fG.mC.fC.mU.fG.mG.fA.mG.fG.mG
351	PmU.fG.mG.fC.mC.fA.mG.fC.mA.fU.mG.fC.mC.fU.mG.fG.mA.fG.mG
352	PmU.fA.mG.fG.mC.fC.mA.fG.mC.fA.mU.fG.mC.fC.mU.fG.mG.fA.mG
353	PmU.fG.mA.fG.mG.fC.mC.fA.mG.fC.mA.fU.mG.fC.mC.fU.mG.fG.mA
354	PmU.fG.mG.fA.mG.fG.mC.fC.mA.fG.mC.fA.mU.fG.mC.fC.mU.fG.mG
355	PmU.fG.mG.fG.mA.fG.mG.fC.mC.fA.mG.fC.mA.fU.mG.fC.mC.fU.mG
356	PmU.fU.mG.fG.mG.fA.mG.fG.mC.fC.mA.fG.mC.fA.mU.fG.mC.fC.mU
357	PmU.fA.mU.fU.mG.fG.mG.fA.mG.fG.mC.fC.mA.fG.mC.fA.mU.fG.mC
358	PmU.fU.mA.fU.mU.fG.mG.fG.mA.fG.mG.fC.mC.fA.mG.fC.mA.fU.mG
359	PmU.fU.mU.fA.mU.fU.mG.fG.mG.fA.mG.fG.mC.fC.mA.fG.mC.fA.mU
360	PmU.fU.mU.fU.mA.fU.mU.fG.mG.fG.mA.fG.mG.fC.mC.fA.mG.fC.mA
361	PmU.fC.mU.fU.mU.fA.mU.fU.mG.fG.mG.fA.mG.fG.mC.fC.mA.fG.mC
362	PmU.fG.mC.fU.mU.fU.mA.fU.mU.fG.mG.fG.mA.fG.mG.fC.mC.fA.mG
363	PmU.fA.mG.fC.mU.fU.mU.fA.mU.fU.mG.fG.mG.fA.mG.fG.mC.fC.mA
364	PmU.fC.mA.fG.mC.fU.mU.fU.mA.fU.mU.fG.mG.fG.mA.fG.mG.fC.mC
365	PmU.fC.mC.fA.mG.fC.mU.fU.mU.fA.mU.fU.mG.fG.mG.fA.mG.fG.mC
366	PmU.fU.mC.fC.mA.fG.mC.fU.mU.fU.mA.fU.mU.fG.mG.fG.mA.fG.mG
367	PmU.fG.mU.fC.mC.fA.mG.fC.mU.fU.mU.fA.mU.fU.mG.fG.mG.fA.mG
368	PmU.fU.mU.fG.mU.fC.mC.fA.mG.fC.mU.fU.mU.fA.mU.fU.mG.fG.mG
369	PmU.fC.mU.fU.mG.fU.mC.fC.mA.fG.mC.fU.mU.fU.mA.fU.mU.fG.mG
370	PmU.fU.mC.fU.mU.fG.mU.fC.mC.fA.mG.fC.mU.fU.mU.fA.mU.fU.mG
371	PmU.fU.mU.fC.mU.fU.mG.fU.mC.fC.mA.fG.mC.fU.mU.fU.mA.fU.mU
372	PmU.fC.mU.fU.mC.fU.mU.fG.mU.fC.mC.fA.mG.fC.mU.fU.mU.fA.mU
373	PmU.fG.mC.fU.mU.fC.mU.fU.mG.fU.mC.fC.mA.fG.mC.fU.mU.fU.mA
374	PmU.fG.mC.fA.mG.fC.mU.fU.mC.fU.mU.fG.mU.fC.mC.fA.mG.fC.mU
375	PmU.fU.mA.fG.mC.fA.mG.fC.mU.fU.mC.fU.mU.fG.mU.fC.mC.fA.mG
376	PmU.fA.mU.fA.mG.fC.mA.fG.mC.fU.mU.fC.mU.fU.mG.fU.mC.fC.mA

Table 1c: Nucleobase sequences of the sense strands of 376 exemplary constructs:

#	Nucleobase sequence
1	AGUUCAUCCCUAGAA
2	GUUCAUCCCUAGAGA
3	UUCAUCCCUAGAGGA
4	UCAUCCCUAGAGGCA
5	CAUCCCUAGAGGCAA

6	AUCCCUAGAGGCAGA
7	UCCCUAGAGGCAGCA
8	CCCUAGAGGCAGCUA
9	CUAGAGGCAGCUGCA
10	UAGAGGCAGCUGCUA
11	AGAGGCAGCUGCUCA
12	GAGGCAGCUGCUCCA
13	CUGCUCCAGGAACAA
14	UGCUCCAGGAACAGA
15	UCCAGGAACAGAGGA
16	CCAGGAACAGAGGUA
17	CAGGAACAGAGGUGA
18	AGGAACAGAGGUGCA
19	GGAACAGAGGUGCCA
20	GAACAGAGGUGCCAA
21	AACAGAGGUGCCAUA
22	ACAGAGGUGCCAUGA
23	AGAGGUGCCAUGCAA
24	GAGGUGCCAUGCAGA
25	AGGUGCCAUGCAGCA
26	GGUGCCAUGCAGCCA
27	GUGCCAUGCAGCCCA
28	GGUACUCCUUGUUGA
29	GUACUCCUUGUUGUA
30	UACUCCUUGUUGUUA
31	ACUCCUUGUUGUUGA
32	CUCCUUGUUGUUGCA
33	UCCUUGUUGUUGCCA
34	CCUUGUUGUUGCCCA
35	CUUGUUGUUGCCCUA
36	UUGUUGUUGCCCUCA
37	UGUUGUUGCCCUCCA
38	GUUGUUGCCCUCCUA
39	UUGUUGCCCUCCUGA
40	UGUUGCCCUCCUGGA
41	GUUGCCCUCCUGGCA
42	UUGCCCUCCUGGCGA
43	UGCCCUCCUGGCGCA
44	GCCCUCCUGGCGCUA
45	CCCUCCUGGCGCUCA
46	CCUCCUGGCGCUCCA
47	CUCCUGGCGCUCCUA
48	CUGGCGCUCCUGGCA
49	CGCUCCUGGCCUCUA
50	GCUCCUGGCCUCUGA
51	CUCCUGGCCUCUGCA
52	UCCUGGCCUCUGCCA
53	CCUGGCCUCUGCCCA
54	UGGCCUCUGCCCGAA
55	GGCCUCUGCCCGAGA
56	GCCUCUGCCCGAGCA
57	CCUCUGCCCGAGCUA
58	CUCUGCCCGAGCUUA
59	UCUGCCCGAGCUUCA
60	CUGCCCGAGCUUCAA
61	UGCCCGAGCUUCAGA
62	GCCCGAGCUUCAGAA

63	CCCGAGCUUCAGAGA
64	CCGAGCUUCAGAGGA
65	CGAGCUUCAGAGGCA
66	GAGCUUCAGAGGCCA
67	AGCUUCAGAGGCCGA
68	GCUUCAGAGGCCGAA
69	CUUCAGAGGCCGAGA
70	UUCAGAGGCCGAGGA
71	UCAGAGGCCGAGGAA
72	CAGAGGCCGAGGAUA
73	AGAGGCCGAGGAUGA
74	GAGGCCGAGGAUGCA
75	AGGCCGAGGAUGCCA
76	GGCCGAGGAUGCCUA
77	GCCGAGGAUGCCUCA
78	CCGAGGAUGCCUCCA
79	CGAGGAUGCCUCCCA
80	GAGGAUGCCUCCCUA
81	AGGAUGCCUCCCUUA
82	GGAUGCCUCCCUUCA
83	GAUGCCUCCCUUCUA
84	AUGCCUCCCUUCUCA
85	UGCCUCCCUUCUCAA
86	GCCUCCCUUCUCAGA
87	CCUCCCUUCUCAGCA
88	CUCCCUUCUCAGCUA
89	CCUUCUCAGCUUCAA
90	CUUCUCAGCUUCAUA
91	UUCUCAGCUUCAUGA
92	UCUCAGCUUCAUGCA
93	CUCAGCUUCAUGCAA
94	UCAGCUUCAUGCAGA
95	CAGCUUCAUGCAGGA
96	AGCUUCAUGCAGGGA
97	GCUUCAUGCAGGGUA
98	CUUCAUGCAGGGUUA
99	UUCAUGCAGGGUUAA
100	UCAUGCAGGGUUACA
101	CAUGCAGGGUUACAA
102	AUGCAGGGUUACAUA
103	UGCAGGGUUACAUGA
104	GCAGGGUUACAUGAA
105	CAGGGUUACAUGAAA
106	AGGGUUACAUGAAGA
107	GGGUUACAUGAAGCA
108	GGUUACAUGAAGCAA
109	GUUACAUGAAGCACA
110	UUACAUGAAGCACGA
111	UACAUGAAGCACGCA
112	ACAUGAAGCACGCCA
113	CAUGAAGCACGCCAA
114	AUGAAGCACGCCACA
115	UGAAGCACGCCACCA
116	GAAGCACGCCACCAA
117	AAGCACGCCACCAAA
118	AGCACGCCACCAAGA
119	GCACGCCACCAAGAA

120	CACGCCACCAAGACA
121	ACGCCACCAAGACCA
122	CGCCACCAAGACCGA
123	GCCACCAAGACCGCA
124	CCACCAAGACCGCCA
125	CACCAAGACCGCCAA
126	ACCAAGACCGCCAAA
127	CCAAGACCGCCAAGA
128	CAAGACCGCCAAGGA
129	AAGACCGCCAAGGAA
130	AGACCGCCAAGGAUA
131	GACCGCCAAGGAUGA
132	ACCGCCAAGGAUGCA
133	CCGCCAAGGAUGCAA
134	CGCCAAGGAUGCACA
135	GCCAAGGAUGCACUA
136	CCAAGGAUGCACUGA
137	CAAGGAUGCACUGAA
138	AAGGAUGCACUGAGA
139	AGGAUGCACUGAGCA
140	GGAUGCACUGAGCAA
141	GAUGCACUGAGCAGA
142	AUGCACUGAGCAGCA
143	UGCACUGAGCAGCGA
144	GCACUGAGCAGCGUA
145	CACUGAGCAGCGUGA
146	ACUGAGCAGCGUGCA
147	CUGAGCAGCGUGCAA
148	UGAGCAGCGUGCAGA
149	GAGCAGCGUGCAGGA
150	AGCAGCGUGCAGGAA
151	CAGCGUGCAGGAGUA
152	CGUGCAGGAGUCCCA
153	GUGCAGGAGUCCCAA
154	UGCAGGAGUCCCAGA
155	GCAGGAGUCCCAGGA
156	CAGGAGUCCCAGGUA
157	AGGAGUCCCAGGUGA
158	GGAGUCCCAGGUGGA
159	GUCCCAGGUGGCCCA
160	UCCCAGGUGGCCCAA
161	CAGGUGGCCCAGCAA
162	AGGUGGCCCAGCAGA
163	UGGCCCAGCAGGCCA
164	CCCAGCAGGCCAGGA
165	UGGGUGACCGAUGGA
166	GGGUGACCGAUGGCA
167	GGUGACCGAUGGCUA
168	GUGACCGAUGGCUUA
169	UGACCGAUGGCUUCA
170	GACCGAUGGCUUCAA
171	ACCGAUGGCUUCAGA
172	CCGAUGGCUUCAGUA
173	CGAUGGCUUCAGUUA
174	GAUGGCUUCAGUUCA
175	AUGGCUUCAGUUCCA
176	UGGCUUCAGUUCCCA

177	GGCUUCAGUUCCCUA
178	GCUUCAGUUCCCUGA
179	CUUCAGUUCCCUGAA
180	UUCAGUUCCCUGAAA
181	UCAGUUCCCUGAAAA
182	CAGUUCCCUGAAAGA
183	AGUUCCCUGAAAGAA
184	GUUCCCUGAAAGACA
185	UUCCCUGAAAGACUA
186	UCCCUGAAAGACUAA
187	CCCUGAAAGACUACA
188	CCUGAAAGACUACUA
189	CUGAAAGACUACUGA
190	UGAAAGACUACUGGA
191	GAAAGACUACUGGAA
192	AAAGACUACUGGAGA
193	AAGACUACUGGAGCA
194	AGACUACUGGAGCAA
195	GACUACUGGAGCACA
196	ACUACUGGAGCACCA
197	CUACUGGAGCACCGA
198	UACUGGAGCACCGUA
199	ACUGGAGCACCGUUA
200	CUGGAGCACCGUUAA
201	UGGAGCACCGUUAAA
202	GGAGCACCGUUAAGA
203	GAGCACCGUUAAGGA
204	AGCACCGUUAAGGAA
205	GCACCGUUAAGGACA
206	CACCGUUAAGGACAA
207	ACCGUUAAGGACAAA
208	CCGUUAAGGACAAGA
209	CGUUAAGGACAAGUA
210	GUUAAGGACAAGUUA
211	UUAAGGACAAGUUCA
212	UAAGGACAAGUUCUA
213	AAGGACAAGUUCUCA
214	AGGACAAGUUCUCUA
215	GGACAAGUUCUCUGA
216	GACAAGUUCUCUGAA
217	ACAAGUUCUCUGAGA
218	CAAGUUCUCUGAGUA
219	AAGUUCUCUGAGUUA
220	AGUUCUCUGAGUUCA
221	UUCUCUGAGUUCUGA
222	UCUCUGAGUUCUGGA
223	CUCUGAGUUCUGGGA
224	UCUGAGUUCUGGGAA
225	CUGAGUUCUGGGAUA
226	UGAGUUCUGGGAUUA
227	GAGUUCUGGGAUUUA
228	AGUUCUGGGAUUUGA
229	GUUCUGGGAUUUGGA
230	UUCUGGGAUUUGGAA
231	UCUGGGAUUUGGACA
232	CUGGGAUUUGGACCA
233	UGGGAUUUGGACCCA

234	GGGAUUUGGACCCUA
235	GGAUUUGGACCCUGA
236	GAUUUGGACCCUGAA
237	UGGACCCUGAGGUCA
238	GGACCCUGAGGUCAA
239	GACCCUGAGGUCAGA
240	ACCCUGAGGUCAGAA
241	CCCUGAGGUCAGACA
242	CCUGAGGUCAGACCA
243	CUGAGGUCAGACCAA
244	UGAGGUCAGACCAAA
245	GAGGUCAGACCAACA
246	AGGUCAGACCAACUA
247	GGUCAGACCAACUUA
248	GUCAGACCAACUUCA
249	UCAGACCAACUUCAA
250	CAGACCAACUUCAGA
251	GACCAACUUCAGCCA
252	ACCAACUUCAGCCGA
253	CCAACUUCAGCCGUA
254	CAACUUCAGCCGUGA
255	AACUUCAGCCGUGGA
256	ACUUCAGCCGUGGCA
257	UUCAGCCGUGGCUGA
258	UCAGCCGUGGCUGCA
259	CAGCCGUGGCUGCCA
260	AGCCGUGGCUGCCUA
261	GCCGUGGCUGCCUGA
262	GUGGCUGCCUGAGAA
263	UGGCUGCCUGAGACA
264	GGCUGCCUGAGACCA
265	GCUGCCUGAGACCUA
266	UGCCUGAGACCUCAA
267	GCCUGAGACCUCAAA
268	CCUGAGACCUCAAUA
269	CUGAGACCUCAAUAA
270	UGAGACCUCAAUACA
271	GAGACCUCAAUACCA
272	AGACCUCAAUACCCA
273	AGUCCACCUGCCUAA
274	GUCCACCUGCCUAUA
275	UCCACCUGCCUAUCA
276	CCACCUGCCUAUCCA
277	CACCUGCCUAUCCAA
278	ACCUGCCUAUCCAUA
279	CCUGCCUAUCCAUCA
280	CUGCCUAUCCAUCCA
281	UGCCUAUCCAUCCUA
282	GCCUAUCCAUCCUGA
283	CCUAUCCAUCCUGCA
284	CUAUCCAUCCUGCGA
285	UAUCCAUCCUGCGAA
286	AUCCAUCCUGCGAGA
287	UCCAUCCUGCGAGCA
288	CCAUCCUGCGAGCUA
289	CAUCCUGCGAGCUCA
290	AUCCUGCGAGCUCCA

291	UCCUGCGAGCUCCUA
292	CCUGCGAGCUCCUUA
293	CUGCGAGCUCCUUGA
294	UGCGAGCUCCUUGGA
295	GCGAGCUCCUUGGGA
296	CGAGCUCCUUGGGUA
297	GAGCUCCUUGGGUCA
298	AGCUCCUUGGGUCCA
299	GCUCCUUGGGUCCUA
300	CUCCUUGGGUCCUGA
301	UCCUUGGGUCCUGCA
302	CCUUGGGUCCUGCAA
303	CUUGGGUCCUGCAAA
304	UUGGGUCCUGCAAUA
305	UGGGUCCUGCAAUCA
306	GGGUCCUGCAAUCUA
307	GGUCCUGCAAUCUCA
308	GUCCUGCAAUCUCCA
309	UCCUGCAAUCUCCAA
310	CCUGCAAUCUCCAGA
311	CUGCAAUCUCCAGGA
312	UGCAAUCUCCAGGGA
313	GCAAUCUCCAGGGCA
314	CAAUCUCCAGGGCUA
315	AAUCUCCAGGGCUGA
316	AUCUCCAGGGCUGCA
317	UCUCCAGGGCUGCCA
318	CUCCAGGGCUGCCCA
319	GUAGGUUGCUUAAAA
320	UAGGUUGCUUAAAAA
321	AGGUUGCUUAAAAGA
322	GGUUGCUUAAAAGGA
323	GUUGCUUAAAAGGGA
324	UUGCUUAAAAGGGAA
325	UGCUUAAAAGGGACA
326	UUAAAAGGGACAGUA
327	UAAAAGGGACAGUAA
328	AAAAGGGACAGUAUA
329	AAAGGGACAGUAUUA
330	AAGGGACAGUAUUCA
331	AGGGACAGUAUUCUA
332	GGGACAGUAUUCUCA
333	GGACAGUAUUCUCAA
334	GACAGUAUUCUCAGA
335	ACAGUAUUCUCAGUA
336	CAGUAUUCUCAGUGA
337	AGUAUUCUCAGUGCA
338	GUAUUCUCAGUGCUA
339	UAUUCUCAGUGCUCA
340	AUUCUCAGUGCUCUA
341	UUCUCAGUGCUCUCA
342	UCUCAGUGCUCUCCA
343	CUCAGUGCUCUCCUA
344	UCAGUGCUCUCCUAA
345	CAGUGCUCUCCUACA
346	AGUGCUCUCCUACCA
347	GUGCUCUCCUACCCA

348	CCUCAUGCCUGGCCA
349	CUCAUGCCUGGCCCA
350	CCAGGCAUGCUGGCA
351	CAGGCAUGCUGGCCA
352	AGGCAUGCUGGCCUA
353	GGCAUGCUGGCCUCA
354	GCAUGCUGGCCUCCA
355	CAUGCUGGCCUCCCA
356	AUGCUGGCCUCCCAA
357	GCUGGCCUCCCAAUA
358	CUGGCCUCCCAAUAA
359	UGGCCUCCCAAUAAA
360	GGCCUCCCAAUAAAA
361	GCCUCCCAAUAAAGA
362	CCUCCCAAUAAAGCA
363	CUCCCAAUAAAGCUA
364	UCCCAAUAAAGCUGA
365	CCCAAUAAAGCUGGA
366	CCAAUAAAGCUGGAA
367	CAAUAAAGCUGGACA
368	AUAAAGCUGGACAAA
369	UAAAGCUGGACAAGA
370	AAAGCUGGACAAGAA
371	AAGCUGGACAAGAAA
372	AGCUGGACAAGAAGA
373	GCUGGACAAGAAGCA
374	GGACAAGAAGCUGCA
375	ACAAGAAGCUGCUAA
376	CAAGAAGCUGCUAUA

Table 1d: Nucleobase sequences and sugar-phosphate backbone modifications of the sense strands of 376 exemplary constructs:

#	Nucleobase sequence and backbone modification
1	fA.mG.fU.mU.fC.mA.fU.mC.fC.mC.fU.mA.fG.mA.fA
2	fG.mU.fU.mC.fA.mU.fC.mC.fC.mU.fA.mG.fA.mG.fA
3	fU.mU.fC.mA.fU.mC.fC.mC.fU.mA.fG.mA.fG.mG.fA
4	fU.mC.fA.mU.fC.mC.fC.mU.fA.mG.fA.mG.fG.mC.fA
5	fC.mA.fU.mC.fC.mC.fU.mA.fG.mA.fG.mG.fC.mA.fA
6	fA.mU.fC.mC.fC.mU.fA.mG.fA.mG.fG.mC.fA.mG.fA
7	fU.mC.fC.mC.fU.mA.fG.mA.fG.mG.fC.mA.fG.mC.fA
8	fC.mC.fC.mU.fA.mG.fA.mG.fG.mC.fA.mG.fC.mU.fA
9	fC.mU.fA.mG.fA.mG.fG.mC.fA.mG.fC.mU.fG.mC.fA
10	fU.mA.fG.mA.fG.mG.fC.mA.fG.mC.fU.mG.fC.mU.fA
11	fA.mG.fA.mG.fG.mC.fA.mG.fC.mU.fG.mC.fU.mC.fA
12	fG.mA.fG.mG.fC.mA.fG.mC.fU.mG.fC.mU.fC.mC.fA
13	fC.mU.fG.mC.fU.mC.fC.mA.fG.mG.fA.mA.fC.mA.fA
14	fU.mG.fC.mU.fC.mC.fA.mG.fG.mA.fA.mC.fA.mG.fA
15	fU.mC.fC.mA.fG.mG.fA.mA.fC.mA.fG.mA.fG.mG.fA
16	fC.mC.fA.mG.fG.mA.fA.mC.fA.mG.fA.mG.fG.mU.fA
17	fC.mA.fG.mG.fA.mA.fC.mA.fG.mA.fG.mG.fU.mG.fA
18	fA.mG.fG.mA.fA.mC.fA.mG.fA.mG.fG.mU.fG.mC.fA
19	fG.mG.fA.mA.fC.mA.fG.mA.fG.mG.fU.mG.fC.mC.fA
20	fG.mA.fA.mC.fA.mG.fA.mG.fG.mU.fG.mC.fC.mA.fA
21	fA.mA.fC.mA.fG.mA.fG.mG.fU.mG.fC.mC.fA.mU.fA
22	fA.mC.fA.mG.fA.mG.fG.mU.fG.mC.fC.mA.fU.mG.fA

23	fA.mG.fA.mG.fG.mU.fG.mC.fC.mA.fU.mG.fC.mA.fA
24	fG.mA.fG.mG.fU.mG.fC.mC.fA.mU.fG.mC.fA.mG.fA
25	fA.mG.fG.mU.fG.mC.fC.mA.fU.mG.fC.mA.fG.mC.fA
26	fG.mG.fU.mG.fC.mC.fA.mU.fG.mC.fA.mG.fC.mC.fA
27	fG.mU.fG.mC.fC.mA.fU.mG.fC.mA.fG.mC.fC.mC.fA
28	fG.mG.fU.mA.fC.mU.fC.mC.fU.mU.fG.mU.fU.mG.fA
29	fG.mU.fA.mC.fU.mC.fC.mU.fU.mG.fU.mU.fG.mU.fA
30	fU.mA.fC.mU.fC.mC.fU.mU.fG.mU.fU.mG.fU.mU.fA
31	fA.mC.fU.mC.fC.mU.fU.mG.fU.mU.fG.mU.fU.mG.fA
32	fC.mU.fC.mC.fU.mU.fG.mU.fU.mG.fU.mU.fG.mC.fA
33	fU.mC.fC.mU.fU.mG.fU.mU.fG.mU.fU.mG.fC.mC.fA
34	fC.mC.fU.mU.fG.mU.fU.mG.fU.mU.fG.mC.fC.mC.fA
35	fC.mU.fU.mG.fU.mU.fG.mU.fU.mG.fC.mC.fC.mU.fA
36	fU.mU.fG.mU.fU.mG.fU.mU.fG.mC.fC.mC.fU.mC.fA
37	fU.mG.fU.mU.fG.mU.fU.mG.fC.mC.fC.mU.fC.mC.fA
38	fG.mU.fU.mG.fU.mU.fG.mC.fC.mC.fU.mC.fC.mU.fA
39	fU.mU.fG.mU.fU.mG.fC.mC.fC.mU.fC.mC.fU.mG.fA
40	fU.mG.fU.mU.fG.mC.fC.mC.fU.mC.fC.mU.fG.mG.fA
41	fG.mU.fU.mG.fC.mC.fC.mU.fC.mC.fU.mG.fG.mC.fA
42	fU.mU.fG.mC.fC.mC.fU.mC.fC.mU.fG.mG.fC.mG.fA
43	fU.mG.fC.mC.fC.mU.fC.mC.fU.mG.fG.mC.fG.mC.fA
44	fG.mC.fC.mC.fU.mC.fC.mU.fG.mG.fC.mG.fC.mU.fA
45	fC.mC.fC.mU.fC.mC.fU.mG.fG.mC.fG.mC.fU.mC.fA
46	fC.mC.fU.mC.fC.mU.fG.mG.fC.mG.fC.mU.fC.mC.fA
47	fC.mU.fC.mC.fU.mG.fG.mC.fG.mC.fU.mC.fC.mU.fA
48	fC.mU.fG.mG.fC.mG.fC.mU.fC.mC.fU.mG.fG.mC.fA
49	fC.mG.fC.mU.fC.mC.fU.mG.fG.mC.fC.mU.fC.mU.fA
50	fG.mC.fU.mC.fC.mU.fG.mG.fC.mC.fU.mC.fU.mG.fA
51	fC.mU.fC.mC.fU.mG.fG.mC.fC.mU.fC.mU.fG.mC.fA
52	fU.mC.fC.mU.fG.mG.fC.mC.fU.mC.fU.mG.fC.mC.fA
53	fC.mC.fU.mG.fG.mC.fC.mU.fC.mU.fG.mC.fC.mC.fA
54	fU.mG.fG.mC.fC.mU.fC.mU.fG.mC.fC.mC.fG.mA.fA
55	fG.mG.fC.mC.fU.mC.fU.mG.fC.mC.fC.mG.fA.mG.fA
56	fG.mC.fC.mU.fC.mU.fG.mC.fC.mC.fG.mA.fG.mC.fA
57	fC.mC.fU.mC.fU.mG.fC.mC.fC.mG.fA.mG.fC.mU.fA
58	fC.mU.fC.mU.fG.mC.fC.mC.fG.mA.fG.mC.fU.mU.fA
59	fU.mC.fU.mG.fC.mC.fC.mG.fA.mG.fC.mU.fU.mC.fA
60	fC.mU.fG.mC.fC.mC.fG.mA.fG.mC.fU.mU.fC.mA.fA
61	fU.mG.fC.mC.fC.mG.fA.mG.fC.mU.fU.mC.fA.mG.fA
62	fG.mC.fC.mC.fG.mA.fG.mC.fU.mU.fC.mA.fG.mA.fA
63	fC.mC.fC.mG.fA.mG.fC.mU.fU.mC.fA.mG.fA.mG.fA
64	fC.mC.fG.mA.fG.mC.fU.mU.fC.mA.fG.mA.fG.mG.fA
65	fC.mG.fA.mG.fC.mU.fU.mC.fA.mG.fA.mG.fG.mC.fA
66	fG.mA.fG.mC.fU.mU.fC.mA.fG.mA.fG.mG.fC.mC.fA
67	fA.mG.fC.mU.fU.mC.fA.mG.fA.mG.fG.mC.fC.mG.fA
68	fG.mC.fU.mU.fC.mA.fG.mA.fG.mG.fC.mC.fG.mA.fA
69	fC.mU.fU.mC.fA.mG.fA.mG.fG.mC.fC.mG.fA.mG.fA
70	fU.mU.fC.mA.fG.mA.fG.mG.fC.mC.fG.mA.fG.mG.fA
71	fU.mC.fA.mG.fA.mG.fG.mC.fC.mG.fA.mG.fG.mA.fA
72	fC.mA.fG.mA.fG.mG.fC.mC.fG.mA.fG.mG.fA.mU.fA
73	fA.mG.fA.mG.fG.mC.fC.mG.fA.mG.fG.mA.fU.mG.fA
74	fG.mA.fG.mG.fC.mC.fG.mA.fG.mG.fA.mU.fG.mC.fA
75	fA.mG.fG.mC.fC.mG.fA.mG.fG.mA.fU.mG.fC.mC.fA
76	fG.mG.fC.mC.fG.mA.fG.mG.fA.mU.fG.mC.fC.mU.fA
77	fG.mC.fC.mG.fA.mG.fG.mA.fU.mG.fC.mC.fU.mC.fA
78	fC.mC.fG.mA.fG.mG.fA.mU.fG.mC.fC.mU.fC.mC.fA
79	fC.mG.fA.mG.fG.mA.fU.mG.fC.mC.fU.mC.fC.mC.fA

80	fG.mA.fG.mG.fA.mU.fG.mC.fC.mU.fC.mC.fC.mU.fA
81	fA.mG.fG.mA.fU.mG.fC.mC.fU.mC.fC.mC.fU.mU.fA
82	fG.mG.fA.mU.fG.mC.fC.mU.fC.mC.fC.mU.fU.mC.fA
83	fG.mA.fU.mG.fC.mC.fU.mC.fC.mC.fU.mU.fC.mU.fA
84	fA.mU.fG.mC.fC.mU.fC.mC.fC.mU.fU.mC.fU.mC.fA
85	fU.mG.fC.mC.fU.mC.fC.mC.fU.mU.fC.mU.fC.mA.fA
86	fG.mC.fC.mU.fC.mC.fC.mU.fU.mC.fU.mC.fA.mG.fA
87	fC.mC.fU.mC.fC.mC.fU.mU.fC.mU.fC.mA.fG.mC.fA
88	fC.mU.fC.mC.fC.mU.fU.mC.fU.mC.fA.mG.fC.mU.fA
89	fC.mC.fU.mU.fC.mU.fC.mA.fG.mC.fU.mU.fC.mA.fA
90	fC.mU.fU.mC.fU.mC.fA.mG.fC.mU.fU.mC.fA.mU.fA
91	fU.mU.fC.mU.fC.mA.fG.mC.fU.mU.fC.mA.fU.mG.fA
92	fU.mC.fU.mC.fA.mG.fC.mU.fU.mC.fA.mU.fG.mC.fA
93	fC.mU.fC.mA.fG.mC.fU.mU.fC.mA.fU.mG.fC.mA.fA
94	fU.mC.fA.mG.fC.mU.fU.mC.fA.mU.fG.mC.fA.mG.fA
95	fC.mA.fG.mC.fU.mU.fC.mA.fU.mG.fC.mA.fG.mG.fA
96	fA.mG.fC.mU.fU.mC.fA.mU.fG.mC.fA.mG.fG.mG.fA
97	fG.mC.fU.mU.fC.mA.fU.mG.fC.mA.fG.mG.fG.mU.fA
98	fC.mU.fU.mC.fA.mU.fG.mC.fA.mG.fG.mG.fU.mU.fA
99	fU.mU.fC.mA.fU.mG.fC.mA.fG.mG.fG.mU.fU.mA.fA
100	fU.mC.fA.mU.fG.mC.fA.mG.fG.mG.fU.mU.fA.mC.fA
101	fC.mA.fU.mG.fC.mA.fG.mG.fG.mU.fU.mA.fC.mA.fA
102	fA.mU.fG.mC.fA.mG.fG.mG.fU.mU.fA.mC.fA.mU.fA
103	fU.mG.fC.mA.fG.mG.fG.mU.fU.mA.fC.mA.fU.mG.fA
104	fG.mC.fA.mG.fG.mG.fU.mU.fA.mC.fA.mU.fG.mA.fA
105	fC.mA.fG.mG.fG.mU.fU.mA.fC.mA.fU.mG.fA.mA.fA
106	fA.mG.fG.mG.fU.mU.fA.mC.fA.mU.fG.mA.fA.mG.fA
107	fG.mG.fG.mU.fU.mA.fC.mA.fU.mG.fA.mA.fG.mC.fA
108	fG.mG.fU.mU.fA.mC.fA.mU.fG.mA.fA.mG.fC.mA.fA
109	fG.mU.fU.mA.fC.mA.fU.mG.fA.mA.fG.mC.fA.mC.fA
110	fU.mU.fA.mC.fA.mU.fG.mA.fA.mG.fC.mA.fC.mG.fA
111	fU.mA.fC.mA.fU.mG.fA.mA.fG.mC.fA.mC.fG.mC.fA
112	fA.mC.fA.mU.fG.mA.fA.mG.fC.mA.fC.mG.fC.mC.fA
113	fC.mA.fU.mG.fA.mA.fG.mC.fA.mC.fG.mC.fC.mA.fA
114	fA.mU.fG.mA.fA.mG.fC.mA.fC.mG.fC.mC.fA.mC.fA
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122	fC.mG.fC.mC.fA.mC.fC.mA.fA.mG.fA.mC.fC.mG.fA
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132	fA.mC.fC.mG.fC.mC.fA.mA.fG.mG.fA.mU.fG.mC.fA
133	fC.mC.fG.mC.fC.mA.fA.mG.fG.mA.fU.mG.fC.mA.fA
134	fC.mG.fC.mC.fA.mA.fG.mG.fA.mU.fG.mC.fA.mC.fA
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140	fG.mG.fA.mU.fG.mC.fA.mC.fU.mG.fA.mG.fC.mA.fA
141	fG.mA.fU.mG.fC.mA.fC.mU.fG.mA.fG.mC.fA.mG.fA
142	fA.mU.fG.mC.fA.mC.fU.mG.fA.mG.fC.mA.fG.mC.fA
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153	fG.mU.fG.mC.fA.mG.fG.mA.fG.mU.fC.mC.fC.mA.fA
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155	fG.mC.fA.mG.fG.mA.fG.mU.fC.mC.fC.mA.fG.mG.fA
156	fC.mA.fG.mG.fA.mG.fU.mC.fC.mC.fA.mG.fG.mU.fA
157	fA.mG.fG.mA.fG.mU.fC.mC.fC.mA.fG.mG.fU.mG.fA
158	fG.mG.fA.mG.fU.mC.fC.mC.fA.mG.fG.mU.fG.mG.fA
159	fG.mU.fC.mC.fC.mA.fG.mG.fU.mG.fG.mC.fC.mC.fA
160	fU.mC.fC.mC.fA.mG.fG.mU.fG.mG.fC.mC.fC.mA.fA
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162	fA.mG.fG.mU.fG.mG.fC.mC.fC.mA.fG.mC.fA.mG.fA
163	fU.mG.fG.mC.fC.mC.fA.mG.fC.mA.fG.mG.fC.mC.fA
164	fC.mC.fC.mA.fG.mC.fA.mG.fG.mC.fC.mA.fG.mG.fA
165	fU.mG.fG.mG.fU.mG.fA.mC.fC.mG.fA.mU.fG.mG.fA
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167	fG.mG.fU.mG.fA.mC.fC.mG.fA.mU.fG.mG.fC.mU.fA
168	fG.mU.fG.mA.fC.mC.fG.mA.fU.mG.fG.mC.fU.mU.fA
169	fU.mG.fA.mC.fC.mG.fA.mU.fG.mG.fC.mU.fU.mC.fA
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171	fA.mC.fC.mG.fA.mU.fG.mG.fC.mU.fU.mC.fA.mG.fA
172	fC.mC.fG.mA.fU.mG.fG.mC.fU.mU.fC.mA.fG.mU.fA
173	fC.mG.fA.mU.fG.mG.fC.mU.fU.mC.fA.mG.fU.mU.fA
174	fG.mA.fU.mG.fG.mC.fU.mU.fC.mA.fG.mU.fU.mC.fA
175	fA.mU.fG.mG.fC.mU.fU.mC.fA.mG.fU.mU.fC.mC.fA
176	fU.mG.fG.mC.fU.mU.fC.mA.fG.mU.fU.mC.fC.mC.fA
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178	fG.mC.fU.mU.fC.mA.fG.mU.fU.mC.fC.mC.fU.mG.fA
179	fC.mU.fU.mC.fA.mG.fU.mU.fC.mC.fC.mU.fG.mA.fA
180	fU.mU.fC.mA.fG.mU.fU.mC.fC.mC.fU.mG.fA.mA.fA
181	fU.mC.fA.mG.fU.mU.fC.mC.fC.mU.fG.mA.fA.mA.fA
182	fC.mA.fG.mU.fU.mC.fC.mC.fU.mG.fA.mA.fA.mG.fA
183	fA.mG.fU.mU.fC.mC.fC.mU.fG.mA.fA.mA.fG.mA.fA
184	fG.mU.fU.mC.fC.mC.fU.mG.fA.mA.fA.mG.fA.mC.fA
185	fU.mU.fC.mC.fC.mU.fG.mA.fA.mA.fG.mA.fC.mU.fA
186	fU.mC.fC.mC.fU.mG.fA.mA.fA.mG.fA.mC.fU.mA.fA
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190	fU.mG.fA.mA.fA.mG.fA.mC.fU.mA.fC.mU.fG.mG.fA
191	fG.mA.fA.mA.fG.mA.fC.mU.fA.mC.fU.mG.fG.mA.fA
192	fA.mA.fA.mG.fA.mC.fU.mA.fC.mU.fG.mG.fA.mG.fA
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226	fU.mG.fA.mG.fU.mU.fC.mU.fG.mG.fG.mA.fU.mU.fA
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229	fG.mU.fU.mC.fU.mG.fG.mG.fA.mU.fU.mU.fG.mG.fA
230	fU.mU.fC.mU.fG.mG.fG.mA.fU.mU.fU.mG.fG.mA.fA
231	fU.mC.fU.mG.fG.mG.fA.mU.fU.mU.fG.mG.fA.mC.fA
232	fC.mU.fG.mG.fG.mA.fU.mU.fU.mG.fG.mA.fC.mC.fA
233	fU.mG.fG.mG.fA.mU.fU.mU.fG.mG.fA.mC.fC.mC.fA
234	fG.mG.fG.mA.fU.mU.fU.mG.fG.mA.fC.mC.fC.mU.fA
235	fG.mG.fA.mU.fU.mU.fG.mG.fA.mC.fC.mC.fU.mG.fA
236	fG.mA.fU.mU.fU.mG.fG.mA.fC.mC.fC.mU.fG.mA.fA
237	fU.mG.fG.mA.fC.mC.fC.mU.fG.mA.fG.mG.fU.mC.fA
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240	fA.mC.fC.mC.fU.mG.fA.mG.fG.mU.fC.mA.fG.mA.fA
241	fC.mC.fC.mU.fG.mA.fG.mG.fU.mC.fA.mG.fA.mC.fA
242	fC.mC.fU.mG.fA.mG.fG.mU.fC.mA.fG.mA.fC.mC.fA
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246	fA.mG.fG.mU.fC.mA.fG.mA.fC.mC.fA.mA.fC.mU.fA
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253	fC.mC.fA.mA.fC.mU.fU.mC.fA.mG.fC.mC.fG.mU.fA
254	fC.mA.fA.mC.fU.mU.fC.mA.fG.mC.fC.mG.fU.mG.fA
255	fA.mA.fC.mU.fU.mC.fA.mG.fC.mC.fG.mU.fG.mG.fA
256	fA.mC.fU.mU.fC.mA.fG.mC.fC.mG.fU.mG.fG.mC.fA
257	fU.mU.fC.mA.fG.mC.fC.mG.fU.mG.fG.mC.fU.mG.fA
258	fU.mC.fA.mG.fC.mC.fG.mU.fG.mG.fC.mU.fG.mC.fA
259	fC.mA.fG.mC.fC.mG.fU.mG.fG.mC.fU.mG.fC.mC.fA
260	fA.mG.fC.mC.fG.mU.fG.mG.fC.mU.fG.mC.fC.mU.fA
261	fG.mC.fC.mG.fU.mG.fG.mC.fU.mG.fC.mC.fU.mG.fA
262	fG.mU.fG.mG.fC.mU.fG.mC.fC.mU.fG.mA.fG.mA.fA
263	fU.mG.fG.mC.fU.mG.fC.mC.fU.mG.fA.mG.fA.mC.fA
264	fG.mG.fC.mU.fG.mC.fC.mU.fG.mA.fG.mA.fC.mC.fA
265	fG.mC.fU.mG.fC.mC.fU.mG.fA.mG.fA.mC.fC.mU.fA
266	fU.mG.fC.mC.fU.mG.fA.mG.fA.mC.fC.mU.fC.mA.fA
267	fG.mC.fC.mU.fG.mA.fG.mA.fC.mC.fU.mC.fA.mA.fA
268	fC.mC.fU.mG.fA.mG.fA.mC.fC.mU.fC.mA.fA.mU.fA
269	fC.mU.fG.mA.fG.mA.fC.mC.fU.mC.fA.mA.fU.mA.fA
270	fU.mG.fA.mG.fA.mC.fC.mU.fC.mA.fA.mU.fA.mC.fA
271	fG.mA.fG.mA.fC.mC.fU.mC.fA.mA.fU.mA.fC.mC.fA
272	fA.mG.fA.mC.fC.mU.fC.mA.fA.mU.fA.mC.fC.mC.fA
273	fA.mG.fU.mC.fC.mA.fC.mC.fU.mG.fC.mC.fU.mA.fA
274	fG.mU.fC.mC.fA.mC.fC.mU.fG.mC.fC.mU.fA.mU.fA
275	fU.mC.fC.mA.fC.mC.fU.mG.fC.mC.fU.mA.fU.mC.fA
276	fC.mC.fA.mC.fC.mU.fG.mC.fC.mU.fA.mU.fC.mC.fA
277	fC.mA.fC.mC.fU.mG.fC.mC.fU.mA.fU.mC.fC.mA.fA
278	fA.mC.fC.mU.fG.mC.fC.mU.fA.mU.fC.mC.fA.mU.fA
279	fC.mC.fU.mG.fC.mC.fU.mA.fU.mC.fC.mA.fU.mC.fA
280	fC.mU.fG.mC.fC.mU.fA.mU.fC.mC.fA.mU.fC.mC.fA
281	fU.mG.fC.mC.fU.mA.fU.mC.fC.mA.fU.mC.fC.mU.fA
282	fG.mC.fC.mU.fA.mU.fC.mC.fA.mU.fC.mC.fU.mG.fA
283	fC.mC.fU.mA.fU.mC.fC.mA.fU.mC.fC.mU.fG.mC.fA
284	fC.mU.fA.mU.fC.mC.fA.mU.fC.mC.fU.mG.fC.mG.fA
285	fU.mA.fU.mC.fC.mA.fU.mC.fC.mU.fG.mC.fG.mA.fA
286	fA.mU.fC.mC.fA.mU.fC.mC.fU.mG.fC.mG.fA.mG.fA
287	fU.mC.fC.mA.fU.mC.fC.mU.fG.mC.fG.mA.fG.mC.fA
288	fC.mC.fA.mU.fC.mC.fU.mG.fC.mG.fA.mG.fC.mU.fA
289	fC.mA.fU.mC.fC.mU.fG.mC.fG.mA.fG.mC.fU.mC.fA
290	fA.mU.fC.mC.fU.mG.fC.mG.fA.mG.fC.mU.fC.mC.fA
291	fU.mC.fC.mU.fG.mC.fG.mA.fG.mC.fU.mC.fC.mU.fA
292	fC.mC.fU.mG.fC.mG.fA.mG.fC.mU.fC.mC.fU.mU.fA
293	fC.mU.fG.mC.fG.mA.fG.mC.fU.mC.fC.mU.fU.mG.fA
294	fU.mG.fC.mG.fA.mG.fC.mU.fC.mC.fU.mU.fG.mG.fA
295	fG.mC.fG.mA.fG.mC.fU.mC.fC.mU.fU.mG.fG.mG.fA
296	fC.mG.fA.mG.fC.mU.fC.mC.fU.mU.fG.mG.fG.mU.fA
297	fG.mA.fG.mC.fU.mC.fC.mU.fU.mG.fG.mG.fU.mC.fA
298	fA.mG.fC.mU.fC.mC.fU.mU.fG.mG.fG.mU.fC.mC.fA
299	fG.mC.fU.mC.fC.mU.fU.mG.fG.mG.fU.mC.fC.mU.fA
300	fC.mU.fC.mC.fU.mU.fG.mG.fG.mU.fC.mC.fU.mG.fA
301	fU.mC.fC.mU.fU.mG.fG.mG.fU.mC.fC.mU.fG.mC.fA
302	fC.mC.fU.mU.fG.mG.fG.mU.fC.mC.fU.mG.fC.mA.fA
303	fC.mU.fU.mG.fG.mG.fU.mC.fC.mU.fG.mC.fA.mA.fA
304	fU.mU.fG.mG.fG.mU.fC.mC.fU.mG.fC.mA.fA.mU.fA
305	fU.mG.fG.mG.fU.mC.fC.mU.fG.mC.fA.mA.fU.mC.fA
306	fG.mG.fG.mU.fC.mC.fU.mG.fC.mA.fA.mU.fC.mU.fA
307	fG.mG.fU.mC.fC.mU.fG.mC.fA.mA.fU.mC.fU.mC.fA

308	fG.mU.fC.mC.fU.mG.fC.mA.fA.mU.fC.mU.fC.mC.fA
309	fU.mC.fC.mU.fG.mC.fA.mA.fU.mC.fU.mC.fC.mA.fA
310	fC.mC.fU.mG.fC.mA.fA.mU.fC.mU.fC.mC.fA.mG.fA
311	fC.mU.fG.mC.fA.mA.fU.mC.fU.mC.fC.mA.fG.mG.fA
312	fU.mG.fC.mA.fA.mU.fC.mU.fC.mC.fA.mG.fG.mG.fA
313	fG.mC.fA.mA.fU.mC.fU.mC.fC.mA.fG.mG.fG.mC.fA
314	fC.mA.fA.mU.fC.mU.fC.mC.fA.mG.fG.mG.fC.mU.fA
315	fA.mA.fU.mC.fU.mC.fC.mA.fG.mG.fG.mC.fU.mG.fA
316	fA.mU.fC.mU.fC.mC.fA.mG.fG.mG.fC.mU.fG.mC.fA
317	fU.mC.fU.mC.fC.mA.fG.mG.fG.mC.fU.mG.fC.mC.fA
318	fC.mU.fC.mC.fA.mG.fG.mG.fC.mU.fG.mC.fC.mC.fA
319	fG.mU.fA.mG.fG.mU.fU.mG.fC.mU.fU.mA.fA.mA.fA
320	fU.mA.fG.mG.fU.mU.fG.mC.fU.mU.fA.mA.fA.mA.fA
321	fA.mG.fG.mU.fU.mG.fC.mU.fU.mA.fA.mA.fA.mG.fA
322	fG.mG.fU.mU.fG.mC.fU.mU.fA.mA.fA.mA.fG.mG.fA
323	fG.mU.fU.mG.fC.mU.fU.mA.fA.mA.fA.mG.fG.mG.fA
324	fU.mU.fG.mC.fU.mU.fA.mA.fA.mA.fG.mG.fG.mA.fA
325	fU.mG.fC.mU.fU.mA.fA.mA.fA.mG.fG.mG.fA.mC.fA
326	fU.mU.fA.mA.fA.mA.fG.mG.fG.mA.fC.mA.fG.mU.fA
327	fU.mA.fA.mA.fA.mG.fG.mG.fA.mC.fA.mG.fU.mA.fA
328	fA.mA.fA.mA.fG.mG.fG.mA.fC.mA.fG.mU.fA.mU.fA
329	fA.mA.fA.mG.fG.mG.fA.mC.fA.mG.fU.mA.fU.mU.fA
330	fA.mA.fG.mG.fG.mA.fC.mA.fG.mU.fA.mU.fU.mC.fA
331	fA.mG.fG.mG.fA.mC.fA.mG.fU.mA.fU.mU.fC.mU.fA
332	fG.mG.fG.mA.fC.mA.fG.mU.fA.mU.fU.mC.fU.mC.fA
333	fG.mG.fA.mC.fA.mG.fU.mA.fU.mU.fC.mU.fC.mA.fA
334	fG.mA.fC.mA.fG.mU.fA.mU.fU.mC.fU.mC.fA.mG.fA
335	fA.mC.fA.mG.fU.mA.fU.mU.fC.mU.fC.mA.fG.mU.fA
336	fC.mA.fG.mU.fA.mU.fU.mC.fU.mC.fA.mG.fU.mG.fA
337	fA.mG.fU.mA.fU.mU.fC.mU.fC.mA.fG.mU.fG.mC.fA
338	fG.mU.fA.mU.fU.mC.fU.mC.fA.mG.fU.mG.fC.mU.fA
339	fU.mA.fU.mU.fC.mU.fC.mA.fG.mU.fG.mC.fU.mC.fA
340	fA.mU.fU.mC.fU.mC.fA.mG.fU.mG.fC.mU.fC.mU.fA
341	fU.mU.fC.mU.fC.mA.fG.mU.fG.mC.fU.mC.fU.mC.fA
342	fU.mC.fU.mC.fA.mG.fU.mG.fC.mU.fC.mU.fC.mC.fA
343	fC.mU.fC.mA.fG.mU.fG.mC.fU.mC.fU.mC.fC.mU.fA
344	fU.mC.fA.mG.fU.mG.fC.mU.fC.mU.fC.mC.fU.mA.fA
345	fC.mA.fG.mU.fG.mC.fU.mC.fU.mC.fC.mU.fA.mC.fA
346	fA.mG.fU.mG.fC.mU.fC.mU.fC.mC.fU.mA.fC.mC.fA
347	fG.mU.fG.mC.fU.mC.fU.mC.fC.mU.fA.mC.fC.mC.fA
348	fC.mC.fU.mC.fA.mU.fG.mC.fC.mU.fG.mG.fC.mC.fA
349	fC.mU.fC.mA.fU.mG.fC.mC.fU.mG.fG.mC.fC.mC.fA
350	fC.mC.fA.mG.fG.mC.fA.mU.fG.mC.fU.mG.fG.mC.fA
351	fC.mA.fG.mG.fC.mA.fU.mG.fC.mU.fG.mG.fC.mC.fA
352	fA.mG.fG.mC.fA.mU.fG.mC.fU.mG.fG.mC.fC.mU.fA
353	fG.mG.fC.mA.fU.mG.fC.mU.fG.mG.fC.mC.fU.mC.fA
354	fG.mC.fA.mU.fG.mC.fU.mG.fG.mC.fC.mU.fC.mC.fA
355	fC.mA.fU.mG.fC.mU.fG.mG.fC.mC.fU.mC.fC.mC.fA
356	fA.mU.fG.mC.fU.mG.fG.mC.fC.mU.fC.mC.fC.mA.fA
357	fG.mC.fU.mG.fG.mC.fC.mU.fC.mC.fC.mA.fA.mU.fA
358	fC.mU.fG.mG.fC.mC.fU.mC.fC.mC.fA.mA.fU.mA.fA
359	fU.mG.fG.mC.fC.mU.fC.mC.fC.mA.fA.mU.fA.mA.fA
360	fG.mG.fC.mC.fU.mC.fC.mC.fA.mA.fU.mA.fA.mA.fA
361	fG.mC.fC.mU.fC.mC.fC.mA.fA.mU.fA.mA.fA.mG.fA
362	fC.mC.fU.mC.fC.mC.fA.mA.fU.mA.fA.mA.fG.mC.fA
363	fC.mU.fC.mC.fC.mA.fA.mU.fA.mA.fA.mG.fC.mU.fA
364	fU.mC.fC.mC.fA.mA.fU.mA.fA.mA.fG.mC.fU.mG.fA

365	fC.mC.fC.mA.fA.mU.fA.mA.fA.mG.fC.mU.fG.mG.fA
366	fC.mC.fA.mA.fU.mA.fA.mA.fG.mC.fU.mG.fG.mA.fA
367	fC.mA.fA.mU.fA.mA.fA.mG.fC.mU.fG.mG.fA.mC.fA
368	fA.mU.fA.mA.fA.mG.fC.mU.fG.mG.fA.mC.fA.mA.fA
369	fU.mA.fA.mA.fG.mC.fU.mG.fG.mA.fC.mA.fA.mG.fA
370	fA.mA.fA.mG.fC.mU.fG.mG.fA.mC.fA.mA.fG.mA.fA
371	fA.mA.fG.mC.fU.mG.fG.mA.fC.mA.fA.mG.fA.mA.fA
372	fA.mG.fC.mU.fG.mG.fA.mC.fA.mA.fG.mA.fA.mG.fA
373	fG.mC.fU.mG.fG.mA.fC.mA.fA.mG.fA.mA.fG.mC.fA
374	fG.mG.fA.mC.fA.mA.fG.mA.fA.mG.fC.mU.fG.mC.fA
375	fA.mC.fA.mA.fG.mA.fA.mG.fC.mU.fG.mC.fU.mA.fA
376	fC.mA.fA.mG.fA.mA.fG.mC.fU.mG.fC.mU.fA.mU.fA

Tables 2a to 2d below show nucleobase sequences and sugar-phosphate backbone modifications of antisense and sense strands of a further 15 exemplary constructs. For corresponding entries in the sequence listing, the following applies: entry number in Table 2a + 376 = entry number in the sequence listing; entry number in Table 2c + 776 = entry number in the sequence listing.

Table 2a: Nucleobase sequences of the antisense strands of 15 further exemplary constructs:

#	AS unmodified
1	UAACUCAGAGAACUUGUCC
2	UUGUCCUUAACGGUGCUCC
3	UAAUCCCAGAACUCAGAGA
4	UCCUUGGCGGUCUUGGUGG
5	UCUGAAGCCAUCGGUCACC
6	UCAGAGAACUUGUCCUUAA
7	UACUCAGAGAACUUGUCCU
8	UGAACUCAGAGAACUUGUC
9	UACUUGUCCUUAACGGUGC
10	UCUCAGAGAACUUGUCCUU
11	UUUGUCCUUAACGGUGCUC
12	UUCCUUGGCGGUCUUGGUG
13	UGCUCCAGUAGUCUUUCAG
14	UCAUCCUCGGCCUCUGAAG
15	UUGGUGGCGUGCUUCAUGU

Table 2b: Nucleobase sequences and sugar-phosphate backbone modifications of the antisense strands of 15 further exemplary constructs:

#	Antisense strand modified
1	[mU][#][fA][#][mA][#][fC][mU][fC][mA][fG][mA][fG][mA][fA][mC][fU][#][mU][#][fG][#][mU][#][fC][#]rC
2	[mU][#][fU][#][mG][#][fU][mC][fC][mU][fU][mA][fA][mC][fG][mG][fU][#][mG][#][fC][#][mU][#][fC][#]rC
3	[mU][#][fA][#][mA][#][fU][mC][fC][mC][fA][mG][fA][mA][fC][mU][fC][#][mA][#][fG][#][mA][#][fG][#]rA
4	[mU][#][fC][#][mC][#][fU][mU][fG][mG][fC][mG][fG][mU][fC][mU][fU][#][mG][#][fG][#][mU][#][fG][#]rG
5	[mU][#][fC][#][mU][#][fG][mA][fA][mG][fC][mC][fA][mU][fC][mG][fG][#][mU][#][fC][#][mA][#][fC][#]rC
6	[mU][#][fC][#][mA][#][fG][mA][fG][mA][fA][mC][fU][mU][fG][mU][fC][#][mC][#][fU][#][mU][#][fA][#]rA
7	[mU][#][fA][#][mC][#][fU][mC][fA][mG][fA][mG][fA][mA][fC][mU][fU][#][mG][#][fU][#][mC][#][fC][#]rU
8	[mU][#][fG][#][mA][#][fA][mC][fU][mC][fA][mG][fA][mG][fA][mA][fC][#][mU][#][fU][#][mG][#][fU][#]rC
9	[mU][#][fA][#][mC][#][fU][mU][fG][mU][fC][mC][fU][mU][fA][mA][fC][#][mG][#][fG][#][mU][#][fG][#]rC
10	[mU][#][fC][#][mU][#][fC][mA][fG][mA][fG][mA][fA][mC][fU][mU][fG][#][mU][#][fC][#][mC][#][fU][#]rU
11	[mU][#][fU][#][mU][#][fG][mU][fC][mC][fU][mU][fA][mA][fC][mG][fG][#][mU][#][fG][#][mC][#][fU][#]rC
12	[mU][#][fU][#][mC][#][fC][mU][fU][mG][fG][mC][fG][mG][fU][mC][fU][#][mU][#][fG][#][mG][#][fU][#]rG
13	[mU][#][fG][#][mC][#][fU][mC][fC][mA][fG][mU][fA][mG][fU][mC][fU][#][mU][#][fU][#][mC][#][fA][#]rG
14	[mU][#][fC][#][mA][#][fU][mC][fC][mU][fC][mG][fG][mC][fC][mU][fC][#][mU][#][fG][#][mA][#][fA][#]rG

15	[mU][#][fU][#][mG][#][fG][mU][fG][mG][fC][mG][fU][mG][fC][mU][fU][#][mC][#][fA][#][mU][#][fG][#]rU

Table 2c: Nucleobase sequences of the sense strands of 15 further exemplary constructs:

#	SS unmodified
1	AGUUCUCUGAGUUA
2	ACCGUUAAGGACAA
3	GAGUUCUGGGAUUA
4	AAGACCGCCAAGGA
5	CCGAUGGCUUCAGA
6	GACAAGUUCUCUGA
7	AAGUUCUCUGAGUA
8	GUUCUCUGAGUUCA
9	GUUAAGGACAAGUA
10	CAAGUUCUCUGAGA
11	CCGUUAAGGACAAA
12	AGACCGCCAAGGAA
13	AGACUACUGGAGCA
14	GAGGCCGAGGAUGA
15	AAGCACGCCACCAA

Table 2d: Nucleobase sequences and sugar-phosphate backbone modifications of the sense strands of 15 further exemplary constructs:

#	Sense strand modified
1	[mA][#][fG][#][mU][fU][mC][fU][mC][fU][mG][fA][mG][fU][#][mU][#][fA][#][3xGalNac]
2	[mA][#][fC][#][mC][fG][mU][fU][mA][fA][mG][fG][mA][fC][#][mA][#][fA][#][3xGalNac]
3	[mG][#][fA][#][mG][fU][mU][fC][mU][fG][mG][fG][mA][fU][#][mU][#][fA][#][3xGalNac]
4	[mA][#][fA][#][mG][fA][mC][fC][mG][fC][mC][fA][mA][fG][#][mG][#][fA][#][3xGalNac]
5	[mC][#][fC][#][mG][fA][mU][fG][mG][fC][mU][fU][mC][fA][#][mG][#][fA][#][3xGalNac]
6	[mG][#][fA][#][mC][fA][mA][fG][mU][fU][mC][fU][mC][fU][#][mG][#][fA][#][3xGalNac]
7	[mA][#][fA][#][mG][fU][mU][fC][mU][fC][mU][fG][mA][fG][#][mU][#][fA][#][3xGalNac]
8	[mG][#][fU][#][mU][fC][mU][fC][mU][fG][mA][fG][mU][fU][#][mC][#][fA][#][3xGalNac]
9	[mG][#][fU][#][mU][fA][mA][fG][mG][fA][mC][fA][mA][fG][#][mU][#][fA][#][3xGalNac]
10	[mC][#][fA][#][mA][fG][mU][fU][mC][fU][mC][fU][mG][fA][#][mG][#][fA][#][3xGalNac]
11	[mC][#][fC][#][mG][fU][mU][fA][mA][fG][mG][fA][mC][fA][#][mA][#][fA][#][3xGalNac]
12	[mA][#][fG][#][mA][fC][mC][fG][mC][fC][mA][fA][mG][fG][#][mA][#][fA][#][3xGalNac]
13	[mA][#][fG][#][mA][fC][mU][fA][mC][fU][mG][fG][mA][fG][#][mC][#][fA][#][3xGalNac]
14	[mG][#][fA][#][mG][fG][mC][fC][mG][fA][mG][fG][mA][fU][#][mG][#][fA][#][3xGalNac]
15	[mA][#][fA][#][mG][fC][mA][fC][mG][fC][mC][fA][mC][fC][#][mA][#][fA][#][3xGalNac]

Tables 3a to 3b below show nucleobase sequences and sugar-phosphate backbone modifications of 12 further exemplary constructs.

Table 3a: Nucleobase sequences of the strands of 12 further exemplary constructs.

#	Strands unmodified
A277(15)	uuggauaggc agguggacuc accugccuau ccaa
A28(15)	ucaacaagga guacccgggg guacuccuug uuga
A277(14)	uuggauaggc agguggacua ccugccuauc caa
A28(14)	ucaacaagga guacccgggg uacuccuugu uga
A277(12-5)	uuggauaggc agguggacug ccuauccaa

A277(13-4)	uuggauaggc agguggacuu gccuauccaa
A28(14-4)	ucaacaagga guacccgggu acuccuuguu ga
A277(14)mF	uuggauaggc agguggacua ccugccuauc caa
A28(14)mF	ucaacaagga guacccgggg uacuccuugu uga
A277(12-5)mF	uuggauaggc agguggacug ccuauccaa
A277(13-4)mF	uuggauaggc agguggacuu gccuauccaa
A28(14-4)mF	ucaacaagga guacccgggu acuccuuguu ga

Table 3b: Nucleobase sequences and sugar-phosphate backbone modifications of the strands of 12 further exemplary constructs:

#	**Strands modified**
A277(15)	[mU][#][fU][#][mG][fG][mA][fU][mA][fG][mG][fC][mA][fG][mG][fU][mG][#][fG][#][mA][#][fC][#][mU][#][fC][mA][fC][mC][fU][mG][fC][mC][fU][mA][fU][mC][mC][#][mA][#][mA][#][3XGalNAc]
A28(15)	[mU][#][fC][#][mA][fA][mC][fA][mA][fG][mG][fA][mG][fU][mA][fC][mC][#][fC][#][mG][#][fG][#][mG][#][fG][mG][fU][mA][fC][mU][fC][mC][fU][mU][fG][mU][mU][#][mG][#][mA][#][3XGalNAc]
A277(14)	[mU][#][fU][#][mG][fG][mA][fU][mA][fG][mG][fC][mA][fG][mG][fU][#][mG][#][fG][#][mA][#][fC][#][mU][#][mA][fC][mC][fU][mG][fC][mC][fU][mA][fU][mC][mC][#][mA][#][mA][#][3XGalNAc]
A28(14)	[mU][#][fC][#][mA][fA][mC][fA][mA][fG][mG][fA][mG][fU][mA][fC][#][mC][#][fC][#][mG][#][fG][#][mG][#][mG][fU][mA][fC][mU][fC][mC][fU][mU][fG][mU][mU][#][mG][#][mA][#][3XGalNAc]
A277(12-5)	[mU][#][fU][#][mG][fG][mA][fU][mA][fG][mG][fC][mA][fG][#][mG][#][fU][mG][#][fG][#][mA][#][fC][fU][mG][fC][mC][fU][mA][fU][mC][mC][#][mA][#][mA][#][3XGalNAc]
A277(13-4)	[mU][#][fU][#][mG][fG][mA][fU][mA][fG][mG][fC][mA][fG][mG][#][fU][#][mG][#][fG][#][mA][#][fC][mU][fU][mG][fC][mC][fU][mA][fU][mC][mC][#][mA][#][mA][#][3XGalNac]
A28(14-4)	[mU][#][fC][#][mA][fA][mC][fA][mA][fG][mG][fA][mG][fU][mA][fC][#][mC][#][fC][#][mG][#][fG][#][mG][fU][mA][fC][mU][fC][mC][fU][mU][fG][mU][mU][#][mG][#][mA][#][3XGalNAc]
A277(14)mF	[mU][#][fU][#][mG][mG][mA][mU][mA][mG][mG][mC][mA][mG][mG][fU][#][mG][#][mG][#][mA][#][mC][#][mU][#][mA][fC][fC][fU][mG][mC][mC][mU][mA][mU][mC][mC][#][mA][#][mA][#][3XGalNac]
A28(14)mF	[mU][#][fC][#][mA][mA][mC][mA][mA][mG][mG][mA][mG][mU][mA][fC][#][mC][#][mC][#][mG][#][mG][#][mG][#][mG][fU][fA][fC][mU][mC][mC][mU][mU][mG][mU][mU][#][mG][#][mA][#][3XGalNAc]
A277(12-5)mF	[mU][#][fU][#][mG][mG][mA][mU][mA][mG][mG][mC][mA][mG][#][mG][#][fU][mG][#][mG][#][fA][#][fC][fU][mG][mC][mC][mU][mA][mU][mC][mC][#][mA][#][mA][#][3XGalNAc]

A277(13-4)mF	[mU][#][fU][#][mG][mG][mA][mU][mA][mG][mG][mC][mA][mG][mG][#][fU][#][mG][#][mG][#][mA][#][fC][fU][fU][mG][mC][mC][mU][mA][mU][mC][mC][#][mA][#][mA][#][3XGalNAc]
A28(14-4)mF	[mU][#][fC][#][mA][mA][mC][mA][mA][mG][mG][mA][mG][mU][mA][fC][#][mC][#][mC][#][mG][#][mG][#][mG][fU][fA][fC][mU][mC][mC][mU][mU][mG][mU][mU][#][mG][#][mA][#][3XGalNAc]

It should also be noted that the scope of the compositions and methods described herein extends to sequences that correspond to those in the Tables above, and wherein the 5' nucleoside of the antisense (guide) strand (first region as defined in the items herein) can include any nucleobase that can be present in an RNA molecule, in other words can be any of adenine (A), uracil (U), guanine (G) or cytosine (C). Additionally, the scope of the present compositions and methods extends to sequences that correspond to those in Table 1a or Table 1b, and wherein the 3' nucleoside of the sense (passenger) strand (second region as defined in the items herein) can include any nucleobase that can be present in an RNA molecule, in other words can be any of adenine (A), uracil (U), guanine (G) or cytosine (C), preferably however a nucleobase that is complementary to the 5' nucleobase of the antisense (guide) strand (first region as defined in the items herein).

While the methods are shown and described as being a series of acts that are performed in a particular sequence, it is to be understood and appreciated that the methods are not limited by the order of the sequence. For example, some acts can occur in a different order than what is described herein. In addition, an act can occur concurrently with another act. Further, in some instances, not all acts may be required to implement a method described herein.

The order of the steps of the methods described herein is exemplary, but the steps may be carried out in any suitable order, or simultaneously where appropriate. Additionally, steps may be added or substituted in, or individual steps may be deleted from any of the methods without departing from the scope of the subject matter described herein. Aspects of any of the Examples described above may be combined with aspects of any of the other Examples described to form further Examples.

It will be understood that the above description of a preferred embodiment is given by way of example only and that various modifications may be made by those skilled in the art. What has been described above includes Examples of one or more embodiments. It is, of course, not possible to describe every conceivable modification and alteration of the above compounds, compositions or methods for purposes of describing the aforementioned aspects, but one of ordinary skill in the art can recognize that many further modifications and permutations of various aspects are possible. Accordingly, the described aspects are intended to embrace all such alterations, modifications, and variations that fall within the scope of the appended claims.

Examples

The following Examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the generic application of those specific embodiments is contemplated. For example, disclosure of an oligonucleotide having a particular motif or

modification patterns provides reasonable support for additional oligonucleotides having the same or similar motif or modification patterns.

The syntheses of the RNAi constructs as disclosed herein have been carried out using synthesis methods known to the person skilled in the art, such as synthesis methods disclosed in https://en.wikipedia.org/wiki/Oligonucleotide_synthesis {retrieved on 16 February 2022}, wherein the methods disclosed on this website are incorporated by reference herein in their entirety. The only difference to the synthesis method disclosed in this reference is that GalNac phosphoramidite immobilized on a support is used in the synthesis method during the first synthesis step.

Example 1:

Materials and Methods

Cell Culture:

HepG2 (ATCC cat. 85011430) cells were maintained by biweekly passing in EMEM supplemented with 10% FBS, 20 mM L-glutamine, 10 mM HEPES pH 7.2, 1 mM sodium pyruvate, 1x MEM non-essential amino acids, and 1x Pen/Strep (EMEM complete).

APOC3 Target identification and duplex preparation:

Targets to APOC3 were identified by bioinformatic analysis on human APOC3 mRNA sequence as given in RefSeq sequence ID NM_000040, wherein *inter alia* it has been taken into consideration that constructs as described herein should target APOC3 mRNA irrespective of splice variants and isoforms. 376 targets were selected for synthesis as asymmetric duplexes (14 nucleotide sense strand, 19 nucleotide antisense strand). Compounds were dissolved to 50uM in molecular biology grade water and annealed by heating at 95C for 5 minutes followed by gradual cooling to room temperature.

APOC3 - Primary Screen:

On the day of transfection, HepG2 cells were collected by trypsinization, counted, and seeded in 96 well tissue culture treated plates at 10,000 cells per well in 50uL complete EMEM with 20% FBS. Cells were allowed to rest for 4 hours before transfection with 2 pmoles of each respective APOC3 duplex in triplicate via RNAiMax (ThermoFisher). In brief, 8 pmoles of each duplex were diluted in 100 uL OptiMEM and mixed gently with 0.8 uL of RNAiMax in 100 uL OptiMEM to make 200 uL total complex. 50 uL of each RNAiMax complexed duplex was added to each respective triplicate well of HepG2 cells for a final mixture of 20 nM duplex in a volume of 100uL, 50/50 EMEM/OptiMEM at 10% FBS.

72 hours post transfection, cells were harvested and RNA isolated using the PureLink Pro 96 total RNA Purification Kit (ThermoFisher, 12173011A) according to the manufacturer protocol. Harvested RNA was assayed for APOC3 expression via Taqman qPCR using the Luna Universal Probe One-Step RT-qPCR Kit (NEB, E3006). Two separate qPCR assays were performed for each sample using two separate APOC3 Taqman probe sets multiplexed with a common GAPDH VIC probe (ThermoFisher, 4326317E). Thermocycling and data acquisition was performed with an Applied Biosystems QuantStudio 3 Real-Time PCR System. Based on the results of the primary screen, a subset of 77 oligomeric compounds was selected which exhibit at least 70% target knockdown when assessed with either probe. These 77 compounds are defined by above items 3 and 4.

APOC3 - Secondary Screen:

Based on data from the primary screen, a yet narrower set of the best performing 30 APOC3 duplexes were tested in dose curves. As before, HepG2 cells were collected by trypsinization and seeded in 96 well tissue culture plates at 10,000 cells per well in 50uL complete EMEM with 20% FBS and allowed to rest for 4 hours. Transfection complexes were formed by gently mixing 36 pmoles of each duplex in 180 uL OptiMEM with 2.16 uL RNAiMax in 180 uL OptiMEM to make 360 uL total complex. A two fold dilution series was then performed with basal OptiMEM. 50 uL of each dilution was added to respective triplicates of HepG2 cells to make a final dilution series of 50 nM down to 0.32 nM in a volume of 100uL, 50/50 EMEM/OptiMEM at 10% FBS.

72 hours post transfection, cells were harvested and RNA isolated using the PureLink Pro 96 total RNA Purification Kit (ThermoFisher, 12173011A) according to the manufacturer protocol. Harvested RNA was assayed for APOC3 expression via Taqman qPCR using the Luna Universal Probe One-Step RT-qPCR Kit (NEB, E3006). A single qPCR assay was performed for each sample using APOC3 Taqman probe set multiplexed with a common GAPDH VIC probe (ThermoFisher, 4326317E). Thermocycling and data acquisition was performed with an Applied Biosystems QuantStudio 3 Real-Time PCR System.

Example 2:

Results

Table 4 below shows IC50 values (in nM) for the 30 constructs selected in accordance with the Examples.

Sequence ID	% k/d at the highest conc.	IC50
AP277	93.44	3.29
AP337	93.10	4.10
AP028	90.64	4.53
AP343	93.10	4.70
AP369	90.15	4.86
AP366	95.63	5.56
AP274	89.43	5.89
AP367	88.85	5.99
AP336	92.76	6.13
AP332	90.23	6.35
AP293	84.99	6.44
AP373	89.76	6.46
AP280	78.85	6.71
AP221	92.66	6.84
AP334	90.35	6.85
AP286	83.77	6.89
AP149	90.36	7.77

AP193	91.30	7.83
AP328	87.02	7.85
AP175	94.58	8.28
AP262	84.65	8.72
AP254	90.79	9.11
AP185	88.83	9.20
AP328	88.99	9.44
AP271	78.49	9.49
AP137	86.09	9.79
AP225	81.11	10.74
AP167	84.77	11.13
AP297	84.99	13.28
AP191	84.23	14.27

The IC50 data in the single- to double-digit nanomolar range demonstrate outstanding performance of numerous constructs as described herein.

Example 3

Materials and Methods

Cell culture:

Human primary hepatocytes (5 donor pooled - Sekisui XenoTech, HPCH05+) were thawed immediately prior to experimentation and cultured in 1x complete Williams medium (Gibco, A1217601) supplemented with Hepatocytes plating supplement pack (Gibco, CM3000). FBS concentration was modified from manufacture recipe to a final 2.5% (as opposed to 5%) for compound stability.

1x Complete WEM: 2.5% FBS, 1 µM Dexamethasone, Pen/Strep (100 U/mL /100 µg/mL), 4 µg/ml Human Insulin, 2 mM GlutaMAX, 15 mM HEPES, pH 7.4).

Hepatocytes were plated on Collagen I (rat tail) coated 96 well tissue culture plates (Gibco, A1142803).

APOC3 compound preparation:

Compounds were dissolved to 10 mg/mL in PBS and annealed by heating at 95C for 5 minutes followed by rapid cooling on ice.

APOC3 compound transfections:

On the day of transfection, primary human hepatocytes were thawed in 45mL of human OptiThaw (Sekisui Xenotech, K8000) and centrifuged down at 200g for 5 minutes. Cells were resuspended in 2x complete WEM and counted. Cell were then plated in 50 uL of 2x complete WEM at 25,000 cells per well on 96 well type 1 rat tail Collagen plates and allowed to rest and attach for four hours before transfection.

Compounds were diluted further to 2 uM in basal WEM. A seven step, five fold dilution series was prepared in basal WEM from 2 uM to 0.000128 uM. 50 uL of each dilution was added to respective triplicates of the plated hepatocytes for a final dilution series of 1 uM down to 0.000064 uM in a volume of 100uL 1x complete WEM.

72 hours post transfection, cells were harvested and RNA isolated using the PureLink Pro 96 total RNA Purification Kit (ThermoFisher, 12173011A) according to the manufacturer protocol. Harvested RNA was assayed for APOC3 expression via Taqman qPCR using the Luna Universal Probe One-Step RT-qPCR Kit (NEB, E3006). A single qPCR assay was performed for each sample using an APOC3 Taqman probe set (Hs00906501_g1-FAM) multiplexed with a common GAPDH VIC probe (ThermoFisher, 4326317E). Thermocycling and data acquisition was performed with an Applied Biosystems QuantStudio 3/5 Real-Time PCR System.

Table 5: Constructs used as positive control

A277(15)dup	5' [mU][#][fU][#][mG][fG][mA][fU][mA][fG][mG][fC][mA][fG][mG][fU][mG][#][fG][#][mA][#][fC][#][rU]
	5' [fC][#][mA][#][fC][mC][fU][mG][fC][mC][fU][mA][fU][mC][mC][#][mA][#][mA][#][3XGalNAc]
A28(15)dup	5' [mU][#][fC][#][mA][fA][mC][fA][mA][fG][mG][fA][mG][fU][mA][fC][mC][#][fC][#][mG][#][fG][#][rG]
	5' [fG][#][mG][#][fU][mA][fC][mU][fC][mC][fU][mU][fG][mU][mU][#][mG][#][mA][#][3XGalNAc]
P29-A28	5' [mU][#][fG][#][mC][fA][mA][fA][mA][fC][mA][fG][mG][fU][mC][fU][#][mA][#][fG][#][mA][#][fA][#][rA][mG][#][fU][#][mA][fC][mU][fC][mC][fU][mU][fG][mU][mU][#][mG][#][mA][#][3XGalNAc]
	5' [mU][#][fC][#][mA][fA][mC][fA][mA][fG][mG][fA][mG][fU][mA][fC][#][mC][#][fC][#][mG][#][fG][#][rG][mA][#][fG][#][mA][fC][mC][fU][mG][fU][mU][fU][mU][mG][#][mC][#][mA][#][3XGalNAc]
P29-A277	5' [mU][#][fG][#][mC][fA][mA][fA][mA][fC][mA][fG][mG][fU][mC][fU][#][mA][#][fG][#][mA][#][fA][#][rA][mA][#][fC][#][mC][fU][mG][fC][mC][fU][mA][fU][mC][mC][#][mA][#][mA][#][3XGalNac]
	5' [mU][#][fU][#][mG][fG][mA][fU][mA][fG][mG][fC][mA][fG][mG][fU][#][mG][#][fG][#][mA][#][fC][#][rU][mA][#][fG][#][mA][fC][mC][fU][mG][fU][mU][fU][mU][mG][#][mC][#][mA][#][3XGalNAc]
TMPRSS6	5' vP[mA][fA][mC][fC][mA][fG][mA][fA][mG][fA][mA][fG][mC][fA][mG][fG][mU][fG][iN][fC][mU][fG][fC][fU][mU][fC][mU][fU][mC][fU][mG][fG][mU][fU]#[3XGalNAc]

Note: vP = vinyl-phosphonate; iN = inverted with 2'OH

Results

As can be seen from Figure 1a, several variations of both A28 and A277 structures demonstrated excellent activities.

As can be seen from Figure 1b, all molecules produced excellent activities.

Example 4

STUDY PROTOCOL

The following study protocol for the study entitled "mxRNA Leads for Candidate Screening Study in Male human liver-uPA-SCID mice, non-GLP" has been drafted before the animal experiments and studies have been completed and therefore uses the future tense. However, as said study has already been completely carried out, each usage of "future tense" should be considered as the "past tense" in the following description of the study protocol.

STUDY OBJECTIVE(S)

The objective of this non-GLP study was to evaluate the dose and duration response effect of two selected mxRNA leads for candidate GalNAc-siRNA constructs targeting APOC3 using the human liver-uPA-SCID mice models. The compounds were administered subcutaneously and the mice survived for 14-days and 42-days.

Prior to necropsy, plasma and serum were collected. At necropsy, 3 liver biopsies (2 mm) per animal were preserved in separate vials in RNAlater, flash frozen, and stored at -80°C. Three more liver biopsies (2mm) were taken, flash frozen in the same vial, and stored at -80°C.

REGULATORY COMPLIANCE

This non-GLP study will not be conducted in accordance with the Food and Drug Administration's Good Laboratory Practice (GLP) regulations (21 CFR Part 58).

ANIMAL WELFARE COMPLIANCE

The procedures described and performed below will be conducted in accordance with the Guide for the Care and Use of Laboratory Animals, USDA APHIS, Animal Welfare Act and/or in accordance with the Standard Operating Procedures.

This protocol has been reviewed and approved by the Test Facility IACUC Committee.

STUDY SCHEDULE

Acclimatization/Quarantine End Date:	≥ 5 days
Baseline Procedure Date:	No baseline procedures Procedure Start Day 0 Date: Tentative: December Waiting on test material.
Necropsy Start:	On Day 14- and 42-days post treatment.
In-Life Study Completion:	6 weeks post treatment
Preliminary Report:	None required by Sponsor, Data only
Final Report Issued:	None required

TEST SYSTEM INFORMATION

Animal Test

Common Name: Mouse

Breed/Class: Rodent – human liver-uPA-SCID mouse

Number of Animals (by gender): 36 Male, all naïve

Age Range: 14-19 weeks

Weight Range: Approx. 20 grams

The mice used in this study were human liver-uPA-SCID mice. About 80% of the hepatocytes of each mouse have been replaced by human hepatocytes. The skilled person is aware of ways of producing such mice; wherein at least some of these ways are shown and referenced in P. Meuleman and G. Leroux-Roels in Antiviral Res. 2008 Dec;80(3):231-8 which is incorporated herein by reference in its entirety.

Acclimation Period:

Duration:

All animals will be acclimated for a minimum period of five (5) days prior to release by the Attending veterinarian, at which time the overall health of the animals will be evaluated. Animals which are not released from acclimation will be treated accordingly and further evaluation will be performed prior to release. All records from the acclimation period will remain in the study file.

Animal Identification Method and Location:

Animals will be assigned sequential numbers. The animals will be ear notched to permanently identify each animal. This method involves punching holes or notches in the ear pinna while anesthetized. Alternatively, the animals may have a tattoo placed on their tail. A cage card will also be affixed to each animal cage denoting the animal number, gender, vendor, strain, study director, and study number

STUDY DESIGN

Design Details

This study will have one type of mice, 36 human liver-uPA-SCID mice. Animals will be grouped by treatment type, dosage, and survival period. Each animal will be treated by subcutaneous injection of test material. Groups 1A and 1B will have four animals receive a control dose of PBS. Groups 2A, 2B, 2C, 3A, 3B, and 3C will receive one dose (10 or 30 mg/kg) with four animals for each dose amount. All animals will be kept alive for 14 or 42 days. See study Table 6 below for details.

Table 6: Study Table

Group	Number of human liver-uPA-SCID mice animals	Treatment Subcutaneous Injection Day 0	Survival Days	Blood	Pre-Euthanasia and Necropsy
1A	4	Control (PBS)	14	Plasma and serum will be collected for all animals on necropsy days 14 and 42. Send Plasma and serum to Sponsor.	Pre-Euthanasia: Plasma and serum collection. Necropsy: 2 mm biopsy of left, middle and right liver lobes in separate vials, in RNAlater for 15 min, flash freeze then stored at -80°C. 2 mm biopsy of left, middle and right liver all in one vial, flash freeze then stored at -80°C. Rest of liver, flash freeze then stored at -80°C.
1B	4	Control (PBS)	42		
2A	4	A28 mxRNA (10 mg/kg)	14		
2B	4	A28 mxRNA (30 mg/kg)	14		
2C	4	A28 mxRNA (10 mg/kg)	42		
3A	4	A277 mxRNA (10 mg/kg)	14		
3B	4	A277 mxRNA (30 mg/kg)	14		
3C	4	A277 mxRNA (10 mg/kg)	42		
Spares	4				
Total	36				

Prior to necropsy, the animals will be deeply anesthetized and a terminal blood draw will be performed through the vena cava. The target blood volume to be collected per animal is as much blood as possible with a minimum of 1.2 mL which will be split equally between a serum and plasma separation tube. After separation (see section 14.10) the serum will be split equally in two separate vials and plasma also will be separated in two separate vials (see example below).

- 1.2 mL of blood= 0.6 mL for serum and 0.6 mL for plasma separation tubes

- Serum (0.3 mL after separation)= 0.15 mL x 2 vials
- Plasma (0.3 mL after separation)= 0.15 mL x 2 vials.

Above serum and plasma samples will be labelled, flash frozen and stored at -80ºC.

Additional blood collected over the minimum 1.2 mL volume will be placed in a serum separation tube, processed, serum transferred to a labelled vile, refrigerated at 4°C for rodent lipid analysis.

Note: serum and plasma will be used to measure protein, caution should be taken to avoid hemolysis or clot formation.

At necropsy, three 2 mm biopsy punches will be taken from the left, middle and right liver lobes, placed in separate vials, soaked in RNAlater for 15 minutes, flash frozen and stored at -80°C. Another three 2mm liver biopsies from the left, middle and right liver lobes will be placed into one vial, flash frozen and stored at -80°C. The rest of the liver will be flash frozen and stored in 10mL conical tubes at -80°C.

Alteration of Study Design

Alterations of this protocol may be made as the study progresses. Changes (to the protocol) that have the potential to negatively impact the study or the safety of the study subjects would require IACUC approval.

Animal Inclusion and Exclusion Criteria

Any animals that are deemed unhealthy during veterinary pre-screen will be excluded from the study and replaced with a spare animal if available. For survival animals found dead or moribund after treatment may be replaced via study protocol amendment by a spare animal if available.

Animal Disposition

At the end of the study, the animals will be euthanized.

Route of Administration

Subcutaneous injection in the scruff. An injection volume of 200 uL.

RESULTS

Fig. 3 highlights the dose-response effect on the percent reduction of APOC3 mRNA in the liver tissues and APOC3 protein levels in the plasma of the animals treated with the different mxRNA constructs at Day 14 as compared to the control animals.

In addition, the following notes apply to Fig. 3:

A28(14-4)mF-10 = A28(14-4)mF 10mg/kg dose group

A28(14-4)mF-30 = A28(14-4)mF 30mg/kg dose group

A277(12-5)-10 = A277(12-5) 10mg/kg dose group

A277(12-5)-30 = A277(12-5) 30mg/kg dose group

Fig. 4 highlights the dose -response effect on the mean percent reduction of Triglycerides and Total Cholesterol in the serum of the animals treated with the different APOC-3 targeting mxRNA constructs at Day 14 as compared to the control animals.

Figs. 5a and 5b highlight the duration effect on the mean percent reduction of APOC3 mRNA in liver tissues and APOC3 protein levels in the plasma of the animals treated with the different APOC3-targeting mxRNA (10mg/kg) constructs at Day 14 (Week 2) and at Week 6 as compared to the control animals. Moreover, it is noted with respect to these Figures that an outlier from the A277(12-5) group is excluded.

Figs. 6a and 6b highlight the duration effect on the mean percent reduction of triglycerides (TGs) and total cholesterol (TC) in the serum of the animals treated with the different APOC3-targeting mxRNA (10mg/kg) constructs at Day 14 (Week 2) and at Week 6 as compared to the control animals. With respect to these Figures it is noted, that an outlier from the A277(12-5) group is excluded.

Summary of Results

A28(14-4)mF APOC3-targeting mxRNA construct:

- 88% suppression of APOC3 mRNA as compared to control group at week 2 that was maintained at 78% on Week 6.
- 90% reduction in plasma APOC3 levels as compared to control group at week 6 that was sustained at 85% on Week 6.
- 32% reduction in serum triglycerides levels as compared to control group at week 2 that increased to 41% reduction on Week 6.
- 43% reduction in serum total cholesterol levels as compared to control group at week 2 that was maintained at 33% on Week 6.

A277(12-5) APOC3-targeting mxRNA construct:

- 56% suppression of APOC3 mRNA as compared to control group at week 2 that was maintained at 42% on Week 6.
- 83% reduction in plasma APOC3 levels as compared to control group at week 6 that was sustained at 84% on Week 6.
- 8% reduction in serum triglycerides levels as compared to control group at week 2that increased to 52% reduction on Week 6.
- 36% reduction in serum total cholesterol levels as compared to control group at week 2 that was lost on Week 6.

CONCLUSIONS

Construct A28(14-4)mF produced outstanding activity, with 98% of the targeted protein downregulation at 2-week timepoint at 30 mg/kg dosing. Furthermore, construct A28(14-4)mF sustained excellent (protein knockdown) activity at 10 mg/kg dosing both on week 2 and week 6.

Example 5

Following the protocol described in detail in Example 4, the effects of compound A28(14-4)mF (also designated STP125G) have been observed over a longer period of time. See Figure 7 for an overview of this extended study. The corresponding results are displayed in Figures 8a and 8b (APOC3 mRNA and protein knockdown, respectively), and Figures 9a and 9b (triglyceride and total cholesterol levels). Several aspects are notable:

- A single dose of 10 mg/kg is sufficient for knockdown of mRNA and protein for a period of six weeks with a rebound becoming slowly apparent toward the end of the study.
- Not only triglycerides (fat levels in blood primarily considered to be associated with APOC3) but also total cholesterol are downregulated.
- In the assessment of the latter findings, the properties of the mice used for the study must be considered. Figure 10 shows that an estimated fraction of 20 to 25 percent of the cells of the humanized liver remain murine (mouse) cells. A28A(14-4)mF does not target murine APOC3.

As a consequence, the non-silenced murine APOC3 contributes to the observed triglyceride and total cholesterol levels. Thus, the downregulation of these two blood fats in a purely human system is expected to exceed the results observed in this study.

Claims

1. An oligomeric compound capable of inhibiting expression of APOC3, wherein said compound comprises at least a first region of linked nucleosides having at least a first nucleobase sequence that is at least partially complementary to at least a portion of RNA transcribed from an APOC3 gene, wherein said first nucleobase sequence is selected from the following sequences, or a portion thereof: sequences of Tables 1a and 2a (SEQ ID NOs: 1 to 391), wherein said portion preferably has a length of at least 18 nucleotides.

2. The oligomeric compound according to claim 1, which further comprises at least a second region of linked nucleosides having at least a second nucleobase sequence that is at least partially complementary to said first nucleobase sequence and is selected from the following sequences, or a portion thereof: sequences of Tables 1c and 2c (SEQ ID NOs: 401 to 791), wherein said portion preferably has a length of at least 8, 9, 10 or 11 nucleotides, more preferably at least 10 nucleotides.

3. The oligomeric compound according to claim 1 or 2, wherein said first nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 175, 293, 262, 297, 277, 366, 337, 254, 274, 286, 137, 149, 280, 343, 225, 221, 185, 373, 121, 281, 331, 367, 296, 28, 345, 328, 339, 278, 271, 212, 223, 369, 276, 332, 300, 341, 334, 138, 193, 340, 31, 167, 275, 191, 336, 90, 346, 219, 283, 213, 23, 24, 285, 347, 370, 206, 282, 342, 272, 303, 220, 209, 29, 89, 291, 117, 372, 218, 368, 148, 217, 128, 338, 171, 94, 324, and 299.

4. The oligomeric compound according to claim 3, wherein said second nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 575, 693, 662, 697, 677, 766, 737, 654, 674, 686, 537, 549, 680, 743, 625, 621, 585, 773, 521, 681, 731, 767, 696, 428, 745, 728, 739, 678, 671, 612, 623, 769, 676, 732, 700, 741, 734, 538, 593, 740, 431, 567, 675, 591, 736, 490, 746, 619, 683, 613, 423, 424, 685, 747, 770, 606, 682, 742, 672, 703, 620, 609, 429, 489, 691, 517, 772, 618, 768, 548, 617, 528, 738, 571, 494, 724, and 699.

5. The oligomeric compound according to any of claims 1 to 4, wherein said first nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 277, 337, 28, 343, 369, 366, 274, 367, 336, 332, 293, 373, 280, 221, 334, 286, 149, 193, 328, 175, 262, 254, 185, 328, 271, 137, 225, 167, 297, and 191.

6. The oligomeric compound according to claim 5, wherein said second nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 677, 737, 428, 743, 769, 766, 674, 767, 736, 732, 693, 773, 680, 621, 734, 686, 549, 593, 728, 575, 662, 654, 585, 728, 671, 537, 625, 567, 697, and 591.

7. The oligomeric compound according to any of claims 1 to 6, wherein said first nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 28, 277, 336, 337, 366, 367, and 369.

8. The oligomeric compound according to claim 7, wherein said second nucleobase sequence is selected from the following sequences, or a portion thereof: SEQ ID NOs: 428, 677, 736, 737, 766, 767, and 769

9. The oligomeric compound according to any of claims 1 to 8, wherein said first region of linked nucleosides consists essentially of 18 to 35, preferably 18 to 20, more preferably 18 or 19, and yet more preferably 19 linked nucleosides.

10. The oligomeric compound according to any of claims 2 to 9, wherein said second region of linked nucleosides consists essentially of 10 to 35, preferably 10 to 20, more preferably 10 to 16, and yet more preferably 10 to 15 linked nucleosides.

11. The oligomeric compound according to any of claims 2 to 10, which comprises at least one complementary duplex region that comprises at least a portion of said first nucleoside region directly or indirectly linked to at least a portion of said second nucleoside region, wherein optionally said duplex region has a length of 10 to 19, 12 to 19, 12 to 15 base pairs, or 14 base pairs, wherein optionally there is one mismatch within said duplex region.

12. The oligomeric compound according to claim 11, wherein each of said first and second nucleoside regions has a 5' to 3' directionality thereby defining 5' and 3' regions respectively thereof.

13. The oligomeric compound according to claim 12, wherein the 5' region of said first nucleoside region is directly or indirectly linked to the 3' region of said second nucleoside region, for example by complementary base pairing, wherein preferably the 5' terminal nucleoside of said first nucleoside region base pairs with the 3' terminal nucleoside of said second nucleoside region.

14. The oligomeric compound according to claim 12 or 13, wherein the 3' region of said first nucleoside region is directly or indirectly linked to the 5' region of said second nucleoside region, wherein preferably said first nucleoside region is directly and covalently linked to said second nucleoside region such as by a phosphate, a phosphorothioate, or a phosphorodithoate.

15. The oligomeric compound according to any of claims 1 to 14, which further comprises one or more ligands.

16. The oligomeric compound according to claim 15, wherein said one or more ligands are conjugated to said second nucleoside region and/or said first nucleoside region.

17. The oligomeric compound according to claim 16, as dependent on claim 12, wherein said one or more ligands are conjugated at the 3' region, preferably to the 3' end of the second nucleoside region and/or of the first nucleoside region, and/or to the 5' end of said second nucleoside region.

18. The oligomeric compound according to any of claims 15 to 17, wherein said one or more ligands are any cell directing moiety, such as lipids, carbohydrates, aptamers, vitamins and / or peptides that bind cellular membrane or a specific target on cellular surface.

19. The oligomeric compound according to claim 18, wherein said one or more ligands comprise one or more carbohydrates.

20. The oligomeric compound according to claim 19, wherein said one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide or polysaccharide.

21. The oligomeric compound according to claim 20, wherein said one or more carbohydrates comprise or consist of one or more hexose moieties.

22. The oligomeric compound according to claim 21, wherein said one or more hexose moieties are one or more galactose moieties, one or more lactose moieties, one or more N-Acetyl-Galactosamine moieties, and / or one or more mannose moieties.

23. The oligomeric compound according to claim 22, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

24. The oligomeric compound according to claim 23, which comprises two or three N-Acetyl-Galactosamine moieties, preferably three.

25. The oligomeric compound according to any of claims 15 to 24, wherein said one or more ligands are attached to said oligomeric compound, preferably to the second nucleoside region thereof, in a linear configuration, or in a branched configuration.

26. The oligomeric compound according to claim 25, wherein said one or more ligands are attached to said oligomeric compound as a biantennary or triantennary configuration.

27. The oligomeric compound according to any one of claims 1 to 26, wherein said compound consists of said first region of linked nucleosides and said second region of linked nucleosides.

28. The oligomeric compound according to claim 11, wherein said oligomeric compound comprises a single strand comprising said first and second nucleoside regions, wherein at least a portion of said first nucleoside region is directly or indirectly linked to at least a portion of said second nucleoside region so as to form said at least partially complementary duplex region.

29. The oligomeric compound according to claim 28, wherein said first nucleoside region has a greater number of linked nucleosides compared to the second nucleoside region, whereby the additional number of linked nucleosides of the first nucleoside region form a hairpin loop linking the first and second nucleoside regions.

30. The oligomeric compound according to claim 29, as dependent on claim 12, whereby said hairpin loop is present at the 3' region of said first nucleoside region.

31. The oligomeric compound according to claim 29 or 30, wherein said hairpin loop comprises 4 or 5 linked nucleosides.

32. The oligomeric compound according to any one of claims 28 to 31, wherein said single strand has a nucleobase sequence selected from SEQ ID NOs: 792 to 803, SEQ ID NOs: 792, 793, 796, 800 and 803, preferably from SEQ ID NOs: 796 and 803, or SEQ ID No: 803.

33. The oligomeric compound according to claim 32, wherein said single strand is selected from Table 3b and optionally is one of constructs A28(14-4)mF or A277(12-5),

34. The oligomeric compound according to any of claims 1 to 33, which comprises internucleoside linkages and wherein at least one internucleoside linkage is a modified internucleoside linkage.

35. The oligomeric compound according to claim 34, wherein said modified internucleoside linkage is a phosphorothioate or phosphorodithioate internucleoside linkage.

36. The oligomeric compound according to claim 35, which comprises 1 to 15 phosphorothioate or phosphorodithioate internucleoside linkages.

37. The oligomeric compound according to claim 36, which comprises 7, 8, 9 or 10 phosphorothioate or phosphorodithioate internucleoside linkages.

38. The oligomeric compound according to any of claims 35 to 37, as dependent on claim 12, which comprises one or more phosphorothioate or phosphorodithioate internucleoside linkages at the 5' region of the first nucleoside region.

39. The oligomeric compound according to any of claims 35 to 38, as dependent on claim 12, which comprises one or more phosphorothioate or phosphorodithioate internucleoside linkages at the 5' region of the second nucleoside region.

40. The oligomeric compound according to any of claims 35 to 39, as dependent on claim 29, which comprises phosphorothioate or phosphorodithioate internucleoside linkages between at least two, preferably at least three, preferably at least four, preferably at least five, adjacent nucleosides of the hairpin loop, dependent on the number of nucleotides present in the hairpin loop.

41. The oligomeric compound according to claim 40, which comprises a phosphorothioate or phosphorodithioate internucleoside linkage between each adjacent nucleoside that is present in said hairpin loop.

42. The oligomeric compound according to any of claims 1 to 41, wherein at least one nucleoside comprises a modified sugar.

43. The oligomeric compound according to claim 42, wherein said modified sugar is selected from 2' modified sugars, locked nucleic acid (LNA) sugar, (S)-constrained ethyl bicyclic nucleic acid sugar, tricyclo-DNA sugar, morpholino, unlocked nucleic acid (UNA) sugar, and glycol nucleic acid (GNA) sugar.

44. The oligomeric compound according to claim 43, wherein said 2' modified sugar is selected from 2'-O-methyl modified sugar, 2'-O-methoxyethyl modified sugar, 2'-F modified sugar, 2'-arabino-fluoro modified sugar, 2'-O-benzyl modified sugar, and 2'-O-methyl-4-pyridine modified sugar.

45. The oligomeric compound according to claim 44, wherein at least one modified sugar is a 2'-O-methyl modified sugar.

46. The oligomeric compound according to claim 44 or 45, wherein at least one modified sugar is a 2'-F modified sugar.

47. The oligomeric compound of claim 45 or 46, wherein the sugar is ribose.

48. The oligomeric compound according to any of claims 45 to 47, as dependent on claim 12, wherein sugars of the nucleosides at any of positions 2 and 14 downstream from the first nucleoside of the 5' region of the first nucleoside region, do not contain 2'-O-methyl modifications.

49. The oligomeric compound according to any of claims 45 to 48, as dependent on claim 12, wherein sugars of the nucleosides of the second nucleoside region, that correspond in position to any of the nucleosides of the first nucleoside region at any of positions 9 to 11 downstream from the first nucleotide of the 5' region of the first nucleoside region, contain 2 or 1 2'-O-methyl modifications or do not contain 2'-O-methyl modifications.

50. The oligomeric compound according to claim 49, wherein sugars of the nucleosides at any of positions 2 and 14 downstream from the first nucleoside of the 5' region of the first nucleoside region, contain 2'-F modifications.

51. The oligomeric compound according to any of claims 49 to 50, wherein sugars of the nucleosides of the second nucleoside region, that correspond in position to 1, 2, or any of the nucleosides of the first nucleoside region at any of positions 9 to 11 downstream from the first nucleoside of the 5' region of the first nucleoside region, contain 2'-F modifications.

52. The oligomeric compound of claim 50 or 51, wherein the 3' terminal position of the second nucleoside region contains a 2'-F modification.

53. The oligomeric compound according to any of claims 47 to 52, as dependent on claim 12, wherein one or more of the odd numbered nucleosides starting from the 5' region of the first nucleoside region are modified, and / or wherein one or more of the even numbered nucleotides starting from the 5' region of the first nucleoside region are modified, wherein typically the modification of the even numbered nucleotides is a second modification that is different from the modification of odd numbered nucleotides.

54. The oligomeric compound according to claim 53, wherein one or more of the odd numbered nucleosides starting from the 3' region of the second nucleoside region are modified by a modification that is different from the modification of odd numbered nucleosides of the first nucleoside region.

55. The oligomeric compound according to claim 53 or 54, wherein one or more of the even numbered nucleosides starting from the 3' region of the second nucleoside region are modified by a modification that is different from the modification of even numbered nucleosides of the first nucleoside region according to claim 54.

56. The oligomeric compound according to any of claims 53 to 55, wherein at least one or more of the modified even numbered nucleosides of the first nucleoside region is adjacent to at least one or more of the differently modified odd numbered nucleosides of the first nucleoside region.

57. The oligomeric compound according to any of claims 53 to 56, wherein at least one or more of the modified even numbered nucleosides of the second nucleoside region is adjacent to at least one or more of the differently modified odd numbered nucleosides of the second nucleoside region.

58. The oligomeric compound according to any of claims 53 to 57, wherein sugars of one or more of the odd numbered nucleosides starting from the 5' region of the first nucleoside region are 2'-O-methyl modified sugars.

59. The oligomeric compound according to any of claims 53 to 58, wherein one or more of the even numbered nucleosides starting from the 5' region of the first nucleoside region are 2'-F modified sugars.

60. The oligomeric compound according to any of claims 53 to 59, wherein sugars of one or more of the odd numbered nucleosides starting from the 3' region of the second nucleoside region are 2'-F modified sugars.

61. The oligomeric compound according to any of claims 53 to 61, wherein one or more of the even numbered nucleosides starting from the 3' region of the second nucleoside region are 2'-O-methyl modified sugars.

62. The oligomeric compound according to any of claims 42 to 61, wherein sugars of a plurality of adjacent nucleosides of the first nucleoside region are modified by a common modification.

63. The oligomeric compound according to any of claims 42 to 62, wherein sugars of a plurality of adjacent nucleosides of the second nucleoside region are modified by a common modification.

64. The oligomeric compound according to any of claims 53 to 63, as dependent on claim 29, wherein sugars of a plurality of adjacent nucleosides of the hairpin loop are modified by a common modification.

65. The oligomeric compound according to any of claims 62 to 64, wherein said common modification is a 2'-F modified sugar.

66. The oligomeric compound according to any of claims 62 to 64, wherein said common modification is a 2'-O-methyl modified sugar.

67. The oligomeric compound according to claim 66, wherein said plurality of adjacent 2'-O-methyl modified sugars are present in at least eight adjacent nucleosides of said first and / or second nucleoside regions.

68. The oligomeric compound according to claim 66, wherein said plurality of adjacent 2'-O-methyl modified sugars are present in three or four adjacent nucleosides of said hairpin loop.

69. The oligomeric compound according to claim 42, as dependent on claim 29, wherein said hairpin loop comprises at least one nucleoside having a modified sugar.

70. The oligomeric compound according to claim 69, wherein said at least one nucleoside is adjacent a nucleoside with a differently modified sugar.

71. The oligomeric compound according to claim 70, wherein said modified sugar is a 2'-O-methyl modified sugar, and said differently modifies sugar is a 2'-F modified sugar.

72. The oligomeric compound according to any of claims 1 to 71, which comprises one or more nucleosides having an un-modified sugar moiety.

73. The oligomeric compound according to claim 72, wherein said unmodified sugar is present in the 5' region of the second nucleoside region.

74. The oligomeric compound according to claim 72 or 73, as dependent on claim 29, wherein said unmodified sugar is present in the hairpin loop.

75. The oligomeric compound according to any of claims 1 to 74, wherein one or more nucleosides of the first nucleoside region and / or the second nucleoside region is an inverted nucleoside and is attached to an adjacent nucleoside via the 3' carbon of its sugar and the 3' carbon of the sugar of the adjacent nucleoside, and / or one or more nucleosides of the first nucleoside region and / or the second nucleoside region is an inverted nucleoside and is attached to an adjacent nucleoside via the 5' carbon of its sugar and the 5' carbon of the sugar of the adjacent nucleoside.

76. The oligomeric compound according to any of claims 1 to 75, which is blunt ended.

77. The oligomeric compound according to any of claims 1 to 75, wherein either the first or second nucleoside region has an overhang.

78. The oligomeric compound according to any one of the preceding claims, wherein the first region of linked nucleotides is selected from Table 1b or Table 2b, preferably from the entries in Table 1b which have a nucleobase sequence as defined in any one of claim 3, 5 or 7.

79. The oligomeric compound according to any one of the preceding claims, wherein the second region of linked nucleotides is selected from Table 1d or Table 2d, preferably from the entries in Table 1b which have a nucleobase sequence as defined in any one of claims 4, 6 or 8.

80. A composition comprising an oligomeric compound according to any of claims 1 to 79, and a physiologically acceptable excipient.

81. A pharmaceutical composition comprising an oligomeric compound according to any of claims 1 to 79.

82. The pharmaceutical composition of claim 81, further comprising a pharmaceutically acceptable excipient, diluent, antioxidant, and/or preservative.

83. The pharmaceutical composition of claim 81 or 82, wherein said oligomeric compound is the only pharmaceutically active agent.

84. The pharmaceutical composition of claim 83, wherein said pharmaceutical composition is to be administered to patients or individuals which are statin-intolerant and/or for whom statins are contraindicated.

85. The pharmaceutical composition of claim 81 or 82, wherein said pharmaceutical composition furthermore comprises one or more further pharmaceutically active agents.

86. The pharmaceutical composition of claim 85, wherein said further pharmaceutically active agent(s) is/are a further oligomeric compound which is directed to a target different from APOC3, preferably PCSK9; Vascepa; Vupanorsen; statins such as Rosuvastatin and Simvastatin; fibrates such fenofibrate; and/or LDL-cholesterol lowering compounds such as statins and ezetimib.

87. The pharmaceutical composition of claim 85 or 86, wherein said oligomeric compound and said further pharmaceutically active agent(s) are to be administered concomitantly or in any order.

88. An oligomeric compound according to any of claims 1 to 79, for use in human or veterinary medicine or therapy.

89. An oligomeric compound according to any of claims 1 to 79, for use in a method of treating, ameliorating and/or preventing a disease or disorder.

90. The compound for use of claim 89, wherein said disease or disorder is an APOC3-associated disease or disorder, or a disease or disorder requiring reduction of APOC3 expression levels, said disease or disorder preferably being selected from dyslipidemia including mixed dyslipidemia; hyperchylomicronemia including familial hyperchylomicronemia; hypertriglyceridemia, preferably severe hypertriglyceridemia and/or hypertriglyceridemia with blood triglyceride levels above 500 mg/dl; inflammation including low-grade inflammation; atherosclerosis; atherosclerotic cardiovascular diseases (ASCVD) including major adverse cardiovascular events (MACE) such as myocardial infarction, stroke and peripheral arterial disease; and pancreatitis including acute pancreatitis.

91. A method of treating a disease or disorder comprising administration of an oligomeric compound according to any of claims 1 to 79, to an individual in need of treatment.

92. The method according to claim 91, wherein the oligomeric compound is administered subcutaneously or intravenously to the individual.

93. Use of an oligomeric compound according to any of claims 1 to 79, for use in research as a gene function analysis tool.

94. Use of an oligomeric compound according to any of claims 1 to 79 in the manufacture of a medicament for a treatment of a disease or disorder.

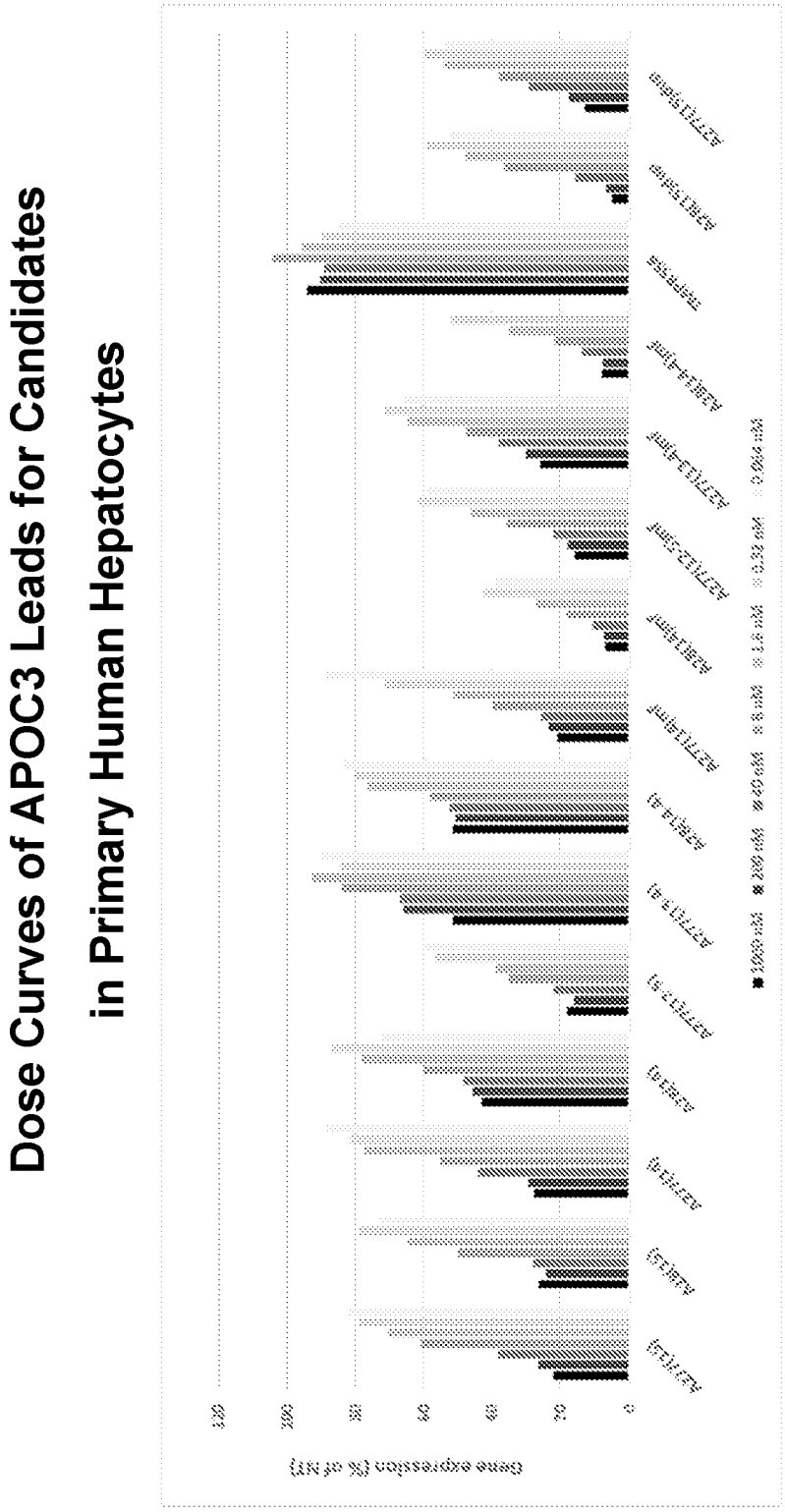

Dose Curves of APOC3 Leads for Candidates
in Primary Human Hepatocytes
Gene expression (% of NT)
100
80
60
40
20
0
1000 nM
200 nM
40 nM
8 nM
1.6 nM
0.32 nM
0.064 nM
AD-1763
AD-65213
AD-65214
AD-65215
AD-65216
AD-65217
AD-65218
AD-65219
AD-65220
AD-65221
AD-65222
AD-65223
AD-65224
AD-65225
AD-65226

Fig. 1a

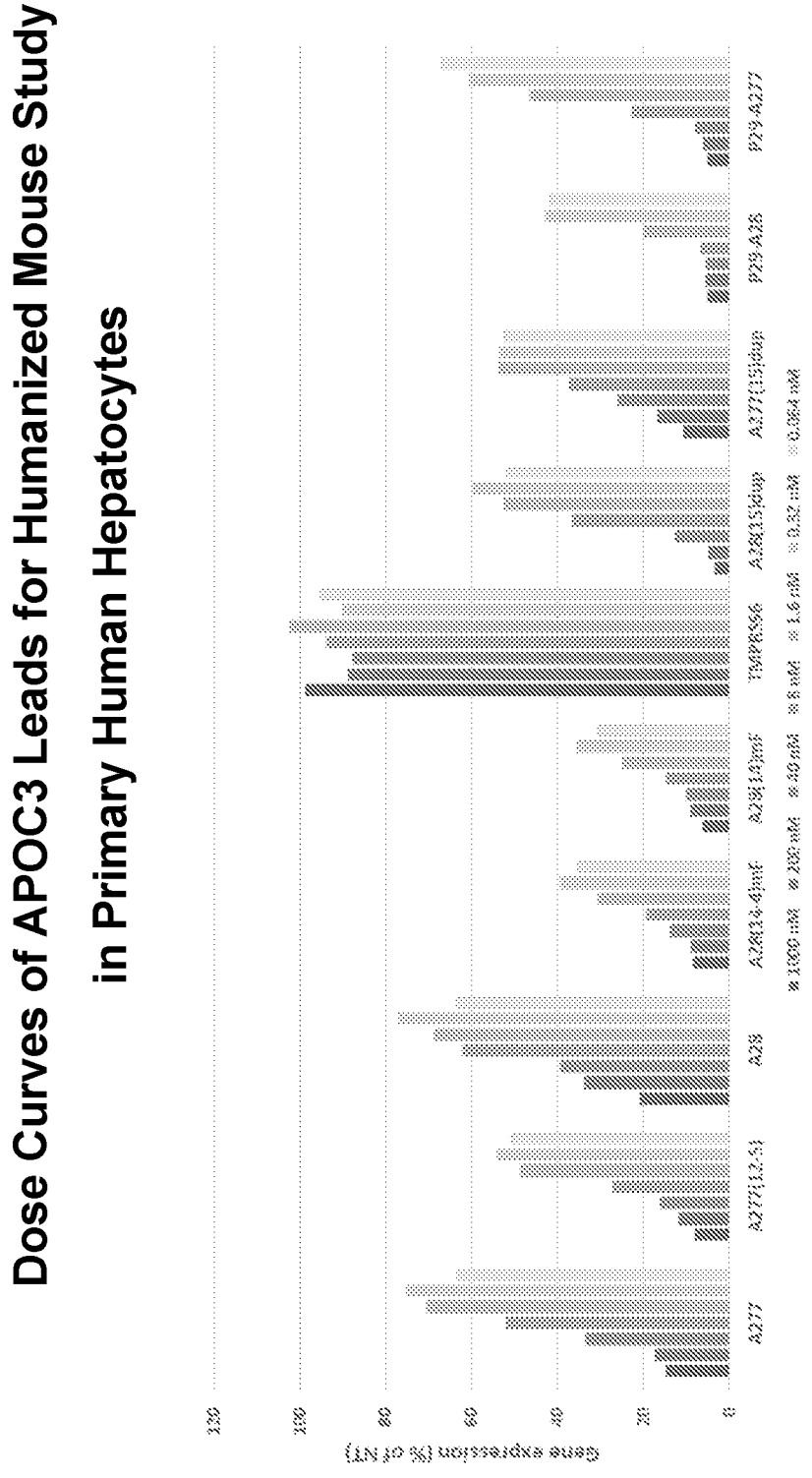

Dose Curves of APOC3 Leads for Humanized Mouse Study in Primary Human Hepatocytes
Gene expression (% of NT)
0
20
40
60
80
100
120
A277
A277(13-5)
A28
A28(14-4)mf
A28(14)mf
TRiPR566
A28(15)dup
A277(15)dup
P29 A28
P29 A277
1000 nM
200 nM
40 nM
8 nM
1.6 nM
0.32 nM
0.064 nM

Fig. 1b

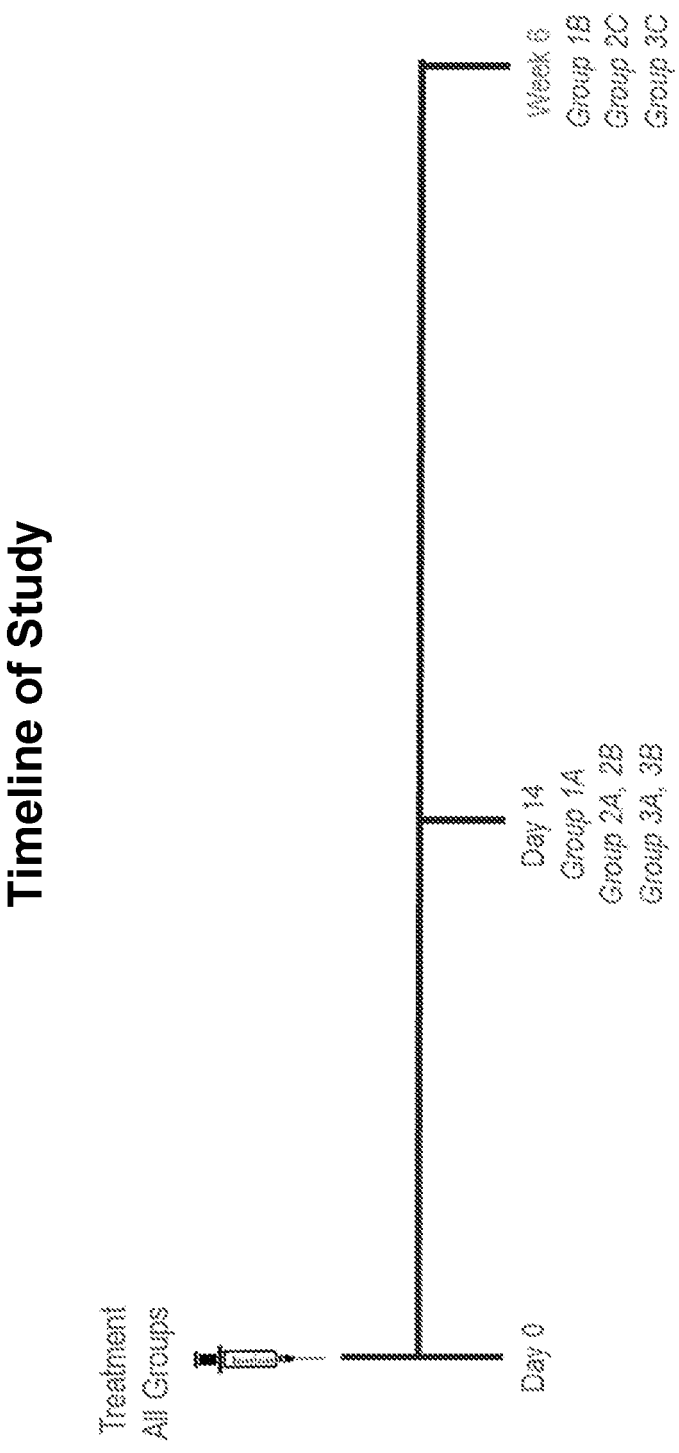

Timeline of Study
Treatment
All Groups
Day 0
Day 14
Group 1A
Group 2A, 2B
Group 3A, 3B
Week 6
Group 1B
Group 2C
Group 3C

Fig. 2

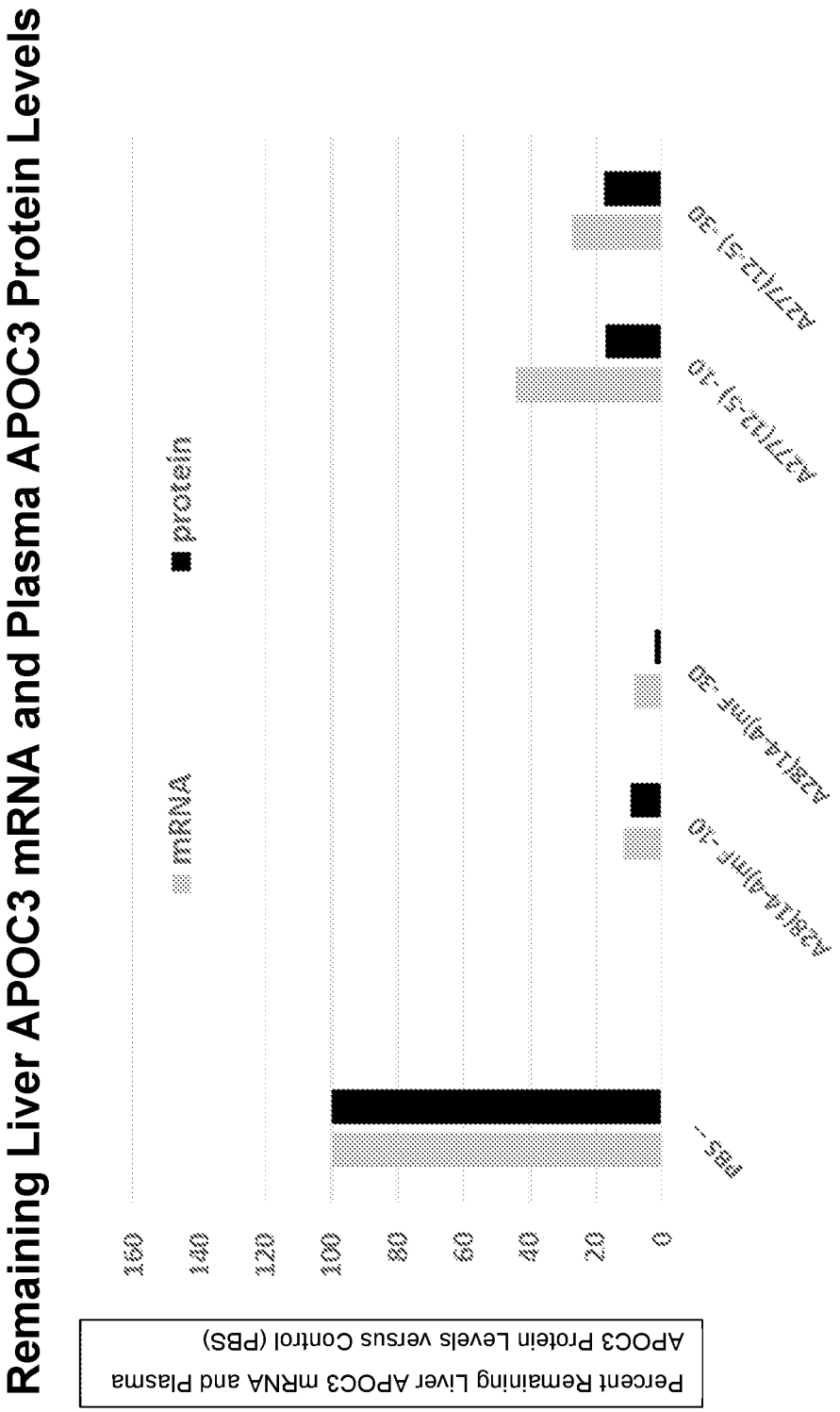

Remaining Liver APOC3 mRNA and Plasma APOC3 Protein Levels
Percent Remaining Liver APOC3 mRNA and Plasma APOC3 Protein Levels versus Control (PBS)
mRNA
protein
0
20
40
60
80
100
120
140
160
PBS
A2ML1-4bMF-10
A2ML1-4bMF-30
A2TTR-(2-5)-10
A2TTR-(2-5)-30

Fig. 3

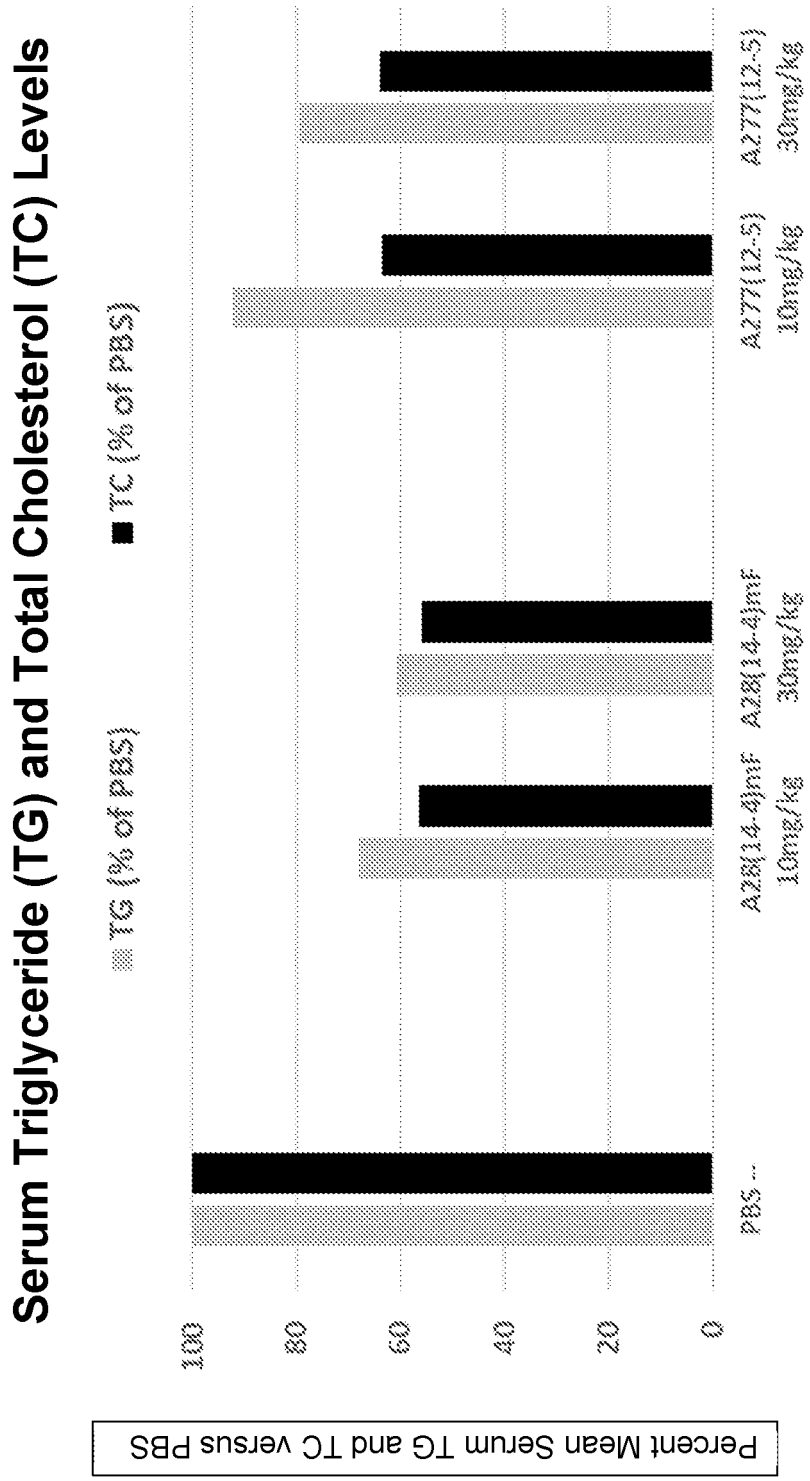

Serum Triglyceride (TG) and Total Cholesterol (TC) Levels
TG (% of PBS)
TC (% of PBS)
Percent Mean Serum TG and TC versus PBS
100
80
60
40
20
0
PBS --
A28(14-4)mf 10mg/kg
A28(14-4)mf 30mg/kg
A277(12-5) 10mg/kg
A277(12-5) 30mg/kg

Fig. 4

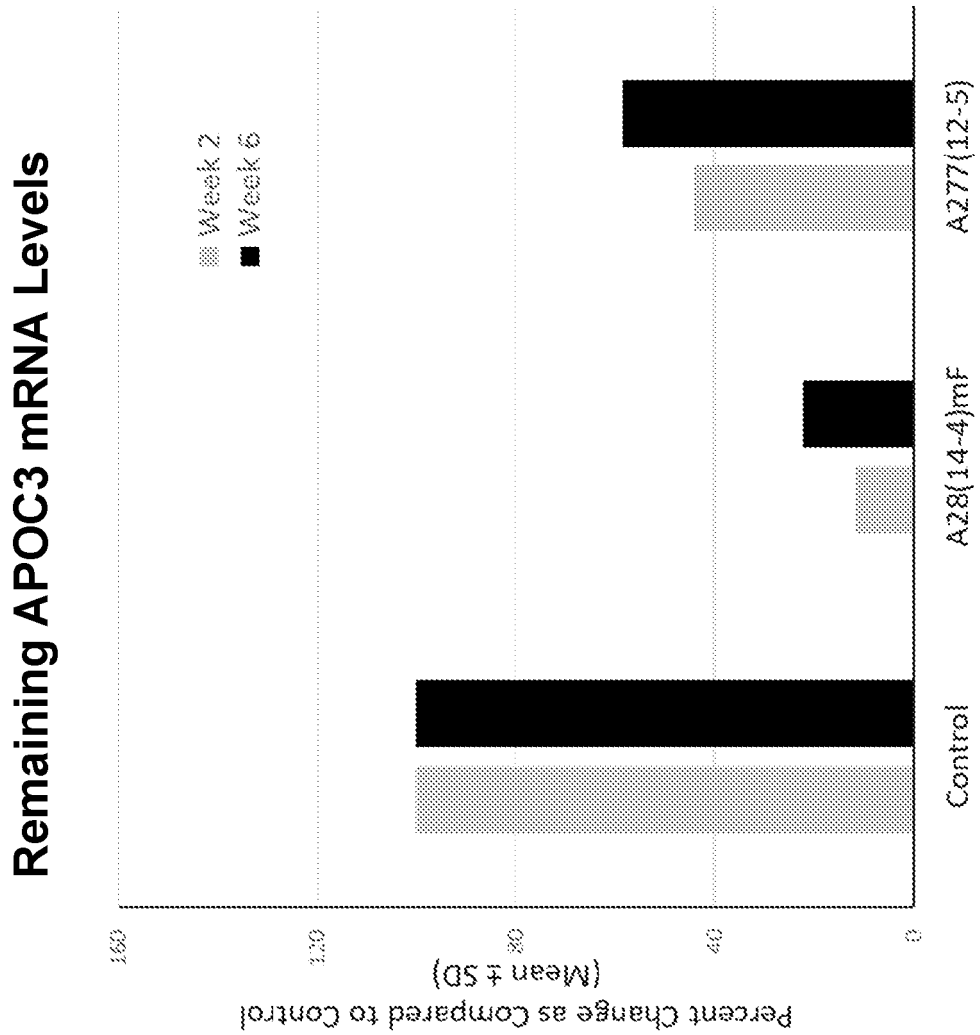

Remaining APOC3 mRNA Levels
Week 2
Week 6
Percent Change as Compared to Control
(Mean ± SD)
160
120
80
40
0
Control
A28(14-4)mF
A277(12-5)

Fig. 5a

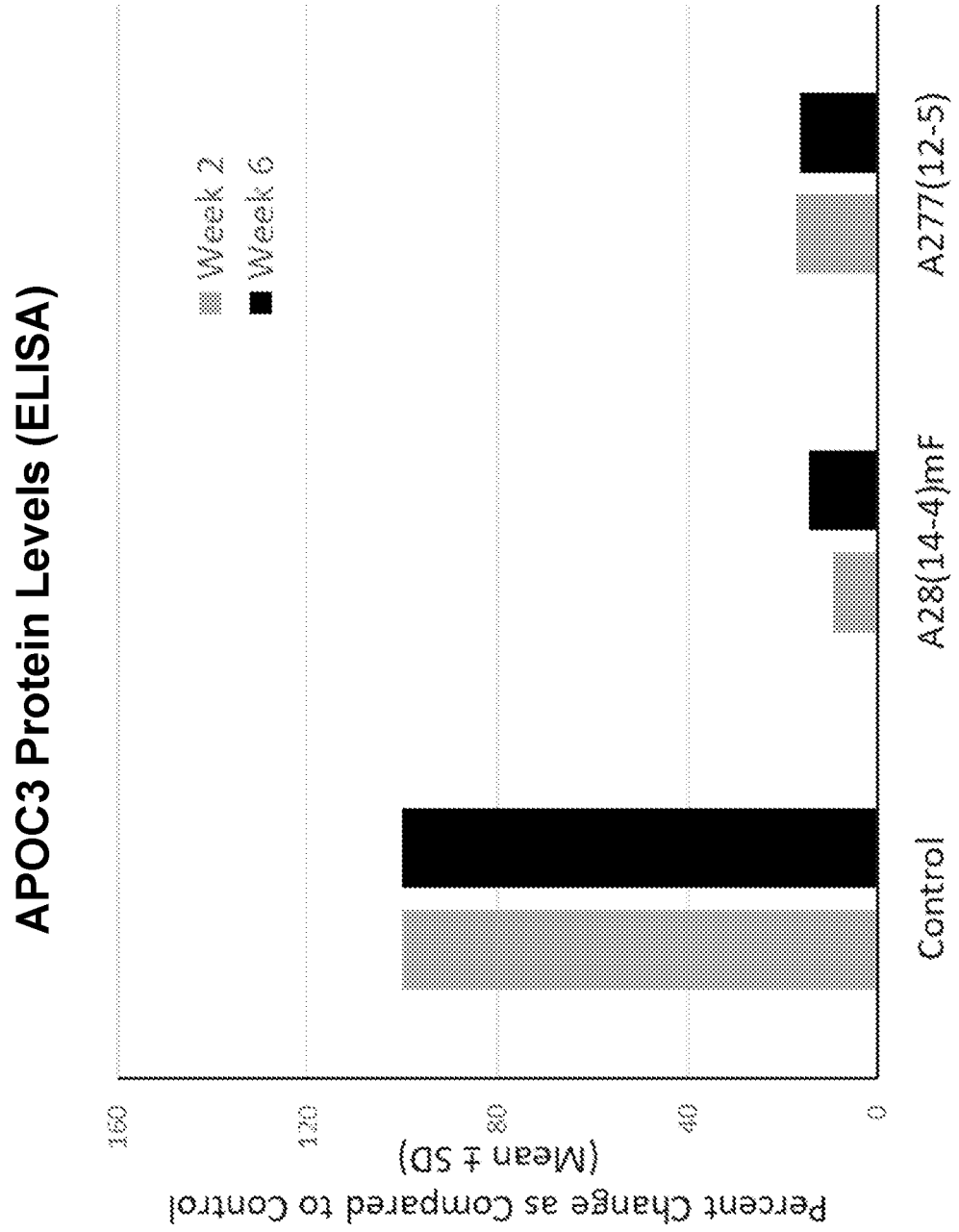

APOC3 Protein Levels (ELISA)
Week 2
Week 6
Percent Change as Compared to Control
(Mean ± SD)
160
120
80
40
0
Control
A28(14-4)mF
A277(12-5)

Fig. 5b

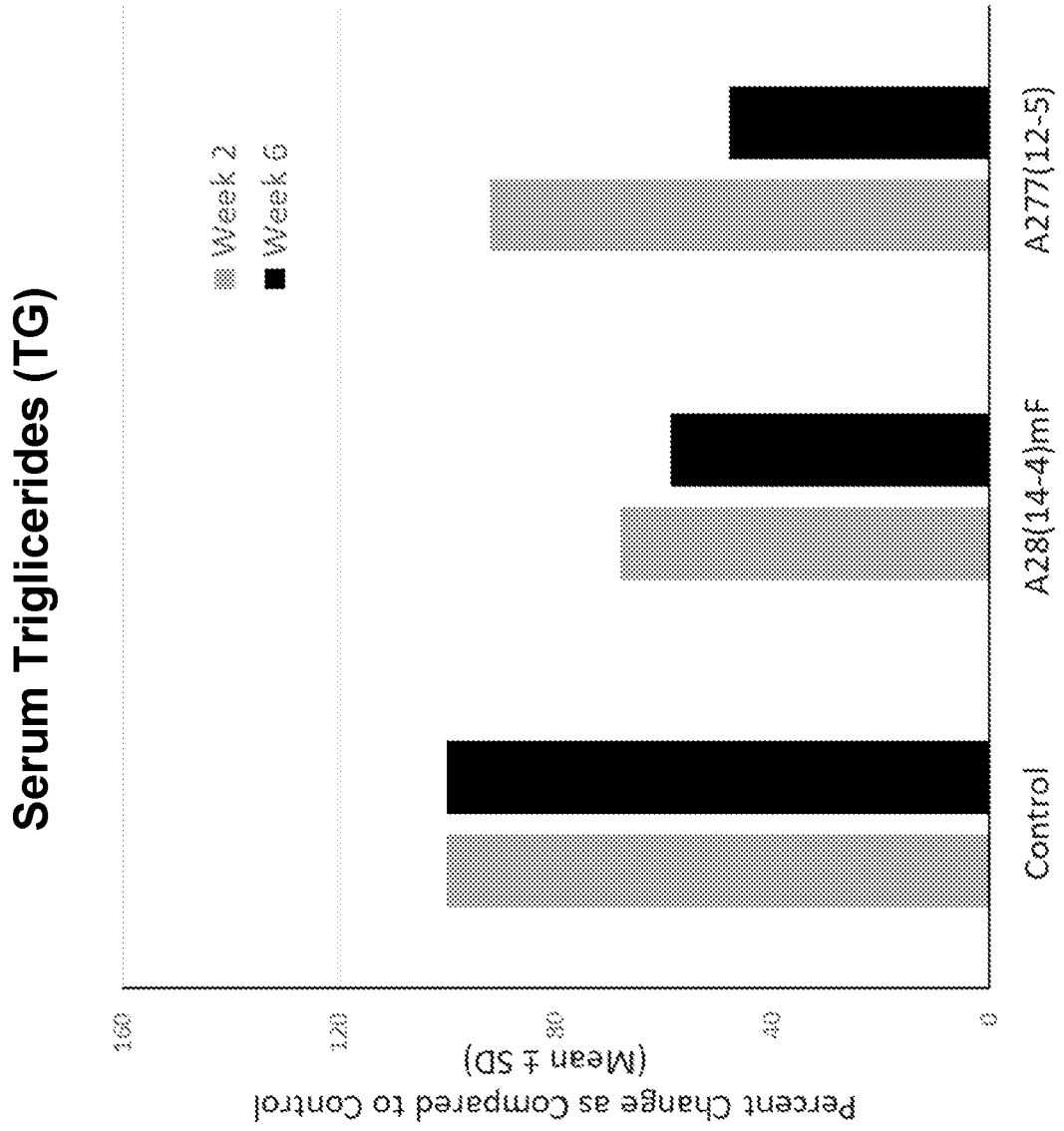

Serum Triglicerides (TG)
Week 2
Week 6
Percent Change as Compared to Control
(Mean ± SD)
160
120
80
40
0
Control
A28(14-4)mf
A277(12-5)

Fig. 6a

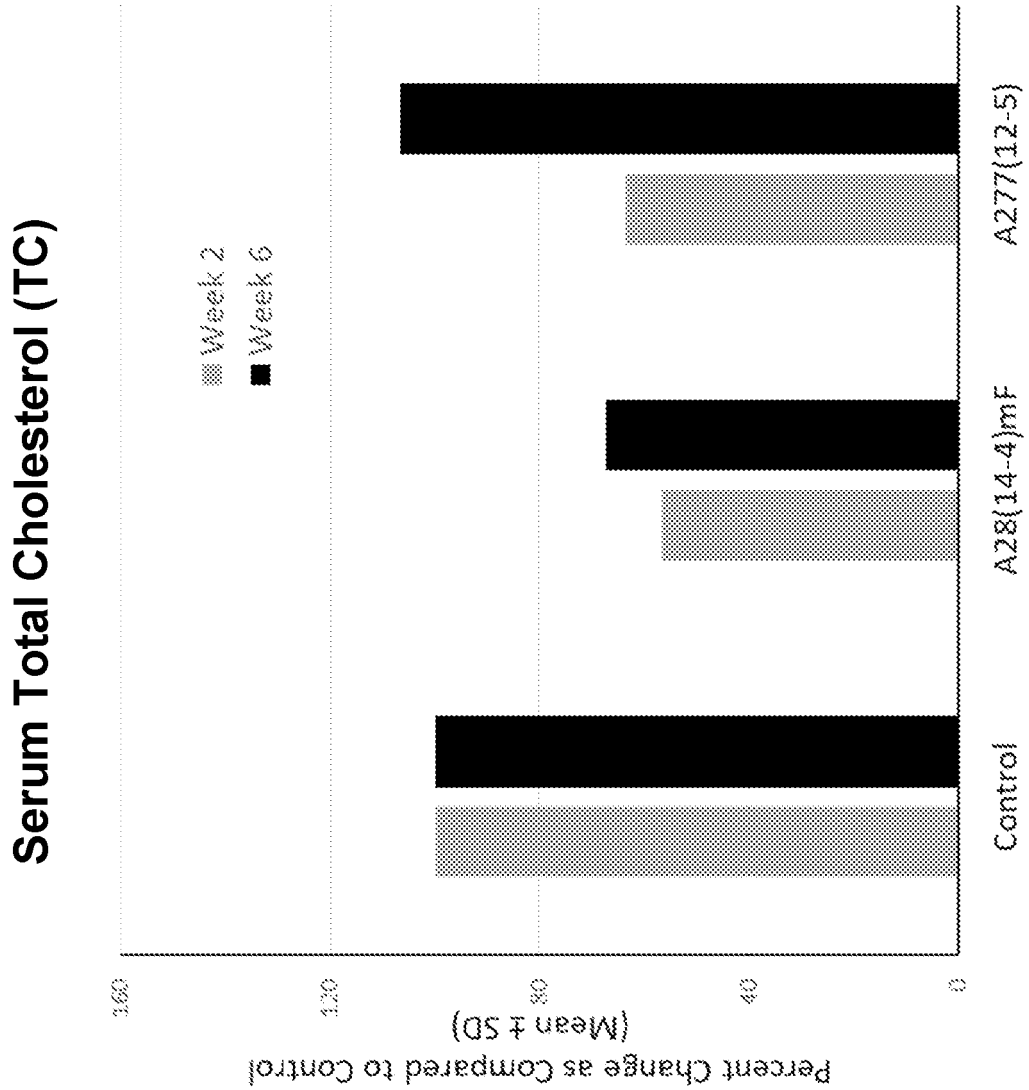

Serum Total Cholesterol (TC)
Week 2
Week 6
Control
A28(14-4)mF
A277(12-5)
Percent Change as Compared to Control
(Mean ± SD)
160
120
80
40
0

Fig. 6b

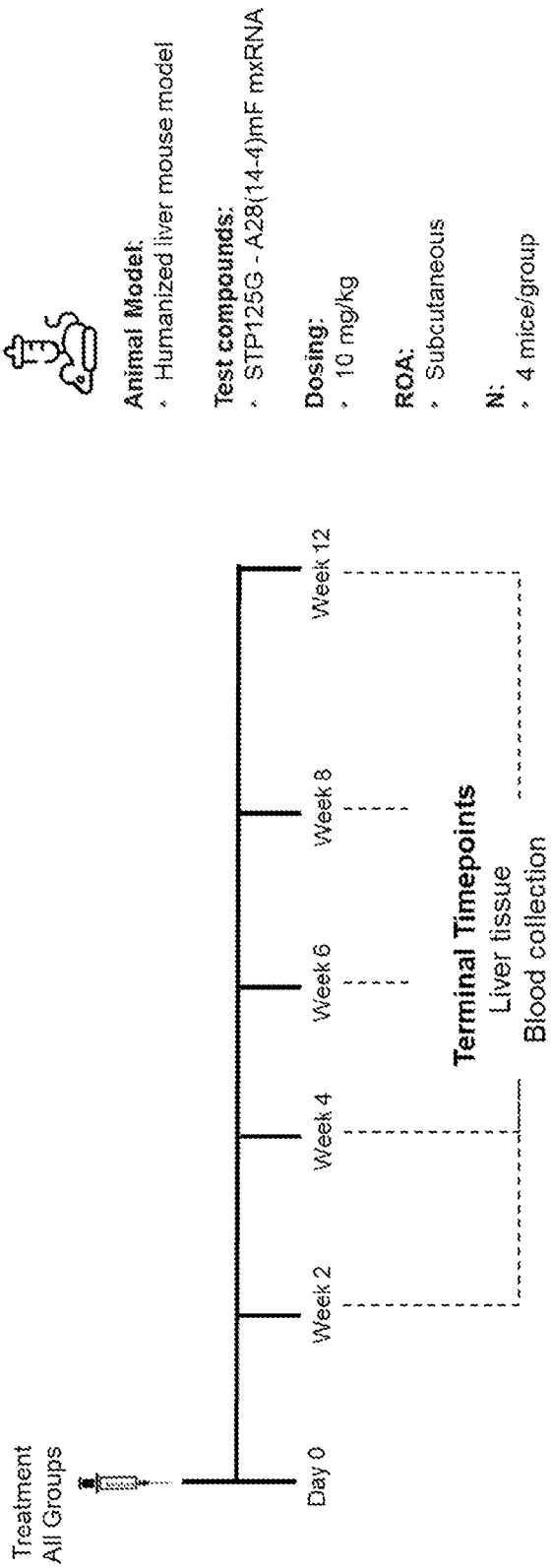

Animal Model:
Humanized liver mouse model
Test compounds:
STP125G - A28(14-4)mF mxRNA
Dosing:
10 mg/kg
ROA:
Subcutaneous
N:
4 mice/group
Terminal Endpoints:
2, 4, 6, 8 and 10-weeks
Readouts:
qPCR (mRNA)
ELISA (protein)
Triglycerides
Treatment
All Groups
Day 0
Week 2
Week 4
Week 6
Week 8
Week 12
Terminal Timepoints
Liver tissue
Blood collection

Fig. 7

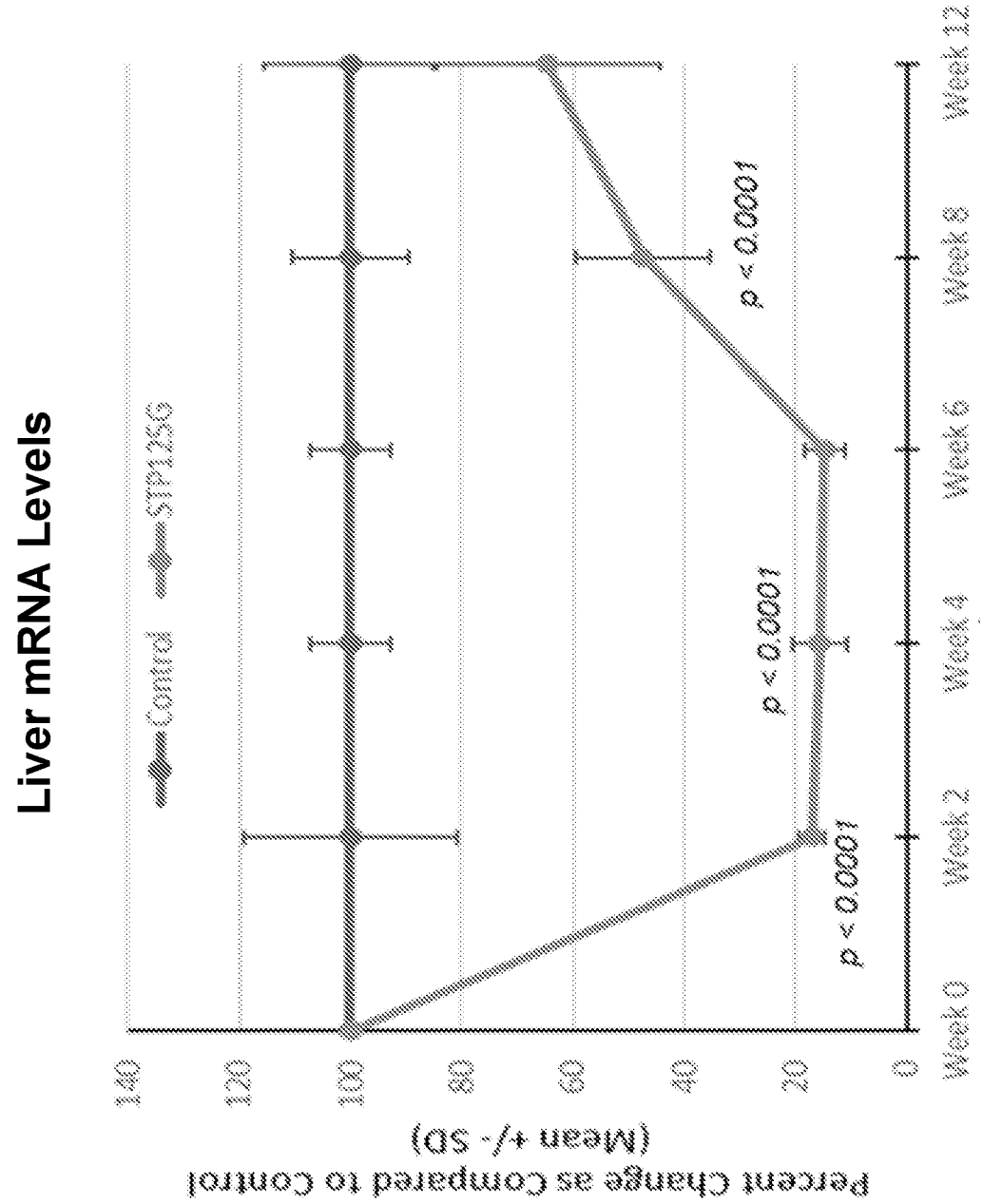

Liver mRNA Levels
Control
STP1256
Percent Change as Compared to Control
(Mean +/- SD)
140
120
100
80
60
40
20
0
Week 0
Week 2
Week 4
Week 6
Week 8
Week 12
p < 0.0001
p < 0.0001
p < 0.0001

Fig. 8a

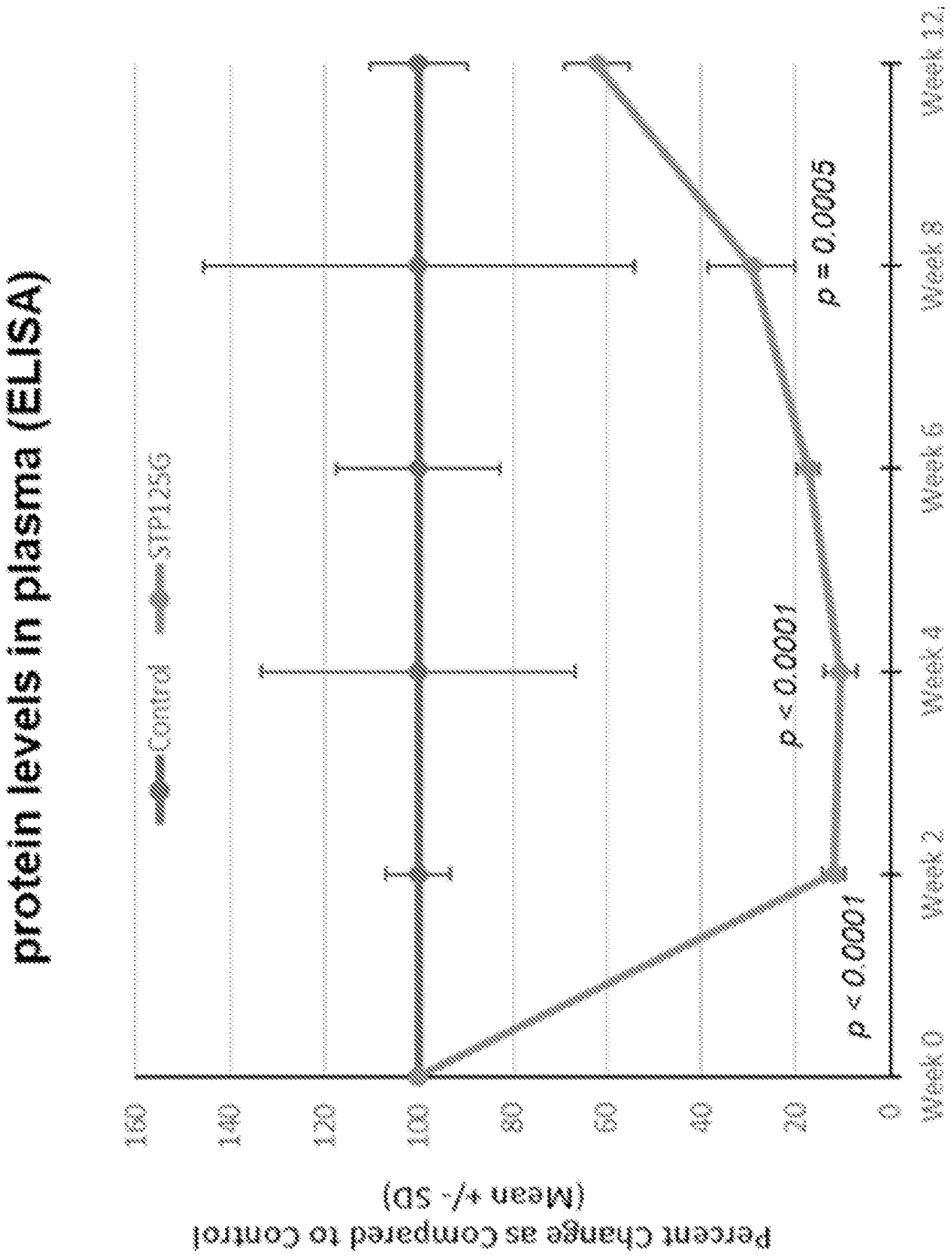

protein levels in plasma (ELISA)
Control
STP1256
Percent Change as Compared to Control
(Mean +/- SD)
160
140
120
100
80
60
40
20
0
Week 0
Week 2
Week 4
Week 6
Week 8
Week 12
p < 0.0001
p < 0.0001
p = 0.0005

Fig. 8b

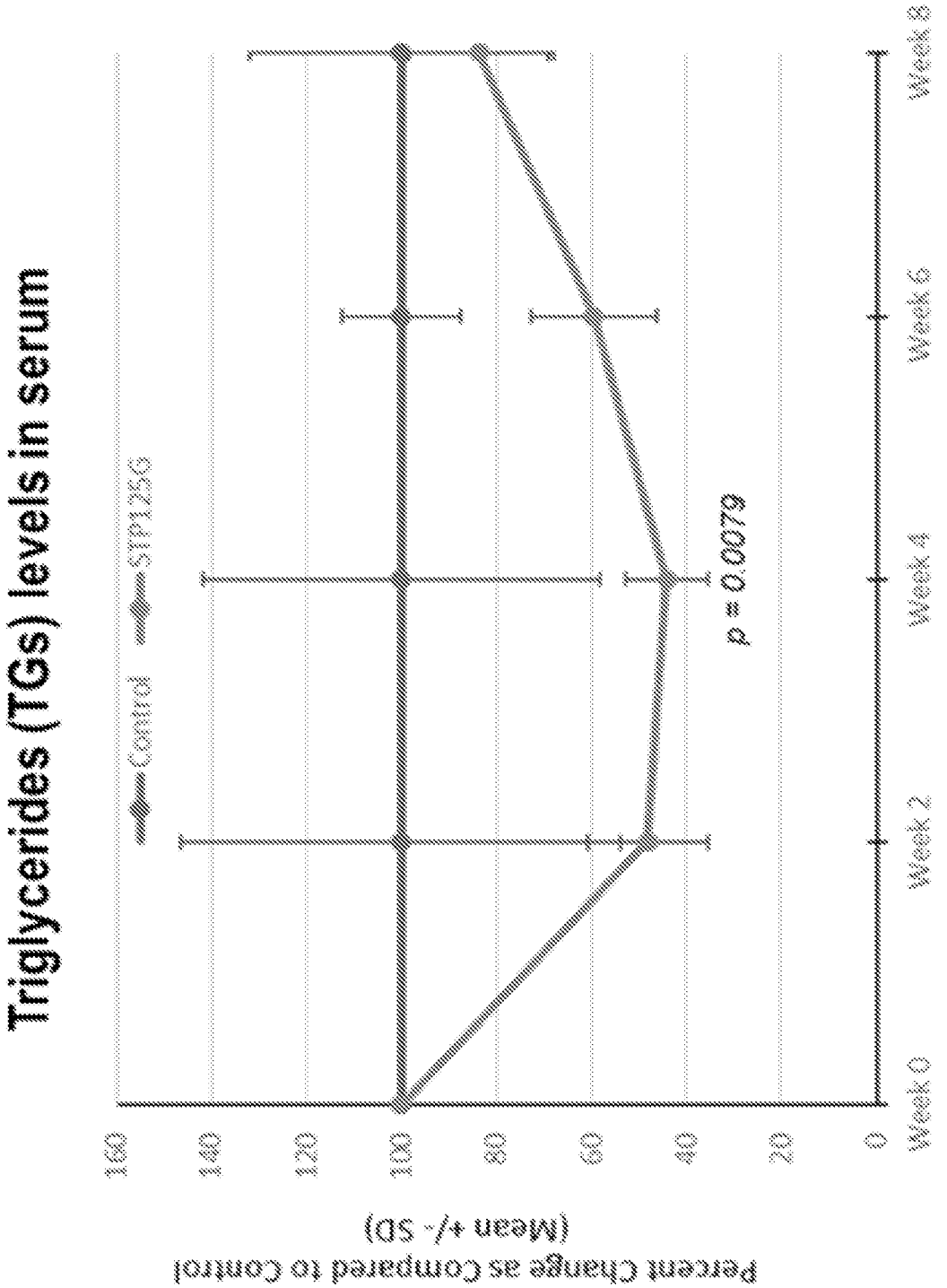

Triglycerides (TGs) levels in serum
Control
STP1250
p = 0.0079
Week 0
Week 2
Week 4
Week 6
Week 8
0
20
40
60
80
100
120
140
160
Percent Change as Compared to Control
(Mean +/- SD)

Fig. 9a

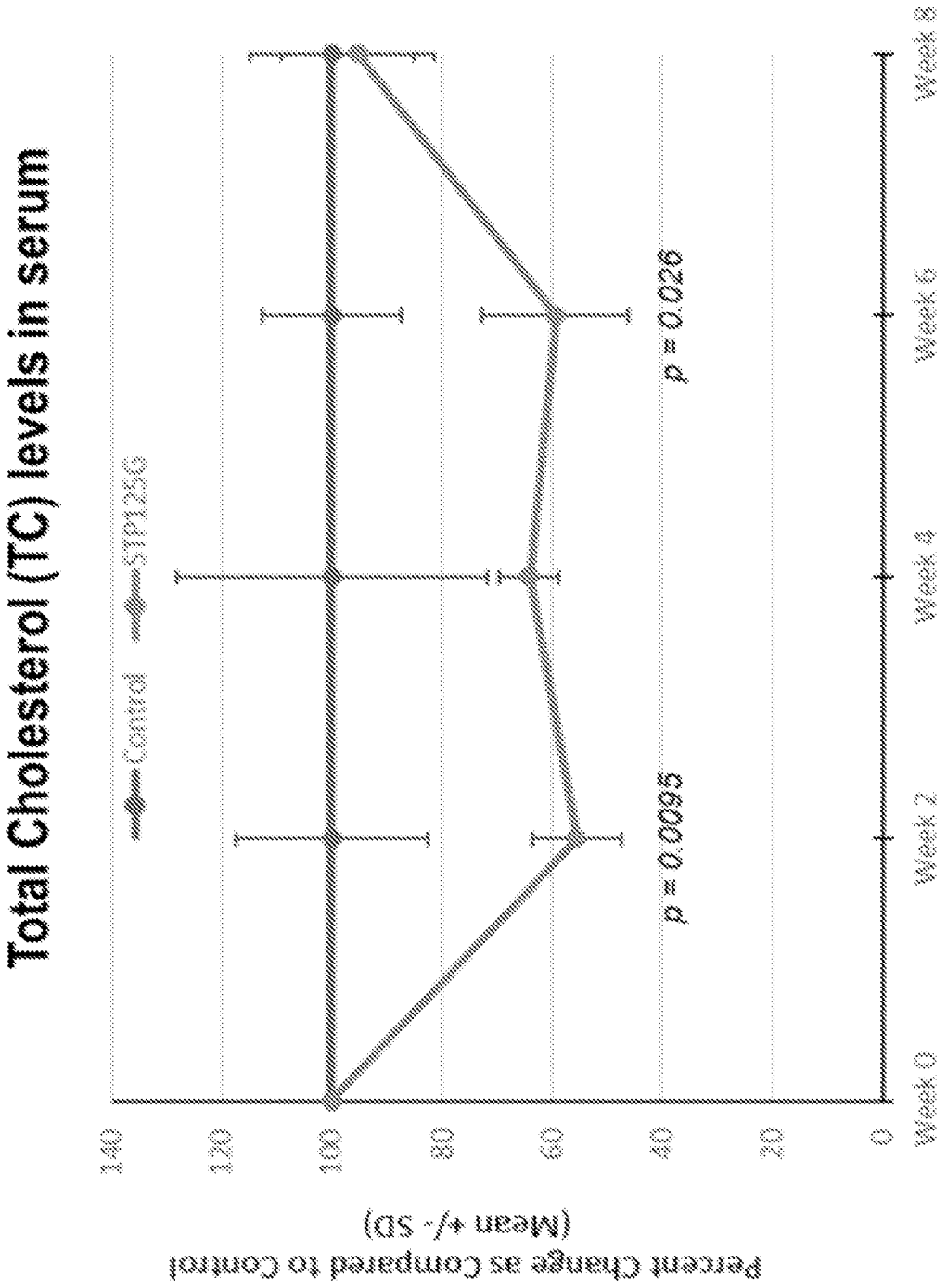

Total Cholesterol (TC) levels in serum
Control
S1P1250
p = 0.0095
p = 0.026
Week 0
Week 2
Week 4
Week 6
Week 8
0
20
40
60
80
100
120
140
Percent change as compared to control
(Mean +/- SD)

Fig. 9b

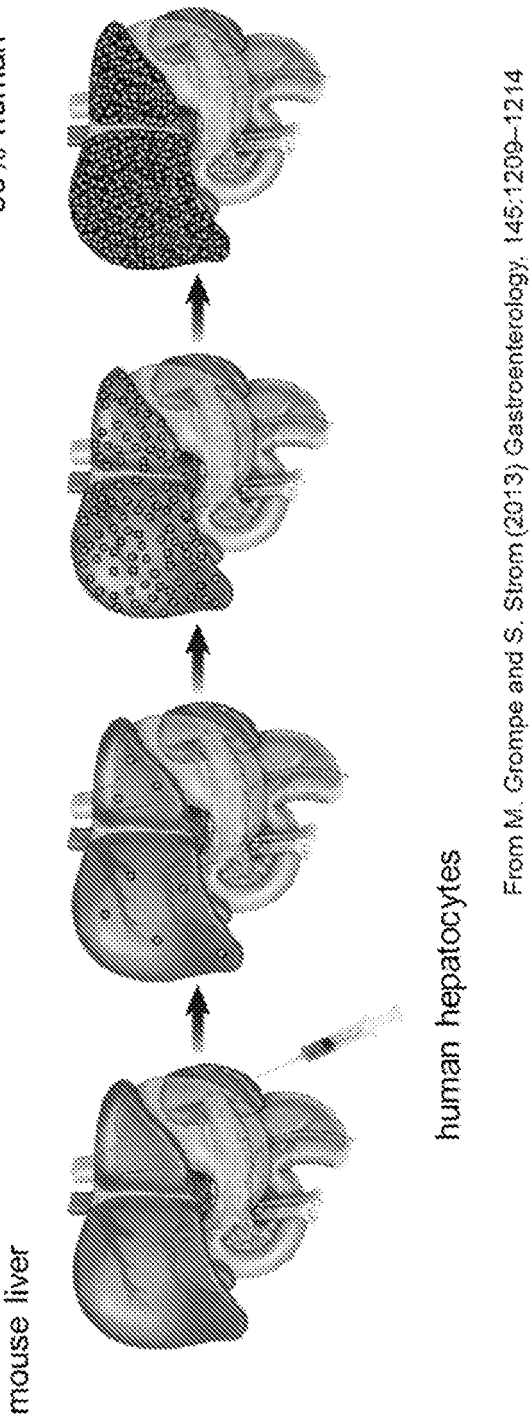

Mouse Humanized Liver
20% mouse
80% human
mouse liver
human hepatocytes
From M. Grompe and S. Strom (2013) Gastroenterology. 145:1209–1214

Fig. 10