

INHIBITORS OF EXPRESSION AND/OR FUNCTION

FIELD

The present invention provides inhibitors, such as nucleic acid compounds, such as siRNAs, suitable for therapeutic use. Additionally, the present invention provides methods of making these compounds, as well
5 as methods of using such compounds for the treatment of various diseases and conditions.

BACKGROUND OF THE INVENTION

Inhibitors, such as oligonucleoside / oligonucleotide compounds which are inhibitors of gene expression and/or expression or function of other targets such as LNCRNAs, can have important therapeutic applications in medicine. Oligonucleotides/ oligonucleosides can be used to silence genes that are
10 responsible for a particular disease. Gene-silencing prevents formation of a protein (or other gene product such as a regulatory non-coding RNA) by inhibiting translation. Importantly, gene-silencing agents are a promising alternative to traditional small, organic compounds that inhibit the function of the protein (or gene product) linked to the disease. siRNA, antisense RNA, and micro-RNA are oligonucleoside /oligonucleotides that prevent the formation of proteins by gene-silencing.

15 A number of modified siRNA compounds in particular have been developed in the last two decades for diagnostic and therapeutic purposes, including siRNA / RNAi therapeutic agents for the treatment of various diseases including central-nervous-system diseases, inflammatory diseases, metabolic disorders, oncology, infectious diseases, and ocular diseases.

The present invention relates to inhibitors, such oligomers e.g. nucleic acids, e.g. oligonucleoside
20 /oligonucleotide compounds, and their use in the treatment and / or prevention of disease.

The *SLC25A5* gene belongs to the ANT gene family, which itself belongs to the superfamily that includes genes encoding brown fat mitochondrial uncoupling proteins and mitochondrial phosphate carrier proteins. This gene is a member of the mitochondrial carrier subfamily of solute carrier protein genes. The product of this gene, adenine nucleotide translocator 2 (ANT2), functions as a major constituent of the
25 mitochondrial permeability-transition pore complex and catalyses the exchange of mitochondrial ATP with cytosolic ADP. As a result of its antiporter function, ANT2 maintains mitochondrial membrane potential by regulating ADP/ATP ratios in oxidative phosphorylation. ANT2 facilitates uncoupling of the mitochondrial membrane when acylated by SIRT4. Though uncoupling the membrane potential typically leads to apoptosis, ANT2 was found to be antiapoptotic. As a result, it is postulated to mediate the TFIIFH-
30 dependent response to DNA damage as a component of the MMS19-XPB.

STATEMENTS OF INVENTION

The invention is defined as in the claims and relates to, *inter alia*:

In one aspect, the invention relates to an inhibitor of expression and / or function of SLC25A5/ANT2, for use in a method of prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in a method of reducing adipogenesis, wherein the method comprises administering the inhibitor and administering at least one other therapeutic agent.

In another aspect, the invention relates to a method of prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or a method of reducing adipogenesis, the method comprising administering the inhibitor and administering at least one other therapeutic agent.

In another aspect, the invention relates to a combination comprising an inhibitor of expression and / or function of SLC25A5/ANT2 and at least one other therapeutic agent.

In another aspect, the invention relates to an inhibitor of expression and / or function of SLC25A5/ANT2, wherein said inhibitor is conjugated to one or more ligand moieties and is to be used in combination with at least one other therapeutic agent.

In another aspect, the invention relates to a pharmaceutical composition comprising an inhibitor as defined herein in combination with a pharmaceutically acceptable excipient or carrier, for use in a method of prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in a method of reducing adipogenesis, wherein the method comprises administering the pharmaceutical composition and administering at least one other therapeutic agent.

In another aspect, the invention relates to a method of prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or a method of reducing adipogenesis, the method comprising administering a pharmaceutical composition comprising an inhibitor as described herein, in combination with a pharmaceutically acceptable excipient or carrier, and administering at least one other therapeutic agent.

In another aspect, the invention relates to a pharmaceutical composition comprising a combination comprising an inhibitor as described herein and at least one other therapeutic, in combination with a pharmaceutically acceptable excipient or carrier.

In another aspect, the invention relates to a pharmaceutical composition comprising an inhibitor as described herein in combination with a pharmaceutically acceptable excipient or carrier, wherein the

inhibitor is conjugated to one or more ligand moieties and wherein the pharmaceutical composition to be used in combination with at least one other therapeutic agent.

In another aspect, the invention relates to a method of predicting susceptibility to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or in reducing adipogenesis in a patient, said method comprising:

- (a) obtaining a sample from the patient,
- (b) detecting the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,
- 10 (c) predicting susceptibility to a disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis, based on the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,
- (d) preferably administering to the diagnosed patient an effective amount of an inhibitor of SLC25A5/ANT2 and at least one other therapeutic agent.

In another aspect, the invention relates to an inhibitor, inhibitor for use, combination, combination for use, composition or composition for use as described herein, in the preparation of a medicament for use in the treatment of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis.

In another aspect, the invention relates to a kit comprising an inhibitor as described herein and at least one other therapeutic agent as described herein.

Certain aspects of the current invention include:

- 25 In one aspect, the invention relates to an inhibitor of expression and / or function of SLC25A5/ANT2, wherein said inhibitor is conjugated to one or more ligand moieties.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein said inhibitor is an siRNA oligomer.

- 30 In another aspect, the invention relates to an inhibitor of expression and / or function of SLC25A5/ANT2, wherein said inhibitor is an siRNA oligomer.

In a further aspect, the invention relates to an inhibitor according to the invention, wherein said inhibitor comprises an siRNA oligomer conjugated to one or more ligand moieties.

In a further aspect, the invention relates to an inhibitor according to the invention, for use in prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the inhibitor is to be used in combination with a GLP-1 agonist and/or a THR-beta agonist.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the inhibitor is to be used in combination with a GLP-1 agonist and/or an FGF-21 analogue.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the GLP-1 agonist is a GLP-1/GIP dual agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR dual agonist, or a GLP-1/GIP/GCGR triple agonist.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the GLP-1 agonist is semaglutide.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the THR-beta agonist is resmetirom.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the GLP-1/GIP dual agonist is tirzepatide.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the FGF-21 analogue is efruxifermin.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the inhibitor is to be used in combination with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belapectin), and/or a PPAR α agonist (such as elafibrinor), and/or a PPAR γ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPAR α and/or δ and/or γ agonist, and/or a pan PPAR $\alpha\gamma\delta$ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase

(ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).

In a further aspect, the invention relates to an inhibitor according to the invention, wherein said one or more ligand moieties comprise one or more GalNAc ligands or comprise one or more GalNAc ligand derivatives.

- 5 In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein said one or more ligand moieties comprise one or more GalNAc ligand derivatives.

In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the target of the inhibitor is SLC25A5/ANT2.

- 10 In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, which is an siRNA oligomer having a first and a second strand wherein:

i) the first strand of the siRNA has a length in the range of 15 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 23 or 25; even more preferably 23; and / or

ii) the second strand of the siRNA has a length in the range of 15 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 21 nucleosides.

- 15 In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the second sense strand further comprises one or more abasic nucleosides in a terminal region of the second strand, and wherein said abasic nucleoside(s) is / are connected to an adjacent nucleoside through a reversed internucleoside linkage.

- 20 In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the second strand comprises:

i) 2, or more than 2, abasic nucleosides in a terminal region of the second strand; and / or

ii) 2, or more than 2, abasic nucleosides in either the 5' or 3' terminal region of the second strand; and / or

- 25 iii) 2, or more than 2, abasic nucleosides in either the 5' or 3' terminal region of the second strand, wherein the abasic nucleosides are present in an overhang as herein described; and / or

iv) 2, or more than 2, consecutive abasic nucleosides in a terminal region of the second strand, wherein preferably one such abasic nucleoside is a terminal nucleoside; and / or

- 30 v) 2, or more than 2, consecutive abasic nucleosides in either the 5' or 3' terminal region of the second strand, wherein preferably one such abasic nucleoside is a terminal nucleoside in either the 5' or 3' terminal region of the second strand; and / or

- vi) a reversed internucleoside linkage connects at least one abasic nucleoside to an adjacent basic nucleoside in a terminal region of the second strand; and / or
- vii) a reversed internucleoside linkage connects at least one abasic nucleoside to an adjacent basic nucleoside in either the 5' or 3' terminal region of the second strand; and / or
- 5 viii) an abasic nucleoside as the penultimate nucleoside which is connected via the reversed linkage to the nucleoside which is not the terminal nucleoside (called the antepenultimate nucleoside herein); and / or
- ix) abasic nucleosides as the 2 terminal nucleosides connected via a 5'-3' linkage when reading the strand in the direction towards that terminus;
- 10 x) abasic nucleosides as the 2 terminal nucleosides connected via a 3'-5' linkage when reading the strand in the direction towards the terminus comprising the terminal nucleosides;
- xi) abasic nucleosides as the terminal 2 positions, wherein the penultimate nucleoside is connected via the reversed linkage to the antepenultimate nucleoside, and wherein the reversed linkage is a 5-5' reversed linkage or a 3'-3' reversed linkage;
- 15 xii) abasic nucleosides as the terminal 2 positions, wherein the penultimate nucleoside is connected via the reversed linkage to the antepenultimate nucleoside, and wherein either
- (1) the reversed linkage is a 5-5' reversed linkage and the linkage between the terminal and penultimate abasic nucleosides is 3'5' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides; or
- 20 (2) the reversed linkage is a 3-3' reversed linkage and the linkage between the terminal and penultimate abasic nucleosides is 5'3' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the reversed internucleoside linkage is at a terminal region which is distal to the 5' terminal region
25 of the second strand, or at a terminal region which is distal to the 3' terminal region of the second strand.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the reversed internucleoside linkage is a 3'3 reversed linkage.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the reversed internucleoside linkage is a 5'5 reversed linkage.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein one or more nucleosides on the first strand and / or the second strand is / are modified, to form modified nucleosides.

5 In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the first strand comprises a 2'-F at any of position 14, position 2, position 6, or any combination thereof, counting from position 1 of said first strand.

10 In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the second strand comprises a 2'-F modification at position 7 and / or 9, and / or 11 and / or 13, counting from position 1 of said second strand.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

15 In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, which is an siRNA, wherein the siRNA comprises at least one thermally destabilizing modification, suitably at one or more of positions 1 to 9 of the first strand counting from position 1 of the first strand, and / or at one or more of positions on the second strand aligned with positions 1 to 9 of the first strand, wherein the destabilizing modification is selected from a modified unlocked nucleic acid (UNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid.
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In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the siRNA comprises at least one thermally destabilizing modification at position 7 of the first strand, counting from position 1 of the first strand.

25 In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, which is an siRNA, wherein the siRNA comprises 3 or more 2'-F modifications at positions 7 to 13 of the second strand, such as 4, 5, 6 or 7 2'-F modifications at positions 7 to 13 of the second strand, counting from position 1 of said second strand

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, which is an siRNA, wherein said second strand comprises at least 3, such as 4, 5 or 6, 2'-Me modifications
30 at positions 1 to 6 of the second strand, counting from position 1 of said second strand.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, which is an siRNA, wherein said first strand comprises at least 5 2'-Me consecutive modifications at the 3'

terminal region, preferably including the terminal nucleoside at the 3' terminal region, or at least within 1 or 2 nucleosides from the terminal nucleoside at the 3' terminal region.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, which is an siRNA wherein said first strand comprises 7 2'-Me consecutive modifications at the 3' terminal region, preferably including the terminal nucleoside at the 3' terminal region.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the siRNA oligomer further comprises one or more phosphorothioate internucleoside linkages.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein said one or more phosphorothioate internucleoside linkages are respectively between at least three consecutive positions in a 5' or 3' near terminal region of the second strand, whereby said near terminal region is preferably adjacent said terminal region wherein said one or more abasic nucleosides of said second strand is / are located as defined herein.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein said one or more phosphorothioate internucleoside linkages are respectively between at least three consecutive positions in a 5' and / or 3' terminal region of the first strand, whereby preferably a terminal position at the 5' and / or 3' terminal region of said first strand is attached to its adjacent position by a phosphorothioate internucleoside linkage.

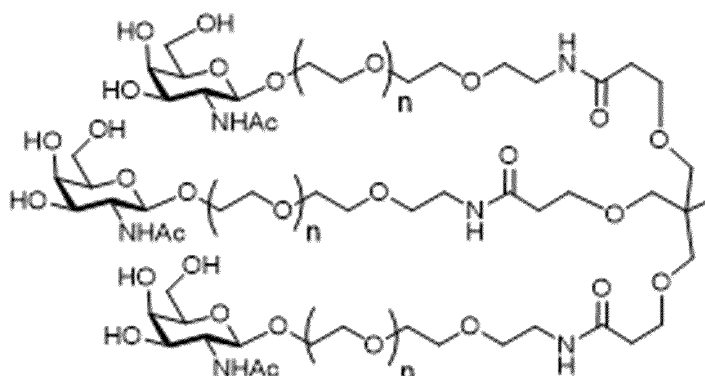
In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the oligomer is an siRNA and the second strand of the siRNA is conjugated directly or indirectly to one or more ligand moiety(s), wherein said ligand moiety is typically present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the ligand moiety comprises

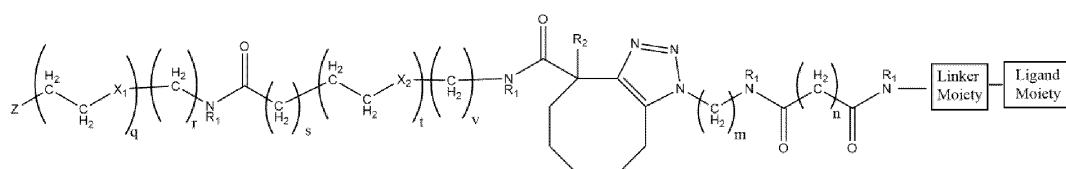
- i) one or more GalNAc ligands; and / or
- ii) one or more GalNAc ligand derivatives; and / or
- iii) one or more GalNAc ligands and / or GalNAc ligand derivatives conjugated to said SiRNA through a linker.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein said one or more GalNAc ligands and / or GalNAc ligand derivatives are conjugated directly or indirectly to the 5' or 3' terminal region of the second strand of the siRNA oligomer, preferably at the 3' terminal region thereof.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the ligand moiety comprises



In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, having the structure:



wherein:

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, $-OC_{1-3}alkyl$, $-C(=O)OC_{1-3}alkyl$, halo and nitro;

X_1 and X_2 at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

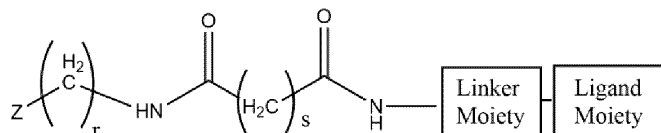
q , r , s , t , v are independently integers from 0 to 4, with the proviso that:

(i) q and r cannot both be 0 at the same time; and

(ii) s , t and v cannot all be 0 at the same time;

Z is an oligomer

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, having the structure



5 wherein:

r and s are independently an integer selected from 1 to 16; and

Z is an oligomer.

In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, formulated as a pharmaceutical composition with an excipient and / or carrier.

10 In another aspect, the invention relates to a combination comprising an inhibitor according to the invention and at least one other therapeutic agent.

In a further aspect, the invention relates to a combination according to the invention, for use in prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

In a further aspect, the invention relates to a combination or combination for use according to the invention, wherein the at least one other therapeutic agent comprises a GLP-1 agonist, a THR-beta agonist, and/or an FGF-21 analogue.

20 As described in the claims, the invention can relate to an inhibitor, an inhibitor for use, a method, a combination, a combination for use, pharmaceutical composition, etc. Unless excluded by context, all features of the invention described herein in relation to one of these aspects applies equally to the other aspects of the invention.

In another aspect, the invention relates to a pharmaceutical composition comprising an inhibitor according to the invention, in combination with a pharmaceutically acceptable excipient or carrier.

25 In a further aspect, the invention relates to a pharmaceutical composition comprising an inhibitor according to the invention, in combination with a pharmaceutically acceptable excipient or carrier, for use in the prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder

associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

In a further aspect, the invention relates to a pharmaceutical composition for use according to the invention, wherein the pharmaceutical composition is to be used in combination with a GLP-1 agonist and/or a THR-
5 beta agonist.

In a further aspect, the invention relates to a pharmaceutical composition for use according to the invention, wherein the pharmaceutical composition is to be used in combination with a GLP-1 agonist and/or an FGF-21 analogue.

In a further aspect, the invention relates to a pharmaceutical composition for use according to the invention, wherein the GLP-1 agonist is a GLP-1/GIP dual agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR
10 dual agonist, or a GLP-1/GIP/GCGR triple agonist.

In a further aspect, the invention relates to a pharmaceutical composition for use according to the invention, wherein the GLP-1 agonist is semaglutide.

In a further aspect, the invention relates to a pharmaceutical composition for use according to the invention, wherein the GLP-1/GIP dual agonist is tirzepatide.
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In a further aspect, the invention relates to a pharmaceutical composition for use according to the invention, wherein the THR-beta agonist is resmetirom.

In a further aspect, the invention relates to a pharmaceutical composition for use according to the invention, wherein the FGF-21 analogue is efruxifermin.

In a further aspect, the invention relates to a pharmaceutical composition for use according to the invention, wherein the composition is to be used in combination with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belapectin), and/or a PPAR α agonist (such as elafibrinor), and/or a PPAR γ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPAR α and/or δ and/or γ agonist, and/or a pan PPAR $\alpha\gamma\delta$ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo
20 lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).
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In another aspect, the invention relates to the use of SLC25A5/ANT2 as a target for identifying one or more therapeutic agents for the treatment or prevention of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

- 5 In another aspect, the invention relates to a method of treating or preventing metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis, which comprises administering to a patient an inhibitor of expression and/or function of SLC25A5/ANT2, such as an inhibitor according to the invention.

- 10 In a further aspect, the invention relates to a method according to the invention, wherein the inhibitor of SLC25A5/ANT2 is administered together with a GLP-1 agonist and/or a THR-beta agonist.

In a further aspect, the invention relates to a method according to the invention, wherein the inhibitor of SLC25A5/ANT2 is administered together with a GLP-1 agonist and/or an FGF-21 analogue.

- 15 In a further aspect, the invention relates to a method according to the invention, wherein the GLP-1 agonist is a GLP-1/GIP dual agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR dual agonist, or a GLP-1/GIP/GCGR triple agonist.

In a further aspect, the invention relates to a method according to the invention, wherein the GLP-1 agonist is semaglutide.

- 20 In a further aspect, the invention relates to a method according to the invention, wherein the GLP-1/GIP dual agonist is tirzepatide.

In a further aspect, the invention relates to a method according to the invention, wherein the THR-beta agonist is resmetirom.

In a further aspect, the invention relates to a method according to the invention, wherein the FGF-21 analogue is efruxifermin.

- 25 In a further aspect, the invention relates to a method according to the invention, wherein the inhibitor is to be used in combination with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a
30 galectin 3 inhibitor (such as belaepectin), and/or a PPAR α agonist (such as elafibrinor), and/or a PPAR γ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPAR α and/or δ and/or γ agonist, and/or a pan PPAR $\alpha\gamma\delta$ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1

inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).

In another aspect, the invention relates to SLC25A5/ANT2 for use as a biomarker of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis.

In another aspect, the invention relates to SLC25A5/ANT2 for use in an *in vivo* method of predicting susceptibility to prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for reducing adipogenesis, typically by monitoring the sequence and/ or level of expression and / or function of SLC25A5/ANT2 in a sample obtained from a patient.

In another aspect, the invention relates to a method of predicting susceptibility to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis, in a patient, said method comprising:

- (a) obtaining a sample from the patient,
- (b) detecting the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,
- (c) predicting susceptibility to a disease related to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis, based on the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,
- (d) preferably administering to the diagnosed patient an effective amount of an inhibitor of SLC25A5/ANT2.

In another aspect, the invention relates to an inhibitor or composition according to the invention, in the preparation of a medicament for use in the treatment or prevention of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis.

FIGURES

Figure 1a shows an exemplary linear configuration for a conjugate.

Figure 1b shows an exemplary branched configuration for a conjugate.

Figures 2-5 show preferred oligomer – linker – ligand constructs of the invention.

Figure 6 shows the detail of the formulae described in Sentences 1-101 disclosed herein.

5 **Figure 7** shows the detail of formulae described in Clauses 1-56 disclosed herein.

Figures 8a and 8b: Inverted abasic constructs that can be used with nucleic acid sequences according to the present invention as described herein. For Figure 8a, a GalNAc linker is attached to the 5' end region of the sense strand in use (not depicted in Figure 8a). For Figure 8b, a GalNAc linker is attached to the 3' end region of the sense strand in use (not depicted in Figure 8b).

10 iaia as shown at the 3' end region of the sense strand in Figure 8a represents (i) two abasic nucleosides provided as the penultimate and terminal nucleosides at the 3' end region of the sense strand, (ii) wherein a 3'-3' reversed linkage is provided between the antepenultimate nucleoside (namely at position 21 of the sense strand, wherein position 1 is the terminal 5' nucleoside of the sense strand) and the adjacent penultimate abasic residue of the sense strand, and (iii) the linkage between the terminal and penultimate
15 abasic nucleosides is 5'-3' when reading towards the 3' end region comprising the terminal and penultimate abasic nucleosides.

iaia as shown at the 5' end region of the sense strand in Figure 8b represents (i) two abasic nucleosides provided as the penultimate and terminal nucleosides at the 5' end region of the sense strand, (ii) wherein a 5'-5' reversed linkage is provided between the antepenultimate nucleoside (namely at position 1 of the
20 sense strand, not including the iaia motif at the 5' end region of the sense strand in the nucleoside position numbering on the sense strand) and the adjacent penultimate abasic residue of the sense strand, and (iii) the linkage between the terminal and penultimate abasic nucleosides is 3'-5' when reading towards the 5' end region comprising the terminal and penultimate abasic nucleosides.

Figures 9a and 9b: Duplex constructs according to Table 5.

25 **Figures 10 and 11** show the NAFLD Activity Scores (NAS) of mice with diet-induced NAFLD in response to different treatments. Liver samples stained with H&E were given a score for NAFLD Activity Score (NAS) using the clinical criteria outlined by Kleiner et al. (2005). Total NAS represents the sum of scores for steatosis, inflammation, and ballooning, and ranges from 0-8. NAS score was determined by Gubra Histopathological Objective Scoring Technology (GHOST) deep learning app developed by Gubra using
30 the VIS software (Visiopharm, Denmark) for a more accurate and objective method for staging disease in DIO-NASH mouse models. Results are presented as change in NAS score (improvement or worsening) at study termination compared to the pre-dose biopsy. Also shown is the percentage of animals with at least a 1- or 2-point improvement in NAS.

Figure 12: ALT and AST were measured in plasma samples after 12 weeks ETX-312 (ETX-M00001378) treatment using commercial kits (Roche Diagnostics), on the cobas c501 autoanalyzer. ALT and AST levels were increased in DIO-NASH mice (vehicle sc, siCtrl, vehicle PO). Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced both ALT and AST levels. Combination therapies demonstrated a significantly enhanced effect compared to semaglutide and resmetirom treatments administered as monotherapies. Results are presented as absolute levels as Mean $\pm$ SEM from n=16 experiment. * $p < 0.05$; *** $p < 0.001$; **** $p < 0.0001$; ns non-significant.

Figure 13: TIMP-1 and PIIINP are non-invasive blood biomarkers for NAFLD/NASH that predict hepatic fibrosis. TIMP-1 was measured in plasma collected in EDTA tubes using a commercial ELISA kit (R&D Systems). PIIINP was measured in plasma collected in EDTA tubes using a commercial ELISA kit (Cusabio). TIMP-1 and PIIINP levels were increased in DIO-NASH mice (vehicle sc, siCtrl, vehicle PO). Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced both TIMP-1 and PIIINP levels. Combination therapies led to a further reduction in TIMP-1 and PIIINP levels when compared to semaglutide and resmetirom treatments alone. Results are presented as absolute levels as Mean $\pm$ SEM from n=16 experiment. An outlier analysis was conducted by comparing the studentised residuals of the linear model fitted to the subcutaneous treatment subset of the data to the critical Bonferroni alpha level ($0.05/88 = \sim 0.00057$). One animal in the semaglutide group was identified as an outlier which was verified by an influence analysis. This animal was concluded as both highly outlying and influential and was excluded from all TIMP-1 and PIIINP analysis. * $p < 0.05$; *** $p < 0.001$; **** $p < 0.0001$; ns non-significant.

Figure 14: Terminal liver weight to body weight ratio demonstrates hepatomegaly in DIO-NASH mice. Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced liver to body weight ratio. No difference was observed between the combination therapies and the monotherapies of semaglutide and resmetirom. Results are presented as percent liver:body weight as Mean $\pm$ SEM from n=16 experiment. ** $p < 0.01$; **** $p < 0.0001$; ns non-significant.

Figure 15: Liver lipid content, or steatosis, is quantified on H&E stained slides by image analysis using the VIS software (Visiopharm, Denmark). Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced liver steatosis. Combination therapies resulted in a significantly greater effect than semaglutide and resmetirom used as monotherapies. Results are presented as a percent area fraction (on the top) and the total level (percent area fraction multiplied by liver weight, on the bottom), as Mean $\pm$ SEM from n=16 experiment. * $p < 0.05$; **** $p < 0.0001$; ns non-significant.

Figure 16: Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced inflammation in liver, a key factor differentiating NASH from NAFLD, as measured by inflammatory foci density, lobular inflammation score, and CD45 staining. Combination therapies exhibited a notably improved effect over semaglutide and resmetirom monotherapies.

Inflammatory foci density and lobular inflammation score were assessed by Gubra Histopathological Objective Scoring Technology (GHOST) deep learning app developed by Gubra, by image analysis of H&E stained slides using the VIS software (Visiopharm, Denmark). Inflammatory foci density is the number of inflammatory foci per surface area, where foci are clusters of more than 3 inflammatory cells.

5 The lobular inflammation score was determined using the clinical criteria outlined by Kleiner et al. (2005). CD45, a surface marker of immune cells, was assessed via immunohistochemistry using a rabbit anti-CD45 primary antibody (AbCam, Cat. Ab10558). CD45-positive staining was quantified using the VIS software (Visiopharm, Denmark), reported as a percent area fraction (bottom left) and the total level (percent area fraction multiplied by liver weight, bottom right). Lobular inflammation scores show changes between pre-

10 dose and post-dose liver biopsies (improvement or worsening), while results for inflammatory foci and CD45 staining are presented as Mean $\pm$ SEM from n=16 experiment. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$; ns non-significant.

Figure 17: Total cholesterol (TC) levels were measured in plasma samples after 12 weeks ETX-312 (ETX-M00001378) treatment using commercial kits (Roche Diagnostics), on the cobas c501 autoanalyzer. GAN

15 diet elevated plasma TC in DIO NASH animals (Vehicle SC, siCtrl, Vehicle PO). Treatment with ETX-312 (ETX-M00001378) alone or in combination with semaglutide or resmetirom significantly reduced plasma TC levels. The combination of semaglutide with ETX-312 further reduced TC compared to semaglutide alone. Results are presented as absolute levels as Mean $\pm$ SEM from n=16 experiment. * $p < 0.05$; **** $p < 0.0001$; ns non-significant.

20 **Figure 18:** Weekly treatment of ETX-312 (ETX-M00001378) for 12 weeks greatly reduced target expression in liver, at both mRNA and protein levels. mRNA or protein was extracted from 50 mg of mouse liver per animal and homogenized in lysis buffer. mRNA expression was analyzed by qPCR in technical triplicates, with TaqMan gene expression assays for the target and the house keeping genes (Mm00846873_g1, Mm99999915_g1, Thermo Fisher Scientific). Relative mRNA expression for each

25 sample was calculated with the ddCt method, normalized to vehicle treated samples. Relative protein abundance was calculated based on quantification of two peptides per liver lysate per animal (QIFLGGVDK – SEQ ID NO: 1390, EQGVLSFWR – SEQ ID NO: 1391). Results are presented as Mean $\pm$ SEM from n=16 experiment. ** $p < 0.01$; **** $p < 0.0001$; ns non-significant.

Figure 19: ALT and AST were measured in plasma samples after 16 weeks ETX-312 (ETX-M00001378)

30 treatment using commercial kits (Roche Diagnostics), on the cobas c501 autoanalyzer. ALT and AST levels were increased in DIO-NASH mice (vehicle sc, siCtrl, vehicle PO). Treatment with ETX-312 (ETX-M00001378) alone or in combination with efruxifermin or tirzepatide significantly reduced both ALT and AST levels. Combination of ETX-312 and Tirzepatide further reduced plasma ALT as compared to tirzepatide alone. Results are presented as absolute levels as Mean $\pm$ SEM from n=18 experiment. ** $p < 0.01$; **** $p < 0.0001$.

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Figure 20: TIMP-1 and PIIINP are non-invasive blood biomarkers for NAFLD/NASH that predict hepatic fibrosis. TIMP-1 was measured in plasma collected in EDTA tubes using a commercial ELISA kit (R&D Systems). PIIINP was measured in plasma collected in EDTA tubes using a commercial ELISA kit (Cusabio). TIMP-1 and PIIINP levels were increased in DIO-NASH mice (vehicle sc, siCtrl, vehicle PO).

5 Treatment with ETX-312 (ETX-M00001378) alone or in combination with efruxifermin or tirzepatide significantly reduced both TIMP-1 and PIIINP levels. Results are presented as absolute levels as Mean $\pm$ SEM from n = 18 experiments for TIMP-1; and n=2 (lean chow vehicle) , n=17 (vehicle sc), n=15 (ETX-312), n=11 (efruxifermin), n=12 (ETX-312 + efruxifermin), n=15 (tirzepatide), n=16 (ETX-312 + tirzepatide) experiment for PIIINP. **** p < 0.0001.

10 **Figure 21:** Terminal liver weight to body weight ratio demonstrates hepatomegaly in DIO-NASH mice. Treatment with ETX-312 (ETX-M00001378) alone or in combination with efruxifermin or tirzepatide significantly reduced liver to body weight ratio. Results are presented as percent liver:body weight as Mean $\pm$ SEM from n=16 experiment. **** p < 0.0001.

Figure 22: Total cholesterol (TC) levels were measured in plasma samples after 16 weeks ETX-312 (ETX-M00001378) treatment using commercial kits (Roche Diagnostics), on the cobas c501 autoanalyzer. GAN diet elevated plasma TC in DIO NASH animals (Vehicle SC, siCtrl, Vehicle PO). Treatment with ETX-312 (ETX-M00001378) alone or in combination with efruxifermin or tirzepatide significantly reduced plasma TC levels. Results are presented as absolute levels as Mean $\pm$ SEM from n=16 experiment. **** p < 0.0001.

20 **Figures 23 and 24:** NAFLD Activity Scores (NAS) in mice with diet-induced NASH following various treatments. NAFLD Activity Scores were assigned to liver samples stained with H&E, using clinical criteria set by Kleiner et al. (2005). The Total NAS, which combines scores for steatosis, inflammation, and ballooning, ranges from 0 to 8. Scoring was conducted with the Gubra Histopathological Objective Scoring Technology (GHOST), a Gubra-developed deep learning tool that utilizes VIS software (Visiopharm, Denmark) for precise, objective staging in DIO-NASH mouse models. Results are shown as changes in NAS score from the pre-dose biopsy to study end: Figure 23 illustrates the absolute changes in NAS scores, while Figure 24 groups animals with NAS improvement of 2 or more points together.

Figures 25 and 26: Liver lipid content, or steatosis, is quantified on H&E stained slides by image analysis using the VIS software (Visiopharm, Denmark). Treatment with ETX-312 (ETX-M00001378) alone or in combination with Efruxifermin or Tirzepatide significantly reduced liver steatosis. Combination therapies resulted in a significantly greater effect than Efruxifermin or Tirzepatide used as monotherapies. Results are presented as a percent area fraction (Figure 25) and the total level (percent area fraction multiplied by liver weight, Figure 26), as Mean $\pm$ SEM from n=18 experiment. **** p < 0.0001.

Figure 27: Treatment with ETX-312 (ETX-M00001378), either alone or in combination with Efruxifermin or Tirzepatide, significantly reduced inflammation in liver, a key factor differentiating NASH from

NAFLD, as measured by post-treatment biopsy inflammatory foci density, change in lobular inflammation score from pre- to post-treatment biopsy, and CD45 staining. Combination with Efruxifermin improved lobular inflammation score and CD45 stained fractional area compared to Efruxifermin monotherapy. Inflammatory foci density and lobular inflammation score were assessed by Gubra Histopathological Objective Scoring Technology (GHOST) deep learning app developed by Gubra, by image analysis of H&E-stained slides using the VIS software (Visiopharm, Denmark). Inflammatory foci density is the number of inflammatory foci per surface area, where foci are clusters of more than 3 inflammatory cells. The lobular inflammation score was determined using the clinical criteria outlined by Kleiner et al. (2005). CD45, a surface marker of immune cells, was assessed via immunohistochemistry using a rabbit anti-CD45 primary antibody (AbCam, Cat. Ab10558). CD45-positive staining was quantified using the VIS software (Visiopharm, Denmark), reported as a percent area fraction excluding steatosis (bottom left) and the total level (percent area fraction multiplied by liver weight, bottom right). Lobular inflammation scores show changes between pre-dose and post-dose liver biopsies (improvement or worsening), while results for inflammatory foci and CD45 staining are presented as Mean $\pm$ SEM from n=18 experiment. ** $p < 0.01$; **** $p < 0.0001$.

Figures 28 and 29: The inhibitor ETX-312 (ETX-M00001378) reduced fibrosis progression, both as monotherapy and in combination, as evidenced by a trend toward reduced 1-point worsening in fibrosis stage (Figure 28) and/or a significantly smaller increase in picrosirius red (PSR) staining (Figure 29) compared to Vehicle control. Liver biopsies were stained with PSR for fibrosis assessment, with pre- and post-treatment samples evaluated. In Figure 28, fibrosis staging was conducted using the Gubra Histopathological Objective Scoring Technology (GHOST), a deep learning application developed by Gubra and implemented in VIS software (Visiopharm, Denmark). GHOST-derived scores were reviewed by a blinded histopathologist to maintain objectivity in the assessment of fibrosis stages. In Figure 29, changes in PSR-positive areas during treatment were analyzed to assess fibrosis progression or potential reversal. Quantitative results excluding steatotic regions are presented as delta area fractions, comparing pre-treatment and post-treatment biopsies, as Mean $\pm$ SEM from n=18 experiment. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figures 30 and 31: The inhibitor ETX-312 (ETX-M00001378), both as monotherapy or in combination, demonstrated a reduction in markers of fibrogenesis and collagen synthesis, supporting its potential impact in fibrosis. Specifically, the inhibitor decreased α -SMA staining (Figure 31), indicating reduced activation of hepatic stellate cells, which play a central role in fibrogenesis. Additionally, the inhibitor, both alone and in combination with Efruxifermin (EFX) or Tirzepatide (TZP), lowered liver Colla1 levels (Figure 30), suggesting a reduction in collagen deposition. Terminal liver biopsies were analyzed histomorphometrically for collagen (Colla1) and activated stellate cells (α -SMA) via immunohistochemistry (IHC). IHC-positive staining for each protein was quantified using image analysis in the VIS software (Visiopharm, Denmark). Results were reported as percent area fractions without steatotic areas, as Mean $\pm$ SEM from n=18 experiment. *** $p < 0.001$; **** $p < 0.0001$.

Figures 32 and 33: Weekly treatment of ETX-312 (ETX-M00001378) for 16 weeks reduced target expression in liver, at both mRNA (Figure 32) and protein (Figure 33) levels. mRNA or protein was extracted from 50 mg of mouse liver per animal and homogenized in the appropriate lysis buffer. mRNA levels were analyzed by qPCR in technical triplicates, with TaqMan gene expression assays for the target and the house keeping genes (Mm00846873_g1, Mm99999915_g1, Thermo Fisher Scientific). Relative mRNA expression for each sample was calculated with the ddCt method, normalized to vehicle treated samples. Relative protein abundance was determined by quantifying two peptides per liver lysate per animal (QIFLGGVDK, EQGVLSFWR). Results are presented as Mean $\pm$ SEM from n=18 experiment. ** p < 0.01; ***p < 0.001; **** p < 0.0001; ns non-significant.

10

DETAILED DESCRIPTION

The present invention, inter alia, provides inhibitors, for example oligomers such as nucleic acids, such as inhibitory RNA molecules (which may be referred to as iRNA or siRNA), and compositions containing the same which can affect expression of a target, for example by binding to mRNA transcribed from a gene. The target may be within a cell, e.g. a cell within a subject, such as a human. The inhibitors can be used to prevent and/or treat medical conditions associated with the e.g. the expression of a target gene.

In particular the present invention identifies inhibitors of expression and/or function of SLC25A5/ANT2 as useful in the prevention and/or treatment of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis.

ADP/ATP translocase 2 (ANT2) is a protein that in humans is encoded by the *SLC25A5* gene on the X chromosome. This protein functions as an antiporter for ADP/ATP exchange between the mitochondrial matrix and cytoplasm.

The present invention relates to an inhibitor of expression and/or function of SLC25A5/ANT2. Accordingly, in certain embodiments, the invention relates to an inhibitor of expression of the *SLC25A5* gene, such as an siRNA that targets an mRNA transcribed from the *SLC25A5* gene. In certain embodiments, the invention relates to an inhibitor of function of the gene product ANT2. Both options are encompassed when it referred herein to an inhibitor of SLC25A5/ANT2 or an inhibitor of the invention.

In humans, ANT2 is encoded by the *SLC25A5* gene (SEQ ID NO: 1381).

SEQ ID NO: 1381 (SLC25A5)

ATCGGCCATTGCTTCGCTCCGCCCCGAGCGCCGGAGTCAAAGCCGGTTCCCCGGCCAGTCCCGTCCT
GCAGCAGTCTGCCTCCTCTTTCAACATGACAGATGCCGCTGTGTCTTCGCCAAGGACTTCCTGGCAGG
TGGAGTGGCCGAGCCATCTCCAAGACGGCGGTAGCGCCCATCGAGCGGGTCAAGCTGCTGCTGCAG
GTACGTCTGGGATCCAGGAGCCCAACCAGGAAGTGGGGGGAAGGGTCGCACAGAAGGCGGGCGCCC
5 GAGGGGTGGCGGGGAGCGAACTCTAAAGACATGGCCAGGGAAGCGGCTTAGGAGAGGCCAGAGCGG
GGCGCAGAGGCAGAACAGAAAGTCAAACCTGGTGGGAGGCGCCTTTAGTGACCTGAAGTAGTGAGTCTA
GGAAGGGGCGGGGGCAGAGGGCAGGACCAGGCTCTCGGCATCTCCGAGGCGGCGGACTCGGATGG
AGCAGTTTCTGAGTGACGGCTCCCCGGGCTGGGCGTCAAGGGCGAAGGCCGAAAGCCGGCGTTAG
AAAGAGGAACGCCAGTTCTTACCGAAGACCTCAAGGTCGCGGCAAGGAGATAACTGCCCGGGGGAGG
10 CCATGCGCCCCGGGTCCAGCGGCCTCCCAGCCCGCGGACGCGCTCAAACCTCGCCGGGCGCGGAAGCCG
GCGCCGGGAAGCGCGTGTGCCTTTTACGTCCGCCCCCGCGCAGCCGCGGCGCTGCCGCCGCGTCTCC
GCCTGCCTCCCTGCGCCGCGCGCTCTCCAGTGCCGGCTCTAGAGGGCGCTCCTGGGCTAGCGTGTAGG
GCTGGCGGGCGGCGGCGCTCGGGTCACCTCTGGGAGCGGAGTGGGGGCGGAGCGAGACGGAAGCAGCT
CAGGAGACTTGAGGCGTAGGCTGCGGTCCCCAAGGTGACCGCGCCCTATGTGGGACTCGCCCTAATGC
15 CTCTGAACCTGGGTTTGAGGTAATGACCTTTCTCCTAGGTCTGAAGGTACGGGTCCGCTGGAGGATG
CCCCCTCTCCACTCAGAGGGGTGGAGGCTTAATGCTACTGGTGCAGATCACCTCTTCCCTGTGACAGC
CTCAGAGGGTTGGGAGGGTCCAGCCAGTATGATATACGAAGACTAGATTTGAGAGAGGGGAGCCTAC
CTTAAAGGGCATTGATCGAGATGGCATAAGCTCTTCTCTTCCCTTCCCAGTGGTTATAACTGTCCCTG
TTGGCTTCCTTCTGTCTGTTAGGTGCAGCATGCCAGCAAGCAGATCACTGCAGATAAGCAATACAAA
20 GGCATTATAGACTGCGTGGTCCGTATTCCCAAGGAGCAGGGAGTTCTGTCTTCTGGCGCGGTAACCT
GGCCAATGTCATCAGATACTTCCCCACCCAGGCTCTTAACTTCGCTTCAAAGATAAATACAAGCAGA
TCTTCTGGGTGGTGTGGACAAGAGAACCAGTTTTGGCTCTACTTTGCAGGGAATCTGGCATCGGGT
GGTGCCGCAGGGGCCACATCCCTGTGTTTTGTGTACCCTCTTGATTTTGCCCGTACCCGTCTAGCAGCT
GATGTGGGTAAAGCTGGAGCTGAAAGGAATTCCGAGGCTCGGTGACTGCCTGGTTAAGATCTACA
25 AATCTGATGGGATTAAGGGCCTGTACCAAGGCTTTAACGTGTCTGTGCAGGGTATTATCATCTACCGA
GCCGCCTACTTCGGTATCTATGACACTGCAAAGGGTAAGTTTGCTGTGGGCTTTAACGTTGTGTTCTTA
GGAGACAGTTTTAAAGAGCATTGTACCAACCTAACAGTCCAAGAGCTAAAGAGTTGTTTTTTAATTG
CTAAAGGAAGCCAAGATCATCCAATGCAACCCTTGTGTACAGATGACGTGTTTAGGGGATGTGGGGA
AAGGAAGTCAGTAAACTCTGCTTTTTGGTAAAAGCATCTCTTCCCTATTCCAGGAATGCTTCCGGAT
30 CCCAAGAACACTCACATCGTCATCAGCTGGATGATCGCACAGACTGTCACTGCTGTTGCCGGGTTGAC
TTCCTATCCATTTGACACTGTTCCCGCCCGCATGATGATGCAGTCAGGGCGCAAAGGAAGTAAGTTCC
ACTTGAGCAGAAGATAAAGTTGTAGTCGTGGGGCAATCTGCTGCCACAACTGGTGATACATACCTTT
AAAATGGCTGTCTGTCCAAGTCAAGGGATGGGGTTGATAGCATCTGTGTCTGTTCCACAACCTGCCTTTG
AGCTGGCCCTTCAGATGCCTATGAATGAGGGTGCTTAAATGGTGTTAGAGGTTAAGACCAATGGGTA
35 TCTGTATTCTGTGGTCATAGCATTAAATATTTAGTGTTGCCCATGCTAATGTGTGAATGTTGGATTTA
AAGCTGACGTTCTTAGAGGTGGGGCTCTGCTTTATTTAGCCTAGTGAATCTTAGGATTTTTTCATCGGCC
TTCAGTCACTAACTCCATGTCTTTATTCTTTGACGCTGACATCATGTACACAGGCACGCTTGACTGCTG
GCGGAAGATTGCTCGTGATGAAGGAGGCAAGCTTTTTTCAAGGGTGCATGGTCCAATGTTCTCAGAG
GCATGGGTGGTGTCTTTGTGCTTGTCTTGTATGATGAAATCAAGAAGTACACATAAGTTATTTCTAGG
40 ATTTTTCCCCCTGTGAACAGGCATGTTGTATTATATAACATATCTTGAGCATTCTTGACAGACTCCTGG
CTGTCAGTTTTCTCAGTGGCAACTATTTACTGGTTGAAAATGGGAAGCAATAATATTCATCTGACCAGTT
TTCTCTTAAAGCCATTTCCATGATGATGATGATGGGACTCAATTGTATTTTTTATTTAGTCACTCCTGA
TAAATAACAAATTTGGAGAAATAAAAATATCTAAAATAAATTTTGTCTGCAGTATATTTTCATATAAAA
AATGCATATTTGAGTGCTACATTGCAATAAAATACTACCTTTTTAGTGAA
45

The inventors employed network analysis that allows them to allocate multiple genes or proteins to a smaller number of driver processes; and to mine these processes for impactful drug targets. The approach takes advantage of information that is usually ignored in standard gene set analyses – the known and predicted interactions between genes (and proteins) and the inclusion of other genes in the same or related
50 pathways. In particular, the inventors analysed Genome Wide Association Studies (GWAS) metanalyses for Non-Alcoholic Fatty Liver Disease (NAFLD) using network models which highlighted SLC25A5/ANT2 as a preferred target for NAFLD among other known targets associated with NAFLD.

The inhibition disclosed herein may be of the gene or protein resulting from expression of the SLC25A5 gene and reference to SLC25A5/ANT2 hereby explicitly incorporates a reference to inhibition of the expression or function of the gene and, separately, of the protein product.

DEFINITIONS

5 The “first strand”, also called the antisense strand or guide strand herein and which can be used interchangeably herein, refers to the nucleic acid strand, e.g. the strand of an siRNA, e.g. a dsRNA, which includes a region that is substantially complementary to a target sequence, e.g. to an mRNA. As used herein, the term “region of complementarity” refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence. Where the region of complementarity is not
10 fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the molecule. In some embodiments, a double stranded nucleic acid e.g. an siRNA agent of the invention includes a nucleotide mismatch in the antisense strand.

The “second strand” (also called the sense strand or passenger strand herein, and which can be used interchangeably herein), refers to the strand of a nucleic acid e.g. siRNA that includes a region that is
15 substantially complementary to a region of the antisense strand as that term is defined herein.

In the context of molecule comprising a nucleic acid provided with a ligand moiety, optionally also with a linker moiety, the nucleic acid of the invention may be referred to as an oligonucleotide moiety or oligonucleoside moiety

Oligonucleotides are short nucleic acid polymers. Whilst oligonucleotides contain phosphodiester bonds
20 between the nucleoside component thereof (base plus sugar), the present invention is not limited to oligonucleotides always joined by such a phosphodiester bond between adjacent nucleosides, and other oligomers of nucleosides joined by bonds which are bonds other than a phosphate bond are contemplated. For example, a bond between nucleotides may be a phosphorothioate bond. Therefore, the term “oligonucleoside” herein covers both oligonucleotides and other oligomers of nucleosides. An
25 oligonucleoside which is a nucleic acid having at least a portion which is an oligonucleotide is preferred according to the present invention. An oligonucleoside having one or more, or a majority of, phosphodiester backbone bonds between nucleosides is also preferred according to the present invention. An oligonucleoside having one or more, or a majority of, phosphodiester backbone bonds between nucleosides, and also having one or more phosphorothioate backbone bonds between nucleosides (typically in a terminal
30 region of the first and / or second strands) is also preferred according to the present invention.

In some embodiments, a double stranded nucleic acid e.g. siRNA agent of the invention includes a nucleoside mismatch in the sense strand. In some embodiments, the nucleoside mismatch is, for example, within 5, 4, 3, 2, or 1 nucleosides from the 3'-end of the nucleic acid e.g. siRNA.

In another embodiment, the nucleoside mismatch is, for example, in the 3'-terminal nucleoside of the nucleic acid e.g. siRNA.

5 A "target sequence" (which may be called a target RNA or a target mRNA) refers to a contiguous portion of the nucleoside sequence of an mRNA molecule formed during the transcription of a gene, including mRNA that is a product of RNA processing of a primary transcription product, or can be a contiguous portion of the nucleotide sequence of any RNA molecule such as a LNCrRNA which it is desired to inhibit.

The target sequence may be from about 10-35 nucleosides in length, e.g., about 15-30 nucleosides in length. For example, the target sequence can be from about 15-30 nucleosides, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 10 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleosides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

The term "ribonucleoside" or "nucleoside" can also refer to a modified nucleoside as further detailed below.

15 A nucleic acid can be a DNA or an RNA, and can comprise modified nucleosides. RNA is a preferred nucleic acid.

The terms "iRNA", "siRNA", "RNAi agent", and "iRNA agent", "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA, and which mediates the targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. siRNA directs the sequence-specific degradation of mRNA through RNA interference (RNAi). 20

A double stranded RNA is referred to herein as a "double stranded siRNA (dsiRNA) agent", "double stranded siRNA (dsiRNA) molecule", "double stranded RNA (dsRNA) agent", "double stranded RNA (dsRNA) molecule", "dsiRNA agent", "dsiRNA molecule", or "dsiRNA", which refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having "sense" and "antisense" orientations with respect to a target RNA. The majority of nucleosides of each strand of the nucleic acid, e.g. a dsRNA molecule, are preferably ribonucleosides, but in that case each or both strands can also include one or more non-ribonucleosides, e.g., a deoxyribonucleoside or a modified ribonucleoside. In addition, as used in this specification, an "siRNA" may include ribonucleosides with chemical modifications. 25

30 The term "modified nucleoside" refers to a nucleoside having, independently, a modified sugar moiety, a modified internucleoside linkage, or modified nucleobase, or any combination thereof. Thus, the term modified nucleoside encompasses substitutions, additions or removal of, e.g., a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. Any such modifications, as used in a siRNA

type molecule, are encompassed by "iRNA" or "RNAi agent" or "siRNA" or "siRNA agent" for the purposes of this specification and claims.

The duplex region of a nucleic acid of the invention e.g. a dsRNA may range from about 9 to 40 base pairs in length such as 9 to 36 base pairs in length, e.g., about 15- 30 base pairs in length, for example, about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 base pairs in length, such as about 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18- 27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21- 30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length.

The two strands forming the duplex structure may be different portions of one larger molecule, or they may be separate molecules e.g. RNA molecules.

The term "nucleoside overhang" refers to at least one unpaired nucleoside that extends from the duplex structure of a double stranded nucleic acid. A ds nucleic acid can comprise an overhang of at least one nucleoside; alternatively the overhang can comprise at least two nucleosides, at least three nucleosides, at least four nucleosides, at least five nucleosides, or more. A nucleoside overhang can comprise or consist of a nucleoside analog, including a deoxynucleoside. The overhang(s) can be on the sense strand, the antisense strand, or any combination thereof. Furthermore, the /nucleoside(s) of an overhang can be present on the 5'-end, 3'-end, or both ends of either an antisense or sense strand.

In certain embodiments, the antisense strand has a 1-10 nucleoside, e.g., 0-3, 1-3, 2-4, 2-5, 4-10, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleoside overhang at the 3'-end or the 5'-end.

"Blunt" or "blunt end" means that there are no unpaired nucleoside at that end of the double stranded nucleic acid, i.e., no nucleoside overhang. The nucleic acids of the invention include those with no nucleoside overhang at one end or with no nucleoside overhangs at either end.

Unless otherwise indicated, the term "complementary," when used to describe a first nucleoside sequence in relation to a second nucleoside sequence, refers to the ability of an oligonucleoside comprising the first nucleoside sequence to hybridize and form a duplex structure under certain conditions with an oligonucleoside or polynucleoside comprising the second nucleoside sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions can include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing (see, e.g., "Molecular Cloning: A Laboratory Manual, Sambrook, et al. (1989) Cold Spring Harbor Laboratory Press).

Complementary sequences within nucleic acid e.g. a dsRNA, as described herein, include base-pairing of the oligonucleoside or polynucleoside comprising a first nucleoside sequence to an oligonucleoside or

polynucleoside comprising a second nucleoside sequence over the entire length of one or both nucleoside sequences. Such sequences can be referred to as "fully complementary" with respect to each other herein. However, where a first sequence is referred to as "substantially complementary" or "partially complementary" with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more mismatched base pairs, such as 2, 4, or 5 mismatched base pairs, but preferably not more than 5, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, e.g., inhibition of gene expression via a RISC pathway. Overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a nucleic acid e.g. dsRNA comprising one oligonucleoside 17 nucleosides in length and another oligonucleoside 19 nucleosides in length, wherein the longer oligonucleoside comprises a sequence of 17 nucleosides that is fully complementary to the shorter oligonucleoside, can yet be referred to as "fully complementary".

"Complementary" sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs or base pairs formed from non-natural and modified nucleosides, in so far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs include, but are not limited to, G:U Wobble or Hoogsteen base pairing.

The terms "complementary," "fully complementary" and "substantially/partially complementary" herein can be used with respect to the base matching between the sense strand and the antisense strand of a nucleic acid e.g. dsRNA, or between the antisense strand of a double stranded nucleic acid e.g. siRNA agent and a target sequence.

Within the present invention, the second strand of the nucleic acid according to the invention, in particular a dsRNA for inhibiting SLC25A5/ANT2, is at least partially complementary to the first strand of said nucleic acid. In certain embodiments, a first and second strand of a nucleic acid according to the invention are partially complementary if they form a duplex region having a length of at least 17 base pairs and comprising not more than 1, 2, 3, 4, or 5 mismatched base pairs.

In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 19 base pairs and comprising not more than 1, 2, 3, 4, or 5 mismatched base pairs. In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 21 base pairs comprising not more than 1, 2, 3, 4, or 5 mismatched base pairs.

Alternatively, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of at least 17 base pairs, wherein at least 14, 15, 16 or 17 of said base pairs are complementary base pairs, in particular Watson-Crick base pairs.

In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 19 base pairs, wherein at least 14, 15, 16,

17, 18 or all 19 base pairs are complementary base pairs, in particular Watson-Crick base pairs. In certain embodiments, a first and second strand of the nucleic acid according to the invention are partially complementary if they form a duplex region having a length of 21 base pairs, wherein at least 16, 17, 18, 19, 20 or all 21 base pairs are complementary base pairs, in particular Watson-Crick base pairs. As used
5 herein, a nucleic acid that is "substantially complementary" or "partially complementary" to at least part of a messenger RNA (mRNA) refers to a polynucleoside that is substantially or partially complementary to a contiguous portion of the mRNA of interest (e.g., an mRNA encoding a gene). In certain embodiments, the contiguous portion of the mRNA is a sequence as listed in Table 1, i.e., any one of SEQ ID NOs: 1-276. For example, a polynucleoside is complementary to at least a part of an mRNA of a gene of interest if the
10 sequence is substantially or partially complementary to a non-interrupted portion of an mRNA encoding that gene.

Accordingly, in some preferred embodiments, the antisense oligonucleosides as disclosed herein are fully complementary to the target gene sequence.

In other embodiments, the antisense oligonucleosides disclosed herein are substantially or partially
15 complementary to a target RNA sequence and comprise a contiguous nucleoside sequence which is at least about 80% complementary over its entire length to the equivalent region of the target RNA sequence, such as at least about 85%, 86%, 87%, 88%, 89%, about 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary or 100% complementary.

In certain embodiments, the first (antisense) strand of a nucleic acid according to the invention is partially
20 or fully complementary to a contiguous portion of RNA transcribed from the *SLC25A5* gene. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of at least 17 nucleosides of the *SLC25A5* mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of the *SLC25A5* mRNA.
25 In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of any one of the sequences as listed in Table 1, i.e., any one of SEQ ID NOs: 1-276.

In certain embodiments, the first (antisense) strand of the nucleic acid according to the invention is partially complementary to a contiguous portion of the *SLC25A5* mRNA if it comprises a contiguous nucleoside
30 sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of the *SLC25A5* mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences
35 listed in Table 1, i.e., any one of SEQ ID NOs: 1-276. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 19 nucleosides, wherein at

least 14, 15, 16, 17, 18 or all 19 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 1-276. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 23 nucleosides, wherein at least 18, 19, 20, 21, 22 or all 23 nucleosides of said
5 contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 1-276.

In some embodiments, a nucleic acid e.g. an siRNA of the invention includes a sense strand that is substantially or partially complementary to an antisense polynucleoside which, in turn, is complementary to a target gene sequence and comprises a contiguous nucleoside sequence which is at least about 80%
10 complementary over its entire length to the equivalent region of the nucleoside sequence of the antisense strand, such as about 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

In some embodiments, a nucleic acid e.g. an siRNA of the invention includes an antisense strand that is substantially or partially complementary to the target sequence and comprises a contiguous nucleoside
15 sequence which is at least 80% complementary over its entire length to the target sequence such as about 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% complementary, or 100% complementary.

As used herein, a "subject" is an animal, such as a mammal, including a primate (such as a human, a non-human primate, e.g., a monkey, and a chimpanzee), or a non-primate or a bird that expresses the target
20 gene, either endogenously or heterologously, when the target gene sequence has sufficient complementarity to the nucleic acid e.g. iRNA agent to promote target knockdown. In certain preferred embodiments, the subject is a human.

The terms "treating" or "treatment" refer to a beneficial or desired result including, but not limited to, alleviation or amelioration of one or more symptoms associated with gene expression. "Treatment" can also
25 mean prolonging survival as compared to expected survival in the absence of treatment. Treatment can include prevention of development of co-morbidities, e.g. reduced liver damage in a subject with a hepatic infection.

"Therapeutically effective amount," as used herein, is intended to include the amount of a nucleic acid e.g. an iRNA that, when administered to a patient for treating a subject having disease, is sufficient to effect
30 treatment of the disease (e.g., by diminishing, ameliorating or maintaining the existing disease or one or more symptoms of disease or its related comorbidities).

The phrase "pharmaceutically acceptable" is employed herein to refer to compounds, materials, compositions, or dosage forms which are suitable for use in contact with the tissues of human subjects and

animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

5 The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically- acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated.

10 Where a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article.

The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

15 The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise. For example, "sense strand or antisense strand" is understood as "sense strand or antisense strand or sense strand and antisense strand."

20 The term "about" is used herein to mean within the typical ranges of tolerances in the art. For example, "about" can be understood as about 2 standard deviations from the mean. In certain embodiments, about means +10%. In certain embodiments, about means +5%. When about is present before a series of numbers or a range, it is understood that "about" can modify each of the numbers in the series or range.

25 The term "at least" prior to a number or series of numbers is understood to include the number adjacent to the term "at least", and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, "at least 18 nucleosides of a 21 nucleoside nucleic acid molecule" means that 18, 19, 20, or 21 nucleosides have the indicated property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

30 As used herein, "no more than" or "less than" is understood as the value adjacent to the phrase and logical lower values or integers, as logical from context, to zero. For example, a duplex with an overhang of "no more than 2 nucleosides" has a 2, 1, or 0 nucleoside overhang. When "no more than" is present before a series of numbers or a range, it is understood that "no more than" can modify each of the numbers in the series or range.

The terminal region of a strand is the last 5 nucleotides from the 5' or the 3' end.

A nucleobase sequence is the sequence of the bases of the nucleic acid in an oligomer.

Various embodiments of the invention can be combined as determined appropriate by one of skill in the art.

TARGET

- 5 A target for inhibition disclosed herein may be, without limitation, an mRNA, polypeptide, protein, or gene.

These targets are a target the inhibition of which helps in the prevention and/or treatment of a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

- 10 The target for inhibition is the gene SLC25A5 or a gene product thereof, such as an mRNA transcribed from the SLC25A5 gene or the ANT2 protein, and inhibition may be effected by inhibition of expression or function of the SLC25A5/ANT2 gene or protein or both.

In a preferred embodiment, the target in an mRNA expressed from the SLC25A5 gene. Exemplary target sequences on the SLC25A5 mRNA are listed below in Table 1.

Table 1

SEQ ID NO	Oligonucleotide mRNA target sequence 5' → 3'	Starting position on ENST00000317881.9
SEQ ID NO: 1	ACUAAUUACUGGUUGAAAAUGGG	1072
SEQ ID NO: 2	UACAAAGGCAUUAUAGACUGCGU	223
SEQ ID NO: 3	UAUGAUGAAAUCAAGAAGUACAC	943
SEQ ID NO: 4	AUGAUGAUGGGACUCAAUUGUAU	1146
SEQ ID NO: 5	AGGCAUUAUAGACUGCGUGGUCC	228
SEQ ID NO: 6	CAGUCACUCCUGAUAAUAACAA	1178
SEQ ID NO: 7	CAAUACAAAGGCAUUAUAGACUG	220
SEQ ID NO: 8	GAGCCGCCUACUUCGGUAUCUAU	635
SEQ ID NO: 9	CGAGCCGCCUACUUCGGUAUCUA	634
SEQ ID NO: 10	AUAGACUGCGUGGUCCGUUUCC	235
SEQ ID NO: 11	AACACUCACAUCGUCAUCAGCUG	691
SEQ ID NO: 12	UAACUUCGCCUUCAAAGAUAAAU	333
SEQ ID NO: 13	GCCUACUUCGGUAUCUAUGACAC	640
SEQ ID NO: 14	UAUUUACUGGUUGAAAAUGGGAA	1074
SEQ ID NO: 15	UUUGCCCGUACCCGUCUAGCAGC	478
SEQ ID NO: 16	GCAGUCAGGGCGCAAAGGAACUG	792
SEQ ID NO: 17	AUUUACUGGUUGAAAAUGGGAAG	1075

SEQ ID NO: 18	CCGAGCCGCCUACUUCGGUAUCU	633
SEQ ID NO: 19	GGCCUCGGUGACUGCCUGGUAA	538
SEQ ID NO: 20	CACAUCGUCAUCAGCUGGAUGAU	697
SEQ ID NO: 21	UAUUUCAGUCACUCCUGAUAAAU	1173
SEQ ID NO: 22	GCUGGAUGAUCGCACAGACUGUC	710
SEQ ID NO: 23	AAGCAAUACAAAGGCAUUUAUAGA	217
SEQ ID NO: 24	AGGCCUCGGUGACUGCCUGGUAA	537
SEQ ID NO: 25	GGCUUUAAACGUGUCUGUGCAGGG	598
SEQ ID NO: 26	ACAAAGGCAUUUAUAGACUGCGUG	224
SEQ ID NO: 27	CUGUGAACAGGCAUGUUGUAUUA	993
SEQ ID NO: 28	UCAUCUGACCAGUUUUCUCUAA	1107
SEQ ID NO: 29	CAAGGCUUUAAACGUGUCUGUGCA	595
SEQ ID NO: 30	AUGCAGUCAGGGCGCAAAGGAAC	790
SEQ ID NO: 31	UGGAUGAUCGCACAGACUGUCAC	712
SEQ ID NO: 32	AAAGGCAUUUAUAGACUGCGUGGU	226
SEQ ID NO: 33	GAUGAUCGCACAGACUGUCACUG	714
SEQ ID NO: 34	GACUGCGUGGUCCGUAUUCCCAA	238
SEQ ID NO: 35	AGCAAUACAAAGGCAUUUAUAGAC	218
SEQ ID NO: 36	GUCAUCAGCUGGAUGAUCGCACA	703
SEQ ID NO: 37	GCAUUUAUAGACUGCGUGGUCCGU	230
SEQ ID NO: 38	AUUUUGCCCGUACCCGUCUAGCA	476
SEQ ID NO: 39	UCACAUCGUCAUCAGCUGGAUGA	696
SEQ ID NO: 40	CCUCUUGAUUUUGCCCGUACCCG	469
SEQ ID NO: 41	UUUAUAGACUGCGUGGUCCGUUU	233
SEQ ID NO: 42	GCCGCCUACUUCGGUAUCUAUGA	637
SEQ ID NO: 43	UAGACUGCGUGGUCCGUUUUCCC	236
SEQ ID NO: 44	CGUCAUCAGCUGGAUGAUCGCAC	702
SEQ ID NO: 45	CAUUUAUAGACUGCGUGGUCCGUA	231
SEQ ID NO: 46	CGCCUACUUCGGUAUCUAUGACA	639
SEQ ID NO: 47	UUUUAAUUCAGUCACUCCUGAUA	1170
SEQ ID NO: 48	UCGUCAUCAGCUGGAUGAUCGCA	701
SEQ ID NO: 49	UGAUUUUGCCCGUACCCGUCUAG	474
SEQ ID NO: 50	UGCAAAGGGAAUGCUUCCGGAUC	663
SEQ ID NO: 51	CCAAGGCUUUAAACGUGUCUGUGC	594
SEQ ID NO: 52	CAAAGGCAUUUAUAGACUGCGUGG	225
SEQ ID NO: 53	UCUUGAUUUUGCCCGUACCCGUC	471
SEQ ID NO: 54	ACCGAGCCGCCUACUUCGGUAUC	632
SEQ ID NO: 55	UUAUCAUCUACCGAGCCGCCUAC	623
SEQ ID NO: 56	CUUGAUUUUGCCCGUACCCGUCU	472
SEQ ID NO: 57	AUUAUCAUCUACCGAGCCGCCUA	622
SEQ ID NO: 58	AUCAUCUACCGAGCCGCCUACUU	625

SEQ ID NO: 59	GGCUCUUAACUUCGCCUUCAAAG	327
SEQ ID NO: 60	CCCCACCCAGGCUCUUAACUUCG	318
SEQ ID NO: 61	GUCCGUAAUCCCCAAGGAGCAGGG	247
SEQ ID NO: 62	AGGAGCAGGGAGUUCUGUCCUUC	260
SEQ ID NO: 63	AUUCCCAAGGAGCAGGGAGUUCU	253
SEQ ID NO: 64	GGUCCGUAAUCCCAAGGAGCAGG	246
SEQ ID NO: 65	GAGCAGGGAGUUCUGUCCUUCUG	262
SEQ ID NO: 66	UGGUCCGUAAUCCCCAAGGAGCAG	245
SEQ ID NO: 67	GGAGCAGGGAGUUCUGUCCUUCU	261
SEQ ID NO: 68	AAGGAGCAGGGAGUUCUGUCCUU	259
SEQ ID NO: 69	UAUUCCCAAGGAGCAGGGAGUUC	252
SEQ ID NO: 70	CAAGGAGCAGGGAGUUCUGUCCU	258
SEQ ID NO: 71	UCCCCACCCAGGCUCUUAACUUC	317
SEQ ID NO: 72	GCUCUUAACUUCGCCUUCAAAGA	328
SEQ ID NO: 73	AUUUCAGUCACUCCUGAUAAUA	1174
SEQ ID NO: 74	UUCAGUCACUCCUGAUAAUAAC	1176
SEQ ID NO: 75	UUUCAGUCACUCCUGAUAAUAA	1175
SEQ ID NO: 76	GAUGAUGGGACUCAAUUGUAUUU	1148
SEQ ID NO: 77	AUGAUGGGACUCAAUUGUAUUUU	1149
SEQ ID NO: 78	GUCACUCCUGAUAAUAACAAU	1180
SEQ ID NO: 79	AUAUUCACUCGACCAGUUUUCUC	1103
SEQ ID NO: 80	UGAACAGGCAUGUUGUAUUAU	996
SEQ ID NO: 81	AAAGGGAAUGCUUCCGGAUCCCA	666
SEQ ID NO: 82	AAGGGAAUGCUUCCGGAUCCCAA	667
SEQ ID NO: 83	UCCGAGGCCUCGGUGACUGCCUG	533
SEQ ID NO: 84	GAACAGGCAUGUUGUAUUAUA	997
SEQ ID NO: 85	GCAAUACAAAGGCAUUAAGACU	219
SEQ ID NO: 86	UUAUUUCAGUCACUCCUGAUAAA	1172
SEQ ID NO: 87	UGAUGAUGGGACUCAAUUGUAUU	1147
SEQ ID NO: 88	AUCUGACCAGUUUUCUCUAAAAG	1109
SEQ ID NO: 89	UCUGACCAGUUUUCUCUAAAGC	1110
SEQ ID NO: 90	CAGAUAAAGCAAUACAAAGGCAUU	212
SEQ ID NO: 91	AGAUAAAGCAAUACAAAGGCAUUA	213
SEQ ID NO: 92	CUUUAACGUGUCUGUGCAGGGUA	600
SEQ ID NO: 93	UUUAACGUGUCUGUGCAGGGUAU	601
SEQ ID NO: 94	ACUCACAUCGUCAUCAGCUGGAU	694
SEQ ID NO: 95	GAUGAUGAUGGGACUCAAUUGUA	1145
SEQ ID NO: 96	AGACUGCGUGGUCCGUAAUCCCA	237
SEQ ID NO: 97	GUGAACAGGCAUGUUGUAUUAUA	995
SEQ ID NO: 98	UUUAUUUCAGUCACUCCUGAUAA	1171
SEQ ID NO: 99	GAUAAGCAAUACAAAGGCAUUAU	214

SEQ ID NO: 100	ACACUCACAUCGUCAUCAGCUGG	692
SEQ ID NO: 101	AGCCGCCUACUUCGGUAUCUAUG	636
SEQ ID NO: 102	CUCACAUCGUCAUCAGCUGGAUG	695
SEQ ID NO: 103	CCGCCUACUUCGGUAUCUAUGAC	638
SEQ ID NO: 104	GCUUUAACGUGUCUGUGCAGGGU	599
SEQ ID NO: 105	GUUCGCCGCCGAUGAUGAUGCA	772
SEQ ID NO: 106	GGCAUUAUAGACUGCGUGGUCCG	229
SEQ ID NO: 107	ACUGCGUGGUCCGUAUUCCCAAG	239
SEQ ID NO: 108	UCAUCUACCGAGCCGCCUACUUC	626
SEQ ID NO: 109	UUUUGCCCCGUACCCGUCUAGCAG	477
SEQ ID NO: 110	CACUCACAUCGUCAUCAGCUGGA	693
SEQ ID NO: 111	AUUAUAGACUGCGUGGUCCGUAU	232
SEQ ID NO: 112	GAGGCCUCGGUGACUGCCUGGUU	536
SEQ ID NO: 113	CUGGAUGAUCGCACAGACUGUCA	711
SEQ ID NO: 114	UUGAUUUUGCCCGUACCCGUCUA	473
SEQ ID NO: 115	AUGAUCGCACAGACUGUCACUGC	715
SEQ ID NO: 116	GGAUGAUCGCACAGACUGUCACU	713
SEQ ID NO: 117	GAUUUUGCCCGUACCCGUCUAGC	475
SEQ ID NO: 118	UAUCAUCUACCGAGCCGCCUACU	624
SEQ ID NO: 119	UAUAGACUGCGUGGUCCGUAUUC	234
SEQ ID NO: 120	CACUGCAGAUAAAGCAAUACAAAG	207
SEQ ID NO: 121	UCACUGCAGAUAAAGCAAUACAAA	206
SEQ ID NO: 122	AUCACUGCAGAUAAAGCAAUACAA	205
SEQ ID NO: 123	CAGCAAGCAGAUACUGCAGAU	195
SEQ ID NO: 124	AGAUCACUGCAGAUAAAGCAAUAC	203
SEQ ID NO: 125	GAUCACUGCAGAUAAAGCAAUACA	204
SEQ ID NO: 126	AAGCAGAUACUGCAGAUAAAGCA	199
SEQ ID NO: 127	AGCAGAUACUGCAGAUAAAGCAA	200
SEQ ID NO: 128	CCAGCAAGCAGAUACUGCAGAU	194
SEQ ID NO: 129	CAGAUACUGCAGAUAAAGCAAUA	202
SEQ ID NO: 130	UGAUAAAUAACAAAUUUGGAGAA	1188
SEQ ID NO: 131	ACUCCUGAUAAAUAACAAAUUUG	1183
SEQ ID NO: 132	CUGAAAGGGAAUUCGAGGCCUC	521
SEQ ID NO: 133	AUGUUGUAUUUAUAACAUAUCU	1005
SEQ ID NO: 134	AAUUCGAGGCCUCGGUGACUGC	530
SEQ ID NO: 135	UGAAAGGGAAUUCGAGGCCUCG	522
SEQ ID NO: 136	GUUGUAUUUAUAACAUAUCUUG	1007
SEQ ID NO: 137	GGAAUUCGAGGCCUCGGUGACU	528
SEQ ID NO: 138	AAGGGAAUUCGAGGCCUCGGUG	525
SEQ ID NO: 139	GGAGCUGAAAGGGAAUUCGAGG	517
SEQ ID NO: 140	CUGGAGCUGAAAGGGAAUUCGA	515

SEQ ID NO: 141	AGCUGAAAGGGAAUCCGAGGCC	519
SEQ ID NO: 142	UGGAGCUGAAAGGGAAUCCGAG	516
SEQ ID NO: 143	GAGCUGAAAGGGAAUCCGAGGC	518
SEQ ID NO: 144	AGGCAUGUUGUAUUUAUAACAUCU	1001
SEQ ID NO: 145	UGUUGUAUUUAUAACAUAUCUU	1006
SEQ ID NO: 146	UUGUAUUUAUAACAUAUCUUGA	1008
SEQ ID NO: 147	CAGGCAUGUUGUAUUUAUAACA	1000
SEQ ID NO: 148	GAAAGGGAAUCCGAGGCCUCGG	523
SEQ ID NO: 149	GGGAAUCCGAGGCCUCGGUGAC	527
SEQ ID NO: 150	AAAGGGAAUCCGAGGCCUCGGU	524
SEQ ID NO: 151	AGGGAAUCCGAGGCCUCGGUGA	526
SEQ ID NO: 152	GUGCUUGUCUUGUAUGAUGAAU	931
SEQ ID NO: 153	CUUCGCCUUCAAAGAUAAAUACA	336
SEQ ID NO: 154	CUGCCUGGUUAAGAUCUACAAU	549
SEQ ID NO: 155	UAUCUAUGACACUGCAAAGGGAA	651
SEQ ID NO: 156	CUUUUGUGCUUGUCUUGUAUGAU	926
SEQ ID NO: 157	GGUGACUGCCUGGUUAAGAUCUA	544
SEQ ID NO: 158	AUGACACUGCAAAGGGAAUGCUU	656
SEQ ID NO: 159	UUCGGUAUCUAUGACACUGCAA	646
SEQ ID NO: 160	UAUUCAUCUGACCAGUUUCUCU	1104
SEQ ID NO: 161	ACUUCGGUAUCUAUGACACUGCA	644
SEQ ID NO: 162	CUGGUUAAGAUCUACAAUCUGA	553
SEQ ID NO: 163	GUAUCUAUGACACUGCAAAGGGA	650
SEQ ID NO: 164	CAAGGGUGCAUGGUCCAAUGUUC	885
SEQ ID NO: 165	AGAUCUACAAUCUGAUGGGAUU	560
SEQ ID NO: 166	UACUUCGGUAUCUAUGACACUGC	643
SEQ ID NO: 167	CAUGGGUGGUGCUUUUGUGCUUG	915
SEQ ID NO: 168	GGUAUUUAUCAUCUACCGAGCCGC	619
SEQ ID NO: 169	GCGUGGUCCGUUUUCCCAAGGAG	242
SEQ ID NO: 170	AUCUAUGACACUGCAAAGGGAAU	652
SEQ ID NO: 171	UGCUIIUUGUGCUUGUCUUGUAUG	924
SEQ ID NO: 172	UGUACCAAGGCUUUAACGUGUCU	590
SEQ ID NO: 173	GGGUGCAUGGUCCAAUGUUCUCA	888
SEQ ID NO: 174	CGCCUUCAAAGAUAAAUACAAGC	339
SEQ ID NO: 175	CAGGGUAUUUAUCAUCUACCGAGC	616
SEQ ID NO: 176	CCUACUUCGGUAUCUAUGACACU	641
SEQ ID NO: 177	UGGUUAAGAUCUACAAUCUGAU	554
SEQ ID NO: 178	UGUGCAGGGUAUUUAUCAUCUACC	612
SEQ ID NO: 179	AAUCUGAUGGGAUUAAGGGCCUG	569
SEQ ID NO: 180	GUCUGUGCAGGGUAUUUAUCAUCU	609
SEQ ID NO: 181	UCUGAUGGGAUUAAGGGCCUGUA	571

SEQ ID NO: 182	UACCAAGGCUUUAACGUGUCUGU	592
SEQ ID NO: 183	AAUAUUCaucugaccaguuuucu	1102
SEQ ID NO: 184	UGACUGCCUGGUUAAGAUCUACA	546
SEQ ID NO: 185	GGGUUGACUCCUAUCCAUUUGA	745
SEQ ID NO: 186	UCUAUGACACUGCAAAGGGAAUG	653
SEQ ID NO: 187	GGUUAAGAUCUACAAAUcugaug	555
SEQ ID NO: 188	GCAGGGUAUUAUCAUCUACCGAG	615
SEQ ID NO: 189	ACUGCCUGGUUAAGAUCUACAAA	548
SEQ ID NO: 190	AUCUGAUGGGAUUAAGGGCCUGU	570
SEQ ID NO: 191	UCGGUAUCUaugacacugcaaag	647
SEQ ID NO: 192	GUACCCGUCUAGCAGCUGAUGUG	485
SEQ ID NO: 193	GGUAUCUaugacacugcaaaggg	649
SEQ ID NO: 194	AGCUGAUGUGGGUAAAGCUGGAG	498
SEQ ID NO: 195	CGUCUAGCAGCUGAUGUGGGUAA	490
SEQ ID NO: 196	AAGGGCCUGUACCAAGGCUUUA	583
SEQ ID NO: 197	UGCCCGUACCCGUCUAGCAGCUG	480
SEQ ID NO: 198	AGCAGCUGAUGUGGGUAAAGCUG	495
SEQ ID NO: 199	GCCCGUACCCGUCUAGCAGCUGA	481
SEQ ID NO: 200	CAGCUGAUGUGGGUAAAGCUGGA	497
SEQ ID NO: 201	AGGGUAUUAUCAUCUACCGAGCC	617
SEQ ID NO: 202	UAUUAUCAUCUACCGAGCCGCCU	621
SEQ ID NO: 203	CCGUACCCGUCUAGCAGCUGAUG	483
SEQ ID NO: 204	CUGAUGGGAUUAAGGGCCUGUAC	572
SEQ ID NO: 205	GUGUCUGUGCAGGGUAUUAUCAU	607
SEQ ID NO: 206	CUGCGUGGUCCGUAUUCCCAAGG	240
SEQ ID NO: 207	UGCGUGGUCCGUAUUCCCAAGGA	241
SEQ ID NO: 208	CCUGGUUAAGAUCUACAAAUcug	552
SEQ ID NO: 209	GUAUGAUGAAAUCAAGAAGUACA	942
SEQ ID NO: 210	AAGAUCUACAAAUcugaugggau	559
SEQ ID NO: 211	CUGUGCAGGGUAUUAUCAUCUAC	611
SEQ ID NO: 212	CUGUACCAAGGCUUUAACGUGUC	589
SEQ ID NO: 213	UAGCAGCUGAUGUGGGUAAAGCU	494
SEQ ID NO: 214	GCAUGGGUGGUGCUUUUGUGCUU	914
SEQ ID NO: 215	CUCGGUGACUGCCUGGUUAAGAU	541
SEQ ID NO: 216	GUCUAGCAGCUGAUGUGGGUAAA	491
SEQ ID NO: 217	UCUACAAAUcugaugggauuaag	563
SEQ ID NO: 218	CUACUUCGGUAUCUAUGACACUG	642
SEQ ID NO: 219	GCAGCUGAUGUGGGUAAAGCUGG	496
SEQ ID NO: 220	CCCGUACCCGUCUAGCAGCUGAU	482
SEQ ID NO: 221	UGUCUGUGCAGGGUAUUAUCAUC	608
SEQ ID NO: 222	UGUGCUUGUCUUGUAUGAUGAAA	930

SEQ ID NO: 223	GUACCAAGGCUUUAACGUGUCUG	591
SEQ ID NO: 224	AAGGGUGCAUGGUCCAAUGUUCU	886
SEQ ID NO: 225	GUGACUGCCUGGUUAAGAUCUAC	545
SEQ ID NO: 226	CUGAUGUGGGUAAAGCUGGAGCU	500
SEQ ID NO: 227	CGUGGUCCGUAUUCCCAAGGAGC	243
SEQ ID NO: 228	UGACACUGCAAAGGGAAUGCUUC	657
SEQ ID NO: 229	GGGAUUAAGGGCCUGUACCAAGG	577
SEQ ID NO: 230	UCUGUGCAGGGUAAUUAUCAUCUA	610
SEQ ID NO: 231	UUAACGUGUCUGUGCAGGGUAUU	602
SEQ ID NO: 232	AGGGCCUGUACCAAGGCUUUAAC	584
SEQ ID NO: 233	UAUGACACUGCAAAGGGAAUGCU	655
SEQ ID NO: 234	CCUCGGUGACUGCCUGGUUAAGA	540
SEQ ID NO: 235	GUGCUUUUGUGCUUGUCUUGUAU	923
SEQ ID NO: 236	UGGGUGGUGCUUUUGUGCUUGUC	917
SEQ ID NO: 237	CCCGUCUAGCAGCUGAUGUGGGU	488
SEQ ID NO: 238	UAAGGGCCUGUACCAAGGCUUUA	582
SEQ ID NO: 239	UUGUGCUUGUCUUGUAUGAUGAA	929
SEQ ID NO: 240	ACAAAUCUGAUGGGAAUUAAGGGC	566
SEQ ID NO: 241	AUCUACAAAUCUGAUGGGAAUUA	562
SEQ ID NO: 242	UGCAGGGUAAUUAUCAUCUACCGA	614
SEQ ID NO: 243	GCCUGUACCAAGGCUUUAACGUG	587
SEQ ID NO: 244	UAAGAUCUACAAAUCUGAUGGGA	558
SEQ ID NO: 245	GCUUUUGUGCUUGUCUUGUAUGA	925
SEQ ID NO: 246	CUACAAAUCUGAUGGGAAUUAAGG	564
SEQ ID NO: 247	UUCAAGGGUGCAUGGUCCAAUGU	883
SEQ ID NO: 248	UGGGAUUAAGGGCCUGUACCAAG	576
SEQ ID NO: 249	CUUCGGUAUCUAUGACACUGCAA	645
SEQ ID NO: 250	ACCAAGGCUUUAACGUGUCUGUG	593
SEQ ID NO: 251	GGCAUGGGUGGUGCUUUUGUGCU	913
SEQ ID NO: 252	GUUAAGAUCUACAAAUCUGAUGG	556
SEQ ID NO: 253	UACCCGUCUAGCAGCUGAUGUGG	486
SEQ ID NO: 254	CUAUGACACUGCAAAGGGAAUGC	654
SEQ ID NO: 255	UCUAGCAGCUGAUGUGGGUAAAG	492
SEQ ID NO: 256	CUGCAAAGGGAAUGCUUCCGGAU	662
SEQ ID NO: 257	UUGCCCGUACCCGUCUAGCAGCU	479
SEQ ID NO: 258	GGGUAAUUAUCAUCUACCGAGCCG	618
SEQ ID NO: 259	CCCUCUUGAUUUUGCCCGUACCC	468
SEQ ID NO: 260	CGUACCCGUCUAGCAGCUGAUGU	484
SEQ ID NO: 261	UACAAAUCUGAUGGGAAUUAAGGG	565
SEQ ID NO: 262	GUGUACCCUCUUGAUUUUGCCCG	463
SEQ ID NO: 263	GGCCUGUACCAAGGCUUUAACGU	586

SEQ ID NO: 264	GAUGGGAUUAAGGGCCUGUACCA	574
SEQ ID NO: 265	GUAUUAUCAUCUACCGAGCCGCC	620
SEQ ID NO: 266	GGGCCUGUACCAAGGCUUUAACG	585
SEQ ID NO: 267	UGAUGGGAUUAAGGGCCUGUACC	573
SEQ ID NO: 268	UAACGUGUCUGUGCAGGGUAUUA	603
SEQ ID NO: 269	AAGGCAUUAUAGACUGCGUGGUC	227
SEQ ID NO: 270	ACUUCCCCACCCAGGCUCUUAAC	314
SEQ ID NO: 271	CAAUGUCAUCAGAUACUCCCCCA	300
SEQ ID NO: 272	AUGUCAUCAGAUACUCCCCACC	302
SEQ ID NO: 273	AAUGUCAUCAGAUACUCCCCAC	301
SEQ ID NO: 274	CCAAUGUCAUCAGAUACUCCCC	299
SEQ ID NO: 275	UACUCCCCACCCAGGCUCUUA	313
SEQ ID NO: 276	AUCUACCGAGCCGCCUACUUCGG	628

It is to be understood that SEQ ID NOs: 1 to 276 relate to human (Homo sapiens) mRNA sequences.

DISEASE/CONDITIONS

The present invention further provides methods of treatment of a subject in need thereof. The treatment methods of the invention include administering, in a therapeutically effective amount, an inhibitor of expression of the SLC25A5 gene, such as an siRNA that targets an mRNA transcribed from the SLC25A5 gene, to a subject, e.g., a subject that would benefit from a reduction or inhibition of the expression of the SLC25A5 gene. Alternatively, the treatment methods of the invention include administering, in a therapeutically effective amount, an inhibitor of function of the gene product of SLC25A5 gene, i.e., the protein ANT2, to a subject, e.g., a subject that would benefit from a reduction or inhibition of the function of ANT2.

The disease to be treated is related to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or adipogenesis.

The inhibitor according to the invention may be used in the prevention and/or treatment of a metabolic disease or disorder. As used herein, the term "metabolic disease" refers to a disease or condition affecting a metabolic process in a subject and is often caused by disruption of normal metabolism.

The patient to be treated may be a patient that already has a metabolic disease or disorder or that is at risk of developing a metabolic disease or disorder. That is, in certain embodiments, the inhibitor of the present invention may be used in the treatment and/or management of an existing metabolic disease or disorder. Treatment and/or management of an existing metabolic disease or disorder with the inhibitor of the present invention may prevent worsening of the metabolic disease or disorder and/or reverse the metabolic disease

or disorder. In some instances, treatment of an existing metabolic disease or disorder with the inhibitor of the present invention may even cure the metabolic disease or disorder. In certain embodiments, the inhibitor of the present invention may be used to prevent manifestation of a metabolic disease or disorder in a patient that is at risk of developing a metabolic disease or disorder.

- 5 The skilled person is capable of diagnosing whether a patient has a metabolic disease or disorder or is at risk of developing a metabolic disease or disorder. For example, a metabolic disease or disorder may be diagnosed based weight gain and/or one or more blood markers, including, without limitation, blood glucose levels, blood insulin levels, blood free fatty acid levels, blood HbA1c levels, blood fibrinogen levels, blood cholesterol levels and blood triglyceride levels. The skilled person is aware of threshold values
10 of one or more blood markers that indicate the presence of a metabolic disease or disorder or the risk of developing a metabolic disease or disorder.

- In certain embodiments, the metabolic disease is fatty liver disease, in particular non-alcoholic fatty liver disease (NAFLD). As used herein "fatty-liver disease" refers to a disease wherein fat is excessively accumulated in the liver and can cause severe diseases such as chronic hepatitis and hepatic cirrhosis. In
15 patients with fatty liver disease, lipids, particularly neutral fat, accumulate in hepatocytes to the extent that the amount exceeds the physiologically permissible range. From a biochemical point of view, a standard for judgment of fatty liver is that the weight of neutral fat is about 10% (100 mg/g wet weight) or more of the wet weight of hepatic tissue. Fatty liver disease is generally detected by observation of elevated serum levels of liver-specific enzymes such as the transaminases ALT and AST, which serve as indices of
20 hepatocyte injury, as well as by presentation of symptoms, which include fatigue and pain in the region of the liver, though definitive diagnosis often requires a biopsy and may be supported by imaging such as ultrasound and/or MRI. The term "NAFLD" or "non-alcoholic fatty liver disease", as used herein, relates to a condition occurring when fat is deposited in the liver (steatosis) not due to excessive alcohol use. It is related to insulin resistance and the metabolic syndrome.

- 25 In a preferred embodiment, the fatty liver disease is Non-Alcoholic SteatoHepatitis (NASH). NASH, as used herein, refers to a liver disease characterized by an accumulation of fat (lipid droplets), along with inflammation and degeneration of hepatocytes. Once initiated, the disease is accompanied with a high risk of cirrhosis, a state wherein liver functions are altered that can progress to liver insufficiency. Thereafter, NASH often progresses to liver cancer.

- 30 In certain embodiments, the metabolic disease is obesity. The term "obesity" as used herein refers to a condition in which the natural energy reserve, stored in the fatty tissue of animals, in particular humans and other mammals, is increased to a point where it is associated with certain health conditions or increased mortality. The term "obese" as used herein is defined for an adult human as having a body mass index (BMI) greater than 30. Obesity is commonly associated with excessive body weight gain, in particular diet-
35 induced body weight gain. "(Diet-induced) body weight gain" is defined herein as body weight gain resulting from an excessive dietary intake, including an excessive dietary intake of fat, in particular

saturated fat, and optionally an excessive dietary intake of simple sugars, including sucrose and fructose. For a given subject, an excessive dietary intake, in particular of fat and optionally of simple sugars, refers to the consumption of an amount of diet, in particular of fat and optionally of simple sugars, higher than the amount necessary to meet the physiological needs and maintain the energy balance of said subject. The effect of a treatment on reduction of - or prevention - of diet-induced body weight gain in a subject can be assessed by comparing body weight gain observed in a subject receiving the treatment with those observed in the same subject without treatment receiving the same diet and having the same level of physical activity.

In certain embodiments, a patient is at risk of developing obesity if the patient has a BMI greater than 25. In certain embodiments, a patient is obese if the patient has a BMI greater than 30.

The term “body mass index” as used herein means the ratio of weight in kg divided by the height in metres, squared.

A “disease associated with adipogenesis” refers to a medical condition characterized by the abnormal proliferation and differentiation of adipocytes (fat cells) within the body, leading to an excessive accumulation of adipose tissue. This condition often results in health complications such as obesity, metabolic disorders, and associated comorbidities.

Within the present invention, a “reduction of adipogenesis” refers to a medical or pharmaceutical intervention designed to decrease the formation and accumulation of adipocytes within the body. A reduction in adipogenesis may be determined and/or quantified based on the size and/or number of adipocytes in a tissue sample obtained from a patient. Alternatively, or in addition, a reduction in adipogenesis may be determined and/or quantified by gene expression analysis, measurement of adipogenic markers (i.e., by ELISA), assessment of lipid accumulation in a sample and/or measurement of triglyceride levels in cells or tissues.

Thus, in a particular embodiment, the invention relates to an inhibitor suitable for use, or for use, in prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

INHIBITORS

Inhibitors of the invention include nucleic acids such as siRNAs, antibodies and antigen binding fragments thereof, e.g., monoclonal antibodies, polypeptides, antibody–drug conjugates, and small molecules.

Preferred are nucleic acids such as siRNA.

Certain preferred features of inhibitors of the invention, where these are oligonucleosides such as siRNA, are given below.

In certain embodiments, the nucleic acid comprises a first strand comprising a sequence that is at least partially complementary to a portion of RNA transcribed from the *SLC25A5* gene (SEQ ID NO: 1381). In a preferred embodiment, the nucleic acid comprises a first strand comprising a sequence that is at least partially complementary to an *SLC25A5* mRNA.

- 5 In certain embodiments, the nucleic acid for inhibiting expression of the *SLC25A5* gene comprises a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is:

(i) at least partially complementary to a portion of RNA transcribed from the *SLC25A5* gene, and

- (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of
10 SEQ ID NO:277-552.

In certain embodiments, the first strand comprises nucleosides 2-18 of any one of the sequences set forth in SEQ ID NO: 277-552.

In certain embodiments, the first strand comprises any one of SEQ ID NO: 277-552.

- 15 In certain embodiments, the nucleic acid for inhibiting expression of the *SLC25A5* gene comprises a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is:

(i) at least partially complementary to a portion of RNA transcribed from the *SLC25A5* gene, and

(ii) comprises at least 21 contiguous nucleosides differing by 0 or 1 nucleosides from any one of
SEQ ID NO: 277-552.

- 20 In certain embodiments, the first strand comprises nucleosides 2-22 of any one of the sequences set forth in SEQ ID NO: 277-552.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO:553-828; wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

- 25 In certain embodiments, the second strand comprises any one of SEQ ID NO: 553-828.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 19 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 553-828; wherein the second strand has a region of at least 85% complementarity over the 19 contiguous nucleosides to the first strand.

In certain embodiments, the second strand comprises a nucleoside sequence of at least 21 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 553-828; wherein the second strand has a region of at least 85% complementarity over the 21 contiguous nucleosides to the first strand.

In certain embodiments, the nucleic acid comprises a first strand that comprises, consists of, or consists essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of SEQ ID NO: 277-552;
 5 and a second strand that comprises, consists of, or consists essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of SEQ ID NO: 553-828.

It is preferred herein that the duplex region is formed between a first (antisense) strand and a complementary second (sense) strand. Exemplary pairs of complementary antisense and sense strands are listed in Table 2
 10 below:

Table 2:

SEQ ID NO (AS)	Antisense Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO (SS)	Sense Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleotide Sequence)	Correspondi ng positions on ENST00000 317881.9
SEQ ID NO: 277	CCCAUUUUAACACAGUAAAUAGU	SEQ ID NO: 553	UAUUUACUGGUUGAA AAUGGG	1072-1094
SEQ ID NO: 278	ACGCAGUCUAUAAUGCCUUUGUA	SEQ ID NO: 554	CAAAGGCAUUUAUAGA CUGCGU	223-245
SEQ ID NO: 279	GUGUACUUCUUGAUUUCAUCAUA	SEQ ID NO: 555	UGAUGAAAUCAAGAA GUACAC	943-965
SEQ ID NO: 280	AUACAAUUGAGUCCCAUCAUCAU	SEQ ID NO: 556	GAUGAUGGGACUCAA UUGUAU	1146-1168
SEQ ID NO: 281	GGACCACGCAGUCUAUAAUGCCU	SEQ ID NO: 557	GCAUUAUAGACUGCG UGGUCC	228-250
SEQ ID NO: 282	UUGUUAUUUAUCAGGAGUGACUG	SEQ ID NO: 558	GUCACUCCUGAUAAA UAACAA	1178-1200
SEQ ID NO: 283	CAGUCUAUAAUGCCUUUGUAUUG	SEQ ID NO: 559	AUACAAAGGCAUUAU AGACUG	220-242
SEQ ID NO: 284	AUAGAUACCGAAGUAGGCGGCUC	SEQ ID NO: 560	GCCGCCUACUUCGGUA UCUAU	635-657
SEQ ID NO: 285	UAGAUACCGAAGUAGGCGGCUCG	SEQ ID NO: 561	AGCCGCCUACUUCGGU AUCUA	634-656
SEQ ID NO: 286	GGAAUACGGACCACGCAGUCUAU	SEQ ID NO: 562	AGACUGCGUGGUCCG UAUUC	235-257

SEQ ID NO: 287	CAGCUGAUGACGAUGUGAGUGUU	SEQ ID NO: 563	CACUCACAUCGUCAUC AGCUG	691-713
SEQ ID NO: 288	AUUUAUCUUUGAAGGCGAAGUUA	SEQ ID NO: 564	ACUUCGCCUUCAAAAG AUAAAU	333-355
SEQ ID NO: 289	GUGUCAUAGAUACCGAAGUAGGC	SEQ ID NO: 565	CUACUUCGGUAUCUA UGACAC	640-662
SEQ ID NO: 290	UUCCCAUUUUCAACCAGUAAAUA	SEQ ID NO: 566	UUUACUGGUUGAAAA UGGGAA	1074-1096
SEQ ID NO: 291	GCUGCUAGACGGGUACGGGCAAA	SEQ ID NO: 567	UGCCCGUACCCGUCUA GCAGC	478-500
SEQ ID NO: 292	CAGUUCUUUGCGCCCUGACUGC	SEQ ID NO: 568	AGUCAGGGCGCAAAG GAACUG	792-814
SEQ ID NO: 293	CUUCCCAUUUUCAACCAGUAAAUA	SEQ ID NO: 569	UUACUGGUUGAAAAU GGGAAG	1075-1097
SEQ ID NO: 294	AGAUACCGAAGUAGGCGGCUCGG	SEQ ID NO: 570	GAGCCGCCUACUUCGG UAUCU	633-655
SEQ ID NO: 295	UUAACCAGGCAGUCACCGAGGCC	SEQ ID NO: 571	CCUCGGUGACUGCCUG GUUAA	538-560
SEQ ID NO: 296	AUCAUCCAGCUGAUGACGAUGUG	SEQ ID NO: 572	CAUCGUCAUCAGCUG GAUGAU	697-719
SEQ ID NO: 297	AUUUAUCAGGAGUGACUGAAAUA	SEQ ID NO: 573	UUUCAGUCACUCCUG AUAAAU	1173-1195
SEQ ID NO: 298	GACAGUCUGUGCGAUCAUCCAGC	SEQ ID NO: 574	UGGAUGAUCGCACAG ACUGUC	710-732
SEQ ID NO: 299	UCUAUAAUGCCUUUGUAUUGCUU	SEQ ID NO: 575	GCAAUACAAAGGCAU UAUAGA	217-239
SEQ ID NO: 300	UAACCAGGCAGUCACCGAGGCCU	SEQ ID NO: 576	GCCUCGGUGACUGCCU GGUUA	537-559
SEQ ID NO: 301	CCCUGCACAGACACGUUAAAGCC	SEQ ID NO: 577	CUUUAACGUGUCUGU GCAGGG	598-620
SEQ ID NO: 302	CACGCAGUCUAUAAUGCCUUUGU	SEQ ID NO: 578	AAAGGCAUUAUAGAC UGCGUG	224-246
SEQ ID NO: 303	UAAUACAACAUGCCUGUUCACAG	SEQ ID NO: 579	GUGAACAGGCAUGUU GUAUUA	993-1015
SEQ ID NO: 304	UUAAGAGAAAACUGGUCAGAUGA	SEQ ID NO: 580	AUCUGACCAGUUUUC UCUUA	1107-1129
SEQ ID NO: 305	UGCACAGACACGUUAAAGCCUUG	SEQ ID NO: 581	AGGCUUUAACGUGUC UGUGCA	595-617
SEQ ID NO: 306	GUUCCUUUGCGCCCUGACUGCAU	SEQ ID NO: 582	GCAGUCAGGGCGCAA AGGAAC	790-812

SEQ ID NO: 307	GUGACAGUCUGUGCGAUCAUCCA	SEQ ID NO: 583	GAUGAUCGCACAGAC UGUCAC	712-734
SEQ ID NO: 308	ACCACGCAGUCUAUAAUGCCUUU	SEQ ID NO: 584	AGGCAUUAUAGACUG CGUGGU	226-248
SEQ ID NO: 309	CAGUGACAGUCUGUGCGAUCAUC	SEQ ID NO: 585	UGAUCGCACAGACUG UCACUG	714-736
SEQ ID NO: 310	UUGGGAAUACGGACCACGCAGUC	SEQ ID NO: 586	CUGCGUGGUCCGUU UCCCAA	238-260
SEQ ID NO: 311	GUCUAUAAUGCCUUUGUAUUGCU	SEQ ID NO: 587	CAAUACAAAGGCAUU AUAGAC	218-240
SEQ ID NO: 312	UGUGCGAUCAUCCAGCUGAUGAC	SEQ ID NO: 588	CAUCAGCUGGAUGAU CGCACA	703-725
SEQ ID NO: 313	ACGGACCACGCAGUCUAUAAUGC	SEQ ID NO: 589	AUUAUAGACUGCGUG GUCCGU	230-252
SEQ ID NO: 314	UGCUAGACGGGUACGGGCAAAAU	SEQ ID NO: 590	UUUGCCCGUACCCGUC UAGCA	476-498
SEQ ID NO: 315	UCAUCCAGCUGAUGACGAUGUGA	SEQ ID NO: 591	ACAUCGUCAUCAGCU GGAUGA	696-718
SEQ ID NO: 316	CGGGUACGGGCAAAAUCAAGAGG	SEQ ID NO: 592	UCUUGAUUUUGCCCG UACCCG	469-491
SEQ ID NO: 317	AAUACGGACCACGCAGUCUAUAA	SEQ ID NO: 593	AUAGACUGCGUGGUC CGUAUU	233-255
SEQ ID NO: 318	UCAUAGAUACCGAAGUAGGCGGC	SEQ ID NO: 594	CGCCUACUUCGGUAUC UAUGA	637-659
SEQ ID NO: 319	GGGAAUACGGACCACGCAGUCUA	SEQ ID NO: 595	GACUGCGUGGUCCGU AUUCCC	236-258
SEQ ID NO: 320	GUGCGAUCAUCCAGCUGAUGACG	SEQ ID NO: 596	UCAUCAGCUGGAUGA UCGCAC	702-724
SEQ ID NO: 321	UACGGACCACGCAGUCUAUAAUG	SEQ ID NO: 597	UUAUAGACUGCGUGG UCCGUA	231-253
SEQ ID NO: 322	UGUCAUAGAUACCGAAGUAGGCG	SEQ ID NO: 598	CCUACUUCGGUAUCU AUGACA	639-661
SEQ ID NO: 323	UAUCAGGAGUGACUGAAAUAAAA	SEQ ID NO: 599	UUAUUUCAGUCACUC CUGAUA	1170-1192
SEQ ID NO: 324	UGCGAUCAUCCAGCUGAUGACGA	SEQ ID NO: 600	GUCAUCAGCUGGAUG AUCGCA	701-723
SEQ ID NO: 325	CUAGACGGGUACGGGCAAAAUCA	SEQ ID NO: 601	AUUUUGCCCGUACCCG UCUAG	474-496
SEQ ID NO: 326	GAUCCGGAAGCAUUCCCUUUGCA	SEQ ID NO: 602	CAAAGGGAAUGCUUC CGGAUC	663-685

SEQ ID NO: 327	GCACAGACACGUUAAAGCCUUGG	SEQ ID NO: 603	AAGGCUUUAACGUGU CUGUGC	594-616
SEQ ID NO: 328	CCACGCAGUCUAUAAUGCCUUUG	SEQ ID NO: 604	AAGGCAUUAUAGACU GCGUGG	225-247
SEQ ID NO: 329	GACGGGUACGGGCAAAAUCAAGA	SEQ ID NO: 605	UUGAUUUUGCCCGUA CCCGUC	471-493
SEQ ID NO: 330	GAUACCGAAGUAGGCGGCUCGGU	SEQ ID NO: 606	CGAGCCGCCUACUUCG GUAUC	632-654
SEQ ID NO: 331	GUAGGCGGCUCGGUAGAUGAUAA	SEQ ID NO: 607	AUCAUCUACCGAGCCG CCUAC	623-645
SEQ ID NO: 332	AGACGGGUACGGGCAAAAUCAAG	SEQ ID NO: 608	UGAUUUUGCCCGUAC CCGUCU	472-494
SEQ ID NO: 333	UAGGCGGCUCGGUAGAUGAUAAU	SEQ ID NO: 609	UAUCAUCUACCGAGCC GCCUA	622-644
SEQ ID NO: 334	AAGUAGGCGGCUCGGUAGAUGAU	SEQ ID NO: 610	CAUCUACCGAGCCGCC UACUU	625-647
SEQ ID NO: 335	CUUUGAAGGCGAAGUUAAGAGCC	SEQ ID NO: 611	CUCUUAACUUCGCCUU CAAAG	327-349
SEQ ID NO: 336	CGAAGUUAAGAGCCUGGGUGGGG	SEQ ID NO: 612	CCACCCAGGCUCUUA CUUCG	318-340
SEQ ID NO: 337	CCCUGCUCCUUGGGAAUACGGAC	SEQ ID NO: 613	CCGUAUUCCCAAGGA GCAGGG	247-269
SEQ ID NO: 338	GAAGGACAGAACUCCUGCUCCU	SEQ ID NO: 614	GAGCAGGGAGUUCUG UCCUUC	260-282
SEQ ID NO: 339	AGAACUCCUGCUCCUUGGGAAU	SEQ ID NO: 615	UCCCAAGGAGCAGGG AGUUCU	253-275
SEQ ID NO: 340	CCUGCUCCUUGGGAAUACGGACC	SEQ ID NO: 616	UCCGUAUUCCCAAGG AGCAGG	246-268
SEQ ID NO: 341	CAGAAGGACAGAACUCCUGCUC	SEQ ID NO: 617	GCAGGGAGUUCUGUC CUUCUG	262-284
SEQ ID NO: 342	CUGCUCCUUGGGAAUACGGACCA	SEQ ID NO: 618	GUCCGUAUUCCCAAG GAGCAG	245-267
SEQ ID NO: 343	AGAAGGACAGAACUCCUGCUCC	SEQ ID NO: 619	AGCAGGGAGUUCUGU CCUUCU	261-283
SEQ ID NO: 344	AAGGACAGAACUCCUGCUCCU	SEQ ID NO: 620	GGAGCAGGGAGUUCU GUCCUU	259-281
SEQ ID NO: 345	GAACUCCUGCUCCUUGGGAAUA	SEQ ID NO: 621	UUCCCAAGGAGCAGG GAGUUC	252-274
SEQ ID NO: 346	AGGACAGAACUCCUGCUCCUUG	SEQ ID NO: 622	AGGAGCAGGGAGUUC UGUCCU	258-280

SEQ ID NO: 347	GAAGUUAAGAGCCUGGGUGGGGA	SEQ ID NO: 623	CCCACCCAGGCUCUUA ACUUC	317-339
SEQ ID NO: 348	UCUUUGAAGGCGAAGUUAAGAGC	SEQ ID NO: 624	UCUUAACUUCGCCUUC AAAGA	328-350
SEQ ID NO: 349	UAUUUAUCAGGAGUGACUGAAAU	SEQ ID NO: 625	UUCAGUCACUCCUGA UAAUA	1174-1196
SEQ ID NO: 350	GUUAUUUAUCAGGAGUGACUGAA	SEQ ID NO: 626	CAGUCACUCCUGAUA AAUAAC	1176-1198
SEQ ID NO: 351	UUAUUUUAUCAGGAGUGACUGAAA	SEQ ID NO: 627	UCAGUCACUCCUGAU AAAUAA	1175-1197
SEQ ID NO: 352	AAAUACAAUUGAGUCCCAUCAUC	SEQ ID NO: 628	UGAUGGGACUCAAUU GUUUU	1148-1170
SEQ ID NO: 353	AAAAUACAAUUGAGUCCCAUCAU	SEQ ID NO: 629	GAUGGGACUCAAUUG UAUUUU	1149-1171
SEQ ID NO: 354	AUUUGUUAUUUAUCAGGAGUGAC	SEQ ID NO: 630	CACUCCUGAUAAAUA ACAAAU	1180-1202
SEQ ID NO: 355	GAGAAAACUGGUCAGAUAUAU	SEQ ID NO: 631	AUUCAUCUGACCAGU UUUCUC	1103-1125
SEQ ID NO: 356	AUAUAAUACAACAUGCCUGUUA	SEQ ID NO: 632	AACAGGCAUGUUGUA UUAUAU	996-1018
SEQ ID NO: 357	UGGGAUCCGGAAGCAUUCCCUU	SEQ ID NO: 633	AGGGAAUGCUUCCGG AUCCCA	666-688
SEQ ID NO: 358	UUGGGAUCCGGAAGCAUUCCCU	SEQ ID NO: 634	GGGAAUGCUUCCGGA UCCCAA	667-689
SEQ ID NO: 359	CAGGCAGUCACCGAGGCCUCGGA	SEQ ID NO: 635	CGAGGCCUCGGUGAC UGCCUG	533-555
SEQ ID NO: 360	UAUAUAAUACAACAUGCCUGUUC	SEQ ID NO: 636	ACAGGCAUGUUGUAU UAUAUA	997-1019
SEQ ID NO: 361	AGUCUAUAAUGCCUUUGUAUUGC	SEQ ID NO: 637	AAUACAAAGGCAUUA UAGACU	219-241
SEQ ID NO: 362	UUUAUCAGGAGUGACUGAAUAA	SEQ ID NO: 638	AUUUCAGUCACUCCU GAUAAA	1172-1194
SEQ ID NO: 363	AAUACAAUUGAGUCCCAUCAUCA	SEQ ID NO: 639	AUGAUGGGACUCAAU UGUAUU	1147-1169
SEQ ID NO: 364	CUUUAAAGAGAAAACUGGUCAGAU	SEQ ID NO: 640	CUGACCAGUUUUCUC UUAAG	1109-1131
SEQ ID NO: 365	GCUUUAAAGAGAAAACUGGUCAGA	SEQ ID NO: 641	UGACCAGUUUUCUCU UAAAGC	1110-1132
SEQ ID NO: 366	AAUGCCUUUGUAUUGCUUAUCUG	SEQ ID NO: 642	GAUAAGCAAUACAAA GGCAUU	212-234

SEQ ID NO: 367	UAAUGCCUUUGUAUUGCUUAUCU	SEQ ID NO: 643	AUAAGCAAUACAAAG GCAUUA	213-235
SEQ ID NO: 368	UACCCUGCACAGACACGUUAAAG	SEQ ID NO: 644	UUAACGUGUCUGUGC AGGGUA	600-622
SEQ ID NO: 369	AUACCCUGCACAGACACGUUAAA	SEQ ID NO: 645	UAACGUGUCUGUGCA GGGUAU	601-623
SEQ ID NO: 370	AUCCAGCUGAUGACGAUGUGAGU	SEQ ID NO: 646	UCACAUCGUCAUCAGC UGGAU	694-716
SEQ ID NO: 371	UACAAUUGAGUCCCAUCAUCAUC	SEQ ID NO: 647	UGAUGAUGGGACUCA AUUGUA	1145-1167
SEQ ID NO: 372	UGGGAAUACGGACCACGCAGUCU	SEQ ID NO: 648	ACUGCGUGGUCCGUA UUCCCA	237-259
SEQ ID NO: 373	UAUAAUACAACAUGCCUGUUCAC	SEQ ID NO: 649	GAACAGGCAUGUUGU AUUUAU	995-1017
SEQ ID NO: 374	UUAUCAGGAGUGACUGAAUAAA	SEQ ID NO: 650	UAUUUCAGUCACUCC UGAUAA	1171-1193
SEQ ID NO: 375	AUAAUGCCUUUGUAUUGCUUAUC	SEQ ID NO: 651	UAAGCAAUACAAAGG CAUUAU	214-236
SEQ ID NO: 376	CCAGCUGAUGACGAUGUGAGUGU	SEQ ID NO: 652	ACUCACAUCGUCAUCA GCUGG	692-714
SEQ ID NO: 377	CAUAGAUACCGAAGUAGGCGGCU	SEQ ID NO: 653	CCGCCUACUUCGGUAU CUAUG	636-658
SEQ ID NO: 378	CAUCCAGCUGAUGACGAUGUGAG	SEQ ID NO: 654	CACAUCGUCAUCAGCU GGAUG	695-717
SEQ ID NO: 379	GUCAUAGAUACCGAAGUAGGCGG	SEQ ID NO: 655	GCCUACUUCGGUAUC UAUGAC	638-660
SEQ ID NO: 380	ACCCUGCACAGACACGUUAAAGC	SEQ ID NO: 656	UUUAACGUGUCUGUG CAGGGU	599-621
SEQ ID NO: 381	UGCAUCAUCAUGCGGCGGCGAAC	SEQ ID NO: 657	UCGCCGCCGCAUGAUG AUGCA	772-794
SEQ ID NO: 382	CGGACCACGCAGUCUAUAAUGCC	SEQ ID NO: 658	CAUUAUAGACUGCGU GGUCCG	229-251
SEQ ID NO: 383	CUUGGGAAUACGGACCACGCAGU	SEQ ID NO: 659	UGCGUGGUCCGUAAU CCCAAG	239-261
SEQ ID NO: 384	GAAGUAGGCGGCUCGGUAGAUGA	SEQ ID NO: 660	AUCUACCGAGCCGCCU ACUUC	626-648
SEQ ID NO: 385	CUGCUAGACGGGUACGGGCAAAA	SEQ ID NO: 661	UUGCCCGUACCCGUCU AGCAG	477-499
SEQ ID NO: 386	UCCAGCUGAUGACGAUGUGAGUG	SEQ ID NO: 662	CUCACAUCGUCAUCAG CUGGA	693-715

SEQ ID NO: 387	AUACGGACCACGCAGUCUAUAAU	SEQ ID NO: 663	UAUAGACUGCGUGGU CCGU AU	232-254
SEQ ID NO: 388	AACCAGGCAGUCACCGAGGCCUC	SEQ ID NO: 664	GGCCUCGGUGACUGCC UGGUU	536-558
SEQ ID NO: 389	UGACAGUCUGUGCGAUCAUCCAG	SEQ ID NO: 665	GGAUGAUCGCACAGA CUGUCA	711-733
SEQ ID NO: 390	UAGACGGGUACGGGCAAAAUCAA	SEQ ID NO: 666	GAUUUUGCCCGUACCC GUCUA	473-495
SEQ ID NO: 391	GCAGUGACAGUCUGUGCGAUCAU	SEQ ID NO: 667	GAUCGCACAGACUGU CACUGC	715-737
SEQ ID NO: 392	AGUGACAGUCUGUGCGAUCAUCC	SEQ ID NO: 668	AUGAUCGCACAGACU GUCACU	713-735
SEQ ID NO: 393	GCUAGACGGGUACGGGCAAAAUUC	SEQ ID NO: 669	UUUUGCCCGUACCCGU CUAGC	475-497
SEQ ID NO: 394	AGUAGGCGGCUCGGUAGAUGAU	SEQ ID NO: 670	UCAUCUACCGAGCCGC CUACU	624-646
SEQ ID NO: 395	GAAUACGGACCACGCAGUCUAUA	SEQ ID NO: 671	UAGACUGCGUGGUCC GUAUUC	234-256
SEQ ID NO: 396	CUUUGUAUUGCUUAUCUGCAGUG	SEQ ID NO: 672	CUGCAGAUAAAGCAAU ACAAAG	207-229
SEQ ID NO: 397	UUUGUAUUGCUUAUCUGCAGUGA	SEQ ID NO: 673	ACUGCAGAUAAAGCAA UACAAA	206-228
SEQ ID NO: 398	UUGUAUUGCUUAUCUGCAGUGAU	SEQ ID NO: 674	CACUGCAGAUAAAGCAA AUACAA	205-227
SEQ ID NO: 399	UAUCUGCAGUGAUCUGCUUGCUG	SEQ ID NO: 675	GCAAGCAGAUACACUG CAGAU	195-217
SEQ ID NO: 400	GU AUUGCUUAUCUGCAGUGAUCU	SEQ ID NO: 676	AUCACUGCAGAUAAAG CAAUAC	203-225
SEQ ID NO: 401	UGUAUUGCUUAUCUGCAGUGAUC	SEQ ID NO: 677	UCACUGCAGAUAAAGC AAUACA	204-226
SEQ ID NO: 402	UGC UUAUCUGCAGUGAUCUGCUU	SEQ ID NO: 678	GCAGAUACUGCAGAU UAAGCA	199-221
SEQ ID NO: 403	UUGCUUAUCUGCAGUGAUCUGCU	SEQ ID NO: 679	CAGAUACUGCAGAU AAGCAA	200-222
SEQ ID NO: 404	AUCUGCAGUGAUCUGCUUGCUGG	SEQ ID NO: 680	AGCAAGCAGAUACU GCAGAU	194-216
SEQ ID NO: 405	UAUUGCUUAUCUGCAGUGAUCUG	SEQ ID NO: 681	GAUCACUGCAGAUAA GCAAUA	202-224
SEQ ID NO: 406	UUCUCCAAAUUUGUUAUUUAUCA	SEQ ID NO: 682	AUAAAUAACAAUUU GGAGAA	1188-1210

SEQ ID NO: 407	CAAAUUUGUUAUUUAUCAGGAGU	SEQ ID NO: 683	UCCUGAUAAAUAACA AAUUUG	1183-1205
SEQ ID NO: 408	GAGGCCUCGGAAUCCCUUUCAG	SEQ ID NO: 684	GAAAGGGAAUCCGA GGCCUC	521-543
SEQ ID NO: 409	AGAU AUGUUAUAUAAUACAACAU	SEQ ID NO: 685	GUUGAUUAUAUAAC AUAUCU	1005-1027
SEQ ID NO: 410	GCAGUCACCGAGGCCUCGGAAUU	SEQ ID NO: 686	UCCGAGGCCUCGGU GACUGC	530-552
SEQ ID NO: 411	CGAGGCCUCGGAAUCCCUUUCA	SEQ ID NO: 687	AAAGGGAAUCCGAG GCCUCG	522-544
SEQ ID NO: 412	CAAGAU AUGUUAUAUAAUACAAC	SEQ ID NO: 688	UGAUUAUAUAACAU AUCUUG	1007-1029
SEQ ID NO: 413	AGUCACCGAGGCCUCGGAAUCC	SEQ ID NO: 689	AAUCCGAGGCCUCG GUGACU	528-550
SEQ ID NO: 414	CACCGAGGCCUCGGAAUCCCUU	SEQ ID NO: 690	GGGAAUCCGAGGCC UCGGUG	525-547
SEQ ID NO: 415	CCUCGGAAUCCCUUUCAGCUCC	SEQ ID NO: 691	AGCUGAAAGGGAAUU CCGAGG	517-539
SEQ ID NO: 416	UCGGAAUCCCUUUCAGCUCCAG	SEQ ID NO: 692	GGAGCUGAAAGGGAA UCCGA	515-537
SEQ ID NO: 417	GGCCUCGGAAUCCCUUUCAGCU	SEQ ID NO: 693	CUGAAAGGGAAUCC GAGGCC	519-541
SEQ ID NO: 418	CUCGGAAUCCCUUUCAGCUCCA	SEQ ID NO: 694	GAGCUGAAAGGGAAU UCCGAG	516-538
SEQ ID NO: 419	GCCUCGGAAUCCCUUUCAGCUC	SEQ ID NO: 695	GCUGAAAGGGAAUUC CGAGGC	518-540
SEQ ID NO: 420	AUGUUAUAUAAUACAACAUGCCU	SEQ ID NO: 696	GCAUGUUGUAUUAUA UAACAU	1001-1023
SEQ ID NO: 421	AAGAU AUGUUAUAUAAUACAACA	SEQ ID NO: 697	UUGAUUAUAUAACA UAUCUU	1006-1028
SEQ ID NO: 422	UCAAGAU AUGUUAUAUAAUACAA	SEQ ID NO: 698	GUAUUAUAUAACAU UCUUGA	1008-1030
SEQ ID NO: 423	UGUUAUAUAAUACAACAUGCCUG	SEQ ID NO: 699	GGCAUGUUGUAUUAU AUAACA	1000-1022
SEQ ID NO: 424	CCGAGGCCUCGGAAUCCCUUUC	SEQ ID NO: 700	AAGGGAAUCCGAGG CCUCGG	523-545
SEQ ID NO: 425	GUCACCGAGGCCUCGGAAUCCCC	SEQ ID NO: 701	GAAUCCGAGGCCUC GGUGAC	527-549
SEQ ID NO: 426	ACCGAGGCCUCGGAAUCCCUUU	SEQ ID NO: 702	AGGGAAUCCGAGGC CUCGGU	524-546

SEQ ID NO: 427	UCACCGAGGCCUCGGAAUCCCU	SEQ ID NO: 703	GGAAUCCGAGGCCU CGGUGA	526-548
SEQ ID NO: 428	AUUUCAUCAUACAAGACAAGCAC	SEQ ID NO: 704	GCUUGUCUUGUAUGA UGAAAU	931-953
SEQ ID NO: 429	UGUAUUUAUCUUUGAAGGCGAAG	SEQ ID NO: 705	UCGCCUCAAAGAUA AAUACA	336-358
SEQ ID NO: 430	AUUUGUAGAUCUUAACCAGGCAG	SEQ ID NO: 706	GCCUGGUUAAGAUCU ACAAAU	549-571
SEQ ID NO: 431	UCCCCUUUGCAGUGUCAUAGAU	SEQ ID NO: 707	UCUAGACACUGCAA AGGGAA	651-673
SEQ ID NO: 432	AUCAUACAAGACAAGCACAAAAG	SEQ ID NO: 708	UUUGUGCUUGUCUUG UAUGAU	926-948
SEQ ID NO: 433	UAGAUUUUAACCAGGCAGUCACC	SEQ ID NO: 709	UGACUGCCUGGUUAA GAUCUA	544-566
SEQ ID NO: 434	AAGCAUCCCUUUGCAGUGUCAU	SEQ ID NO: 710	GACACUGCAAAGGGA AUGCUU	656-678
SEQ ID NO: 435	UUUGCAGUGUCAUAGAUACCGAA	SEQ ID NO: 711	CGGUAUCUAUGACAC UGCAA	646-668
SEQ ID NO: 436	AGAGAAAACUGGUCAGAUGAAUA	SEQ ID NO: 712	UUCAUCUGACCAGUU UUCUCU	1104-1126
SEQ ID NO: 437	UGCAGUGUCAUAGAUACCGAAGU	SEQ ID NO: 713	UUCGGUAUCUAUGAC ACUGCA	644-666
SEQ ID NO: 438	UCAGAUUUGUAGAUCUUAACCAG	SEQ ID NO: 714	GGUUAAGAUCUACAA AUCUGA	553-575
SEQ ID NO: 439	UCCCUUUGCAGUGUCAUAGAUAC	SEQ ID NO: 715	AUCUAUGACACUGCA AAGGGA	650-672
SEQ ID NO: 440	GAACAUUGGACCAUGCACCCUUG	SEQ ID NO: 716	AGGGUGCAUGGUCCA AUGUUC	885-907
SEQ ID NO: 441	AAUCCCAUCAGAUUUGUAGAUCU	SEQ ID NO: 717	AUCUACAAAUCUGAU GGGAUU	560-582
SEQ ID NO: 442	GCAGUGUCAUAGAUACCGAAGUA	SEQ ID NO: 718	CUUCGGUAUCUAUGA CACUGC	643-665
SEQ ID NO: 443	CAAGCACAAAAGCACCAACCAUG	SEQ ID NO: 719	UGGGUGGUGCUUUUG UGCUUG	915-937
SEQ ID NO: 444	GCGGCUCGGUAGAUGAUAAUACC	SEQ ID NO: 720	UAUUAUCAUCUACCG AGCCGC	619-641
SEQ ID NO: 445	CUCCUUGGGAAUACGGACCACGC	SEQ ID NO: 721	GUGGUCCGAUUUCCC AAGGAG	242-264
SEQ ID NO: 446	AUCCCCUUUGCAGUGUCAUAGAU	SEQ ID NO: 722	CUAUGACACUGCAAA GGGAAU	652-674

SEQ ID NO: 447	CAUACAAGACAAGCACAAAAGCA	SEQ ID NO: 723	CUUUUGUGCUUGUCU UGUAUG	924-946
SEQ ID NO: 448	AGACACGUUAAAGCCUUGGUACA	SEQ ID NO: 724	UACCAAGGCUUUAAC GUGUCU	590-612
SEQ ID NO: 449	UGAGAACAUUGGACCAUGCACCC	SEQ ID NO: 725	GUGCAUGGUCCAAUG UUCUCA	888-910
SEQ ID NO: 450	GCUUGUAUUUAUCUUUGAAGGCG	SEQ ID NO: 726	CCUUCAAAGAUAAAU ACAAGC	339-361
SEQ ID NO: 451	GCUCGGUAGAUGAUAAUACCCUG	SEQ ID NO: 727	GGGUAAUAUCAUCUA CCGAGC	616-638
SEQ ID NO: 452	AGUGUCAUAGAUACCGAAGUAGG	SEQ ID NO: 728	UACUUCGGUAUCUAU GACACU	641-663
SEQ ID NO: 453	AUCAGAUUUGUAGAUCUUAACCA	SEQ ID NO: 729	GUUAAGAUCUACAAA UCUGAU	554-576
SEQ ID NO: 454	GGUAGAUGAUAAUACCCUGCACA	SEQ ID NO: 730	UGCAGGGUAUUAUCA UCUACC	612-634
SEQ ID NO: 455	CAGGCCCUUAAUCCCAUCAGAUU	SEQ ID NO: 731	UCUGAUGGGAUUAAG GGCCUG	569-591
SEQ ID NO: 456	AGAUGAUAAUACCCUGCACAGAC	SEQ ID NO: 732	CUGUGCAGGGUAUUA UCAUCU	609-631
SEQ ID NO: 457	UACAGGCCCUUAAUCCCAUCAGA	SEQ ID NO: 733	UGAUGGGAUUAAGGG CCUGUA	571-593
SEQ ID NO: 458	ACAGACACGUUAAAGCCUUGGUA	SEQ ID NO: 734	CCAAGGCUUUAACGU GUCUGU	592-614
SEQ ID NO: 459	AGAAAACUGGUCAGAUGAAUAAU	SEQ ID NO: 735	UAUUCAUCUGACCAG UUUUCU	1102-1124
SEQ ID NO: 460	UGUAGAUCUUAACCAGGCAGUCA	SEQ ID NO: 736	ACUGCCUGGUUAAGA UCUACA	546-568
SEQ ID NO: 461	UCAAUUGGAUAGGAAGUCAACCC	SEQ ID NO: 737	GUUGACUCCUAUCC AUUUGA	745-767
SEQ ID NO: 462	CAUUCCCUUUGCAGUGUCAUAGA	SEQ ID NO: 738	UAUGACACUGCAAAG GGAAUG	653-675
SEQ ID NO: 463	CAUCAGAUUUGUAGAUCUUAACC	SEQ ID NO: 739	UUAAGAUCUACAAAU CUGAUG	555-577
SEQ ID NO: 464	CUCGGUAGAUGAUAAUACCCUGC	SEQ ID NO: 740	AGGGUAUUAUCAUCU ACCGAG	615-637
SEQ ID NO: 465	UUUGUAGAUCUUAACCAGGCAGU	SEQ ID NO: 741	UGCCUGGUUAAGAUC UACAAA	548-570
SEQ ID NO: 466	ACAGGCCCUUAAUCCCAUCAGAU	SEQ ID NO: 742	CUGAUGGGAUUAAGG GCCUGU	570-592

SEQ ID NO: 467	CUUUGCAGUGUCAUAGAUACCGA	SEQ ID NO: 743	GGUAUCUAUGACACU GCAAAG	647-669
SEQ ID NO: 468	CACAUCAGCUGCUAGACGGGUAC	SEQ ID NO: 744	ACCCGUCUAGCAGCUG AUGUG	485-507
SEQ ID NO: 469	CCCUUUGCAGUGUCAUAGAUACC	SEQ ID NO: 745	UAUCUAUGACACUGC AAAGGG	649-671
SEQ ID NO: 470	CUCCAGCUUUACCCACAUCAGCU	SEQ ID NO: 746	CUGAUGUGGGUAAAG CUGGAG	498-520
SEQ ID NO: 471	UUACCCACAUCAGCUGCUAGACG	SEQ ID NO: 747	UCUAGCAGCUGAUGU GGGUAA	490-512
SEQ ID NO: 472	UUAAAGCCUUGGUACAGGCCCUU	SEQ ID NO: 748	GGGCCUGUACCAAGG CUUUA	583-605
SEQ ID NO: 473	CAGCUGCUAGACGGGUACGGGCA	SEQ ID NO: 749	CCCGUACCCGUCUAGC AGCUG	480-502
SEQ ID NO: 474	CAGCUUUACCCACAUCAGCUGCU	SEQ ID NO: 750	CAGCUGAUGUGGGUA AAGCUG	495-517
SEQ ID NO: 475	UCAGCUGCUAGACGGGUACGGGC	SEQ ID NO: 751	CCGUACCCGUCUAGCA GCUGA	481-503
SEQ ID NO: 476	UCCAGCUUUACCCACAUCAGCUG	SEQ ID NO: 752	GCUGAUGUGGGUAAA GCUGGA	497-519
SEQ ID NO: 477	GGCUCGGUAGAUGAUAAUACCCU	SEQ ID NO: 753	GGUAUUAUCAUCUAC CGAGCC	617-639
SEQ ID NO: 478	AGGCGGCUCGGUAGAUGAUAAUA	SEQ ID NO: 754	UUAUCAUCUACCGAG CCGCCU	621-643
SEQ ID NO: 479	CAUCAGCUGCUAGACGGGUACGG	SEQ ID NO: 755	GUACCCGUCUAGCAGC UGAUG	483-505
SEQ ID NO: 480	GUACAGGCCCUAAUCCCAUCAG	SEQ ID NO: 756	GAUGGGAUUAAGGGC CUGUAC	572-594
SEQ ID NO: 481	AUGAUAAUACCCUGCACAGACAC	SEQ ID NO: 757	GUCUGUGCAGGGUAU UAUCAU	607-629
SEQ ID NO: 482	CCUUGGGAUACGGACCACGCAG	SEQ ID NO: 758	GCGUGGUCCGUAUUC CCAAGG	240-262
SEQ ID NO: 483	UCCUUGGGAUACGGACCACGCA	SEQ ID NO: 759	CGUGGUCCGUAUUCCC AAGGA	241-263
SEQ ID NO: 484	CAGAUUUGUAGAUUUAAACCAGG	SEQ ID NO: 760	UGGUUAAGAUCUACA AAUCUG	552-574
SEQ ID NO: 485	UGUACUUCUUGAUUUCAUCAUAC	SEQ ID NO: 761	AUGAUGAAAUCAAGA AGUACA	942-964
SEQ ID NO: 486	AUCCCAUCAGAUUUGUAGAUUU	SEQ ID NO: 762	GAUCUACAAAUCUGA UGGGAU	559-581

SEQ ID NO: 487	GUAGAUGAAUACCCUGCACAG	SEQ ID NO: 763	GUGCAGGGUAUUAUC AUCUAC	611-633
SEQ ID NO: 488	GACACGUUAAAGCCUUGGUACAG	SEQ ID NO: 764	GUACCAAGGCUUUAA CGUGUC	589-611
SEQ ID NO: 489	AGCUUUACCCACAUCAGCUGCUA	SEQ ID NO: 765	GCAGCUGAUGUGGGU AAAGCU	494-516
SEQ ID NO: 490	AAGCACAAAAGCACCACCCAUGC	SEQ ID NO: 766	AUGGGUGGUGCUUUU GUGCUU	914-936
SEQ ID NO: 491	AUCUUAACCAGGCAGUCACCGAG	SEQ ID NO: 767	CGGUGACUGCCUGGU UAAGAU	541-563
SEQ ID NO: 492	UUUACCCACAUCAGCUGCUAGAC	SEQ ID NO: 768	CUAGCAGCUGAUGUG GGUAAA	491-513
SEQ ID NO: 493	CUUAAUCCCAUCAGAUUUGUAGA	SEQ ID NO: 769	UACAAAUCUGAUGGG AUUAAG	563-585
SEQ ID NO: 494	CAGUGUCAUAGAUACCGAAGUAG	SEQ ID NO: 770	ACUUCGGUAUCUAUG ACACUG	642-664
SEQ ID NO: 495	CCAGCUUUACCCACAUCAGCUGC	SEQ ID NO: 771	AGCUGAUGUGGGUAA AGCUGG	496-518
SEQ ID NO: 496	AUCAGCUGCUAGACGGGUACGGG	SEQ ID NO: 772	CGUACCCGUCUAGCAG CUGAU	482-504
SEQ ID NO: 497	GAUGAUAAUACCCUGCACAGACA	SEQ ID NO: 773	UCUGUGCAGGGUAUU AUCAUC	608-630
SEQ ID NO: 498	UUUCAUCAUACAAGACAAGCACA	SEQ ID NO: 774	UGCUUGUCUUGUAUG AUGAAA	930-952
SEQ ID NO: 499	CAGACACGUUAAAGCCUUGGUAC	SEQ ID NO: 775	ACCAAGGCUUUAACG UGUCUG	591-613
SEQ ID NO: 500	AGAACAUUGGACCAUGCACCCUU	SEQ ID NO: 776	GGGUGCAUGGUCCAA UGUUCU	886-908
SEQ ID NO: 501	GUAGAUCUUAACCAGGCAGUCAC	SEQ ID NO: 777	GACUGCCUGGUUAAG AUCUAC	545-567
SEQ ID NO: 502	AGCUCCAGCUUUACCCACAUCAG	SEQ ID NO: 778	GAUGUGGGUAAAGCU GGAGCU	500-522
SEQ ID NO: 503	GCUCCUUGGGAAUACGGACCACG	SEQ ID NO: 779	UGGUCCGUUUUCCCA AGGAGC	243-265
SEQ ID NO: 504	GAAGCAUUCCCUUUGCAGUGUCA	SEQ ID NO: 780	ACACUGCAAAGGGAA UGCUUC	657-679
SEQ ID NO: 505	CCUUGGUACAGGCCCUUAAUCCC	SEQ ID NO: 781	GAUUAAGGGCCUGUA CCAAGG	577-599
SEQ ID NO: 506	UAGAUGAAUACCCUGCACAGA	SEQ ID NO: 782	UGUGCAGGGUAUUAU CAUCUA	610-632

SEQ ID NO: 507	AAUACCCUGCACAGACACGUUAA	SEQ ID NO: 783	AACGUGUCUGUGCAG GGUAUU	602-624
SEQ ID NO: 508	GUUAAAGCCUUGGUACAGGCCCU	SEQ ID NO: 784	GGCCUGUACCAAGGC UUUAAC	584-606
SEQ ID NO: 509	AGCAUUCCCUUUGCAGUGUCAUA	SEQ ID NO: 785	UGACACUGCAAAGGG AAUGCU	655-677
SEQ ID NO: 510	UCUUAACCAGGCAGUCACCGAGG	SEQ ID NO: 786	UCGGUGACUGCCUGG UUAAGA	540-562
SEQ ID NO: 511	AUACAAGACAAGCACAAAAGCAC	SEQ ID NO: 787	GCUUUUGUGCUUGUC UUGUAU	923-945
SEQ ID NO: 512	GACAAGCACAAAAGCACCA	SEQ ID NO: 788	GGUGGUGCUUUUGUG CUUGUC	917-939
SEQ ID NO: 513	ACCCACAUCAGCUGCUAGACGGG	SEQ ID NO: 789	CGUCUAGCAGCUGAU GUGGGU	488-510
SEQ ID NO: 514	UAAAGCCUUGGUACAGGCCCUUA	SEQ ID NO: 790	AGGGCCUGUACCAAG GCUUUA	582-604
SEQ ID NO: 515	UUCAUCAUACAAGACAAGCACAA	SEQ ID NO: 791	GUGCUUGUCUUGUAU GAUGAA	929-951
SEQ ID NO: 516	GCCCUUAAUCCCAUCAGAUUUGU	SEQ ID NO: 792	AAAUCUGAUGGGAUU AAGGGC	566-588
SEQ ID NO: 517	UUAAUCCCAUCAGAUUUGUAGAU	SEQ ID NO: 793	CUACAAAUCUGAUGG GAUUA	562-584
SEQ ID NO: 518	UCGGUAGAUGAUAAUACCCUGCA	SEQ ID NO: 794	CAGGGUAUUAUCAUC UACCGA	614-636
SEQ ID NO: 519	CACGUUAAAGCCUUGGUACAGGC	SEQ ID NO: 795	CUGUACCAAGGCUUU AACGUG	587-609
SEQ ID NO: 520	UCCCAUCAGAUUUGUAGAUUUA	SEQ ID NO: 796	AGAUCUACAAAUCUG AUGGGA	558-580
SEQ ID NO: 521	UCAUACAAGACAAGCACAAAAGC	SEQ ID NO: 797	UUUUGUGCUUGUCUU GUAUGA	925-947
SEQ ID NO: 522	CCUUAUCCCAUCAGAUUUGUAG	SEQ ID NO: 798	ACAAAUCUGAUGGGA UUAAGG	564-586
SEQ ID NO: 523	ACAUUGGACCAUGCACCCUUGAA	SEQ ID NO: 799	CAAGGGUGCAUGGUC CAAUGU	883-905
SEQ ID NO: 524	CUUGGUACAGGCCCUUAAUCCCA	SEQ ID NO: 800	GAUUAAGGGCCUGU ACCAAG	576-598
SEQ ID NO: 525	UUGCAGUGUCAUAGAUACCGAAG	SEQ ID NO: 801	UCGGUAUCUAUGACA CUGCAA	645-667
SEQ ID NO: 526	CACAGACACGUUAAAGCCUUGGU	SEQ ID NO: 802	CAAGGCUUUAACGUG UCUGUG	593-615

SEQ ID NO: 527	AGCACAAAAGCACCACCCAUGCC	SEQ ID NO: 803	CAUGGGUGGUGCUUU UGUGCU	913-935
SEQ ID NO: 528	CCAUCAGAUUUGUAGAUCUUAAC	SEQ ID NO: 804	UAAGAUCUACAAAUC UGAUGG	556-578
SEQ ID NO: 529	CCACAUCAGCUGCUAGACGGGUA	SEQ ID NO: 805	CCCGUCUAGCAGCUGA UGUGG	486-508
SEQ ID NO: 530	GCAUUCCCUUUGCAGUGUCAUAG	SEQ ID NO: 806	AUGACACUGCAAAGG GAAUGC	654-676
SEQ ID NO: 531	CUUUACCCACAUCAGCUGCUAGA	SEQ ID NO: 807	UAGCAGCUGAUGUGG GUAAAG	492-514
SEQ ID NO: 532	AUCCGGAAGCAUUCCCUUUGCAG	SEQ ID NO: 808	GCAAAGGGAAUGCUU CCGGAU	662-684
SEQ ID NO: 533	AGCUGCUAGACGGGUACGGGCAA	SEQ ID NO: 809	GCCCGUACCCGUCUAG CAGCU	479-501
SEQ ID NO: 534	CGGCUCGGUAGAUGAUAAUACCC	SEQ ID NO: 810	GUUUUAUCAUCUACC GAGCCG	618-640
SEQ ID NO: 535	GGGUACGGGCAAAAUCAAGAGGG	SEQ ID NO: 811	CUCUUGAUUUUGCCC GUACCC	468-490
SEQ ID NO: 536	ACAUCAGCUGCUAGACGGGUACG	SEQ ID NO: 812	UACCCGUCUAGCAGCU GAUGU	484-506
SEQ ID NO: 537	CCCUUAAUCCCAUCAGAUUUGUA	SEQ ID NO: 813	CAAUCUGAUGGGAU UAAGGG	565-587
SEQ ID NO: 538	CGGGCAAAAUCAAGAGGGUACAC	SEQ ID NO: 814	GUACCCUCUUGAUUU UGCCCG	463-485
SEQ ID NO: 539	ACGUUAAAGCCUUGGUACAGGCC	SEQ ID NO: 815	CCUGUACCAAGGCUU UAACGU	586-608
SEQ ID NO: 540	UGGUACAGGCCCUUAAUCCCAUC	SEQ ID NO: 816	UGGGAUUAAGGGCCU GUACCA	574-596
SEQ ID NO: 541	GGCGGCUCGGUAGAUGAUAAUAC	SEQ ID NO: 817	AUUAUCAUCUACCGA GCCGCC	620-642
SEQ ID NO: 542	CGUUAAAGCCUUGGUACAGGCC	SEQ ID NO: 818	GCCUGUACCAAGGCU UUAACG	585-607
SEQ ID NO: 543	GGUACAGGCCCUUAAUCCCAUCA	SEQ ID NO: 819	AUGGGAUUAAGGGCC UGUACC	573-595
SEQ ID NO: 544	UAAUACCCUGCACAGACACGUUA	SEQ ID NO: 820	ACGUGUCUGUGCAGG GUUUUA	603-625
SEQ ID NO: 545	GACCACGCAGUCUAUAAUGCCUU	SEQ ID NO: 821	GGCAUUAUAGACUGC GUGGUC	227-249
SEQ ID NO: 546	GUUAAGAGCCUGGGUGGGGAAGU	SEQ ID NO: 822	UUCCCCACCCAGGCUC UUAAC	314-336

SEQ ID NO: 547	UGGGGAAGUAUCUGAUGACAUUG	SEQ ID NO: 823	AUGUCAUCAGAUACU UCCCCA	300-322
SEQ ID NO: 548	GGUGGGGAAGUAUCUGAUGACAU	SEQ ID NO: 824	GUCAUCAGAUACUUC CCCACC	302-324
SEQ ID NO: 549	GUGGGGAAGUAUCUGAUGACAUU	SEQ ID NO: 825	UGUCAUCAGAUACUU CCCCAC	301-323
SEQ ID NO: 550	GGGGAAGUAUCUGAUGACAUUGG	SEQ ID NO: 826	AAUGUCAUCAGAUAC UUCCCC	299-321
SEQ ID NO: 551	UUAAGAGCCUGGGUGGGGAAGUA	SEQ ID NO: 827	CUUCCCCACCCAGGCU CUUAA	313-335
SEQ ID NO: 552	CCGAAGUAGGCGGCUCGGUAGAU	SEQ ID NO: 828	CUACCGAGCCGCCUAC UUCGG	628-650

In a particular embodiment, the invention relates to a nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

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Unmodified first strand	Unmodified second strand
SEQ ID NO:304	SEQ ID NO:580
SEQ ID NO:323	SEQ ID NO:599
SEQ ID NO:439	SEQ ID NO:715
SEQ ID NO:453	SEQ ID NO:729
SEQ ID NO:496	SEQ ID NO:772

In a particular embodiment, the invention relates to a nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

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Unmodified first strand	Unmodified second strand
SEQ ID NO:304	SEQ ID NO:580

In certain embodiments, the nucleic acid for inhibiting expression of the *SLC25A5* gene comprises a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is:

- 15
- (i) at least partially complementary to a portion of RNA transcribed from the *SLC25A5* gene, and
 - (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO:829-1104.

In certain embodiments, the first strand comprises nucleosides 2-18 of any one of the sequences set forth in SEQ ID NO: 829-1104.

In certain embodiments, the nucleic acid for inhibiting expression of the *SLC25A5* gene comprises a duplex region that comprises a first strand and a second strand that is at least partially complementary to the first strand, wherein said first strand is:

- (i) at least partially complementary to a portion of RNA transcribed from the *SLC25A5* gene, and
- (ii) comprises at least 21 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 829-1104.

In certain embodiments, the first strand comprises nucleosides 2-22 of any one of the sequences set forth in SEQ ID NO: 829-1104.

In certain embodiments, the first strand comprises any one of SEQ ID NO: 829-1104.

The modification pattern of the nucleic acids as set forth in SEQ ID NO: 829-1104 is summarized in Table 3 below:

Table 3

Antisense strand ID	Modified Antisense Strand 5' → 3'	SEQ ID NO (AS - mod)	Underlying Base Sequence 5' → 3' (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO (AS - unmod)
ETX-S00003090	CmsCfsCmAmUmUfUmUmCmAmAmCmCmAfGmUfAmAfAmUmAmsGmsUm	SEQ ID NO: 829	CCCAUUUUCAACC AGUAAAUAGU	SEQ ID NO: 277
ETX-S00003094	AmsCfsGmCmAmGfUmCmUmAmUmAmAmUfGmCfCmUfUmUmGmsUmsAm	SEQ ID NO: 830	ACGCAGUCUAUAA UGCCUUUGUA	SEQ ID NO: 278
ETX-S00003098	GmsUfsGmUmAmCfUmUmCmUmUmGmA mUfUmUfCmAfUmCmAmsUmsAm	SEQ ID NO: 831	GUGUACUUCUUGA UUUCAUCAUA	SEQ ID NO: 279
ETX-S00003102	AmsUfsAmCmAmAfUmUmGmAmGmUmCmCfCmAfUmCfAmUmCmsAmsUm	SEQ ID NO: 832	AUACAAUUGAGUC CCAUCAUCAU	SEQ ID NO: 280
ETX-S00003106	GmsGfsAmCmCmAfCmGmCmAmGmUmCmUfAmUfAmAfUmGmCmsCmsUm	SEQ ID NO: 833	GGACCACGCAGUC UAUAAUGCCU	SEQ ID NO: 281
ETX-S00003110	UmsUfsGmUmUmAfUmUmUmAmUmCmA mGfGmAfGmUfGmAmCmsUmsGm	SEQ ID NO: 834	UUGUUAUUUAUCA GGAGUGACUG	SEQ ID NO: 282
ETX-S00003114	CmsAfsGmUmCmUfAmUmAmAmUmGmCmCfUmUfUmGfUmAmUmsUmsGm	SEQ ID NO: 835	CAGUCUAUAAUGC CUUUGUAUUG	SEQ ID NO: 283

ETX-S00003118	AmsUfsAmGmAmUfAmCmCmGmAmAmGmUfAmGfGmCfGmGmCmsUmsCm	SEQ ID NO: 836	AUAGAUACCGAAG UAGGCGGCUC	SEQ ID NO: 284
ETX-S00003122	UmsAfsGmAmUmAfCmCmGmAmAmGmUmAfGmGfCmGfGmCmUmsCmsGm	SEQ ID NO: 837	UAGAUACCGAAGU AGGCGGCUCG	SEQ ID NO: 285
ETX-S00003126	GmsGfsAmAmUmAfCmGmGmAmCmCmA mCfGmCfAmGfUmCmUmsAmsUm	SEQ ID NO: 838	GGAAUACGGACCA CGCAGUCUAU	SEQ ID NO: 286
ETX-S00003130	CmsAfsGmCmUmGfAmUmGmAmCmGmA mUfGmUfGmAfGmUmGmsUmsUm	SEQ ID NO: 839	CAGCUGAUGACGA UGUGAGUGUU	SEQ ID NO: 287
ETX-S00003134	AmsUfsUmUmAmUfCmUmUmUmGmAmA mGfGmCfGmAfAmGmUmsUmsAm	SEQ ID NO: 840	AUUUAUCUUUGAA GGCGAAGUUA	SEQ ID NO: 288
ETX-S00003138	GmsUfsGmUmCmAfUmAmGmAmUmAmC mCfGmAfAmGfUmAmGmsGmsCm	SEQ ID NO: 841	GUGUCAUAGAUAC CGAAGUAGGC	SEQ ID NO: 289
ETX-S00003142	UmsUfsCmCmCmAfUmUmUmUmCmA mCfCmAfGmUfAmAmAmsUmsAm	SEQ ID NO: 842	UUCCCAUUUCAA CCAGUAAAUA	SEQ ID NO: 290
ETX-S00003146	GmsCfsUmGmCmUfAmGmAmCmGmGmG mUfAmCfGmGfGmCmAmsAmsAm	SEQ ID NO: 843	GCUGCUAGACGGG UACGGGCAAA	SEQ ID NO: 291
ETX-S00003150	CmsAfsGmUmUmCfCmUmUmUmGmCmG mCfCmCfUmGfAmCmUmsGmsCm	SEQ ID NO: 844	CAGUUCCUUUGCG CCCUGACUGC	SEQ ID NO: 292
ETX-S00003154	CmsUfsUmCmCmCfAmUmUmUmUmCmA mAfCmCfAmGfUmAmAmsAmsUm	SEQ ID NO: 845	CUUCCCAUUUUCA ACCAGUAAAU	SEQ ID NO: 293
ETX-S00003158	AmsGfsAmUmAmCfCmGmAmAmGmUmA mGfGmCfGmGfCmUmCmsGmsGm	SEQ ID NO: 846	AGAUACCGAAGUA GGCGGCUCGG	SEQ ID NO: 294
ETX-S00003162	UmsUfsAmAmCmCfAmGmGmCmAmGmU mCfAmCfCmGfAmGmGmsCmsCm	SEQ ID NO: 847	UUAACCGAGCAGU CACCGAGGCC	SEQ ID NO: 295
ETX-S00003166	AmsUfsCmAmUmCfCmAmGmCmUmGmA mUfGmAfCmGfAmUmGmsUmsGm	SEQ ID NO: 848	AUCAUCCAGCUGA UGACGAUGUG	SEQ ID NO: 296
ETX-S00003170	AmsUfsUmUmAmUfCmAmGmGmAmGmU mGfAmCfUmGfAmAmAmsUmsAm	SEQ ID NO: 849	AUUUAUCAGGAGU GACUGAAUA	SEQ ID NO: 297
ETX-S00003174	GmsAfsCmAmGmUfCmUmGmUmGmCmG mAfUmCfAmUfCmCmAmsGmsCm	SEQ ID NO: 850	GACAGUCUGUGCG AUCAUCCAGC	SEQ ID NO: 298
ETX-S00003178	UmsCfsUmAmUmAfAmUmGmCmCmUmU mUfGmUfAmUfUmGmCmsUmsUm	SEQ ID NO: 851	UCUAUAAUGCCUU UGUAUUGCUU	SEQ ID NO: 299
ETX-S00003182	UmsAfsAmCmCmAfGmGmCmAmGmUmC mAfCmCfGmAfGmGmCmsCmsUm	SEQ ID NO: 852	UAACCGAGCAGUC ACCGAGGCCU	SEQ ID NO: 300
ETX-S00003186	CmsCfsCmUmGmCfAmCmAmGmAmCmA mCfGmUfUmAfAmAmGmsCmsCm	SEQ ID NO: 853	CCCUGCACAGACA CGUAAAAGCC	SEQ ID NO: 301
ETX-S00003190	CmsAfsCmGmCmAfGmUmCmUmAmUmA mAfUmGfCmCfUmUmUmsGmsUm	SEQ ID NO: 854	CACGCAGUCUAUA AUGCCUUUGU	SEQ ID NO: 302
ETX-S00003194	UmsAfsAmUmAmCfAmAmCmAmUmGmC mCfUmGfUmUfCmAmCmsAmsGm	SEQ ID NO: 855	UAAUACAACAUGC CUGUUCACAG	SEQ ID NO: 303

ETX-S00003198	UmsUfsAmAmGmAfGmAmAmAmAmCmU mGfGmUfCmAfGmAmUmsGmsAm	SEQ ID NO: 856	UUAAGAGAAAACU GGUCAGAUGA	SEQ ID NO: 304
ETX-S00003202	UmsGfsCmAmCmAfGmAmCmAmCmGmU mUfAmAfAmGfCmCmUmsUmsGm	SEQ ID NO: 857	UGCACAGACACGU UAAAGCCUUG	SEQ ID NO: 305
ETX-S00003206	GmsUfsUmCmCmUfUmUmGmCmGmCmC mCfUmGfAmCfUmGmCmsAmsUm	SEQ ID NO: 858	GUUCCUUUGCGCC CUGACUGCAU	SEQ ID NO: 306
ETX-S00003210	GmsUfsGmAmCmAfGmUmCmUmGmUmG mCfGmAfUmCfAmUmCmsCmsAm	SEQ ID NO: 859	GUGACAGUCUGUG CGAUCAUCCA	SEQ ID NO: 307
ETX-S00003214	AmsCfsCmAmCmGfCmAmGmUmCmUmA mUfAmAfUmGfCmCmUmsUmsUm	SEQ ID NO: 860	ACCACGCAGUCUA UAAUGCCUUU	SEQ ID NO: 308
ETX-S00003218	CmsAfsGmUmGmAfCmAmGmUmCmUmG mUfGmCfGmAfUmCmAmsUmsCm	SEQ ID NO: 861	CAGUGACAGUCUG UGCGAUAUC	SEQ ID NO: 309
ETX-S00003222	UmsUfsGmGmGmAfAmUmAmCmGmGmA mCfCmAfCmGfCmAmGmsUmsCm	SEQ ID NO: 862	UUGGGAAUACGGA CCACGCAGUC	SEQ ID NO: 310
ETX-S00003226	GmsUfsCmUmAmUfAmAmUmGmCmCmU mUfUmGfUmAfUmUmGmsCmsUm	SEQ ID NO: 863	GUCUAUAAUGCCU UUGUAUUGCU	SEQ ID NO: 311
ETX-S00003230	UmsGfsUmGmCmGfAmUmCmAmUmCmC mAfGmCfUmGfAmUmGmsAmsCm	SEQ ID NO: 864	UGUGCGAUCAUCC AGCUGAUGAC	SEQ ID NO: 312
ETX-S00003234	AmsCfsGmGmAmCfCmAmCmGmCmAmG mUfCmUfAmUfAmAmUmsGmsCm	SEQ ID NO: 865	ACGGACCACGCAG UCUAUAAUGC	SEQ ID NO: 313
ETX-S00003238	UmsGfsCmUmAmGfAmCmGmGmGmUmA mCfGmGfGmCfAmAmAmsAmsUm	SEQ ID NO: 866	UGCUAGACGGGUA CGGGCAAAAU	SEQ ID NO: 314
ETX-S00003242	UmsCfsAmUmCmCfAmGmCmUmGmAmU mGfAmCfGmAfUmGmUmsGmsAm	SEQ ID NO: 867	UCAUCCAGCUGAU GACGAUGUGA	SEQ ID NO: 315
ETX-S00003246	CmsGfsGmGmUmAfCmGmGmGmCmA mAfAmUfCmAfAmGmAmsGmsGm	SEQ ID NO: 868	CGGGUACGGGCAA AAUCAAGAGG	SEQ ID NO: 316
ETX-S00003250	AmsAfsUmAmCmGfGmAmCmCmAmCmG mCfAmGfUmCfUmAmUmsAmsAm	SEQ ID NO: 869	AAUACGGACCACG CAGUCUAUAA	SEQ ID NO: 317
ETX-S00003254	UmsCfsAmUmAmGfAmUmAmCmCmGmA mAfGmUfAmGfGmCmGmsGmsCm	SEQ ID NO: 870	UCAUAGAUACCGA AGUAGGCGGC	SEQ ID NO: 318
ETX-S00003258	GmsGfsGmAmAmUfAmCmGmGmAmCmC mAfCmGfCmAfGmUmCmsUmsAm	SEQ ID NO: 871	GGGAUACGGACC ACGCAGUCUA	SEQ ID NO: 319
ETX-S00003262	GmsUfsGmCmGmAfUmCmAmUmCmCmA mGfCmUfGmAfUmGmAmsCmsGm	SEQ ID NO: 872	GUGCGAUAUCCA GCUGAUGACG	SEQ ID NO: 320
ETX-S00003266	UmsAfsCmGmGmAfCmCmAmCmGmCmA mGfUmCfUmAfUmAmAmsUmsGm	SEQ ID NO: 873	UACGGACCACGCA GUCUAUAAUG	SEQ ID NO: 321
ETX-S00003270	UmsGfsUmCmAmUfAmGmAmUmAmCmC mGfAmAfGmUfAmGmGmsCmsGm	SEQ ID NO: 874	UGUCAUAGAUACC GAAGUAGGCG	SEQ ID NO: 322
ETX-S00003274	UmsAfsUmCmAmGfGmAmGmUmGmAmC mUfGmAfAmAfUmAmAmsAmsAm	SEQ ID NO: 875	UAUCAGGAGUGAC UGAAAUAAAA	SEQ ID NO: 323

ETX-S00003278	UmsGfsCmGmAmUfCmAmUmCmCmAmGmCfUmGfAmUfGmAmCmsGmsAm	SEQ ID NO: 876	UGCGAUCAUCCAG CUGAUGACGA	SEQ ID NO: 324
ETX-S00003282	CmsUfsAmGmAmCfGmGmGmUmAmCmGmGfGmCfAmAfAmAmUmsCmsAm	SEQ ID NO: 877	CUAGACGGGUACG GGCAAAAUCA	SEQ ID NO: 325
ETX-S00003286	GmsAfsUmCmCmGfGmAmAmGmCmAmUmUfCmCfCmUfUmUmGmsCmsAm	SEQ ID NO: 878	GAUCCGGAAGCAU UCCCUUUGCA	SEQ ID NO: 326
ETX-S00003290	GmsCfsAmCmAmGfAmCmAmCmGmUmUmAfAmAfGmCfCmUmUmsGmsGm	SEQ ID NO: 879	GCACAGACACGUU AAAGCCUUGG	SEQ ID NO: 327
ETX-S00003294	CmsCfsAmCmGmCfAmGmUmCmUmAmUmAfAmUfGmCfCmUmUmsUmsGm	SEQ ID NO: 880	CCACGCAGUCUAU AAUGCCUUUG	SEQ ID NO: 328
ETX-S00003298	GmsAfsCmGmGmGfUmAmCmGmGmGmCmAfAmAfAmUfCmAmAmsGmsAm	SEQ ID NO: 881	GACGGGUACGGGC AAAAUCAAGA	SEQ ID NO: 329
ETX-S00003302	GmsAfsUmAmCmCfGmAmAmGmUmAmGmGfCmGfGmCfUmCmGmsGmsUm	SEQ ID NO: 882	GAUACCGAAGUAG GCGGCUCGGU	SEQ ID NO: 330
ETX-S00003306	GmsUfsAmGmGmCfGmGmCmUmCmGmGmUmUfAmGfAmUfGmAmUmsAmsAm	SEQ ID NO: 883	GUAGGCGGCUCGG UAGAUGAUAA	SEQ ID NO: 331
ETX-S00003310	AmsGfsAmCmGmGfGmUmAmCmGmGmGmCfAmAfAmAfUmCmAmsAmsGm	SEQ ID NO: 884	AGACGGGUACGGG CAAAAUCAAG	SEQ ID NO: 332
ETX-S00003314	UmsAfsGmGmCmGfGmCmUmCmGmGmUmAfGmAfUmGfAmUmAmsAmsUm	SEQ ID NO: 885	UAGGCGGCUCGGU AGAUGAUAAU	SEQ ID NO: 333
ETX-S00003318	AmsAfsGmUmAmGfGmCmGmGmCmUmCmGfGmUfAmGfAmUmGmsAmsUm	SEQ ID NO: 886	AAGUAGGCGGCUC GGUAGAUGAU	SEQ ID NO: 334
ETX-S00003322	CmsUfsUmUmGmAfAmGmGmCmGmAmAmGfUmUfAmAfGmAmGmsCmsCm	SEQ ID NO: 887	CUUUGAAGGCGAA GUUAAGAGCC	SEQ ID NO: 335
ETX-S00003326	CmsGfsAmAmGmUfUmAmAmGmAmGmCmCfUmGfGmGfUmGmGmsGmsGm	SEQ ID NO: 888	CGAAGUUAAGAGC CUGGGUGGGG	SEQ ID NO: 336
ETX-S00003330	CmsCfsCmUmGmCfUmCmCmUmUmGmGmGfAmAfUmAfCmGmGmsAmsCm	SEQ ID NO: 889	CCCUGCUCCUUGG GAAUACGGAC	SEQ ID NO: 337
ETX-S00003334	GmsAfsAmGmGmAfCmAmGmAmAmCmUmCfCmCfUmGfCmUmCmsCmsUm	SEQ ID NO: 890	GAAGGACAGAACU CCCUGCUCCU	SEQ ID NO: 338
ETX-S00003338	AmsGfsAmAmCmUfCmCmCmUmGmCmUmCfCmUfUmGfGmGmAmsAmsUm	SEQ ID NO: 891	AGAACUCCCUGCU CCUUGGGAAU	SEQ ID NO: 339
ETX-S00003342	CmsCfsUmGmCmUfCmCmUmUmGmGmGmAfAmUfAmCfGmGmAmsCmsCm	SEQ ID NO: 892	CCUGCUCCUUGGG AAUACGGACC	SEQ ID NO: 340
ETX-S00003346	CmsAfsGmAmAmGfGmAmCmAmGmAmAmCfUmCfCmCfUmGmCmsUmsCm	SEQ ID NO: 893	CAGAAGGACAGAA CUCCCUGCUC	SEQ ID NO: 341
ETX-S00003350	CmsUfsGmCmUmCfCmUmUmGmGmGmAfUmAfCmGfGmAmCmsCmsAm	SEQ ID NO: 894	CUGCUCCUUGGGA AUACGGACCA	SEQ ID NO: 342
ETX-S00003354	AmsGfsAmAmGmGfAmCmAmGmAmAmCmUfCmCfCmUfGmCmUmsCmsCm	SEQ ID NO: 895	AGAAGGACAGAAC UCCCUGCUCC	SEQ ID NO: 343

ETX-S00003358	AmsAfsGmGmAmCfAmGmAmAmCmUmCmCfCmUfGmCfUmCmCmsUmsUm	SEQ ID NO: 896	AAGGACAGAACUC CCUGCUCCUU	SEQ ID NO: 344
ETX-S00003362	GmsAfsAmCmUmCfCmCmUmGmCmUmCmCfUmUfGmGfGmAmAmsUmsAm	SEQ ID NO: 897	GAACUCCCUGCUC CUUGGGAUA	SEQ ID NO: 345
ETX-S00003366	AmsGfsGmAmCmAfGmAmAmCmUmCmCmCfUmGfCmUfCmCmUmsUmsGm	SEQ ID NO: 898	AGGACAGAACUCC CUGCUCCUUG	SEQ ID NO: 346
ETX-S00003370	GmsAfsAmGmUmUfAmAmGmAmGmCmCmUfGmGfGmUfGmGmGmsGmsAm	SEQ ID NO: 899	GAAGUUAAGAGCC UGGGUGGGGA	SEQ ID NO: 347
ETX-S00003374	UmsCfsUmUmUmGfAmAmGmGmCmGmA mAfGmUfUmAfAmGmAmsGmsCm	SEQ ID NO: 900	UCUUUGAAGGCGA AGUUAAGAGC	SEQ ID NO: 348
ETX-S00003378	UmsAfsUmUmUmAfUmCmAmGmGmAmGmUfGmAfCmUfGmAmAmsAmsUm	SEQ ID NO: 901	UAUUUAUCAGGAG UGACUGAAAU	SEQ ID NO: 349
ETX-S00003382	GmsUfsUmAmUmUfUmAmUmCmAmGmGmAfGmUfGmAfCmUmGmsAmsAm	SEQ ID NO: 902	GUUAUUUAUCAGG AGUGACUGAA	SEQ ID NO: 350
ETX-S00003386	UmsUfsAmUmUmUfAmUmCmAmGmGmA mGfUmGfAmCfUmGmAmsAmsAm	SEQ ID NO: 903	UUAUUUAUCAGGA GUGACUGAAA	SEQ ID NO: 351
ETX-S00003390	AmsAfsAmUmAmCfAmAmUmUmGmAmGmUfCmCfCmAfUmCmAmsUmsCm	SEQ ID NO: 904	AAAUACAAUUGAG UCCCAUCAUC	SEQ ID NO: 352
ETX-S00003394	AmsAfsAmAmUmAfCmAmAmUmUmGmA mGfUmCfCmCfAmUmCmsAmsUm	SEQ ID NO: 905	AAAAUACAAUUGA GUCCCAUCAU	SEQ ID NO: 353
ETX-S00003398	AmsUfsUmUmGmUfUmAmUmUmUmAmU mCfAmGfGmAfGmUmGmsAmsCm	SEQ ID NO: 906	AUUUGUUAUUUAU CAGGAGUGAC	SEQ ID NO: 354
ETX-S00003402	GmsAfsGmAmAmAfAmCmUmGmGmUmCmAfGmAfUmGfAmAmUmsAmsUm	SEQ ID NO: 907	GAGAAAACUGGUC AGAUGAAUAU	SEQ ID NO: 355
ETX-S00003406	AmsUfsAmUmAmAfUmAmCmAmAmCmA mUfGmCfCmUfGmUmUmsCmsAm	SEQ ID NO: 908	AUAUAAUACAACA UGCCUGUUCA	SEQ ID NO: 356
ETX-S00003410	UmsGfsGmGmAmUfCmCmGmGmAmAmGmCfAmUfUmCfCmCmUmsUmsUm	SEQ ID NO: 909	UGGGAUCCGGAAG CAUUCCCUUU	SEQ ID NO: 357
ETX-S00003414	UmsUfsGmGmGmAfUmCmCmGmGmA mGfCmAfUmUfCmCmCmsUmsUm	SEQ ID NO: 910	UUGGGAUCCGGAA GCAUUCCCUU	SEQ ID NO: 358
ETX-S00003418	CmsAfsGmGmCmAfGmUmCmAmCmCmGmAfGmGfCmCfUmCmGmsGmsAm	SEQ ID NO: 911	CAGGCAGUCACCG AGGCCUCGGA	SEQ ID NO: 359
ETX-S00003422	UmsAfsUmAmUmAfAmUmAmCmAmAmCmAfUmGfCmCfUmGmUmsUmsCm	SEQ ID NO: 912	UAUAUAAUACAAC AUGCCUGUUC	SEQ ID NO: 360
ETX-S00003426	AmsGfsUmCmUmAfUmAmAmUmGmCmCmUfUmUfGmUfAmUmUmsGmsCm	SEQ ID NO: 913	AGUCUAUAAUGCC UUUGUAUUGC	SEQ ID NO: 361
ETX-S00003430	UmsUfsUmAmUmCfAmGmGmAmGmUmGmAfCmUfGmAfAmAmUmsAmsAm	SEQ ID NO: 914	UUUAUCAGGAGUG ACUGAAAUAA	SEQ ID NO: 362
ETX-S00003434	AmsAfsUmAmCmAfAmUmUmGmAmGmUmCfCmCfAmUfCmAmUmsCmsAm	SEQ ID NO: 915	AAUACAAUUGAGU CCCAUCAUCA	SEQ ID NO: 363

ETX- S00003438	CmsUfsUmUmAmAfGmAmGmAmAmAmA mCfUmGfGmUfCmAmGmsAmsUm	SEQ ID NO: 916	CUUUAAGAGAAAA CUGGUCAGAU	SEQ ID NO: 364
ETX- S00003442	GmsCfsUmUmUmAfAmGmAmGmAmAmA mAfCmUfGmGfUmCmAmsGmsAm	SEQ ID NO: 917	GCUUUAAGAGAAA ACUGGUCAGA	SEQ ID NO: 365
ETX- S00003446	AmsAfsUmGmCmCfUmUmUmGmUmAmU mUfGmCfUmUfAmUmCmsUmsGm	SEQ ID NO: 918	AAUGCCUUUGUAU UGCUIAUCUG	SEQ ID NO: 366
ETX- S00003450	UmsAfsAmUmGmCfCmUmUmUmGmUmA mUfUmGfCmUfUmAmUmsCmsUm	SEQ ID NO: 919	UAAUGCCUUUGUA UUGCUUAUCU	SEQ ID NO: 367
ETX- S00003454	UmsAfsCmCmCmUfGmCmAmCmAmGmA mCfAmCfGmUfUmAmAmsAmsGm	SEQ ID NO: 920	UACCCUGCACAGA CACGUUAAAAG	SEQ ID NO: 368
ETX- S00003458	AmsUfsAmCmCmCfUmGmCmAmCmAmG mAfCmAfCmGfUmUmAmsAmsAm	SEQ ID NO: 921	AUACCCUGCACAG ACACGUUAAA	SEQ ID NO: 369
ETX- S00003462	AmsUfsCmCmAmGfCmUmGmAmUmGmA mCfGmAfUmGfUmGmAmsGmsUm	SEQ ID NO: 922	AUCCAGCUGAUGA CGAUGUGAGU	SEQ ID NO: 370
ETX- S00003466	UmsAfsCmAmAmUfUmGmAmGmUmCmC mCfAmUfCmAfUmCmAmsUmsCm	SEQ ID NO: 923	UACAAUUGAGUCC CAUCAUCAUC	SEQ ID NO: 371
ETX- S00003470	UmsGfsGmGmAmAfUmAmCmGmGmAmC mCfAmCfGmCfAmGmUmsCmsUm	SEQ ID NO: 924	UGGGAAUACGGAC CACGCAGUCU	SEQ ID NO: 372
ETX- S00003474	UmsAfsUmAmAmUfAmCmAmAmCmAmU mGfCmCfUmGfUmUmCmsAmsCm	SEQ ID NO: 925	UAUAAUACAACAU GCCUGUUCAC	SEQ ID NO: 373
ETX- S00003478	UmsUfsAmUmCmAfGmGmAmGmUmGmA mCfUmGfAmAfAmUmAmsAmsAm	SEQ ID NO: 926	UUAUCAGGAGUGA CUGAAAUAAA	SEQ ID NO: 374
ETX- S00003482	AmsUfsAmAmUmGfCmCmUmUmUmGmU mAfUmUfGmCfUmUmAmsUmsCm	SEQ ID NO: 927	AUAAUGCCUUUGU AUUGCUUAUC	SEQ ID NO: 375
ETX- S00003486	CmsCfsAmGmCmUfGmAmUmGmAmCmG mAfUmGfUmGfAmGmUmsGmsUm	SEQ ID NO: 928	CCAGCUGAUGACG AUGUGAGUGU	SEQ ID NO: 376
ETX- S00003490	CmsAfsUmAmGmAfUmAmCmCmGmAmA mGfUmAfGmGfCmGmGmsCmsUm	SEQ ID NO: 929	CAUAGAUACCGAA GUAGGCGGCU	SEQ ID NO: 377
ETX- S00003494	CmsAfsUmCmCmAfGmCmUmGmAmUmG mAfCmGfAmUfGmUmGmsAmsGm	SEQ ID NO: 930	CAUCCAGCUGAUG ACGAUGUGAG	SEQ ID NO: 378
ETX- S00003498	GmsUfsCmAmUmAfGmAmUmAmCmCmG mAfAmGfUmAfGmGmCmsGmsGm	SEQ ID NO: 931	GUCAUAGAUACCG AAGUAGGCGG	SEQ ID NO: 379
ETX- S00003502	AmsCfsCmCmUmGfCmAmCmAmGmAmC mAfCmGfUmUfAmAmAmsGmsCm	SEQ ID NO: 932	ACCCUGCACAGAC ACGUUAAAGC	SEQ ID NO: 380
ETX- S00003506	UmsGfsCmAmUmCfAmUmCmAmUmGmC mGfGmCfGmGfCmGmAmsAmsCm	SEQ ID NO: 933	UGCAUCAUCAUGC GGCGGCGAAC	SEQ ID NO: 381
ETX- S00003510	CmsGfsGmAmCmCfAmCmGmCmAmGmU mCfUmAfUmAfAmUmGmsCmsCm	SEQ ID NO: 934	CGGACCACGCAGU CUAUAAUGCC	SEQ ID NO: 382
ETX- S00003514	CmsUfsUmGmGmGfAmAmUmAmCmGmG mAfCmCfAmCfGmCmAmsGmsUm	SEQ ID NO: 935	CUUGGGAUACGG ACCACGCAGU	SEQ ID NO: 383

ETX-S00003518	GmsAfsAmGmUmAfGmGmCmGmGmCmUmCfGmGfUmAfGmAmUmsGmsAm	SEQ ID NO: 936	GAAGUAGGCGGCU CGGUAGAUGA	SEQ ID NO: 384
ETX-S00003522	CmsUfsGmCmUmAfGmAmCmGmGmGmUmAfCmGfGmGfCmAmAmsAmsAm	SEQ ID NO: 937	CUGCUAGACGGGU ACGGGCAAAA	SEQ ID NO: 385
ETX-S00003526	UmsCfsCmAmGmCfUmGmAmUmGmAmCmGfAmUfGmUfGmAmGmsUmsGm	SEQ ID NO: 938	UCCAGCUGAUGAC GAUGUGAGUG	SEQ ID NO: 386
ETX-S00003530	AmsUfsAmCmGmGfAmCmCmAmCmGmCmAfGmUfCmUfAmUmAmsAmsUm	SEQ ID NO: 939	AUACGGACCACGC AGUCUAUAAU	SEQ ID NO: 387
ETX-S00003534	AmsAfsCmCmAmGfGmCmAmGmUmCmA mCfCmGfAmGfGmCmCmsUmsCm	SEQ ID NO: 940	AACCAGGCAGUCA CCGAGGCCUC	SEQ ID NO: 388
ETX-S00003538	UmsGfsAmCmAmGfUmCmUmGmUmGmCmGfAmUfCmAfUmCmCmsAmsGm	SEQ ID NO: 941	UGACAGUCUGUGC GAUCAUCCAG	SEQ ID NO: 389
ETX-S00003542	UmsAfsGmAmCmGfGmGmUmAmCmGmGmGfCmAfAmAfAmUmCmsAmsAm	SEQ ID NO: 942	UAGACGGGUACGG GCAAAAUCAA	SEQ ID NO: 390
ETX-S00003546	GmsCfsAmGmUmGfAmCmAmGmUmCmUmGfUmGfCmGfAmUmCmsAmsUm	SEQ ID NO: 943	GCAGUGACAGUCU GUGCGAUCAU	SEQ ID NO: 391
ETX-S00003550	AmsGfsUmGmAmCfAmGmUmCmUmGmUmGfCmGfAmUfCmAmUmsCmsCm	SEQ ID NO: 944	AGUGACAGUCUGU GCGAUCAUCC	SEQ ID NO: 392
ETX-S00003554	GmsCfsUmAmGmAfCmGmGmGmUmAmCmGfGmGfCmAfAmAmAmsUmsCm	SEQ ID NO: 945	GCUAGACGGGUAC GGGCAAAAUUC	SEQ ID NO: 393
ETX-S00003558	AmsGfsUmAmGmGfCmGmGmCmUmCmGmGfUmAfGmAfUmGmAmsUmsAm	SEQ ID NO: 946	AGUAGGCGGCUCG GUAGAUGAUA	SEQ ID NO: 394
ETX-S00003562	GmsAfsAmUmAmCfGmGmAmCmCmAmCmGfCmAfGmUfCmUmAmsUmsAm	SEQ ID NO: 947	GAAUACGGACCAC GCAGUCUAUA	SEQ ID NO: 395
ETX-S00003566	CmsUfsUmUmGmUfAmUmUmGmCmUmUmAfUmCfUmGfCmAmGmsUmsGm	SEQ ID NO: 948	CUUUGUAUUGCUU AUCUGCAGUG	SEQ ID NO: 396
ETX-S00003570	UmsUfsUmGmUmAfUmUmGmCmUmUmAmUfCmUfGmCfAmGmUmsGmsAm	SEQ ID NO: 949	UUUGUAUUGCUUA UCUGCAGUGA	SEQ ID NO: 397
ETX-S00003574	UmsUfsGmUmAmUfUmGmCmUmUmAmUmCfUmGfCmAfGmUmGmsAmsUm	SEQ ID NO: 950	UUGUAUUGCUUAU CUGCAGUGAU	SEQ ID NO: 398
ETX-S00003578	UmsAfsUmCmUmGfCmAmGmUmGmAmUmCfUmGfCmUfUmGmCmsUmsGm	SEQ ID NO: 951	UAUCUGCAGUGAU CUGCUUGCUG	SEQ ID NO: 399
ETX-S00003582	GmsUfsAmUmUmGfCmUmUmAmUmCmUmGfCmAfGmUfGmAmUmsCmsUm	SEQ ID NO: 952	GUAUUGCUUAUCU GCAGUGAUCU	SEQ ID NO: 400
ETX-S00003586	UmsGfsUmAmUmUfGmCmUmUmAmUmCmUfGmCfAmGfUmGmAmsUmsCm	SEQ ID NO: 953	UGUAUUGCUUAUC UGCAGUGAUC	SEQ ID NO: 401
ETX-S00003590	UmsGfsCmUmUmAfUmCmUmGmCmAmGmUfGmAfUmCfUmGmCmsUmsUm	SEQ ID NO: 954	UGCUIAUCUGCAG UGAUCUGCUI	SEQ ID NO: 402
ETX-S00003594	UmsUfsGmCmUmUfAmUmCmUmGmCmA mGfUmGfAmUfCmUmGmsCmsUm	SEQ ID NO: 955	UUGCUUAUCUGCA GUGAUCUGCU	SEQ ID NO: 403

ETX-S00003598	AmsUfsCmUmGmCfAmGmUmGmAmUmC mUfGmCfUmUfGmCmUmsGmsGm	SEQ ID NO: 956	AUCUGCAGUGAUC UGCUUGCUGG	SEQ ID NO: 404
ETX-S00003602	UmsAfsUmUmGmCfUmUmAmUmCmUmG mCfAmGfUmGfAmUmCmsUmsGm	SEQ ID NO: 957	UAUUGCUUAUCUG CAGUGAUCUG	SEQ ID NO: 405
ETX-S00003606	UmsUfsCmUmCmCfAmAmAmUmUmUmG mUfUmAfUmUfUmAmUmsCmsAm	SEQ ID NO: 958	UUCUCCAAAUUUG UUAUUUAUCA	SEQ ID NO: 406
ETX-S00003610	CmsAfsAmAmUmUfUmGmUmUmAmUmU mUfAmUfCmAfGmGmAmsGmsUm	SEQ ID NO: 959	CAAAUUUGUUAUU UAUCAGGAGU	SEQ ID NO: 407
ETX-S00003614	GmsAfsGmGmCmCfUmCmGmGmAmAmU mUfCmCfCmUfUmUmCmsAmsGm	SEQ ID NO: 960	GAGGCCUCGGAAU UCCCUUUCAG	SEQ ID NO: 408
ETX-S00003618	AmsGfsAmUmAmUfGmUmUmAmUmAmU mAfAmUfAmCfAmAmCmsAmsUm	SEQ ID NO: 961	AGAUUAUGUUAUAU AAUACAACAU	SEQ ID NO: 409
ETX-S00003622	GmsCfsAmGmUmCfAmCmCmGmAmGmG mCfCmUfCmGfGmAmAmsUmsUm	SEQ ID NO: 962	GCAGUCACCGAGG CCUCGGAAUU	SEQ ID NO: 410
ETX-S00003626	CmsGfsAmGmGmCfCmUmCmGmGmAmA mUfUmCfCmCfUmUmUmsCmsAm	SEQ ID NO: 963	CGAGGCCUCGGAA UUCCCUUUCA	SEQ ID NO: 411
ETX-S00003630	CmsAfsAmGmAmUfAmUmGmUmUmAmU mAfUmAfAmUfAmCmAmsAmsCm	SEQ ID NO: 964	CAAGAUUAUGUUAU AUAAUACAAC	SEQ ID NO: 412
ETX-S00003634	AmsGfsUmCmAmCfCmGmAmGmGmCmC mUfCmGfGmAfAmUmUmsCmsCm	SEQ ID NO: 965	AGUCACCGAGGCC UCGGAAUUCC	SEQ ID NO: 413
ETX-S00003638	CmsAfsCmCmGmAfGmGmCmCmUmCmG mGfAmAfUmUfCmCmCmsUmsUm	SEQ ID NO: 966	CACCGAGGCCUCG GAAUUCCCUU	SEQ ID NO: 414
ETX-S00003642	CmsCfsUmCmGmGfAmAmUmUmCmCmC mUfUmUfCmAfGmCmUmsCmsCm	SEQ ID NO: 967	CCUCGGAAUUCCC UUUCAGCUCC	SEQ ID NO: 415
ETX-S00003646	UmsCfsGmGmAmAfUmUmCmCmCmUmU mUfCmAfGmCfUmCmCmsAmsGm	SEQ ID NO: 968	UCGGAAUUCCCUU UCAGCUCCAG	SEQ ID NO: 416
ETX-S00003650	GmsGfsCmCmUmCfGmGmAmAmUmUmC mCfCmUfUmUfCmAmGmsCmsUm	SEQ ID NO: 969	GGCCUCGGAAUUC CCUUUCAGCU	SEQ ID NO: 417
ETX-S00003654	CmsUfsCmGmGmAfAmUmUmCmCmCmU mUfUmCfAmGfCmUmCmsCmsAm	SEQ ID NO: 970	CUCGGAAUUCCCU UUCAGCUCCA	SEQ ID NO: 418
ETX-S00003658	GmsCfsCmUmCmGfGmAmAmUmUmCmC mCfUmUfUmCfAmGmCmsUmsCm	SEQ ID NO: 971	GCCUCGGAAUUCC CUUUCAGCUC	SEQ ID NO: 419
ETX-S00003662	AmsUfsGmUmUmAfUmAmUmAmAmUmA mCfAmAfCmAfUmGmCmsCmsUm	SEQ ID NO: 972	AUGUUAUAUAAUA CAACAUGCCU	SEQ ID NO: 420
ETX-S00003666	AmsAfsGmAmUmAfUmGmUmUmAmUmA mUfAmAfUmAfCmAmAmsCmsAm	SEQ ID NO: 973	AAGAUUAUGUUAUA UAAUACAACA	SEQ ID NO: 421
ETX-S00003670	UmsCfsAmAmGmAfUmAmUmGmUmUmA mUfAmUfAmAfUmAmCmsAmsAm	SEQ ID NO: 974	UCAAGAUUAUGUUA UAUAAUACAA	SEQ ID NO: 422
ETX-S00003674	UmsGfsUmUmAmUfAmUmAmAmUmAmC mAfAmCfAmUfGmCmCmsUmsGm	SEQ ID NO: 975	UGUUAUAUAAUAC AACAUGCCUG	SEQ ID NO: 423

ETX-S00003678	CmsCfsGmAmGmGfCmCmUmCmGmGmA mAfUmUfCmCfCmUmUmsUmsCm	SEQ ID NO: 976	CCGAGGCCUCGGA AUUCCCUUUC	SEQ ID NO: 424
ETX-S00003682	GmsUfsCmAmCmCfGmAmGmGmCmCmU mCfGmGfAmAfUmUmCmsCmsCm	SEQ ID NO: 977	GUCACCGAGGCCU CGGAAUUCCC	SEQ ID NO: 425
ETX-S00003686	AmsCfsCmGmAmGfGmCmCmUmCmGmG mAfAmUfUmCfCmCmUmsUmsUm	SEQ ID NO: 978	ACCGAGGCCUCGG AAUCCCUUU	SEQ ID NO: 426
ETX-S00003690	UmsCfsAmCmCmGfAmGmGmCmCmUmC mGfGmAfAmUfUmCmCmsCmsUm	SEQ ID NO: 979	UCACCGAGGCCUC GGAAUUCCCU	SEQ ID NO: 427
ETX-S00003694	AmsUfsUmUmCmAfUmCmAmUmAmCmA mAfGmAfCmAfAmGmCmsAmsCm	SEQ ID NO: 980	AUUUCAUCAUACA AGACAAGCAC	SEQ ID NO: 428
ETX-S00003698	UmsGfsUmAmUmUfUmAmUmCmUmUmU mGfAmAfGmGfCmGmAmsAmsGm	SEQ ID NO: 981	UGUAUUUAUCUUU GAAGGCGAAG	SEQ ID NO: 429
ETX-S00003702	AmsUfsUmUmGmUfAmGmAmUmCmUmU mAfAmCfCmAfGmGmCmsAmsGm	SEQ ID NO: 982	AUUUGUAGAUCUU AACCAGGCAG	SEQ ID NO: 430
ETX-S00003706	UmsUfsCmCmCmUfUmUmGmCmAmGmU mGfUmCfAmUfAmGmAmsUmsAm	SEQ ID NO: 983	UUCCCUUUGCAGU GUCAUAGAU	SEQ ID NO: 431
ETX-S00003710	AmsUfsCmAmUmAfCmAmAmGmAmCmA mAfGmCfAmCfAmAmsAmsGm	SEQ ID NO: 984	AUCAUACAAGACA AGCACAAAAG	SEQ ID NO: 432
ETX-S00003714	UmsAfsGmAmUmCfUmUmAmAmCmCmA mGfGmCfAmGfUmCmAmsCmsCm	SEQ ID NO: 985	UAGAUCUUAACCA GGCAGUCACC	SEQ ID NO: 433
ETX-S00003718	AmsAfsGmCmAmUfUmCmCmCmUmUmU mGfCmAfGmUfGmUmCmsAmsUm	SEQ ID NO: 986	AAGCAUCCCUUU GCAGUGUCAU	SEQ ID NO: 434
ETX-S00003722	UmsUfsUmGmCmAfGmUmGmUmCmAmU mAfGmAfUmAfCmCmGmsAmsAm	SEQ ID NO: 987	UUUGCAGUGUCAU AGAUACCGAA	SEQ ID NO: 435
ETX-S00003726	AmsGfsAmGmAmAfAmAmCmUmGmGmU mCfAmGfAmUfGmAmAmsUmsAm	SEQ ID NO: 988	AGAGAAAACUGGU CAGAUGAAUA	SEQ ID NO: 436
ETX-S00003730	UmsGfsCmAmGmUfGmUmCmAmUmAmG mAfUmAfCmCfGmAmAmsGmsUm	SEQ ID NO: 989	UGCAGUGUCAUAG AUACCGAAGU	SEQ ID NO: 437
ETX-S00003734	UmsCfsAmGmAmUfUmUmGmUmAmGmA mUfCmUfUmAfAmCmCmsAmsGm	SEQ ID NO: 990	UCAGAUUUGUAGA UCUUAACCAG	SEQ ID NO: 438
ETX-S00003738	UmsCfsCmCmUmUfUmGmCmAmGmUmG mUfCmAfUmAfGmAmUmsAmsCm	SEQ ID NO: 991	UCCCUUUGCAGUG UCAUAGAUAC	SEQ ID NO: 439
ETX-S00003742	GmsAfsAmCmAmUfUmGmGmAmCmCmA mUfGmCfAmCfCmCmUmsUmsGm	SEQ ID NO: 992	GAACAUUGGACCA UGCACCCUUG	SEQ ID NO: 440
ETX-S00003746	AmsAfsUmCmCmCfAmUmCmAmGmAmU mUfUmGfUmAfGmAmUmsCmsUm	SEQ ID NO: 993	AAUCCCAUCAGAU UUGUAGAUCU	SEQ ID NO: 441
ETX-S00003750	GmsCfsAmGmUmGfUmCmAmUmAmGmA mUfAmCfCmGfAmAmGmsUmsAm	SEQ ID NO: 994	GCAGUGUCAUAGA UACCGAAGUA	SEQ ID NO: 442
ETX-S00003754	CmsAfsAmGmCmAfCmAmAmAmAmGmC mAfCmCfAmCfCmCmAmsUmsGm	SEQ ID NO: 995	CAAGCACAAAAGC ACCACCCAUG	SEQ ID NO: 443

ETX-S00003758	GmsCfsGmGmCmUfCmGmGmUmAmGmA mUfGmAfUmAfAmUmAmsCmsCm	SEQ ID NO: 996	GCGGCUCGGUAGA UGAUAAUACC	SEQ ID NO: 444
ETX-S00003762	CmsUfsCmCmUmUfGmGmGmAmAmUmA mCfGmGfAmCfCmAmCmsGmsCm	SEQ ID NO: 997	CUCCUUGGGAAUA CGGACCACGC	SEQ ID NO: 445
ETX-S00003766	AmsUfsUmCmCmCfUmUmUmGmCmAmG mUfGmUfCmAfUmAmGmsAmsUm	SEQ ID NO: 998	AUUCCCUUUGCAG UGUCAUAGAU	SEQ ID NO: 446
ETX-S00003770	CmsAfsUmAmCmAfAmGmAmCmAmAmG mCfAmCfAmAfAmAmGmsCmsAm	SEQ ID NO: 999	CAUACAAGACAAG CACAAAAGCA	SEQ ID NO: 447
ETX-S00003774	AmsGfsAmCmAmCfGmUmUmAmAmAmG mCfCmUfUmGfGmUmAmsCmsAm	SEQ ID NO: 1000	AGACACGUUAAAG CCUUGGUACA	SEQ ID NO: 448
ETX-S00003778	UmsGfsAmGmAmAfCmAmUmUmGmGmA mCfCmAfUmGfCmAmCmsCmsCm	SEQ ID NO: 1001	UGAGAACAUUGGA CCAUGCACCC	SEQ ID NO: 449
ETX-S00003782	GmsCfsUmUmGmUfAmUmUmUmAmUmC mUfUmUfGmAfAmGmGmsCmsGm	SEQ ID NO: 1002	GCUUGUAUUUAUC UUUGAAGGCG	SEQ ID NO: 450
ETX-S00003786	GmsCfsUmCmGmGfUmAmGmAmUmGmA mUfAmAfUmAfCmCmCmsUmsGm	SEQ ID NO: 1003	GCUCGGUAGAUGA UAAUACCCUG	SEQ ID NO: 451
ETX-S00003790	AmsGfsUmGmUmCfAmUmAmGmAmUmA mCfCmGfAmAfGmUmAmsGmsGm	SEQ ID NO: 1004	AGUGUCAUAGAU CCGAAGUAGG	SEQ ID NO: 452
ETX-S00003794	AmsUfsCmAmGmAfUmUmUmGmUmAmG mAfUmCfUmUfAmAmCmsCmsAm	SEQ ID NO: 1005	AUCAGAUUUGUAG AUCUUAACCA	SEQ ID NO: 453
ETX-S00003798	GmsGfsUmAmGmAfUmGmAmUmAmAmU mAfCmCfCmUfGmCmAmsCmsAm	SEQ ID NO: 1006	GGUAGAUGAUAAU ACCCUGCACA	SEQ ID NO: 454
ETX-S00003802	CmsAfsGmGmCmCfCmUmUmAmAmUmC mCfCmAfUmCfAmGmAmsUmsUm	SEQ ID NO: 1007	CAGGCCCUUAAUC CCAUCAGAUU	SEQ ID NO: 455
ETX-S00003806	AmsGfsAmUmGmAfUmAmAmUmAmCmC mCfUmGfCmAfCmAmGmsAmsCm	SEQ ID NO: 1008	AGAUGAUAAUACC CUGCACAGAC	SEQ ID NO: 456
ETX-S00003810	UmsAfsCmAmGmGfCmCmCmUmUmAmA mUfCmCfCmAfUmCmAmsGmsAm	SEQ ID NO: 1009	UACAGGCCCUUAA UCCCAUCAGA	SEQ ID NO: 457
ETX-S00003814	AmsCfsAmGmAmCfAmCmGmUmUmAmA mAfGmCfCmUfUmGmGmsUmsAm	SEQ ID NO: 1010	ACAGACACGUUAA AGCCUUGGUA	SEQ ID NO: 458
ETX-S00003818	AmsGfsAmAmAmAfCmUmGmGmUmCmA mGfAmUfGmAfAmUmAmsUmsUm	SEQ ID NO: 1011	AGAAAACUGGUCA GAUGAAUAAU	SEQ ID NO: 459
ETX-S00003822	UmsGfsUmAmGmAfUmCmUmUmAmAmC mCfAmGfGmCfAmGmUmsCmsAm	SEQ ID NO: 1012	UGUAGAUCUUAAC CAGGCAGUCA	SEQ ID NO: 460
ETX-S00003826	UmsCfsAmAmAmUfGmGmAmUmAmGmG mAfAmGfUmCfAmAmCmsCmsCm	SEQ ID NO: 1013	UCAAAUGGAUAGG AAGUCAACCC	SEQ ID NO: 461
ETX-S00003830	CmsAfsUmUmCmCfCmUmUmUmGmCmA mGfUmGfUmCfAmUmAmsGmsAm	SEQ ID NO: 1014	CAUCCCCUUGCA GUGUCAUAGA	SEQ ID NO: 462
ETX-S00003834	CmsAfsUmCmAmGfAmUmUmUmGmUmA mGfAmUfCmUfUmAmAmsCmsCm	SEQ ID NO: 1015	CAUCAGAUUUGUA GAUCUUAACC	SEQ ID NO: 463

ETX-S00003838	CmsUfsCmGmGmUfAmGmAmUmGmAmUmAfAmUfAmCfCmCmUmsGmsCm	SEQ ID NO: 1016	CUCGGUAGAUGAU AAUACCCUGC	SEQ ID NO: 464
ETX-S00003842	UmsUfsUmGmUmAfGmAmUmCmUmUmAmAfCmCfAmGfGmCmAmsGmsUm	SEQ ID NO: 1017	UUUGUAGAUCUUA ACCAGGCAGU	SEQ ID NO: 465
ETX-S00003846	AmsCfsAmGmGmCfCmCmUmUmAmAmUmCfCmCfAmUfCmAmGmsAmsUm	SEQ ID NO: 1018	ACAGGCCCCUAAU CCCAUCAGAU	SEQ ID NO: 466
ETX-S00003850	CmsUfsUmUmGmCfAmGmUmGmUmCmA mUfAmGfAmUfAmCmCmsGmsAm	SEQ ID NO: 1019	CUUUGCAGUGUCA UAGAUACCGA	SEQ ID NO: 467
ETX-S00003854	CmsAfsCmAmUmCfAmGmCmUmGmCmUmAfGmAfCmGfGmGmUmsAmsCm	SEQ ID NO: 1020	CACAUCAGCUGCU AGACGGGUAC	SEQ ID NO: 468
ETX-S00003858	CmsCfsCmUmUmUfGmCmAmGmUmGmUmCfAmUfAmGfAmUmAmsCmsCm	SEQ ID NO: 1021	CCCUUUGCAGUGU CAUAGAUACC	SEQ ID NO: 469
ETX-S00003862	CmsUfsCmCmAmGfCmUmUmUmAmCmCmCfAmCfAmUfCmAmGmsCmsUm	SEQ ID NO: 1022	CUCCAGCUUUACC CACAUCAGCU	SEQ ID NO: 470
ETX-S00003866	UmsUfsAmCmCmCfAmCmAmUmCmAmGmCfUmGfCmUfAmGmAmsCmsGm	SEQ ID NO: 1023	UUACCCACAUCAG CUGCUAGACG	SEQ ID NO: 471
ETX-S00003870	UmsUfsAmAmAmGfCmCmUmUmGmGmUmAfCmAfGmGfCmCmCmsUmsUm	SEQ ID NO: 1024	UUAAAGCCUUGGU ACAGGCCCUU	SEQ ID NO: 472
ETX-S00003874	CmsAfsGmCmUmGfCmUmAmGmAmCmGmGfGmUfAmCfGmGmGmsCmsAm	SEQ ID NO: 1025	CAGCUGCUAGACG GGUACGGGCA	SEQ ID NO: 473
ETX-S00003878	CmsAfsGmCmUmUfUmAmCmCmCmAmCmAfUmCfAmGfCmUmGmsCmsUm	SEQ ID NO: 1026	CAGCUUUACCCAC AUCAGCUGCU	SEQ ID NO: 474
ETX-S00003882	UmsCfsAmGmCmUfGmCmUmAmGmAmCmGmGfGmGfUmAfCmGmGmsGmsCm	SEQ ID NO: 1027	UCAGCUGCUAGAC GGGUACGGGC	SEQ ID NO: 475
ETX-S00003886	UmsCfsCmAmGmCfUmUmUmAmCmCmCmAfCmAfUmCfAmGmCmsUmsGm	SEQ ID NO: 1028	UCCAGCUUUACCC ACAUCAGCUG	SEQ ID NO: 476
ETX-S00003890	GmsGfsCmUmCmGfGmUmAmGmAmUmGmAfUmAfAmUfAmCmCmsCmsUm	SEQ ID NO: 1029	GGCUCGGUAGAUG AUAUACCCU	SEQ ID NO: 477
ETX-S00003894	AmsGfsGmCmGmGfCmUmCmGmGmUmAmGfAmUfGmAfUmAmAmsUmsAm	SEQ ID NO: 1030	AGGCGGCUCGGUA GAUGAUAAUA	SEQ ID NO: 478
ETX-S00003898	CmsAfsUmCmAmGfCmUmGmCmUmAmGmAfCmGfGmGfUmAmCmsGmsGm	SEQ ID NO: 1031	CAUCAGCUGCUAG ACGGGUACGG	SEQ ID NO: 479
ETX-S00003902	GmsUfsAmCmAmGfGmCmCmCmUmUmAmAfUmCfCmCfAmUmCmsAmsGm	SEQ ID NO: 1032	GUACAGGCCCUUA AUCCCAUCAG	SEQ ID NO: 480
ETX-S00003906	AmsUfsGmAmUmAfAmUmAmCmCmCmUmGfCmAfCmAfGmAmCmsAmsCm	SEQ ID NO: 1033	AUGAUAAUACCCU GCACAGACAC	SEQ ID NO: 481
ETX-S00003910	CmsCfsUmUmGmGfGmAmAmUmAmCmGmGfAmCfCmAfCmGmCmsAmsGm	SEQ ID NO: 1034	CCUUGGGAAUACG GACCACGCAG	SEQ ID NO: 482
ETX-S00003914	UmsCfsCmUmUmGfGmGmAmAmUmAmCmGfGmAfCmCfAmCmGmsCmsAm	SEQ ID NO: 1035	UCCUUGGGAAUAC GGACCACGCA	SEQ ID NO: 483

ETX-S00003918	CmsAfsGmAmUmUfUmGmUmAmGmAmUmCfUmUfAmAfCmCmAmsGmsGm	SEQ ID NO: 1036	CAGAUUUGUAGAU CUUAACCAGG	SEQ ID NO: 484
ETX-S00003922	UmsGfsUmAmCmUfUmCmUmUmGmAmUmUfUmCfAmUfCmAmUmsAmsCm	SEQ ID NO: 1037	UGUACUUCUUGAU UUCAUCAUAC	SEQ ID NO: 485
ETX-S00003926	AmsUfsCmCmCmAfUmCmAmGmAmUmUmUfGmUfAmGfAmUmCmsUmsUm	SEQ ID NO: 1038	AUCCCAUCAGAUU UGUAGAUCUU	SEQ ID NO: 486
ETX-S00003930	GmsUfsAmGmAmUfGmAmUmAmAmUmAmCfCmCfUmGfCmAmCmsAmsGm	SEQ ID NO: 1039	GUAGAUGAUAAUA CCCUGCACAG	SEQ ID NO: 487
ETX-S00003934	GmsAfsCmAmCmGfUmUmAmAmAmGmCmCfUmUfGmGfUmAmCmsAmsGm	SEQ ID NO: 1040	GACACGUUAAAGC CUUGGUACAG	SEQ ID NO: 488
ETX-S00003938	AmsGfsCmUmUmUfAmCmCmCmAmCmA mUfCmAfGmCfUmGmCmsUmsAm	SEQ ID NO: 1041	AGCUUUACCCACA UCAGCUGCUA	SEQ ID NO: 489
ETX-S00003942	AmsAfsGmCmAmCfAmAmAmAmGmCmA mCfCmAfCmCfCmAmUmsGmsCm	SEQ ID NO: 1042	AAGCACAAAAGCA CCACCCAUGC	SEQ ID NO: 490
ETX-S00003946	AmsUfsCmUmUmAfAmCmCmAmGmGmC mAfGmUfCmAfCmCmGmsAmsGm	SEQ ID NO: 1043	AUCUUAACCAGGC AGUCACCGAG	SEQ ID NO: 491
ETX-S00003950	UmsUfsUmAmCmCfCmAmCmAmUmCmA mGfCmUfGmCfUmAmGmsAmsCm	SEQ ID NO: 1044	UUUACCCACAUCA GCUGCUAGAC	SEQ ID NO: 492
ETX-S00003954	CmsUfsUmAmAmUfCmCmCmAmUmCmA mGfAmUfUmUfGmUmAmsGmsAm	SEQ ID NO: 1045	CUUAAUCCCAUCA GAUUUGUAGA	SEQ ID NO: 493
ETX-S00003958	CmsAfsGmUmGmUfCmAmUmAmGmAmUmAfCmCfGmAfAmGmUmsAmsGm	SEQ ID NO: 1046	CAGUGUCAUAGAU ACCGAAGUAG	SEQ ID NO: 494
ETX-S00003962	CmsCfsAmGmCmUfUmUmAmCmCmCmA mCfAmUfCmAfGmCmUmsGmsCm	SEQ ID NO: 1047	CCAGCUUUACCCA CAUCAGCUGC	SEQ ID NO: 495
ETX-S00003966	AmsUfsCmAmGmCfUmGmCmUmAmGmA mCfGmGfGmUfAmCmGmsGmsGm	SEQ ID NO: 1048	AUCAGCUGCUAGA CGGGUACGGG	SEQ ID NO: 496
ETX-S00003970	GmsAfsUmGmAmUfAmAmUmAmCmCmC mUfGmCfAmCfAmGmAmsCmsAm	SEQ ID NO: 1049	GAUGAUAAUACCC UGCACAGACA	SEQ ID NO: 497
ETX-S00003974	UmsUfsUmCmAmUfCmAmUmAmCmAmA mGfAmCfAmAfGmCmAmsCmsAm	SEQ ID NO: 1050	UUUCAUCAUACAA GACAAGCACA	SEQ ID NO: 498
ETX-S00003978	CmsAfsGmAmCmAfCmGmUmUmAmAmA mGfCmCfUmUfGmGmUmsAmsCm	SEQ ID NO: 1051	CAGACACGUUAAA GCCUUGGUAC	SEQ ID NO: 499
ETX-S00003982	AmsGfsAmAmCmAfUmUmGmGmAmCmC mAfUmGfCmAfCmCmCmsUmsUm	SEQ ID NO: 1052	AGAACAUUGGACC AUGCACCCUU	SEQ ID NO: 500
ETX-S00003986	GmsUfsAmGmAmUfCmUmUmAmAmCmC mAfGmGfCmAfGmUmCmsAmsCm	SEQ ID NO: 1053	GUAGAUCUUAACC AGGCAGUCAC	SEQ ID NO: 501
ETX-S00003990	AmsGfsCmUmCmCfAmGmCmUmUmUmA mCfCmCfAmCfAmUmCmsAmsGm	SEQ ID NO: 1054	AGCUCCAGCUUUA CCCACAUCAG	SEQ ID NO: 502
ETX-S00003994	GmsCfsUmCmCmUfUmGmGmGmAmAmU mAfCmGfGmAfCmCmAmsCmsGm	SEQ ID NO: 1055	GCUCCUUGGGAAU ACGGACCACG	SEQ ID NO: 503

ETX-S00003998	GmsAfsAmGmCmAfUmUmCmCmCmUmUmUfGmCfAmGfUmGmUmsCmsAm	SEQ ID NO: 1056	GAAGCAUUCUUUGCAGUGUCA	SEQ ID NO: 504
ETX-S00004002	CmsCfsUmUmGmGfUmAmCmAmGmGmCmCfCmUfUmAfAmUmCmsCmsCm	SEQ ID NO: 1057	CCUUGGUACAGGC CCUUAUUCCC	SEQ ID NO: 505
ETX-S00004006	UmsAfsGmAmUmGfAmUmAmAmUmAmCmCfCmUfGmCfAmCmAmsGmsAm	SEQ ID NO: 1058	UAGAUGAUAAUAC CCUGCACAGA	SEQ ID NO: 506
ETX-S00004010	AmsAfsUmAmCmCfCmUmGmCmAmCmA mGfAmCfAmCfGmUmUmsAmsAm	SEQ ID NO: 1059	AAUACCCUGCACA GACACGUUAA	SEQ ID NO: 507
ETX-S00004014	GmsUfsUmAmAmAfGmCmCmUmUmGmGmUfAmCfAmGfGmCmCmsCmsUm	SEQ ID NO: 1060	GUUAAAGCCUUGG UACAGGCCCU	SEQ ID NO: 508
ETX-S00004018	AmsGfsCmAmUmUfCmCmCmUmUmUmGmCfAmGfUmGfUmCmAmsUmsAm	SEQ ID NO: 1061	AGCAUUCUUUG CAGUGUCAUA	SEQ ID NO: 509
ETX-S00004022	UmsCfsUmUmAmAfCmCmAmGmGmCmA mGfUmCfAmCfCmGmAmsGmsGm	SEQ ID NO: 1062	UCUUAACCAGGCA GUCACCGAGG	SEQ ID NO: 510
ETX-S00004026	AmsUfsAmCmAmAfGmAmCmAmAmGmCmAfCmAfAmAfAmGmCmsAmsCm	SEQ ID NO: 1063	AUACAAGACAAGC ACAAAGCAC	SEQ ID NO: 511
ETX-S00004030	GmsAfsCmAmAmGfCmAmCmAmAmAmA mGfCmAfCmCfAmCmCmsCmsAm	SEQ ID NO: 1064	GACAAGCACAAA GCACCACCA	SEQ ID NO: 512
ETX-S00004034	AmsCfsCmCmAmCfAmUmCmAmGmCmUmGfCmUfAmGfAmCmGmsGmsGm	SEQ ID NO: 1065	ACCCACAUCAGCU GCUAGACGGG	SEQ ID NO: 513
ETX-S00004038	UmsAfsAmAmGmCfCmUmUmGmGmUmAmCfAmGfGmCfCmCmUmsUmsAm	SEQ ID NO: 1066	UAAAGCCUUGGUA CAGGCCCUUA	SEQ ID NO: 514
ETX-S00004042	UmsUfsCmAmUmCfAmUmAmCmAmAmGmAfCmAfAmGfCmAmCmsAmsAm	SEQ ID NO: 1067	UUCAUCAUACAAG ACAAGCACAA	SEQ ID NO: 515
ETX-S00004046	GmsCfsCmCmUmUfAmAmUmCmCmCmA mUfCmAfGmAfUmUmUmsGmsUm	SEQ ID NO: 1068	GCCCUAAUCCCA UCAGAUUUGU	SEQ ID NO: 516
ETX-S00004050	UmsUfsAmAmUmCfCmCmAmUmCmAmGmAfUmUfUmGfUmAmGmsAmsUm	SEQ ID NO: 1069	UUAAUCCCAUCAG AUUUGUAGAU	SEQ ID NO: 517
ETX-S00004054	UmsCfsGmGmUmAfGmAmUmGmAmUmAmAfUmAfCmCfCmUmGmsCmsAm	SEQ ID NO: 1070	UCGGUAGAUGAUA AUACCCUGCA	SEQ ID NO: 518
ETX-S00004058	CmsAfsCmGmUmUfAmAmAmGmCmCmUmUfGmGfUmAfCmAmGmsGmsCm	SEQ ID NO: 1071	CACGUUAAAGCCU UGGUACAGGC	SEQ ID NO: 519
ETX-S00004062	UmsCfsCmCmAmUfCmAmGmAmUmUmUmGfUmAfGmAfUmCmUmsUmsAm	SEQ ID NO: 1072	UCCCAUCAGAUUU GUAGAUCUUA	SEQ ID NO: 520
ETX-S00004066	UmsCfsAmUmAmCfAmAmGmAmCmAmAmGfCmAfCmAfAmAmAmsGmsCm	SEQ ID NO: 1073	UCAUACAAGACAA GCACAAAAGC	SEQ ID NO: 521
ETX-S00004070	CmsCfsUmUmAmAfUmCmCmCmAmUmCmAfGmAfUmUfUmGmUmsAmsGm	SEQ ID NO: 1074	CCUUAUUCCCAUC AGAUUUGUAG	SEQ ID NO: 522
ETX-S00004074	AmsCfsAmUmUmGfGmAmCmCmAmUmGmCfAmCfCmCfUmUmGmsAmsAm	SEQ ID NO: 1075	ACAUUGGACCAUG CACCCUUGAA	SEQ ID NO: 523

ETX-S00004078	CmsUfsUmGmGmUfAmCmAmGmGmCmCmCfUmUfAmAfUmCmCmsCmsAm	SEQ ID NO: 1076	CUUGGUACAGGCC CUUAAUCCCA	SEQ ID NO: 524
ETX-S00004082	UmsUfsGmCmAmGfUmGmUmCmAmUmAmGfAmUfAmCfCmGmAmsAmsGm	SEQ ID NO: 1077	UUGCAGUGUCAUA GAUACCGAAG	SEQ ID NO: 525
ETX-S00004086	CmsAfsCmAmGmAfCmAmCmGmUmUmAmAfAmGfCmCfUmUmGmsGmsUm	SEQ ID NO: 1078	CACAGACACGUUA AAGCCUUGGU	SEQ ID NO: 526
ETX-S00004090	AmsGfsCmAmCmAfAmAmAmGmCmAmCmCfAmCfCmCfAmUmGmsCmsCm	SEQ ID NO: 1079	AGCACAAAAGCAC CACCAUGCC	SEQ ID NO: 527
ETX-S00004094	CmsCfsAmUmCmAfGmAmUmUmUmGmUmAfGmAfUmCfUmUmAmsAmsCm	SEQ ID NO: 1080	CCAUCAGAUUUGU AGAUCUUAAC	SEQ ID NO: 528
ETX-S00004098	CmsCfsAmCmAmUfCmAmGmCmUmGmCmUfAmGfAmCfGmGmGmsUmsAm	SEQ ID NO: 1081	CCACAUCAGCUGC UAGACGGGUA	SEQ ID NO: 529
ETX-S00004102	GmsCfsAmUmUmCfCmCmUmUmUmGmCmAfGmUfGmUfCmAmUmsAmsGm	SEQ ID NO: 1082	GCAUCCCCUUGC AGUGUCAUAG	SEQ ID NO: 530
ETX-S00004106	CmsUfsUmUmAmCfCmCmAmCmAmUmCmAfGmCfUmGfCmUmAmsGmsAm	SEQ ID NO: 1083	CUUUACCCACAUC AGCUGCUAGA	SEQ ID NO: 531
ETX-S00004110	AmsUfsCmCmGmGfAmAmGmCmAmUmUmCfCmCfUmUfUmGmCmsAmsGm	SEQ ID NO: 1084	AUCCGGAAGCAUU CCC UUUGCAG	SEQ ID NO: 532
ETX-S00004114	AmsGfsCmUmGmCfUmAmGmAmCmGmGmGfUmAfCmGfGmGmCmsAmsAm	SEQ ID NO: 1085	AGCUGCUAGACGG GUACGGGCAA	SEQ ID NO: 533
ETX-S00004118	CmsGfsGmCmUmCfGmGmUmAmGmAmUmGfAmUfAmAfUmAmCmsCmsCm	SEQ ID NO: 1086	CGGCUCGGUAGAU GAUAAUACCC	SEQ ID NO: 534
ETX-S00004122	GmsGfsGmUmAmCfGmGmGmCmAmAmAmAfUmCfAmAfGmAmGmsGmsGm	SEQ ID NO: 1087	GGGUACGGGCAAA AUCAAGAGGG	SEQ ID NO: 535
ETX-S00004126	AmsCfsAmUmCmAfGmCmUmGmCmUmAmGfAmCfGmGfGmUmAmsCmsGm	SEQ ID NO: 1088	ACAUCAGCUGCUA GACGGGUACG	SEQ ID NO: 536
ETX-S00004130	CmsCfsCmUmUmAfAmUmCmCmCmAmUmCfAmGfAmUfUmUmGmsUmsAm	SEQ ID NO: 1089	CCCUAAUCCCAU CAGAUUUGUA	SEQ ID NO: 537
ETX-S00004134	CmsGfsGmGmCmAfAmAmAmUmCmAmAmGfAmGfGmGfUmAmCmsAmsCm	SEQ ID NO: 1090	CGGGCAAAAUCAA GAGGGUACAC	SEQ ID NO: 538
ETX-S00004138	AmsCfsGmUmUmAfAmAmGmCmCmUmUmGfGmUfAmCfAmGmGmsCmsCm	SEQ ID NO: 1091	ACGUAAAGCCUU GGUACAGGCC	SEQ ID NO: 539
ETX-S00004142	UmsGfsGmUmAmCfAmGmGmCmCmCmUmUfAmAfUmCfCmCmAmsUmsCm	SEQ ID NO: 1092	UGGUACAGGCCCU UAAUCCCAUC	SEQ ID NO: 540
ETX-S00004146	GmsGfsCmGmGmCfUmCmGmGmUmAmGmAfUmGfAmUfAmAmUmsAmsCm	SEQ ID NO: 1093	GGCGGCUCGGUAG AUGAUAAUAC	SEQ ID NO: 541
ETX-S00004150	CmsGfsUmUmAmAfAmGmCmCmUmUmGmGfUmAfCmAfGmGmCmsCmsCm	SEQ ID NO: 1094	CGUAAAGCCUUG GUACAGGCCC	SEQ ID NO: 542
ETX-S00004154	GmsGfsUmAmCmAfGmGmCmCmCmUmUmAfAmUfCmCfCmAmUmsCmsAm	SEQ ID NO: 1095	GGUACAGGCCCUU AAUCCCAUCA	SEQ ID NO: 543

ETX-S00004158	UmsAfsAmUmAmCfCmCmUmGmCmAmCmAfGmAfCmAfCmGmUmsUmsAm	SEQ ID NO: 1096	UAAUACCCUGCACAGACACGUUA	SEQ ID NO: 544
ETX-S00004162	GmsAfsCmCmAmCfGmCmAmGmUmCmUmAfUmAfAmUfGmCmCmsUmsUm	SEQ ID NO: 1097	GACCACGCAGUCUAUAAUGCCUU	SEQ ID NO: 545
ETX-S00004166	GmsUfsUmAmAmGfAmGmCmCmUmGmGmGfUmGfGmGfGmAmAmsGmsUm	SEQ ID NO: 1098	GUUAAGAGCCUGGGUGGGGAAGU	SEQ ID NO: 546
ETX-S00004170	UmsGfsGmGmGmAfAmGmUmAmUmCmUmGfAmUfGmAfCmAmsUmsGm	SEQ ID NO: 1099	UGGGGAAGUAUCUGAUGACAUUG	SEQ ID NO: 547
ETX-S00004174	GmsGfsUmGmGmGfGmAmAmGmUmAmUmCfUmGfAmUfGmAmCmsAmsUm	SEQ ID NO: 1100	GGUGGGGAAGUAUCUGAUGACAU	SEQ ID NO: 548
ETX-S00004178	GmsUfsGmGmGmGfAmAmGmUmAmUmCmUmUfGmAfUmGfAmCmAmsUmsUm	SEQ ID NO: 1101	GUGGGGAAGUAUCUGAUGACAUU	SEQ ID NO: 549
ETX-S00004182	GmsGfsGmGmAmAfGmUmAmUmCmUmGmAfUmGfAmCfAmUmsGmsGm	SEQ ID NO: 1102	GGGGAAGUAUCUGAUGACAUUGG	SEQ ID NO: 550
ETX-S00004186	UmsUfsAmAmGmAfGmCmCmUmGmGmGmUfGmGfGmGfAmAmGmsUmsAm	SEQ ID NO: 1103	UUAAGAGCCUGGGUGGGGAAGUA	SEQ ID NO: 551
ETX-S00004190	CmsCfsGmAmAmGfUmAmGmGmCmGmGmCfUmCfGmGfUmAmGmsAmsUm	SEQ ID NO: 1104	CCGAAGUAGGCGGCUCGGUAGAU	SEQ ID NO: 552

In certain embodiments, the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 1105-1380; wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

- 5 In certain embodiments, the second strand comprises a nucleoside sequence of at least 19 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 1105-1380; wherein the second strand has a region of at least 85% complementarity over the 19 contiguous nucleosides to the first strand.

- In certain embodiments, the second strand comprises a nucleoside sequence of at least 21 contiguous nucleosides differing by 0 or 1 nucleosides from any one of SEQ ID NO: 1105-1380; wherein the second strand has a region of at least 85% complementarity over the 21 contiguous nucleosides to the first strand.
- 10

In certain embodiments, the second strand comprises any one of SEQ ID NO: 1105-1380.

The modification pattern of the nucleic acids as set forth in SEQ ID NO: 1105-1380 is summarized in Table 4 below:

Table 4

Sense strand ID	Modified Sense Strand 5' → 3'	SEQ ID NO (SS - mod)	Underlying Base Sequence 5' → 3' (Shown as an Unmodified Nucleotide Sequence)	SEQ ID NO (SS - unmod)
ETX-S00003089	iaiaUmsAmsUmUmUmAmCmUmGfGfUfU mGmAmAmAmAmUmGmGmGm	SEQ ID NO: 1105	UAUUUACUGGUUG AAAAUGGG	SEQ ID NO: 553
ETX-S00003093	iaiaCmsAmsAmAmGmGmCmAmUfUfAfU mAmGmAmCmUmGmCmGmUm	SEQ ID NO: 1106	CAAAGGCAUUUAU GACUGCGU	SEQ ID NO: 554
ETX-S00003097	iaiaUmsGmsAmUmGmAmAmAmUfCfAfA mGmAmAmGmUmAmCmAmCm	SEQ ID NO: 1107	UGAUGAAAUCAAG AAGUACAC	SEQ ID NO: 555
ETX-S00003101	iaiaGmsAmsUmGmAmUmGmGmGfAfCfU mCmAmAmUmUmGmUmAmUm	SEQ ID NO: 1108	GAUGAUGGGACUC AAUUGUAU	SEQ ID NO: 556
ETX-S00003105	iaiaGmsCmsAmUmUmAmUmAmGfAfCfU mGmCmGmUmGmGmUmCmCm	SEQ ID NO: 1109	GCAUUAUAGACUG CGUGGUCC	SEQ ID NO: 557
ETX-S00003109	iaiaGmsUmsCmAmCmUmCmCmUfGfAfUm AmAmAmUmAmAmCmAmAm	SEQ ID NO: 1110	GUCACUCCUGAUA AAUAACAA	SEQ ID NO: 558
ETX-S00003113	iaiaAmsUmsAmCmAmAmAmGmGfCfAfU mUmAmUmAmGmAmCmUmGm	SEQ ID NO: 1111	AUACAAAGGCAUU AUAGACUG	SEQ ID NO: 559
ETX-S00003117	iaiaGmsCmsCmGmCmCmUmAmCfUfUfCm GmGmUmAmUmCmUmAmUm	SEQ ID NO: 1112	GCCGCCUACUUCG GUAUCUAU	SEQ ID NO: 560
ETX-S00003121	iaiaAmsGmsCmCmGmCmCmUmAfCfUfUm CmGmGmUmAmUmCmUmAm	SEQ ID NO: 1113	AGCCGCCUACUUC GGUAUCUA	SEQ ID NO: 561
ETX-S00003125	iaiaAmsGmsAmCmUmGmCmGmUfGfGfU mCmCmGmUmAmUmUmCmCm	SEQ ID NO: 1114	AGACUGCGUGGUC CGUAUUCC	SEQ ID NO: 562
ETX-S00003129	iaiaCmsAmsCmUmCmAmCmAmUfCfGfUm CmAmUmCmAmGmCmUmGm	SEQ ID NO: 1115	CACUCACAUCGUC AUCAGCUG	SEQ ID NO: 563
ETX-S00003133	iaiaAmsCmsUmUmCmGmCmCmUfUfCfAm AmAmGmAmUmAmAmAmUm	SEQ ID NO: 1116	ACUUCGCCUUCAA AGAUAAAU	SEQ ID NO: 564
ETX-S00003137	iaiaCmsUmsAmCmUmUmCmGmGfUfAfUm CmUmAmUmGmAmCmAmCm	SEQ ID NO: 1117	CUACUUCGGUAUC UAUGACAC	SEQ ID NO: 565
ETX-S00003141	iaiaUmsUmsUmAmCmUmGmGmUfUfGfA mAmAmAmUmGmGmGmAmAm	SEQ ID NO: 1118	UUUACUGGUUGAA AAUGGGAA	SEQ ID NO: 566
ETX-S00003145	iaiaUmsGmsCmCmCmGmUmAmCfCfCfGm UmCmUmAmGmCmAmGmCm	SEQ ID NO: 1119	UGCCCGUACCCGU CUAGCAGC	SEQ ID NO: 567
ETX-S00003149	iaiaAmsGmsUmCmAmGmGmGmCfGfCfAm AmAmGmGmAmAmCmUmGm	SEQ ID NO: 1120	AGUCAGGGCGCAA AGGAACUG	SEQ ID NO: 568
ETX-S00003153	iaiaUmsUmsAmCmUmGmGmUmUfGfAfA mAmAmUmGmGmGmAmAmGm	SEQ ID NO: 1121	UUACUGGUUGAAA AUGGGAAG	SEQ ID NO: 569

ETX-S00003157	iaiaGmsAmsGmCmCmGmCmCmUfAfCfUm UmCmGmGmUmAmUmCmUm	SEQ ID NO: 1122	GAGCCGCCUACUU CGGUAUCU	SEQ ID NO: 570
ETX-S00003161	iaiaCmsCmsUmCmGmGmUmGmAfCfUfGm CmCmUmGmGmUmUmAmAm	SEQ ID NO: 1123	CCUCGGUGACUGC CUGGUUAA	SEQ ID NO: 571
ETX-S00003165	iaiaCmsAmsUmCmGmUmCmAmUfCfAfGm CmUmGmGmAmUmGmAmUm	SEQ ID NO: 1124	CAUCGUCAUCAGC UGGAUGAU	SEQ ID NO: 572
ETX-S00003169	iaiaUmsUmsUmCmAmGmUmCmAfCfUfCm CmUmGmAmUmAmAmAmUm	SEQ ID NO: 1125	UUUCAGUCACUCC UGAUAAAU	SEQ ID NO: 573
ETX-S00003173	iaiaUmsGmsGmAmUmGmAmUmCfGfCfA mCmAmGmAmCmUmGmUmCm	SEQ ID NO: 1126	UGGAUGAUCGCAC AGACUGUC	SEQ ID NO: 574
ETX-S00003177	iaiaGmsCmsAmAmUmAmCmAmAfAfGfG mCmAmUmUmAmUmAmGmAm	SEQ ID NO: 1127	GCAAUACAAAGGC AUUAUAGA	SEQ ID NO: 575
ETX-S00003181	iaiaGmsCmsCmUmCmGmGmUmGfAfCfUm GmCmCmUmGmGmUmUmAm	SEQ ID NO: 1128	GCCUCGGUGACUG CCUGGUUA	SEQ ID NO: 576
ETX-S00003185	iaiaCmsUmsUmUmAmAmCmGmUfGfUfCm UmGmUmGmCmAmGmGmGm	SEQ ID NO: 1129	CUUUAACGUGUCU GUGCAGGG	SEQ ID NO: 577
ETX-S00003189	iaiaAmsAmsAmGmGmCmAmUmUfAfUfA mGmAmCmUmGmCmGmUmGm	SEQ ID NO: 1130	AAAGGCAUUAUAG ACUGCGUG	SEQ ID NO: 578
ETX-S00003193	iaiaGmsUmsGmAmAmCmAmGmGfCfAfU mGmUmUmGmUmAmUmUmAm	SEQ ID NO: 1131	GUGAACAGGCAUG UUGUAUUA	SEQ ID NO: 579
ETX-S00003197	iaiaAmsUmsCmUmGmAmCmCmAfGfUfUm UmUmCmUmCmUmUmAmAm	SEQ ID NO: 1132	AUCUGACCAGUUU UCUCUUA	SEQ ID NO: 580
ETX-S00003201	iaiaAmsGmsGmCmUmUmUmAmAfCfGfU mGmUmCmUmGmUmGmCmAm	SEQ ID NO: 1133	AGGCUUUAACGUG UCUGUGCA	SEQ ID NO: 581
ETX-S00003205	iaiaGmsCmsAmGmUmCmAmGmGfGfCfGm CmAmAmAmGmGmAmAmCm	SEQ ID NO: 1134	GCAGUCAGGGCGC AAAGGAAC	SEQ ID NO: 582
ETX-S00003209	iaiaGmsAmsUmGmAmUmCmGmCfAfCfAm GmAmCmUmGmUmCmAmCm	SEQ ID NO: 1135	GAUGAUCGCACAG ACUGUCAC	SEQ ID NO: 583
ETX-S00003213	iaiaAmsGmsGmCmAmUmUmAmUfAfGfA mCmUmGmCmGmUmGmGmUm	SEQ ID NO: 1136	AGGCAUUAUAGAC UGCGUGGU	SEQ ID NO: 584
ETX-S00003217	iaiaUmsGmsAmUmCmGmCmAmCfAfGfAm CmUmGmUmCmAmCmUmGm	SEQ ID NO: 1137	UGAUCGCACAGAC UGUCACUG	SEQ ID NO: 585
ETX-S00003221	iaiaCmsUmsGmCmGmUmGmGmUfCfCfGm UmAmUmUmCmCmCmAmAm	SEQ ID NO: 1138	CUGCGUGGUCCGU AUUCCCAA	SEQ ID NO: 586
ETX-S00003225	iaiaCmsAmsAmUmAmCmAmAmAfGfGfCm AmUmUmAmUmAmGmAmCm	SEQ ID NO: 1139	CAAUACAAAGGCA UUAUAGAC	SEQ ID NO: 587
ETX-S00003229	iaiaCmsAmsUmCmAmGmCmUmGfGfAfUm GmAmUmCmGmCmAmCmAm	SEQ ID NO: 1140	CAUCAGCUGGAUG AUCGCACA	SEQ ID NO: 588
ETX-S00003233	iaiaAmsUmsUmAmUmAmGmAmCfUfGfC mGmUmGmGmUmCmCmGmUm	SEQ ID NO: 1141	AUUAUAGACUGCG UGGUCCGU	SEQ ID NO: 589

ETX-S00003237	iaiaUmsUmsUmGmCmCmCmGmUfAfCfCm CmGmUmCmUmAmGmCmAm	SEQ ID NO: 1142	UUUGCCCGUACCC GUCUAGCA	SEQ ID NO: 590
ETX-S00003241	iaiaAmsCmsAmUmCmGmUmCmAfUfCfAm GmCmUmGmGmAmUmGmAm	SEQ ID NO: 1143	ACAUCGUCAUCAG CUGGAUGA	SEQ ID NO: 591
ETX-S00003245	iaiaUmsCmsUmUmGmAmUmUmUfUfGfC mCmCmGmUmAmCmCmCmGm	SEQ ID NO: 1144	UCUUGAUUUUGCC CGUACCCG	SEQ ID NO: 592
ETX-S00003249	iaiaAmsUmsAmGmAmCmUmGmCfGfUfG mGmUmCmCmGmUmAmUmUm	SEQ ID NO: 1145	AUAGACUGCGUGG UCCGUAAU	SEQ ID NO: 593
ETX-S00003253	iaiaCmsGmsCmCmUmAmCmUmUfCfGfGm UmAmUmCmUmAmUmGmAm	SEQ ID NO: 1146	CGCCUACUUCGGU AUCUAUGA	SEQ ID NO: 594
ETX-S00003257	iaiaGmsAmsCmUmGmCmGmUmGfGfUfCm CmGmUmAmUmUmCmCmCm	SEQ ID NO: 1147	GACUGCGUGGUCC GUAUCCCC	SEQ ID NO: 595
ETX-S00003261	iaiaUmsCmsAmUmCmAmGmCmUfGfGfAm UmGmAmUmCmGmCmAmCm	SEQ ID NO: 1148	UCAUCAGCUGGAU GAUCGCAC	SEQ ID NO: 596
ETX-S00003265	iaiaUmsUmsAmUmAmGmAmCmUfGfCfG mUmGmGmUmCmCmGmUmAm	SEQ ID NO: 1149	UUAUAGACUGCGU GGUCCGUA	SEQ ID NO: 597
ETX-S00003269	iaiaCmsCmsUmAmCmUmUmCmGfGfUfAm UmCmUmAmUmGmAmCmAm	SEQ ID NO: 1150	CCUACUUCGGUAAU CUAUGACA	SEQ ID NO: 598
ETX-S00003273	iaiaUmsUmsAmUmUmUmCmAmGfUfCfA mCmUmCmCmUmGmAmUmAm	SEQ ID NO: 1151	UUAUUUCAGUCAC UCCUGAUA	SEQ ID NO: 599
ETX-S00003277	iaiaGmsUmsCmAmUmCmAmGmCfUfGfGm AmUmGmAmUmCmGmCmAm	SEQ ID NO: 1152	GUCAUCAGCUGGA UGAUCGCA	SEQ ID NO: 600
ETX-S00003281	iaiaAmsUmsUmUmUmGmCmCmCfGfUfAm CmCmCmGmUmCmUmAmGm	SEQ ID NO: 1153	AUUUUGCCCGUAC CCGUCUAG	SEQ ID NO: 601
ETX-S00003285	iaiaCmsAmsAmAmGmGmGmAmAfUfGfC mUmUmCmCmGmGmAmUmCm	SEQ ID NO: 1154	CAAAGGGAAUGCU UCCGGAUC	SEQ ID NO: 602
ETX-S00003289	iaiaAmsAmsGmGmCmUmUmUmAfAfCfG mUmGmUmCmUmGmUmGmCm	SEQ ID NO: 1155	AAGGCUUUAACGU GUCUGUGC	SEQ ID NO: 603
ETX-S00003293	iaiaAmsAmsGmGmCmAmUmUmAfUfAfG mAmCmUmGmCmGmUmGmGm	SEQ ID NO: 1156	AAGGCAUUAUAGA CUGCGUGG	SEQ ID NO: 604
ETX-S00003297	iaiaUmsUmsGmAmUmUmUmGfCfCfCm GmUmAmCmCmCmGmUmCm	SEQ ID NO: 1157	UUGAUUUUGCCCG UACCCGUC	SEQ ID NO: 605
ETX-S00003301	iaiaCmsGmsAmGmCmCmGmCmCfUfAfCm UmUmCmGmGmUmAmUmCm	SEQ ID NO: 1158	CGAGCCGCCUACU UCGGUAUC	SEQ ID NO: 606
ETX-S00003305	iaiaAmsUmsCmAmUmCmUmAmCfCfGfAm GmCmCmGmCmCmUmAmCm	SEQ ID NO: 1159	AUCAUCUACCGAG CCGCCUAC	SEQ ID NO: 607
ETX-S00003309	iaiaUmsGmsAmUmUmUmGmCfCfCfGm UmAmCmCmCmGmUmCmUm	SEQ ID NO: 1160	UGAUUUUGCCCGU ACCCGUCU	SEQ ID NO: 608
ETX-S00003313	iaiaUmsAmsUmCmAmUmCmUmAfCfCfGm AmGmCmCmGmCmCmUmAm	SEQ ID NO: 1161	UAUCAUCUACCGA GCCGCCUA	SEQ ID NO: 609

ETX- S00003317	iaiaCmsAmsUmCmUmAmCmCmGfAfGfCm CmGmCmCmUmAmCmUmUm	SEQ ID NO: 1162	CAUCUACCGAGCC GCCUACUU	SEQ ID NO: 610
ETX- S00003321	iaiaCmsUmsCmUmUmAmAmCmUfUfCfGm CmCmUmUmCmAmAmAmGm	SEQ ID NO: 1163	CUCUUAACUUCGC CUUCAAAAG	SEQ ID NO: 611
ETX- S00003325	iaiaCmsCmsAmCmCmCmAmGmGfCfUfCm UmUmAmAmCmUmUmCmGm	SEQ ID NO: 1164	CCACCCAGGCUCU UAACUUCG	SEQ ID NO: 612
ETX- S00003329	iaiaCmsCmsGmUmAmUmUmCmCfCfAfAm GmGmAmGmCmAmGmGmGm	SEQ ID NO: 1165	CCGUAAUCCCAAG GAGCAGGG	SEQ ID NO: 613
ETX- S00003333	iaiaGmsAmsGmCmAmGmGmGmAfGfUfU mCmUmGmUmCmCmUmUmCm	SEQ ID NO: 1166	GAGCAGGGAGUUC UGUCCUUC	SEQ ID NO: 614
ETX- S00003337	iaiaUmsCmsCmCmAmAmGmGmAfGfCfAm GmGmGmAmGmUmUmCmUm	SEQ ID NO: 1167	UCCCAAGGAGCAG GGAGUUCU	SEQ ID NO: 615
ETX- S00003341	iaiaUmsCmsCmGmUmAmUmUmCfCfCfAm AmGmGmAmGmCmAmGmGm	SEQ ID NO: 1168	UCCGUAAUCCCAA GGAGCAGG	SEQ ID NO: 616
ETX- S00003345	iaiaGmsCmsAmGmGmGmAmGmUfUfCfU mGmUmCmCmUmUmCmUmGm	SEQ ID NO: 1169	GCAGGGAGUUCUG UCCUUCUG	SEQ ID NO: 617
ETX- S00003349	iaiaGmsUmsCmCmGmUmAmUmUfCfCfCm AmAmGmGmAmGmCmAmGm	SEQ ID NO: 1170	GUCCGUAAUCCCA AGGAGCAG	SEQ ID NO: 618
ETX- S00003353	iaiaAmsGmsCmAmGmGmGmAmGfUfUfC mUmGmUmCmCmUmUmCmUm	SEQ ID NO: 1171	AGCAGGGAGUUCU GUCCUUCU	SEQ ID NO: 619
ETX- S00003357	iaiaGmsGmsAmGmCmAmGmGmGfAfGfU mUmCmUmGmUmCmCmUmUm	SEQ ID NO: 1172	GGAGCAGGGAGUU CUGUCCUU	SEQ ID NO: 620
ETX- S00003361	iaiaUmsUmsCmCmCmAmAmGmGfAfGfCm AmGmGmGmAmGmUmUmCm	SEQ ID NO: 1173	UUCCCAAGGAGCA GGGAGUUC	SEQ ID NO: 621
ETX- S00003365	iaiaAmsGmsGmAmGmCmAmGmGfGfAfG mUmUmCmUmGmUmCmCmUm	SEQ ID NO: 1174	AGGAGCAGGGAGU UCUGUCCU	SEQ ID NO: 622
ETX- S00003369	iaiaCmsCmsCmAmCmCmCmAmGfGfCfUm CmUmUmAmAmCmUmUmCm	SEQ ID NO: 1175	CCCACCCAGGCUC UUAACUUC	SEQ ID NO: 623
ETX- S00003373	iaiaUmsCmsUmUmAmAmCmUmUfCfGfCm CmUmUmCmAmAmAmGmAm	SEQ ID NO: 1176	UCUUAACUUCGCC UUCAAGA	SEQ ID NO: 624
ETX- S00003377	iaiaUmsUmsCmAmGmUmCmAmCfUfCfCm UmGmAmUmAmAmAmUmAm	SEQ ID NO: 1177	UUCAGUCACUCCU GAUAAUA	SEQ ID NO: 625
ETX- S00003381	iaiaCmsAmsGmUmCmAmCmUmCfCfUfGm AmUmAmAmAmUmAmAmCm	SEQ ID NO: 1178	CAGUCACUCCUGA UAAAUAAC	SEQ ID NO: 626
ETX- S00003385	iaiaUmsCmsAmGmUmCmAmCmUfCfCfUm GmAmUmAmAmAmUmAmAm	SEQ ID NO: 1179	UCAGUCACUCCUG AUAAAUAA	SEQ ID NO: 627
ETX- S00003389	iaiaUmsGmsAmUmGmGmGmAmCfUfCfA mAmUmUmGmUmAmUmUmUm	SEQ ID NO: 1180	UGAUGGGACUCAA UUGUAUUU	SEQ ID NO: 628
ETX- S00003393	iaiaGmsAmsUmGmGmGmAmCmUfCfAfA mUmUmGmUmAmUmUmUmUm	SEQ ID NO: 1181	GAUGGGACUCAAU UGUAUUUU	SEQ ID NO: 629

ETX- S00003397	iaiaCmsAmsCmUmCmCmUmGmAfUfAfAm AmUmAmAmCmAmAmAmUm	SEQ ID NO: 1182	CACUCCUGAUAAA UAACAAAU	SEQ ID NO: 630
ETX- S00003401	iaiaAmsUmsUmCmAmUmCmUmGfAfCfCm AmGmUmUmUmUmCmUmCm	SEQ ID NO: 1183	AUUCAUCUGACCA GUUUUCUC	SEQ ID NO: 631
ETX- S00003405	iaiaAmsAmsCmAmGmGmCmAmUfGfUfU mGmUmAmUmUmAmUmAmUm	SEQ ID NO: 1184	AACAGGCAUGUUG UAUUUAU	SEQ ID NO: 632
ETX- S00003409	iaiaAmsGmsGmGmAmAmUmGmCfUfUfC mCmGmGmAmUmCmCmCmAm	SEQ ID NO: 1185	AGGGAAUGCUUCC GGAUCCCA	SEQ ID NO: 633
ETX- S00003413	iaiaGmsGmsGmAmAmUmGmCmUfUfCfCm GmGmAmUmCmCmCmAmAm	SEQ ID NO: 1186	GGGAAUGCUUCCG GAUCCCAA	SEQ ID NO: 634
ETX- S00003417	iaiaCmsGmsAmGmGmCmCmUmCfGfGfUm GmAmCmUmGmCmCmUmGm	SEQ ID NO: 1187	CGAGGCCUCGGUG ACUGCCUG	SEQ ID NO: 635
ETX- S00003421	iaiaAmsCmsAmGmGmCmAmUmGfUfUfG mUmAmUmUmAmUmAmUmAm	SEQ ID NO: 1188	ACAGGCAUGUUGU AUUAUAUA	SEQ ID NO: 636
ETX- S00003425	iaiaAmsAmsUmAmCmAmAmAmGfGfCfA mUmUmAmUmAmGmAmCmUm	SEQ ID NO: 1189	AAUACAAAGGCAU UAUAGACU	SEQ ID NO: 637
ETX- S00003429	iaiaAmsUmsUmUmCmAmGmUmCfAfCfUm CmCmUmGmAmUmAmAmAm	SEQ ID NO: 1190	AUUUCAGUCACUC CUGAUAAA	SEQ ID NO: 638
ETX- S00003433	iaiaAmsUmsGmAmUmGmGmGmAfCfUfC mAmAmUmUmGmUmAmUmUm	SEQ ID NO: 1191	AUGAUGGGACUCA AUUGUAUU	SEQ ID NO: 639
ETX- S00003437	iaiaCmsUmsGmAmCmCmAmGmUfUfUfUm CmUmCmUmUmAmAmAmGm	SEQ ID NO: 1192	CUGACCAGUUUUC UCUAAAAG	SEQ ID NO: 640
ETX- S00003441	iaiaUmsGmsAmCmCmAmGmUmUfUfUfCm UmCmUmUmAmAmAmGmCm	SEQ ID NO: 1193	UGACCAGUUUUCU CUUAAAGC	SEQ ID NO: 641
ETX- S00003445	iaiaGmsAmsUmAmAmGmCmAmAfUfAfC mAmAmAmGmGmCmAmUmUm	SEQ ID NO: 1194	GAUAAGCAAUACA AAGGCAUU	SEQ ID NO: 642
ETX- S00003449	iaiaAmsUmsAmAmGmCmAmAmUfAfCfA mAmAmGmGmCmAmUmUmAm	SEQ ID NO: 1195	AUAAGCAAUACAA AGGCAUUA	SEQ ID NO: 643
ETX- S00003453	iaiaUmsUmsAmAmCmGmUmGmUfCfUfG mUmGmCmAmGmGmGmUmAm	SEQ ID NO: 1196	UUAACGUGUCUGU GCAGGGUA	SEQ ID NO: 644
ETX- S00003457	iaiaUmsAmsAmCmGmUmGmUmCfUfGfU mGmCmAmGmGmGmUmAmUm	SEQ ID NO: 1197	UAACGUGUCUGUG CAGGGUAU	SEQ ID NO: 645
ETX- S00003461	iaiaUmsCmsAmCmAmUmCmGmUfCfAfUm CmAmGmCmUmGmGmAmUm	SEQ ID NO: 1198	UCACAUCGUCAUC AGCUGGAU	SEQ ID NO: 646
ETX- S00003465	iaiaUmsGmsAmUmGmAmUmGmGfGfAfC mUmCmAmAmUmUmGmUmAm	SEQ ID NO: 1199	UGAUGAUGGGACU CAAUUGUA	SEQ ID NO: 647
ETX- S00003469	iaiaAmsCmsUmGmCmGmUmGmGfUfCfCm GmUmAmUmUmCmCmCmAm	SEQ ID NO: 1200	ACUGCGUGGUCCG UAUUCCCA	SEQ ID NO: 648
ETX- S00003473	iaiaGmsAmsAmCmAmGmGmCmAfUfGfU mUmGmUmAmUmUmAmUmAm	SEQ ID NO: 1201	GAACAGGCAUGUU GUAUUAUA	SEQ ID NO: 649

ETX- S00003477	iaiaUmsAmsUmUmUmCmAmGmUfCfAfCm UmCmCmUmGmAmUmAmAm	SEQ ID NO: 1202	UAUUUCAGUCACU CCUGAUAA	SEQ ID NO: 650
ETX- S00003481	iaiaUmsAmsAmGmCmAmAmUmAfCfAfA mAmGmGmCmAmUmUmAmUm	SEQ ID NO: 1203	UAAGCAAUACAAA GGCAUUAU	SEQ ID NO: 651
ETX- S00003485	iaiaAmsCmsUmCmAmCmAmUmCfGfUfCm AmUmCmAmGmCmUmGmGm	SEQ ID NO: 1204	ACUCACAUCGUCA UCAGCUGG	SEQ ID NO: 652
ETX- S00003489	iaiaCmsCmsGmCmCmUmAmCmUfUfCfGm GmUmAmUmCmUmAmUmGm	SEQ ID NO: 1205	CCGCCUACUUCGG UAUCUAUG	SEQ ID NO: 653
ETX- S00003493	iaiaCmsAmsCmAmUmCmGmUmCfAfUfCm AmGmCmUmGmGmAmUmGm	SEQ ID NO: 1206	CACAUCGUCAUCA GCUGGAUG	SEQ ID NO: 654
ETX- S00003497	iaiaGmsCmsCmUmAmCmUmUmCfGfGfUm AmUmCmUmAmUmGmAmCm	SEQ ID NO: 1207	GCCUACUUCGGUA UCUAUGAC	SEQ ID NO: 655
ETX- S00003501	iaiaUmsUmsUmAmAmCmGmUmGfUfCfU mGmUmGmCmAmGmGmGmUm	SEQ ID NO: 1208	UUUAACGUGUCUG UGCAGGGU	SEQ ID NO: 656
ETX- S00003505	iaiaUmsCmsGmCmCmGmCmGfCfAfUm GmAmUmGmAmUmGmCmAm	SEQ ID NO: 1209	UCGCCGCCGCAUG AUGAUGCA	SEQ ID NO: 657
ETX- S00003509	iaiaCmsAmsUmUmAmUmAmGmAfCfUfG mCmGmUmGmGmUmCmCmGm	SEQ ID NO: 1210	CAUUAUAGACUGC GUGGUCCG	SEQ ID NO: 658
ETX- S00003513	iaiaUmsGmsCmGmUmGmGmUmCfCfGfUm AmUmUmCmCmCmAmAmGm	SEQ ID NO: 1211	UGCGUGGUCCGUA UUCCCAAG	SEQ ID NO: 659
ETX- S00003517	iaiaAmsUmsCmUmAmCmCmGmAfGfCfCm GmCmCmUmAmCmUmUmCm	SEQ ID NO: 1212	AUCUACCGAGCCG CCUACUUC	SEQ ID NO: 660
ETX- S00003521	iaiaUmsUmsGmCmCmCmGmUmAfCfCfCm GmUmCmUmAmGmCmAmGm	SEQ ID NO: 1213	UUGCCCGUACCCG UCUAGCAG	SEQ ID NO: 661
ETX- S00003525	iaiaCmsUmsCmAmCmAmUmCmGfUfCfAm UmCmAmGmCmUmGmGmAm	SEQ ID NO: 1214	CUCACAUCGUCAU CAGCUGGA	SEQ ID NO: 662
ETX- S00003529	iaiaUmsAmsUmAmGmAmCmUmGfCfGfU mGmGmUmCmCmGmUmAmUm	SEQ ID NO: 1215	UAUAGACUGCGUG GUCCGUAU	SEQ ID NO: 663
ETX- S00003533	iaiaGmsGmsCmCmUmCmGmGmUfGfAfCm UmGmCmCmUmGmGmUmUm	SEQ ID NO: 1216	GGCCUCGGUGACU GCCUGGUU	SEQ ID NO: 664
ETX- S00003537	iaiaGmsGmsAmUmGmAmUmCmGfCfAfCm AmGmAmCmUmGmUmCmAm	SEQ ID NO: 1217	GGAUGAUCGCACA GACUGUCA	SEQ ID NO: 665
ETX- S00003541	iaiaGmsAmsUmUmUmUmGmCmCfCfGfUm AmCmCmCmGmUmCmUmAm	SEQ ID NO: 1218	GAUUUUGCCCGUA CCCGUCUA	SEQ ID NO: 666
ETX- S00003545	iaiaGmsAmsUmCmGmCmAmCmAfGfAfCm UmGmUmCmAmCmUmGmCm	SEQ ID NO: 1219	GAUCGCACAGACU GUCACUGC	SEQ ID NO: 667
ETX- S00003549	iaiaAmsUmsGmAmUmCmGmCmAfCfAfGm AmCmUmGmUmCmAmCmUm	SEQ ID NO: 1220	AUGAUCGCACAGA CUGUCACU	SEQ ID NO: 668
ETX- S00003553	iaiaUmsUmsUmUmGmCmCmGfUfAfCm CmCmGmUmCmUmAmGmCm	SEQ ID NO: 1221	UUUUGCCCGUACC CGUCUAGC	SEQ ID NO: 669

ETX- S00003557	iaiaUmsCmsAmUmCmUmAmCmCfGfAfGm CmCmGmCmCmUmAmCmUm	SEQ ID NO: 1222	UCAUCUACCGAGC CGCCUACU	SEQ ID NO: 670
ETX- S00003561	iaiaUmsAmsGmAmCmUmGmCmGfUfGfG mUmCmCmGmUmAmUmUmCm	SEQ ID NO: 1223	UAGACUGCGUGGU CCGUAUUC	SEQ ID NO: 671
ETX- S00003565	iaiaCmsUmsGmCmAmGmAmUmAfAfGfCm AmAmUmAmCmAmAmAmGm	SEQ ID NO: 1224	CUGCAGAUAAAGCA AUACAAAG	SEQ ID NO: 672
ETX- S00003569	iaiaAmsCmsUmGmCmAmGmAmUfAfAfG mCmAmAmUmAmCmAmAmAm	SEQ ID NO: 1225	ACUGCAGAUAAAGC AAUACAAA	SEQ ID NO: 673
ETX- S00003573	iaiaCmsAmsCmUmGmCmAmGmAfUfAfAm GmCmAmAmUmAmCmAmAm	SEQ ID NO: 1226	CACUGCAGAUAAAG CAAUACAA	SEQ ID NO: 674
ETX- S00003577	iaiaGmsCmsAmAmGmCmAmGmAfUfCfAm CmUmGmCmAmGmAmUmAm	SEQ ID NO: 1227	GCAAGCAGAUACAC UGCAGAUAA	SEQ ID NO: 675
ETX- S00003581	iaiaAmsUmsCmAmCmUmGmCmAfGfAfUm AmAmGmCmAmAmUmAmCm	SEQ ID NO: 1228	AUCACUGCAGAUAA AGCAAUAC	SEQ ID NO: 676
ETX- S00003585	iaiaUmsCmsAmCmUmGmCmAmGfAfUfAm AmGmCmAmAmUmAmCmAm	SEQ ID NO: 1229	UCACUGCAGAUAA GCAAUACA	SEQ ID NO: 677
ETX- S00003589	iaiaGmsCmsAmGmAmUmCmAmCfUfGfCm AmGmAmUmAmAmGmCmAm	SEQ ID NO: 1230	GCAGAUACAGUCA GAUAAAGCA	SEQ ID NO: 678
ETX- S00003593	iaiaCmsAmsGmAmUmCmAmCmUfGfCfAm GmAmUmAmAmGmCmAmAm	SEQ ID NO: 1231	CAGAUACAGUCAG AUAAGCAA	SEQ ID NO: 679
ETX- S00003597	iaiaAmsGmsCmAmAmGmCmAmGfAfUfCm AmCmUmGmCmAmGmAmUm	SEQ ID NO: 1232	AGCAAGCAGAUCA CUGCAGAU	SEQ ID NO: 680
ETX- S00003601	iaiaGmsAmsUmCmAmCmUmGmCfAfGfAm UmAmAmGmCmAmAmUmAm	SEQ ID NO: 1233	GAUCACUGCAGAU AAGCAAUA	SEQ ID NO: 681
ETX- S00003605	iaiaAmsUmsAmAmAmUmAmAmCfAfAfA mUmUmUmGmGmAmGmAmAm	SEQ ID NO: 1234	AUAAAUAACAAAU UUGGAGAA	SEQ ID NO: 682
ETX- S00003609	iaiaUmsCmsCmUmGmAmUmAmAfAfUfA mAmCmAmAmAmUmUmUmGm	SEQ ID NO: 1235	UCCUGAUAAAUAA CAAUUUG	SEQ ID NO: 683
ETX- S00003613	iaiaGmsAmsAmAmGmGmGmAmAfUfUfC mCmGmAmGmGmCmUmCm	SEQ ID NO: 1236	GAAAGGGAAUUCG GAGGCCUC	SEQ ID NO: 684
ETX- S00003617	iaiaGmsUmsUmGmUmAmUmUmAfUfAfU mAmAmCmAmUmAmUmCmUm	SEQ ID NO: 1237	GUUGUAUUUAUA ACAUUCU	SEQ ID NO: 685
ETX- S00003621	iaiaUmsUmsCmCmGmAmGmGmCfCfUfCm GmGmUmGmAmCmUmGmCm	SEQ ID NO: 1238	UUCCGAGGCCUCG GUGACUGC	SEQ ID NO: 686
ETX- S00003625	iaiaAmsAmsAmGmGmGmAmAmUfUfCfC mGmAmGmGmCmCmUmCmGm	SEQ ID NO: 1239	AAAGGGAAUUCG AGGCCUCG	SEQ ID NO: 687
ETX- S00003629	iaiaUmsGmsUmAmUmUmAmUmAfUfAfA mCmAmUmAmUmCmUmUmGm	SEQ ID NO: 1240	UGUAUUUAUAAC AUAUCUUG	SEQ ID NO: 688
ETX- S00003633	iaiaAmsAmsUmUmCmCmGmAmGfGfCfCm UmCmGmGmUmGmAmCmUm	SEQ ID NO: 1241	AAUUCGAGGCCU CGGUGACU	SEQ ID NO: 689

ETX- S00003637	iaiaGmsGmsGmAmAmUmUmCmCfGfAfG mGmCmCmUmCmGmGmUmGm	SEQ ID NO: 1242	GGGAAUUCCGAGG CCUCGGUG	SEQ ID NO: 690
ETX- S00003641	iaiaAmsGmsCmUmGmAmAmAmGfGfGfA mAmUmUmCmCmGmAmGmGm	SEQ ID NO: 1243	AGCUGAAAGGGAA UUCCGAGG	SEQ ID NO: 691
ETX- S00003645	iaiaGmsGmsAmGmCmUmGmAmAfAfGfG mGmAmAmUmUmCmCmGmAm	SEQ ID NO: 1244	GGAGCUGAAAGGG AAUUCCGA	SEQ ID NO: 692
ETX- S00003649	iaiaCmsUmsGmAmAmAmGmGmGfAfAfU mUmCmCmGmAmGmGmCmCm	SEQ ID NO: 1245	CUGAAAGGGAAUU CCGAGGCC	SEQ ID NO: 693
ETX- S00003653	iaiaGmsAmsGmCmUmGmAmAmAfGfGfG mAmAmUmUmCmCmGmAmGm	SEQ ID NO: 1246	GAGCUGAAAGGGA AUUCCGAG	SEQ ID NO: 694
ETX- S00003657	iaiaGmsCmsUmGmAmAmAmGmGfGfAfA mUmUmCmCmGmAmGmGmCm	SEQ ID NO: 1247	GCUGAAAGGGAAU UCCGAGGC	SEQ ID NO: 695
ETX- S00003661	iaiaGmsCmsAmUmGmUmUmGmUfAfUfU mAmUmAmUmAmAmCmAmUm	SEQ ID NO: 1248	GCAUGUUGUAUUA UAUAACAU	SEQ ID NO: 696
ETX- S00003665	iaiaUmsUmsGmUmAmUmUmAmUfAfUfA mAmCmAmUmAmUmCmUmUm	SEQ ID NO: 1249	UUGUAUUUAUAAA CAUAUCUU	SEQ ID NO: 697
ETX- S00003669	iaiaGmsUmsAmUmUmAmUmAmUfAfAfC mAmUmAmUmCmUmUmGmAm	SEQ ID NO: 1250	GUAUUUAUUAACA UAUCUUGA	SEQ ID NO: 698
ETX- S00003673	iaiaGmsGmsCmAmUmGmUmUmGfUfAfU mUmAmUmAmUmAmAmCmAm	SEQ ID NO: 1251	GGCAUGUUGUAUU AUUAACA	SEQ ID NO: 699
ETX- S00003677	iaiaAmsAmsGmGmGmAmAmUmUfCfCfG mAmGmGmCmCmUmCmGmGm	SEQ ID NO: 1252	AAGGGAAUCCGA GGCCUCGG	SEQ ID NO: 700
ETX- S00003681	iaiaGmsAmsAmUmUmCmCmGmAfGfGfCm CmUmCmGmGmUmGmAmCm	SEQ ID NO: 1253	GAAUCCGAGGCC UCGGUGAC	SEQ ID NO: 701
ETX- S00003685	iaiaAmsGmsGmGmAmAmUmUmCfCfGfA mGmGmCmCmUmCmGmGmUm	SEQ ID NO: 1254	AGGGAAUCCGAG GCCUCGGU	SEQ ID NO: 702
ETX- S00003689	iaiaGmsGmsAmAmUmUmCmCmGfAfGfG mCmCmUmCmGmGmUmGmAm	SEQ ID NO: 1255	GGAAUCCGAGGC CUCGGUGA	SEQ ID NO: 703
ETX- S00003693	iaiaGmsCmsUmUmGmUmCmUmUfGfUfA mUmGmAmUmGmAmAmAmUm	SEQ ID NO: 1256	GCUUGUCUUGUAU GAUGAAU	SEQ ID NO: 704
ETX- S00003697	iaiaUmsCmsGmCmCmUmUmCmAfAfAfGm AmUmAmAmAmUmAmCmAm	SEQ ID NO: 1257	UCGCCUCAAAGA UAAAUACA	SEQ ID NO: 705
ETX- S00003701	iaiaGmsCmsCmUmGmGmUmUmAfAfGfA mUmCmUmAmCmAmAmAmUm	SEQ ID NO: 1258	GCCUGGUUAAGAU CUACAAAU	SEQ ID NO: 706
ETX- S00003705	iaiaUmsCmsUmAmUmGmAmCmAfCfUfGm CmAmAmAmGmGmGmAmAm	SEQ ID NO: 1259	UCUAUGACACUGC AAAGGGAA	SEQ ID NO: 707
ETX- S00003709	iaiaUmsUmsUmGmUmGmCmUmUfGfUfC mUmUmGmUmAmUmGmAmUm	SEQ ID NO: 1260	UUUGUGCUUGUCU UGUAUGAU	SEQ ID NO: 708
ETX- S00003713	iaiaUmsGmsAmCmUmGmCmCmUfGfGfUm UmAmAmGmAmUmCmUmAm	SEQ ID NO: 1261	UGACUGCCUGGUU AAGAUCUA	SEQ ID NO: 709

ETX-S00003717	iaiaGmsAmsCmAmCmUmGmCmAfAfAfGm GmGmAmAmUmGmCmUmUm	SEQ ID NO: 1262	GACACUGCAAAGG GAAUGCUU	SEQ ID NO: 710
ETX-S00003721	iaiaCmsGmsGmUmAmUmCmUmAfUfGfA mCmAmCmUmGmCmAmAmAm	SEQ ID NO: 1263	CGGUAUCUAUGAC ACUGCAAA	SEQ ID NO: 711
ETX-S00003725	iaiaUmsUmsCmAmUmCmUmGmAfCfCfAm GmUmUmUmUmCmUmCmUm	SEQ ID NO: 1264	UUCAUCUGACCAG UUUUCUCU	SEQ ID NO: 712
ETX-S00003729	iaiaUmsUmsCmGmGmUmAmUmCfUfAfU mGmAmCmAmCmUmGmCmAm	SEQ ID NO: 1265	UUCGGUAUCUAUG ACACUGCA	SEQ ID NO: 713
ETX-S00003733	iaiaGmsGmsUmUmAmAmGmAmUfCfUfA mCmAmAmAmUmCmUmGmAm	SEQ ID NO: 1266	GGUUAAGAUCUAC AAAUCUGA	SEQ ID NO: 714
ETX-S00003737	iaiaAmsUmsCmUmAmUmGmAmCfAfCfUm GmCmAmAmAmGmGmGmAm	SEQ ID NO: 1267	AUCUAUGACACUG CAAAGGGA	SEQ ID NO: 715
ETX-S00003741	iaiaAmsGmsGmGmUmGmCmAmUfGfGfU mCmCmAmAmUmGmUmUmCm	SEQ ID NO: 1268	AGGGUGCAUGGUC CAAUGUUC	SEQ ID NO: 716
ETX-S00003745	iaiaAmsUmsCmUmAmCmAmAmAfUfCfUm GmAmUmGmGmGmAmUmUm	SEQ ID NO: 1269	AUCUACAAAUCUG AUGGGAUU	SEQ ID NO: 717
ETX-S00003749	iaiaCmsUmsUmCmGmGmUmAmUfCfUfAm UmGmAmCmAmCmUmGmCm	SEQ ID NO: 1270	CUUCGGUAUCUAAU GACACUGC	SEQ ID NO: 718
ETX-S00003753	iaiaUmsGmsGmGmUmGmGmUmGfCfUfU mUmUmGmUmGmCmUmUmGm	SEQ ID NO: 1271	UGGGUGGUGCUUU UGUGCUUG	SEQ ID NO: 719
ETX-S00003757	iaiaUmsAmsUmUmAmUmCmAmUfCfUfA mCmCmGmAmGmCmCmGmCm	SEQ ID NO: 1272	UAUUAUCAUCUAC CGAGCCGC	SEQ ID NO: 720
ETX-S00003761	iaiaGmsUmsGmGmUmCmCmGmUfAfUfU mCmCmCmAmAmGmGmAmGm	SEQ ID NO: 1273	GUGGUCCGUUUUC CCAAGGAG	SEQ ID NO: 721
ETX-S00003765	iaiaCmsUmsAmUmGmAmCmAmCfUfGfCm AmAmAmGmGmGmAmAmUm	SEQ ID NO: 1274	CUAUGACACUGCA AAGGGAAU	SEQ ID NO: 722
ETX-S00003769	iaiaCmsUmsUmUmUmGmUmGmCfUfUfG mUmCmUmUmGmUmAmUmGm	SEQ ID NO: 1275	CUUUUGUGCUUGU CUUGUAUG	SEQ ID NO: 723
ETX-S00003773	iaiaUmsAmsCmCmAmAmGmGmCfUfUfUm AmAmCmGmUmGmUmCmUm	SEQ ID NO: 1276	UACCAAGGCUUUA ACGUGUCU	SEQ ID NO: 724
ETX-S00003777	iaiaGmsUmsGmCmAmUmGmGmUfCfCfAm AmUmGmUmUmCmUmCmAm	SEQ ID NO: 1277	GUGCAUGGUCCAA UGUUCUCA	SEQ ID NO: 725
ETX-S00003781	iaiaCmsCmsUmUmCmAmAmAmGfAfUfAm AmAmUmAmCmAmAmGmCm	SEQ ID NO: 1278	CCUCAAAGAUAA AUACAAGC	SEQ ID NO: 726
ETX-S00003785	iaiaGmsGmsGmUmAmUmUmAmUfCfAfU mCmUmAmCmCmGmAmGmCm	SEQ ID NO: 1279	GGGUAAUUAUCAUC UACCGAGC	SEQ ID NO: 727
ETX-S00003789	iaiaUmsAmsCmUmUmCmGmGmUfAfUfCm UmAmUmGmAmCmAmCmUm	SEQ ID NO: 1280	UACUUCGGUAUCU AUGACACU	SEQ ID NO: 728
ETX-S00003793	iaiaGmsUmsUmAmAmGmAmUmCfUfAfC mAmAmAmUmCmUmGmAmUm	SEQ ID NO: 1281	GUUAAGAUCUACA AAUCUGAU	SEQ ID NO: 729

ETX- S00003797	iaiaUmsGmsCmAmGmGmGmUmAfUfUfA mUmCmAmUmCmUmAmCmCm	SEQ ID NO: 1282	UGCAGGGUAUUAU CAUCUACC	SEQ ID NO: 730
ETX- S00003801	iaiaUmsCmsUmGmAmUmGmGmGfAfUfU mAmAmGmGmGmCmCmUmGm	SEQ ID NO: 1283	UCUGAUGGGAUUA AGGGCCUG	SEQ ID NO: 731
ETX- S00003805	iaiaCmsUmsGmUmGmCmAmGmGfGfUfA mUmUmAmUmCmAmUmCmUm	SEQ ID NO: 1284	CUGUGCAGGGUAU UAUCAUCU	SEQ ID NO: 732
ETX- S00003809	iaiaUmsGmsAmUmGmGmGmAmUfUfAfA mGmGmGmCmCmUmGmUmAm	SEQ ID NO: 1285	UGAUGGGAUUAAG GGCCUGUA	SEQ ID NO: 733
ETX- S00003813	iaiaCmsCmsAmAmGmGmCmUmUfUfAfAm CmGmUmGmUmCmUmGmUm	SEQ ID NO: 1286	CCAAGGCUUUAAC GUGUCUGU	SEQ ID NO: 734
ETX- S00003817	iaiaUmsAmsUmUmCmAmUmCmUfGfAfCm CmAmGmUmUmUmUmCmUm	SEQ ID NO: 1287	UAUUCAUCUGACC AGUUUUCU	SEQ ID NO: 735
ETX- S00003821	iaiaAmsCmsUmGmCmCmUmGmGfUfUfAm AmGmAmUmCmUmAmCmAm	SEQ ID NO: 1288	ACUGCCUGGUUAA GAUCUACA	SEQ ID NO: 736
ETX- S00003825	iaiaGmsUmsUmGmAmCmUmUmCfCfUfAm UmCmCmAmUmUmUmGmAm	SEQ ID NO: 1289	GUUGACUCCUAU CCAUUUGA	SEQ ID NO: 737
ETX- S00003829	iaiaUmsAmsUmGmAmCmAmCmUfGfCfAm AmAmGmGmGmAmAmUmGm	SEQ ID NO: 1290	UAUGACACUGCAA AGGGAAUG	SEQ ID NO: 738
ETX- S00003833	iaiaUmsUmsAmAmGmAmUmCmUfAfCfA mAmAmUmCmUmGmAmUmGm	SEQ ID NO: 1291	UUAAGAUCUACAA AUCUGAUG	SEQ ID NO: 739
ETX- S00003837	iaiaAmsGmsGmGmUmAmUmUmAfUfCfA mUmCmUmAmCmCmGmAmGm	SEQ ID NO: 1292	AGGGUAUUUAUCAU CUACCGAG	SEQ ID NO: 740
ETX- S00003841	iaiaUmsGmsCmCmUmGmGmUmUfAfAfG mAmUmCmUmAmCmAmAmAm	SEQ ID NO: 1293	UGCCUGGUUAAGA UCUACAAA	SEQ ID NO: 741
ETX- S00003845	iaiaCmsUmsGmAmUmGmGmGmAfUfUfA mAmGmGmGmCmCmUmGmUm	SEQ ID NO: 1294	CUGAUGGGAUUAA GGGCCUGU	SEQ ID NO: 742
ETX- S00003849	iaiaGmsGmsUmAmUmCmUmAmUfGfAfC mAmCmUmGmCmAmAmAmGm	SEQ ID NO: 1295	GGUAUCUAUGACA CUGCAAAG	SEQ ID NO: 743
ETX- S00003853	iaiaAmsCmsCmCmGmUmCmUmAfGfCfAm GmCmUmGmAmUmGmUmGm	SEQ ID NO: 1296	ACCCGUCUAGCAG CUGAUGUG	SEQ ID NO: 744
ETX- S00003857	iaiaUmsAmsUmCmUmAmUmGmAfCfAfCm UmGmCmAmAmAmGmGmGm	SEQ ID NO: 1297	UAUCUAUGACACU GCAAAGGG	SEQ ID NO: 745
ETX- S00003861	iaiaCmsUmsGmAmUmGmUmGmGfGfUfA mAmAmGmCmUmGmGmAmGm	SEQ ID NO: 1298	CUGAUGUGGGUAA AGCUGGAG	SEQ ID NO: 746
ETX- S00003865	iaiaUmsCmsUmAmGmCmAmGmCfUfGfAm UmGmUmGmGmGmUmAmAm	SEQ ID NO: 1299	UCUAGCAGCUGAU GUGGGUAA	SEQ ID NO: 747
ETX- S00003869	iaiaGmsGmsGmCmCmUmGmUmAfCfCfAm AmGmGmCmUmUmUmAmAm	SEQ ID NO: 1300	GGGCCUGUACCAA GGCUUUA	SEQ ID NO: 748
ETX- S00003873	iaiaCmsCmsCmGmUmAmCmCmCfGfUfCm UmAmGmCmAmGmCmUmGm	SEQ ID NO: 1301	CCCGUACCCGUCU AGCAGCUG	SEQ ID NO: 749

ETX- S00003877	iaiaCmsAmsGmCmUmGmAmUmGfUfGfG mGmUmAmAmAmGmCmUmGm	SEQ ID NO: 1302	CAGCUGAUGUGGG UAAAGCUG	SEQ ID NO: 750
ETX- S00003881	iaiaCmsCmsGmUmAmCmCmCmGfUfCfUm AmGmCmAmGmCmUmGmAm	SEQ ID NO: 1303	CCGUACCCGUCUA GCAGCUGA	SEQ ID NO: 751
ETX- S00003885	iaiaGmsCmsUmGmAmUmGmUmGfGfGfU mAmAmAmGmCmUmGmGmAm	SEQ ID NO: 1304	GCUGAUGUGGGUA AAGCUGGA	SEQ ID NO: 752
ETX- S00003889	iaiaGmsGmsUmAmUmUmAmUmCfAfUfC mUmAmCmCmGmAmGmCmCm	SEQ ID NO: 1305	GGUAUUAUCAUCU ACCGAGCC	SEQ ID NO: 753
ETX- S00003893	iaiaUmsUmsAmUmCmAmUmCmUfAfCfCm GmAmGmCmCmGmCmCmUm	SEQ ID NO: 1306	UUAUCAUCUACCG AGCCGCCU	SEQ ID NO: 754
ETX- S00003897	iaiaGmsUmsAmCmCmCmGmUmCfUfAfGm CmAmGmCmUmGmAmUmGm	SEQ ID NO: 1307	GUACCCGUCUAGC AGCUGAUG	SEQ ID NO: 755
ETX- S00003901	iaiaGmsAmsUmGmGmGmAmUmUfAfAfG mGmGmCmCmUmGmUmAmCm	SEQ ID NO: 1308	GAUGGGAUUAAGG GCCUGUAC	SEQ ID NO: 756
ETX- S00003905	iaiaGmsUmsCmUmGmUmGmCmAfGfGfG mUmAmUmUmAmUmCmAmUm	SEQ ID NO: 1309	GUCUGUGCAGGGU AUUAUCAU	SEQ ID NO: 757
ETX- S00003909	iaiaGmsCmsGmUmGmGmUmCmCfGfUfAm UmUmCmCmCmAmAmGmGm	SEQ ID NO: 1310	GCGUGGUCCGUAU UCCCAAGG	SEQ ID NO: 758
ETX- S00003913	iaiaCmsGmsUmGmGmUmCmCmGfUfAfUm UmCmCmCmAmAmGmGmAm	SEQ ID NO: 1311	CGUGGUCCGUAAU CCCAAGGA	SEQ ID NO: 759
ETX- S00003917	iaiaUmsGmsGmUmUmAmAmGmAfUfCfU mAmCmAmAmAmUmCmUmGm	SEQ ID NO: 1312	UGGUUAAGAUCUA CAAAUCUG	SEQ ID NO: 760
ETX- S00003921	iaiaAmsUmsGmAmUmGmAmAmAfUfCfA mAmGmAmAmGmUmAmCmAm	SEQ ID NO: 1313	AUGAUGAAAUCAA GAAGUACA	SEQ ID NO: 761
ETX- S00003925	iaiaGmsAmsUmCmUmAmCmAmAfAfUfCm UmGmAmUmGmGmGmAmUm	SEQ ID NO: 1314	GAUCUACAAAUCU GAUGGGAU	SEQ ID NO: 762
ETX- S00003929	iaiaGmsUmsGmCmAmGmGmGmUfAfUfU mAmUmCmAmUmCmUmAmCm	SEQ ID NO: 1315	GUGCAGGGUAUUA UCAUCUAC	SEQ ID NO: 763
ETX- S00003933	iaiaGmsUmsAmCmCmAmAmGmGfCfUfUm UmAmAmCmGmUmGmUmCm	SEQ ID NO: 1316	GUACCAAGGCUUU AACGUGUC	SEQ ID NO: 764
ETX- S00003937	iaiaGmsCmsAmGmCmUmGmAmUfGfUfG mGmGmUmAmAmAmGmCmUm	SEQ ID NO: 1317	GCAGCUGAUGUGG GUAAAGCU	SEQ ID NO: 765
ETX- S00003941	iaiaAmsUmsGmGmGmUmGmGmUfGfCfU mUmUmUmGmUmGmCmUmUm	SEQ ID NO: 1318	AUGGGUGGUGCUU UUGUGCUU	SEQ ID NO: 766
ETX- S00003945	iaiaCmsGmsGmUmGmAmCmUmGfCfCfUm GmGmUmUmAmAmGmAmUm	SEQ ID NO: 1319	CGGUGACUGCCUG GUUAAGAU	SEQ ID NO: 767
ETX- S00003949	iaiaCmsUmsAmGmCmAmGmCmUfGfAfUm GmUmGmGmGmUmAmAmAm	SEQ ID NO: 1320	CUAGCAGCUGAUG UGGGUAAA	SEQ ID NO: 768
ETX- S00003953	iaiaUmsAmsCmAmAmAmUmCmUfGfAfU mGmGmGmAmUmUmAmAmGm	SEQ ID NO: 1321	UACAAAUCUGAUG GGAUUAAG	SEQ ID NO: 769

ETX- S00003957	iaiaAmsCmsUmUmCmGmGmUmAfUfCfUm AmUmGmAmCmAmCmUmGm	SEQ ID NO: 1322	ACUUCGGUAUCUA UGACACUG	SEQ ID NO: 770
ETX- S00003961	iaiaAmsGmsCmUmGmAmUmGmUfGfGfG mUmAmAmAmGmCmUmGmGm	SEQ ID NO: 1323	AGCUGAUGUGGGU AAAGCUGG	SEQ ID NO: 771
ETX- S00003965	iaiaCmsGmsUmAmCmCmCmGmUfCfUfAm GmCmAmGmCmUmGmAmUm	SEQ ID NO: 1324	CGUACCCGUCUAG CAGCUGAU	SEQ ID NO: 772
ETX- S00003969	iaiaUmsCmsUmGmUmGmCmAmGfGfGfU mAmUmUmAmUmCmAmUmCm	SEQ ID NO: 1325	UCUGUGCAGGGUA UUAUCAUC	SEQ ID NO: 773
ETX- S00003973	iaiaUmsGmsCmUmUmGmUmCmUfUfGfU mAmUmGmAmUmGmAmAmAm	SEQ ID NO: 1326	UGCUUGUCUUGUA UGAUGAAA	SEQ ID NO: 774
ETX- S00003977	iaiaAmsCmsCmAmAmGmGmCmUfUfUfAm AmCmGmUmGmUmCmUmGm	SEQ ID NO: 1327	ACCAAGGCUUUA CGUGUCUG	SEQ ID NO: 775
ETX- S00003981	iaiaGmsGmsGmUmGmCmAmUmGfGfUfC mCmAmAmUmGmUmUmCmUm	SEQ ID NO: 1328	GGGUGCAUGGUCC AAUGUUCU	SEQ ID NO: 776
ETX- S00003985	iaiaGmsAmsCmUmGmCmCmUmGfGfUfUm AmAmGmAmUmCmUmAmCm	SEQ ID NO: 1329	GACUGCCUGGUUA AGAUCUAC	SEQ ID NO: 777
ETX- S00003989	iaiaGmsAmsUmGmUmGmGmUfAfAfA mGmCmUmGmGmAmGmCmUm	SEQ ID NO: 1330	GAUGUGGGUAAAG CUGGAGCU	SEQ ID NO: 778
ETX- S00003993	iaiaUmsGmsGmUmCmCmGmUmAfUfUfCm CmCmAmAmGmGmAmGmCm	SEQ ID NO: 1331	UGGUCCGUUUCC CAAGGAGC	SEQ ID NO: 779
ETX- S00003997	iaiaAmsCmsAmCmUmGmCmAmAfAfGfGm GmAmAmUmGmCmUmUmCm	SEQ ID NO: 1332	ACACUGCAAAGGG AAUGCUUC	SEQ ID NO: 780
ETX- S00004001	iaiaGmsAmsUmUmAmAmGmGmGfCfCfU mGmUmAmCmCmAmAmGmGm	SEQ ID NO: 1333	GAUUAAGGGCCUG UACCAAGG	SEQ ID NO: 781
ETX- S00004005	iaiaUmsGmsUmGmCmAmGmGmGfUfAfU mUmAmUmCmAmUmCmUmAm	SEQ ID NO: 1334	UGUGCAGGGUAUU AUCAUCUA	SEQ ID NO: 782
ETX- S00004009	iaiaAmsAmsCmGmUmGmUmCmUfGfUfG mCmAmGmGmGmUmAmUmUm	SEQ ID NO: 1335	AACGUGUCUGUGC AGGGUAUU	SEQ ID NO: 783
ETX- S00004013	iaiaGmsGmsCmCmUmGmUmAmCfCfAfAm GmGmCmUmUmUmAmAmCm	SEQ ID NO: 1336	GGCCUGUACCAAG GCUUUAAC	SEQ ID NO: 784
ETX- S00004017	iaiaUmsGmsAmCmAmCmUmGmCfAfAfAm GmGmGmAmAmUmGmCmUm	SEQ ID NO: 1337	UGACACUGCAAAG GGAAUGCU	SEQ ID NO: 785
ETX- S00004021	iaiaUmsCmsGmGmUmGmAmCmUfGfCfCm UmGmGmUmUmAmAmGmAm	SEQ ID NO: 1338	UCGGUGACUGCCU GGUUAAGA	SEQ ID NO: 786
ETX- S00004025	iaiaGmsCmsUmUmUmUmGmUmGfCfUfU mGmUmCmUmUmGmUmAmUm	SEQ ID NO: 1339	GCUUUUGUGCUUG UCUUGUAU	SEQ ID NO: 787
ETX- S00004029	iaiaGmsGmsUmGmGmUmGmCmUfUfUfU mGmUmGmCmUmUmGmUmCm	SEQ ID NO: 1340	GGUGGUGCUUUUG UGCUUGUC	SEQ ID NO: 788
ETX- S00004033	iaiaCmsGmsUmCmUmAmGmCmAfGfCfUm GmAmUmGmUmGmGmGmUm	SEQ ID NO: 1341	CGUCUAGCAGCUG AUGUGGGU	SEQ ID NO: 789

ETX- S00004037	iaiaAmsGmsGmGmCmCmUmGmUfAfCfCm AmAmGmGmCmUmUmUmAm	SEQ ID NO: 1342	AGGGCCUGUACCA AGGCUUUA	SEQ ID NO: 790
ETX- S00004041	iaiaGmsUmsGmCmUmUmGmUmCfUfUfG mUmAmUmGmAmUmGmAmAm	SEQ ID NO: 1343	GUGCUUGUCUUGU AUGAUGAA	SEQ ID NO: 791
ETX- S00004045	iaiaAmsAmsAmUmCmUmGmAmUfGfGfG mAmUmUmAmAmGmGmGmCm	SEQ ID NO: 1344	AAAUCUGAUGGGA UUAAGGGC	SEQ ID NO: 792
ETX- S00004049	iaiaCmsUmsAmCmAmAmAmUmCfUfGfAm UmGmGmGmAmUmUmAmAm	SEQ ID NO: 1345	CUACAAAUCUGAU GGGAUUAA	SEQ ID NO: 793
ETX- S00004053	iaiaCmsAmsGmGmGmUmAmUmUfAfUfC mAmUmCmUmAmCmCmGmAm	SEQ ID NO: 1346	CAGGGUAUUAUCA UCUACCGA	SEQ ID NO: 794
ETX- S00004057	iaiaCmsUmsGmUmAmCmCmAmAfGfGfCm UmUmUmAmAmCmGmUmGm	SEQ ID NO: 1347	CUGUACCAAGGCU UUAACGUG	SEQ ID NO: 795
ETX- S00004061	iaiaAmsGmsAmUmCmUmAmCmAfAfAfU mCmUmGmAmUmGmGmGmAm	SEQ ID NO: 1348	AGAUCUACAAUC UGAUGGGA	SEQ ID NO: 796
ETX- S00004065	iaiaUmsUmsUmUmGmUmGmCmUfUfGfU mCmUmUmGmUmAmUmGmAm	SEQ ID NO: 1349	UUUUGUGCUUGUC UUGUAUGA	SEQ ID NO: 797
ETX- S00004069	iaiaAmsCmsAmAmAmUmCmUmGfAfUfG mGmGmAmUmUmAmAmGmGm	SEQ ID NO: 1350	ACAAAUCUGAUGG GAUUAAGG	SEQ ID NO: 798
ETX- S00004073	iaiaCmsAmsAmGmGmGmUmGmCfAfUfG mGmUmCmCmAmAmUmGmUm	SEQ ID NO: 1351	CAAGGGUGCAUGG UCCAAUGU	SEQ ID NO: 799
ETX- S00004077	iaiaGmsGmsAmUmUmAmAmGmGfGfCfC mUmGmUmAmCmCmAmAmGm	SEQ ID NO: 1352	GGAUUAAGGGCCU GUACCAAG	SEQ ID NO: 800
ETX- S00004081	iaiaUmsCmsGmGmUmAmUmCmUfAfUfG mAmCmAmCmUmGmCmAmAm	SEQ ID NO: 1353	UCGGUAUCUAUGA CACUGCAA	SEQ ID NO: 801
ETX- S00004085	iaiaCmsAmsAmGmGmCmUmUmUfAfAfCm GmUmGmUmCmUmGmUmGm	SEQ ID NO: 1354	CAAGGCUUUAACG UGUCUGUG	SEQ ID NO: 802
ETX- S00004089	iaiaCmsAmsUmGmGmGmUmGmGfUfGfC mUmUmUmUmGmUmGmCmUm	SEQ ID NO: 1355	CAUGGGUGGUGCU UUUGUGCU	SEQ ID NO: 803
ETX- S00004093	iaiaUmsAmsAmGmAmUmCmUfAfAfA mAmUmCmUmGmAmUmGmGm	SEQ ID NO: 1356	UAAGAUCUACAAA UCUGAUGG	SEQ ID NO: 804
ETX- S00004097	iaiaCmsCmsCmGmUmCmUmAmGfCfAfGm CmUmGmAmUmGmUmGmGm	SEQ ID NO: 1357	CCCGUCUAGCAGC UGAUGUGG	SEQ ID NO: 805
ETX- S00004101	iaiaAmsUmsGmAmCmAmCmUmGfCfAfAm AmGmGmGmAmAmUmGmCm	SEQ ID NO: 1358	AUGACACUGCAAA GGGAAUGC	SEQ ID NO: 806
ETX- S00004105	iaiaUmsAmsGmCmAmGmCmUmGfAfUfG mUmGmGmGmUmAmAmAmGm	SEQ ID NO: 1359	UAGCAGCUGAUGU GGGUAAAG	SEQ ID NO: 807
ETX- S00004109	iaiaGmsCmsAmAmAmGmGmGmAfAfUfG mCmUmUmCmCmGmGmAmUm	SEQ ID NO: 1360	GCAAAGGGAAUGC UUCCGGAU	SEQ ID NO: 808
ETX- S00004113	iaiaGmsCmsCmCmGmUmAmCmCfCfGfUm CmUmAmGmCmAmGmCmUm	SEQ ID NO: 1361	GCCCGUACCCGUC UAGCAGCU	SEQ ID NO: 809

ETX-S00004117	iaiaGmsUmsAmUmUmAmUmCmAfUfCfU mAmCmCmGmAmGmCmCmGm	SEQ ID NO: 1362	GUAUUAUCAUCA CCGAGCCG	SEQ ID NO: 810
ETX-S00004121	iaiaCmsUmsCmUmUmGmAmUmUfUfUfG mCmCmCmGmUmAmCmCmCm	SEQ ID NO: 1363	CUCUUGAUUUUGC CCGUACCC	SEQ ID NO: 811
ETX-S00004125	iaiaUmsAmsCmCmCmGmUmCmUfAfGfCm AmGmCmUmGmAmUmGmUm	SEQ ID NO: 1364	UACCCGUCUAGCA GCUGAUGU	SEQ ID NO: 812
ETX-S00004129	iaiaCmsAmsAmAmUmCmUmGmAfUfGfG mGmAmUmUmAmAmGmGmGm	SEQ ID NO: 1365	CAAAUCUGAUGGG AUUAAGGG	SEQ ID NO: 813
ETX-S00004133	iaiaGmsUmsAmCmCmCmUmCmUfUfGfAm UmUmUmUmGmCmCmCmGm	SEQ ID NO: 1366	GUACCCUCUUGAU UUUGCCCCG	SEQ ID NO: 814
ETX-S00004137	iaiaCmsCmsUmGmUmAmCmCmAfAfGfGm CmUmUmUmAmAmCmGmUm	SEQ ID NO: 1367	CCUGUACCAAGGC UUUAACGU	SEQ ID NO: 815
ETX-S00004141	iaiaUmsGmsGmGmAmUmUmAmAfGfGfG mCmCmUmGmUmAmCmCmAm	SEQ ID NO: 1368	UGGGAUUAAGGGC CUGUACCA	SEQ ID NO: 816
ETX-S00004145	iaiaAmsUmsUmAmUmCmAmUmCfUfAfCm CmGmAmGmCmCmGmCmCm	SEQ ID NO: 1369	AUUAUCAUCUACC GAGCCGCC	SEQ ID NO: 817
ETX-S00004149	iaiaGmsCmsCmUmGmUmAmCmCfAfAfGm GmCmUmUmUmAmAmCmGm	SEQ ID NO: 1370	GCCUGUACCAAGG CUUUAACG	SEQ ID NO: 818
ETX-S00004153	iaiaAmsUmsGmGmGmAmUmUmAfAfGfG mGmCmCmUmGmUmAmCmCm	SEQ ID NO: 1371	AUGGGAUUAAGGG CCUGUACC	SEQ ID NO: 819
ETX-S00004157	iaiaAmsCmsGmUmGmUmCmUmGfUfGfCm AmGmGmGmUmAmUmUmAm	SEQ ID NO: 1372	ACGUGUCUGUGCA GGGUAAUA	SEQ ID NO: 820
ETX-S00004161	iaiaGmsGmsCmAmUmUmAmUmAfGfAfC mUmGmCmGmUmGmGmUmCm	SEQ ID NO: 1373	GGCAUUAUAGACU GCGUGGUC	SEQ ID NO: 821
ETX-S00004165	iaiaUmsUmsCmCmCmCmAmCmCfCfAfGm GmCmUmCmUmUmAmAmCm	SEQ ID NO: 1374	UUCCCCACCCAGG CUCUUAAC	SEQ ID NO: 822
ETX-S00004169	iaiaAmsUmsGmUmCmAmUmCmAfGfAfU mAmCmUmUmCmCmCmCmAm	SEQ ID NO: 1375	AUGUCAUCAGAU CUUCCCCA	SEQ ID NO: 823
ETX-S00004173	iaiaGmsUmsCmAmUmCmAmGmAfUfAfCm UmUmCmCmCmCmAmCmCm	SEQ ID NO: 1376	GUCAUCAGAUACU UCCCCACC	SEQ ID NO: 824
ETX-S00004177	iaiaUmsGmsUmCmAmUmCmAmGfAfUfA mCmUmUmCmCmCmCmAmCm	SEQ ID NO: 1377	UGUCAUCAGAUAC UUCCCCAC	SEQ ID NO: 825
ETX-S00004181	iaiaAmsAmsUmGmUmCmAmUmCfAfGfA mUmAmCmUmUmCmCmCmCm	SEQ ID NO: 1378	AAUGUCAUCAGAU ACUUCCCC	SEQ ID NO: 826
ETX-S00004185	iaiaCmsUmsUmCmCmCmCmAmCfCfCfAm GmGmCmUmCmUmUmAmAm	SEQ ID NO: 1379	CUUCCCCACCCAG GCUCUUA	SEQ ID NO: 827
ETX-S00004189	iaiaCmsUmsAmCmCmGmAmGmCfCfGfCm CmUmAmCmUmUmCmGmGm	SEQ ID NO: 1380	CUACCGAGCCGCC UACUUCGG	SEQ ID NO: 828

As used herein, and in particular in Tables 3 and 4, the following abbreviations are used for modified nucleosides:

Am stands for 2'-O-methyl-adenosine, Cm stands for 2'-O-methyl-cytidine, Gm stands for 2'-O-methyl-guanosine, Um stands for 2'-O-methyl-uridine, Af stands for 2'-Fluoro-adenosine, Cf stands for 2'-Fluoro-cytidine, Gf stands for 2'-Fluoro-guanosine and Uf stands for 2'-Fluoro-uridine.

Furthermore, the letter “s” is used as abbreviation for a phosphorothioate linkage between two consecutive (modified) nucleosides. For example, the abbreviation “AmsAm” is used for two consecutive 2'-O-methyl-adenosine nucleosides that are linked via a 3'5' phosphorothioate linkage. No abbreviation is used for nucleosides that are linked via a standard 3'5' phosphodiester linkage. For example, the abbreviation “AmAm” is used for two consecutive 2'-O-methyl-adenosine nucleosides that are linked via a 3'5' phosphodiester linkage.

10 In certain embodiments, the nucleic acid comprises a first strand that comprises, consists of, or consists essentially of a (modified) nucleoside sequence differing by 0 or 1 nucleosides from any one of SEQ ID NO: 829-1104;

and a second strand that comprises, consists of, or consists essentially of a (modified) nucleoside sequence differing by 0 or 1 nucleosides from any one of SEQ ID NO: 1105-1380.

15 Preferred combinations of complementary modified antisense (first) and sense (second) strands are listed below in Table 5:

Table 5

Duplex ID	Antisense strand ID	Sense strand ID
ETX-M00001351	ETX-S00003090	ETX-S00003089
ETX-M00001352	ETX-S00003094	ETX-S00003093
ETX-M00001353	ETX-S00003098	ETX-S00003097
ETX-M00001354	ETX-S00003102	ETX-S00003101
ETX-M00001355	ETX-S00003106	ETX-S00003105
ETX-M00001356	ETX-S00003110	ETX-S00003109
ETX-M00001357	ETX-S00003114	ETX-S00003113
ETX-M00001358	ETX-S00003118	ETX-S00003117
ETX-M00001359	ETX-S00003122	ETX-S00003121
ETX-M00001360	ETX-S00003126	ETX-S00003125
ETX-M00001361	ETX-S00003130	ETX-S00003129
ETX-M00001362	ETX-S00003134	ETX-S00003133
ETX-M00001363	ETX-S00003138	ETX-S00003137
ETX-M00001364	ETX-S00003142	ETX-S00003141
ETX-M00001365	ETX-S00003146	ETX-S00003145
ETX-M00001366	ETX-S00003150	ETX-S00003149

ETX-M00001367	ETX-S00003154	ETX-S00003153
ETX-M00001368	ETX-S00003158	ETX-S00003157
ETX-M00001369	ETX-S00003162	ETX-S00003161
ETX-M00001370	ETX-S00003166	ETX-S00003165
ETX-M00001371	ETX-S00003170	ETX-S00003169
ETX-M00001372	ETX-S00003174	ETX-S00003173
ETX-M00001373	ETX-S00003178	ETX-S00003177
ETX-M00001374	ETX-S00003182	ETX-S00003181
ETX-M00001375	ETX-S00003186	ETX-S00003185
ETX-M00001376	ETX-S00003190	ETX-S00003189
ETX-M00001377	ETX-S00003194	ETX-S00003193
ETX-M00001378	ETX-S00003198	ETX-S00003197
ETX-M00001379	ETX-S00003202	ETX-S00003201
ETX-M00001380	ETX-S00003206	ETX-S00003205
ETX-M00001381	ETX-S00003210	ETX-S00003209
ETX-M00001382	ETX-S00003214	ETX-S00003213
ETX-M00001383	ETX-S00003218	ETX-S00003217
ETX-M00001384	ETX-S00003222	ETX-S00003221
ETX-M00001385	ETX-S00003226	ETX-S00003225
ETX-M00001386	ETX-S00003230	ETX-S00003229
ETX-M00001387	ETX-S00003234	ETX-S00003233
ETX-M00001388	ETX-S00003238	ETX-S00003237
ETX-M00001389	ETX-S00003242	ETX-S00003241
ETX-M00001390	ETX-S00003246	ETX-S00003245
ETX-M00001391	ETX-S00003250	ETX-S00003249
ETX-M00001392	ETX-S00003254	ETX-S00003253
ETX-M00001393	ETX-S00003258	ETX-S00003257
ETX-M00001394	ETX-S00003262	ETX-S00003261
ETX-M00001395	ETX-S00003266	ETX-S00003265
ETX-M00001396	ETX-S00003270	ETX-S00003269
ETX-M00001397	ETX-S00003274	ETX-S00003273
ETX-M00001398	ETX-S00003278	ETX-S00003277
ETX-M00001399	ETX-S00003282	ETX-S00003281
ETX-M00001400	ETX-S00003286	ETX-S00003285
ETX-M00001401	ETX-S00003290	ETX-S00003289
ETX-M00001402	ETX-S00003294	ETX-S00003293
ETX-M00001403	ETX-S00003298	ETX-S00003297
ETX-M00001404	ETX-S00003302	ETX-S00003301
ETX-M00001405	ETX-S00003306	ETX-S00003305
ETX-M00001406	ETX-S00003310	ETX-S00003309
ETX-M00001407	ETX-S00003314	ETX-S00003313

ETX-M00001408	ETX-S00003318	ETX-S00003317
ETX-M00001409	ETX-S00003322	ETX-S00003321
ETX-M00001410	ETX-S00003326	ETX-S00003325
ETX-M00001411	ETX-S00003330	ETX-S00003329
ETX-M00001412	ETX-S00003334	ETX-S00003333
ETX-M00001413	ETX-S00003338	ETX-S00003337
ETX-M00001414	ETX-S00003342	ETX-S00003341
ETX-M00001415	ETX-S00003346	ETX-S00003345
ETX-M00001416	ETX-S00003350	ETX-S00003349
ETX-M00001417	ETX-S00003354	ETX-S00003353
ETX-M00001418	ETX-S00003358	ETX-S00003357
ETX-M00001419	ETX-S00003362	ETX-S00003361
ETX-M00001420	ETX-S00003366	ETX-S00003365
ETX-M00001421	ETX-S00003370	ETX-S00003369
ETX-M00001422	ETX-S00003374	ETX-S00003373
ETX-M00001423	ETX-S00003378	ETX-S00003377
ETX-M00001424	ETX-S00003382	ETX-S00003381
ETX-M00001425	ETX-S00003386	ETX-S00003385
ETX-M00001426	ETX-S00003390	ETX-S00003389
ETX-M00001427	ETX-S00003394	ETX-S00003393
ETX-M00001428	ETX-S00003398	ETX-S00003397
ETX-M00001429	ETX-S00003402	ETX-S00003401
ETX-M00001430	ETX-S00003406	ETX-S00003405
ETX-M00001431	ETX-S00003410	ETX-S00003409
ETX-M00001432	ETX-S00003414	ETX-S00003413
ETX-M00001433	ETX-S00003418	ETX-S00003417
ETX-M00001434	ETX-S00003422	ETX-S00003421
ETX-M00001435	ETX-S00003426	ETX-S00003425
ETX-M00001436	ETX-S00003430	ETX-S00003429
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ETX-M00001438	ETX-S00003438	ETX-S00003437
ETX-M00001439	ETX-S00003442	ETX-S00003441
ETX-M00001440	ETX-S00003446	ETX-S00003445
ETX-M00001441	ETX-S00003450	ETX-S00003449
ETX-M00001442	ETX-S00003454	ETX-S00003453
ETX-M00001443	ETX-S00003458	ETX-S00003457
ETX-M00001444	ETX-S00003462	ETX-S00003461
ETX-M00001445	ETX-S00003466	ETX-S00003465
ETX-M00001446	ETX-S00003470	ETX-S00003469
ETX-M00001447	ETX-S00003474	ETX-S00003473
ETX-M00001448	ETX-S00003478	ETX-S00003477

ETX-M00001449	ETX-S00003482	ETX-S00003481
ETX-M00001450	ETX-S00003486	ETX-S00003485
ETX-M00001451	ETX-S00003490	ETX-S00003489
ETX-M00001452	ETX-S00003494	ETX-S00003493
ETX-M00001453	ETX-S00003498	ETX-S00003497
ETX-M00001454	ETX-S00003502	ETX-S00003501
ETX-M00001455	ETX-S00003506	ETX-S00003505
ETX-M00001456	ETX-S00003510	ETX-S00003509
ETX-M00001457	ETX-S00003514	ETX-S00003513
ETX-M00001458	ETX-S00003518	ETX-S00003517
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ETX-M00001466	ETX-S00003550	ETX-S00003549
ETX-M00001467	ETX-S00003554	ETX-S00003553
ETX-M00001468	ETX-S00003558	ETX-S00003557
ETX-M00001469	ETX-S00003562	ETX-S00003561
ETX-M00001470	ETX-S00003566	ETX-S00003565
ETX-M00001471	ETX-S00003570	ETX-S00003569
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ETX-M00001479	ETX-S00003602	ETX-S00003601
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ETX-M00001493	ETX-S00003658	ETX-S00003657
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ETX-M00001563	ETX-S00003938	ETX-S00003937
ETX-M00001564	ETX-S00003942	ETX-S00003941
ETX-M00001565	ETX-S00003946	ETX-S00003945
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ETX-M00001567	ETX-S00003954	ETX-S00003953
ETX-M00001568	ETX-S00003958	ETX-S00003957
ETX-M00001569	ETX-S00003962	ETX-S00003961
ETX-M00001570	ETX-S00003966	ETX-S00003965
ETX-M00001571	ETX-S00003970	ETX-S00003969

ETX-M00001572	ETX-S00003974	ETX-S00003973
ETX-M00001573	ETX-S00003978	ETX-S00003977
ETX-M00001574	ETX-S00003982	ETX-S00003981
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ETX-M00001578	ETX-S00003998	ETX-S00003997
ETX-M00001579	ETX-S00004002	ETX-S00004001
ETX-M00001580	ETX-S00004006	ETX-S00004005
ETX-M00001581	ETX-S00004010	ETX-S00004009
ETX-M00001582	ETX-S00004014	ETX-S00004013
ETX-M00001583	ETX-S00004018	ETX-S00004017
ETX-M00001584	ETX-S00004022	ETX-S00004021
ETX-M00001585	ETX-S00004026	ETX-S00004025
ETX-M00001586	ETX-S00004030	ETX-S00004029
ETX-M00001587	ETX-S00004034	ETX-S00004033
ETX-M00001588	ETX-S00004038	ETX-S00004037
ETX-M00001589	ETX-S00004042	ETX-S00004041
ETX-M00001590	ETX-S00004046	ETX-S00004045
ETX-M00001591	ETX-S00004050	ETX-S00004049
ETX-M00001592	ETX-S00004054	ETX-S00004053
ETX-M00001593	ETX-S00004058	ETX-S00004057
ETX-M00001594	ETX-S00004062	ETX-S00004061
ETX-M00001595	ETX-S00004066	ETX-S00004065
ETX-M00001596	ETX-S00004070	ETX-S00004069
ETX-M00001597	ETX-S00004074	ETX-S00004073
ETX-M00001598	ETX-S00004078	ETX-S00004077
ETX-M00001599	ETX-S00004082	ETX-S00004081
ETX-M00001600	ETX-S00004086	ETX-S00004085
ETX-M00001601	ETX-S00004090	ETX-S00004089
ETX-M00001602	ETX-S00004094	ETX-S00004093
ETX-M00001603	ETX-S00004098	ETX-S00004097
ETX-M00001604	ETX-S00004102	ETX-S00004101
ETX-M00001605	ETX-S00004106	ETX-S00004105
ETX-M00001606	ETX-S00004110	ETX-S00004109
ETX-M00001607	ETX-S00004114	ETX-S00004113
ETX-M00001608	ETX-S00004118	ETX-S00004117
ETX-M00001609	ETX-S00004122	ETX-S00004121
ETX-M00001610	ETX-S00004126	ETX-S00004125
ETX-M00001611	ETX-S00004130	ETX-S00004129
ETX-M00001612	ETX-S00004134	ETX-S00004133

ETX-M00001613	ETX-S00004138	ETX-S00004137
ETX-M00001614	ETX-S00004142	ETX-S00004141
ETX-M00001615	ETX-S00004146	ETX-S00004145
ETX-M00001616	ETX-S00004150	ETX-S00004149
ETX-M00001617	ETX-S00004154	ETX-S00004153
ETX-M00001618	ETX-S00004158	ETX-S00004157
ETX-M00001619	ETX-S00004162	ETX-S00004161
ETX-M00001620	ETX-S00004166	ETX-S00004165
ETX-M00001621	ETX-S00004170	ETX-S00004169
ETX-M00001622	ETX-S00004174	ETX-S00004173
ETX-M00001623	ETX-S00004178	ETX-S00004177
ETX-M00001624	ETX-S00004182	ETX-S00004181
ETX-M00001625	ETX-S00004186	ETX-S00004185
ETX-M00001626	ETX-S00004190	ETX-S00004189

For duplexes of Table 5:

ETX-M00001351 – ETX-M00001626 preferably have a duplex structure according to Figure 8b.

In a particularly preferred embodiment, the invention relates to a nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Duplex ID	Modified first strand	Modified second strand
ETX-M00001378	ETX-S00003198 (SEQ ID NO: 856)	ETX-S00003197 (SEQ ID NO: 1132)
ETX-M00001397	ETX-S00003274 (SEQ ID NO: 875)	ETX-S00003273 (SEQ ID NO: 1151)
ETX-M00001513	ETX-S00003738 (SEQ ID NO: 991)	ETX-S00003737 (SEQ ID NO: 1267)
ETX-M00001527	ETX-S00003794 (SEQ ID NO: 1005)	ETX-S00003793 (SEQ ID NO: 1281)
ETX-M00001570	ETX-S00003966 (SEQ ID NO: 1048)	ETX-S00003965 (SEQ ID NO: 1324)

In an even more preferred embodiment, the invention relates to a nucleic acid comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from any one of the following first and second sequences:

Duplex ID	Modified first strand	Modified second strand
ETX-M00001378	ETX-S00003198 (SEQ ID NO: 856)	ETX-S00003197 (SEQ ID NO: 1132)

In case of ambiguity between the sequences in this specification and the sequences in the attached sequence listing, the sequences provided herein are considered to be the correct sequences.

ABASIC NUCLEOTIDES

5 In certain embodiments, there are 1, e.g. 2, e.g. 3, e.g. 4 or more abasic nucleosides present in nucleic acids according to the invention. Abasic nucleosides are modified nucleosides because they lack the base normally seen at position 1 of the sugar moiety. Typically, there will be a hydrogen at position 1 of the sugar moiety of the abasic nucleosides present in a nucleic acid according to the present invention.

10 The abasic nucleosides are in the terminal region of the second strand, preferably located within the terminal 5 nucleosides of the end of the strand. The terminal region may be the terminal 5 nucleosides, which includes abasic nucleosides.

The second strand may comprise, as preferred features (which are all specifically contemplated in combination unless mutually exclusive):

- 2, or more than 2, abasic nucleosides in a terminal region of the second strand; and/or
- 15 2, or more than 2, abasic nucleosides in either the 5' or 3' terminal region of the second strand; and/or
- 2, or more than 2, abasic nucleosides in either the 5' or 3' terminal region of the second strand, wherein the abasic nucleosides are present in an overhang as herein described; and/or
- 20 2, or more than 2, consecutive abasic nucleosides in a terminal region of the second strand, wherein preferably one such abasic nucleosides is a terminal nucleosides; and/or
- 2, or more than 2, consecutive abasic nucleosides in either the 5' or 3' terminal region of the second strand, wherein preferably one such abasic nucleosides is a terminal nucleosides in either the 5' or 3' terminal region of the second strand; and/or
- 25 a reversed internucleoside linkage connects at least one abasic nucleoside to an adjacent basic nucleoside in a terminal region of the second strand; and/or
- a reversed internucleoside linkage connects at least one abasic nucleoside to an adjacent basic nucleoside in either the 5' or 3' terminal region of the second strand; and/or

an abasic nucleoside as the penultimate nucleoside which is connected via the reversed linkage to the nucleoside which is not the terminal nucleoside (called the antepenultimate nucleoside herein); and/or

5 abasic nucleosides as the 2 terminal nucleosides connected via a 5'-3' linkage when reading the strand in the direction towards the terminus comprising the terminal nucleosides;

abasic nucleosides as the 2 terminal nucleosides connected via a 3'-5' linkage when reading the strand in the direction towards the terminus comprising the terminal nucleosides;

10 abasic nucleosides as the terminal 2 positions, wherein the penultimate nucleoside is connected via the reversed linkage to the antepenultimate nucleoside, and wherein the reversed linkage is a 5-5' reversed linkage or a 3'-3' reversed linkage;

abasic nucleosides as the terminal 2 positions, wherein the penultimate nucleoside is connected via the reversed linkage to the antepenultimate nucleoside, and wherein either

15 (1) the reversed linkage is a 5-5' reversed linkage and the linkage between the terminal and penultimate abasic nucleosides is 3'5' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides; or

(2) the reversed linkage is a 3-3' reversed linkage and the linkage between the terminal and penultimate abasic nucleosides is 5'3' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides.

Preferably there is an abasic nucleoside at the terminus of the second strand.

20 Preferably there are 2 or at least 2 abasic nucleosides in the terminal region of the second strand, preferably at the terminal and penultimate positions.

Preferably 2 or more abasic nucleosides are consecutive, for example all abasic nucleosides may be consecutive. For example, the terminal 1 or terminal 2 or terminal 3 or terminal 4 nucleotides may be abasic nucleosides.

25 An abasic nucleoside may also be linked to an adjacent nucleoside through a 5'-3' phosphodiester linkage or reversed linkage unless there is only 1 abasic nucleoside at the terminus, in which case it will have a reversed linkage to the adjacent nucleoside.

30 A reversed linkage (which may also be referred to as an inverted linkage, which is also seen in the art), comprises either a 5'-5', a 3'-3', a 3'-2' or a 2'-3' phosphodiester linkage between the adjacent sugar moieties of the nucleosides.

Abasic nucleosides which are not terminal will have 2 phosphodiester bonds, one with each adjacent nucleoside, and these may be a reversed linkage or may be a 5'-3' phosphodiester bond or may be one of each.

5 A preferred embodiment comprises 2 abasic nucleosides at the terminal and penultimate positions of the second strand, and wherein the reversed internucleoside linkage is located between the penultimate (abasic) nucleoside and the antepenultimate nucleoside.

Preferably there are 2 abasic nucleosides at the terminal and penultimate positions of the second strand and the penultimate nucleoside is linked to the antepenultimate nucleoside through a reversed internucleoside linkage and is linked to the terminal nucleoside through a 5'-3' or 3'-5' phosphodiester linkage (reading in
10 the direction of the terminus of the molecule).

Different preferred features are as follows:

The reversed internucleoside linkage is a 3'-3' reversed linkage. The reversed internucleoside linkage is at a terminal region which is distal to the 5' terminal phosphate of the second strand.

15 The reversed internucleoside linkage is a 5'-5' reversed linkage. The reversed internucleoside linkage is at a terminal region which is distal to the 3' terminal hydroxide of the second strand.

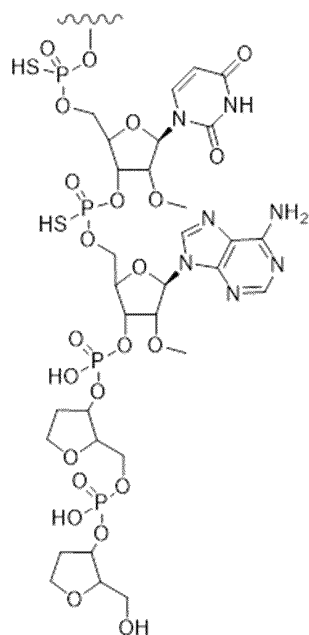
In certain embodiments, the second strand comprises 2 consecutive abasic nucleosides in the 5' terminal region of the second strand, wherein one such abasic nucleoside is a terminal nucleoside at the 5' terminal region of the second strand and the other abasic nucleoside is a penultimate nucleoside at the 5' terminal region of the second strand, wherein: (a) said penultimate abasic nucleoside is connected to an adjacent
20 first basic nucleoside in an adjacent 5' near terminal region through a reversed internucleoside linkage; and (b) the reversed linkage is a 5-5' reversed linkage; and (c) the linkage between the terminal and penultimate abasic nucleosides is 3'5' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides. More typically, (i) the first strand and the second strand each has a length of 23 nucleosides; (ii) two phosphorothioate internucleoside linkages are respectively between three consecutive
25 positions in said 5' near terminal region of the second strand, wherein a first phosphorothioate internucleoside linkage is present between said adjacent first basic nucleoside of (a) and an adjacent second basic nucleoside in said 5' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present between said adjacent second basic nucleoside and an adjacent third basic nucleoside in said 5' near terminal region of the second strand; (iii) two phosphorothioate internucleoside
30 linkages are respectively between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each first 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage; and (iv) the second

strand of the nucleic acid is conjugated directly or indirectly to one or more ligand moieties at the 3' terminal region of the second strand.

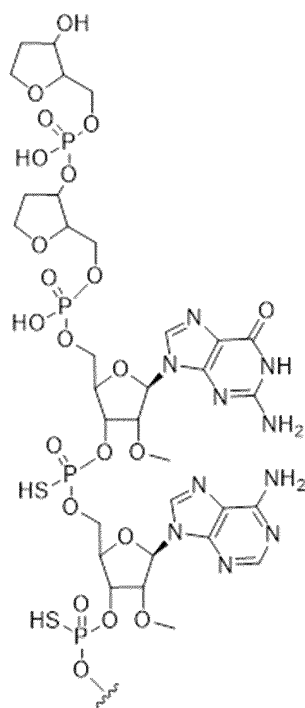
Alternatively the second strand comprises 2 consecutive abasic nucleosides preferably in an overhang in the 3' terminal region of the second strand, wherein one such abasic nucleoside is a terminal nucleoside at the 3' terminal region of the second strand and the other abasic nucleoside is a penultimate nucleoside at the 3' terminal region of the second strand, wherein: (a) said penultimate abasic nucleoside is connected to an adjacent first basic nucleoside in an adjacent 3' near terminal region through a reversed internucleoside linkage; and (b) the reversed linkage is a 3-3' reversed linkage; and (c) the linkage between the terminal and penultimate abasic nucleosides is 5'-3' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides. More typically, (i) the first strand and the second strand each has a length of 23 nucleosides; (ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 3' near terminal region of the second strand, wherein a first phosphorothioate internucleoside linkage is present between said adjacent first basic nucleoside of (a) and an adjacent second basic nucleoside in said 3' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present between said adjacent second basic nucleoside and an adjacent third basic nucleoside in said 3' near terminal region of the second strand; (iii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each first 5' and 3' penultimate nucleoside is attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage; and (iv) the second strand of the nucleic acid is conjugated directly or indirectly to one or more ligand moieties at the 5' terminal region of the second strand.

Examples of the structures are as follows (where the specific RNA nucleosides shown are not limiting and could be any RNA nucleoside):

A A 3'-3' reversed bond (and also showing the 5'-3' direction of the last phosphodiester bond between the two abasic molecules reading towards the terminus of the molecule)



B Illustrating a 5'-5' reversed bond (and also showing the 3'-5' direction of the last phosphodiester bond between the two abasic molecules reading towards the terminus of the molecule)



- 5 The abasic nucleoside or abasic nucleosides present in the nucleic acid are provided in the presence of a reversed internucleoside linkage or linkages, namely a 5'-5' or a 3'-3' reversed internucleoside linkage. A reversed linkage occurs as a result of a change of orientation of an adjacent nucleoside sugar, such that the sugar will have a 3' – 5' orientation as opposed to the conventional 5' – 3' orientation (with reference to

the numbering of ring atoms on the nucleoside sugars). The abasic nucleoside or nucleosides as present in the nucleic acids of the invention preferably include such inverted nucleoside sugars.

In the case of a terminal nucleoside having an inverted orientation, then this will result in an “inverted” end configuration for the overall nucleic acid. Whilst certain structures drawn and referenced herein are represented using conventional 5' - 3' direction (with reference to the numbering of ring atoms on the nucleoside sugars), it will be appreciated that the presence of a terminal nucleoside having a change of orientation and a proximal 3'-3' reversed linkage, will result in a nucleic acid having an overall 5'-5' end structure (i.e. the conventional 3' end nucleoside becomes a 5' end nucleoside). Alternatively, it will be appreciated that the presence of a terminal nucleoside having a change of orientation and a proximal 5'-5' reversed linkage will result in a nucleic acid with an overall 3' - 3' end structure.

The proximal 3'-3' or 5'-5' reversed linkage as herein described, may comprise the reversed linkage being directly adjacent / attached to a terminal nucleoside having an inverted orientation, such as a single terminal nucleoside having an inverted orientation. Alternatively, the proximal 3'-3' or 5'-5' reversed linkage as herein described, may comprise the reversed linkage being adjacent 2, or more than 2, nucleosides having an inverted orientation, such as 2, or more than 2, terminal region nucleosides having an inverted orientation, such as the terminal and penultimate nucleosides. In this way, the reversed linkage may be attached to a penultimate nucleoside having an inverted orientation. While a skilled addressee will appreciate that inverted orientations as described above can result in nucleic acid molecules having overall 3' - 3' or 5'-5' end structures as described herein, it will also be appreciated that with the presence of one or more additional reversed linkages and / or nucleosides having an inverted orientation, then the overall nucleic acid may have 3' - 5' end structures corresponding to the conventionally positioned 5' / 3' ends.

In one aspect the nucleic acid may have a 3'-3' reversed linkage, and the terminal sugar moiety may comprise a 5' OH rather than a 5' phosphate group at the 5' position of that terminal sugar.

A skilled person would therefore clearly understand that 5'-5', 3'-3' and 3'-5' (reading in the direction of that terminus) end variants of the more conventional 5'-3' structures (with reference to the numbering of ring atoms on the end nucleoside sugars) drawn herein are included in the scope of the disclosure, where a reversed linkage or linkages is / are present.

In the situation of e.g. a reversed internucleoside linkage and / or one or more nucleosides having an inverted orientation creating an inverted end, and where the relative position of a linkage (e.g. to a linker) or the location of an internal feature (such as a modified nucleoside) is defined relative to the 5' or 3' end of the nucleic acid, then the 5' or 3' end is the conventional 5' or 3' end which would have existed had a reversed linkage not been in place, and wherein the conventional 5' or 3' end is determined by consideration of the directionality of the majority of the internal nucleoside linkages and / or nucleoside orientation within the nucleic acid. It is possible to tell from these internal bonds and / or nucleoside orientation which ends

of the nucleic acid would constitute the conventional 5' and 3' ends (with reference to the numbering of ring atoms on the end nucleoside sugars) of the molecule absent the reversed linkage.

For example, in the structure shown below there are abasic residues in the first 2 positions located at the "5'" end. Where the terminal nucleoside has an inverted orientation then the "5'" end indicated in the diagram below, which is the conventional 5' end, can in fact comprise a 3' OH in view of the inverted nucleoside at the terminal position. Nevertheless the majority of the molecule will comprise conventional internucleoside linkages that run from the 3' OH of the sugar to the 5' phosphate of the next sugar, when reading in the standard 5' [PO4] to 3' [OH] direction of a nucleic acid molecule (with reference to the numbering of ring atoms on the nucleoside sugars), which can be used to determine the conventional 5' and 3' ends that would be found absent the inverted end configuration.

A 5' A-A-Me-Me-Me-Me-Me-Me-F-Me-F-F-F-Me-Me-Me-Me-Me-Me-Me-Me-Me-Me 3'

The reversed bond is preferably located at the end of the nucleic acid e.g. RNA which is distal to a ligand moiety, such as a GalNAc containing portion, of the molecule.

GalNAc-siRNA constructs with a 5'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

GalNAc-siRNA constructs with a 3'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

NUCLEIC ACID LENGTHS

In one aspect the i) the first strand of the nucleic acid has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 23 nucleosides; and / or ii) the second strand of the nucleic acid has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 21 nucleosides.

Typically the duplex region of the nucleic acid is between 17 and 30 nucleosides in length, more preferably is 19 or 21 nucleosides in length. Similarly, the region of complementarity between the first strand and the portion of RNA transcribed from the *SLC25A5* gene is between 17 and 30 nucleosides in length. Generally, the duplex structure of the nucleic acid e.g. an iRNA is about 15 to 30 base pairs in length, e.g., 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

Similarly, the region of complementarity of an antisense sequence to a target sequence and/or the region of complementarity of an antisense sequence to a sense sequence is about 15 to 30 nucleosides in length, e.g.,

15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleosides in length. Ranges and lengths
 5 intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

In certain preferred embodiments, the region of complementarity of an antisense sequence to a target sequence and/or the region of complementarity of an antisense sequence to a sense sequence is at least 17 nucleosides in length. For example, the region of complementarity between the antisense strand and the target is 19 to 21 nucleosides in length, for example, the region of complementarity is 21 nucleosides in
 10 length.

In preferred embodiments, each strand is no more than 30 nucleosides in length.

In certain preferred embodiments, the duplex structure of the nucleic acid e.g. an siRNA is 19 or 21 base pairs in length.

A nucleic acid e.g. a dsRNA as described herein can further include one or more single-stranded nucleoside overhangs e.g., 1-4, 2-4, 1-3, 2-3, 1, 2, 3, or 4 nucleosides. A nucleoside overhang can comprise or consist
 15 of a nucleoside/nucleoside analog, including a deoxynucleoside/nucleoside. The overhang(s) can be on the sense strand, the antisense strand, or any combination thereof. Furthermore, the nucleoside(s) of an overhang can be present on the 5'-end, 3'-end, or both ends of an antisense or sense strand of a nucleic acid e.g. a dsRNA.

20 In certain preferred embodiments, at least one strand comprises a 3' overhang of at least 1 nucleoside, e.g., , at least one strand comprises a 3' overhang of at least 2 nucleosides. The overhang is suitably on the antisense/ guide strand and/or the sense / passenger strand.

NUCLEIC ACID MODIFICATIONS

In certain embodiments, the nucleic acid e.g. an RNA of the invention e.g., a dsiRNA, does not comprise
 25 further modifications, e.g., chemical modifications or conjugations known in the art and described herein.

In other preferred embodiments, the nucleic acid e.g. RNA of the invention, e.g., a dsiRNA, is further chemically modified to enhance stability or other beneficial characteristics.

In certain embodiments of the invention, substantially all of the nucleosides are modified.

The nucleic acids featured in the invention can be synthesized or modified by methods well established in
 30 the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. et al. (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference.

Modifications include, for example, end modifications, e.g., 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleosides within an RNA, or RNA nucleosides within a DNA, inverted linkages, etc.); base modifications, e.g., replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, conjugated bases; sugar modifications (e.g., at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages.

Specific examples of nucleic acids such as siRNA compounds useful in the embodiments described herein include, but are not limited to RNAs containing modified backbones or no natural internucleoside linkages. Nucleic acids such as RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified nucleic acids e.g., RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified nucleic acid e.g., an siRNA will have a phosphorus atom in its internucleoside backbone.

Modified nucleic acid e.g. RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 5'-3' or 5'-2'. Various salts, mixed salts and free acid forms are also included.

Modified nucleic acids e.g. RNAs can also contain one or more substituted sugar moieties. The nucleic acids e.g. siRNAs, e.g., dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted. 2' O- methyl and 2' -F are preferred modifications.

In certain preferred embodiments, the nucleic acid comprises at least one modified nucleoside.

The nucleic acid of the invention may comprise one or more modified nucleosides on the first strand and/or the second strand.

In some embodiments, substantially all of the nucleosides of the sense strand and all of the nucleosides of the antisense strand comprise a modification.

In some embodiments, all of the nucleosides of the sense strand and substantially all of the nucleosides of the antisense strand comprise a modification.

In some embodiments, all of the nucleosides of the sense strand and all of the nucleosides of the antisense strand comprise a modification.

In one embodiment, at least one of the modified nucleosides is selected from the group consisting of a deoxy- nucleoside, a 3'-terminal deoxy-thymine (dT) nucleoside, a 2'-O-methyl modified nucleoside (also called herein 2'-Me, where Me is a methoxy) , a 2'-fluoro modified nucleoside, a 2'-deoxy- modified nucleoside, a locked nucleoside, an unlocked nucleoside, a conformationally restricted nucleoside, a constrained ethyl nucleoside, an abasic nucleoside, a 2'-amino- modified nucleoside, a 2'- O-allyl- modified nucleoside, 2'-C-alkyl- modified nucleoside, 2'-hydroxly-modified nucleoside, a 2'- methoxyethyl modified nucleoside, a 2'-O-alkyl-modified nucleoside, a morpholino nucleoside, a phosphoramidate, a non-natural base comprising nucleoside, a tetrahydropyran modified nucleoside, a 1,5-anhydrohexitol modified nucleoside, a cyclohexenyl modified nucleoside, a nucleoside comprising a phosphorothioate group, a nucleoside comprising a methylphosphonate group, a nucleoside comprising a 5'-phosphate, and a nucleoside comprising a 5'-phosphate mimic. In another embodiment, the modified nucleosides comprise a short sequence of 3'-terminal deoxy-thymine nucleosides (dT).

Modifications on the nucleosides may preferably be selected from the group including, but not limited to, LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'- hydroxyl, and combinations thereof. In another embodiment, the modifications on the nucleosides are 2'-O-methyl ("2'-Me") or 2'-fluoro modifications.

One preferred modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

In certain embodiments, the nucleic acid e.g., siRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleoside linkage. For example the phosphorothioate or methylphosphonate internucleoside linkage can be at the 3'-terminus or in the terminal region of one strand, i.e., the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

In certain embodiments, the phosphorothioate or methylphosphonate internucleoside linkage is at the 5'-terminus or in the terminal region of one strand, i.e., the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

In certain embodiments, a phosphorothioate or a methylphosphonate internucleoside linkage is at both the 5'- and 3'-terminus or in the terminal region of one strand, i.e., the sense strand or the antisense strand; or at the ends of both strands, the sense strand and the antisense strand.

Any nucleic acid may comprise one or more phosphorothioate (PS) modifications within the nucleic acid, such as at least two PS internucleoside bonds at the ends of a strand.

At least one of the oligoribonucleoside strands preferably comprises at least two consecutive phosphorothioate modifications in the last 3 nucleosides of the oligonucleoside.

The invention therefore also relates to: A nucleic acid disclosed herein which comprises phosphorothioate internucleoside linkages respectively between at least two or three consecutive positions, such as in a 5' and/or 3' terminal region and/or near terminal region of the second strand, whereby said near terminal region is preferably adjacent said terminal region wherein said one or more abasic nucleosides of said second strand is / are located.

A nucleic acid disclosed herein which comprises phosphorothioate internucleoside linkages respectively between at least two or three consecutive positions in a 5' and / or 3' terminal region of the first strand, whereby preferably the terminal position at the 5' and / or 3' terminal region of said first strand is attached to its adjacent position by a phosphorothioate internucleoside linkage.

The nucleic acid strand may be an RNA comprising a phosphorothioate internucleoside linkage between the three nucleosides contiguous with 2 terminally located abasic nucleosides.

A preferred nucleic acid is a double stranded RNA comprising 2 adjacent abasic nucleosides at the 5' terminus of the second strand and a ligand moiety comprising one or more GalNAc ligand moieties at the opposite 3' end of the second strand. Further preferred, the same nucleic acid may also comprise a phosphorothioate bond between nucleotides at positions 3-4 and 4-5 of the second strand, reading from the position 1 of the second strand.

Position 1 of the first or the second strand is the nucleoside which is the closest to the end of the nucleic acid (ignoring any abasic nucleosides) and that is joined to an adjacent nucleoside (at Position 2) via a 3' to 5' internal bond, with reference to the bonds between the sugar moieties of the backbone, and reading in a direction away from that end of the molecule.

It can therefore be seen that "position 1 of the sense strand" is the 5' most nucleoside (not including abasic nucleosides) at the conventional 5' end of the sense strand. Typically, the nucleoside at this position 1 of the sense strand will be equivalent to the 5' nucleoside of the selected target nucleic acid sequence, and more generally the sense strand will have equivalent nucleosides to those of the target nucleic acid sequence starting from this position 1 of the sense strand, whilst also allowing for acceptable mismatches between the sequences.

As used herein, "position 1 of the antisense strand" is the 5' most nucleoside (not including abasic nucleosides) at the conventional 5' end of the antisense strand. As hereinbefore described, there will be a region of complementarity between the sense and antisense strands, and in this way the antisense strand will also have a region of complementarity to the target nucleic acid sequence as referred to above.

Preferred modifications that can be used with sequences according to the present invention can be as follows:

Modification 1:

First strand modification:

5 NmsNfsNmNfNmNfNmNfNmNfNmNmNmNmNfNmNfNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNmNfNmNfNmNmNmNmNmNmNmNfNmNm (5' to 3')

Modification 2:

First strand modification:

10 NmsNfsNmNfNmNfNmNfNmNfNmNmNmNmNfNmNfNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNmNfNmNfNmNmNmNmNmNmNmNfNmNm (5' to 3')

Modification 3:

First strand modification:

15 NmsNfsNmNfNmNfNmNfNmNfNmNmNmNmNfNmNfNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNmNfNmNfNmNmNmNmNmNmNmNfNmNm (5' to 3')

Modification 4:

First strand modification:

20 NmsNfsNmNfNmNfNmNmNmNmNmNmNfNmNfNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNmNfNmNfNmNmNmNmNmNmNmNfNmNm (5' to 3')

Modification 5:

First strand modification:

NmsNfsNmNmNmNfNmNmNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

Modification 6:

- 5 First strand modification:

NmsNfsNmNmNmNfNmNmNmNmNmNmNmNfNmNfNmNfNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

Modification 7:

- 10 First strand modification:

NmsNfsNmNmNmNyNmNmNmNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

Modification 8:

- 15 First strand modification:

NmsNfsNmNmNmNyNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

Modification 9:

- 20 First strand modification:

NmsNfsNmNmNmNfNmNmNmNmNmNmNmNfNmNfNmNmNmNfNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

Modification 10:

First strand modification:

NmsNfsNmNfNmNfNmNmNmNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

5 Modification 11:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

10 Modification 12:

First strand modification:

NmsNfsNmNmNmNfNmNfNfNmNmNmNmNfNmNfNmNfNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

15 Modification 13:

First strand modification:

NmsNfsNmNmNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5' to 3')

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

20 wherein in each of the above modifications:

ia represents an inverted abasic nucleoside;

Nm represents a 2' Me ribose modified nucleoside;

Nf represents a 2' F ribose modified nucleoside;

Ny represents a nucleoside with a thermally destabilizing modification, preferably wherein the destabilizing modification is selected from a modified unlocked nucleic acid (UNA) and a glycol nucleic acid (GNA), more preferably a glycol nucleic acid, most preferably an (S)-glycol nucleic acid;

s represents a phosphorothioate internucleoside bond.

- 5 A particularly preferred modification that can be used with sequences according to the present invention can be:

Modification 6:

First strand modification:

NmsNfsNmNmNmNfNmNmNmNmNmNmNmNfNmNfNmNfNmNmNmsNmsNm (5' to 3')

- 10 Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5' to 3')

wherein in each of the above modifications:

ia represents an inverted abasic nucleoside;

Nm represents a 2'-Me ribose modified nucleoside;

- 15 Nf represents a 2'-F ribose modified nucleoside; and

s represents a phosphorothioate internucleoside bond.

CONJUGATION OF NUCLEIC ACID TO LIGAND

- Another modification of a nucleic acid e.g. RNA e.g. an siRNA of the invention involves linking the nucleic acid e.g. the siRNA to one or more ligand moieties e.g. to enhance the activity, cellular distribution, or cellular uptake of the nucleic acid e.g. siRNA e.g., into a cell.
- 20

In some embodiments, the ligand moiety described can be attached to a nucleic acid e.g. an siRNA oligonucleoside, via a linker that can be cleavable or non-cleavable. The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, e.g., covalently attaches two parts of a compound.

- 25 The ligand can be attached to the 3' or 5' end of the sense strand.

The ligand is preferably conjugated to 3' end of the sense strand of the nucleic acid e.g. an siRNA agent.

The invention therefore relates in a further aspect to a conjugate for inhibiting expression of a target e.g. a target gene, in a cell, said conjugate comprising a nucleic acid portion and one or more ligand moieties, said nucleic acid portion comprising a nucleic acid as disclosed herein.

5 In one aspect the second strand of the nucleic acid is conjugated directly or indirectly (e.g. via a linker) to the one or more ligand moiety(s), wherein said ligand moiety is typically present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

In certain embodiments, the ligand moiety comprises a GalNAc or GalNAc derivative attached to the nucleic acid e.g. dsRNA through a linker.

Therefore, the invention relates to a conjugate wherein the ligand moiety comprises

- 10 i) one or more GalNAc ligands; and/or
- ii) one or more GalNAc ligand derivatives; and/or
- iii) one or more GalNAc ligands conjugated to said nucleic acid through a linker.

Said GalNAc ligand may be conjugated directly or indirectly to the 5' or 3' terminal region of the second strand of the nucleic acid, preferably at the 3' terminal region thereof.

15 GalNAc ligands are well known in the art and described in, inter alia, EP3775207A1.

In some embodiments, the ligand moiety comprises one or more ligands.

In some embodiments, the ligand moiety comprises one or more carbohydrate ligands.

In some embodiments, the one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and / or polysaccharide.

20 In some embodiments, the one or more carbohydrates comprise one or more galactose moieties, one or more lactose moieties, one or more N-AcetylGalactosamine moieties, and / or one or more mannose moieties.

In some embodiments, the one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

25 In some embodiments, the compounds as described anywhere herein comprise two or three N-AcetylGalactosamine moieties.

In some embodiments, the one or more ligands are attached in a linear configuration, or in a branched configuration, for example each configuration being respectively attached to a branch point in an overall linker.

Exemplary linear configurations and Exemplary branched configurations are shown in Figures 1a and 1b:

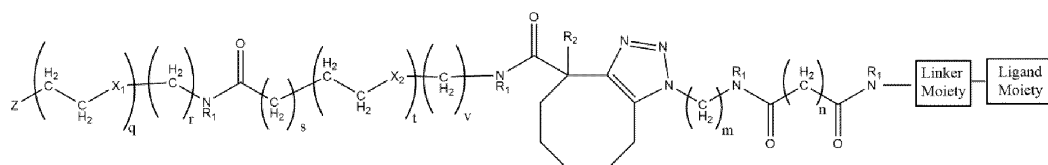
In Fig 1a, (linear), (a) and / or (b) can typically represent connecting bonds or groups, such as phosphate or phosphorothioate groups.

- 5 In Fig 1b, (branched), in some embodiments, the one or more ligands are attached as a biantennary or triantennary branched configuration. Typically, a triantennary branched configuration can be preferred, such as an N-AcetylGalactosamine triantennary branched configuration.

LINKER

Exemplary compounds of the invention comprise a 'linker moiety', such as that as depicted in Formula (I), that is part of an overall 'linker'.

10 Formula I



wherein:

R₁ at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

- 15 R₂ is selected from the group consisting of hydrogen, hydroxy, -OC₁₋₃alkyl, -C(=O)OC₁₋₃alkyl, halo and nitro;

X₁ and X₂ at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

- 20 q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(i) q and r cannot both be 0 at the same time; and

(ii) s, t and v cannot all be 0 at the same time;

Z is an oligonucleoside moiety.

As will be further understood in the art, exemplary compounds of the invention comprise an overall linker that is located between the oligonucleoside moiety and the ligand moiety of these compounds. The overall linker, thereby 'links' the oligonucleoside moiety and the ligand moiety to each other.

The overall linker is often notionally envisaged as comprising one or more linker building blocks. For example, there is a linker portion that is depicted as the 'linker moiety' as represented in Formula (I) positioned adjacent the ligand moiety and attaching the ligand moiety, typically via a branch point, directly or indirectly to the oligonucleoside moiety. The linker moiety as depicted in Formula (I) can also often be referred to as the 'ligand arm or arms' of the overall linker. There can also, but not always, be a further linker portion between the oligonucleoside moiety and the branch point, that is often referred to as the 'tether moiety' of the overall linker, 'tethering' the oligonucleoside moiety to the remainder of the conjugated compound. Such 'ligand arms' and / or 'linker moieties' and / or 'tether moieties' can be envisaged by reference to the linear and / or branched configurations as set out above.

As can be seen from the claims, and the remainder of the patent specification, the scope of the present invention extends to linear or branched configurations, and with no limitation as to the number of individual ligands that might be present. Furthermore, the addressee will also be aware that there are many structures that could be used as the linker moiety, based on the state of the art and the expertise of an oligonucleoside chemist.

The remainder of the overall linker (other than the linker moiety) as set out in the claims, and the remainder of the patent specification, is shown by its chemical constituents in Formula (I), which the inventors consider to be particularly unique to the current invention. In more general terms, however, these chemical constituents could be described as a 'tether moiety' as hereinbefore described, wherein the 'tether moiety' is that portion of the overall linker which comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety as depicted in Formula (I).

Tether moiety of Formula I

In relation to Formula (I), the 'tether moiety' comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety.

In some embodiments, R₁ is hydrogen at each occurrence. In some embodiments, R₁ is methyl. In some embodiments, R₁ is ethyl.

In some embodiments, R₂ is hydroxy. In some embodiments, R₂ is halo. In some embodiments, R₂ is fluoro. In some embodiments, R₂ is chloro. In some embodiments, R₂ is bromo. In some embodiments, R₂ is iodo. In some embodiments, R₂ is nitro.

In some embodiments, X₁ is methylene. In some embodiments, X₁ is oxygen. In some embodiments, X₁ is sulfur.

In some embodiments, X_2 is methylene. In some embodiments, X_2 is oxygen. In some embodiments, X_2 is sulfur.

In some embodiments, $m = 3$.

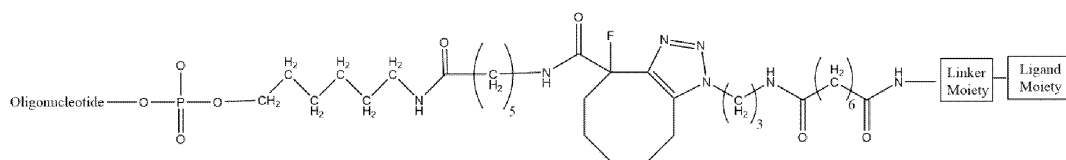
In some embodiments, $n = 6$.

- 5 In some embodiments, X_1 is oxygen and X_2 is methylene. In some embodiments, both X_1 and X_2 are methylene.

In some embodiments, $q = 1$, $r = 2$, $s = 1$, $t = 1$, $v = 1$. In some embodiments, $q = 1$, $r = 3$, $s = 1$, $t = 1$, $v = 1$.

- 10 In some embodiments, R_1 is hydrogen at each occurrence, $n = 6$, $m = 3$, R_2 is fluoro, X_2 is methylene, $v = 1$, $t = 1$, $s = 1$, X_1 is methylene, $q = 1$ and $r = 2$.

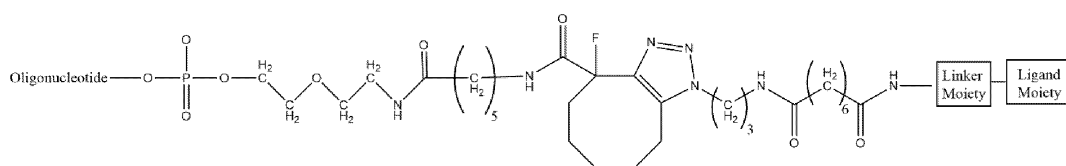
Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (IV)

- 15 In some embodiments, R_1 is hydrogen at each occurrence, $n = 6$, $m = 3$, R_2 is fluoro, X_2 is methylene, $v = 1$, $t = 1$, $s = 1$, X_1 is oxygen, $q = 1$ and $r = 2$.

Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (II)

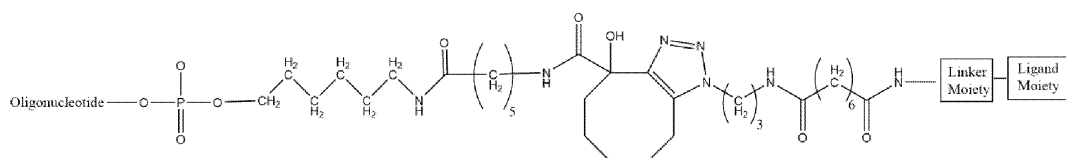
Alternative tether moieties

- 20 During the synthesis of compounds of the present invention, alternative tether moiety structures may arise. In some embodiments, alternative tether moieties have a change of one or more atoms in the tether moiety of the overall linker compared to tether moieties described anywhere herein.

In some embodiments, the alternative tether moiety is a compound of Formula (I) as described anywhere herein, wherein R_2 is hydroxy.

In some embodiments, R_1 is hydrogen at each occurrence, $n = 6$, $m = 3$, R_2 is hydroxy, X_2 is methylene, $v = 1$, $t = 1$, $s = 1$, X_1 is methylene, $q = 1$ and $r = 2$.

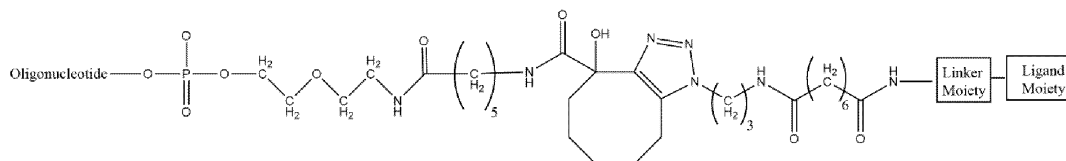
- 5 Thus, in some embodiments, compounds of the invention comprise the following structure:



Formula (V)

In some embodiments, R_1 is hydrogen at each occurrence, $n = 6$, $m = 3$, R_2 is hydroxy, X_2 is methylene, $v = 1$, $t = 1$, $s = 1$, X_1 is oxygen, $q = 1$ and $r = 2$.

- 10 Thus, in some embodiments, compounds of the invention comprise the following structure:

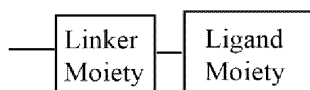


Formula (III)

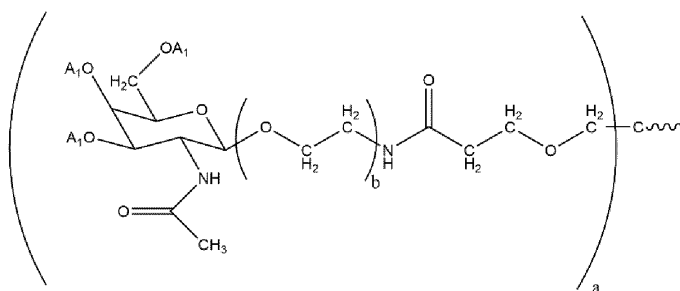
Linker moiety

- 15 In relation to Formula (I), the 'linker moiety' as depicted in Formula (I) comprises the group of atoms located between the tether moiety as described anywhere herein, and the ligand moiety as described anywhere herein.

In some embodiments:



- 20 as depicted in Formula (I) as described anywhere herein is any of Formulae (VIa), (VIb) or (VIc), preferably Formula (VIa):



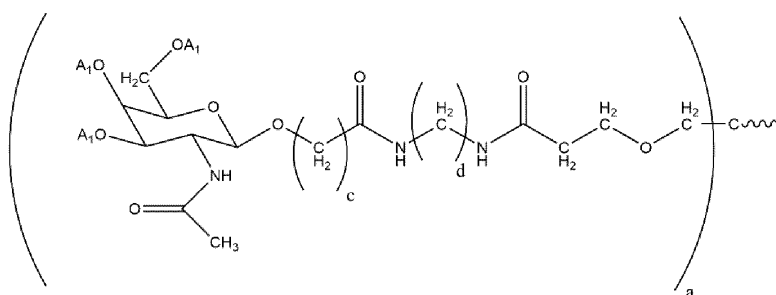
Formula (VIa)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

5 a is an integer of 2 or 3; and

b is an integer of 2 to 5; or



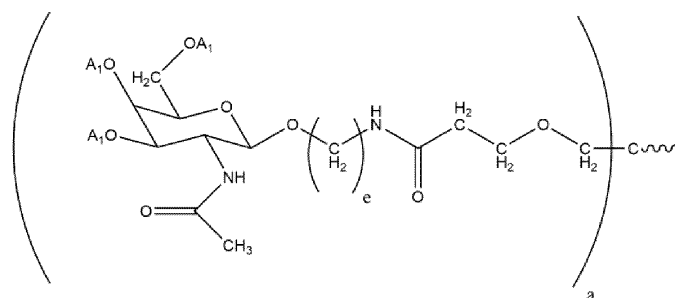
Formula (VIb)

wherein:

10 A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

c and d are independently integers of 1 to 6; or



Formula (VIc)

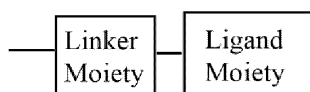
wherein:

A_1 is hydrogen, or a suitable hydroxy protecting group;

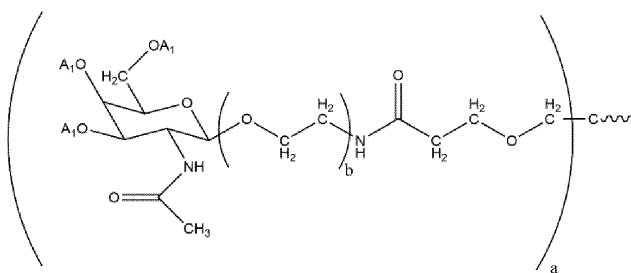
a is an integer of 2 or 3; and

5 e is an integer of 2 to 10.

In some embodiments, the moiety:



as depicted in Formula (I) is Formula (VIa):



10

Formula (VIa)

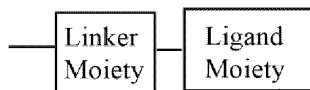
wherein:

A_1 is hydrogen, or a suitable hydroxy protecting group;

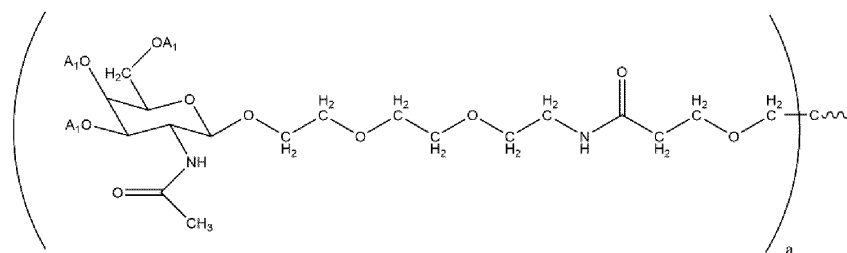
a is 3; and

b is an integer of 3.

15 In some embodiments, the moiety:



as depicted in Formula (I) as described anywhere herein is Formula (VII):



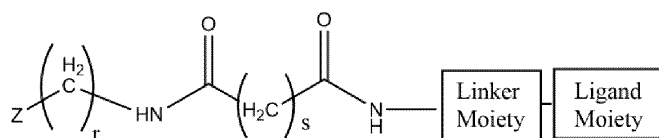
Formula (VII)

wherein:

A₁ is hydrogen;

- 5 a is an integer of 2 or 3, preferably 3.

Other exemplary compounds of the invention comprise a 'linker moiety', as depicted in Formula (I*), that is part of an overall 'linker'.



Formula I*

- 10 Where:

r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety.

- As will be further understood in the art, exemplary compounds of the invention comprise an overall linker that is located between the oligonucleoside moiety and the ligand moiety of these compounds. The overall linker, thereby 'links' the oligonucleoside moiety and the ligand moiety to each other.
- 15

- The overall linker is often notionally envisaged as comprising one or more linker building blocks. For example, there is a linker portion that is depicted as the 'linker moiety' as represented in Formula (I*) positioned adjacent the ligand moiety and attaching the ligand moiety, typically via a branch point, directly or indirectly to the oligonucleoside moiety. The linker moiety as depicted in Formula (I*) can also often be referred to as the 'ligand arm or arms' of the overall linker. There can also, but not always, be a further linker portion between the oligonucleoside moiety and the branch point, that is often referred to as the 'tether moiety' of the overall linker, 'tethering' the oligonucleoside moiety to the remainder of the
- 20

conjugated compound. Such 'ligand arms' and / or 'linker moieties' and / or 'tether moieties' can be envisaged by reference to the linear and / or branched configurations as set out above.

As can be seen from the claims, and the reminder of the patent specification, the scope of the present invention extends to linear or branched configurations, and with no limitation as to the number of individual
 5 ligands that might be present. Furthermore, the addressee will also be aware that there are many structures that could be used as the linker moiety, based on the state of the art and the expertise of an oligonucleoside chemist.

The remainder of the overall linker (other than the linker moiety) as set out in the claims, and the remainder of the patent specification, is shown by its chemical constituents in Formula (I), which the inventors
 10 consider to be particularly unique to the current invention. In more general terms, however, these chemical constituents could be described as a 'tether moiety' as hereinbefore described, wherein the 'tether moiety' is that portion of the overall linker which comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety as depicted in Formula (I).

Tether moiety

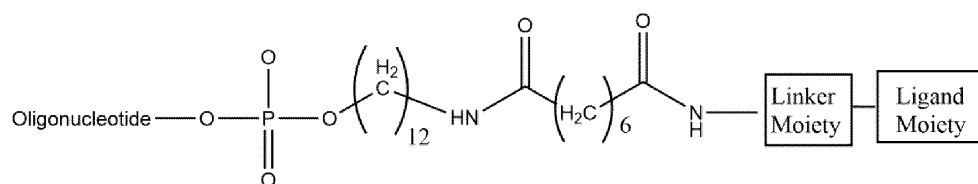
15 In relation to Formula (I*), the 'tether moiety' comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety.

In some embodiments, s is an integer selected from 4 to 12. In some embodiments, s is 6.

In some embodiments, r is an integer selected from 4 to 14. In some embodiments, r is 6. In some embodiments, r is 12.

20 In some embodiments, r is 12 and s is 6.

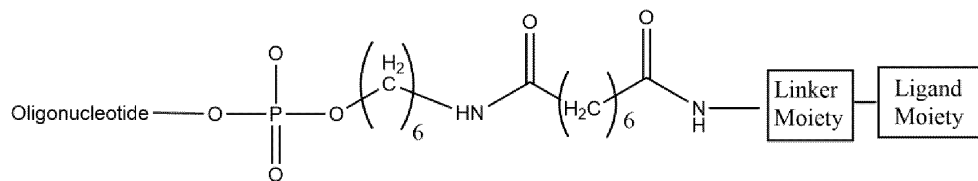
Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (II*)

In some embodiments, r is 6 and s is 6.

25 Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:

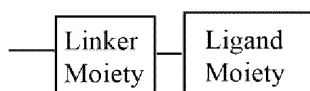


Formula (III*)

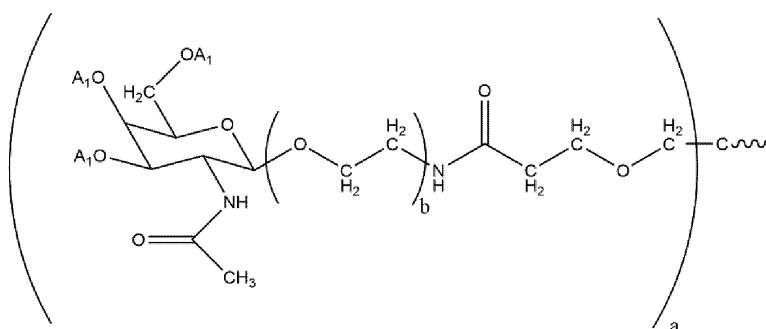
Linker moiety

In relation to Formula (I*), the 'linker moiety' as depicted in Formula (I) comprises the group of atoms
 5 located between the tether moiety as described anywhere herein, and the ligand moiety as described anywhere herein.

In some embodiments, the moiety:



as depicted in Formula (I*) as described anywhere herein is any of Formulae (IV*), (V*) or (VI*),
 10 preferably Formula (IV*):



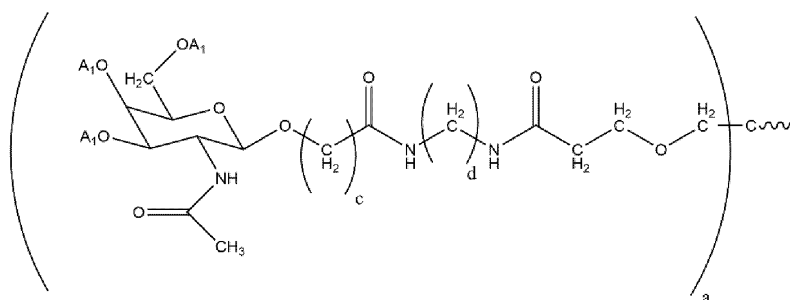
Formula (IV*)

wherein:

A_1 is hydrogen, or a suitable hydroxy protecting group;

15 a is an integer of 2 or 3; and

b is an integer of 2 to 5; or



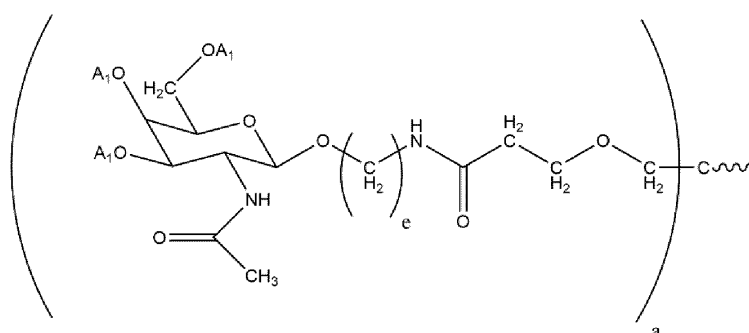
Formula (V*)

wherein:

A_1 is hydrogen, or a suitable hydroxy protecting group;

5 a is an integer of 2 or 3; and

c and d are independently integers of 1 to 6; or



Formula (VI*)

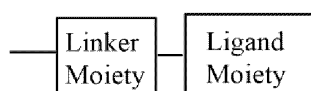
wherein:

10 A_1 is hydrogen, or a suitable hydroxy protecting group;

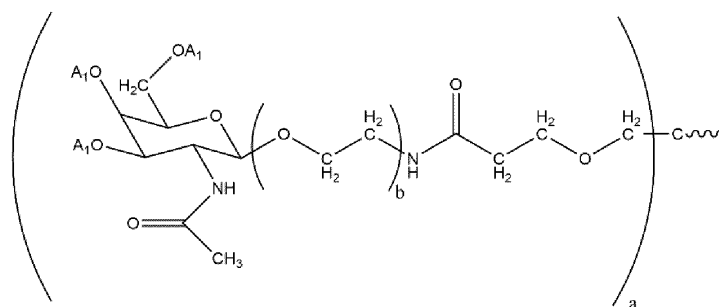
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

In some embodiments, the moiety:



15 as depicted in Formula (I) is Formula (VIa*):



Formula (VIa*)

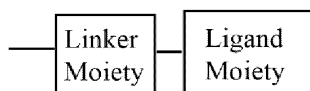
wherein:

A₁ is hydrogen, or a suitable hydroxy protecting group;

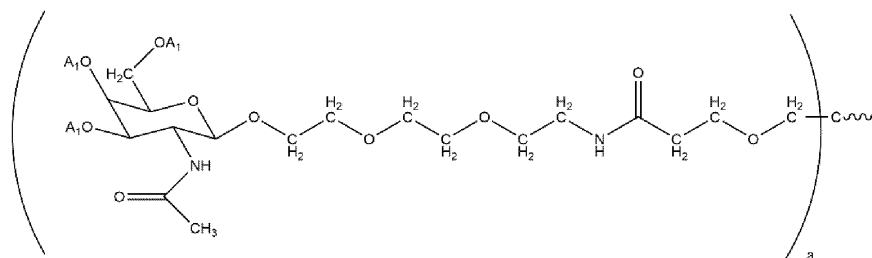
5 a is 3; and

b is an integer of 3.

In some embodiments, the moiety:



as depicted in Formula (I) as described anywhere herein is Formula (VII*):



10

Formula (VII*)

wherein:

A₁ is hydrogen;

a is an integer of 2 or 3.

15 In some embodiments, a = 2. In some embodiments, a = 3. In some embodiments, b = 3.

VECTOR AND CELL

In one aspect, the invention provides a cell containing a nucleic acid, such as inhibitory RNA [RNAi] as described herein.

In one aspect, the invention provides a cell comprising a vector as described herein.

- 5 In one aspect the invention provides a vector comprising an oligonucleotide inhibitor, e.g. an iRNA e.g. siRNA.

PHARMACEUTICALLY ACCEPTABLE COMPOSITIONS

- 10 In one aspect, the invention provides a pharmaceutical composition for inhibiting expression of a target gene, the composition comprising an inhibitor such as an oligomer such as a nucleic acid as disclosed herein.

The pharmaceutically acceptable composition may comprise an excipient and or carrier.

- Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or poly anhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

- 25 Typical pharmaceutical carriers include, but are not limited to, binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, etc.); fillers (e.g., lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, etc.); lubricants (e.g., magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, etc.); disintegrants (e.g., starch, sodium starch glycolate, etc.); and wetting agents (e.g., sodium lauryl sulphate, etc).

Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present invention. Suitable pharmaceutically acceptable excipients include, but are not limited to, water,

salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone, and the like.

Formulations for topical administration of nucleic acids can include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions can also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used.

In one embodiment, the nucleic acid or composition is administered in an unbuffered solution. In certain embodiments, the unbuffered solution is saline or water. In other embodiments, the nucleic acid e.g. RNAi agent is administered in a buffered solution. In such embodiments, the buffer solution can comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. For example, the buffer solution can be phosphate buffered saline (PBS).

DOSAGES

The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of a gene or modify the expression or function of a target. In general, where the composition comprising a nucleic acid, a suitable dose of a nucleic acid e.g. an siRNA of the invention will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day. Typically, a suitable dose of a nucleic acid e.g. an siRNA of the invention will be in the range of about 0.1 mg/kg to about 5.0 mg/kg, e.g., about 0.3 mg/kg and about 3.0 mg/kg.

A repeat-dose regimen may include administration of a therapeutic amount of a nucleic acid e.g. siRNA on a regular basis, such as every other day or once a year. In certain embodiments, the nucleic acid e.g. siRNA is administered about once per month to about once per quarter (i.e., about once every three months).

In various embodiments, the nucleic acid e.g. siRNA agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg. In some embodiments, the nucleic acid e.g. siRNA agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In certain embodiments, the nucleic acid e.g. siRNA agent is administered at a dose selected from about 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg, and 30 mg/kg. In certain embodiments, the nucleic acid e.g. siRNA agent is administered about once per week, once per month, once every other two months, or once a quarter (i.e., once every three months) at a dose of about 0.1 mg/kg to about 5.0 mg/kg. In certain embodiments, the nucleic acid e.g. siRNA agent is administered to the subject once a week. In certain embodiments, the nucleic acid e.g. siRNA agent is administered to the subject once a month. In certain embodiments, the nucleic acid e.g. siRNA agent is administered once per quarter (i.e., every three months).

After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration weekly or biweekly for three months, administration can be repeated once per month, for six months, or a year; or longer.

5 The pharmaceutical composition can be administered once daily, or administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In that case, the nucleic acid e.g. siRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, e.g., using a conventional sustained release formulation which provides sustained release of the nucleic acid e.g. siRNA over a several day period. Sustained release
10 formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as could be used with the agents of the present invention. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

In other embodiments, a single dose of the pharmaceutical compositions can be long lasting, such that subsequent doses are administered at not more than 3, 4, or 5 day intervals, or at not more than 1, 2, 3, or 4
15 week intervals. In some embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered once per week. In other embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered bimonthly. In certain embodiments, the siRNA is administered about once per month to about once per quarter (i.e., about once every three months), or even every 6 months or 12 months.

20 Estimates of effective dosages and *in vivo* half-lives for the individual nucleic acid e.g. siRNAs encompassed by the invention can be made using conventional methodologies or on the basis of *in vivo* testing using an appropriate animal model, as known in the art.

The pharmaceutical compositions of the present invention can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated.
25 Administration can be topical {e.g., by a transdermal patch), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal, or intramuscular injection or infusion; subdermal, e.g., via an implanted device; or intracranial, e.g., by intraparenchymal, intrathecal or intraventricular administration. In certain preferred embodiments, the
30 compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection.

In one embodiment, the nucleic acid e.g. siRNA agent is administered to the subject subcutaneously.

The inhibitor e.g. nucleic acid e.g. siRNA can be delivered in a manner to target a particular tissue (e.g. in particular liver cells).

METHODS FOR INHIBITING GENE EXPRESSION OR INHIBITION OF TARGET EXPRESSION
OR FUNCTION IN VITRO

The present invention also provides methods of inhibiting expression of SLC25A5 gene in a cell. The methods include contacting a cell with a nucleic acid of the invention e.g. siRNA agent, such as double stranded siRNA agent, in an amount effective to inhibit expression of the SLC25A5 gene in the cell, thereby inhibiting expression of the SLC25A5 gene in the cell. It is to be noted that a nucleic acid "for inhibiting the expression of SLC25A5" is a nucleic acid that is capable of inhibiting SLC25A5 expression, preferably as described herein below.

Contacting of a cell with the nucleic acid e.g. an siRNA, such as a double stranded siRNA agent, may be done in vitro or in vivo. Contacting a cell in vivo with nucleic acid e.g. includes contacting a cell or group of cells within a subject, e.g., a human subject, with the nucleic acid e.g. siRNA. Combinations of in vitro and in vivo methods of contacting a cell are also possible. Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished via a targeting ligand moiety, including any ligand moiety described herein or known in the art. In preferred embodiments, the targeting ligand moiety is a carbohydrate moiety, e.g. a GalNAc3 ligand, or any other ligand moiety that directs the siRNA agent to a site of interest.

The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating", "suppressing", and other similar terms, and includes any level of inhibition.

In some embodiments of the methods of the invention, expression of SLC25A5 gene is inhibited by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay, preferably when determined by qPCR as described herein and/or when the siRNA is introduced into the target cell by transfection. In certain embodiments, the methods include a clinically relevant inhibition of expression of SLC25A5 target gene e.g. as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of the gene.

In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 gene with an IC₅₀ value lower than 2500 pM, 2400 pM, 2300 pM, 2200 pM, 2100 pM, 2000 pM, 1900 pM, 1800 pM, 1700 pM, 1600 pM, 1500 pM, 1400 pM, 1300 pM, 1200 pM, 1100 pM, 1000 pM, 900 pM, 800 pM, 700 pM, 600 pM, 500 pM, 400 pM, 300 pM, 200 pM or 100 pM, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

In a preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 gene with an IC₅₀ value lower than 2500 pM. In a more preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 gene with an IC₅₀ value lower than 1000 pM. In an even more preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 gene with an IC₅₀ value lower

than 500 pM. In a most preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the SLC25A5 gene with an IC₅₀ value lower than 100 pM.

Inhibition of expression of the SLC25A5 gene may be quantified by the following method:

Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) may be maintained in
5 Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS and 1% non-essential amino acids at 37°C in an atmosphere of 5% CO₂. Cells may then be transfected with siRNA duplexes targeting SLC25A5 mRNA or a negative control siRNA (siRNA-control; sense strand 5'-GCCUGUACCAAGGCUUAA-3' (SEQ ID NO: 1383), antisense strand 5'-UUAAGCCUUGGUACAGGC-3' (SEQ ID NO: 1382)) using six 10-fold serial dilutions over a final
10 duplex concentration range of 3 nM to 0.03 pM. Transfection may be carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture may be incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells may be incubated for 24 hours at 37°C/5% CO₂ prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex may be tested by
15 transfection in duplicate wells in a single experiment.

cDNA synthesis may be performed using FastKing RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) may be performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human SLC25A5 (forward: ACTGACATCATGTACACAGGCAC (SEQ ID NO: 1384), reverse: ACCCATGCCTCTGAGAACATT (SEQ ID NO: 1385)) and human GAPDH (forward: GAAGGTGAAGGTCGGAGTC (SEQ ID NO: 1386), reverse: GAAGATGGTGATGGGATTTC (SEQ
20 ID NO: 1387)) using a SensiFAST SYBR Hi-ROX kit (Meridian).

qPCR may be performed in duplicate on cDNA derived from each well and the mean cycle threshold (Ct) calculated. Relative SLC25A5 expression may be calculated from mean Ct values using the comparative Ct ($\Delta\Delta C_t$) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of
25 SLC25A5 expression and IC₅₀ values may be calculated using a four parameter (variable slope) model using GraphPad Prism 9.

Alternatively or in addition, a pEC₅₀ value may be calculated to quantify and or compare the inhibitory potential of the siRNAs according to the invention.

In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression
30 of the SLC25A5 gene with an pEC₅₀ value lower than 5, 6, 7, 8, 9 or 10, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

For that, Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) may be maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS and 1% non-

essential amino acids at 37°C, 5% CO₂, 95% humidity. Cells may be transfected with siRNA duplexes targeting either SLC25A5 mRNA or a negative control siRNA (siRNA-control; sense strand 5'-GCCUGUACCAAGGCUUUA-3' (SEQ ID NO: 1383), antisense strand 5'-UUAAGCCUUGGUACAGGC-3' (SEQ ID NO: 1382)) in a 6-point, log dose response curve to give
5 final in assay concentrations of 3nM to 0.03pM. Transfection may be carried out by diluting Lipofectamine RNAiMAX (ThermoFisher) in Opti-MEM (ThermoFisher) medium at a ratio of 48.5:1.5. This solution may be added to an equal volume of siRNA, diluted to the required concentration in phosphate buffered saline. The lipofectamine RNAiMAX and siRNA mixture may be incubated at room temperature for 15 minutes before 20 µL may be added to wells of a 96 well plate. Huh7 cells may be dissociated from flasks
10 using trypsin and resuspended at a density of 200,000 cells/mL. 100 µL of Huh7 cell suspension may be added to each well of the siRNA-containing 96-well plates. Cells may be incubated for 24 hours at 37°C, 5% CO₂, 95% humidity. Each siRNA may be tested in triplicate wells and on two separate days for a total of six replicates.

Intracellular RNA may be isolated using an Rneasy kit (Qiagen) according to the manufacturer's
15 instructions. cDNA synthesis may be performed using a FastKing RT kit, with gDNase (Tiangen). Target cDNA may be quantified by qPCR on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human SLC25A5 (forward: ACTGACATCATGTACACAGGCAC (SEQ ID NO: 1384), reverse: ACCCATGCCTCTGAGAACATT (SEQ ID NO: 1385)) and human GAPDH (forward: GAAGGTGAAGGTCGGAGTC (SEQ ID NO: 1386), reverse: GAAGATGGTGATGGGATTTC (SEQ
20 ID NO: 1387)) using a SensiFAST SYBR Hi-ROX kit (Meridian).

qPCR may be performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative SLC25A5 expression may be calculated from mean Ct values using the comparative Ct ($\Delta\Delta C_t$) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of SLC25A5 expression and pEC50 values ($-\log_{10}$ of the EC50) may be calculated using a four parameter (variable slope) model
25 using NumPy (Python).

Alternatively or in addition, inhibition of expression of the SLC25A5 gene may be characterized by a reduction of mean relative expression of the SLC25A5 gene.

In some embodiments, when cells are transfected with 0.1 nM of the nucleic acid of the invention, the mean relative expression of SLC25A5 is below 1, 0.9, 0.8, 0.7, 0.6, 0.5, or 0.4, preferably when determined by
30 qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

In some embodiments, when cells are transfected with 5 nM of the nucleic acid of the invention, the mean relative expression of SLC25A5 is below 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4 or 0.3, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

Mean relative expression of the SLC25A5 gene may be quantified by the following method:

Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) may be maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37°C in an atmosphere of 5% CO₂. Cells may be transfected with siRNA duplexes targeting SLC25A5 mRNA or a negative control siRNA (siRNA-control; sense strand 5'-GCCUGUACCAAGGCUUUA-3' (SEQ ID NO: 1383),
 5 antisense strand 5'- UUAAAGCCUUGGUACAGGC-3' (SEQ ID NO: 1382)) at a final duplex concentration of 5 nM and 0.1 nM. Transfection may be carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture may be incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells may be incubated for 24 hours at 37°C/5%
 10 CO₂ prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex may be tested by transfection in duplicate wells in two independent experiments.

cDNA synthesis may be performed using FastKing RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) may be performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human SLC25A5 (forward: ACTGACATCATGTACACAGGCAC (SEQ ID NO: 1384), reverse:
 15 ACCCATGCCTCTGAGAACATT (SEQ ID NO: 1385)) and human GAPDH (forward: GAAGGTGAAGGTCGGAGTC (SEQ ID NO: 1386), reverse: GAAGATGGTGATGGGATTTC (SEQ ID NO: 1387)) using a SensiFAST SYBR Hi-ROX kit (Meridian).

qPCR may be performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative SLC25A5 expression may be calculated from mean Ct values using the comparative Ct ($\Delta\Delta C_t$) method,
 20 normalised to GAPDH and relative to untreated cells.

Inhibition of the expression of SLC25A5 gene may be manifested by a reduction of the amount of mRNA of the target SLC25A5 gene in comparison to a suitable control.

In other embodiments, inhibition of the expression of SLC25A5 gene may be assessed in terms of a reduction of a parameter that is functionally linked to gene expression, e.g., protein expression or signaling
 25 pathways.

METHODS OF TREATING OR PREVENTING DISEASES ASSOCIATED WITH GENE EXPRESSION/ EXPRESSION OF FUNCTION OF A TARGET.

The present invention also provides methods of using nucleic acid e.g. an siRNA of the invention or a composition containing nucleic acid e.g. an siRNA of the invention to reduce or inhibit gene expression in
 30 a cell or reduce expression or function of a target. The methods include contacting the cell with a nucleic acid e.g. dsRNA of the invention and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcript of a gene, thereby inhibiting expression of the gene in the cell. Reduction in gene expression or function of a target can be assessed by any methods known in the art. In a preferred embodiment, the gene is *SLC25A5*.

In the methods of the invention the cell may be contacted *in vitro* or *in vivo*, i.e., the cell may be within a subject.

A cell suitable for treatment using the methods of the invention may be any cell that expresses a gene of interest or target of interest associated with disease.

- 5 The *in vivo* methods of the invention may include administering to a subject a composition containing a nucleic acid of the invention e.g. an iRNA, where the nucleic acid e.g. siRNA includes a nucleoside sequence that is complementary to at least a part of an RNA transcript of the gene of the mammal to be treated, or complementary to another nucleic acid the expression and /or function of which is associated with diseases.
- 10 The present invention further provides methods of treatment of a subject in need thereof. The treatment methods of the invention include administering a nucleic acid such as an siRNA of the invention to a subject, e.g., a subject that would benefit from a reduction or inhibition of the expression of a gene and/or expression and/or function of a target, in a therapeutically effective amount e.g. a nucleic acid such as an siRNA targeting a gene or a pharmaceutical composition comprising the nucleic acid targeting a gene.
- 15 A nucleic acid e.g. siRNA of the invention may be administered as a "free" nucleic acid or "free" siRNA, administered in the absence of a pharmaceutical composition. The naked nucleic acid may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolality of the buffer solution can be adjusted such that it is suitable for administering to a subject.
- 20

Alternatively, a nucleic acid e.g. siRNA of the invention may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

- In one embodiment, the method includes administering a composition featured herein such that expression of the target gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 18, 24 hours, 28, 32, or about
- 25 36 hours. In one embodiment, expression of the target gene is decreased for an extended duration, e.g., at least about two, three, four days or more, e.g., about one week, two weeks, three weeks, or four weeks or longer, e.g., about 1 month, 2 months, or 3 months.

Subjects can be administered a therapeutic amount of nucleic acid e.g. siRNA, such as about 0.01 mg/kg to about 200 mg/kg.

- 30 The nucleic acid e.g. siRNA can be administered by intravenous infusion over a period of time, on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. Administration of the siRNA can reduce gene product levels of a target gene, e.g., in a cell or tissue of the patient by at least about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%,

75%, 80%, 85%, 90%, or 95%, or below the level of detection of the assay method used. In certain embodiments, administration results in clinical stabilization or preferably clinically relevant reduction of at least one sign or symptom of a gene-associated disorder.

Alternatively, the nucleic acid e.g. siRNA can be administered subcutaneously, i.e., by subcutaneous injection. One or more injections may be used to deliver the desired daily dose of nucleic acid e.g. siRNA to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimen may include administration of a therapeutic amount of nucleic acid on a regular basis, such as every other day or to once a year. In certain embodiments, the nucleic acid is administered about once per month to about once per quarter (i.e., about once every three months). Administration of the siRNA can reduce gene product levels of a target gene, e.g., in a cell or tissue of the patient by at least about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or below the level of detection of the assay method used.

COMBINATION THERAPIES

The inhibitor of the present invention may be combined with other therapeutic agents for use in therapy, in particular for use in treatment of any of the metabolic diseases or disorders disclosed herein.

In certain embodiments, the inhibitor of the present invention, such as any of the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist, including, without limitation, GLP-1/GIP dual agonists, GLP-1/FGF21 dual agonists, GLP-1/GCGR dual agonists and GLP-1/GIP/GCGR triple agonists, and/or a THR-beta agonist.

That is, in certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term “GLP-1 agonist” as used herein refers to a compound, which fully or partially activates the human GLP-1 receptor. The term is thus equal to the term “GLP-1 receptor agonist” used in other documents. The term GLP-1 agonist as well as the specific GLP-1 agonists described herein also encompass salt forms thereof.

It follows that the GLP-1 agonist should display “GLP-1 activity” which refers to the ability of the compound, i.e. a GLP-1 analogue or a compound comprising a GLP-1 analogue, to bind to the GLP-1 receptor and initiate a signal transduction pathway resulting in insulinotropic action or other physiological effects as is known in the art. In some embodiments the “GLP-1 agonist” binds to a GLP-1 receptor, e.g., with an affinity constant (K_D) or activate the receptor with a potency (EC_{50}) of below 1 mM, e.g. below

100 nM as measured by methods known in the art (see e.g. WO 98/08871) and exhibits insulinotropic activity, where insulinotropic activity may be measured in vivo or in vitro assays known to those of ordinary skill in the art. For example, the GLP-1 agonist may be administered to an animal with increased blood glucose (e.g. obtained using an Intravenous Glucose Tolerance Test (IVGTT). A person skilled in the art will be able to determine a suitable glucose dosage and a suitable blood sampling regime, e.g. depending on the species of the animal, for the IVGTT) and measure the plasma insulin concentration overtime. Suitable assays have been described in such as WO2015/155151.

The term half maximal effective concentration (EC_{50}) generally refers to the concentration which induces a response halfway between the baseline and maximum, by reference to the dose response curve. EC_{50} is used as a measure of the potency of a compound and represents the concentration where 50% of its maximal effect is observed. Due to the albumin binding effects of GLP-1 agonists comprising a substituent as described herein, it is important to pay attention to if the assay includes human serum albumin or not.

The in vitro potency of the GLP-1 agonist may be determined as described in WO 2015/155151, example 29 without Human Serum Albumin (HSA), and the EC_{50} determined. The lower the EC_{50} value, the better the potency. In one embodiment, the potency (EC_{50}) as determined (without HSA) is 5-1000 pM, such as 10-750 pM, 10-500 pM or 10-200 pM. In one embodiment the EC_{50} (without HSA) is at most 500 pM, such as at most 300 pM, such as at most 200 pM.

In one embodiment the EC_{50} (without HSA) is comparable to human GLP-1 (7-37).

In one embodiment the EC_{50} (without HSA) is at most 50 pM. In a further such embodiment the EC_{50} is at most 40 pM, such as at most 30 pM such as at most 20 pM, such as at most 10 pM. In one embodiment the EC_{50} is around 10 pM

Also, or alternatively, the binding of the GLP-1 agonist to albumin may be measured using the in vitro potency assay of Example 29 of WO 2015/155151 including HSA. An increase of the in vitro potency, EC_{50} value, in the presence of serum albumin reflects the affinity to serum albumin.

In one embodiment the potency (EC_{50}) as determined (with 1 % HSA) is 5-1000 pM, such as 100-750 pM, 200-500 pM or 100-400 pM. In one embodiment the EC_{50} (with 1 % HSA) is at most 750 pM, such as at most 500 pM, such as at most 400 pM, such as at most 300 or such as at most 250 pM.

If desired, the fold variation in relation to a known GLP-1 receptor agonist may be calculated as $EC_{50}(\text{test analogue})/EC_{50}(\text{known analogue})$, and if this ratio is such as 0.5- 1.5, or 0.8-1.2 the potencies are considered to be equivalent.

In one embodiment the potency, EC_{50} (without HSA), is equivalent to the potency of liraglutide. In one embodiment the potency, EC_{50} (without HSA), is equivalent to the potency of semaglutide.

In some embodiments the GLP-1 agonist is a GLP-1 analogue, optionally comprising "one substituent". The term "analogue" as used herein referring to a GLP-1 peptide (hereafter "peptide") means a peptide wherein at least one amino acid residue of the peptide has been substituted with another amino acid residue and/or wherein at least one amino acid residue has been deleted from the peptide and/or wherein at least one amino acid residue has been added to the peptide and/or wherein at least one amino acid residue of the peptide has been modified. Such addition or deletion of amino acid residues may take place at the N- terminal of the peptide and/or at the C-terminal of the peptide.

In some embodiments the term "GLP-1 analogue" or "analogue of GLP-1" as used herein refers to a peptide, or a compound, which is a variant of the human Glucagon-Like Peptide-1 (GLP-1 (7-37)). GLP-1 (7-37) has the sequence HAEGTFTSDV SSYLEGQAAKEFIAWLVKGRG (SEQ ID NO: 1388). In some embodiments the term "variant" refers to a compound which comprises one or more amino acid substitutions, deletions, additions and/or insertions.

In one embodiment the GLP-1 agonist exhibits at least 60%, 65%, 70%, 80% or 90% sequence identity to GLP-1 (7-37) over the entire length of GLP-1 (7-37).

In general, the term GLP-1 agonist is meant to encompass the GLP-1 agonist and any pharmaceutically acceptable salt, amide, or ester thereof. In some embodiments the composition comprises the GLP-1 agonist or a pharmaceutically acceptable salt, amide, or ester thereof. In some embodiments the composition comprises the GLP-1 agonist and one or more pharmaceutically acceptable counter ions.

In certain embodiments, the inhibitor of the present invention, in particular the siRNA molecules of the present invention, may be administered with a GLP-1 agonist selected from one or more of the GLP-1 agonists disclosed in W093/19175, W096/29342, W098/08871, W099/43707, W099/43706, W099/43341, W099/43708, W02005/027978, W02005/058954, W02005/058958, W02006/005667, W02006/037810, W02006/037811, W02006/097537, W02006/097538, W02008/023050, W02009/030738, W02009/030771, W02009/030774 and WO2021/219710, which are incorporated herein by reference in their entirety.

In certain embodiments, the inhibitor of the present invention, in particular the siRNA molecules of the present invention, may be administered with a GLP-1 agonist selected from the group consisting of: Dulaglutide (Trulicity®), Exenatide (Byetta®), Exenatide extended-release (Bydureon®), Liraglutide (Victoza®), Lixisenatide (Adlyxin®), Semaglutide injection (Ozempic®), and Semaglutide tablets (Rybelsus®).

In some embodiments, the GLP-1 agonist is semaglutide having a formula of N- epsilon26-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)butyrylamino]ethoxy}ethoxy)acetylaminolamino]ethoxy}ethoxy)acetyl] [Aib8,Arg34]GLP-1 (7-37).

The term "GLP-1 agonist" as used herein also encompasses dual or triple agonists that can activate more than one receptor. These dual or triple agonists may be molecules that have the ability to activate the GLP-1 receptor and at least one further receptor. In some embodiments, the dual or triple agonist may be a chimeric molecule comprising a first portion that activates the GLP-1 receptor and further portions that
5 activate further receptors. In certain embodiments, the GLP-1 agonist is a dual or triple agonist that, in addition to the GLP-1 receptor, further activates one or more of: a glucose-dependent insulinotropic polypeptide (GIP) receptor, a Fibroblast growth factor 21 (FGF21) receptor, and a glucagon receptor (GCGR).

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein,
10 may be combined with a GLP-1/GIP dual agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GIP dual agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "GLP-1/GIP dual agonist" as used in the context of the present invention refers to a substance or
15 ligand that can activate the GLP-1 receptor and the glucose-dependent insulinotropic polypeptide (GIP) receptor. GLP-1/GIP receptor co-agonists and their potential medical uses are described in several patent applications such as WO 2010/011439, WO 2013/164483, WO 2014/192284, WO 2015/067715, WO 2015/022420, WO 2015/086728, WO 2015/086729, WO 2016/111971, WO 2020/023386, US 9745360, US 2014/162945, US 2014/0357552, WO 2021/150673,
20 WO 2021/260530, WO 2022/018185, and WO 2022/079639, which are fully incorporated herein by reference.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the GLP-1/GIP dual agonist tirzepatide (Mounjaro®) for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA
25 molecules disclosed herein, may be combined with the GLP-1/GIP dual agonist tirzepatide (Mounjaro®) for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

As used herein, "tirzepatide" means a GLP-1/GIP dual agonist peptide as described in U.S. Pat. No. 9,474,780 and described by CAS Registry Number: 2023788-19-2. Tirzepatide is described in Example 1 of U.S. Pat. No. 9,474,780, with the following sequence:

30 YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLMGGPSSGAPPPS (SEQ ID NO: 1389)

wherein X₁ is α -amino isobutyric acid (Aib); X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with (2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)₁-CO—(CH₂)₁₈—CO₂H; and the C-terminal amino acid is amidated as a C-terminal primary amide.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the FGF-21 analogue (analog) efruxifermin for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the FGF-21 analogue efruxifermin for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/ FGF21 dual agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/FGF21 dual agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "GLP-1/FGF21 dual agonist" as used in the context of the present invention refers to a substance or ligand that can activate the GLP-1 receptor and the Fibroblast growth factor 21 (FGF21) receptor. Preferably, the GLP-1/FGF21 dual agonist is a chimeric molecule comprising a GLP-1 agonist as defined herein above and the molecule FGF21 or a functionally active variant or analogue thereof. In certain embodiments, the GLP-1/FGF21 dual agonist may further comprise an antibody Fc region.

GLP-1/ FGF21 receptor co-agonists and their potential medical uses are described in several patent applications such as WO 2010/142665, WO2014/037373, WO 2018/115401, WO 2018/166461, WO 2019/243557, and WO 2022/002408, which are fully incorporated herein by reference.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/ GCGR dual agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GCGR dual agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "GLP-1/ GCGR dual agonist" as used in the context of the present invention refers to a substance or ligand that can activate the GLP-1 receptor and the glucagon receptor (GCGR). GLP-1/GCGR receptor co-agonists and their potential medical uses are described in several patent applications such as, WO 2008/101017, WO 2009/155258, WO 2011/075393, WO 2011/160630, WO 2014/056872, WO 2014/091316, WO 2015/086733, WO 2017/181452, WO 2018/100174, WO 2019/030268, WO 2019/060660 and WO 2023/006923, which are fully incorporated herein by reference.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the GLP-1/ GCGR dual agonist Survodutide (BI 456906) for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with the GLP-1/ GCGR dual agonist Survodutide (BI 456906) for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GIP/GCGR triple agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1/GIP/GCGR dual agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "GLP-1/GIP/GCGR triple agonist" as used in the context of the present invention refers to a substance or ligand that can activate the GLP-1 receptor, the GIP receptor and the glucagon receptor (GCGR). GLP-1/GIP/GCGR receptor co-agonists and their potential medical uses are described in several patent applications such as, WO 2014/096150, WO 2015/067716, WO 2019/125292, WO 2022/090447, and WO 2022/268029, which are fully incorporated herein by reference.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with Retatrutid (LY-3437943) for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with Retatrutid (LY-3437943) for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The person skilled in the art is aware of ways to formulate GLP-1 agonists, including dual and triple agonists, for any suitable route of administration. In certain embodiments, the GLP-1 agonist may be administered orally or by injection, e.g., by subcutaneous injection.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a THR-beta agonist for the treatment of metabolic diseases or disorders. In a particular embodiment, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a THR-beta agonist for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The term "THR-beta agonist" as used herein refers to a compound, which fully or partially activates the human thyroid hormone receptor- β . The term THR-beta agonist as well as the specific THR-beta agonists described herein also encompass salt forms thereof.

Various THR-beta agonists have been described in the art and have been summarized, inter alia, by Zucchi (Thyroid Hormone Analogues: An Update, Thyroid. August 2020; 30(8): 1099–1105), which is incorporated herein by reference in its entirety.

In certain embodiments, the THR-beta agonist that is to be administered in combination with the inhibitor of the invention is MGL-3196 (resmetirom), KB-2115 (eprotirome), GC-1 (sobetirome) or MB07344/VK2809, as, for example, described by Zucchi.

In certain embodiments, the THR-beta agonist is MGL-3196 (resmetirom) or any of the compounds disclosed in WO 2014/043706, which is incorporated herein by reference in its entirety. Resmetirom is a thyroid hormone receptor (THR) β -selective agonist. Disclosures related to resmetirom can further be found in US Patent No. 9,266,861, US Patent Application Serial No. 16/343,065, and PCT Application
5 Serial No. PCT/US2019/040276, the contents of each of which are incorporated herein by reference in their entireties.

In certain embodiments, the THR-beta agonist is KB-2115 (eprotirome) or any of the compounds disclosed in WO 2007/110226 or WO 2009/077147, which are incorporated herein by reference in their entirety.

The person skilled in the art is aware of ways to formulate THR-beta agonists for any suitable route of
10 administration.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist, such as any one of the GLP-1 agonists disclosed herein above, including dual or triple agonists, and a THR-beta agonist, such as any one of the THR-beta agonists disclosed herein above, for the treatment of metabolic diseases or disorders. In a particular embodiment,
15 the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be combined with a GLP-1 agonist, such as any one of the GLP-1 agonists disclosed herein above, including dual or triple agonists, and a THR-beta agonist, such as any one of the THR-beta agonists disclosed herein above, for the treatment of fatty liver diseases, in particular NAFLD and/or NASH.

The inhibitor of the invention, in particular the siRNA molecules disclosed herein, may alternatively, or in
20 addition, be combined and/or co-administered with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belapectin), and/or a PPAR α agonist (such as elafibrinor),
25 and/or a PPAR γ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPAR α and/or δ and/or γ agonist, and/or a pan PPAR $\alpha\gamma\delta$ agonist (such as lanafibrinor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA
30 carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin); preferably for the treatment of any of the metabolic diseases or disorders disclosed herein, more preferably for the treatment of NAFLD.

In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein,
35 may be used for the treatment of any of the metabolic diseases or disorders disclosed herein, more

- preferably for the treatment of NAFLD, in combination with any of the molecules disclosed in Fig.1 of Nathani and Bansal (Gastroenterol Hepatol (NY). 2023 Jul; 19(7): 371–381; incorporated by reference), in particular one or more of: a THR-beta agonist (such as resmetirom, VK2809 or TERN-501), a PPAR agonist (such as Lanifibranor, Saroglitazar, or Elafibranor), a GLP-1 agonist (such as Liraglutide, Semaglutide or Tirzepatide), a CCR2/5 inhibitor (such as Cenicriviroc), an ASK1 inhibitor (such as Selonsertib), an ACC inhibitor (such as Firsocostat or PF-05221304), an SCD inhibitor (such as Aramchol), an FGF21 analogue (such as Efruxifermin or Pegbelfermin), a Galectin-3 inhibitor (such as Belapectin), a LOXL2 inhibitor (such as Simtuzumab), an FXR agonists (such as Obeticholic acid, Tropicifexor, Cilofexor, EDP-305, or MET409), and/or an FGF19 analogue (such as Aldafermina).
- 10 In certain embodiments, the inhibitor of the invention, in particular the siRNA molecules disclosed herein, may be used for the treatment of any of the metabolic diseases or disorders disclosed herein, more preferably for the treatment of NAFLD, in combination with any of the molecules disclosed in Batchuluun et al. (Nat Rev Drug Discov, 2022, 21(4):283-305. doi: 10.1038/s41573-021-00367-2.; incorporated by reference), in particular one or more of: a citrate/isocitrate carrier (CIC) inhibitor (such as Benzenetricarboxylate, CPTI-1 or CPTI-2), an ATP-citrate lyase (ACLY) inhibitor (such as Bempedoic acid, Hydroxycitrate, BMS-303141, Emodin derivatives, Furan carboxylate derivatives, MEDICA 16, SB-204990, or NDI-091143), an acetyl-CoA carboxylase (ACC) inhibitor (such as Firsocostat, PF-05221304, PF-05175157, MK-4074, A-908292, Carboxamide derivative-1k, CP-640186, Monocyclic derivative-1q, ND-654, ND-646, Olefin derivative-2e, (S)-9c, Soraphen A, TOFA, or WZ66), and/or a fatty acid synthase (FAS) inhibitor (such as Orlistat, TVB-2640, FT-4101, BI-99179, Cerulenin, C75, Fasnall, GSK2194069, IPI-9119, MP-ML-24-N1, or TVB-3166).

A combination therapy, or a “combination” contemplated herein includes the co-administration of an inhibitor according to the invention, in particular an siRNA according to the invention, with one or more additional therapeutic agent, preferably one or more of the additional therapeutic agents disclosed herein above. The inhibitor according to the invention may be administered prior to, after, or at the same time as the one or more additional therapeutic agent.

In certain embodiments, the inhibitor according to the invention, in particular the siRNA according to the invention, may be co-administered with a GLP-1 agonist, including GLP-1/GIP dual agonists, GLP-1/FGF21 dual agonists, GLP-1/GCGR dual agonists and GLP-1/GIP/GCGR triple agonists, and/or a THR-beta agonist, wherein the inhibitor according to the invention may be administered prior to, after, or at the same time as the GLP-1 agonist and/or the THR-beta agonist.

In an exemplary embodiment, the co-administration includes administering an siRNA according to the invention and any of the GLP-1 agonists, including GLP-1/GIP dual agonists, GLP-1/FGF21 dual agonists, GLP-1/GCGR dual agonists and GLP-1/GIP/GCGR triple agonists, disclosed herein or incorporated herein by reference. In another exemplary embodiment, the co-administration includes administering an siRNA according to the invention and the GLP-1 agonist semaglutide. In another exemplary embodiment, the co-

administration includes administering an siRNA according to the invention and the GLP-1/GIP dual agonist terzapetide.

In yet another exemplary embodiment, the co-administration includes administering an siRNA according to the invention and any of the THR-beta agonists disclosed herein or incorporated herein by reference. In

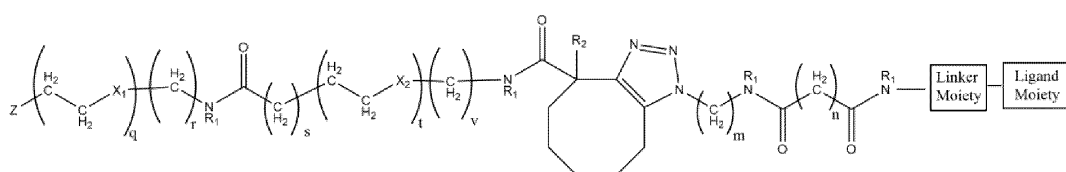
5 another exemplary embodiment, the co-administration includes administering an siRNA according to the invention and the THR-beta agonist resmetirom.

In another exemplary embodiment, the co-administration includes administering an siRNA according to the invention, the GLP-1 agonists semaglutide or terzapetide, and the THR-beta agonist resmetirom.

The combination therapy of the disclosure comprising the inhibitor according to the invention and at least
 10 one more additional therapeutic agent may be administered via any route. In some embodiments, the inhibitor according to the invention and the at least one more additional therapeutic agent may be delivered orally, subcutaneously, intravenously, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonary, vaginally, rectally, or intraocularly. In exemplary embodiments, the inhibitor according to the invention may be administered intravenously (IV) and/or subcutaneously, and the GLP-1 agonist may
 15 be administered subcutaneously.

In one aspect the present invention may be applied in the compounds, processes, compositions or uses of the following Sentences numbered 1-101 (wherein reference to any Formula in the Sentences 1-101 refers only to those Formulas that are defined within Sentences 1-101. These formulae are reproduced in Figure 6)

20 1. A compound comprising the following structure:



Formula (I)

wherein:

R₁ at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

25 R₂ is selected from the group consisting of hydrogen, hydroxy, -OC₁₋₃alkyl, -C(=O)OC₁₋₃alkyl, halo and nitro;

X₁ and X₂ at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

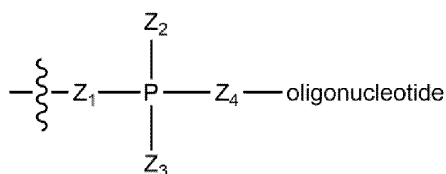
(i) q and r cannot both be 0 at the same time; and

5 (ii) s, t and v cannot all be 0 at the same time;

Z is an oligonucleoside moiety.

2. A compound according to Sentence 1, wherein R₁ is hydrogen at each occurrence.
3. A compound according to Sentence 1, wherein R₁ is methyl.
4. A compound according to Sentence 1, wherein R₁ is ethyl.
- 10 5. A compound according to any of Sentences 1 to 4, wherein R₂ is hydroxy.
6. A compound according to any of Sentences 1 to 4, wherein R₂ is halo.
7. A compound according to Sentence 6, wherein R₂ is fluoro.
8. A compound according to Sentence 6, wherein R₂ is chloro.
9. A compound according to Sentence 6, wherein R₂ is bromo.
- 15 10. A compound according to Sentence 6, wherein R₂ is iodo.
11. A compound according to Sentence 6, wherein R₂ is nitro.
12. A compound according to any of Sentences 1 to 11, wherein X₁ is methylene.
13. A compound according to any of Sentences 1 to 11, wherein X₁ is oxygen.
14. A compound according to any of Sentences 1 to 11, wherein X₁ is sulfur.
- 20 15. A compound according to any of Sentences 1 to 14, wherein X₂ is methylene.
16. A compound according to any of Sentences 1 to 15, wherein X₂ is oxygen.
17. A compound according to any of Sentences 1 to 16, wherein X₂ is sulfur.
18. A compound according to any of Sentences 1 to 17, wherein m = 3.
19. A compound according to any of Sentences 1 to 18, wherein n = 6.

20. A compound according to Sentences 13 and 15, wherein X_1 is oxygen and X_2 is methylene, and preferably wherein:
- $q = 1$,
- $r = 2$,
- 5 $s = 1$,
- $t = 1$,
- $v = 1$.
21. A compound according to Sentences 12 and 15, wherein both X_1 and X_2 are methylene, and preferably wherein:
- 10 $q = 1$,
- $r = 3$,
- $s = 1$,
- $t = 1$,
- $v = 1$.
- 15 22. A compound according to any of Sentences 1 to 21, wherein Z is:



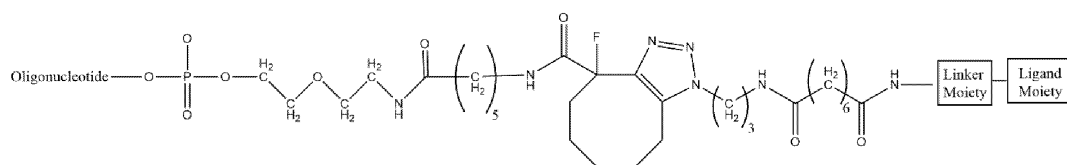
wherein:

Z_1, Z_2, Z_3, Z_4 are independently at each occurrence oxygen or sulfur; and

one the bonds between P and Z_2 , and P and Z_3 is a single bond and the other bond is a double bond.

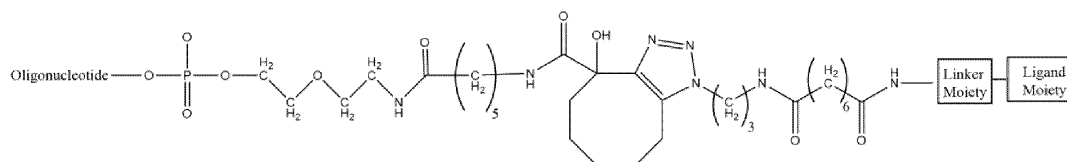
- 20 23. A compound according to Sentence 22, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.
24. A compound according to Sentence 23, wherein said RNA compound comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends.
- 25

25. A compound according to Sentence 24, wherein the RNA compound is attached at the 5' end of its second strand to the adjacent phosphate.
26. A compound according to Sentence 24, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.
- 5 27. A compound of Formula (II):



Formula (II)

28. A compound of Formula (III):



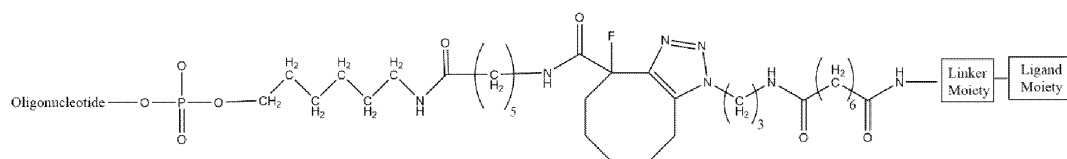
Formula (III)

10

29. A compound according to Sentence 27 or 28, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.
- 15

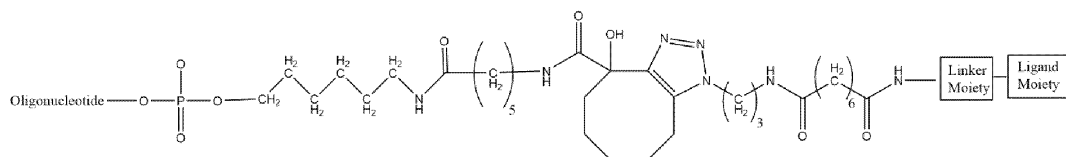
30. A composition comprising a compound of Formula (II) as defined in Sentence 27, and a compound of Formula (III) as defined in Sentence 28, optionally dependent on Sentence 29.
31. A composition according to Sentence 30, wherein said compound of Formula (III) as defined in Sentence 28 is present in an amount in the range of 10 to 15% by weight of said composition.
- 20

32. A compound of Formula (IV):



Formula (IV)

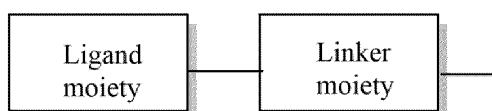
33. A compound of Formula (V):



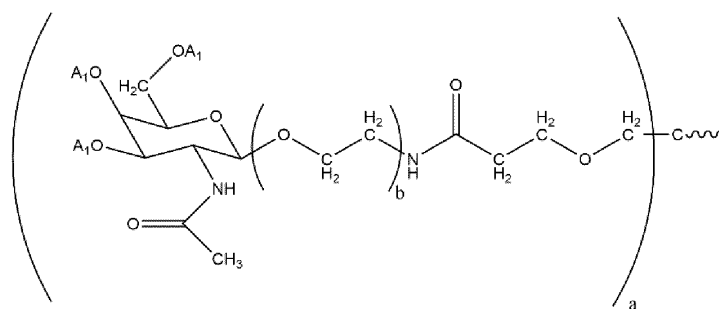
Formula (V)

34. A compound according to Sentence 32 or 33, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.
35. A composition comprising a compound of Formula (IV) as defined in Sentence 32, and a compound of Formula (V) as defined in Sentence 33, optionally dependent on Sentence 34.
36. A composition according to Sentence 35, wherein said compound of Formula (V) as defined in Sentence 33 is present in an amount in the range of 10 to 15% by weight of said composition.
37. A compound as defined in any of Sentences 1 to 29, or 32 to 34, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.
38. A compound according to Sentence 37, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.
39. A compound according to any of Sentences 1 to 29, or 32 to 34, or 37 to 38, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.
40. A compound according to Sentence 39, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside linkages, phosphorodithioate internucleoside linkages and inverted abasic nucleosides, wherein said inverted abasic nucleosides are present at the distal end of the strand that carries the ligand moieties.

41. A compound according to any of Sentences 1 to 29, or 32 to 34, or 37 to 40, wherein said ligand moiety as depicted in Formula (I) in Sentence 1 comprises one or more ligands.
42. A compound according to Sentence 41, wherein said ligand moiety as depicted in Formula (I) in Sentence 1 comprises one or more carbohydrate ligands.
- 5 43. A compound according to Sentence 42, wherein said one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide or polysaccharide.
44. A compound according to Sentence 43, wherein said one or more carbohydrates comprise one or more galactose moieties, one or more lactose moieties, one or more N-AcetylGalactosamine moieties, and / or one or more mannose moieties.
- 10 45. A compound according to Sentence 44, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.
46. A compound according to Sentence 45, which comprises two or three N-AcetylGalactosamine moieties.
47. A compound according to any of Sentences 41 to 46, wherein said one or more ligands are
- 15 attached in a linear configuration, or in a branched configuration.
48. A compound according to Sentence 47, wherein said one or more ligands are attached as a biantennary or triantennary branched configuration.
49. A compound according to Sentences 46 to 48, wherein said moiety:



- 20 as depicted in Formula (I) in Sentence 1 is any of formulae (VIa), (VIb) or (VIc), preferably formula (VIa):



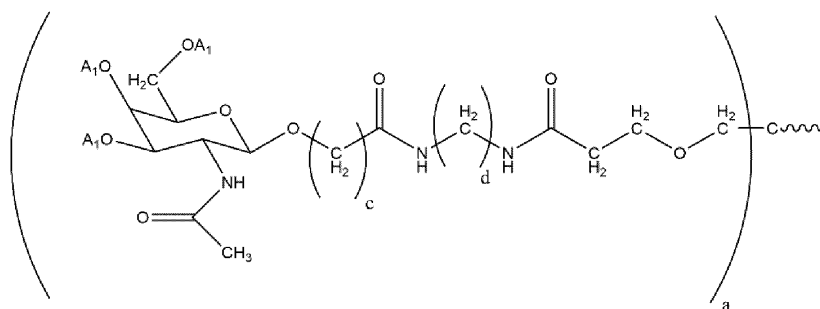
Formula (VIa)

wherein:

A_1 is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

5 b is an integer of 2 to 5; or



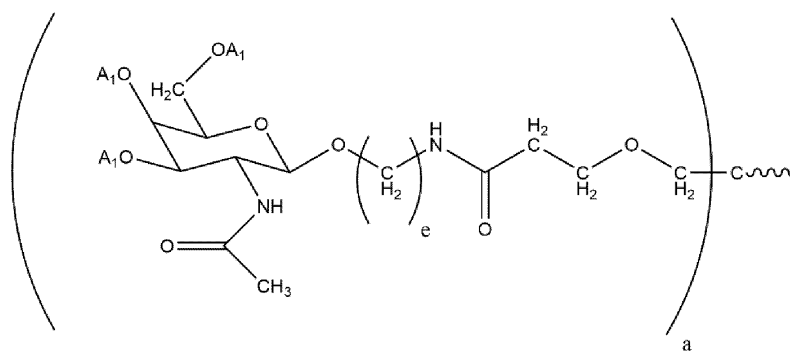
Formula (VIb)

wherein:

A_1 is hydrogen, or a suitable hydroxy protecting group;

10 a is an integer of 2 or 3; and

c and d are independently integers of 1 to 6; or



Formula (VIc)

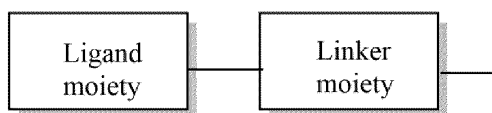
wherein:

15 A_1 is hydrogen, or a suitable hydroxy protecting group;

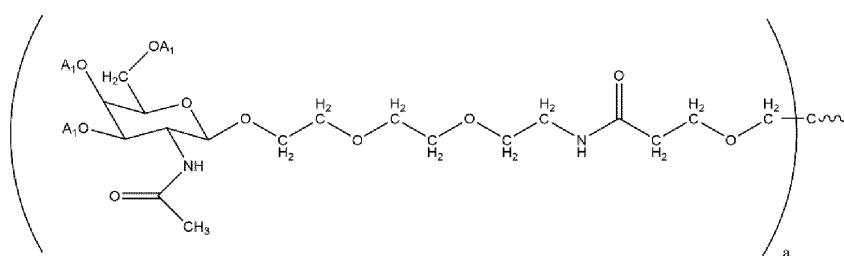
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

50. A compound according to Sentences 46 to 48, wherein said moiety:



5 as depicted in Formula (I) in Sentence 1 is Formula (VII):



Formula (VII)

wherein:

A_1 is hydrogen;

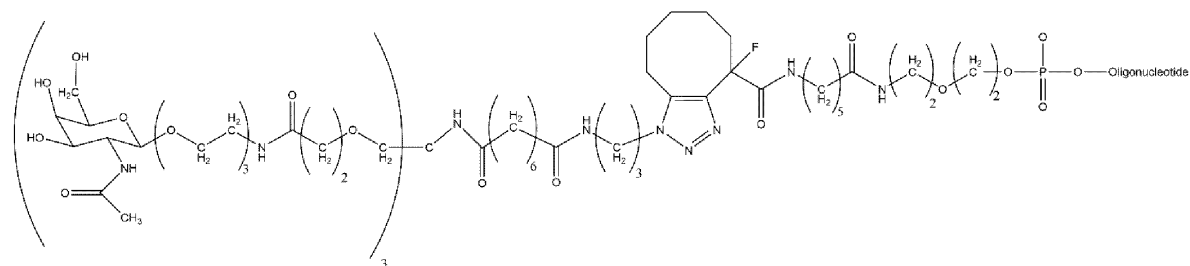
10 a is an integer of 2 or 3.

51. A compound according to Sentence 49 or 50, wherein $a = 2$.

52. A compound according to Sentence 49 or 50, wherein $a = 3$.

53. A compound according to Sentence 49, wherein $b = 3$.

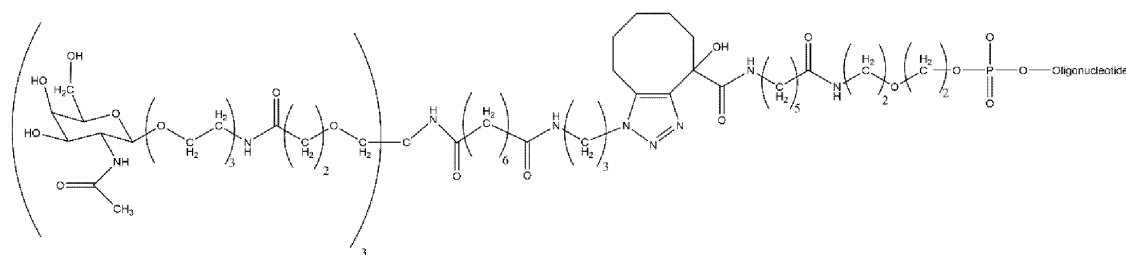
54. A compound of Formula (VIII):



15

Formula (VIII)

55. A compound of Formula (IX):



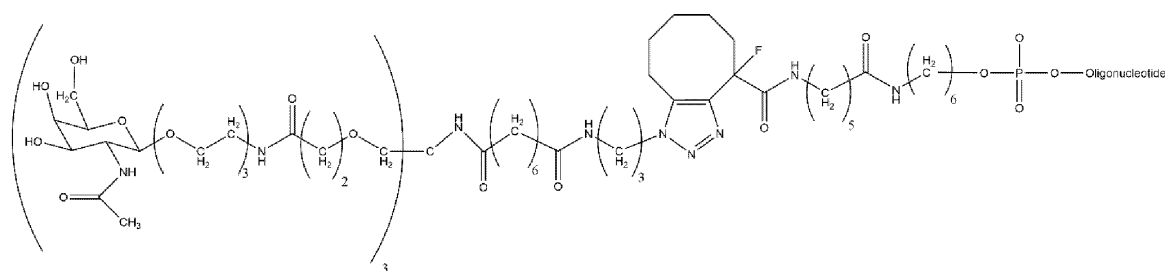
Formula (IX)

56. A compound according to Sentence 54 or 55, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

57. A composition comprising a compound of Formula (VIII) as defined in Sentence 54, and a compound of Formula (IX) as defined in Sentence 55, optionally dependent on Sentence 56.

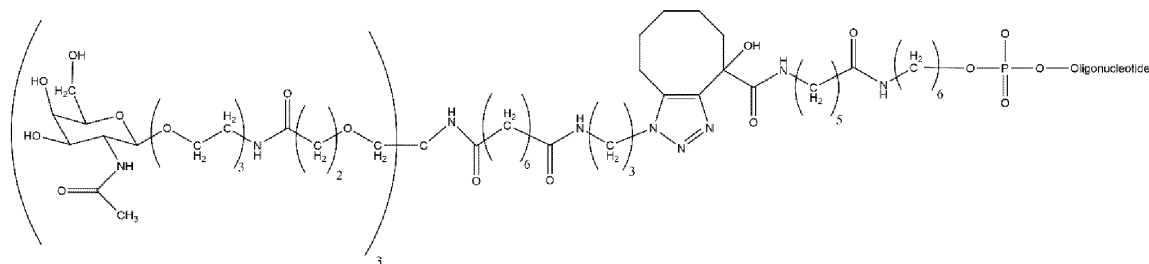
58. A composition according to Sentence 57, wherein said compound of Formula (IX) as defined in Sentence 55 is present in an amount in the range of 10 to 15% by weight of said composition.

59. A compound of Formula (X):



Formula (X)

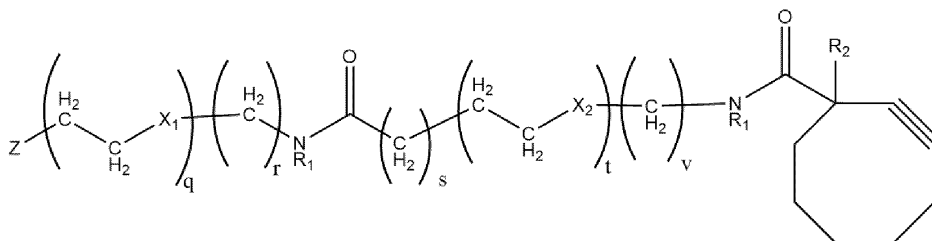
60. A compound of Formula (XI):



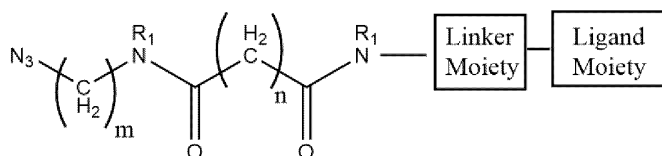
Formula (XI)

61. A compound according to Sentence 59 or 60, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.
62. A composition comprising a compound of Formula (X) as defined in Sentence 59, and a compound of Formula (XI) as defined in Sentence 60, optionally dependent on Sentence 61.
63. A composition according to Sentence 62, wherein said compound of Formula (XI) as defined in Sentence 60 is present in an amount in the range of 10 to 15% by weight of said composition.
64. A compound as defined in any of Sentences 54 to 63, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.
65. A compound according to Sentence 64, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.
66. A compound according to any of Sentences 54 to 65, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.
67. A compound according to Sentence 66, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside linkages, phosphorodithioate internucleoside linkages and inverted abasic nucleosides, wherein said inverted abasic nucleosides are present at the distal end of the strand that carries the ligand moieties, as shown in any of Formulae (VIII), (IX), (X) or (XI) in any of Sentences 54, 55, 59 or 60.

68. A process of preparing a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62, 63, which comprises reacting compounds of Formulae (XII) and (XIII):



5 Formula (XII)



Formula (XIII)

herein:

R₁ at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

- 10 R₂ is selected from the group consisting of hydrogen, hydroxy, -OC₁₋₃alkyl, -C(=O)OC₁₋₃alkyl, halo and nitro;

X₁ and X₂ at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

m is an integer of from 1 to 6;

- 15 n is an integer of from 1 to 10;

q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

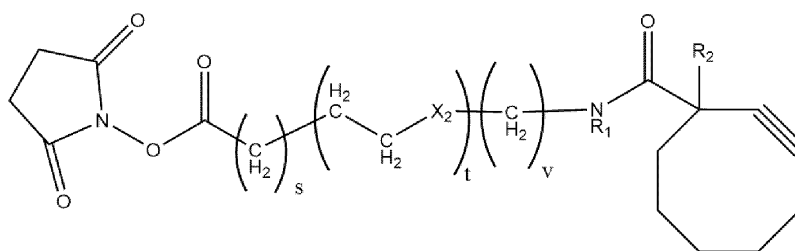
(i) q and r cannot both be 0 at the same time; and

(ii) s, t and v cannot all be 0 at the same time;

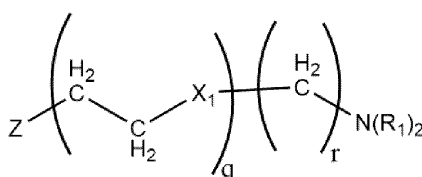
Z is an oligonucleoside moiety;

- 20 and where appropriate carrying out deprotection of the ligand and / or annealing of a second strand for the oligonucleoside moiety.

69. A process according to Sentence 68, wherein a compound of Formula (XII) is prepared by reacting compounds of Formulae (XIV) and (XV):



Formula (XIV)



Formula (XV)

5

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, $-OC_{1-3}alkyl$, $-C(=O)OC_{1-3}alkyl$, halo and nitro;

- 10 X_1 and X_2 at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

q , r , s , t , v are independently integers from 0 to 4, with the proviso that:

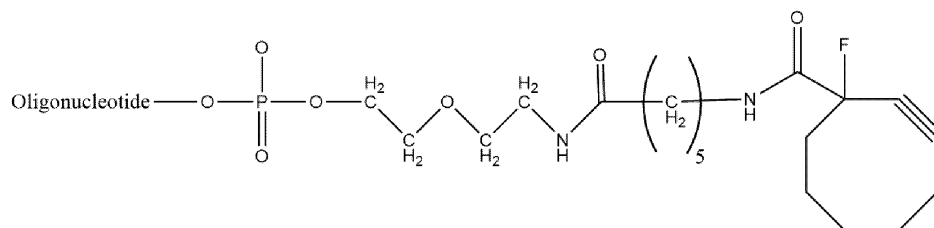
(i) q and r cannot both be 0 at the same time; and

(ii) s , t and v cannot all be 0 at the same time;

- 15 Z is an oligonucleoside moiety.

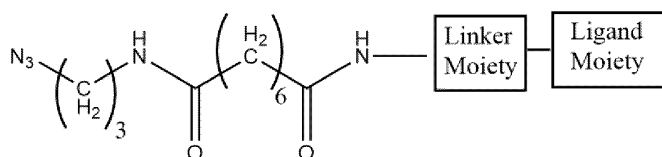
70. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 27, 29, 54, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

compound of Formula (XII) is Formula (XIIa):



Formula (XIIa)

and compound of Formula (XIII) is Formula (XIIIa):



5

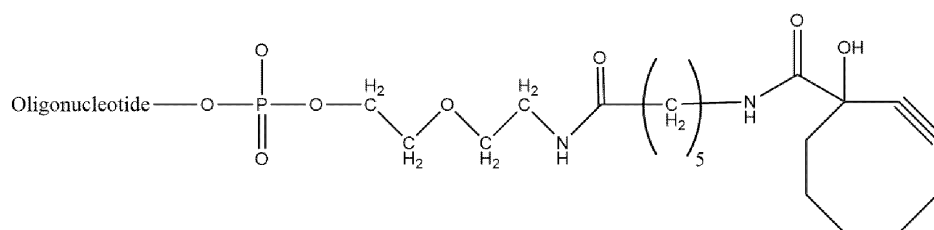
Formula (XIIIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

10

71. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 28, 29, 55, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

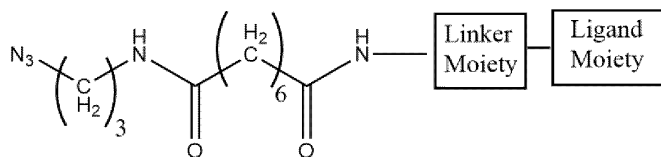
compound of Formula (XII) is Formula (XIIb):



15

Formula (XIIb)

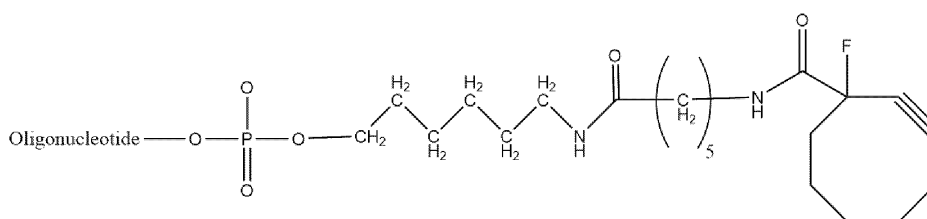
and compound of Formula (XIII) is Formula (XIIIa):



Formula (XIIIa)

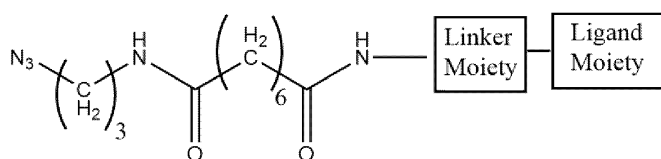
wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

72. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 32, 34, 59, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:
- 10 compound of Formula (XII) is Formula (XIIc):



Formula (XIIc)

and compound of Formula (XIII) is Formula (XIIIa):



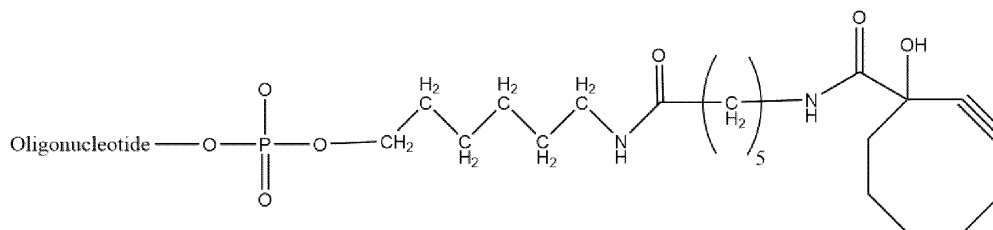
15 Formula (XIIIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

20

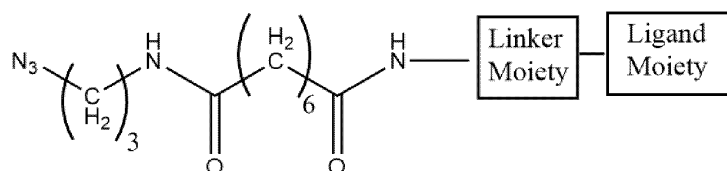
73. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 33, 34, 60, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

compound of Formula (XII) is Formula (XIId):



Formula (XIId)

and compound of Formula (XIII) is Formula (XIIIa):

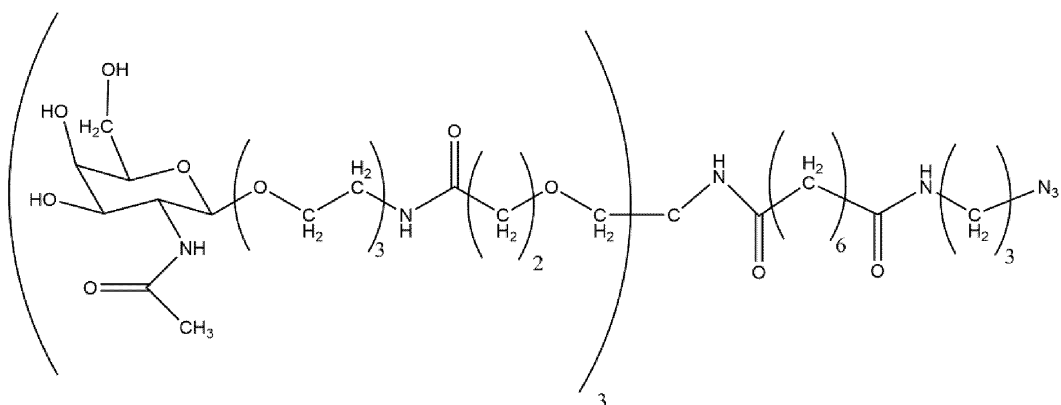


Formula (XIIIa)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

74. A process according to any of Sentences 70 to 73, wherein:

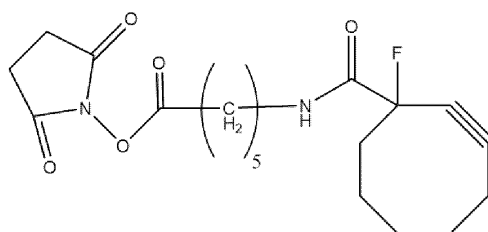
compound of Formula (XIIIa) is Formula (XIIIb):



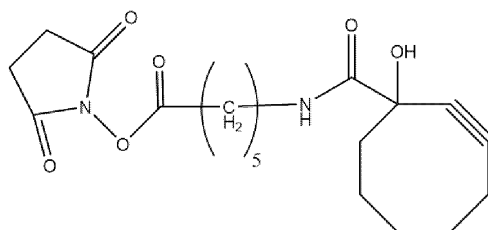
Formula (XIIIb)

75. A process according to Sentences 69, as dependent on Sentences 70 to 73, wherein:

compound of Formula (XIV) is either Formula (XIVa) or Formula (XIVb):

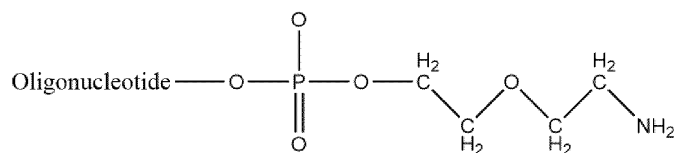


Formula (XIVa)

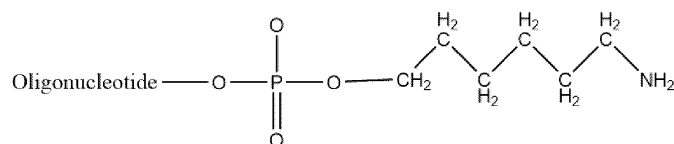


Formula (XIVb)

and compound of Formula (XV) is either Formula (XVa) or Formula (XIVb):



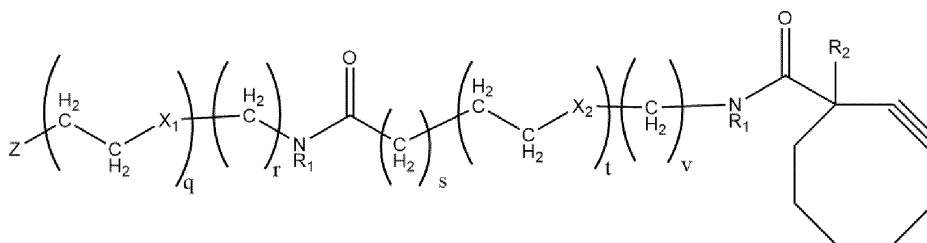
Formula (XVa)



Formula (XVb)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein (i) said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate in Formula (XVa), or (ii) said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate in Formula (XVb).

76. A compound of Formula (XII):



Formula (XII)

wherein:

R₁ at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R₂ is selected from the group consisting of hydrogen, hydroxy, -OC₁₋₃alkyl, -C(=O)OC₁₋₃alkyl, halo and nitro;

X₁ and X₂ at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

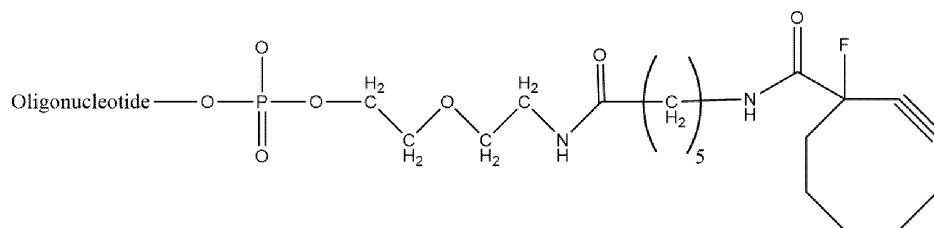
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(i) q and r cannot both be 0 at the same time; and

(ii) s, t and v cannot all be 0 at the same time;

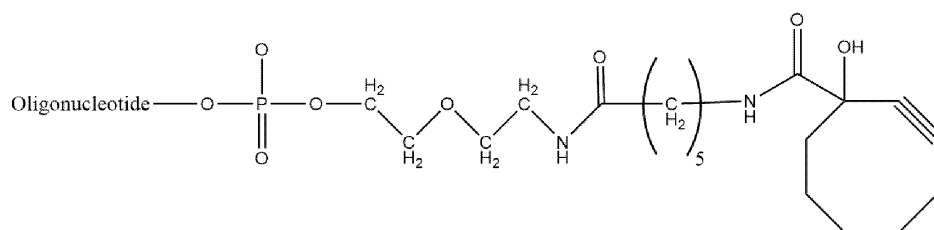
Z is an oligonucleoside moiety.

77. A compound of Formula (XIIa):



Formula (XIIa)

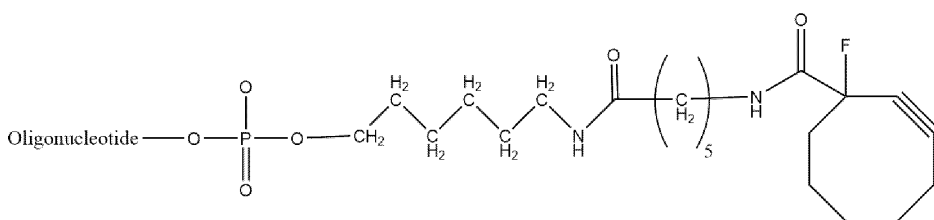
78. A compound of Formula (XIIb):



5

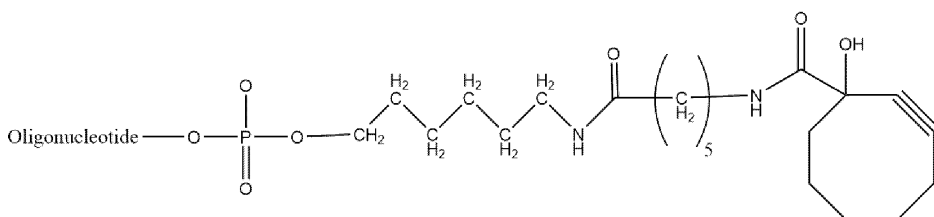
Formula (XIIb)

79. A compound of Formula (XIIf):



Formula (XIIf)

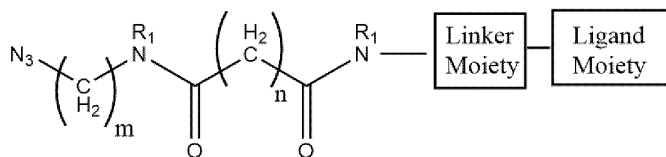
80. A compound of Formula (XIId):



10

Formula (XIId)

81. A compound of Formula (XIII):



Formula (XIII)

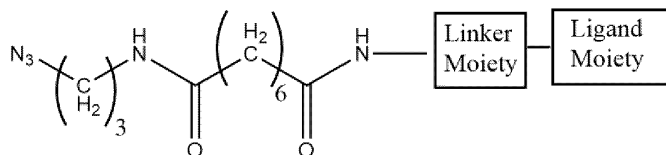
wherein:

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

5 m is an integer of from 1 to 6;

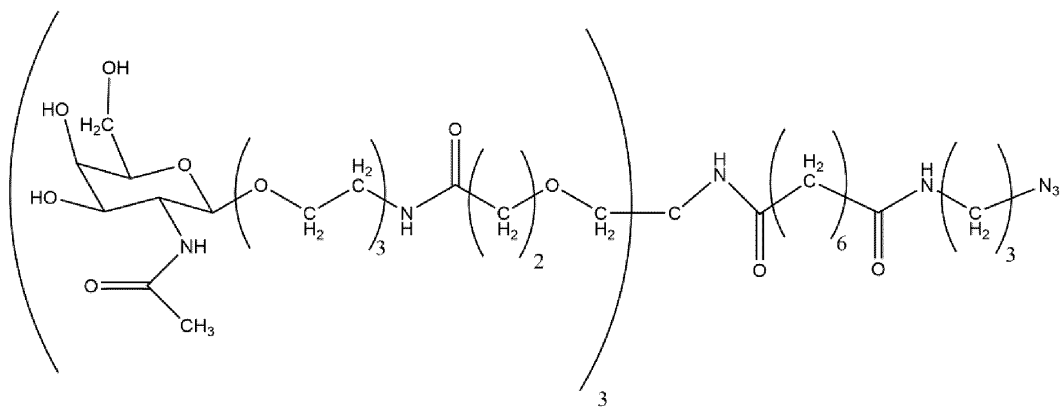
n is an integer of from 1 to 10.

82. A compound of Formula (XIIIa):



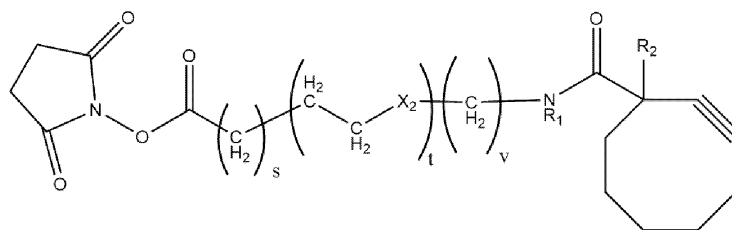
Formula (XIIIa)

10 83. A compound of Formula (XIIIb):



Formula (XIIIb)

84. A compound of Formula (XIV):



Formula (XIV)

wherein:

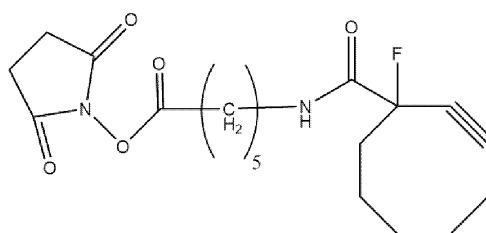
R_1 is selected from the group consisting of hydrogen, methyl and ethyl;

- 5 R_2 is selected from the group consisting of hydrogen, hydroxy, $-OC_{1-3}alkyl$, $-C(=O)OC_{1-3}alkyl$, halo and nitro;

X_2 is selected from the group consisting of methylene, oxygen and sulfur;

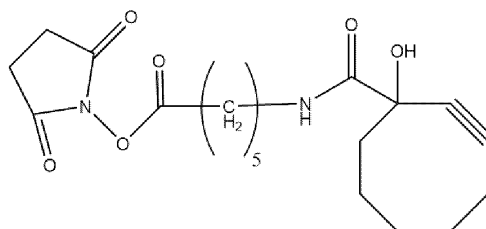
s , t , v are independently integers from 0 to 4, with the proviso that s , t and v cannot all be 0 at the same time.

- 10 85. A compound of Formula (XIVa):



Formula (XIVa)

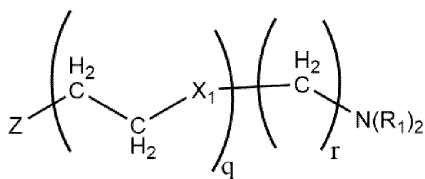
86. A compound of Formula (XIVb):



Formula (XIVb)

15

87. A compound of Formula (XV):



Formula (XV)

wherein:

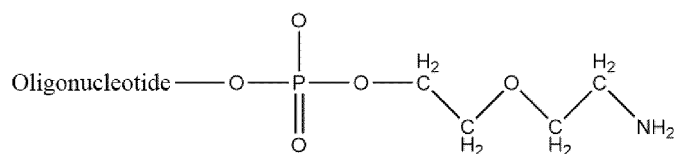
R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

- 5 X_1 is selected from the group consisting of methylene, oxygen and sulfur;

q and r are independently integers from 0 to 4, with the proviso that q and r cannot both be 0 at the same time;

Z is an oligonucleoside moiety.

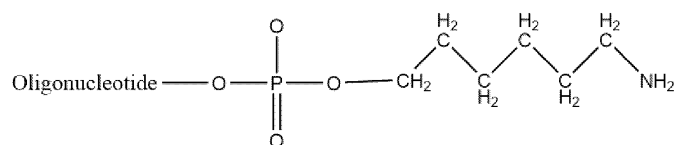
88. A compound of formula (XVa):



10

Formula (XVa)

89. A compound of Formula (XVb):



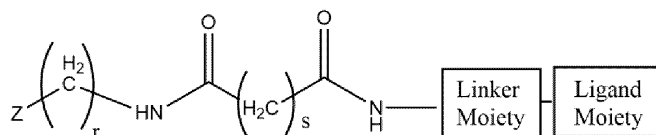
Formula (XVb)

- 15 90. Use of a compound according to any of Sentences 76, 81 to 84, 87, for the preparation of a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63.
91. Use of a compound according to Sentence 85, for the preparation of a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63, wherein $\text{R}_2 = \text{F}$.
- 20

92. Use of a compound according to Sentence 86, for the preparation of a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63, wherein $R_2 = OH$.
- 5 93. Use of a compound according to Sentence 77, for the preparation of a compound according to any of Sentences 20, 25, 27, 29, 54, 56, and / or a composition according to any of Sentences 30, 31, 57, 58.
94. Use of a compound according to Sentence 78, for the preparation of a compound according to any of Sentences 20, 25, 28, 29, 55, 56, and / or a composition according to any of Sentences 30, 31, 57, 58.
- 10 95. Use of a compound according to Sentence 79, for the preparation of a compound according to any of Sentences 21, 26, 32, 34, 59, 61, and / or a composition according to any of Sentences 35, 36, 62, 63.
96. Use of a compound according to Sentence 80, for the preparation of a compound according to any of Sentences 21, 26, 33, 34, 60, 61, and / or a composition according to any of Sentences 35, 36, 62, 63.
- 15 97. Use of a compound according to Sentence 88, for the preparation of a compound according to any of Sentences 20, 25, 27 to 29, 54 to 56, and / or a composition according to any of Sentences 30, 31, 57, 58.
98. Use of a compound according to Sentence 89, for the preparation of a compound according to any of Sentences 21, 26, 32 to 34, 59 to 61, and / or a composition according to any of Sentences 35, 36, 62, 63.
- 20 99. A compound or composition obtained, or obtainable by a process according to any of Sentences 68 to 75.
100. A pharmaceutical composition comprising of a compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63, together with a pharmaceutically acceptable carrier, diluent or excipient.
- 25
- A compound according to any of Sentences 1 to 29, 32 to 34, 37 to 56, 59 to 61, and 64 to 67, and / or a composition according to any of Sentences 30, 31, 35, 36, 57, 58, 62 and 63, for use
- 30 in therapy.

In another aspect the present invention may be applied in the compounds, processes, compositions or uses of the following Clauses numbered 1-56 (wherein reference to any Formula in the Clauses refers only to those Formulas that are defined within Clause 1-56. These formulae are reproduced in Figure 7).

1. A compound comprising the following structure:



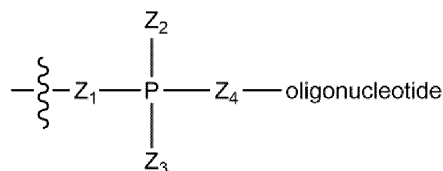
Formula (I*)

wherein:

r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety.

- 10 2. A compound according to Clause 1, wherein s is an integer selected from 4 to 12.
3. A compound according to Clause 2, wherein s is 6.
4. A compound according to any of Clauses 1 to 3, wherein r is an integer selected from 4 to 14.
5. A compound according to Clause 4, wherein r is 6.
6. A compound according to Clause 4, wherein r is 12.
- 15 7. A compound according to Clause 5, which is dependent on Clause 3.
8. A compound according to Clause 6, which is dependent on Clause 3.
9. A compound according to any of Clauses 1 to 8, wherein Z is:

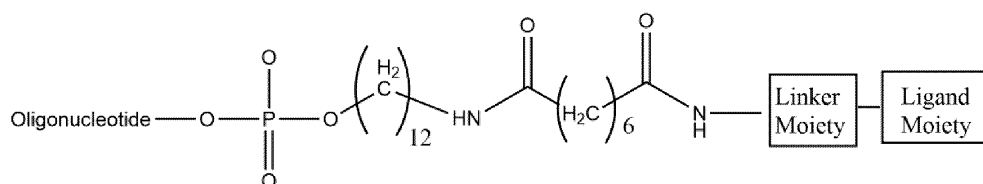


wherein:

- 20 Z_1, Z_2, Z_3, Z_4 are independently at each occurrence oxygen or sulfur; and

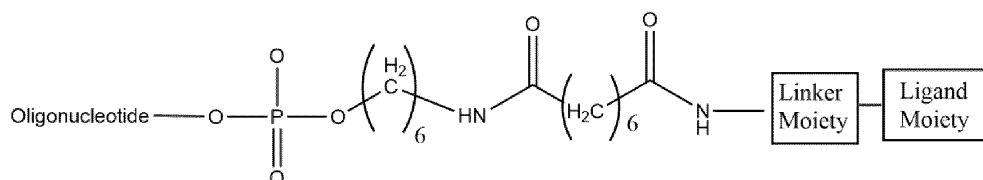
one the bonds between P and Z_2 , and P and Z_3 is a single bond and the other bond is a double bond.

10. A compound according to any of Claims 1 to 9, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.
11. A compound according to any of Claim 10, wherein said RNA compound comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends.
12. A compound according to Claim 11, preferably also dependent on Claims 3 and 6, wherein the RNA compound is attached at the 5' end of its second strand to the adjacent phosphate.
13. A compound according to Claim 11, preferably also dependent on Claims 3 and 5, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.
14. A compound of Formula (II*), preferably dependent on Claim 12:



Formula (II*)

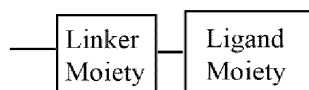
15. A compound of Formula (III*), preferably dependent on Claim 13:



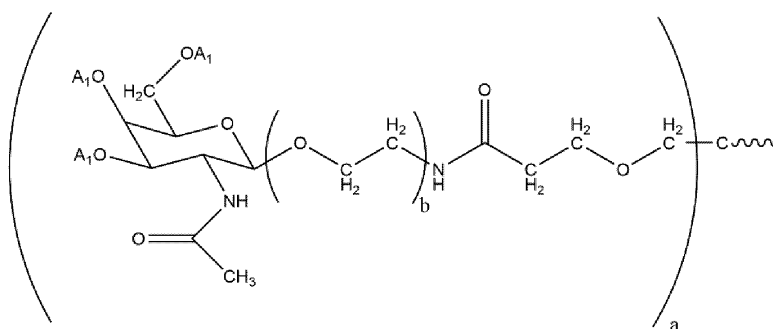
Formula (III*)

16. A compound as defined in any of Claims 1 to 15, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.
17. A compound according to Claim 16, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.
18. A compound according to any of Claims 1 to 17, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

19. A compound according to Clause 18, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the linker / ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside linkages, phosphorodithioate internucleoside linkages and inverted abasic nucleosides, wherein said inverted abasic nucleosides are present at the distal end of the same strand to the end that carries the linker / ligand moieties.
20. A compound according to any of Clauses 1 to 19, wherein said ligand moiety as depicted in Formula (I*) in Clause 1 comprises one or more ligands.
21. A compound according to Clause 20, wherein said ligand moiety as depicted in Formula (I*) in Clause 1 comprises one or more carbohydrate ligands.
22. A compound according to Clause 21, wherein said one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide or polysaccharide.
23. A compound according to Clause 22, wherein said one or more carbohydrates comprise one or more galactose moieties, one or more lactose moieties, one or more N-AcetylGalactosamine moieties, and / or one or more mannose moieties.
24. A compound according to Clause 23, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.
25. A compound according to Clause 24, which comprises two or three N-AcetylGalactosamine moieties.
26. A compound according to any of the preceding Clauses, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.
27. A compound according to Clause 26, wherein said one or more ligands are attached as a biantennary or triantennary branched configuration.
28. A compound according to Clauses 20 to 27, wherein said moiety:



as depicted in Formula (I*) in Clause 1 is any of Formulae (IV*), (V*) or (VI*), preferably Formula (IV*):



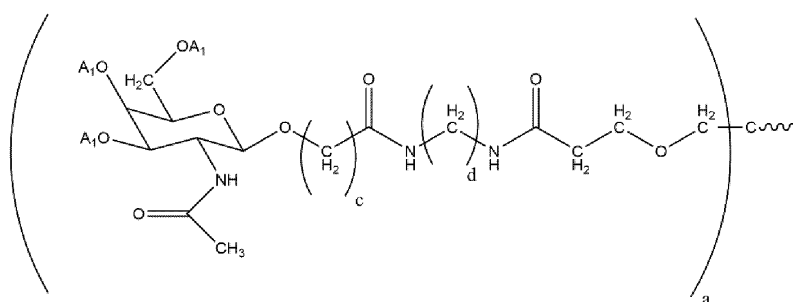
Formula (IV*)

wherein:

A_1 is hydrogen, or a suitable hydroxy protecting group;

5 a is an integer of 2 or 3; and

b is an integer of 2 to 5; or



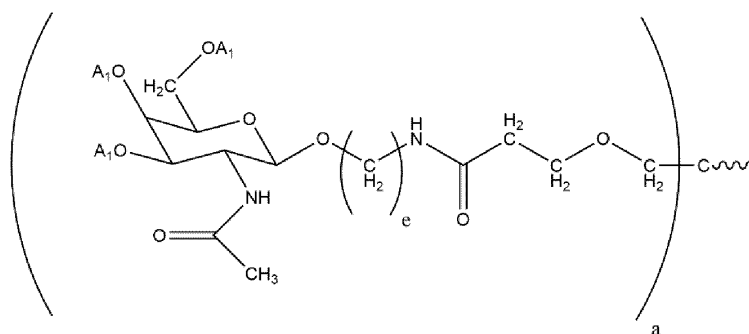
Formula (V*)

wherein:

10 A_1 is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

c and d are independently integers of 1 to 6; or



Formula (VI*)

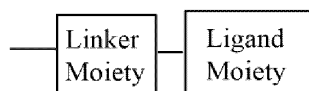
wherein:

A₁ is hydrogen, or a suitable hydroxy protecting group;

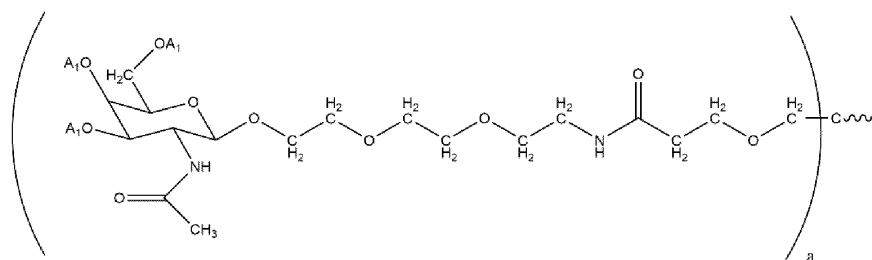
5 a is an integer of 2 or 3; and

e is an integer of 2 to 10.

29. A compound according to any of Clauses 1 to 28, wherein said moiety:



as depicted in Formula (I*) in Clause 1 is Formula (VII*):



10

Formula (VII*)

wherein:

A₁ is hydrogen;

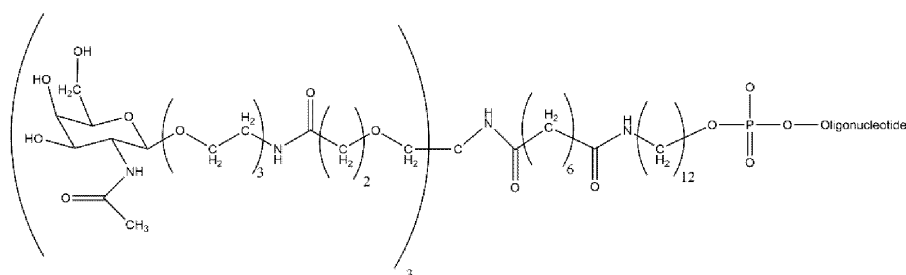
a is an integer of 2 or 3.

15 30. A compound according to Clause 28 or 29, wherein a = 2.

31. A compound according to Clause 28 or 29, wherein $a = 3$.

32. A compound according to Clause 28, wherein $b = 3$.

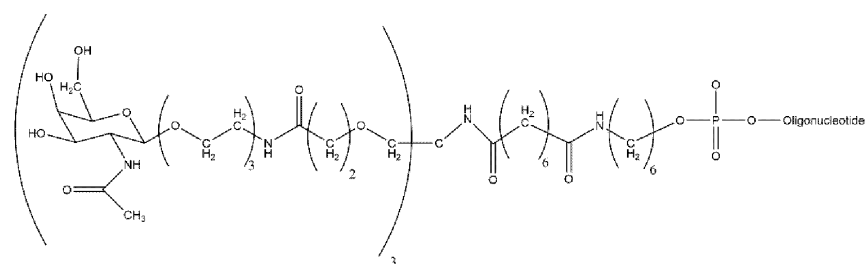
33. A compound of Formula (VIII*):



5

Formula (VIII*)

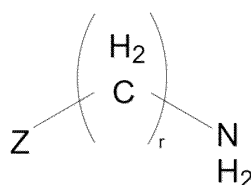
34. A compound of Formula (IX*):



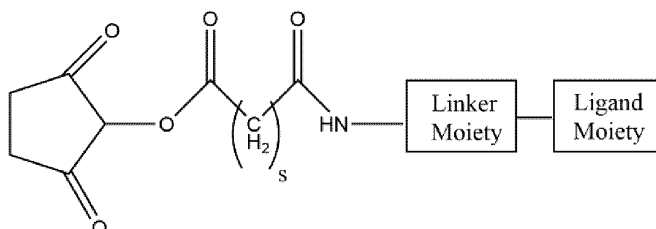
Formula (IX*)

35. A compound according to Clause 33 or 34, wherein the oligonucleoside comprises an RNA duplex which further comprises one or more riboses modified at the 2' position, preferably a plurality of riboses modified at the 2' position.
36. A compound according to Clause 35, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.
37. A compound according to any of Clauses 33 to 36, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.
38. A compound according to Clause 37, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the linker / ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside linkages, phosphorodithioate internucleoside linkages and inverted abasic nucleosides, wherein said inverted abasic nucleosides are present at the distal end of the same strand to the end that carries the linker / ligand moieties.

39. A compound according to Clause 33, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.
40. A compound according to Clause 34, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.
41. A process of preparing a compound according to any of Clauses 1 to 40, which comprises reacting compounds of Formulae (X*) and (XI*):



Formula (X*)



Formula (XI*)

wherein:

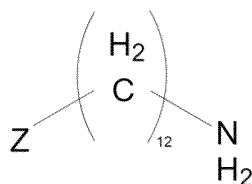
r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety;

- and where appropriate carrying out deprotection of the ligand and / or annealing of a second strand for the oligonucleoside.

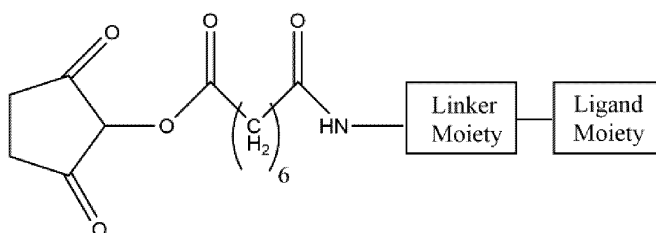
42. A process according to Clause 41, to prepare a compound according to any of Clauses 6, 8 to 14, 16 to 33, and 35 to 40, wherein:

compound of Formula (X*) is Formula (Xa*):



Formula (Xa*)

and compound of formula (XI*) is Formula (XIa*):



5

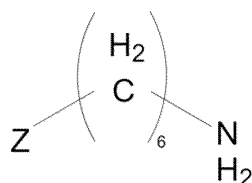
Formula (XIa*)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 5' end of its second strand to the adjacent phosphate.

10

43. A process according to Clause 41, to prepare a compound according to any of Clauses 5, 7, 9 to 13, 15 to 32, and 34 to 40, wherein:

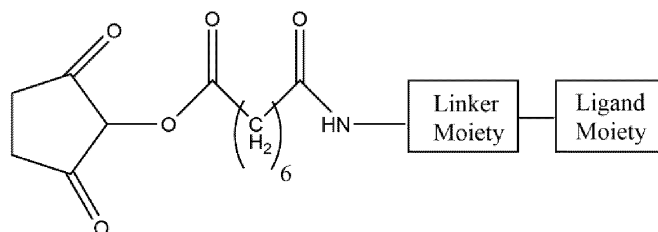
compound of Formula (X*) is Formula (Xb*):



15

Formula (Xb*)

and compound of formula (XI*) is Formula (XIa*):

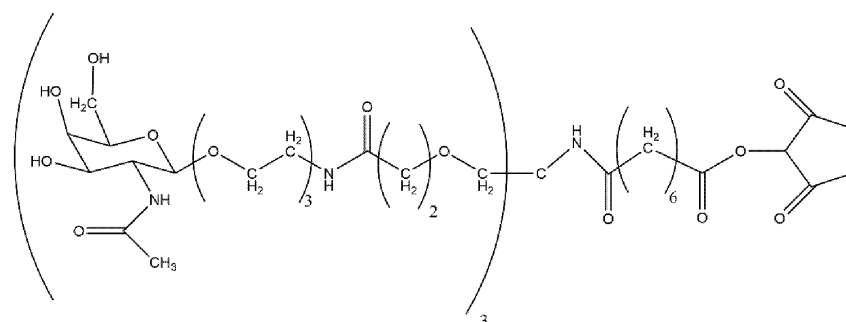


Formula (XIa*)

wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand, and wherein each of the first and second strands have 5' and 3' ends, and wherein said RNA duplex is attached at the 3' end of its second strand to the adjacent phosphate.

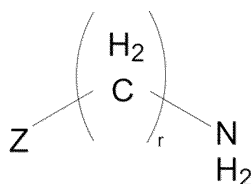
44. A process according to Clauses 42 or 43, wherein:

compound of Formula (XIa*) is Formula (XIb*):



Formula (XIb*)

45. A compound of Formula (X*):



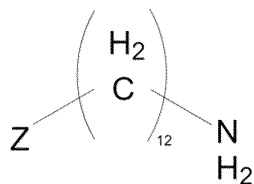
Formula (X*)

15 wherein:

r is independently an integer selected from 1 to 16; and

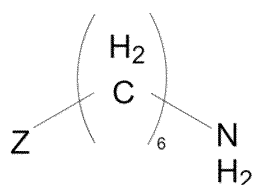
Z is an oligonucleoside moiety.

46. A compound of Formula (Xa*):



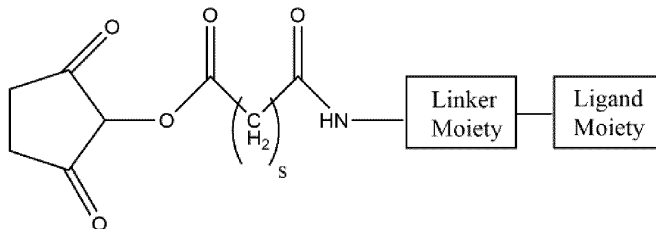
Formula (Xa*)

5 47. A compound of Formula (Xb*):



Formula (Xb*)

48. A compound of Formula (XI*):



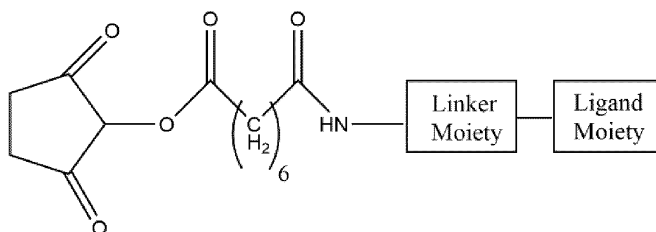
Formula (XI*)

wherein:

s is independently an integer selected from 1 to 16; and

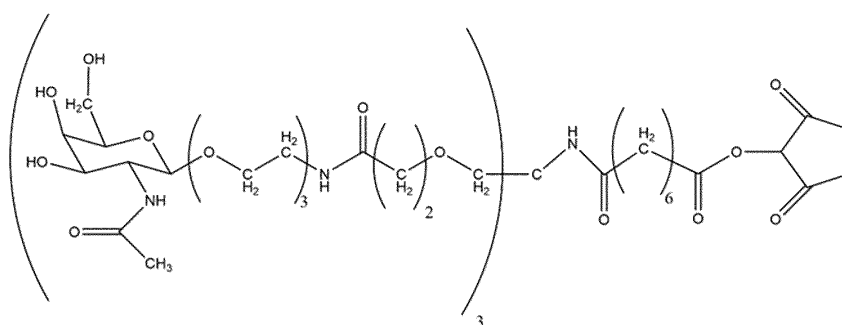
Z is an oligonucleoside moiety.

49. A compound of Formula (XIa*):



Formula (XIa*)

50. A compound of Formula (XIb*):



Formula (XIb*)

51. Use of a compound according to any of Clauses 45 and 48 to 50, for the preparation of a compound according to any of Clauses 1 to 40.
52. Use of a compound according to Clause 46, for the preparation of a compound according to any of Clauses 6, 8 to 14, 16 to 33, and 35 to 40.
- 10 53. Use of a compound according to Clause 47, for the preparation of a compound according to any of Clauses 5, 7, 9 to 13, 15 to 32, and 34 to 40.
54. A compound or composition obtained, or obtainable by a process according to any of Clauses 41 to 44.
55. A pharmaceutical composition comprising of a compound according to any of Clauses 1 to 40,
15 together with a pharmaceutically acceptable carrier, diluent or excipient.

A compound according to any of Clauses 1 to 40, for use in therapy.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. It is understood that the examples and

embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

EXAMPLE 1 – TARGET IDENTIFICATION

5 Background

All biological functions arise from the co-ordinated interaction of hundreds of interacting molecules – primarily proteins – and can be thought of as the emergent functional consequence of protein-protein interaction networks where each node in the network is a protein and each edge linking the proteins can represent a range of possible interaction types from complex formation to catalytic activation etc.

10 Historically such functions have been represented as simplistic linear pathways. As knowledge has grown however, it has become clear that pathways are more complex and that the minimum level of complexity that adequately represents the functional properties of a biological process, and can capture the characteristics of resilience to perturbation and robustness to random damage of individual components, is a network.

15 Networks subserving biological function may consist of several interacting canonical pathways as well as additional proteins that are primarily engaged when the canonical function is perturbed. It is therefore critical to develop approaches that can model this complexity in a meaningful and tractable way; and generate target hypotheses that take account of the inherent resistance to change that is a consequence of network robustness.

20 Oversimplification of biology and the failure to make rational drug target choices based on realistic models of biological processes has contributed to the poor success rate of drug discovery. Furthermore, there has been a lack of rigorous objective methods both for making network models of processes and for prioritising protein targets within these models. As a consequence target selection decisions are frequently made on an ad hoc basis based on preference or evidence unrelated to the functional model.

25 Process for identifying processes and targets

The starting point for the identification of the target SLC25A5/ANT2 was Genome Wide Association Studies (GWAS) metanalyses for Non-Alcoholic Fatty Liver Disease (NAFLD).

The GWAS metanalyses were QC'ed for sample size, target population, and quality of statistical analysis. More specifically, a sample size of more than 1,000 was used as a cut-off,

30 SNPs were taken forward if the p-value was reflecting multiple testing corrections. Finally, sex-combined and all-ancestries SNPs were selected (continental European, UK, other); SNPs with gender-specific significance were excluded.

The resulting selected GWAS were used to extract the SNPs with strong association with the trait of interest, in this case NAFLD pathophysiology as well as associated metabolic dysfunction (for example, NAFLD and cardiometabolic diseases or steatosis and risk of NAFLD).

5 As a subsequent step, the SNPs were mapped to genes using the Variant-to-Gene (V2G) pipeline data from Open Targets Genetics (<https://genetics.opentargets.org/>). More specifically, for each SNP of interest the gene with the highest score (or genes, in case of a top-score tie) based on the V2G pipeline were selected, along with those genes with a score above 0.2.

10 The collated gene set was used as input for network construction, based on a proprietary ETX algorithm (algorithm A). Impact analysis (algorithm B) is then applied on the networks, to identify the biological processes that the gene set is involved in. This method takes canonical pathways and evaluates the impact they have on the network; they are then clustered. The resulting clustered processes represented in the networks were assessed by an internal team.

15 The most relevant processes for NAFLD biology were taken forward; their proteins were used with a proprietary ETX algorithm (algorithm C) to make directed networks. The nodes of each directed network were scored for the degree and type of influence they have on the network based on a set of proprietary ETX metrics. In addition, the nodes were filtered for those genes that are expressed in hepatocytes and scored above a proprietary threshold in the metrics of choice.

20 As a subsequent step, based on the aforementioned ranking, the top-scoring genes per directed network were assessed by an internal ETX team to identify targets of interest for the treatment of NAFLD metabolic diseases.

ANT2 was identified in the network process (Supercluster) 574, annotated by the ETX algorithm as "Adipogenesis/Non-alcoholic fatty liver disease", having scored above a proprietary threshold in one of the proprietary ETX metrics.

25 The inventors have thus analysed these network models using proprietary analytical methods. These methods use the directional information to capture key 'target' properties such as whether a protein is an integrator of information, a key conduit of information to other parts of the network, an influencer of key proteins and the extent to which an influencer is influenced or influences other proteins (based on absolute and relative number and direction of inputs and outputs). The directional information also enables hierarchical relationships between proteins to be imputed. Proteins higher in the hierarchy and with certain
30 properties may be preferred over others with otherwise similar properties. The relative specificity and magnitude of each property relative to the others made it possible for the inventors to score and rank proteins in terms of their target suitability.

The ability to characterise the properties of these targets in terms of network relationships enables judgements to be made on the selectivity and magnitude of effect in the chosen context and hence the suitability of each for a given indication.

- Proprietary analytical techniques were then applied to the network models to identify pharmacologically viable targets from within the networks whose knockdown will have a significant influence on the network and by extension on the biological function being modelled. The algorithms make extensive use of directional information and hierarchical relationships to identify targets with a range of specific properties that will make them good siRNA targets. Targets were then further filtered by protein class and hepatocyte specific properties according to the therapeutic requirements.
- The above workflow leveraging proprietary data resources and network node metrics has identified the provided target for the provided uses.

The outcome of the network approach is shown in Table 6. ANT2 was surprisingly identified as a drug target for NAFLD among various other targets that have been previously associated with metabolic disorders, such NAFLD (APOA5, HMDH, APOC3, NR1H3, MTP, PCSK9, SOAT1 and ABCA1).

Table 6

Protein name	Accession number	Prediction score for NAFLD	Hepatocellular expression rank
APOA5	Q6Q788	93.6	0.46
HMDH	P04035	91.3	0.54
APOC3	P02656	91.2	0.95
NR1H3	Q13133	91.1	0.22
MTP	P55157	88.1	0.96
ANT2	P05141	80	0.98
PCSK9	Q8NBP7	79.3	0.21
SOAT1	P35610	77.7	0.27
ABCA1	O095477	77.0	0.46

EXAMPLE 2: SYNTHESIS OF TETHER 1

General Experimental conditions:

- Thin layer chromatography (TLC) was performed on silica-coated aluminium plates with fluorescence indicator 254 nm from Macherey-Nagel. Compounds were visualized under UV light (254 nm), or after spraying with the 5% H₂SO₄ in methanol (MeOH) or ninhydrin reagent according to Stahl (from Sigma-Aldrich), followed by heating. Flash chromatography was performed with a Biotage Isolera One flash

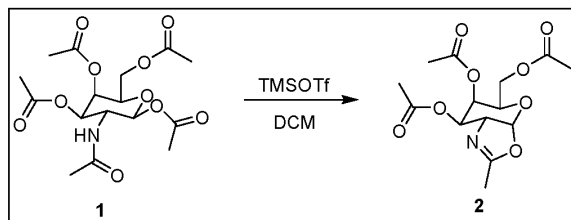
chromatography instrument equipped with a dual variable UV wavelength detector (200-400 nm) using Biotage Sfär Silica 10, 25, 50 or 100 g columns (Uppsala, Sweden).

All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents were purchased from Sigma-Aldrich and solvents from Carl Roth GmbH + Co. KG. D-Galactosamine pentaacetate was purchased from AK scientific.

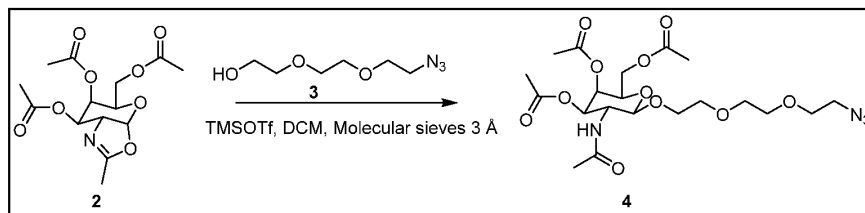
HPLC/ESI-MS was performed on a Dionex UltiMate 3000 RS UHPLC system and Thermo Scientific MSQ Plus Mass spectrometer using an Acquity UPLC Protein BEH C4 column from Waters (300Å, 1.7 µm, 2.1 x 100 mm) at 60 °C. The solvent system consisted of solvent A with H₂O containing 0.1% formic acid and solvent B with acetonitrile (ACN) containing 0.1% formic acid. A gradient from 5-100% of B over 15 min with a flow rate of 0.4 mL/min was employed. Detector and conditions: Corona ultra-charged aerosol detection (from esa). Nebulizer Temp.: 25 °C. N₂ pressure: 35.1 psi. Filter: Corona.

¹H and ¹³C NMR spectra were recorded at room temperature on a Varian spectrometer at 500 MHz (¹H NMR) and 125 MHz (¹³C NMR). Chemical shifts are given in ppm referenced to the solvent residual peak (CDCl₃ – ¹H NMR: δ at 7.26 ppm and ¹³C NMR δ at 77.2 ppm; DMSO-d₆ – ¹H NMR: δ at 2.50 ppm and ¹³C NMR δ at 39.5 ppm). Coupling constants are given in Hertz. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t) or multiplet (m).

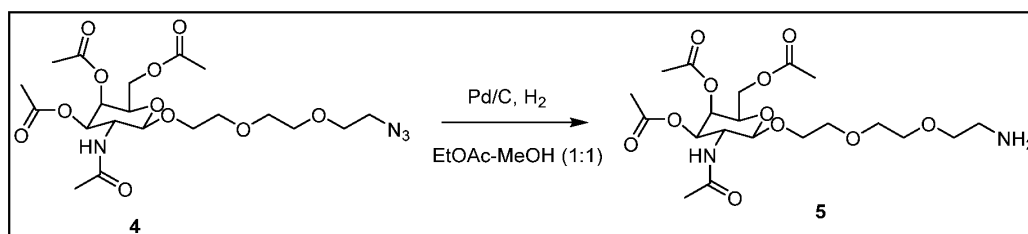
Synthesis route for the conjugate building block TriGalNAc_Tether1:



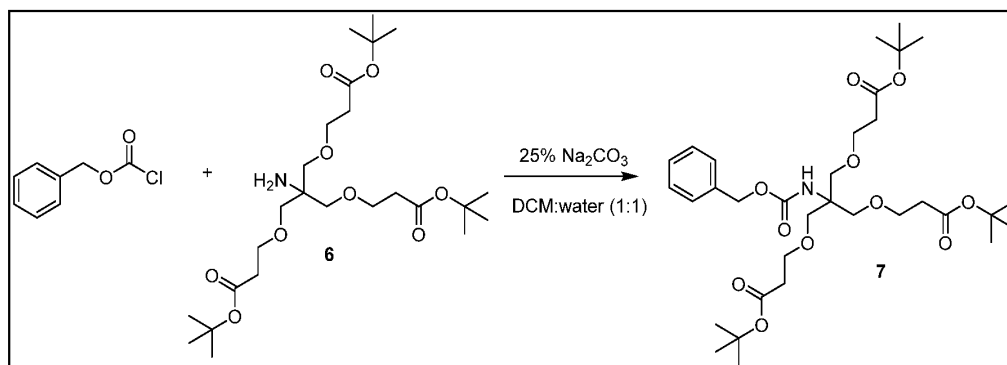
Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM (50 mL) and washed with cold saturated aq. NaHCO₃ (100 mL) and water (100 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated to afford the title compound as yellow oil, which was purified by flash chromatography (gradient elution: 0-10% MeOH in DCM in 10 CV). The product was obtained as colourless oil (2.5 g, 98%, rf= 0.45 (2% MeOH in DCM)).



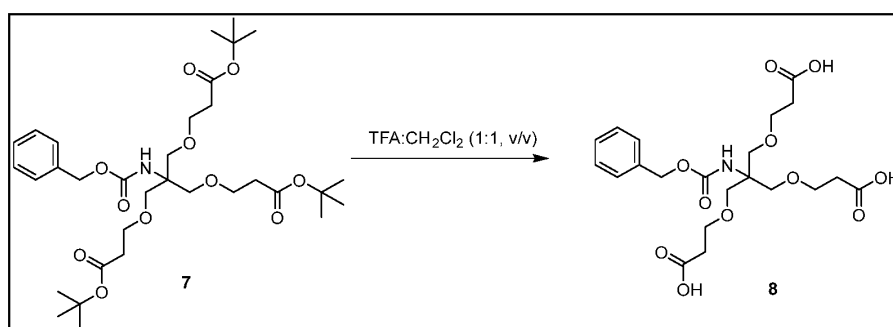
Preparation of compound 4: Compound 2 (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 0.5 eq.) was then added to the mixture and the reaction was stirred overnight. The molecular sieves were filtered, the filtrate was diluted with DCM (100 mL) and washed with cold saturated aq. NaHCO₃ (100 mL) and water (100 mL). The organic layer was separated, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (gradient elution: 0-3% MeOH in DCM in 10 CV) to afford the title product as light yellow oil (3.10 g, 88%, rf = 0.25 (2% MeOH in DCM)). MS: calculated for C₂₀H₃₂N₄O₁₁, 504.21. Found 505.4. ¹H NMR (500 MHz, CDCl₃) δ 6.21-6.14 (m, 1H), 5.30 (dd, J = 3.4, 1.1 Hz, 1H), 5.04 (dd, J = 11.2, 3.4 Hz, 1H), 4.76 (d, J = 8.6 Hz, 1H), 4.23-4.08 (m, 3H), 3.91-3.80 (m, 3H), 3.74-3.59 (m, 9H), 3.49-3.41 (m, 2H), 2.14 (s, 3H), 2.02 (s, 3H), 1.97 (d, J = 4.2 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 170.6 (C), 170.5 (C), 170.4 (C), 170.3 (C), 102.1 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.5 (CH), 70.3 (CH₂), 69.7 (CH₂), 68.5 (CH₂), 66.6 (CH₂), 61.5 (CH₂), 23.1 (CH₃), 20.7 (3xCH₃).



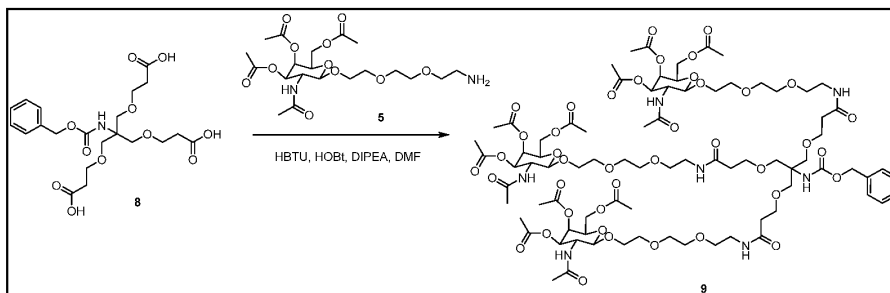
Preparation of compound 5: Compound 4 (1.00 g, 1.98 mmol, 1.0 eq.) was dissolved in a mixture of ethyl acetate (EtOAc) and MeOH (30 mL 1:1 v/v) and Pd/C (100 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The reaction mixture was filtered through celite and washed with EtOAc (30 mL). The solvent was removed under reduced pressure to afford the title compound as colourless oil (0.95 g, quantitative yield, rf = 0.25 (10% MeOH in DCM)). The compound was used without further purification. MS: calculated for C₂₀H₃₄N₂O₁₁, 478.2. Found 479.4.



- Preparation of compound 7: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine 6 (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na₂CO₃ (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 mmol, 3.10 eq.) was added dropwise to the previous mixture and the reaction was stirred at room temperature for 24 h. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and washed with water (100 mL). The organic layer was separated and dried over Na₂SO₄. The solvent was removed under reduced pressure and the resulting crude material was purified by flash chromatography (gradient elution: 0-10% EtOAc in cyclohexane in 12 CV) to afford the title compound as pale yellowish oil (3.9 g, 91%, rf = 0.56 (10% EtOAc in cyclohexane)).
- MS: calculated for C₃₃H₅₃NO₁₁, 639.3. Found 640.9. ¹H NMR (500 MHz, DMSO-d₆) δ 7.38-7.26 (m, 5H), 4.97 (s, 2H), 3.54 (t, 6H), 3.50 (s, 6H), 2.38 (t, 6H), 1.39 (s, 27H). ¹³C NMR (125 MHz, DMSO-d₆) δ 170.3 (3xC), 154.5 (C), 137.1 (C), 128.2 (2xCH), 127.7 (CH), 127.6 (2xCH), 79.7 (3xC), 68.4 (3xCH₂), 66.8 (3xCH₂), 64.9 (C), 58.7 (CH₂), 35.8 (3xCH₂), 27.7 (9xCH₃).



- Preparation of compound 8: Cbz-NH-tris-Boc-ester 7 (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 3 times with toluene (5 mL) and dried under high vacuum to get the compound as its TFA salt (0.183 g, 98%). The compound was used without further purification. MS: calculated for C₂₁H₂₉NO₁₁, 471.6. Found 472.4.

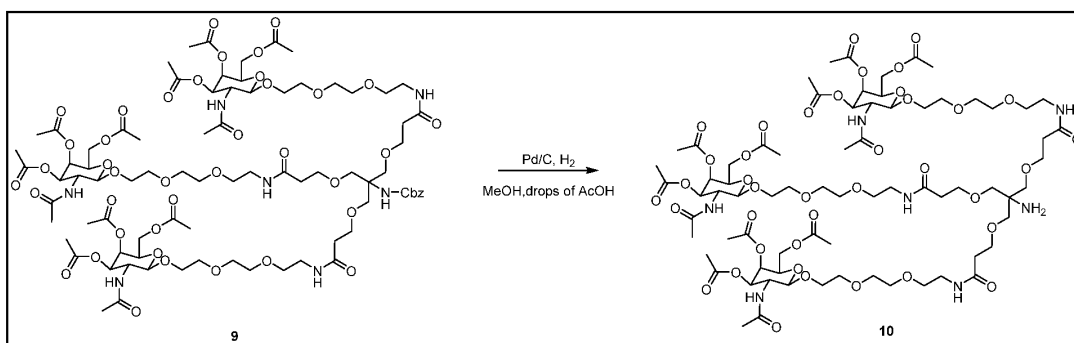


Preparation of compound 9: CbzNH-tris-COOH **8** (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH₂ **5** (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in N,N-dimethylformamide (DMF) (25 mL). Then N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 mmol, 5.0 eq.),

5 1-hydroxybenzotriazole hydrate (HOBT) (1.05 g, 7.44 mmol, 5.0 eq.) and N,N-diisopropylethylamine (DIPEA) (2.07 mL, 11.9 mmol, 8.0 eq.) were added to the solution and the reaction was stirred for 72 h. The solvent was removed under reduced pressure, the residue was dissolved in DCM (100 mL) and washed with saturated aq. NaHCO₃ (100 mL). The organic layer was dried over Na₂SO₄, the solvent evaporated and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 14

10 CV). The product was obtained as pale yellowish oil (1.2 g, 43%, rf = 0.20 (5% MeOH in DCM)). MS: calculated for C₈₁H₁₂₅N₇O₄₁, 1852.9. Found 1854.7. ¹H NMR (500 MHz, DMSO-d₆) δ 7.90-7.80 (m, 10H), 7.65-7.62 (m, 4H), 7.47-7.43 (m, 3H), 7.38-7.32 (m, 8H), 5.24-5.22 (m, 3H), 5.02-4.97 (m, 4H), 4.60-4.57 (m, 3 H), 4.07-3.90 (m 10H), 3.67-3.36 (m, 70H), 3.23-3.07 (m, 25H), 2.18 (s, 10H), 2.00 (s, 13H), 1.89 (s, 11H), 1.80-1.78 (m, 17H). ¹³C NMR (125 MHz, DMSO-d₆) δ 170.1 (C), 169.8 (C), 169.7 (C), 169.4 (C),

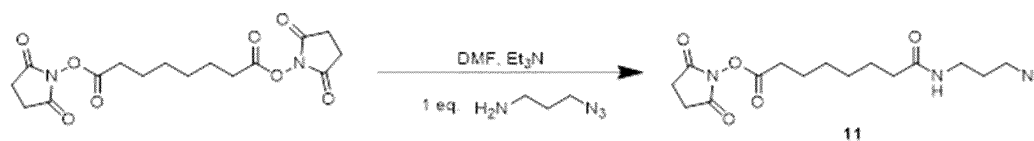
15 169.2 (C), 169.1 (C), 142.7 (C), 126.3 (CH), 123.9 (CH), 118.7 (CH), 109.7 (CH), 100.8 (CH), 70.5 (CH), 69.8 (CH), 69.6 (CH), 69.5 (CH), 69.3 (CH₂), 69.0 (CH₂), 68.2 (CH₂), 67.2 (CH₂), 66.7 (CH₂), 61.4 (CH₂), 22.6 (CH₂), 22.4 (3xCH₃), 20.7 (9xCH₃).



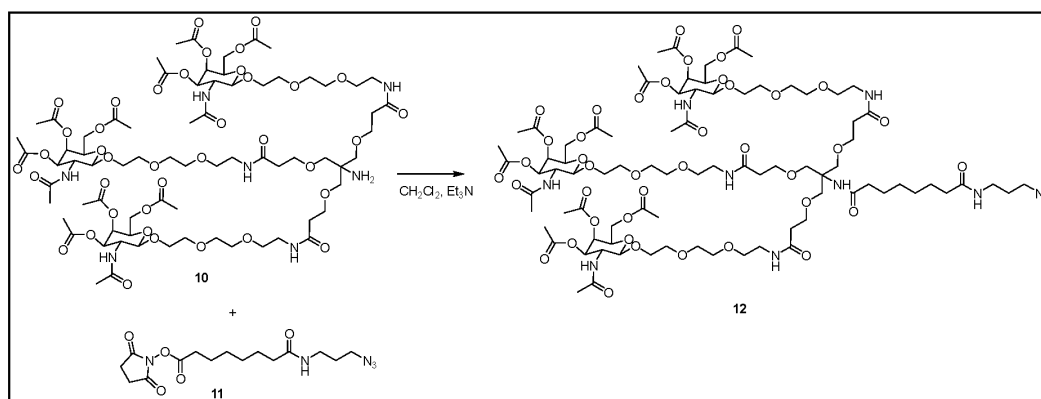
Preparation of compound 10: Triantennary GalNAc compound **9** (0.27 g, 0.14 mmol, 1.0 eq.) was dissolved

20 in MeOH (15 mL), 3 drops of acetic acid (AcOH) and Pd/C (30 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction was followed by mass spectrometry and the resulting mixture was filtered through a thin pad of celite. The solvent was evaporated and the residue obtained was dried under high

vacuum and used for the next step without further purification. The product was obtained as pale yellowish oil (0.24 g, quantitative yield). MS: calculated for $C_{73}H_{119}N_7O_{39}$, 1718.8. Found 1719.3.



Preparation of compound 11: Commercially available suberic acid bis(N-hydroxysuccinimide ester) (3.67 g, 9.9 mmol, 1.0 eq.) was dissolved in DMF (5 mL) and triethylamine (1.2 mL) was added. To this solution was added dropwise a solution of 3-azido-1-propylamine (1.0 g, 9.9 mmol, 1.0 eq.) in DMF (5 mL). The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (50 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 16 CV). The product was obtained as white solid (1.54 g, 43%, $rf = 0.71$ (5% MeOH in DCM)). MS: calculated for $C_{15}H_{23}N_3O_5$, 353.4. Found 354.3.



Preparation of TriGalNAc (12): Triantennary GalNAc compound 10 (0.35 g, 0.24 mmol, 1.0 eq.) and compound 11 (0.11 g, 0.31 mmol, 1.5 eq.) were dissolved in DCM (5 mL) under argon and triethylamine (0.1 mL, 0.61 mmol, 3.0 eq.) was added. The reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was dissolved in EtOAc (100 mL) and washed with water (100 mL). The organic layer was separated and dried over Na_2SO_4 . The solvent was evaporated and the resulting crude material was purified by flash chromatography (elution gradient: 0-10% MeOH in DCM in 20 CV) to afford the title compound as white fluffy solid (0.27 g, 67%, $rf = 0.5$ (10% MeOH in DCM)). MS: calculated for $C_{84}H_{137}N_{11}O_{41}$, 1957.1. Found 1959.6.

Conjugation of Tether 1 to a siRNA strand: Monofluoro cyclooctyne (MFCO) conjugation at 5'-or 3'-end

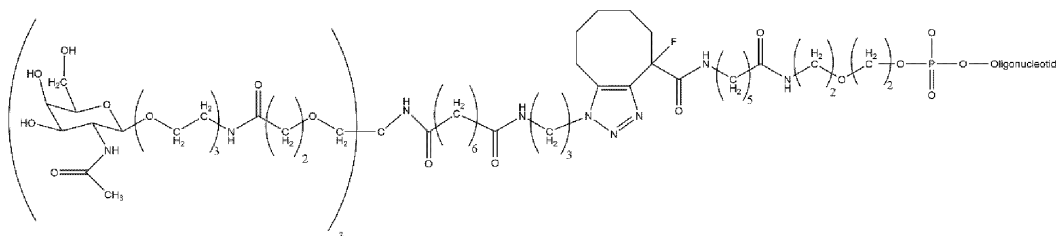
5'-end MFCO conjugation



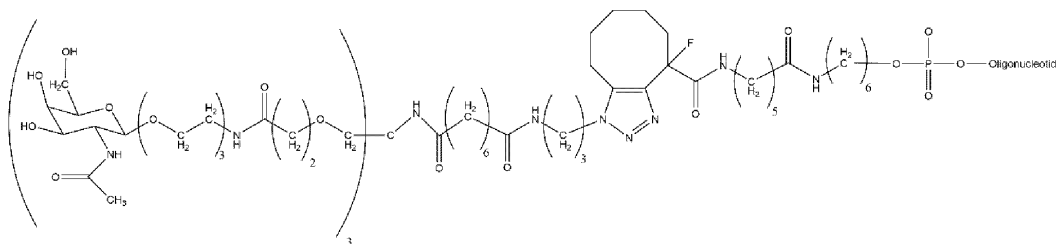
Purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM TEAAc pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

Fractions containing full length conjugated oligonucleotide were pooled, precipitated in the freezer with 3 M NaOAc, pH 5.2 and 85% ethanol and the collected pellet was dissolved in water. Samples were desalted by size exclusion chromatography and concentrated using a speed-vac concentrator to yield the conjugated oligonucleotide in an isolated yield of 40–80%.

5'-GalNAc-T1 conjugates



3'-GalNAc-T1 conjugates



General procedure for TriGalNAc conjugation: MFCO-modified single strand was dissolved at 2000 OD/mL in water and to this solution was added one equivalent solution of compound 12 (10 mM) in DMF. The reaction was carried out at room temperature and after 3 h 0.7 molar equivalent of the compound 12 solution was added. The reaction was allowed to proceed overnight and completion was monitored by LCMS. The conjugate was diluted 15-fold in water, filtered through a 1.2 µm filter from Sartorius and then purified by RP HPLC on an Äkta Pure instrument (GE Healthcare).

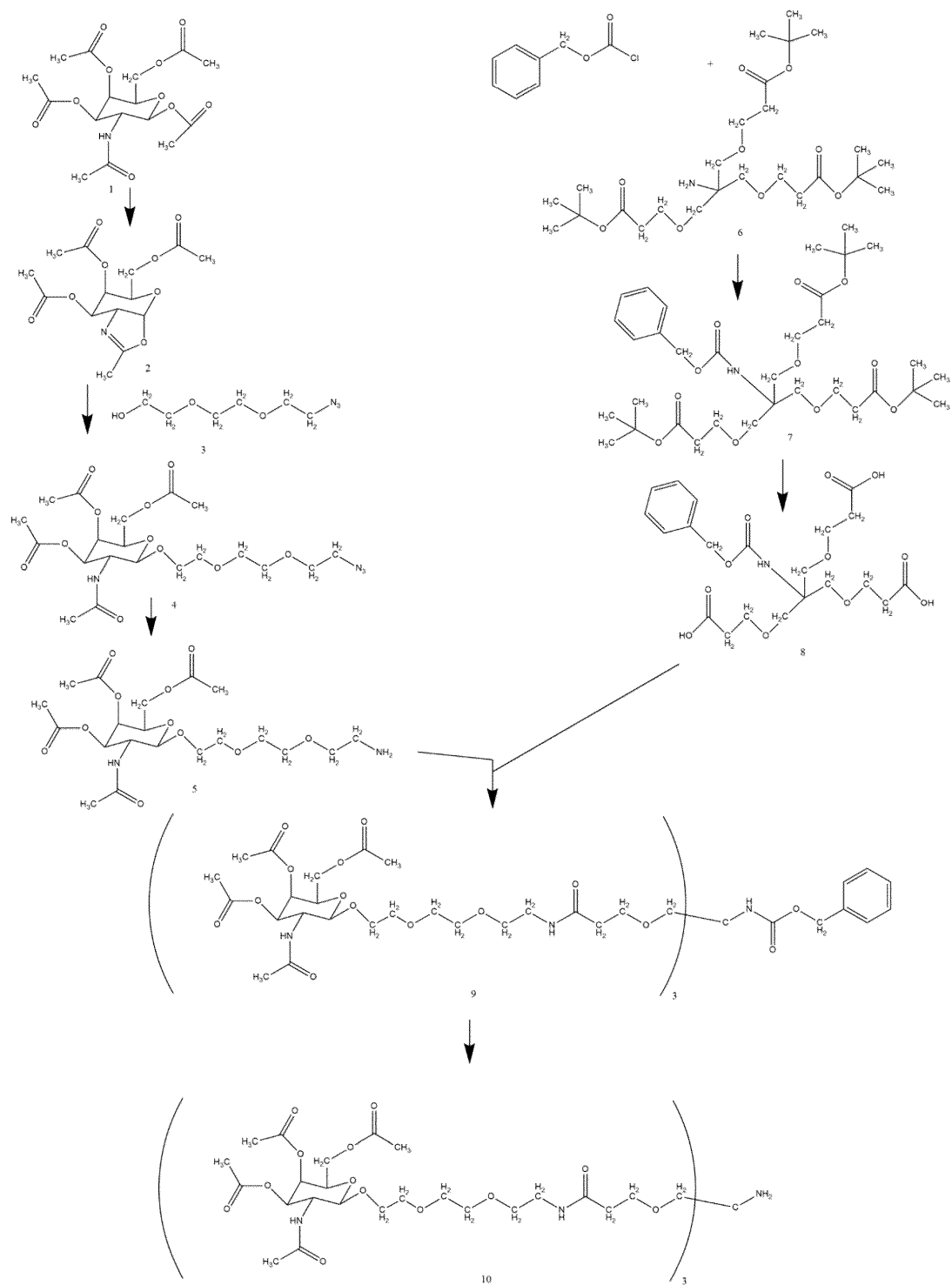
RP HPLC purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM triethylammonium acetate pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

Fractions containing full-length conjugated oligonucleotide were pooled, precipitated in the freezer with 3 M NaOAc, pH 5.2 and 85% ethanol and the collected pellet was dissolved in water to give an oligonucleotide solution of about 1000 OD/mL. The O-acetates were removed by adding 20% aqueous ammonia. Quantitative removal of these protecting groups was verified by LC-MS.

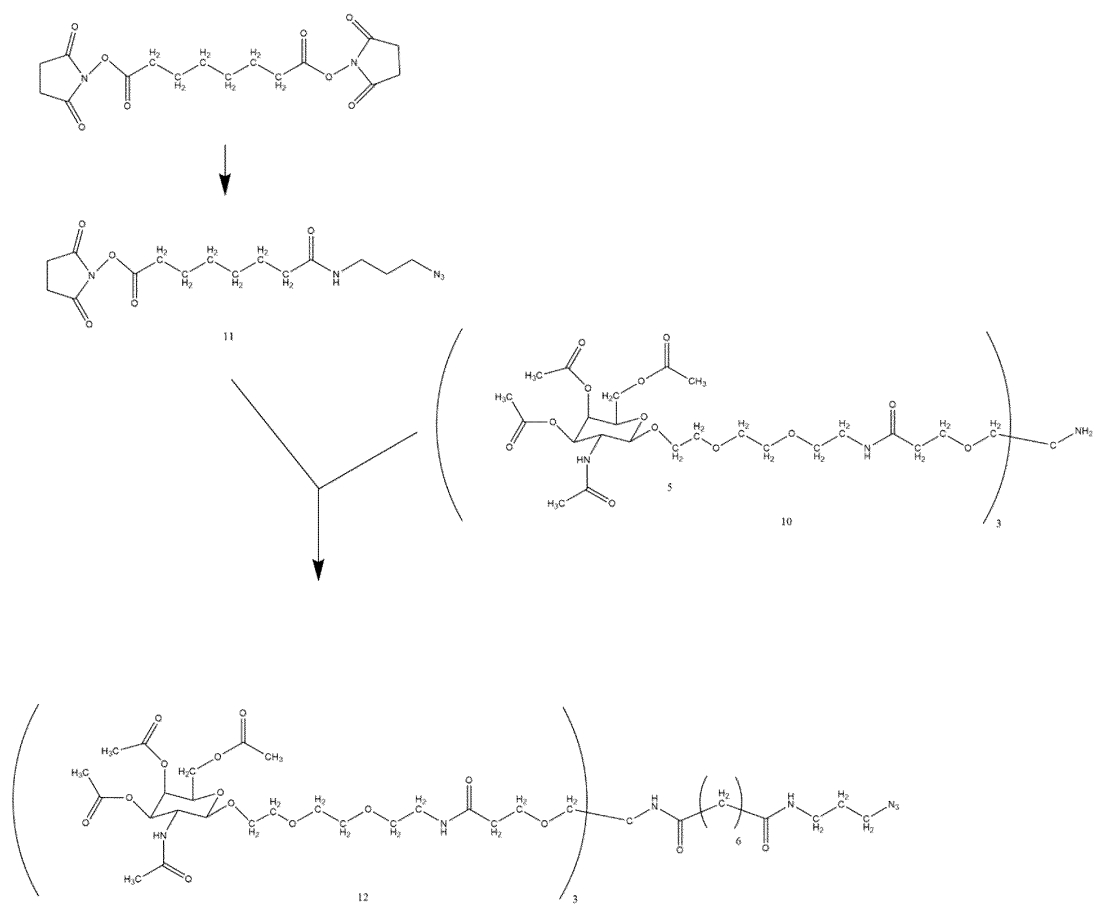
The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 50–70%.

The following schemes further set out the routes of synthesis:

Scheme 1:

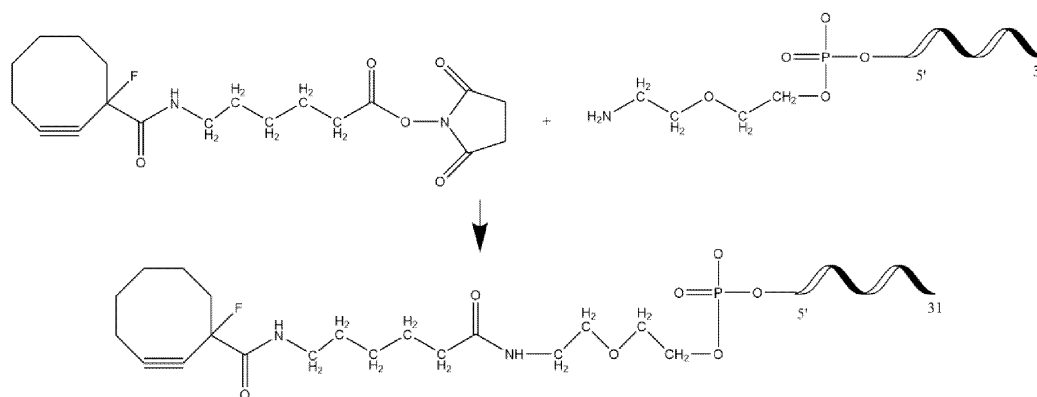


Scheme 2:

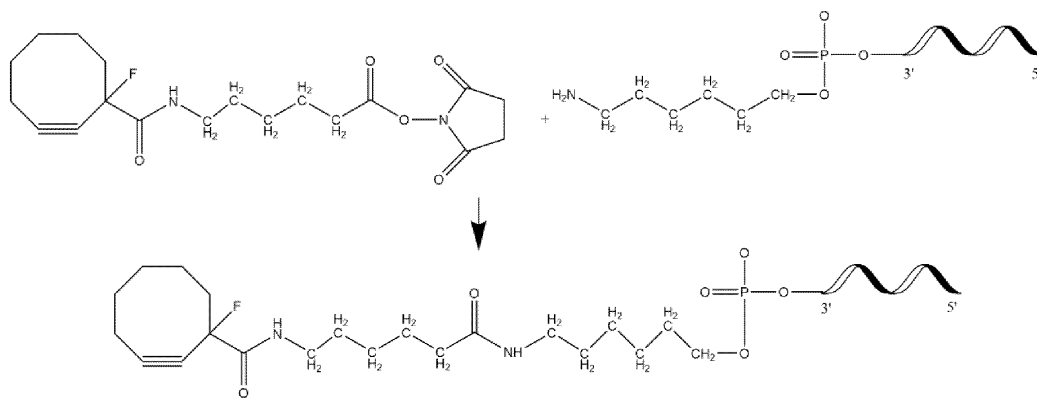


Scheme 3:

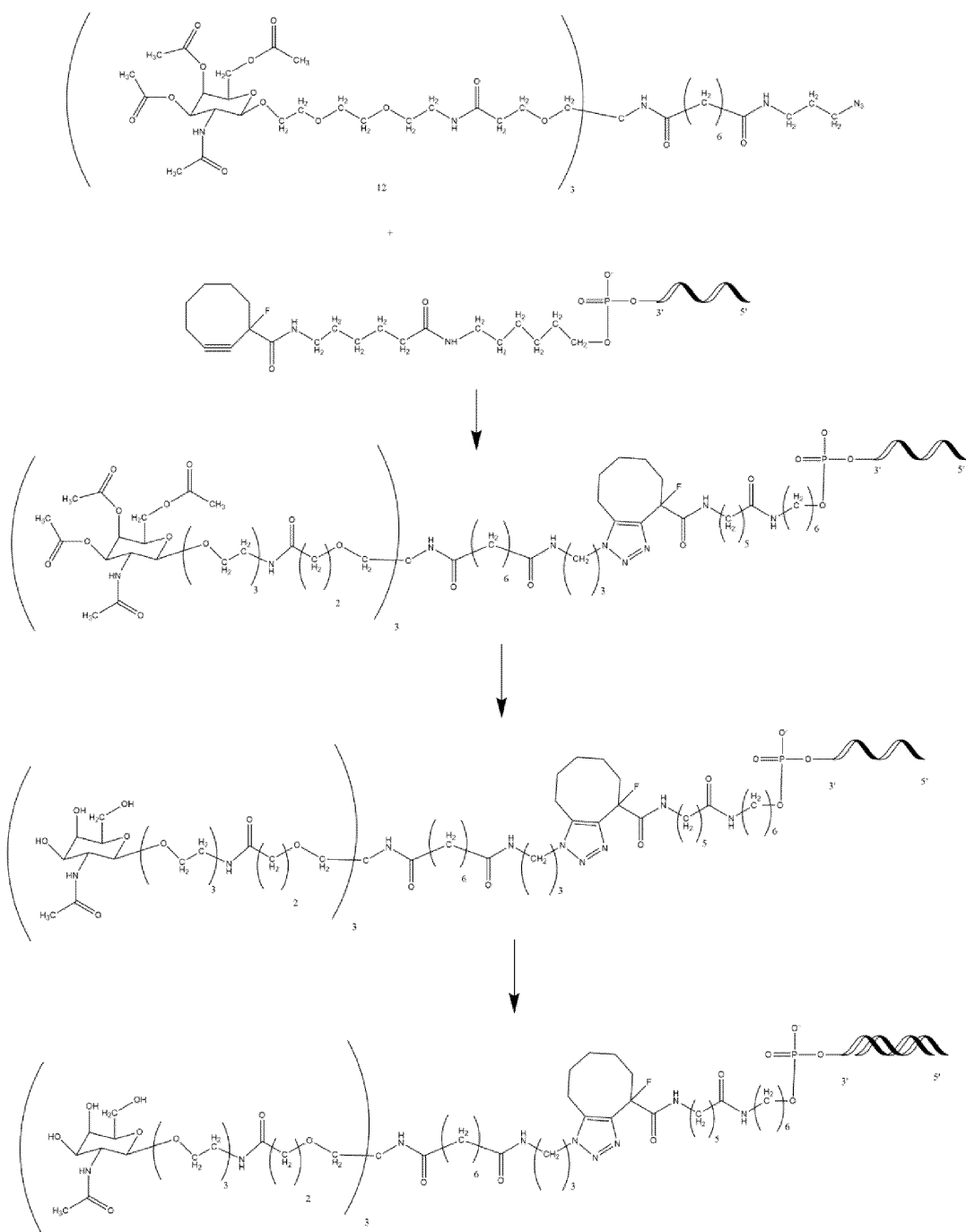
5' end MFCO conjugation



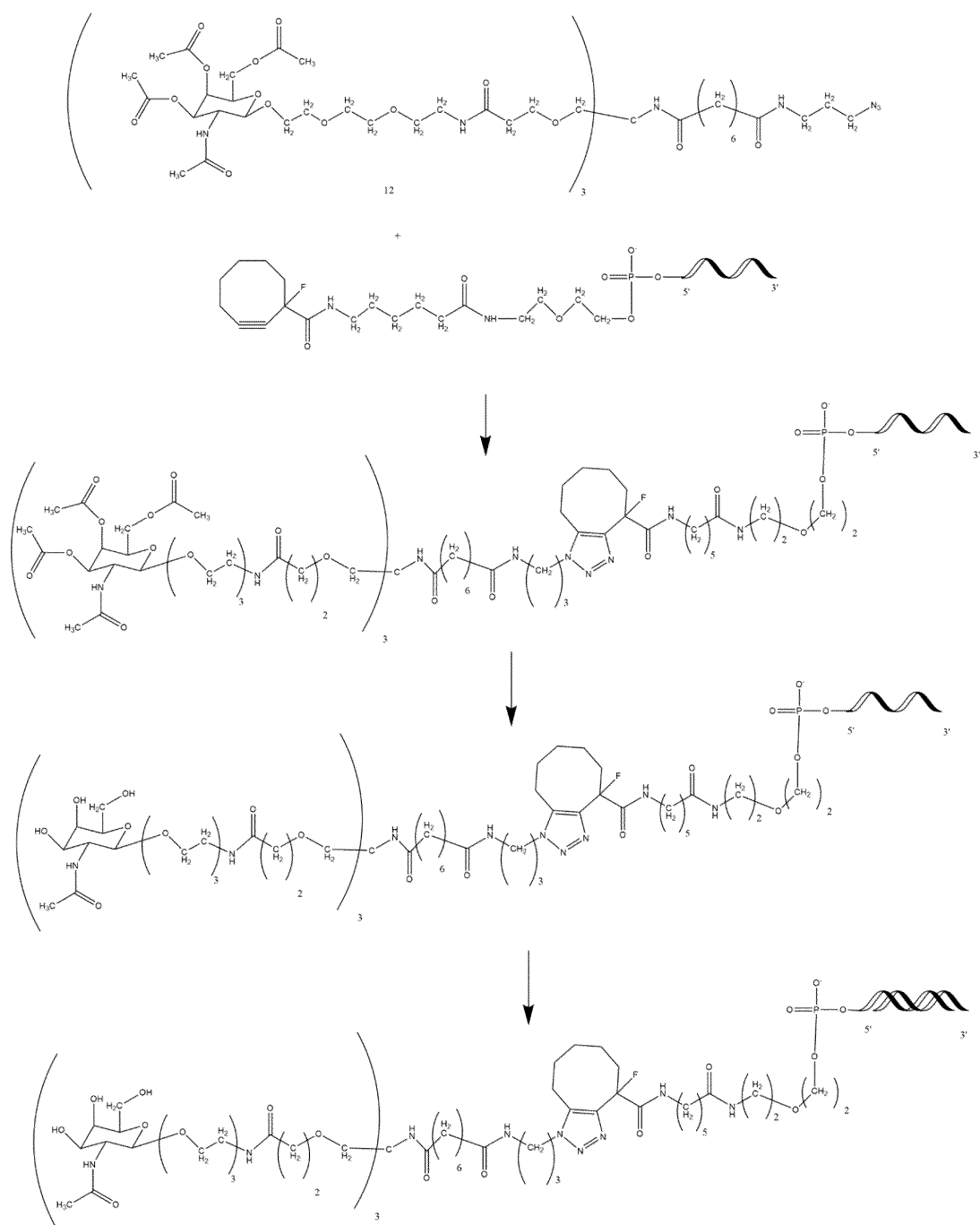
3' end MFCO conjugation



Scheme 4:



Scheme 5:



EXAMPLE 3: DUPLEX ANNEALING

To generate the desired siRNA duplex, the two complementary strands were annealed by combining equimolar aqueous solutions of both strands. The mixtures were placed into a water bath at 70°C for 5 minutes and subsequently allowed to cool to ambient temperature within 2 h. The duplexes were lyophilized for 2 days and stored at -20°C.

The duplexes were analyzed by analytical SEC HPLC on Superdex™ 75 Increase 5/150 GL column 5 x 153-158 mm (Cytiva) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system. Mobile phase consisted of 1x PBS containing 10% acetonitrile. An isocratic gradient was run in 10 min at a flow rate of 1.5 mL/min at room temperature. UV traces at 260 and 280 nm were recorded. Water (LC-MS grade) was purchased from Sigma-Aldrich and Phosphate-buffered saline (PBS; 10x, pH 7.4) was purchased from GIBCO (Thermo Fisher Scientific).

EXAMPLE 4: SYNTHESIS OF TETHER 2General Experimental conditions:

Thin layer chromatography (TLC) was performed on silica-coated aluminium plates with fluorescence indicator 254 nm from Macherey-Nagel. Compounds were visualized under UV light (254 nm), or after spraying with the 5% H₂SO₄ in methanol (MeOH) or ninhydrin reagent according to Stahl (from Sigma-Aldrich), followed by heating. Flash chromatography was performed with a Biotage Isolera One flash chromatography instrument equipped with a dual variable UV wavelength detector (200-400 nm) using Biotage Sfär Silica 10, 25, 50 or 100 g columns (Uppsala, Sweden).

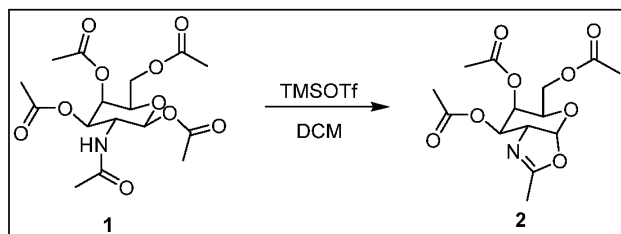
All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents were purchased from Sigma-Aldrich and solvents from Carl Roth GmbH + Co. KG. D-Galactosamine pentaacetate was purchased from AK scientific.

HPLC/ESI-MS was performed on a Dionex UltiMate 3000 RS UHPLC system and Thermo Scientific MSQ Plus Mass spectrometer using an Acquity UPLC Protein BEH C4 column from Waters (300Å, 1.7 µm, 2.1 x 100 mm) at 60 °C. The solvent system consisted of solvent A with H₂O containing 0.1% formic acid and solvent B with acetonitrile (ACN) containing 0.1% formic acid. A gradient from 5-100% of B over 15 min with a flow rate of 0.4 mL/min was employed. Detector and conditions: Corona ultra-charged aerosol detection (from esa). Nebulizer Temp.: 25 °C. N₂ pressure: 35.1 psi. Filter: Corona.

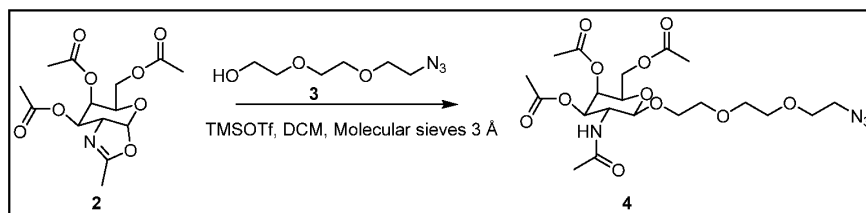
¹H and ¹³C NMR spectra were recorded at room temperature on a Varian spectrometer at 500 MHz (¹H NMR) and 125 MHz (¹³C NMR). Chemical shifts are given in ppm referenced to the solvent residual peak (CDCl₃ – ¹H NMR: δ at 7.26 ppm and ¹³C NMR δ at 77.2 ppm; DMSO-d₆ – ¹H NMR: δ at 2.50 ppm and

^{13}C NMR δ at 39.5 ppm). Coupling constants are given in Hertz. Signal splitting patterns are described as singlet (s), doublet (d), triplet (t) or multiplet (m).

Synthesis route for the conjugate building block TriGalNAc_Tether2:

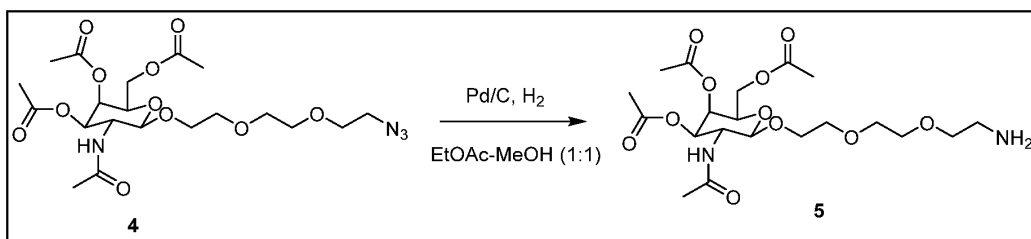


- 5 Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM (50 mL) and washed with cold saturated aq. NaHCO_3 (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 , and concentrated to afford the title compound as yellow oil, which was purified by flash chromatography (gradient elution: 0-10% MeOH in DCM in 10 CV). The product was obtained as colourless oil (2.5 g, 98%, rf= 0.45 (2% MeOH in DCM)).

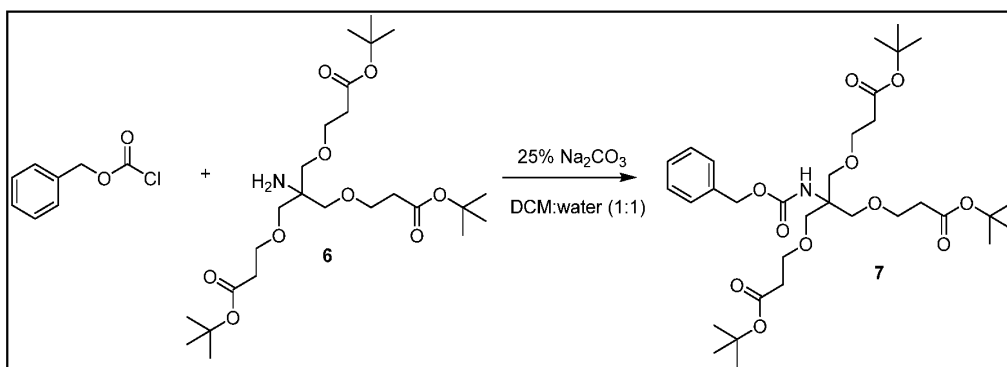


- 15 Preparation of compound 4: Compound 2 (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 0.5 eq.) was then added to the mixture and the reaction was stirred overnight. The molecular sieves were filtered, the filtrate was diluted with DCM (100 mL) and washed with cold saturated aq. NaHCO_3 (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (gradient elution: 0-3% MeOH in DCM in 10 CV) to afford the title product as light-yellow oil (3.10 g, 88%, rf = 0.25 (2% MeOH in DCM)). MS: calculated for $\text{C}_{20}\text{H}_{32}\text{N}_4\text{O}_{11}$, 504.21. Found 505.4. ^1H NMR (500 MHz, CDCl_3) δ 6.21-6.14 (m, 1H), 5.30 (dd, J = 3.4, 1.1 Hz, 1H), 5.04 (dd, J = 11.2, 3.4 Hz, 1H), 4.76 (d, J = 8.6 Hz, 1H), 4.23-4.08 (m, 3H), 3.91-3.80 (m, 3H), 3.74-3.59 (m, 9H), 3.49-3.41 (m, 2H), 2.14 (s, 3H), 2.02 (s, 3H), 1.97 (d, J = 4.2 Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.6 (C), 170.5 (C), 170.4 (C), 170.3

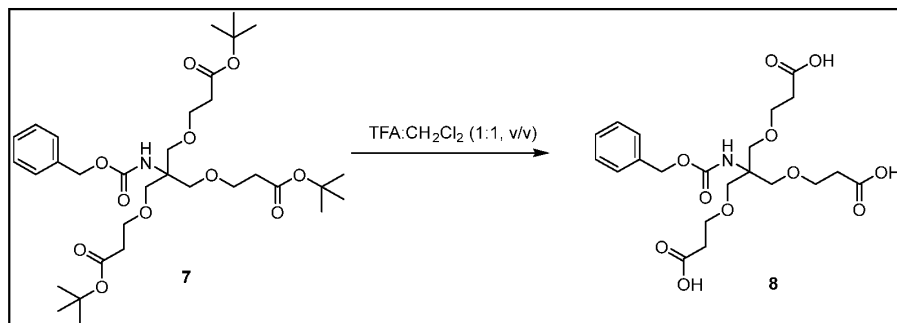
(C), 102.1 (CH), 71.6 (CH), 70.8 (CH), 70.6 (CH), 70.5 (CH), 70.3 (CH₂), 69.7 (CH₂), 68.5 (CH₂), 66.6 (CH₂), 61.5 (CH₂), 23.1 (CH₃), 20.7 (3xCH₃).



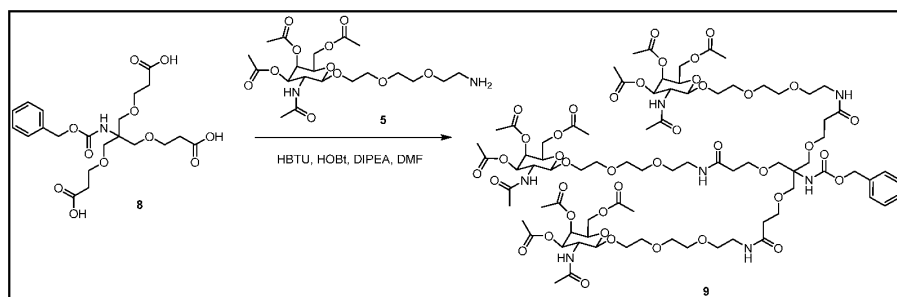
Preparation of compound 5: Compound 4 (1.00 g, 1.98 mmol, 1.0 eq.) was dissolved in a mixture of ethyl acetate (EtOAc) and MeOH (30 mL 1:1 v/v) and Pd/C (100 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The reaction mixture was filtered through celite and washed with EtOAc (30 mL). The solvent was removed under reduced pressure to afford the title compound as colourless oil (0.95 g, quantitative yield, rf = 0.25 (10% MeOH in DCM)). The compound was used without further purification. MS: calculated for C₂₀H₃₄N₂O₁₁, 478.2. Found 479.4.



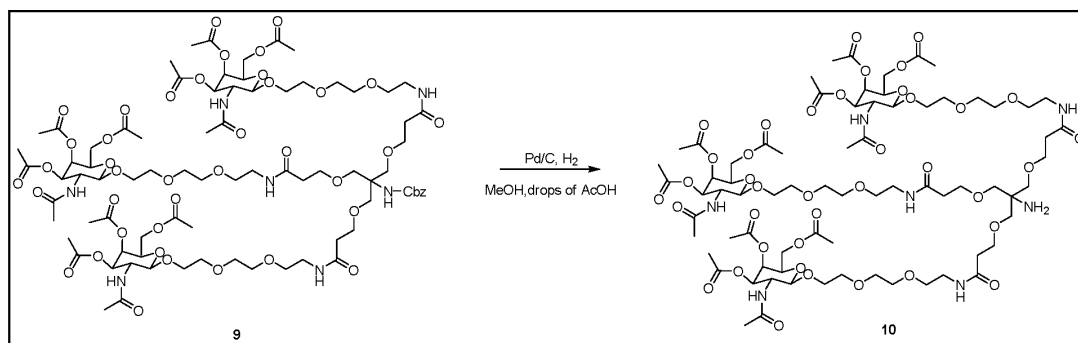
Preparation of compound 7: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine 6 (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na₂CO₃ (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 mmol, 3.10 eq.) was added dropwise to the previous mixture and the reaction was stirred at room temperature for 24 h. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and washed with water (100 mL). The organic layer was separated and dried over Na₂SO₄. The solvent was removed under reduced pressure and the resulting crude material was purified by flash chromatography (gradient elution: 0-10% EtOAc in cyclohexane in 12 CV) to afford the title compound as pale yellowish oil (3.9 g, 91%, rf = 0.56 (10% EtOAc in cyclohexane)). MS: calculated for C₃₃H₅₃NO₁₁, 639.3. Found 640.9. ¹H NMR (500 MHz, DMSO-d₆) δ 7.38-7.26 (m, 5H), 4.97 (s, 2H), 3.54 (t, 6H), 3.50 (s, 6H), 2.38 (t, 6H), 1.39 (s, 27H). ¹³C NMR (125 MHz, DMSO-d₆) δ 170.3 (3xC), 154.5 (C), 137.1 (C), 128.2 (2xCH), 127.7 (CH), 127.6 (2xCH), 79.7 (3xC), 68.4 (3xCH₂), 66.8 (3xCH₂), 64.9 (C), 58.7 (CH₂), 35.8 (3xCH₂), 27.7 (9xCH₃).



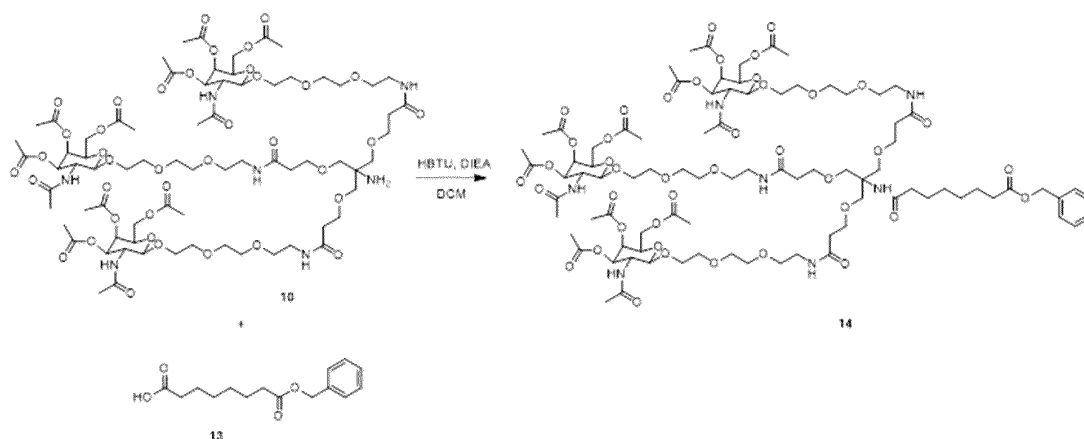
Preparation of compound 8: Cbz-NH-tris-Boc-ester **7** (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 3 times with toluene (5 mL) and dried under high vacuum to get the compound as its TFA salt (0.183 g, 98%).
 5 The compound was used without further purification. MS: calculated for C₂₁H₂₉NO₁₁, 471.6. Found 472.4.



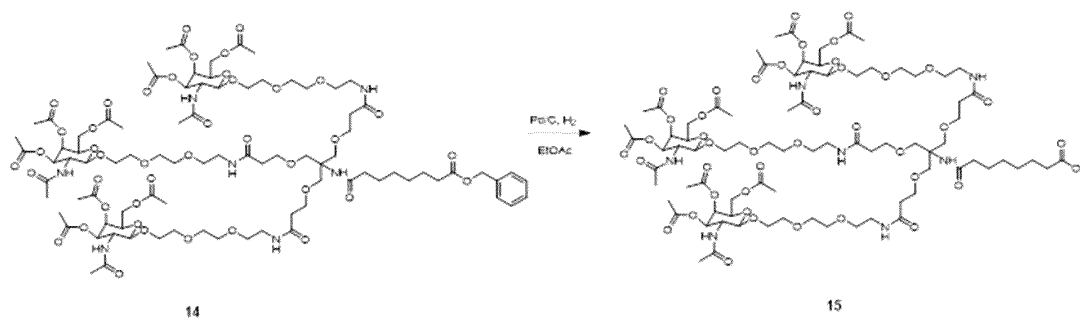
Preparation of compound 9: CbzNH-tris-COOH **8** (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH₂ **5** (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in N,N-dimethylformamide (DMF) (25 mL). Then N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 mmol, 5.0 eq.), 1-hydroxybenzotriazole hydrate (HOBT) (1.05 g, 7.44 mmol, 5.0 eq.) and N,N-diisopropylethylamine (DIPEA) (2.07 mL, 11.9 mmol, 8.0 eq.) were added to the solution and the reaction was stirred for 72 h. The solvent was removed under reduced pressure, the residue was dissolved in DCM (100 mL) and washed with saturated aq. NaHCO₃ (100 mL). The organic layer was dried over Na₂SO₄, the solvent evaporated and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 14 CV). The product was obtained as pale yellowish oil (1.2 g, 43%, rf = 0.20 (5% MeOH in DCM)). MS: calculated for C₈₁H₁₂₅N₇O₄₁, 1852.9. Found 1854.7. ¹H NMR (500 MHz, DMSO-d₆) δ 7.90-7.80 (m, 10H), 7.65-7.62 (m, 4H), 7.47-7.43 (m, 3H), 7.38-7.32 (m, 8H), 5.24-5.22 (m, 3H), 5.02-4.97 (m, 4H), 4.60-4.57 (m, 3H), 4.07-3.90 (m 10H), 3.67-3.36 (m, 70H), 3.23-3.07 (m, 25H), 2.18 (s, 10H), 2.00 (s, 13H), 1.89 (s, 11H), 1.80-1.78 (m, 17H). ¹³C NMR (125 MHz, DMSO-d₆) δ 170.1 (C), 169.8 (C), 169.7 (C), 169.4 (C), 169.2 (C), 169.1 (C), 142.7 (C), 126.3 (CH), 123.9 (CH), 118.7 (CH), 109.7 (CH), 100.8 (CH), 70.5 (CH), 69.8 (CH), 69.6 (CH), 69.5 (CH), 69.3 (CH₂), 69.0 (CH₂), 68.2 (CH₂), 67.2 (CH₂), 66.7 (CH₂), 61.4 (CH₂), 22.6 (CH₂), 22.4 (3xCH₃), 20.7 (9xCH₃).
 15
 20



Preparation of compound 10: Triantennary GalNAc compound 9 (0.27 g, 0.14 mmol, 1.0 eq.) was dissolved in MeOH (15 mL), 3 drops of acetic acid (AcOH) and Pd/C (30 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction was followed by mass spectrometry and the resulting mixture was filtered through a thin pad of celite. The solvent was evaporated, and the residue obtained was dried under high vacuum and used for the next step without further purification. The product was obtained as pale yellowish oil (0.24 g, quantitative yield). MS: calculated for $C_{73}H_{119}N_7O_{39}$, 1718.8. Found 1719.3.



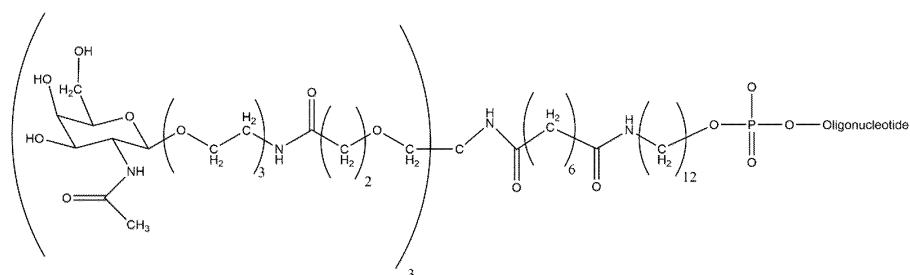
Preparation of compound 14: Triantennary GalNAc compound 10 (0.45 g, 0.26 mmol, 1.0 eq.), HBTU (0.19 g, 0.53 mmol, 2.0 eq.) and DIPEA (0.23 mL, 1.3 mmol, 5.0 eq.) were dissolved in DCM (10 mL) under argon. To this mixture, it was added dropwise a solution of compound 13 (0.14 g, 0.53 mmol, 2.0 eq.) in DCM (5 mL). The reaction was stirred at room temperature overnight. The solvent was removed, and the residue was dissolved in EtOAc (50 mL), washed with water (50 mL) and dried over Na₂SO₄. The solvent was evaporated, and the crude material was purified by flash chromatography (gradient elution: 0-5% MeOH in DCM in 20 CV). The product was obtained as white fluffy solid (0.25 g, 48%, rf = 0.4 (10% MeOH in DCM)). MS: calculated for C₈₈H₁₃₇N₇O₄₂, 1965.1. Found 1965.6.



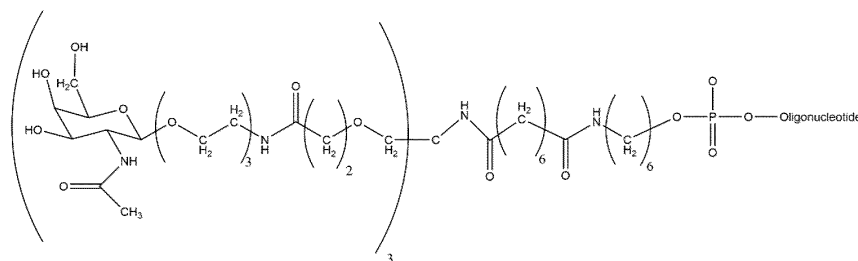
Preparation of TriGalNAc (15): Triantennary GalNAc compound 14 (0.31 g, 0.15 mmol, 1.0 eq.) was dissolved in EtOAc (15 mL) and Pd/C (40 mg) was added. The reaction mixture was degassed by using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction was monitored by mass spectrometry and the resulting mixture was filtered through a thin pad of celite. The solvent was removed under reduced pressure and the resulting residue was dried under high vacuum overnight. The residue was used for conjugations to oligonucleosides without further purification (0.28 g, quantitative yield). MS: calculated for $C_{81}H_{131}N_7O_{42}$, 1874.9. Found 1875.3.

Conjugation of Tether 2 to a siRNA strand: TriGalNAc tether 2 (GalNAc-T2) conjugation at 5'-end or 3'-end

5'-GalNAc-T2 conjugates



3'-GalNAc-T2 conjugates



Preparation of TriGalNAc tether 2 NHS ester: To a solution of carboxylic acid tether 2 (compound 15, 227 mg, 121 μ mol) in DMF (2.1 mL), N-hydroxysuccinimide (NHS) (15.3 mg, 133 μ mol) and N,N'-

diisopropylcarbodiimide (DIC) (19.7 μ L, 127 μ mol) were added. The solution was stirred at room temperature for 18 h and used without purification for the subsequent conjugation reactions.

General procedure for triGalNAc tether 2 conjugation: Amine-modified single strand was dissolved at 700 OD/mL in 50 mM carbonate/bicarbonate buffer pH 9.6/DMSO 4:6 (v/v) and to this solution was added one molar equivalent of Tether 2 NHS ester (57 mM) solution in DMF. The reaction was carried out at room temperature and after 1 h another molar equivalent of the NHS ester solution was added. The reaction was allowed to proceed for one more hour and reaction progress was monitored by LCMS. At least two molar equivalent excess of the NHS ester reagent relative to the amino modified oligonucleoside were needed to achieve quantitative consumption of the starting material. The reaction mixture was diluted 15-fold with water, filtered once through 1.2 μ m filter from Sartorius and then purified by reserve phase (RP HPLC) on an Äkta Pure (GE Healthcare) instrument.

The purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM TEAA pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0–100% B within 60 column volumes was employed.

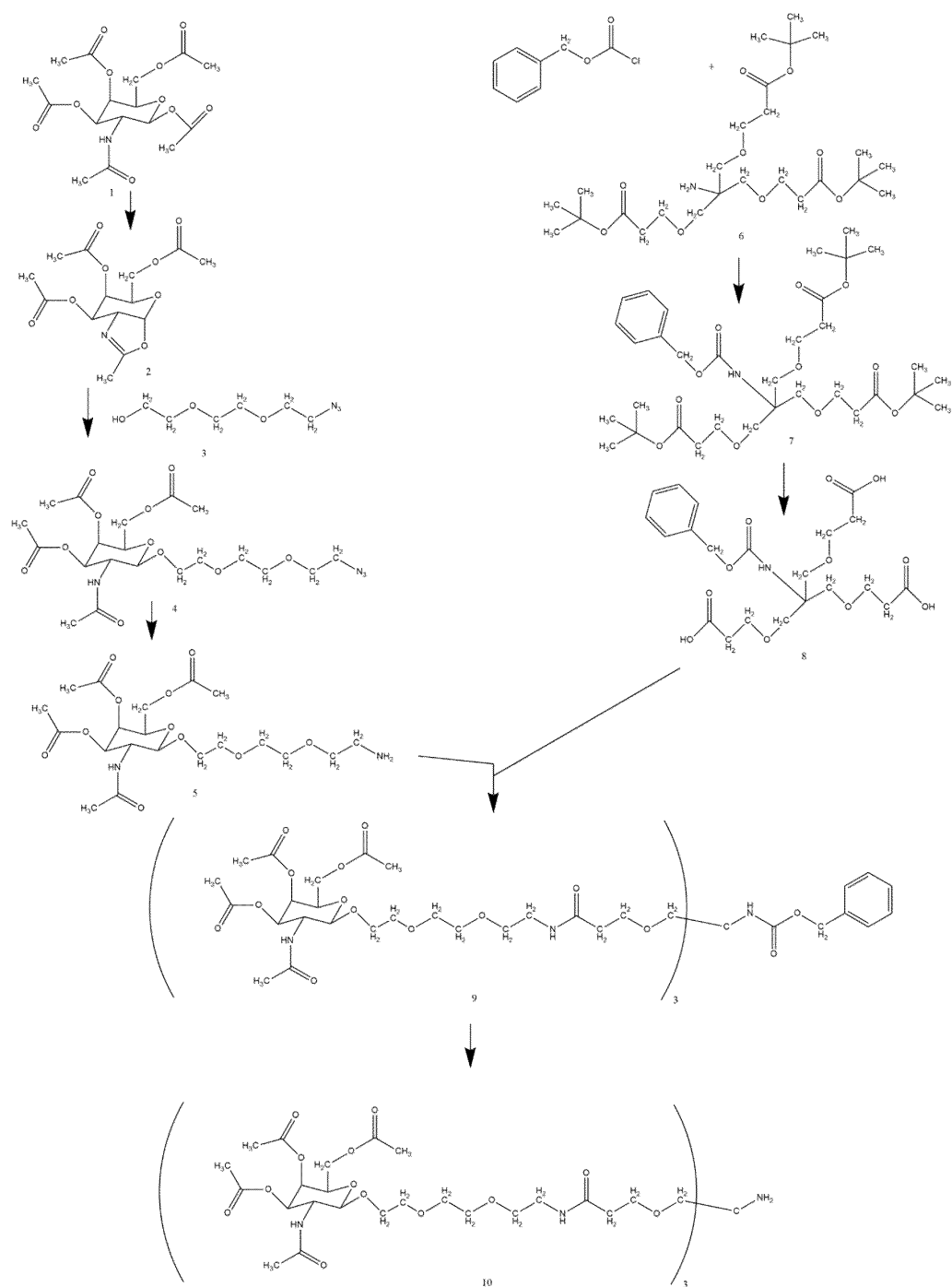
Fractions containing full-length conjugated oligonucleosides were pooled together, precipitated in the freezer with 3 M NaOAc, pH 5.2 and 85% ethanol and then dissolved at 1000 OD/mL in water. The O-acetates were removed with 20% ammonium hydroxide in water until completion (monitored by LC-MS).

The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 60–80%.

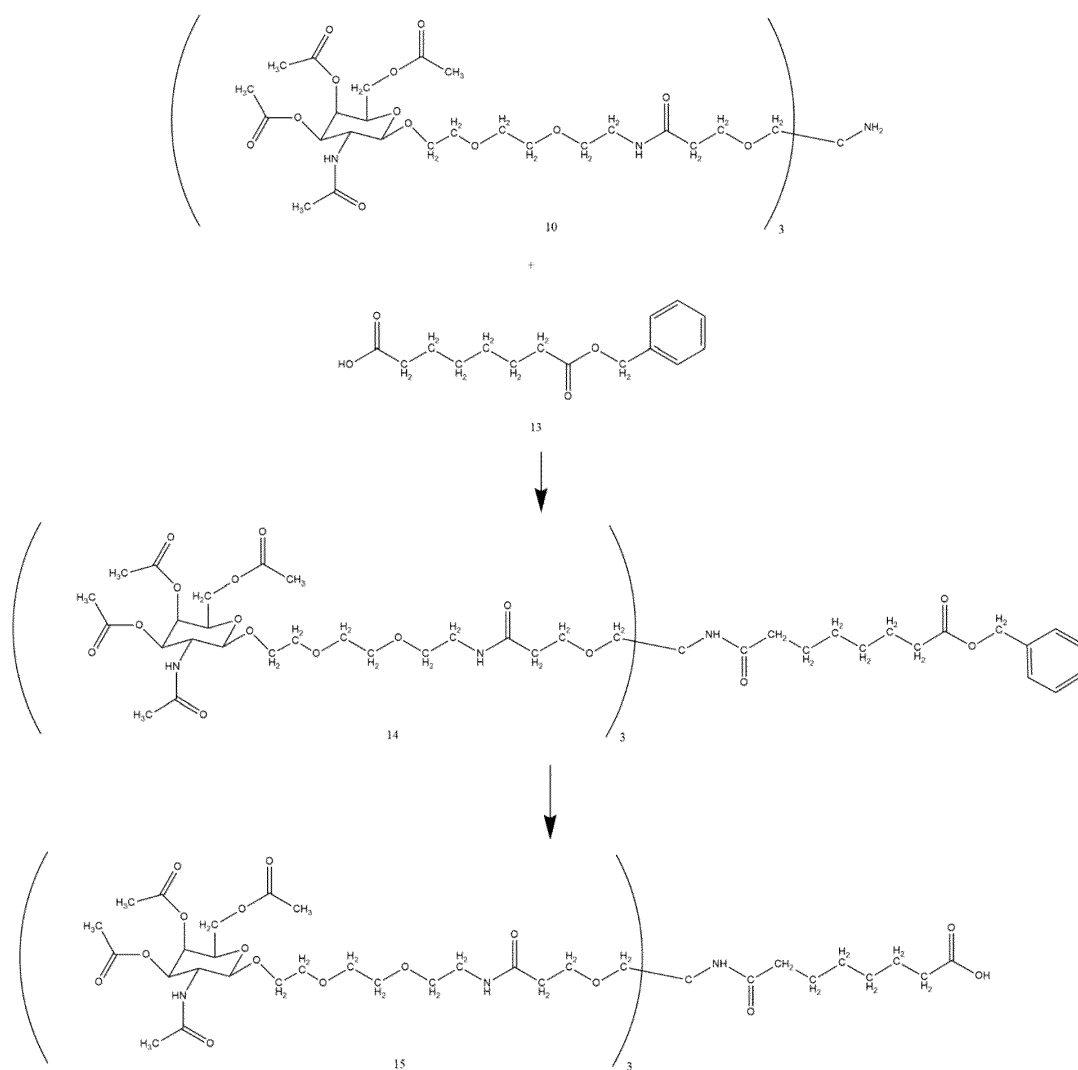
The conjugates were characterized by HPLC–MS analysis with a 2.1 x 50 mm XBridge C18 column (Waters) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system equipped with a Compact ESI-Qq-TOF mass spectrometer (Bruker Daltonics). Buffer A was 16.3 mM triethylamine, 100 mM HFIP in 1% MeOH in H₂O and buffer B contained 95% MeOH in buffer A. A flow rate of 250 μ L/min and a temperature of 60°C were employed. UV traces at 260 and 280 nm were recorded. A gradient of 1–100% B within 31 min was employed.

The following schemes further set out the routes of synthesis:

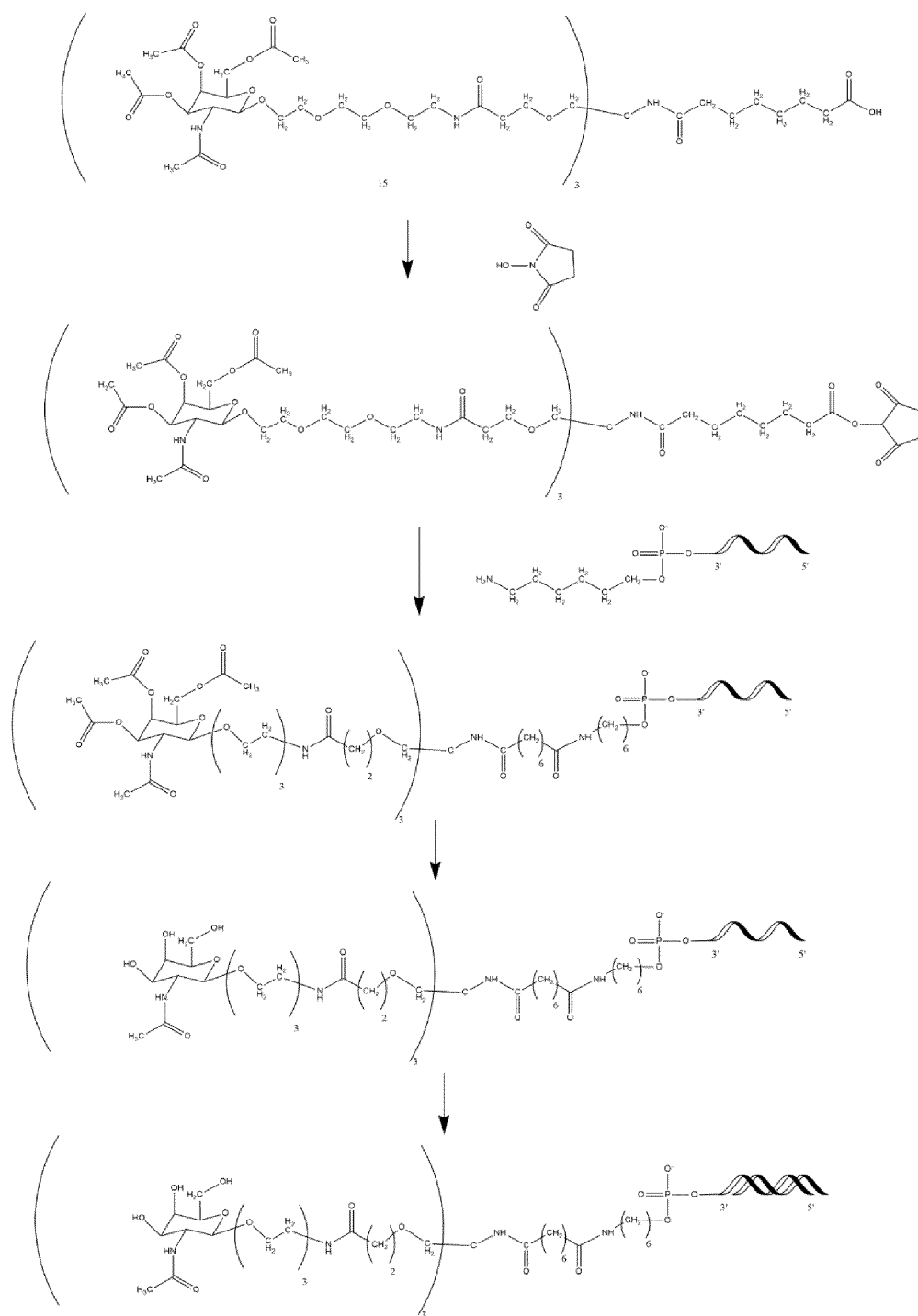
Scheme 6:



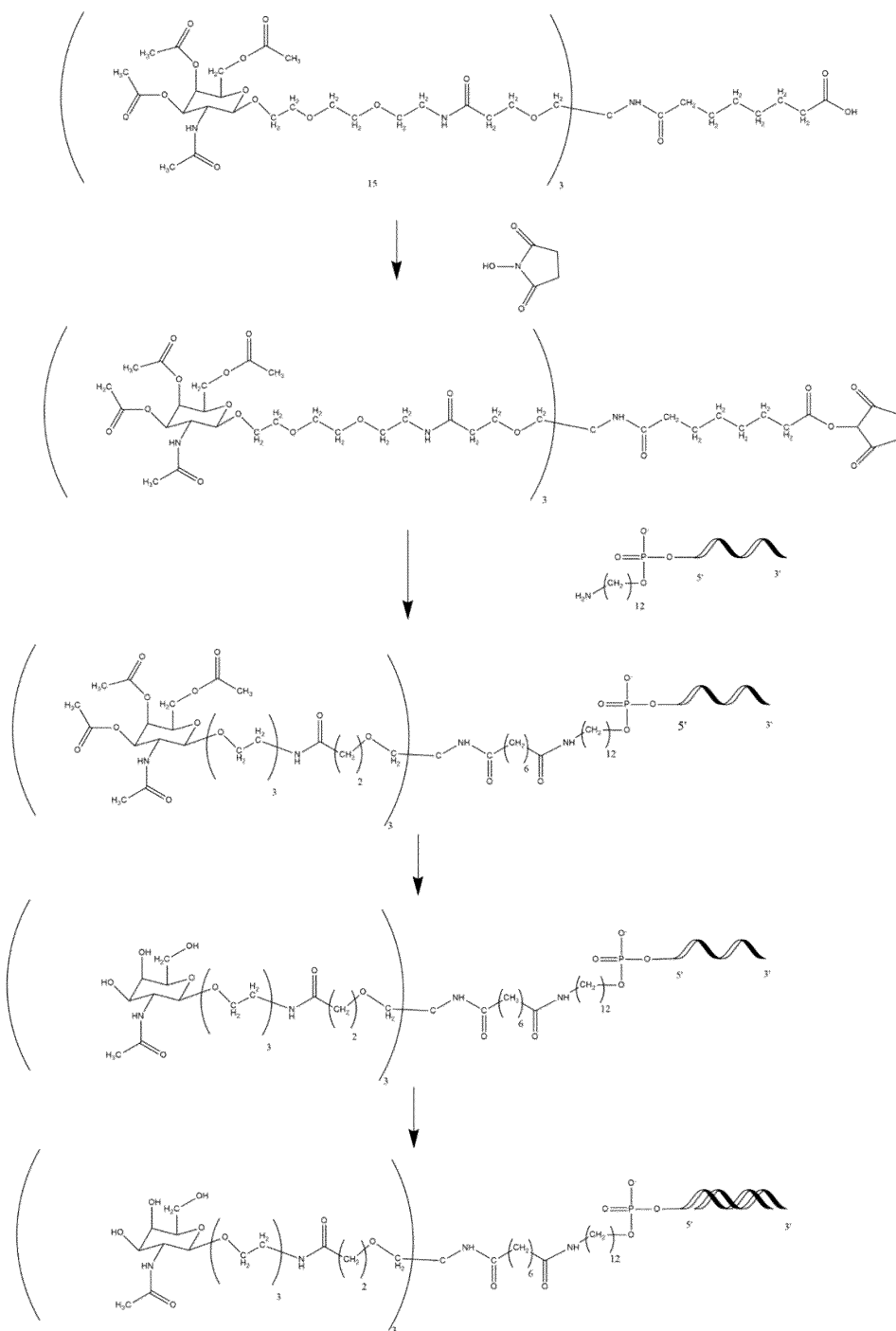
Scheme 7:



Scheme 8:



Scheme 9:

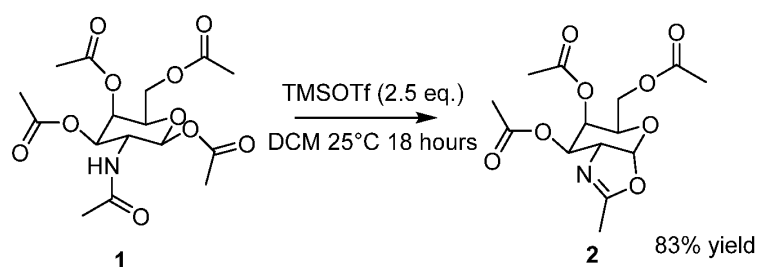


EXAMPLE 5: DUPLEX ANNEALING

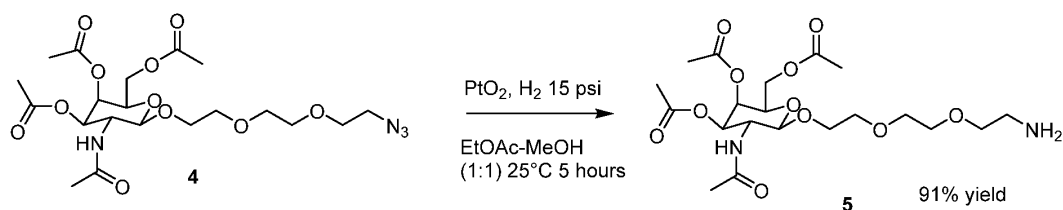
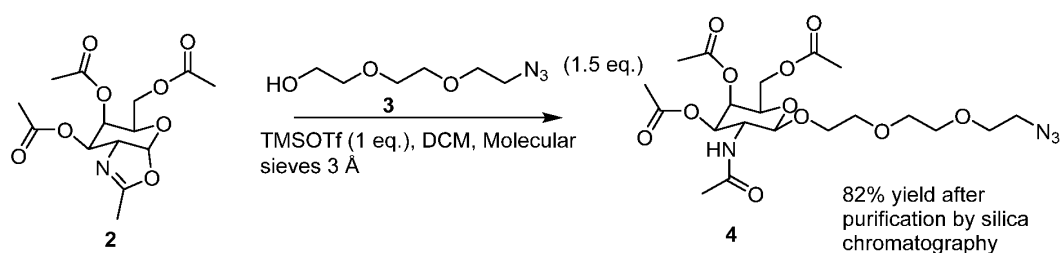
To generate the desired siRNA duplex, the two complementary strands were annealed by combining equimolar aqueous solutions of both strands. The mixtures were placed into a water bath at 70°C for 5 minutes and subsequently allowed to cool to ambient temperature within 2 h. The duplexes were lyophilized for 2 days and stored at -20°C.

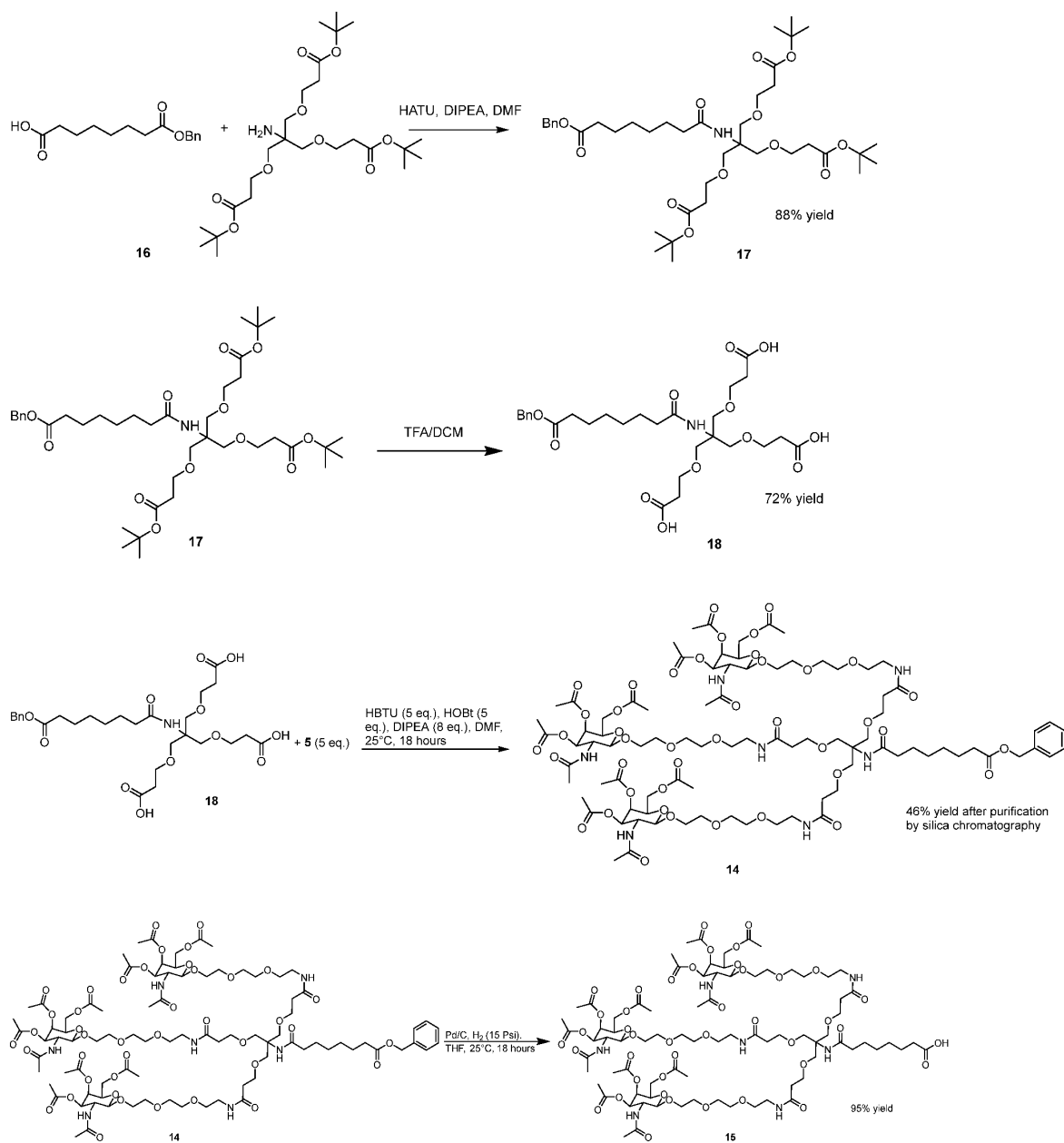
The duplexes were analyzed by analytical SEC HPLC on Superdex™ 75 Increase 5/150 GL column 5 x 153-158 mm (Cytiva) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system. Mobile phase consisted of 1x PBS containing 10% acetonitrile. An isocratic gradient was run in 10 min at a flow rate of 1.5 mL/min at room temperature. UV traces at 260 and 280 nm were recorded. Water (LC-MS grade) was purchased from Sigma-Aldrich and Phosphate-buffered saline (PBS; 10x, pH 7.4) was purchased from GIBCO (Thermo Fisher Scientific).

EXAMPLE 6: ALTERNATIVE SYNTHESIS ROUTE FOR THE CONJUGATE BUILDING BLOCK
TRIGALNAC_TETHER2:



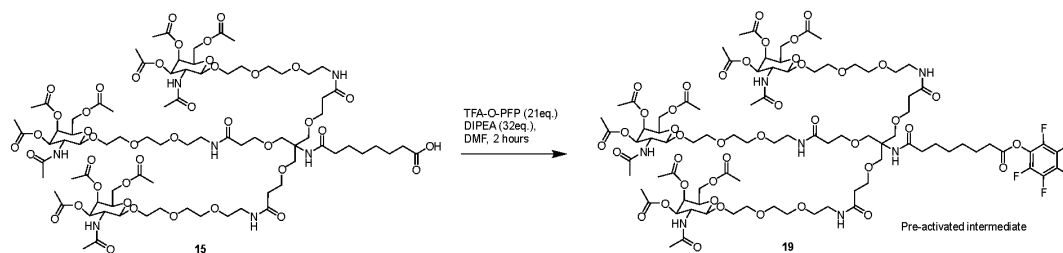
15





Conjugation of Tether 2 to a siRNA strand: TriGalNAc tether 2 (GalNAc-T2) conjugation at 5'-end or 3'-end

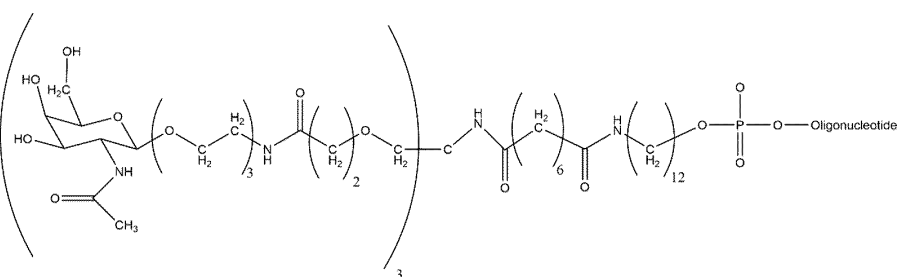
Conjugation conditions



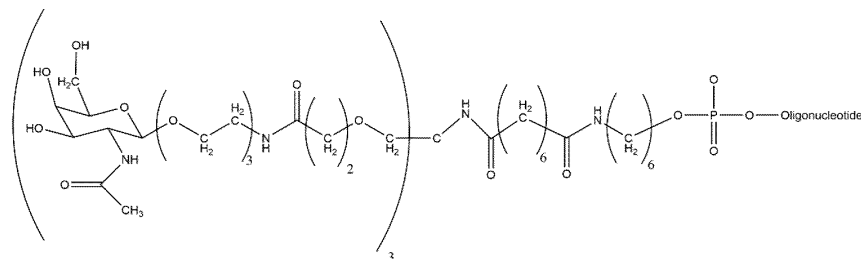
5

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5'-GalNAc-T2 conjugates



3'-GalNAc-T2 conjugates



15

EXAMPLE 7: SOLID PHASE SYNTHESIS METHOD: SCALE $\leq 1\mu\text{MOL}$

Syntheses of siRNA sense and antisense strands were performed on a MerMade192X synthesiser with commercially available solid supports made of controlled pore glass with universal linker (Universal CPG, with a loading of 40 µmol/g; LGC Biosearch or Glen Research).

RNA phosphoramidites were purchased from ChemGenes or Hongene.

5 The 2'-O-Methyl phosphoramidites used were the following: 5'-(4,4'-dimethoxytrityl)-N-benzoyl-adenosine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-N-acetyl-cytidine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-N-isobutyryl-guanosine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-uridine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite.

The 2'-F phosphoramidites used were the following: 5'-dimethoxytrityl-N-benzoyl-deoxyadenosine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-dimethoxytrityl-N-acetyl-deoxycytidine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-dimethoxytrityl-N-isobutyryl-deoxyguanosine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite and 5'-dimethoxytrityl-deoxyuridine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite.

All phosphoramidites were dissolved in anhydrous acetonitrile (Honeywell Research Chemicals) at a concentration of 0.05M, except 2'-O-methyl-uridine phosphoramidite which was dissolved in DMF/MeCN (1:4, v/v). Iodine at 0.02M in acetonitrile/Pyridine/H₂O (DNAchem) was used as oxidizing reagent. Thiolation for phosphorothioate linkages was performed with 0.2 M PADS (TCI) in acetonitrile/pyridine 1:1 v/v. 5-Ethyl thiotetrazole (ETT), 0.25M mM in acetonitrile was used as activator solution.

Inverted abasic phosphoramidite, 3-O-Dimethoxytrityl-2-deoxyribose-5'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite were purchased from Chemgenes (ANP-1422) or Hongene (OP-040).

At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

The coupling time was 180 seconds. The oxidizer contact time was set to 80 seconds and thiolation time was 2*100 seconds.

At the end of the synthesis, the oligonucleotides were cleaved from the solid support using a NH₄OH:EtOH solution 4:1 (v/v) for 20 hours at 45°C (TCI). The solid support was then filtered off, the filter was thoroughly washed with H₂O and the volume of the combined solution was reduced by evaporation under reduced pressure.

30 Oligonucleotide were treated to form the sodium salt by ultracentrifugation using Amicon Ultra-2 Centrifugal Filter Unit; PBS buffer (10x, Teknova, pH 7.4, Sterile) or by EtOH precipitation from 1M sodium acetate.

The single strands identity were assessed by MS ESI- and then, were annealed in water to form the final duplex siRNA and duplex purity were assessed by size exclusion chromatography.

EXAMPLE 8: SOLID PHASE SYNTHESIS METHOD: SCALE ≥ 5 μ MOL

Syntheses of siRNA sense and antisense strands were performed on a MerMade12 synthesiser with
 5 commercially available solid supports made of controlled pore glass with universal linker (Universal CPG, with a loading of 40 μ mol/g; LGC Biosearch or Glen Research) at 5 μ mol scale. Sense strand destined to 3' conjugation were synthesised at 12 μ mol on 3'-PT-Amino-Modifier C6 CPG 500 Å solid support with a loading of 86 μ mol/g (LGC).

RNA phosphoramidites were purchased from ChemGenes or Hongene.

10 The 2'-O-Methyl phosphoramidites used were the following: 5'-(4,4'-dimethoxytrityl)-N-benzoyl-adenosine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-N-acetyl-cytidine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-N-isobutyryl-guanosine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-(4,4'-dimethoxytrityl)-uridine 2'-O-methyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-
 15 phosphoramidite.

The 2'-F phosphoramidites used were the following: 5'-dimethoxytrityl-N-benzoyl-deoxyadenosine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-dimethoxytrityl-N-acetyl-deoxycytidine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-dimethoxytrityl-N-isobutyryl-deoxyguanosine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite and 5'-dimethoxytrityl-deoxyuridine 2'-fluoro-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite.
 20

Inverted abasic phosphoramidite, 3-O-Dimethoxytrityl-2-deoxyribose-5'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite were purchased from Chemgenes (ANP-1422) or Hongene (OP-040).

All phosphoramidites were dissolved in anhydrous acetonitrile (Honeywell Research Chemicals) at a concentration of 0.05M, except 2'-O-methyl-uridine phosphoramidite which was dissolved in DMF/MeCN
 25 (1:4, v/v). Iodine at 0.02M in acetonitrile/Pyridine/H₂O (DNAchem) was used as oxidizing reagent. Thiolation for phosphorothioate linkages was performed with 0.2 M PADS (TCI) in acetonitrile/pyridine 1:1 v/v. 5-Ethyl thiotetrazole (ETT), 0.25M mM in acetonitrile was used as activator solution.

At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

For strands synthesised on universal CPG the coupling was performed with 8 eq. of amidite for 130 seconds.
 30 The oxidation time was 47 seconds, the thiolation time was 210 seconds.

For strands synthesised on 3'-PT-Amino-Modifier C6 CPG the coupling was performed with 8 eq. of amidite for 2*150 seconds. The oxidation time was 47 seconds, the thiolation time was 250 seconds

At the end of the synthesis, the oligonucleotides were cleaved from the solid support using a NH₄OH:EtOH solution 4:1 (v/v) for 20 hours at 45°C (TCI). The solid support was then filtered off, the filter was thoroughly washed with H₂O and the volume of the combined solution was reduced by evaporation under reduced pressure.

- 5 Oligonucleotide were treated to form the sodium salt by EtOH precipitation from 1M sodium acetate.

The single strand oligonucleotides were purified by IP-RP HPLC on Xbridge BEH C18 5 µm, 130 Å, 19x150 mm (Waters) column with an increasing gradient of B in A. Mobile phase A: 240 mM HFIP, 7 mM TEA and 5% methanol in water; mobile phase B: 240 mM HFIP, 7 mM TEA in methanol.

- 10 The single strands purity and identity were assessed by UPLC/MS ESI- on Xbridge BEH C18 2.5 µm, 3x50 mm (Waters) column with an increasing gradient of B in A. Mobile phase A: 100 mM HFIP, 5 mM TEA in water; mobile phase B: 20% mobile phase A: 80% Acetonitrile (v/v).

Sense strands were conjugated as per protocol provided in any of Examples 2, 4, 6.

Sense and Antisense strands were then annealed in water to form the final duplex siRNA and duplex purity were assessed by size exclusion chromatography.

15 EXAMPLE 9: PHARMACOLOGICAL STUDY IN MICE

- In this Example, the activity of ETX-312 (ETX-M00001378 (ETX-M00001751)), an inhibitor of ANT2/SLC25A5, specifically an inhibitor of expression of ANT2/SLC25A5 on metabolic parameters, hepatic pathology, and NAFLD Activity Score (NAS) including fibrosis stage in male biopsy-confirmed GAN DIO-NASH mice was tested. A total of 9 DIO-NASH groups (n=16) and 1 LEAN-CHOW group (n=10) of male C57BL/6JRj mice were fed 40% HFD, 40% carbohydrate (22% fructose), 2% Cholesterol (GAN) diet or normal chow (Altromin 1324) for 34 weeks prior to study start.

- 25 All mice were pre-biopsied at week -4 and stratified based on liver biopsy (only animals with fibrosis stage =F2-F3, steatosis score =3 and inflammation score ≥2 were included). Mice were anesthetized by inhalation anesthesia using isoflurane (2-3%). A small abdominal incision was made in the midline and the left lateral lobe of the liver exposed. A cone shaped wedge of liver tissue (approximately 50 mg) was excised from the distal portion of the lobe and fixated in 10% neutral buffered formalin (10% NBF) for histology. The cut surface of the liver was instantly electrocoagulated using bipolar coagulation (ERBE VIO 100 electrosurgical unit). The liver was returned to the abdominal cavity, the abdominal wall sutured and the skin closed with staplers. For post-operative recovery, mice received carprofen (5mg/kg) administered subcutaneously on the day of the procedure and on post-operation days 1 and 2.

Animals were randomized into groups based on fibrosis stage and picosirius red (PSR) staining (% fractional area). Mice received a total of 12 weeks of dosing and were divided into the following groups: 1) LEAN-CHOW control (saline) (subcutaneous (SC), once weekly (QW)), 2) DIO-NASH control (saline)

(SC, QW), 3) SiCtrl, 5 mg/kg (SC, QW), 4) ETX-312, 5 mg/kg (SC, QW), 5) Semaglutide, 30 nmol/kg (SC, once daily (QD)), 6) Semaglutide, 30 nmol/kg (SC, QD) + ETX-312, 5 mg/kg (SC, QW), 7) Vehicle (oral (PO), QD), 8) HU6, 5 mg/kg (PO, QD), 9) Resmetirom, 3 mg/kg (PO, QD), 10) Resmetirom, 3 mg/kg (PO, QD) + ETX-312, 5 mg/kg (SC, QW). Semaglutide (Ozempic®) was diluted to achieve the required concentration in PBS supplemented with 0.1% BSA and let stand for 1 hour to obtain a homogeneous solution. Semaglutide was dose titrated during week 1 as follows to reach a final dose level of 30 nmol/kg for all remaining doses: 0.6 nmol/kg day 1; 1.2 nmol/kg day 2; 2.4 nmol/kg day 3; 4.8 nmol/kg day 4; 12 nmol/kg day 5, 30 nmol/kg day 6. HU6 stock solution was prepared in DMSO and diluted in 0.5% MC/0.2% Tween 80 resulting in 5% DMSO/0.5% MC/0.2% Tween 80. Resmetirom (MGL-3196) was mixed with a small volume of 0.5% CMC + 0.1% Tween80 (500µL) and crushed with a spatula. Vehicle PO (0.5 % CMC/ 0.1% Tween80) was added to obtain the required concentration of Resmetirom. The suspension was stirred for 2 hours to obtain orange/beige microsuspension.

Body weight was recorded daily and food intake recorded once weekly for 24 hours during the study period.

At the end of the study period, preterminal tail vein blood collection was conducted for non-fasting plasma Alanine transaminase (ALT), Aspartate transaminase (AST), Triglycerides (TG) and Total Cholesterol (TC) analysis. Tail-vein, tongue or cheek blood was collected in heparinized tubes and mixed by inversion 5 times. Blood was placed at 4°C until it was centrifuged at 3000 g for 10 minutes. The plasma supernatants were transferred to new tubes and immediately frozen on dry ice. The samples were stored at -70°. Terminal plasma samples were prepared during anesthesia with isoflurane with the abdominal cavity opened and cardiac blood drawn with a syringe into a Microvette/Vacurette of appropriate dimensions with anticoagulant and mixed by inversion 5 times. Blood was placed at 4°C until it was centrifuged at 3000 g for 10 minutes. The plasma supernatants were transferred to new tubes and immediately frozen on dry ice. The samples were stored at -70°C.

ALT, AST, TG, and TC assays were measured using commercial kits (Roche Diagnostics), on the Cobas c 501 autoanalyzer. TIMP-1 was measured in plasma collected in EDTA tubes using a commercial ELISA kit (R&D Systems). PIIINP was measured in plasma collected in EDTA tubes using a commercial ELISA kit (Cusabio).

After study termination, the liver was collected and weighed. Specific liver samples and biopsies were dissected and prepared as follows. The liver was divided into a left lateral lobe, medial lobe, right lateral lobe, and caudate lobe. The Post-biopsy piece (~200 mg, less than 0.7 x 0.5 cm) was cut from the left lateral lobe, 4 mm from the prebiopsy site with an edge. The tissue was collected in 10% neutral buffered formalin. Two liver samples collected for future analysis of protein expression (~ 50 mg per piece) were dissected from the left medial lobe, collected in tubes and frozen in liquid nitrogen. A third piece of liver was dissected from the center of the left lateral lobe (~ 50 mg), put in a tube, stored in RNAlater for 24h at 4°C and stored at -70°C.

Data were analysed via fitting of a simple linear model with fitted coefficients for the mean effect of the treatment on the biomarker, compared to a baseline comparator. p-values correspond to one-tailed t-tests on the regression coefficients, testing the alternate hypothesis that the coefficient in question is less than 0 (one-tailed) for non-control groups (equivalent to testing there being a reductive effect versus the comparator) and not equal to 0 (two-tailed) for the SiCtrl group (equivalent to testing there being no difference versus the comparator). Where significant heteroskedasticity was observed between treatment groups, p-values were calculated using robust estimation to the variance-covariance matrix. p-values were subsequently corrected for multiple comparisons via the FDR method. The following biomarkers were tested for increases or decreases (i.e. two-tailed) in the treatment groups: mRNA, Protein.

FFPE biopsies were placed in 10% neutral buffered formalin (10% NBF) for approximately 24 hours and then transferred to 70% ethanol and stored at 4°C. The FFPE biopsies were then placed in the Histokinette to infiltrate prior to embedding in blocks. Biopsy tissues were cut at 3µm on a microtome and the sections were mounted on Superfrost Plus slides and stored at 4 °C.

Glass slides with paraffin embedded sections were deparaffinated in xylene and rehydrated in series of graded ethanol. For Hematoxylin & Eosin (H&E) staining, slides are incubated in Mayer's Hematoxylin (Dako), washed in tap water, stained in Eosin Y solution (Sigma-Aldrich), dehydrated in graded ethanol and cover slipped. For Picrosirius red (PSR) staining, slides were incubated in Weigert's iron hematoxylin (Sigma-Aldrich), washed in tap water, stained in Picrosirius red (Sigma-Aldrich) and washed twice in acidified water. Excess water was removed by shaking the slides and the slides were then dehydrated in three changes of 100% ethanol, cleared in xylene and cover slipped. Immunohistochemistry (IHC) was performed using standard procedures. Briefly, after antigen retrieval and blocking of endogenous peroxidase activity, slides were incubated with primary antibody. The primary antibody was detected using a polymeric HRP-linker antibody conjugate. Next, the primary antibody was visualized with DAB as chromogen. Finally, sections were counterstained in hematoxylin and cover slipped. Slides were scanned under a 20x objective in a ScanScope AT slide scanner (Aperio).

Antibodies Used:

Antigen	Primary Antibody	Vendor
Colla1	Goat anti-type I Collagen	Southern Biotech, Cat. 1310-01
Galectin-3 (mouse)	Rat anti-Galectin 3	Biolegend, Cat. 125402
α-SMA	Rabbit anti-alpha smooth muscle actin [EPR5368]	Abcam, Cat. ab124964
CD45	Rabbit anti-CD45	AbCam, Cat. Ab10558

Liver samples stained with H&E or PSR were given a score for NAFLD Activity Score (NAS) and fibrosis stage, respectively, using the clinical criteria outlined by Kleiner et al. (Design and validation of a histological scoring system for nonalcoholic fatty liver disease, Hepatology, 2005) shown in the table below. Total NAS represents the sum of scores for steatosis, inflammation, and ballooning, and ranges from 0-8. NAS and fibrosis stage was determined by Gubra Histopathological Objective Scoring Technology (GHOST) deep learning app developed by Gubra using the VIS software (Visiopharm, Denmark) for a more accurate and objective method for staging disease in DIO-NASH mouse models. The app scores were reviewed by a histopathologist blinded to the results. Terminal liver biopsy histomorphometric analysis was also conducted by immunohistochemistry (IHC) for inflammation (Gal-3 and CD45), Collagen (Colla1), and activated stellate cells (α-SMA).

NAS Scoring:

Feature	Degree	Score
Steatosis (percentage of hepatocytes with lipid droplets)	<5%	0
	5-33%	1
	>33-66%	2
	>66%	3
Lobular inflammation	No foci	0
	<2 foci/200x	1
	2-4 foci/200x	2
	>4 foci/200x	3
Ballooning degeneration	None	0
	Few	1
	Many cells/prominent ballooning	2
Fibrosis stage	None	0
	Perisinusoidal or periportal	1
	Perisinusoidal and portal/periportal	2
	portal/periportal	3
	Bridging fibrosis	4
	Cirrhosis	

For mRNA extraction, 50 mg of mouse liver per animal was homogenized in lysis buffer and DTT (MagMAX™ mirVana™ Total RNA Isolation Kit, Thermo Fisher Scientific; Tissue Lyser II, QIAGEN). mRNA were isolated using an automated system (KingFisher Apex, Thermo Fisher Scientific), and cDNA synthesis was performed after genomic DNA removal (HiScript® III RT SuperMix for qPCR with gDNA wiper, Vazyme). qPCR was performed in technical triplicates, with TaqMan gene expression assays for the

target and the house keeping genes (Mm00846873_g1, Mm99999915_g1, Thermo Fisher Scientific) and a PCR kit (Universal PCR Master Mix, Roche), using the Applied Biosystems QuantStudio Flex by Thermo Fisher Scientific. Relative gene expression for each sample was calculated with the ddCt method, normalized to vehicle treated samples.

- 5 For protein extraction, 50 mg of mouse liver per animal was homogenized in RIPA buffer supplemented with protease inhibitor, phosphatase inhibitor and PMSF (Tissue Lyzer, QIAGEN). Protein digestion was performed with 100 ug of liver lysate per animal, using DTT and IAA as reductant and alkylation reagent. (S-Trap 96- well MS sample prep kit, ProtiFi). 500 ng of peptide per liver sample was run on a 60 min LC method in Easy Nano 1200 (mobile phase A: 0.1% formic acid in H₂O, mobile phase B: 0.1% formic acid in 80% acetonitrile). The separation gradient was: 7-18% B from 0 to 16 minutes, 18-40% B from 16 to 49 minutes, 40-100% B from 49-52 minutes and maintain at 100 % B to the end. A 25 cm of C18 column was used for peptide separation. The eluted peptide was analyzed with PRM-MS/MS method (Orbitrap Eclipse, Thermo Fisher Scientific). Candidate peptides were identified based on the following criteria: 1. Peptide must be unique for targeted protein; 2. Trypsin digested peptide with no missed cleavage; 3. Peptide with no potential modification sites; 4. M/Z range between 400-1000. The raw data was processed in Skyline, and the peptide quality was manually checked. The protein database from UniProt was used for the library search. Peptides were selected based on: 1. Elution peak without tailing; 2. Well-matched product ions; 3. Quantified peak area greater than 1e6. Consequently, the following two peptides: QIFLGGVDK and EQGVLSFWR were quantified. Relative abundance for each peptide in each liver sample was quantified by averaging the peak area of top three most intense product ions, normalized to the vehicle control, and relative abundances for the two peptides were averaged for final relative protein abundance.
- 10
- 15
- 20

As shown in Figures 10 and 11, the inhibitor ETX-312 resulted in a significant improvement of the NAFLD activity score (NAS). Of note, the effect obtained with ETX-312 was greater than the effects obtained with both positive controls, i.e., the GLP-1 agonist semaglutide and the THR-beta agonist resmetirom. Surprisingly, the most significant improvement was obtained when ETX-312 was combined with semaglutide or resmetirom.

25

ETX-312 significantly reduced levels of the blood markers ALT, AST, TIMP-1, and PIIINP, whether administered alone or in combination with semaglutide or resmetirom. The combination therapies demonstrated a significantly enhanced effect compared to monotherapies with semaglutide or resmetirom. Additionally, ETX-312, either alone or in combination with semaglutide or resmetirom, significantly improved hepatomegaly and plasma total cholesterol levels. The impact of the inhibitor ETX-312 on the blood markers ALT, AST, TIMP-1 and PIIINP is shown in Figures 12 and 13. The terminal liver weight to body weight ratio in DIO-NASH mice that received different treatments is shown in Figure 14.

30

EXAMPLE 10: FURTHER PHARMACOLOGICAL STUDY IN MICE

In this Example, the activity of ETX-312 (ETX-M00001378 also known as ETX-M00001751), an inhibitor of ANT2/SLC25A5, specifically expression of ANT2/SLC25A5 on metabolic parameters, hepatic pathology, NAFLD Activity Score (NAS) and fibrosis stage in male biopsy-confirmed GAN DIO-NASH mice was tested. A total of 6 DIO-NASH groups (n=18) and 1 LEAN-CHOW group (n=10) of male C57BL/6JRj mice were fed 40% HFD, 40% carbohydrate (22% fructose), 2% Cholesterol (GAN) diet (D09100310, Ssniff) or normal chow (Altromin 1324, Bro-garden) for 32 weeks prior to study start.

All mice were pre-biopsied at week -4 as per example 9 and stratified based on liver biopsy (only animals with fibrosis stage =F2-F3, steatosis score =3 and inflammation score ≥ 2 were included).

Animals were randomized into groups based on fibrosis stage and picrosirius red (PSR) staining (% fractional area). Mice received a total of 16 weeks of dosing and were divided into the following groups: 1) LEAN-CHOW control (saline) (subcutaneous (SC), once weekly (QW)), 2) DIO-NASH Vehicle (saline) (SC, QW), 3) ETX-312, 5 mg/kg (SC, QW), 4) Efruxifermin, 1 mg/kg (SC, QW), 5) Efruxifermin, 1 mg/kg (SC, QW) + ETX-312, 5 mg/kg (SC, QW), 6) Tirzepatide, 10 nmol/kg (SC, QD), 7) Tirzepatide, 10 nmol/kg (SC, QD) + ETX-312, 5 mg/kg (SC, QW). Efruxifermin was supplied as a stock solution of 4.8 mg/ml in 20 mM HEPES, 150 mM NaCl, 240 mM Sucrose, pH 7.2. It was diluted with 10 mM TRIS-base containing 2.32% l-lysine and 0.008% polysorbate 20 to desired concentration. Tirzepatide (hydrochloride) stock solution was prepared and then diluted to the required dosing solution in 50 mM phosphate buffer with 3.5% mannitol, pH 7.4. Efruxifermin was administered at 3 mg/kg for groups 4 and 5 on Day 1 and Day 7 then reduced to 1 mg/kg for all remaining doses. Tirzepatide was dose titrated during week 1 as follows to reach a final dose level of 10 nmol/kg for all remaining doses: 0.6 nmol/kg on Day 1, 1.2 nmol/kg on Day 2, 2.4 nmol/kg on Day 3, 4.8 nmol/kg on Day 4, and 10 nmol/kg on Day 5.

Body weight was recorded daily and food intake recorded once weekly for 24 hours during the study period.

At the end of the study period, plasma Alanine transaminase (ALT), Aspartate transaminase (AST), Triglycerides (TG) and Total Cholesterol (TC), TIMP-1 and PIIINP levels were measured as per example 9. One animal was excluded from TIMP-1 analysis due to high percent CV. PIIINP could be measured in 83 out of 117 samples due to small sample volume or readings below the limit of quantification.

After study termination, the liver was collected and weighed as per example 9. FFPE biopsies were prepared and stained, as per example 9.

NAFLD Activity Score (NAS) and fibrosis stage were calculated as per Example 9. Terminal liver biopsy histomorphometric analysis for inflammation (Gal-3 and CD45), collagen (Colla1), and activated stellate cells (α -SMA) was performed using immunohistochemistry (IHC) with the same antibodies as in Example 9. IHC-positive staining for each protein was quantified by image analysis with VIS software (Visiopharm, Denmark). Results for each protein were reported as a percent area fraction (PFA) with calculations both

including and excluding steatotic areas; data excluding steatotic areas were presented separately. Total estimation (PFA multiplied by liver weight) was calculated only for values including steatotic areas to provide an overall quantification.

The quantitative estimates of PSR-positive staining were calculated by image analysis using the VIS software (Visiopharm, Denmark), including or excluding steatotic areas (ie. with or without steatosis). Results excluding steatotic areas were reported as delta area fractions between pre-treatment and post-treatment biopsies for evaluating fibrosis progression and/or reversal.

Post-dosing liver tissues were collected for assessment of the target gene expression (50 +/- 10 mg per piece). Tissue samples collected for mRNA analysis were stored in RNeasy lysis buffer for 24 hours at 4°C, and then stored at -70°C after removal of RNeasy lysis buffer, while tissue samples collected for protein analysis were quick frozen in liquid nitrogen and stored at -70°C. Samples were shipped to Wuxi AppTec where they were processed.

The mRNA extraction and RT-PCR were performed as per Example 9, with the AceQ Universal U+ Probe Master Mix V2 by Vazyme, using the Applied Biosystems QuantStudio Flex by Thermo Fisher Scientific. Relative gene expression for each sample was calculated with the ddCt method, normalized to vehicle treated samples.

Protein extraction and digestion were performed as per Example 9. 500 ng of peptide per liver sample was run on a 65 min LC method in Easy Nano Vanquish (mobile phase A: 0.1% formic acid in H₂O, mobile phase B: 0.1% formic acid in acetonitrile). The separation gradient was: 4% B hold for 2 minutes, 4-12% B from 2 to 17 minutes, 12-32 % B from 17 to 57 minutes, 32-90% B from 57-60 minutes and maintain at 90 % B to the end. A 25 cm of C18 column was used for peptide separation. The eluted peptide was analyzed with PRM-MS/MS method (Orbitrap explorer 240, Thermo Fisher Scientific). Selected peptides were quantified, and data analysis for calculating relative protein abundances was carried out as per Example 9.

Statistical analyses were performed as per Example 9 except for ALT and AST endpoints which were log-transformed for statistical analysis due to observed positive skew. Transformations were supported by significant ($p < 0.05$) improvements in fitted model log-likelihoods. Additionally, outlier analyses were carried out for each measurand as follows: studentized residuals from the linear models were extracted and used to calculate p-values for all observations, which were subsequently adjusted for multiple comparisons via the FDR method. Any observation corresponding to a $p\text{-value} \leq 0.05$ was excluded from analysis. Specifically, the exclusions included one animal from TG, one animal from mRNA, three animals from CD45-positive fractional area, one animal from total CD45 estimations, and one animal from lipid fractional area analyses.

The inhibitor ETX-312, as demonstrated in Figure 23 and Figure 24, significantly improved the NAFLD activity score (NAS). Notably, the most pronounced effect occurred when ETX-312 administered in

combination with Efruxifermin or Tirzepatide. The observed reduction in NAS was primarily driven by decreases in steatosis and lobular inflammation, as evidenced by reductions in liver lipid content (Figure 25 and Figure 26), as well as post-treatment biopsy inflammatory foci density, lobular inflammation score and CD45 staining (Figure 27).

- 5 As shown in Figure 19, the inhibitor ETX-312 resulted in a significant improvement of the blood markers ALT and AST, alone or in combination with Efruxifermin or Tirzepatide. Figure 21 depicts the terminal liver weight to body weight ratio in DIO-NASH mice that received different treatments showing that ETX-312 alone or in combination with Efruxifermin or Tirzepatide significantly reduced hepatomegaly. As shown in Figure 28 and Figure 29, ETX-312 also slowed fibrosis progression, both as a monotherapy and
- 10 in combination, with a trend toward less 1-point worsening of fibrosis stage and smaller increase in PSR staining compared to the Vehicle control. The inhibitor also, whether used alone or in combination, effectively lowered plasma and tissue markers of fibrogenesis and fibrosis, underscoring its impact on fibrosis progression. This is evidenced by reductions in TIMP-1 and PIIINP (Figure 20) and by decreases in Col1a1 and α -SMA (Figure 30 and Figure 31).
- 15 ETX-312 alone or in combination with either Efruxifermin or Tirzepatide reduced plasma total cholesterol levels as shown in Figure 22.

Weekly treatment with ETX-312 for 16 weeks reduced target expression in the liver by approximately 90% at both the mRNA and protein levels, confirming its ability to inhibit the intended target (Figure 32 and Figure 33).

- 20 The present invention is not intended to be limited in scope to the particular disclosed embodiments, which are provided, for example, to illustrate various aspects of the invention. Various modifications to the compositions and methods described will become apparent from the description and teachings herein. Such variations may be practiced without departing from the true scope and spirit of the disclosure and are intended to fall within the scope of the present disclosure.

CLAIMS

1. An inhibitor of expression and / or function of SLC25A5/ANT2, for use in a method of prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in a method of reducing adipogenesis, wherein the method comprises administering the inhibitor and administering at least one other therapeutic agent.
2. A method of prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or a method of reducing adipogenesis, the method comprising administering the inhibitor and administering at least one other therapeutic agent.
3. A combination comprising an inhibitor of expression and / or function of SLC25A5/ANT2 and at least one other therapeutic agent.
4. An inhibitor of expression and / or function of SLC25A5/ANT2, wherein said inhibitor is conjugated to one or more ligand moieties and is to be used in combination with at least one other therapeutic agent.
5. The inhibitor for use according to claim 1, the method according to claim 2, the combination according to claim 3 or the inhibitor of claim 4, wherein said inhibitor is an siRNA oligomer.
6. The inhibitor for use, method, combination or inhibitor according to claim 5, wherein said inhibitor comprises an siRNA oligomer conjugated to one or more ligand moieties.
7. The inhibitor for use, method, combination or inhibitor according to any one of the preceding claims, wherein the at least one other therapeutic agent comprises a GLP-1 agonist and/or a THR-beta agonist.
8. The inhibitor for use, method, combination or inhibitor according to any one of the preceding claims, wherein the at least one other therapeutic agent comprises a GLP-1 agonist and/or an FGF-21 analogue.
9. The inhibitor for use, method, combination or inhibitor according to claim 7 or claim 8, wherein the GLP-1 agonist is a GLP-1/GIP dual agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR dual agonist, or a GLP-1/GIP/GCGR triple agonist.
10. The inhibitor for use, method, combination or inhibitor according to any one of claims 7-9, wherein the GLP-1 agonist is semaglutide.

11. The inhibitor for use, method, combination or inhibitor according to any one of claims 7-9, wherein the GLP-1/GIP dual agonist is tirzepatide.
12. The inhibitor for use, method, combination or inhibitor according to any one of claims 7 and 9-11, wherein the THR-beta agonist is resmetirom.
- 5 13. The inhibitor for use, method, combination or inhibitor according to any one of claims 8-11, wherein the FGF-21 analogue is efruxifermin.
14. The inhibitor for use, method, combination or inhibitor according to any one of the preceding claims, wherein the at least one other therapeutic agent comprises one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belapectin), and/or a PPAR α agonist (such as elafibrinor), and/or a PPAR γ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPAR α and/or δ and/or γ agonist, and/or a pan PPAR $\alpha\gamma\delta$ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).
- 10 15. The inhibitor for use, method, combination or inhibitor according to any one of claims 4-14, wherein said one or more ligand moieties comprise one or more GalNAc ligands or comprise one more GalNAc ligand derivatives.
16. The inhibitor for use, method, combination or inhibitor according to one or more preceding claims, wherein the target of the inhibitor is SLC25A5/ANT2.
- 25 17. The inhibitor for use, method, combination or inhibitor according to one or more preceding claims, wherein the inhibitor is an siRNA oligomer having a first and a second strand wherein:
- i) the first strand of the siRNA has a length in the range of 15 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 23 or 25; even more preferably 23; and / or
- ii) the second strand of the siRNA has a length in the range of 15 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 21 nucleosides.
- 30 18. The inhibitor for use, method, combination or inhibitor according to claim 17, wherein the second sense strand further comprises one or more abasic nucleosides in a terminal region of the second strand,

and wherein said abasic nucleoside(s) is / are connected to an adjacent nucleoside through a reversed internucleoside linkage.

19. The inhibitor for use, method, combination or inhibitor according to claim 18, wherein the second strand comprises:

- 5 i 2, or more than 2, abasic nucleosides in a terminal region of the second strand; and / or
- ii 2, or more than 2, abasic nucleosides in either the 5' or 3' terminal region of the second strand; and / or
- iii 2, or more than 2, abasic nucleosides in either the 5' or 3' terminal region of the second strand, wherein the abasic nucleosides are present in an overhang as herein described; and / or
- 10 iv 2, or more than 2, consecutive abasic nucleosides in a terminal region of the second strand, wherein preferably one such abasic nucleoside is a terminal nucleoside; and / or
- v 2, or more than 2, consecutive abasic nucleosides in either the 5' or 3' terminal region of the second strand, wherein preferably one such abasic nucleoside is a terminal nucleoside in either the 5' or 3' terminal region of the second strand; and / or
- 15 vi a reversed internucleoside linkage connects at least one abasic nucleoside to an adjacent basic nucleoside in a terminal region of the second strand; and / or
- vii a reversed internucleoside linkage connects at least one abasic nucleoside to an adjacent basic nucleoside in either the 5' or 3' terminal region of the second strand; and / or
- viii an abasic nucleoside as the penultimate nucleoside which is connected via the reversed linkage to the nucleoside which is not the terminal nucleoside (called the antepenultimate nucleoside herein); and / or
- 20 ix abasic nucleosides as the 2 terminal nucleosides connected via a 5'-3' linkage when reading the strand in the direction towards that terminus;
- x abasic nucleosides as the 2 terminal nucleosides connected via a 3'-5' linkage when reading the strand in the direction towards the terminus comprising the terminal nucleosides;
- 25 xi abasic nucleosides as the terminal 2 positions, wherein the penultimate nucleoside is connected via the reversed linkage to the antepenultimate nucleoside, and wherein the reversed linkage is a 5-5' reversed linkage or a 3'-3' reversed linkage;
- xii abasic nucleosides as the terminal 2 positions, wherein the penultimate nucleoside is connected via the reversed linkage to the antepenultimate nucleoside, and wherein either
- 30

(1) the reversed linkage is a 5-5' reversed linkage and the linkage between the terminal and penultimate abasic nucleosides is 3'5' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides; or

5 (2) the reversed linkage is a 3-3' reversed linkage and the linkage between the terminal and penultimate abasic nucleosides is 5'3' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides.

20. The inhibitor for use, method, combination or inhibitor according claim 18 or 19, wherein the reversed internucleoside linkage is at a terminal region which is distal to the 5' terminal region of the second strand, or at a terminal region which is distal to the 3' terminal region of the second strand.

10 21. The inhibitor for use, method, combination or inhibitor according to any one of claims 18 to 20, wherein the reversed internucleoside linkage is a 3'3 reversed linkage.

22. The inhibitor for use, method, combination or inhibitor according to any one of claims 18 to 20, wherein the reversed internucleoside linkage is a 5'5 reversed linkage.

15 23. The inhibitor for use, method, combination or inhibitor according to any one of claims 17 to 22, wherein one or more nucleosides on the first strand and / or the second strand is / are modified, to form modified nucleosides.

24. The inhibitor for use, method, combination or inhibitor according to claim 23, wherein the modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

20 25. The inhibitor for use, method, combination or inhibitor according to claim 23 or 24, wherein the first strand comprises a 2'-F at any of position 14, position 2, position 6, or any combination thereof, counting from position 1 of said first strand.

25 26. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 25, wherein the second strand comprises a 2'-F modification at position 7 and / or 9, and / or 11 and / or 13, counting from position 1 of said second strand.

27. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 26, wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

30 28. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 27, wherein the inhibitor is an siRNA, wherein the siRNA comprises at least one thermally destabilizing modification, suitably at one or more of positions 1 to 9 of the first strand counting from position 1 of the first strand, and / or at one or more of positions on the second strand aligned with positions 1 to 9 of the

first strand, wherein the destabilizing modification is selected from a modified unlocked nucleic acid (UNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid.

29. The inhibitor for use, method, combination or inhibitor according to claim 28, wherein the siRNA comprises at least one thermally destabilizing modification at position 7 of the first strand, counting from position 1 of the first strand.

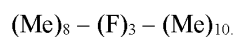
30. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 29, wherein the inhibitor is an siRNA, wherein the siRNA comprises 3 or more 2'-F modifications at positions 7 to 13 of the second strand, such as 4, 5, 6 or 7 2'-F modifications at positions 7 to 13 of the second strand, counting from position 1 of said second strand

31. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 30, wherein the inhibitor is an siRNA, wherein said second strand comprises at least 3, such as 4, 5 or 6, 2'-Me modifications at positions 1 to 6 of the second strand, counting from position 1 of said second strand.

32. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 31, wherein the inhibitor is an siRNA, wherein said first strand comprises at least 5 2'-Me consecutive modifications at the 3' terminal region, preferably including the terminal nucleoside at the 3' terminal region, or at least within 1 or 2 nucleosides from the terminal nucleoside at the 3' terminal region.

33. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 32, wherein the inhibitor is an siRNA wherein said first strand comprises 7 2'-Me consecutive modifications at the 3' terminal region, preferably including the terminal nucleoside at the 3' terminal region.

34. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 29, wherein the inhibitor is an siRNA, wherein said modified nucleosides of said second strand comprise a modification pattern according to any one of the following (5'-3'):



35. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 29 or 34, wherein the inhibitor is an siRNA, wherein nucleosides of said first strand comprise a 2' sugar modification pattern wherein said modifications are selected at least from 2'-Me and 2'-F sugar modifications, provided that the overall number of 2'-F sugar modifications in the first strand does not consist of four, or six, 2'-F modifications.

36. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 29 or 34 to 35, wherein the inhibitor is an siRNA, wherein said modifications are selected at least from 2'-Me and 2'-F sugar modifications, wherein the overall number of 2'-F sugar modifications in the first strand consists of three, five or seven 2'-F modifications.

37. The inhibitor for use, method, combination or inhibitor according to any one of claims 23 to 36, wherein the siRNA oligomer further comprises one or more phosphorothioate internucleoside linkages.

38. The inhibitor for use, method, combination or inhibitor according to claim 37, wherein said one or more phosphorothioate internucleoside linkages are respectively between at least three consecutive positions in a 5' or 3' near terminal region of the second strand, whereby said near terminal region is preferably adjacent said terminal region wherein said one or more abasic nucleosides of said second strand is / are located according to at least claim 18.

39. The inhibitor for use, method, combination or inhibitor according to claim 37 or 38, wherein said one or more phosphorothioate internucleoside linkages are respectively between at least three consecutive positions in a 5' and / or 3' terminal region of the first strand, whereby preferably a terminal position at the 5' and / or 3' terminal region of said first strand is attached to its adjacent position by a phosphorothioate internucleoside linkage.

40. The inhibitor for use, method, combination or inhibitor according to any one of claims 17 to 39, wherein the oligomer is an siRNA and the second strand of the siRNA is conjugated directly or indirectly to one or more ligand moiety(s), wherein said ligand moiety is typically present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

41. The inhibitor for use, method, combination or inhibitor according to claim 40, wherein the ligand moiety comprises

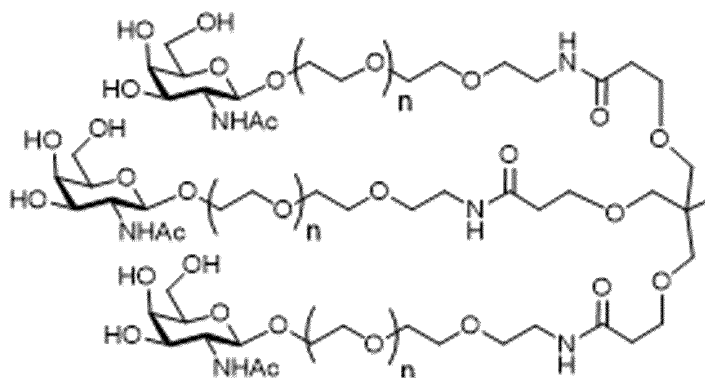
i) one or more GalNAc ligands; and / or

ii) one or more GalNAc ligand derivatives; and / or

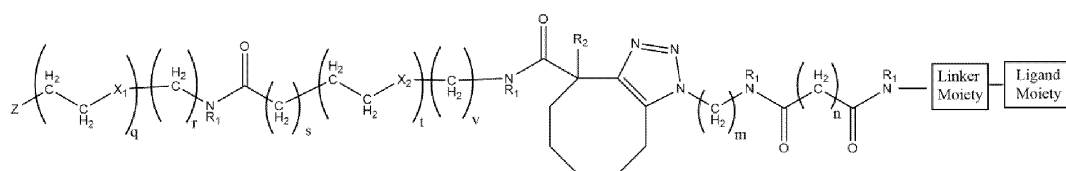
iii) one or more GalNAc ligands and / or GalNAc ligand derivatives conjugated to said siRNA through a linker.

42. The inhibitor for use, method, combination or inhibitor wherein said one or more GalNAc ligands and / or GalNAc ligand derivatives are conjugated directly or indirectly to the 5' or 3' terminal region of the second strand of the siRNA oligomer, preferably at the 3' terminal region thereof.

43. The inhibitor for use, method, combination or inhibitor according to claim 41 or 42, wherein the ligand moiety comprises:



44. The inhibitor for use, method, combination or inhibitor according to claim 41 or 42, wherein the inhibitor has the structure:



5 wherein:

R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

R_2 is selected from the group consisting of hydrogen, hydroxy, $-OC_{1-3}alkyl$, $-C(=O)OC_{1-3}alkyl$, halo and nitro;

10 X_1 and X_2 at each occurrence are independently selected from the group consisting of methylene, oxygen and sulfur;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

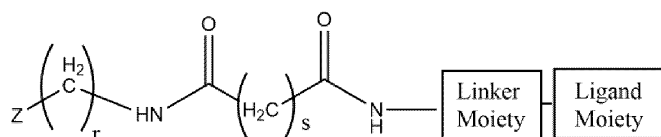
q , r , s , t , v are independently integers from 0 to 4, with the proviso that:

(i) q and r cannot both be 0 at the same time; and

15 (ii) s , t and v cannot all be 0 at the same time;

Z is an oligomer

45. The inhibitor for use, method, combination or inhibitor according to claim 41 or 42, wherein the inhibitor has the structure:



wherein:

r and s are independently an integer selected from 1 to 16; and

Z is an oligomer.

46. The inhibitor for use, method, combination or inhibitor according to one or more preceding claims, wherein the inhibitor is formulated as a pharmaceutical composition with an excipient and / or carrier.

47. The inhibitor for use, method, combination or inhibitor according to any one of the preceding claims, wherein the inhibitor and the at least one other therapeutic agent are for concurrent, sequential or separate administration, or are administered concurrently, sequentially or separately.

48. The combination or inhibitor of any one of claims 3-47, for use in prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis.

49. The inhibitor for use, method, combination, inhibitor or combination for use according to any one of the preceding claims, wherein the therapeutic agent is a GLP-1 agonist, a THR-beta agonist, and/or an FGF-21 analogue.

50. A pharmaceutical composition comprising an inhibitor as defined in any one of the preceding claims, in combination with a pharmaceutically acceptable excipient or carrier, for use in a method of prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in a method of reducing adipogenesis, wherein the method comprises administering the pharmaceutical composition and administering at least one other therapeutic agent.

51. A method of prevention and/or treatment of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or a method of reducing adipogenesis, the method comprising administering a pharmaceutical composition comprising an inhibitor as defined in any one of the preceding claims, in combination with a pharmaceutically acceptable excipient or carrier, and administering at least one other therapeutic agent.

52. A pharmaceutical composition comprising a combination comprising an inhibitor as defined in any one of the preceding claims and at least one other therapeutic, in combination with a pharmaceutically acceptable excipient or carrier.

53. A pharmaceutical composition comprising an inhibitor as defined in any one of the preceding
5 claims in combination with a pharmaceutically acceptable excipient or carrier, wherein the inhibitor is conjugated to one or more ligand moieties and wherein the pharmaceutical composition to be used in combination with at least one other therapeutic agent.

54. The pharmaceutical composition of claim 52 or claim 53, for use in prevention and/or treatment
10 of metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or for use in reducing adipogenesis. 55. The pharmaceutical composition or pharmaceutical composition for use according to any one of claims 52-54, wherein the at least one or therapeutic agent comprises a GLP-1 agonist and/or a THR-beta agonist.

56. The pharmaceutical composition or pharmaceutical composition for use according to any one of
15 claims 52-55, wherein the at least one or therapeutic agent comprises a GLP-1 agonist and/or an FGF-21 analogue.

57. The pharmaceutical composition or pharmaceutical composition for use according to claim 55 or claim 56, wherein the GLP-1 agonist is a GLP-1/GIP dual agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR dual agonist, or a GLP-1/GIP/GCGR triple agonist.

20 58. The pharmaceutical composition for use according to any one of claims 55-57, wherein the GLP-1 agonist is semaglutide.

59. The pharmaceutical composition for use according to any one of claims 55-57, wherein the GLP-1/GIP dual agonist is tirzepatide.

60. The pharmaceutical composition for use according to any one of claims 55 and 57-59, wherein the
25 THR-beta agonist is resmetirom.

61. The pharmaceutical composition for use according to any one of claims 56 to 59, wherein the FGF-21 analogue is efruxifermin.

62. The pharmaceutical composition or pharmaceutical composition for use according to any one of
30 claims 52-54, wherein the composition is to be used in combination with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist

- (such as aldafermin), and/or a galectin 3 inhibitor (such as belaepectin), and/or a PPAR α agonist (such as elafibrinor), and/or a PPAR γ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPAR α and/or δ and/or γ agonist, and/or a pan PPAR $\alpha\gamma\delta$ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab),
- 5 and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).
- 10 63. A method according to any one of claims 2, 5-47 and 49, wherein the inhibitor of SLC25A5/ANT2 is administered together with a GLP-1 agonist and/or a THR-beta agonist.
64. A method according to any one of claims 2, 5-47 and 49, wherein the inhibitor of SLC25A5/ANT2 is administered together with a GLP-1 agonist and/or an FGF-21 analogue.
65. A method according to claim 63 or claim 64, wherein the GLP-1 agonist is a GLP-1/GIP dual
15 agonist, a GLP-1/FGF21 dual agonist, a GLP-1/GCGR dual agonist, or a GLP-1/GIP/GCGR triple agonist.
66. A method according to any one of claims 63 to 65, wherein the GLP-1 agonist is semaglutide.
67. A method according to any one of claims 63 to 65, wherein the GLP-1/GIP dual agonist is tirzepatide.
68. A method according to any one of claims 63 and 65 to 67, wherein the THR-beta agonist is
20 resmetirom.
69. A method according to any one of claims 64 to 67, wherein the FGF-21 analogue is efruxifermin.
70. A method according to any one of claims 62 to 69, wherein the inhibitor is to be used in combination with one or more of: an amylin receptor agonist (such as pramlintide), and/or a dual amylin + calcitonin receptor agonist, and/or a glucagon receptor agonist, and/or an FXR receptor agonist (such as cilofexor or obeticholic acid), and/or an FGF-21 analogue or FGF-21 receptor agonist (such as efruxifermin), and/or an FGF-19 analogue or FGF-19 receptor agonist (such as aldafermin), and/or a galectin 3 inhibitor (such as belaepectin), and/or a PPAR α agonist (such as elafibrinor), and/or a PPAR γ agonist (such as pioglitazone or rosiglitazone), and/or a mixed PPAR α and/or δ and/or γ agonist, and/or a pan PPAR $\alpha\gamma\delta$ agonist (such as lanafibranor), and/or an acetyl CoA desaturase activator, and/or an ASK1
25 inhibitor (such as selonsertib), and/or an LOXL2 inhibitor (such as simtuzumab), and/or a dual CCR2/5 inhibitor (such as cenicriviroc), and/or an inhibitor of an enzyme in the de novo lipogenesis (DNL) pathway including citrate/isocitrate carrier (CIC), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and
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fatty acid synthase (FAS), and/or an inhibitor of an enzyme in the cholesterol biosynthesis pathway (such as an HMGCoA reductase inhibitor, such as atorvastatin).

71. A method of predicting susceptibility to a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis and/or in reducing adipogenesis in a patient, said method comprising:

- (a) obtaining a sample from the patient,
- (b) detecting the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,
- (c) predicting susceptibility to a disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis, based on the sequence and / or expression and / or function of SLC25A5/ANT2 in said sample obtained from the patient,
- (d) preferably administering to the diagnosed patient an effective amount of an inhibitor of SLC25A5/ANT2 and at least one other therapeutic agent.

72. An inhibitor, inhibitor for use, combination, combination for use, composition or composition for use according to any one of claims 1, 3-50 and 52-62, in the preparation of a medicament for use in the treatment of a metabolic disease or disorder, such as a metabolic disease or disorder associated with non-alcoholic fatty liver disease (NAFLD) and/or obesity and/or a disease or disorder associated with adipogenesis.

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74. A kit comprising an inhibitor as defined in any one of the preceding claims and at least one other therapeutic agent as defined in any one of the preceding claims.