INHIBITORS OF EXPRESSION AND/OR FUNCTION

TECHNICAL FIELD

[0001] The disclosure relates generally to biology and medicine, and more particularly it provides inhibitors, such as nucleic acid compounds, such as siRNA, suitable for therapeutic use. Such use is the inhibition, reduction, or beneficial modulation certain gene(s). Additionally, the present invention provides methods of making these compounds, as well as methods of using such compounds for the treatment of various diseases and conditions.

BACKGROUND OF THE INVENTION

[0002] 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 responsible for a particular disease, condition or related disorder. Gene-silencing prevents formation of a protein by inhibiting translation. Importantly, gene-silencing agents are a promising alternative to traditional small, organic compounds that inhibit the function of the protein linked to the disease. siRNA, antisense RNA, and micro-RNA are oligonucleoside/oligonucleotides that prevent the formation of proteins by gene-silencing.

[0003] 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 liver diseases, central-nervous-system diseases, inflammatory diseases, metabolic disorders, oncology, infectious diseases, and ocular diseases.

[0004] The present invention relates to inhibitors, such oligomers *e.g.*, nucleic acids, *e.g.*, oligonucleoside / oligonucleotide compounds, and their use in the treatment and / or prevention of disease.

[0005] The present invention relates to nucleic acid compounds that inhibit the expression of the gene NR3C2, for use in the treatment and / or prevention of disease.

[0006] In humans the NR3C2 gene is located on chromosome 4 at q31.23 and encodes the nuclear receptor subfamily 3 group C member 2 protein, also known as mineralocorticoid receptor. The protein functions as a ligand-dependent transcription factor that mediates the effects of aldosterone in a variety of target tissues, including the distal parts of the nephron, the distal colon, the cardiovascular and central nervous systems, and brown adipose tissue. In addition, the target tissues include the heart and liver.

STATEMENTS OF INVENTION

[0007] The invention is defined as in the claims and relates to, *inter alia*:

[0008] In one aspect (Aspect A), there is provided a nucleic acid for inhibiting expression of NR3C2, comprising 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 NR3C2 gene, and (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

[0009] In a further aspect (Aspect B), there is provided a nucleic acid for inhibiting expression of NR3C2, comprising 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 NR3C2 gene, and (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand modified sequences as listed in Table 3.

[0010] In a further aspect, there is provided a nucleic acid as described herein, wherein the first strand comprises nucleosides 2-18 of any one of the sequences according to the above Aspect A or Aspect B of the present invention, in particular wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in Tables 2 or 3.

[0011] In a further aspect, there is provided a nucleic acid according to the above Aspect A of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0012] In a further aspect, there is provided a nucleic acid according to the above Aspect B of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0013] In a further aspect, there is provided a nucleic acid according to the above Aspect A of the present invention, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

[0014] In a further aspect, there is provided a nucleic acid according to the above Aspect B of the present invention, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.

[0015] In a further aspect, there is provided a nucleic acid according to the above Aspect A of the present invention, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

[0016] In a further aspect, there is provided a nucleic acid according to the above Aspect B of the present invention, wherein the second strand comprises any one of the second strand modified sequences as listed in Table 4.

[0017] In a further aspect, there is provided a nucleic acid according to the invention, wherein the first strand has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 23 nucleosides.

[0018] In a further aspect, there is provided a nucleic acid according to the invention, wherein the second strand has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 21 or 23 nucleosides.

[0019] In a further aspect, there is provided a nucleic acid according to the invention, wherein the duplex region of the nucleic acid is between 17 and 30 nucleosides in length, more preferably is 19 or 21 or 23 nucleosides in length.

[0020] In a further aspect, there is provided a nucleic acid according to the invention, wherein the region of complementarity between the first strand and the portion of RNA transcribed from the NR3C2 gene is between 17 and 30 nucleosides in length.

[0021] In a further aspect, there is provided a nucleic acid according to the invention, wherein the nucleic acid further comprises one or more single-stranded nucleoside overhangs, optionally wherein the overhang is present on the first or second strand, preferably at the 3' terminus of the first or second strand, and/or wherein the overhang comprises 1 to 4 nucleosides, more preferably 2 nucleosides.

[0022] In a further aspect, there is provided a nucleic acid according to the invention, wherein the nucleic acid is an siRNA oligonucleoside.

[0023] In a further aspect, there is provided a nucleic acid according to the invention, wherein 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 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.

[0024] In a further aspect, there is provided a nucleic acid according to the invention, wherein:

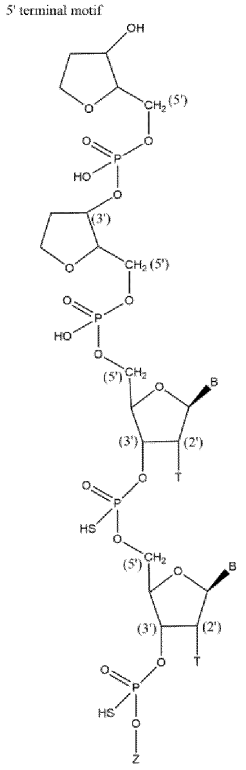
(i) the first strand and the second strand each has a length of 23 nucleosides;

(ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 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 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.

[0025] In a further aspect, there is provided a nucleic acid according to the invention, wherein the 2 consecutive inverted abasic nucleosides in the 5' terminal region of the second strand present as the following 5' terminal motif:



wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of the second strand, and

Z represents the remaining 19 contiguous basic nucleosides of said second strand.

[0026] In a further aspect, there is provided a nucleic acid according to the invention, wherein the nucleic acid is conjugated directly or indirectly to one or more ligand moieties, optionally wherein said ligand moiety is present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

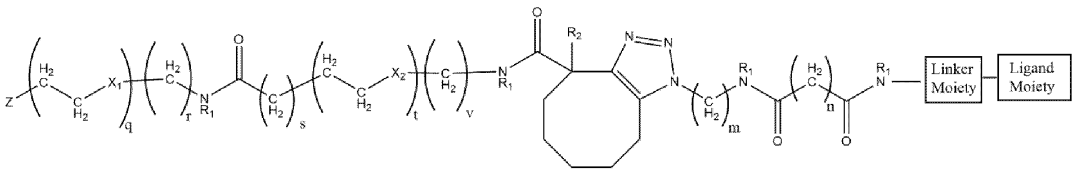
[0027] In a further aspect, there is provided a nucleic acid according to the invention, wherein the ligand moiety comprises:

(i) one or more N-acetyl galactosamine (GalNAc) ligands, and / or

(ii) one or more N-acetyl galactosamine (GalNAc) ligand derivatives.

[0028] In a further aspect, there is provided a nucleic acid 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 nucleic acid, preferably at the 3' terminal region thereof.

[0029] In a further aspect, there is provided a nucleic acid according to the invention, comprising the structure:



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;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

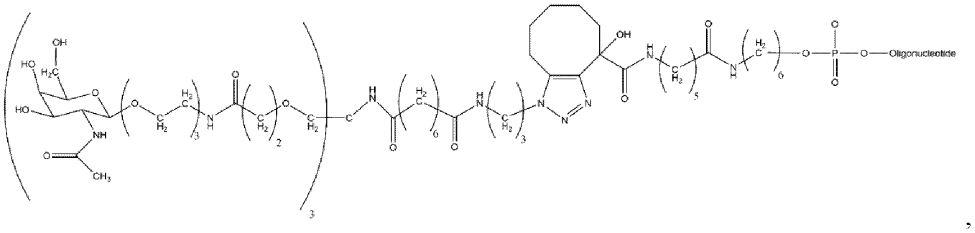
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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;

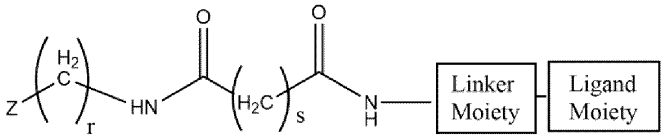
Z is an oligonucleoside moiety.

[0030] In a further aspect, there is provided a nucleic acid according to the invention, comprising the structure:



wherein oligonucleotide represents the contiguous nucleosides of the second strand.

[0031] In a further aspect, there is provided a nucleic acid according to the invention, comprising the structure:

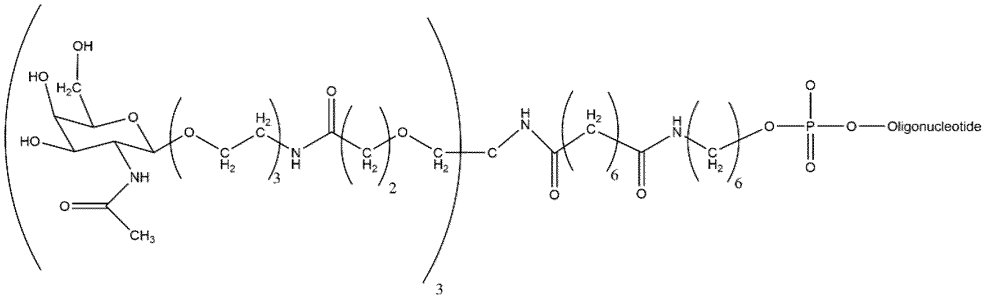


wherein:

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

Z is an oligonucleoside moiety.

[0032] In a further aspect, there is provided a nucleic acid according to the invention, comprising the structure:



,

wherein oligonucleotide represents the contiguous nucleosides of the second strand.

[0033] In a further aspect, there is provided a nucleic acid according to the invention, wherein the structure is conjugated to the 3' terminal region of the second strand.

[0034] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 290, SEQ ID NO: 270, SEQ ID NO: 238, SEQ ID NO: 245, SEQ ID NO: 283, SEQ ID NO: 235, SEQ ID NO: 226, SEQ ID NO: 335, SEQ ID NO: 228 or SEQ ID NO: 410.

[0035] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 290, SEQ ID NO: 270, SEQ ID NO: 238, SEQ ID NO: 245 or SEQ ID NO: 283.

[0036] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 290.

[0037] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 270.

[0038] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 736, SEQ ID NO: 716, SEQ ID NO: 684, SEQ ID NO: 691, SEQ ID NO: 729, SEQ ID NO: 681, SEQ ID NO: 672, SEQ ID NO: 781, SEQ ID NO: 674 or SEQ ID NO: 856.

[0039] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 736, SEQ ID NO: 716, SEQ ID NO: 684, SEQ ID NO: 691 or SEQ ID NO: 729.

[0040] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 736.

[0041] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 716.

[0042] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 513, SEQ ID NO: 493, SEQ ID NO: 461, SEQ ID NO: 468, SEQ ID NO: 506, SEQ ID NO: 458, SEQ ID NO: 449, SEQ ID NO: 558, SEQ ID NO: 451 or SEQ ID NO: 633.

[0043] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 513, SEQ ID NO: 493, SEQ ID NO: 461, SEQ ID NO: 468 or SEQ ID NO: 506.

[0044] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO: 513.

[0045] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO: 493.

[0046] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 959, SEQ ID NO: 939, SEQ ID NO: 907, SEQ ID NO: 914, SEQ ID NO: 952, SEQ ID NO: 904, SEQ ID NO: 895, SEQ ID NO: 1004, SEQ ID NO: 897, SEQ ID NO: 897 or SEQ ID NO: 1079.

[0047] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 959, SEQ ID NO: 939, SEQ ID NO: 907, SEQ ID NO: 914 or SEQ ID NO: 952.

[0048] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO: 959.

[0049] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO: 939.

[0050] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513
SEQ ID NO: 270	SEQ ID NO: 493
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 283	SEQ ID NO: 506
SEQ ID NO: 235	SEQ ID NO: 458
SEQ ID NO: 226	SEQ ID NO: 449
SEQ ID NO: 335	SEQ ID NO: 558
SEQ ID NO: 228	SEQ ID NO: 451
SEQ ID NO: 410	SEQ ID NO: 633

[0051] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513
SEQ ID NO: 270	SEQ ID NO: 493
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 283	SEQ ID NO: 506

[0052] In a further aspect, the invention relates to an inhibitor according to the invention, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513

[0053] In a further aspect, the invention relates to an inhibitor according to the invention, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 270	SEQ ID NO: 493

[0054] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 736	SEQ ID NO: 959
SEQ ID NO: 716	SEQ ID NO: 939
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 729	SEQ ID NO: 952
SEQ ID NO: 681	SEQ ID NO: 904
SEQ ID NO: 672	SEQ ID NO: 895
SEQ ID NO: 781	SEQ ID NO: 1004
SEQ ID NO: 674	SEQ ID NO: 897
SEQ ID NO: 856	SEQ ID NO: 1079

[0055] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 736	SEQ ID NO: 959
SEQ ID NO: 716	SEQ ID NO: 939
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 729	SEQ ID NO: 952

[0056] In a further aspect, the invention relates to an inhibitor according to the invention, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Modified first strand	Modified second strand
SEQ ID NO: 736	SEQ ID NO: 959

[0057] In a further aspect, the invention relates to an inhibitor according to the invention, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Modified first strand	Modified second strand
SEQ ID NO: 716	SEQ ID NO: 939

[0058] In a further aspect, there is provided a conjugate for inhibiting expression of NR3C2 target gene in a cell, said conjugate comprising a nucleic acid as disclosed herein and one or more ligand moieties.

[0059] In a further aspect, there is provided a pharmaceutical composition comprising a nucleic acid as disclosed herein, in combination with a pharmaceutically acceptable excipient or carrier.

[0060] In a further aspect, there is provided a nucleic acid or pharmaceutical composition, for use in therapy.

[0061] In a further aspect, there is provided a nucleic acid or pharmaceutical composition, for use in the treatment of heart failure with reduced ejection fraction (HFrEF), such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or for use in the treatment of heart failure with preserved ejection fraction (HFpEF) and/or symptoms thereof.

[0062] In a further aspect, there is provided a nucleic acid or pharmaceutical composition as disclosed herein, wherein the nucleic acid or the pharmaceutical composition is administered after myocardial infarction.

[0063] In one aspect, the invention relates to an inhibitor of expression and / or function of NR3C2, wherein said inhibitor is conjugated to one or more ligand moieties.

[0064] In a further aspect, the invention relates to an inhibitor according to the invention, wherein said inhibitor is an siRNA oligomer.

[0065] In another aspect, the invention relates to an inhibitor of expression and / or function of NR3C2, wherein said inhibitor is an siRNA oligomer.

[0066] 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.

[0067] In a further aspect, the invention relates to an inhibitor according to the invention, for use in prevention or treatment of an ischaemic heart disease, such as myocardial infarction.

[0068] In a particular aspect of the invention, the inhibitor according to the invention is for use in the treatment of an ischaemic heart disease, such as myocardial infarction, whereby the inhibitor alleviates symptoms of an ischaemic heart disease, in particular myocardial infarction, more particularly an acute myocardial infarction. Within the present invention, the inhibitor of the invention may be administered after myocardial infarction, in particular for cardioprotection, for reducing infarct size and/or reducing reperfusion arrhythmias.

[0069] In a particular aspect of the invention, the inhibitor according to the invention is for use in the treatment of heart failure with reduced ejection fraction (HFrEF) and/or heart failure with preserved ejection fraction (HFpEF).

[0070] 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.

[0071] 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.

[0072] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the target of the inhibitor is NR3C2.

[0073] In a further aspect (Aspect C), there is provided a nucleic acid for inhibiting expression of NR3C2, comprising 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 NR3C2 gene, and (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

[0074] In a further aspect (Aspect D), there is provided a nucleic acid for inhibiting expression of NR3C2, comprising 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 NR3C2 gene, and (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand modified sequences as listed in Table 3.

[0075] In a further aspect, there is provided a nucleic acid as described herein, wherein the first strand comprises nucleosides 2-18 of any one of the sequences according to the above Aspect C or Aspect D of the present invention.

[0076] In a further aspect, there is provided a nucleic acid according to the above Aspect C of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0077] In a further aspect, there is provided a nucleic acid according to the above Aspect C of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the duplex region comprises at least 14, 15, 16 or 17 complementary base pairs.

[0078] In a further aspect, there is provided a nucleic acid according to the above Aspect D of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0079] In a further aspect, there is provided a nucleic acid according to the above further Aspect D of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the duplex region comprises at least 14, 15, 16 or 17 complementary base pairs.

[0080] In a further aspect, there is provided a nucleic acid according to the above Aspect C of the present invention, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

[0081] In a further aspect, there is provided a nucleic acid according to the above Aspect D of the present invention, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.

[0082] In a further aspect, there is provided a nucleic acid according to the above Aspect C of the present invention, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

[0083] In a further aspect, there is provided a nucleic acid according to the above Aspect D of the present invention, wherein the second strand comprises any one of the second strand modified sequences as listed in Table 4.

[0084] In a further aspect, there is provided a conjugate for inhibiting expression of NR3C2 target gene in a cell, said conjugate comprising a nucleic acid as disclosed herein and one or more ligand moieties.

[0085] In a further aspect, there is provided a pharmaceutical composition comprising a nucleic acid as disclosed herein, in combination with a pharmaceutically acceptable excipient or carrier.

[0086] In a further aspect, there is provided a nucleic acid or pharmaceutical composition, for use in therapy.

[0087] In a further aspect, there is provided a nucleic acid or pharmaceutical composition, for use in the treatment of an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof.

[0088] In a further aspect, there is provided a nucleic acid or pharmaceutical composition, for use in the treatment of heart failure with reduced ejection fraction (HFrEF) and/or heart failure with preserved ejection fraction (HFpEF). In a further aspect, there is provided a nucleic acid or pharmaceutical composition as

disclosed herein, wherein the nucleic acid or the pharmaceutical composition is administered after myocardial infarction.

[0089] 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.

[0090] 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.

[0091] 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

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

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

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; and / or

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; and / or

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; and / or

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

(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.

[0092] 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 of the second strand, or at a terminal region which is distal to the 3' terminal region of the second strand.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] 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.

[0100] 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 (IMUNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid.

[0101] 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.

[0102] 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.

[0103] 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 at positions 1 to 6 of the second strand, counting from position 1 of said second strand.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the ligand moiety comprises

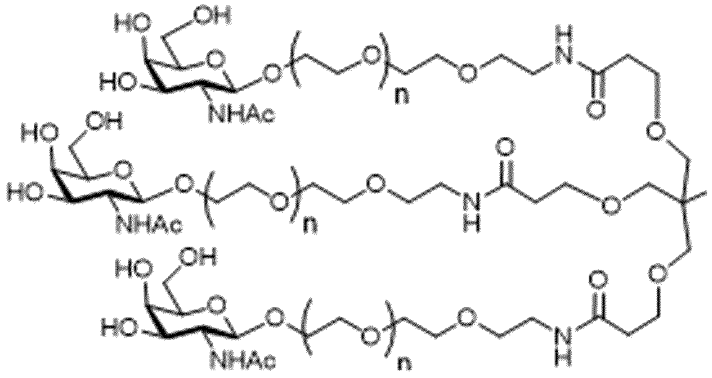
i) one or more GalNAc ligands; and / or

ii) one or more GalNAc ligand derivatives; and / or

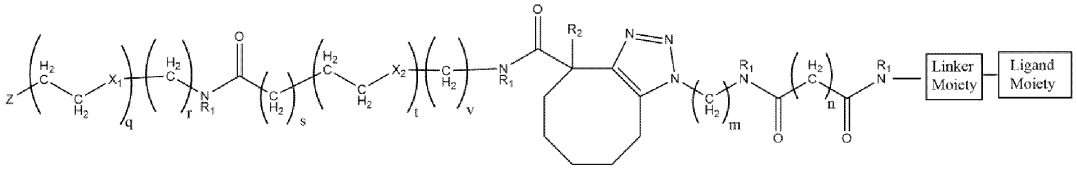
iii) one or more GalNAc ligands and / or GalNAc ligand derivatives conjugated to said siRNA through a linker.

[0111] 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.

[0112] In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, wherein the ligand moiety comprises:



[0113] 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;

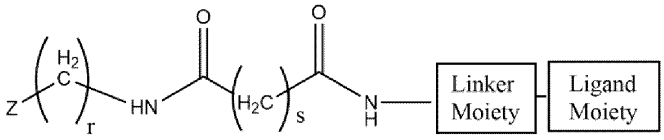
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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.

[0114] In a further aspect, the invention relates to an inhibitor or an inhibitor for use according to the invention, having the structure:



wherein:

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

Z is an oligomer.

[0115] 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.

[0116] In another aspect, the invention relates to a pharmaceutical composition comprising an inhibitor according to one or more preceding claims, in combination with a pharmaceutically acceptable excipient or carrier.

[0117] 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 treatment of an ischaemic heart disease, such as myocardial infarction. In a particular aspect of the invention, the pharmaceutical composition according to the invention is for use in the treatment of an ischaemic heart disease, such as myocardial infarction, whereby the pharmaceutical composition alleviates symptoms of an ischaemic heart disease, in particular myocardial infarction, more particularly an acute myocardial infarction. Within the present invention, the pharmaceutical composition of the invention may be administered after myocardial infarction, in particular for cardioprotection, for reducing infarct size and/or reducing reperfusion arrhythmias.

[0118] In another aspect, the invention relates to the use of NR3C2 as a target for identifying one or more therapeutic agents for the treatment of an ischaemic heart disease, such as myocardial infarction.

[0119] In another aspect, the invention relates to a method of treating or preventing a disease or disorder related to an ischaemic heart disease, such as myocardial infarction, which comprises administering to a patient an inhibitor of NR3C2, such as an inhibitor as defined according to one or more preceding aspects.

[0120] In another aspect, the invention relates to NR3C2 for use as a biomarker of heart failure with reduced ejection fraction (HFrEF) and associated conditions such as ischaemic heart disease, such as myocardial infarction.

[0121] In another aspect, the invention relates to NR3C2 for use as a biomarker of heart failure with preserved ejection fraction (HFpEF).

[0122] In another aspect, the invention relates to NR3C2 for use in an *in vivo* method of predicting susceptibility to an ischaemic heart disease, such as myocardial infarction, typically by monitoring the sequence and/ or level of expression and / or function of NR3C2 in a sample obtained from a patient.

[0123] In another aspect, the invention relates to a method of predicting susceptibility to an ischaemic heart disease, such as myocardial infarction, and optionally treating an ischaemic heart disease, such as myocardial infarction, in a patient, said method comprising:

(a) obtaining a sample from the patient,

(b) detecting the sequence and / or expression and / or function of NR3C2 in said sample obtained from the patient,

(c) predicting susceptibility to an ischaemic heart disease, such as myocardial infarction, based on the sequence and / or expression and / or function of NR3C2 in said sample obtained from the patient,

(d) preferably administering to the diagnosed patient an effective amount of an inhibitor of NR3C2.

[0124] 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 of an ischaemic heart disease, such as myocardial infarction.

[0125] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 228, SEQ ID NO: 238, SEQ ID NO: 243, SEQ ID NO: 235, SEQ ID NO: 245 and SEQ ID NO: 250.

[0126] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 238.

[0127] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 245.

[0128] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 674, SEQ ID NO: 684, SEQ ID NO: 689, SEQ ID NO: 681, SEQ ID NO: 691 and SEQ ID NO: 696.

[0129] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 684.

[0130] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the first strand comprises SEQ ID NO: 691.

[0131] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 451, SEQ ID NO: 461, SEQ ID NO: 466, SEQ ID NO: 458, SEQ ID NO: 468 and SEQ ID NO: 473.

[0132] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO: 461.

[0133] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO: 468.

[0134] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 897, SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919.

[0135] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO: 907.

[0136] In a further aspect, the invention relates to an inhibitor according to the invention, wherein the second strand comprises SEQ ID NO: 914.

[0137] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 228	SEQ ID NO: 451
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 243	SEQ ID NO: 466
SEQ ID NO: 235	SEQ ID NO: 458
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 250	SEQ ID NO: 473

[0138] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 238	SEQ ID NO: 461

[0139] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 245	SEQ ID NO: 468

[0140] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 674	SEQ ID NO: 897
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 689	SEQ ID NO: 912
SEQ ID NO: 681	SEQ ID NO: 904
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 696	SEQ ID NO: 919

[0141] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 684	SEQ ID NO: 907

[0142] In a further aspect, the invention relates to an inhibitor according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 691	SEQ ID NO: 914

[0143] In one aspect, the invention relates to an inhibitor of expression and / or function of NR3C2, for use in the treatment of heart failure with preserved ejection fraction (HFpEF).

[0144] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein said inhibitor is an siRNA oligomer.

[0145] 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 ligands or comprise one or more GalNAc ligand derivatives.

[0146] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the target of the inhibitor is NR3C2.

[0147] In a further aspect (Aspect E), there is provided a nucleic acid for inhibiting expression of NR3C2, for use in the treatment of heart failure with preserved ejection fraction (HFpEF), comprising 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 NR3C2 gene, and (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

[0148] In a further aspect (Aspect F), there is provided a nucleic acid for inhibiting expression of NR3C2, for use in the treatment of heart failure with preserved ejection fraction (HFpEF), comprising 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 NR3C2 gene, and (ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand modified sequences as listed in Table 3.

[0149] In a further aspect, there is provided a nucleic acid for use as described herein, wherein the first strand comprises nucleosides 2-18 of any one of the sequences according to the above Aspect E or Aspect F of the present invention.

[0150] In a further aspect, there is provided a nucleic acid for use according to the above Aspect E of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0151] In a further aspect, there is provided a nucleic acid for use according to the above Aspect E of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the duplex region comprises at least 14, 15, 16 or 17 complementary base pairs.

[0152] In a further aspect, there is provided a nucleic acid for use according to the above Aspect F of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0153] In a further aspect, there is provided a nucleic acid for use according to the above further Aspect F of the present invention, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified

sequences as listed in Table 4, and wherein the duplex region comprises at least 14, 15, 16 or 17 complementary base pairs.

[0154] In a further aspect, there is provided a nucleic acid for use according to the above Aspect E of the present invention, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

[0155] In a further aspect, there is provided a nucleic acid for use according to the above Aspect F of the present invention, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.

[0156] In a further aspect, there is provided a nucleic acid for use according to the above Aspect E of the present invention, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

[0157] In a further aspect, there is provided a nucleic acid for use according to the above Aspect F of the present invention, wherein the second strand comprises any one of the second strand modified sequences as listed in Table 4.

[0158] In a further aspect, there is provided a conjugate for inhibiting expression of NR3C2 target gene in a cell, for use in the treatment of heart failure with preserved ejection fraction (HFpEF), said conjugate comprising a nucleic acid as disclosed herein and one or more ligand moieties.

[0159] In a further aspect, there is provided a pharmaceutical composition comprising a nucleic acid for use as disclosed herein, in combination with a pharmaceutically acceptable excipient or carrier.

[0160] In a further aspect, there is provided a nucleic acid or pharmaceutical composition, for use in the treatment of heart failure with preserved ejection fraction (HFpEF) and/or symptoms thereof.

[0161] In a further aspect, the invention relates to 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.

[0162] In a further aspect, the invention relates to 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.

[0163] In a further aspect, the invention relates to 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

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

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

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;

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;

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

(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.

[0164] In a further aspect, the invention relates to 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 of the second strand, or at a terminal region which is distal to the 3' terminal region of the second strand.

[0165] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the reversed internucleoside linkage is a 3'3 reversed linkage.

[0166] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the reversed internucleoside linkage is a 5'5 reversed linkage.

[0167] In a further aspect, the invention relates to 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.

[0168] In a further aspect, the invention relates to 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.

[0169] In a further aspect, the invention relates to 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.

[0170] In a further aspect, the invention relates to 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.

[0171] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

[0172] In a further aspect, the invention relates to 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 (IMUNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid.

[0173] In a further aspect, the invention relates to 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.

[0174] In a further aspect, the invention relates to 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

[0175] In a further aspect, the invention relates to 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 at positions 1 to 6 of the second strand, counting from position 1 of said second strand.

[0176] In a further aspect, the invention relates to 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.

[0177] In a further aspect, the invention relates to 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.

[0178] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the siRNA oligomer further comprises one or more phosphorothioate internucleoside linkages.

[0179] In a further aspect, the invention relates to 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.

[0180] In a further aspect, the invention relates to 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.

[0181] In a further aspect, the invention relates to 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.

[0182] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the ligand moiety comprises:

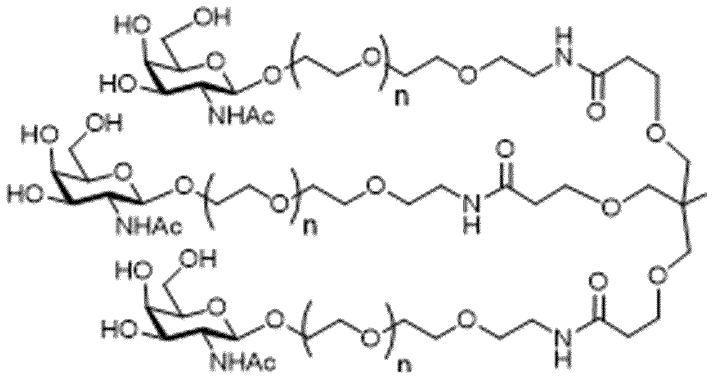
i) one or more GalNAc ligands; and / or

ii) one or more GalNAc ligand derivatives; and / or

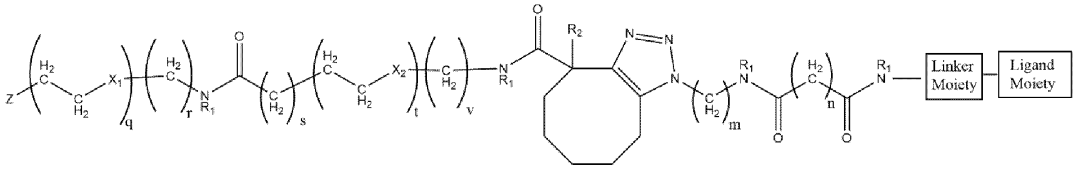
iii) one or more GalNAc ligands and / or GalNAc ligand derivatives conjugated to said siRNA through a linker.

[0183] In a further aspect, the invention relates to 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.

[0184] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the ligand moiety comprises:



[0185] In a further aspect, the invention relates to 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;

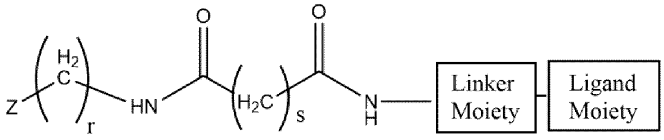
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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.

[0186] In a further aspect, the invention relates to an inhibitor for use according to the invention, having the structure:



wherein:

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

Z is an oligomer.

[0187] In a further aspect, the invention relates to an inhibitor for use according to the invention, formulated as a pharmaceutical composition with an excipient and / or carrier.

[0188] 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, for use in the treatment of heart failure with preserved ejection fraction (HFpEF).

[0189] In another aspect, the invention relates to the use of NR3C2 as a target for identifying one or more therapeutic agents for the treatment of heart failure with preserved ejection fraction (HFpEF).

[0190] In another aspect, the invention relates to a method of treating or preventing a disease or disorder related to heart failure with preserved ejection fraction (HFpEF), which comprises administering to a patient an inhibitor of NR3C2, such as an inhibitor as defined according to the invention.

[0191] In another aspect, the invention relates to NR3C2 for use as a biomarker of heart failure with preserved ejection fraction (HFpEF) and associated conditions such as restrictive and hypertrophic cardiomyopathies of any etiology, constrictive pericarditis, and valvular heart disease.

[0192] In another aspect, the invention relates to NR3C2 for use in an *in vivo* method of predicting susceptibility to HFpEF, typically by monitoring the sequence and/ or level of expression and / or function of NR3C2 in a sample obtained from a patient.

[0193] In another aspect, the invention relates to a method of predicting susceptibility to HFpEF, and optionally treating HFpEF, in a patient, said method comprising:

(a) obtaining a sample from the patient,

(b) detecting the sequence and / or expression and / or function of NR3C2 in said sample obtained from the patient,

(c) predicting susceptibility to HFpEF based on the sequence and / or expression and / or function of NR3C2 in said sample obtained from the patient,

(d) preferably administering to the diagnosed patient an effective amount of an inhibitor of NR3C2.

[0194] 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 of HFpEF.

[0195] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 228, SEQ ID NO: 238, SEQ ID NO: 243, SEQ ID NO: 235, SEQ ID NO: 245 and SEQ ID NO: 250.

[0196] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the first strand comprises SEQ ID NO: 238.

[0197] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the first strand comprises SEQ ID NO: 245.

[0198] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 674, SEQ ID NO: 684, SEQ ID NO: 689, SEQ ID NO: 681, SEQ ID NO: 691 and SEQ ID NO: 696.

[0199] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the first strand comprises SEQ ID NO: 684.

[0200] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the first strand comprises SEQ ID NO: 691.

[0201] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 451, SEQ ID NO: 461, SEQ ID NO: 466, SEQ ID NO: 458, SEQ ID NO: 468 and SEQ ID NO: 473.

[0202] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the second strand comprises SEQ ID NO: 461.

[0203] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the second strand comprises SEQ ID NO: 468.

[0204] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 897, SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919.

[0205] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the second strand comprises SEQ ID NO: 907.

[0206] In a further aspect, the invention relates to an inhibitor for use according to the invention, wherein the second strand comprises SEQ ID NO: 914.

[0207] In a further aspect, the invention relates to an inhibitor for use according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 228	SEQ ID NO: 451
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 243	SEQ ID NO: 466
SEQ ID NO: 235	SEQ ID NO: 458
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 250	SEQ ID NO: 473

[0208] In a further aspect, the invention relates to an inhibitor for use according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 238	SEQ ID NO: 461

[0209] In a further aspect, the invention relates to an inhibitor for use according to the invention, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 245	SEQ ID NO: 468

[0210] In a further aspect, the invention relates to an inhibitor for use according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 674	SEQ ID NO: 897
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 689	SEQ ID NO: 912
SEQ ID NO: 681	SEQ ID NO: 904
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 696	SEQ ID NO: 919

[0211] In a further aspect, the invention relates to an inhibitor for use according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 684	SEQ ID NO: 907

[0212] In a further aspect, the invention relates to an inhibitor for use according to the invention, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 691	SEQ ID NO: 914

[0213] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 290, SEQ ID NO: 270, SEQ ID NO: 238, SEQ ID NO: 245, SEQ ID NO: 283, SEQ ID NO: 235, SEQ ID NO: 226, SEQ ID NO: 335, SEQ ID NO: 228 or SEQ ID NO: 410.

[0214] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 290, SEQ ID NO: 270, SEQ ID NO: 238, SEQ ID NO: 245 or SEQ ID NO: 283.

[0215] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the first strand comprises SEQ ID NO: 290.

[0216] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the first strand comprises SEQ ID NO: 270.

[0217] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 736, SEQ ID NO: 716, SEQ ID NO: 684, SEQ ID NO: 691, SEQ ID NO: 729, SEQ ID NO: 681, SEQ ID NO: 672, SEQ ID NO: 781, SEQ ID NO: 674 or SEQ ID NO: 856.

[0218] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 736, SEQ ID NO: 716, SEQ ID NO: 684, SEQ ID NO: 691 or SEQ ID NO: 729.

[0219] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the first strand comprises SEQ ID NO: 736.

[0220] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the first strand comprises SEQ ID NO: 716.

[0221] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 513, SEQ ID NO: 493, SEQ ID NO: 461, SEQ ID NO: 468, SEQ ID NO: 506, SEQ ID NO: 458, SEQ ID NO: 449, SEQ ID NO: 558, SEQ ID NO: 451 or SEQ ID NO: 633.

[0222] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 513, SEQ ID NO: 493, SEQ ID NO: 461, SEQ ID NO: 468 or SEQ ID NO: 506.

[0223] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the second strand comprises SEQ ID NO: 513.

[0224] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the second strand comprises SEQ ID NO: 493.

[0225] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 959, SEQ ID NO: 939, SEQ ID NO: 907, SEQ ID NO: 914, SEQ ID NO: 952, SEQ ID NO: 904, SEQ ID NO: 895, SEQ ID NO: 1004, SEQ ID NO: 897, SEQ ID NO: 897 or SEQ ID NO: 1079.

[0226] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 959, SEQ ID NO: 939, SEQ ID NO: 907, SEQ ID NO: 914 or SEQ ID NO: 952.

[0227] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the second strand comprises SEQ ID NO: 959.

[0228] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, wherein the second strand comprises SEQ ID NO: 939.

[0229] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513
SEQ ID NO: 270	SEQ ID NO: 493
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 283	SEQ ID NO: 506
SEQ ID NO: 235	SEQ ID NO: 458
SEQ ID NO: 226	SEQ ID NO: 449
SEQ ID NO: 335	SEQ ID NO: 558
SEQ ID NO: 228	SEQ ID NO: 451
SEQ ID NO: 410	SEQ ID NO: 633

[0230] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513
SEQ ID NO: 270	SEQ ID NO: 493
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 283	SEQ ID NO: 506

[0231] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513

[0232] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 270	SEQ ID NO: 493

[0233] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 736	SEQ ID NO: 959
SEQ ID NO: 716	SEQ ID NO: 939
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 729	SEQ ID NO: 952
SEQ ID NO: 681	SEQ ID NO: 904
SEQ ID NO: 672	SEQ ID NO: 895
SEQ ID NO: 781	SEQ ID NO: 1004
SEQ ID NO: 674	SEQ ID NO: 897
SEQ ID NO: 856	SEQ ID NO: 1079

[0234] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 736	SEQ ID NO: 959
SEQ ID NO: 716	SEQ ID NO: 939
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 729	SEQ ID NO: 952

[0235] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Modified first strand	Modified second strand
SEQ ID NO: 736	SEQ ID NO: 959

[0236] In a further aspect, the invention relates to an inhibitor for use in the treatment of HFpEF, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Modified first strand	Modified second strand
SEQ ID NO: 716	SEQ ID NO: 939

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES

[0237] **Figure 1:** Linker and ligand portions of constructs suitable for use according to the present invention including tether 1a. While Figure 1 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

[0238] It should also be understood that while Figure 1 depicts as a product molecules based on the linker and ligand portions as specifically depicted in Figure 1 attached to an oligonucleoside moiety as also depicted herein, this product may alternatively further comprise, or consist essentially of, molecules wherein the linker and ligand portions are essentially as depicted in Figure 1 attached to an oligonucleoside moiety but having the F substituent as shown in Figure 1 on the cyclo-octyl ring replaced by a substituent, which could occur as a result of hydrolytic displacement, such as an OH substituent, or the OH substituent could be synthesized as a linker in its own right. In this way, (a) tether 1a constructs can consist essentially of molecules having linker and ligand portions specifically as depicted in Figure 1, with a F substituent on the cyclo-octyl ring; or (b) tether 1a constructs can consist essentially of molecules having linker and ligand portions essentially as depicted in Figure 1 but having the F substituent as shown in Figure 1 on the cyclo-octyl ring replaced by an OH substituent, or (c) tether 1a constructs can comprise a mixture of molecules as defined in (a) and/or (b).

[0239] **Figure 2:** Linker and ligand portions of constructs suitable for use according to the present invention including tether 1b. While Figure 2 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

[0240] The comments made in relation to Figure 1 and the possible replacement of the F substituent as shown in Figure 1 on the cyclo-octyl ring replaced by a substituent, which could occur as a result of hydrolytic displacement, such as an OH substituent, or the OH substituent could be synthesized as a linker in its own right, apply equally to tether 1b constructs. In this way, (a) tether 1b constructs can consist essentially of molecules having linker and ligand portions specifically as depicted in Figure 2, with a F substituent on the cyclo-octyl ring; or (b) tether 1b constructs can consist essentially of molecules having

linker and ligand portions essentially as depicted in Figure 2 but having the F substituent as shown in Figure 2 on the cyclo-octyl ring replaced by an OH substituent, or (c) tether 1b constructs can comprise a mixture of molecules as defined in (a) and/or (b).

[0241] Figure 3: Linker and ligand portions of constructs suitable for use according to the present invention including tether 2a. While Figure 3 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

[0242] Figure 4: Linker and ligand portions of constructs suitable for use according to the present invention including tether 2b. While Figure 4 depicts the linker to be conjugated to an oligonucleotide, it is to be understood that the present invention also encompasses conjugates of the same linker with an oligonucleoside as disclosed herein.

[0243] Figure 5: Relevant formulae.

[0244] Figure 6: Further formulae.

[0245] Figures 7a and 7b: Inverted abasic constructs that can be used with nucleic acid sequences according to the present invention as described herein. For Figure 7a, a GalNAc linker is attached to the 5' end region of the sense strand in use (not depicted in Figure 7a). For Figure 7b, a GalNAc linker is attached to the 3' end region of the sense strand in use (not depicted in Figure 7b).

[0246] iaia as shown at the 3' end region of the sense strand in Figure 7a 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 abasic nucleosides is 5'-3' when reading towards the 3' end region comprising the terminal and penultimate abasic nucleosides.

[0247] iaia as shown at the 5' end region of the sense strand in Figure 7b 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 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.

[0248] Figures 8a and 8b: Duplex constructs according to Table 5.

[0249] Figure 9: The correlation between predicted and experimentally determined siRNA efficacy values i.e. maximum RNA knockdown where 1 represents maximum knockdown and 0 is no reduction in mRNA levels. Data displayed are for the test dataset in the best performing siRNAdesignR model.

[0250] Figure 10: Performance metrics for the best performing siRNAdesignR model in the test data set and also the validation dataset. In both cases the model scored above 0.5 in the Precision@20 metric, and the best performing siRNA (experimentally determined) was in the top 20 predictions of the model (nSiRNAsForBest).

[0251] Figure 11: siRNAdesignR ranking for 276 siRNAs. These rankings were tested in an *in vitro* model (Huh7 cells) demonstrating strong correlation (Spearman correlation coefficient 0.743).

[0252] Figure 12: A dose response curve of SLC25A5 mRNA knockdown following 24-hour exposure to siRNA. Cells were tested in triplicate repeats on two separate days (replicates 1 and 2). Data are mean +/- standard deviation with knockdown normalised to untreated wells.

[0253] Figure 13: Change in SLC25A5 mRNA knockdown over 28 days following one subcutaneous dose of siRNA at day 0. As mRNA measurements are taken from liver tissue measurements are taken from different mice at each time point. Data are mean +/- standard deviation from 16 mice per timepoint per dose, normalised to saline control.

[0254] Figure 14: Change in SLC25A5 protein expression over 28 days following one subcutaneous dose of siRNA at day 0. As mRNA measurements are taken from liver tissue measurements are taken from different mice at each time point. Data are mean +/- standard deviation from 16 mice per timepoint per dose, normalized to saline control.

[0255] Figure 15a shows an exemplary linear configuration for a conjugate.

[0256] Figure 15b shows an exemplary branched configuration for a conjugate.

[0257] Figures 16-19 show preferred oligomer – linker – ligand constructs of the invention.

[0258] Figure 20: Hepatic target mRNA knockdown in mice following injection of GalNAc-siRNA.

[0259] Figure 21: No change in markers of liver health following injection of GalNAc-siRNAs.

[0260] Figure 22: Hepatic knockdown and trend towards increased FGF21 levels with ETXM-2590 treatment.

[0261] Figure 23: No treatment effects on survival, body weight or food intake in the MI mouse model.

[0262] Figure 24: Improvements in main parameters of cardiac function and structure post-MI in mice treated with GalNAc-siRNA to reduce hepatic NR3C2 expression.

[0263] Figure 25: Reduced hepatic expression of human NR3C2 in a hydrodynamic injection (HDI) mouse model injected with GalNAc siRNAs.

[0264] Figure 26: Results of an *in vitro* screen showing siRNA activity against NR3C2 in primary human hepatocytes. 0.01nM and 1.0nM siRNA were transfected into Primary Human Hepatocytes for 48 hours. Relative expression levels (mean +/- SEM) of NR3C2 were determined *via* qPCR using b-actin as a housekeeping gene.

[0265] Figure 27: Overview of the hydrodynamic injection (HDI) study in mice.

[0266] Figure 28: Results of an siRNA molecule screen targeting the expression of human NR3C2 following hydrodynamic injection in BALB/c mice. Mice were injected with a single subcutaneous 0.5 mg/kg of each of the 54 siRNAs followed by HDI with the plasmid containing the human NR3C2 cDNA. Numerous siRNAs resulted in statistically significant knockdown of NR3C2. Statistical significance relative to vehicle control *p< 0.05, ***p < 0.001, ****p < 0.0001.

[0267] Figure 29: Serum levels of FGF21 (pg/ml) at termination of experiment.

[0268] Figure 30: Left ventricle (LV) geometry assessed by echocardiography after 6 weeks of treatments with vehicle or ETX-M00002590 at 10 mg/kg or eplerenone at 1 g/kg diet or empagliflozin at 10mg/kg in mice. A, B) posterior wall thickness in diastole and systole (LVPWd and LVPWs), C, D) anterior wall thickness in diastole and systole (LVAWd and LVAWs). Statistical significance relative to vehicle *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

[0269] Figure 31: Left ventricle (LV) diastolic function assessed after 6 weeks of treatments with vehicle or ETX-M00002590 at 10 mg/kg or eplerenone at 1g/kg diet or empagliflozin at 10mg/kg in mice. A) E'/A' ratio, B) E/E' ratio, C) Diastolic Arterial Pressure, D) Systolic Arterial Pressure E) Mean Arterial Pressure F) LV End-Diastolic Pressure G) Min dP/dT H) Max dP/dT I) Relaxation Index Tau (ms). Statistical significance relative to vehicle control *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

[0270] Figure 32: Plasma biomarkers in mice treated with vehicle or siRNA at 10 mg/kg or eplerenone at 1 g/kg diet or empagliflozin at 10 mg/kg in mice. A) serum potassium (mmol/l, mean +/- SEM). B) Serum glucose (mmol/l, mean +/- SEM). Statistical significance relative to vehicle control **p<0.01, ***p<0.001.

[0271] Figure 33: Liver weight to tibia length ratio (g/mm mean +/- SEM) 17 weeks after diet induction in mice treated with vehicle or siRNA at 10 mg/kg or eplerenone at 1 g/kg diet or empagliflozin at 10 mg/kg in mice. Statistical significance relative to vehicle control **p<0.01.

DETAILED DESCRIPTION

[0272] 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.

[0273] The present invention identifies inhibitors of NR3C2 as useful in the prevention and/or treatment of an ischaemic heart disease, such as myocardial infarction and/or the disorder or diseases as a symptom of myocardial infarction.

[0274] In particular, the present invention identifies inhibitors of NR3C2 as useful in the prevention and/or treatment of heart failure with preserved ejection fraction (HFpEF) and/or heart failure with reduced ejection fraction (HFrEF).

[0275] The mineralocorticoid receptor (MR or NR3C2) is a protein/receptor that belongs to the nuclear receptor family. As such, binding of the ligand to NR3C2 affects specific gene expression in the nucleus of human cells. In humans, NR3C2 is encoded by the NR3C2 gene (ENSG00000151623).

[0276] The inhibition disclosed herein may be of the gene or protein resulting from expression of the gene and reference to NR3C2 hereby explicitly incorporates a reference to inhibition of the expression or function of the gene and, separately, of the protein product.

[0277] Ischemic heart disease is the primary etiology of heart failure with reduced ejection fraction (HFrEF). The present invention extends equally to other indications associated with, or resulting from, HFrEF or ischemic heart disease. References herein to ischemic heart disease can be applied equally to HFrEF and associated indications.

[0278] Other etiologies of HFrEF include valvular disease, hypertension, and cardiomyopathies. The present invention also extends equally to such other etiologies of HFrEF. References herein to ischemic heart disease can be applied equally to these.

[0279] Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome with diverse phenotypes. Approximately 50% of patients with heart failure are classified as having HFpEF or associated disorders including restrictive and hypertrophic cardiomyopathies of any etiology, constrictive pericarditis, and valvular heart disease. The present invention extends equally to other indications associated with, or resulting from, HFpEF. References herein to HFpEF can be applied equally to such associated indications.

DEFINITIONS

[0280] 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 dsiRNA, 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 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.

[0281] 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 substantially complementary to a region of the antisense strand as that term is defined herein.

[0282] 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.

[0283] Oligonucleotides are short nucleic acid polymers. Whilst oligonucleotides contain phosphodiester bonds 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 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 having one or more phosphorothioate backbone bonds between nucleosides (typically in a terminal region of the first and / or second strands) is also preferred according to the present invention.

[0284] It is preferred herein that the nucleic acid according to the invention is a double stranded oligonucleoside comprising one or more phosphorothioate backbone bonds between nucleosides. Accordingly, in all instances in which the present application refers to an oligonucleotide, particularly in the chemical structures disclosed herein, the oligonucleotide may equally be an oligonucleoside as defined herein.

[0285] 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.

[0286] In another embodiment, the nucleoside mismatch is, for example, in the 3'- terminal nucleoside of the nucleic acid *e.g.,* siRNA.

[0287] 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 LNCRNA which it is desired to inhibit.

[0288] 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, 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.

[0289] The term “ribonucleoside” or “nucleoside” can also refer to a modified nucleoside as further detailed below.

[0290] A nucleic acid can be a DNA or an RNA and can comprise modified nucleosides. RNA is a preferred nucleic acid.

[0291] The terms "iRNA", “siRNA”, "RNAi agent," "iRNA agent," and "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).

[0292] 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.

[0293] 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.

[0294] 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.

[0295] 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.

[0296] 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.

[0297] 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.

[0298] 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 overhangs at the 3'-end or the 5'-end.

[0299] "Blunt" or "blunt end" means that there are no unpaired nucleosides 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.

[0300] 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).

[0301] Complementary sequences within nucleic acid *e.g.,* a dsiRNA, 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" 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".

[0302] "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 Hoogstein base pairing.

[0303] The terms "complementary," "fully complementary" and "substantially 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.,* dsiRNA, or between the antisense strand of a double stranded nucleic acid *e.g.,* siRNA agent and a target sequence.

[0304] Within the present invention, the second strand of the nucleic acid according to the invention, in particular a dsiRNA for inhibiting expression of NR3C2, 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.

[0305] 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.

[0306] 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.

[0307] 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.

[0308] As used herein, a nucleic acid that is "substantially complementary" to at least part of a messenger RNA (mRNA) refers to a polynucleoside that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.,* an mRNA encoding a gene). For example, a polynucleoside is complementary to at least a part of an mRNA of a gene of interest if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding that gene.

[0309] Accordingly, in some preferred embodiments, the antisense oligonucleosides as disclosed herein are fully complementary to the target gene sequence.

[0310] In other embodiments, the antisense oligonucleosides disclosed herein are substantially 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.

[0311] In certain embodiments, the first (antisense) strand of a nucleic acid according to the invention is partially or fully complementary to a contiguous portion of RNA transcribed from the NR3C2 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 NR3C2 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 NR3C2 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 any one of the sequences as listed in Table 1, i.e., any one of SEQ ID NOs:1-223.

[0312] In certain embodiments, the first (antisense) strand of the nucleic acid according to the invention is partially complementary to a contiguous portion of the NR3C2 mRNA if it 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 the NR3C2 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 listed in Table 1, i.e., any one of SEQ ID NOs: 1-223. 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: 1-223. 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 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: 1-223.

[0313] In some embodiments, a nucleic acid *e.g.,* an siRNA of the invention includes a sense strand that is substantially 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% 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.

[0314] In some embodiments, a nucleic acid *e.g.,* an siRNA of the invention includes an antisense strand that is substantially complementary to the target sequence and comprises a contiguous nucleoside 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.

[0315] 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 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.

[0316] 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 mean prolonging survival as compared to expected survival in the absence of treatment. Treatment can include prevention of development of co-morbidities. As used herein, the term “treatment”, in particular treatment of myocardial infarction, HFrEF and/or HFpEF, encompasses the treatment of consequences/symptoms of myocardial infarction, HFrEF and/or HFpEF respectively, such as damage of heart muscle tissue. As such, the inhibitors of the invention, have cardioprotective effect and, *inter alia*, reduce infarct size and/or reperfusion arrythmias.

[0317] The terms “prevent” or “prevention” as used herein are defined as eliminating or reducing the likelihood of occurrence of one or more symptoms of a disease or disorder. For example, the inhibitor disclosed herein can be used to prevent the occurrence of ischaemic heart diseases, in particular myocardial infarction, and/or symptoms thereof, HFrEF and/or symptoms thereof and/or HFpEF and/or symptoms thereof.

[0318] "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 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).

[0319] 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.

[0320] 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.

[0321] 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.

[0322] 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.

[0323] The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

[0324] 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".

[0325] 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.

[0326] 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.

[0327] 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.

[0328] The terminal region of a strand is the last 5 nucleotides from the 5' or the 3' end.

[0329] A nucleobase sequence is the sequence of the bases of the nucleic acid in an oligomer.

[0330] Various embodiments of the invention can be combined as determined appropriate by one of skill in the art.

TARGET

[0331] A target for inhibition disclosed herein may be, without limitation, an mRNA, polypeptide, protein, or gene.

[0332] These targets are a target the inhibition of which helps in the prevention or treatment of an ischaemic heart disease such as myocardial infarction. These targets are a target the inhibition of which helps in the prevention or treatment of HFpEF and/or HFrEF.

[0333] The target for inhibition is NR3C2, and inhibition may be effected by inhibition of expression or function of the NR3C2 gene or protein or both.

DISEASE/CONDITIONS

[0334] The invention relates to an inhibitor suitable for use, or for use, in treatment of an ischaemic heart disease, in particular myocardial infarction.

[0335] The invention relates to an inhibitor suitable for use, or for use, in treatment of heart failure with preserved ejection fraction (HFpEF).

[0336] The invention relates to an inhibitor suitable for use, or for use, in treatment of heart failure with reduced ejection fraction (HFrEF).

[0337] Inhibitors disclosed herein, including the specific oligonucleotide sequences disclosed herein, may be used in the treatment of any of the diseases disclosed herein, included HFrEF and HFpEF.

INHIBITORS

[0338] 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.

[0339] Certain preferred features of inhibitors of the invention, where these are oligonucleosides such as siRNA, are given below.

[0340] 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 NR3C2 gene (SEQ ID NO: 1116). In a preferred embodiment, the nucleic acid comprises a first strand comprising a sequence that is at least partially complementary to a NR3C2 mRNA.

[0341] In certain embodiments, the nucleic acid for inhibiting expression of NR3C2 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 at least partially complementary to a portion of RNA transcribed from the NR3C2 gene.

[0342] In certain embodiments, the nucleic acid for inhibiting expression of NR3C2 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 at least partially complementary to a portion of RNA transcribed from the NR3C2 gene.

ABASIC NUCLEOTIDES

[0343] The invention specifically contemplates the use of abasic nucleosides as disclosed in PCT/US22/74223 (WO 2023/059948). In particular, it specifically contemplates the use of abasic nucleosides as described in paragraphs [0141] - [0165] (pages 34 - 40) of the published PCT specification, the disclosure of which is hereby incorporated by reference.

[0344] Preferably a nucleic acid according to the present invention comprises one or more abasic nucleosides, optionally wherein the one or more abasic nucleosides are in a terminal region of the second strand, and/or wherein at least one abasic nucleoside is linked to an adjacent basic nucleoside through a reversed internucleoside linkage.

[0345] Typically, 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

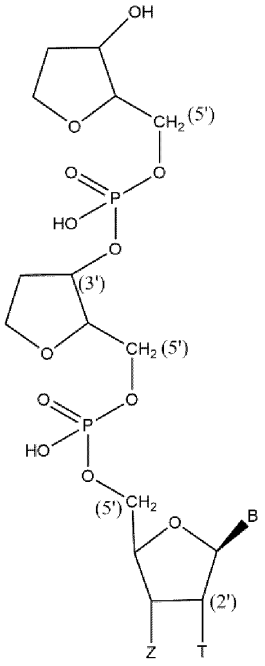
the second strand, wherein: (a) said penultimate abasic nucleoside is connected to an adjacent first basic nucleoside in an adjacent 5' near terminal region through a reversed internucleoside linkage; and (b) the reversed linkage is a 5-5' reversed linkage; and (c) the linkage between the terminal and 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 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 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.

[0346] 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.

[0347] In some embodiments, the second (sense) strand of the nucleic acid according to the invention comprises 2 consecutive abasic nucleosides in the 5' terminal region as shown in the following 5' terminal motif:

5' terminal motif



wherein:

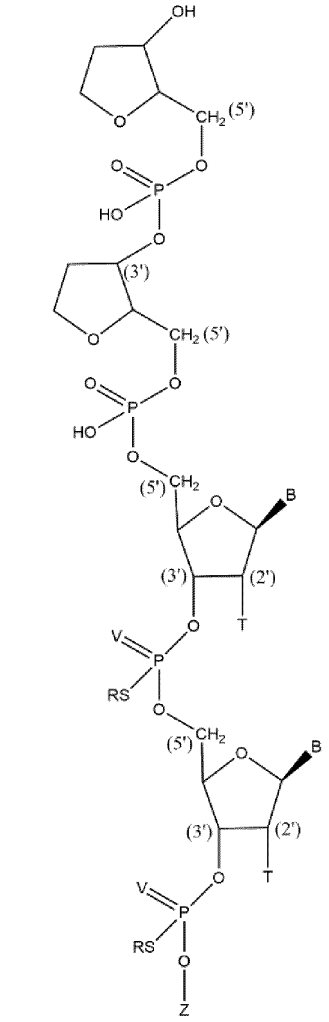
B represents a nucleoside base,

T represent H, OH or a 2' ribose modification,

Z represents the remaining nucleosides of said second strand.

[0348] In some embodiments, the second (sense) strand of the nucleic acid according to the invention comprises 2 consecutive abasic nucleosides in the 5' terminal region as shown in the following 5' terminal motif:

5' terminal motif



wherein:

B represents a nucleoside base,

T represents H, OH or a 2' ribose modification (preferably a 2' ribose modification, more preferably a 2'Me or 2'F ribose modification),

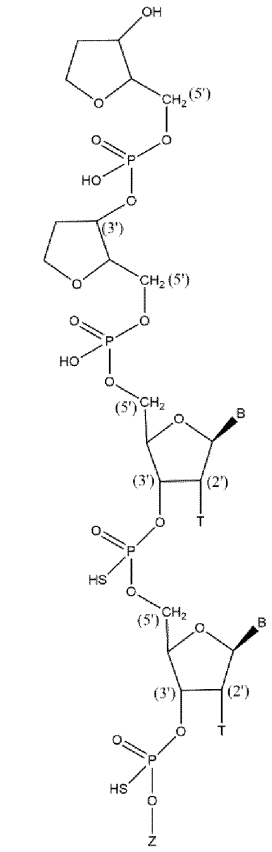
V represents O or S (preferably O),

R represents H or C1-4 alkyl (preferably H),

Z represents the remaining nucleosides of said second strand,

more preferably the following 5' terminal motif:

5' terminal motif



wherein:

B represents a nucleoside base,

T represents a 2' ribose modification (preferably a 2'Me or 2'F ribose modification),

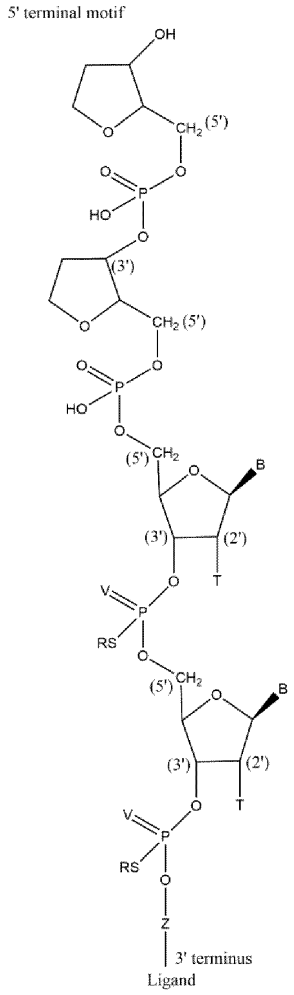
Z represents the remaining nucleosides of said second strand.

[0349] 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.

[0350] GalNAc-siRNA constructs with a 5'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[0351] GalNAc-siRNA constructs with a 3'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[0352] In a preferred embodiment, the second (sense) strand of the nucleic acid according to the invention comprises 2 consecutive abasic nucleosides in the 5' terminal region as shown in the following 5' terminal motif:



wherein:

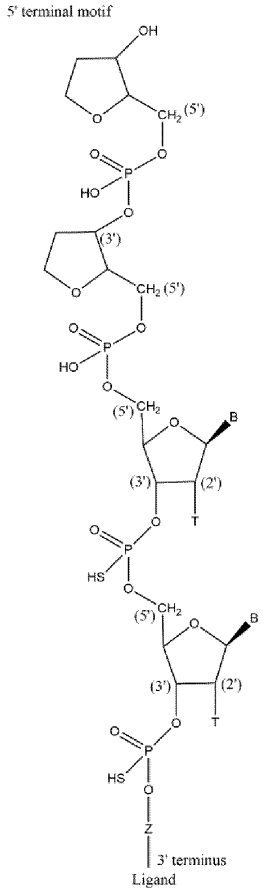
B represents a nucleoside base,

T represent H, OH or a 2' ribose modification (preferably a 2' ribose modification, more preferably a 2'Me or 2'F ribose modification),

V represent O or S (preferably O),

R represent H or C1-4 alkyl (preferably H),

Z comprises 11 to 26 contiguous nucleosides, preferably 15 to 21 contiguous nucleosides, and more preferably 19 contiguous nucleosides, more preferably the following 5' terminal motif:



wherein:

B represents a nucleoside base,

T represents a 2' ribose modification (preferably a 2'Me or 2'F ribose modification),

Z comprises 19 contiguous nucleosides.

NUCLEIC ACID LENGTHS

[0353] In one aspect 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.

[0354] 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 NR3C2 gene is between 17 and 30 nucleosides in length.

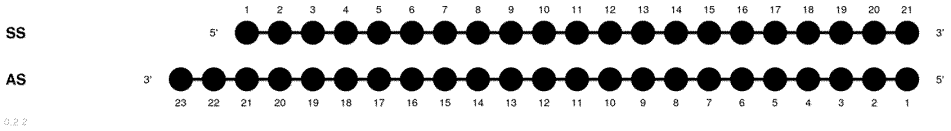
[0355] Generally, the duplex structure of the nucleic acid *e.g.,* an iRNA is about 15 to 30 base pairs in length, *e.g.,* 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 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.

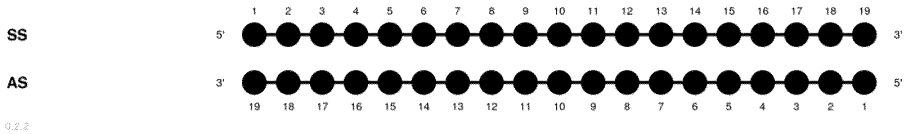
[0356] Similarly, the region of complementarity of an antisense sequence to a target sequence and/or the region of complementarity of an antisense sequence to a sense sequence is about 15 to 30 nucleosides in length, *e.g.,* 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 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 intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

[0357] 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 length.

[0358] In preferred embodiments, each strand is no more than 30 nucleosides in length.

[0359] In certain preferred embodiments, the duplex structure of the nucleic acid *e.g.,* an siRNA is 19 or 21 base pairs in length. In a particularly preferred embodiment, the duplex may have one of the following structures:





[0360] 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 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.

[0361] 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

[0362] In certain embodiments, the nucleic acid *e.g.,* an RNA of the invention *e.g.,* a dsiRNA, does not comprise further modifications, *e.g.,* chemical modifications or conjugations known in the art and described herein.

[0363] 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.

[0364] In certain embodiments of the invention, substantially all of the nucleosides are modified.

[0365] The nucleic acids featured in the invention can be synthesized or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. et al. ((Eds.), John Wiley & Sons, Inc., New York, NY, USA), which is hereby incorporated herein by reference.

[0366] The invention specifically contemplates the use of nucleic acid modifications as disclosed in PCT/US22/74223 (WO 2023/059948). In particular, it specifically contemplates the use of nucleic acid modifications as described in paragraphs [0175] - [0188] and [0225] - [0236] (pages 41 - 43 and 50 - 51) of the published PCT specification, the disclosure of which is hereby incorporated by reference.

[0367] Preferred modifications that can be used with sequences according to the present invention can be as follows:

Modification 1:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNfNfNfNfNmNmNmNmNmNmNmNfNmNm (5’ to 3’)

Modification 2:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNfNfNmNfNfNfNfNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 3:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNmNfNfNfNfNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 4:

First strand modification:

NmsNfsNmNfNmNfNmNmNmNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNfNmNfNfNfNfNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 5:

First strand modification:

NmsNfsNmNmNmNfNmNmNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 6:

First strand modification:

NmsNfsNmNmNmNfNmNmNmNmNmNmNmNfNmNfNmNfNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 7:

First strand modification:

NmsNfsNmNmNmNyNmNmNmNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 8:

First strand modification:

NmsNfsNmNmNmNyNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 9:

First strand modification:

NmsNfsNmNmNmNfNmNmNmNmNmNmNmNfNmNfNmNmNmNfNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 10:

First strand modification:

NmsNfsNmNfNmNfNmNmNmNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 11:

First strand modification:

NmsNfsNmNfNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 12:

First strand modification:

NmsNfsNmNmNmNfNmNfNfNmNmNmNmNfNmNfNmNfNmNmNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

Modification 13:

First strand modification:

NmsNfsNmNmNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNfNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNmNm (5’ to 3’)

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.

[0368] In a preferred embodiment, the nucleic acid according to the invention has the following modification pattern:

Modification 13:

First strand modification:

NmsNfsNmNmNmNfNmNfNfNmNmNmNmNfNmNfNmNmNmNfNmsNmsNm (5’ to 3’)

Second strand modification:

iaiaNmsNmsNmNmNmNmNmNmNfNfNfNmNmNmNmNmNmNmNmNmNm (5’ to 3’).

[0369] In certain embodiments, the nucleic acid comprises a 5’ vinylphosphonate (5’VP) modification. The 5’VP modification is preferably on the antisense strand, but can be on the sense strand as well, or instead. Preferably, the 5’VP modification is a 5’-(E)-vinylphosphonate (5’-(E)-VP) modification.

[0370] A 5'-VP modification is a stable phosphate mimic added at the 5' end of an oligonucleoside. It is a modification in which the 5' carbon forms a double bond to a 6' carbon linked to the phosphorus. Such modifications are described in Haraszti et al 2017 (Haraszti et al., *5′-Vinylphosphonate improves tissue accumulation and efficacy of conjugated siRNAs in vivo*. NUCLEIC ACIDS RES. 2017 Jul 27;45(13):7581-7592. doi: 10.1093/nar/gkx507. PMID: 28591791; PMCID: PMC5570069).

CONJUGATION OF NUCLEIC ACID TO LIGAND

[0371] 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.

[0372] 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.

[0373] The ligand can be attached to the 3' or 5’ end of the sense strand.

[0374] The ligand is preferably conjugated to 3’ end of the sense strand of the nucleic acid *e.g.,* an siRNA agent.

[0375] 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.

[0376] 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.

[0377] In certain embodiments, the ligand moiety comprises a GalNAc or GalNAc derivative attached to the nucleic acid *e.g.,* dsiRNA through a linker.

[0378] Therefore, the invention relates to a conjugate 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 conjugated to said nucleic acid through a linker.

[0379] 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.

[0380] GalNAc ligands are well known in the art and described in, *inter alia*, EP3775207A1.

[0381] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, *via* a phosphodiester bond.

[0382] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, *via* a phosphodiester bond.

[0383] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" may be any nucleic acid disclosed herein. Accordingly, the "oligonucleotide" may comprise other bonds than a phosphodiester bond, such as one or more phosphorothioate bonds. Preferably, the nucleic acid according to the invention is a double stranded oligonucleoside as defined herein and the linker is conjugated to the second strand, more preferably to the 3' terminal region of the second strand, *via* a phosphodiester bond.

[0384] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified or unmodified second strand comprising or consisting of any one of SEQ ID NO:447 to SEQ ID NO:669, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:447 to SEQ ID NO:669, *via* a phosphodiester bond.

[0385] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified or unmodified second strand comprising or consisting of any one of SEQ ID NO:447 to SEQ ID NO:669, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:447 to SEQ ID NO:669, *via* a phosphodiester bond.

[0386] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified or unmodified second strand comprising or consisting of any one of SEQ ID NO:447 to SEQ ID NO:669, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one SEQ ID NO:447 to SEQ ID NO:669, *via* a phosphodiester bond.

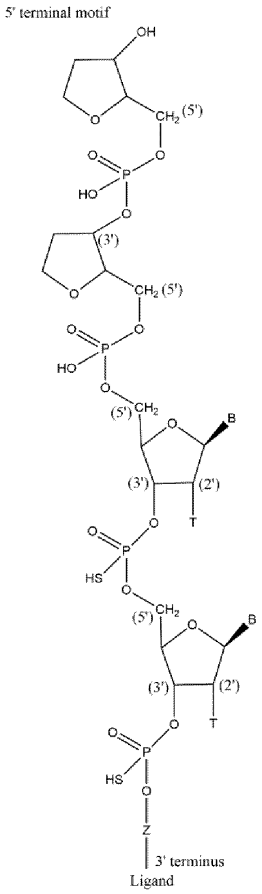
[0387] In some embodiments, the GalNAc ligand is comprised in any one of the linkers shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand comprising or consisting of any one of SEQ ID NO:893 to SEQ ID NO:1115, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:893 to SEQ ID NO:1115, *via* a phosphodiester bond.

[0388] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand comprising or consisting of any one of SEQ ID NO:893 to SEQ ID NO:1115, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:893 to SEQ ID NO:1115, *via* a phosphodiester bond.

[0389] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand comprising or consisting of any one of SEQ ID NO:893 to SEQ ID NO:1115, preferably wherein the linker is conjugated to the 3' terminal region of the second strand, i.e., to the 3' terminal region of any one of SEQ ID NO:893 to SEQ ID NO:1115, *via* a phosphodiester bond.

[0390] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figures 1 to 4 or Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand comprising or consisting of any one of SEQ ID NO:893 to SEQ ID NO:1115, preferably of any one of SEQ ID NO: 897,

SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919, more preferably SEQ ID NO: 907 or SEQ ID NO: 914, wherein the second strand has the following structure:



wherein:

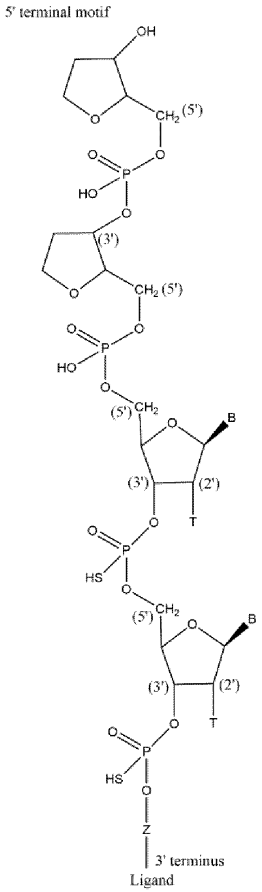
T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of any one of SEQ ID NO:893 to SEQ ID NO:1115, preferably of any one of SEQ ID NO: 897, SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919, more preferably SEQ ID NO: 907 or SEQ ID NO: 914, and

Z represents the remaining 19 contiguous basic nucleosides of any one of SEQ ID NO:893 to SEQ ID NO:1115, preferably of any one of SEQ ID NO: 897, SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919, more preferably SEQ ID NO: 907 or SEQ ID NO: 914.

[0391] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 5 (Formula XI), wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid according to the invention comprises a modified second strand comprising or consisting of any one of

SEQ ID NO:893 to SEQ ID NO:1115, preferably of any one of SEQ ID NO: 897, SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919, more preferably SEQ ID NO: 907 or SEQ ID NO: 914, wherein the second strand has the following structure:



wherein:

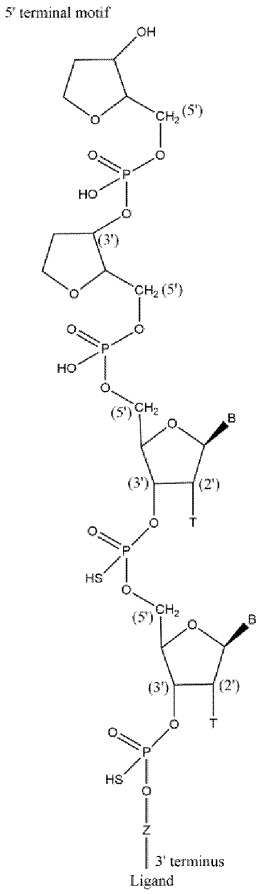
T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of any one of SEQ ID NO:893 to SEQ ID NO:1115, preferably of any one of SEQ ID NO: 897, SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919, more preferably SEQ ID NO: 907 or SEQ ID NO: 914, and

Z represents the remaining 19 contiguous basic nucleosides of any one of SEQ ID NO:893 to SEQ ID NO:1115, preferably of any one of SEQ ID NO: 897, SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919, more preferably SEQ ID NO: 907 or SEQ ID NO: 914.

[0392] In some embodiments, the GalNAc ligand is comprised in the linker shown in Figure 3, wherein the "oligonucleotide" represents a nucleic acid according to the invention, wherein the nucleic acid

according to the invention comprises a modified second strand comprising or consisting of any one of SEQ ID NO:893 to SEQ ID NO:1115, wherein the second strand has the following structure:



wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of any one of SEQ ID NO:893 to SEQ ID NO:1115, and

Z represents the remaining 19 contiguous basic nucleosides of any one of SEQ ID NO:893 to SEQ ID NO:1115, respectively.

[0393] In some embodiments, the ligand moiety comprises one or more ligands.

[0394] In some embodiments, the ligand moiety comprises one or more carbohydrate ligands.

[0395] In some embodiments, the one or more carbohydrates can be a monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and / or polysaccharide.

[0396] 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.

[0397] In some embodiments, the one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

[0398] In some embodiments, the compounds as described anywhere herein comprise two or three N-AcetylGalactosamine moieties.

[0399] 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.

[0400] Exemplary linear configurations and Exemplary branched configurations are shown in Figures 15a and 15b:

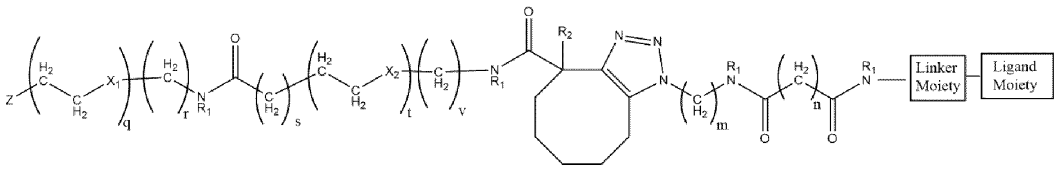
[0401] In Fig 15a, (linear), (a) and / or (b) can typically represent connecting bonds or groups, such as phosphate or phosphorothioate groups.

[0402] In Fig 15b, (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

[0403] Exemplary compounds of the invention comprise a 'linker moiety', such as that as depicted in Formula (I), that is part of an overall 'linker'.

Formula I



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 oligonucleoside moiety.

[0404] 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.

[0405] 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, which 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.

[0406] 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 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.

[0407] 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

[0408] In relation to Formula (I), the 'tether moiety' comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety.

[0409] In some embodiments, R_1 is hydrogen at each occurrence. In some embodiments, R_1 is methyl. In some embodiments, R_1 is ethyl.

[0410] In some embodiments, R_2 is hydroxy. In some embodiments, R_2 is halo. In some embodiments, R_2 is fluoro. In some embodiments, R_2 is chloro. In some embodiments, R_2 is bromo. In some embodiments, R_2 is iodo. In some embodiments, R_2 is nitro.

[0411] In some embodiments, X_1 is methylene. In some embodiments, X_1 is oxygen. In some embodiments, X_1 is sulfur.

[0412] In some embodiments, X_2 is methylene. In some embodiments, X_2 is oxygen. In some embodiments, X_2 is sulfur.

[0413] In some embodiments, m = 3.

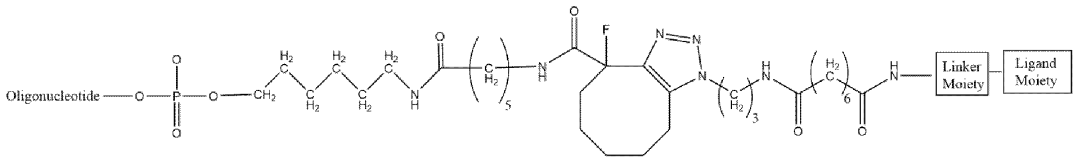
[0414] In some embodiments, n = 6.

[0415] In some embodiments, X_1 is oxygen and X_2 is methylene. In some embodiments, both X_1 and X_2 are methylene.

[0416] 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.

[0417] 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.

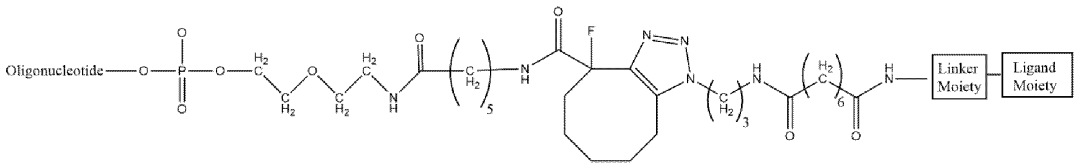
[0418] Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (IV)

[0419] 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.

[0420] Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (II)

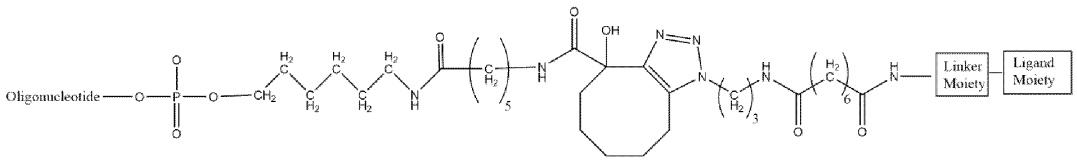
Alternative tether moieties

[0421] 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.

[0422] In some embodiments, the alternative tether moiety is a compound of Formula (I) as described anywhere herein, wherein R_2 is hydroxy.

[0423] 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.

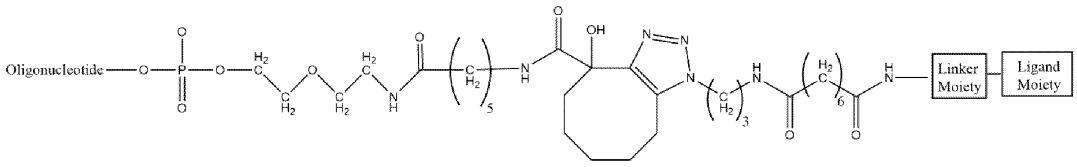
[0424] Thus, in some embodiments, compounds of the invention comprise the following structure:



Formula (V)

[0425] 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.

[0426] Thus, in some embodiments, compounds of the invention comprise the following structure:

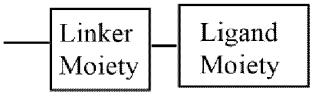


Formula (III)

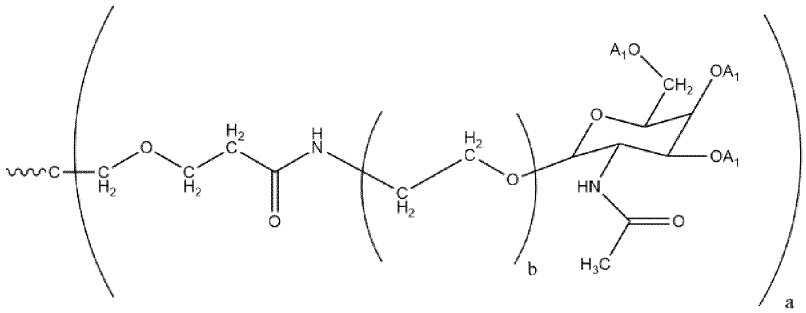
Linker moiety

[0427] 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.

[0428] In some embodiments:



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



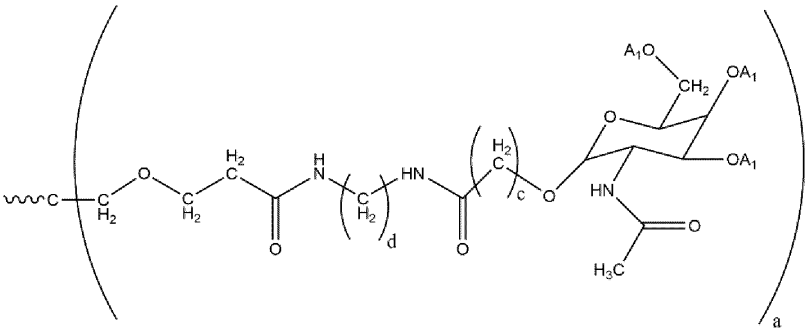
Formula (VIa)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

b is an integer of 2 to 5; or



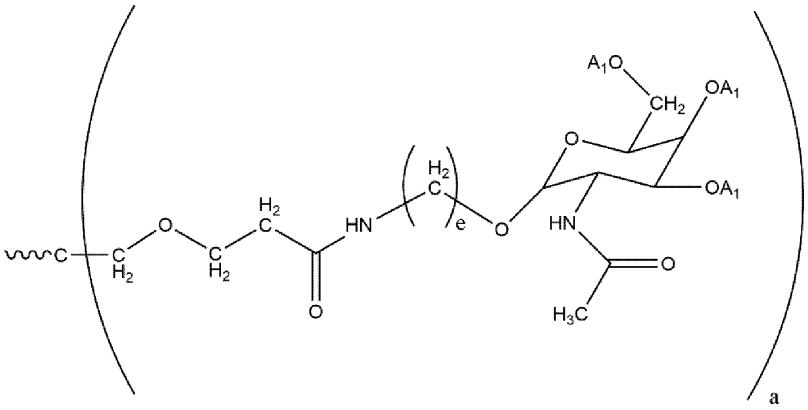
Formula (VIb)

wherein:

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)

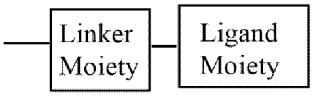
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

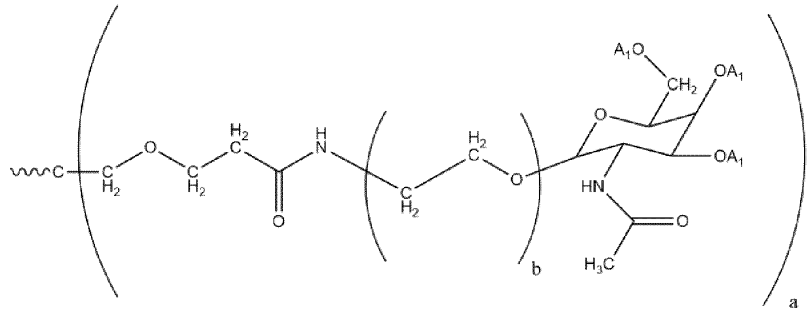
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

[0429] In some embodiments, the moiety:



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



Formula (VIa)

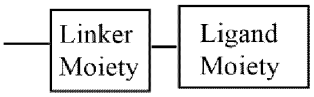
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

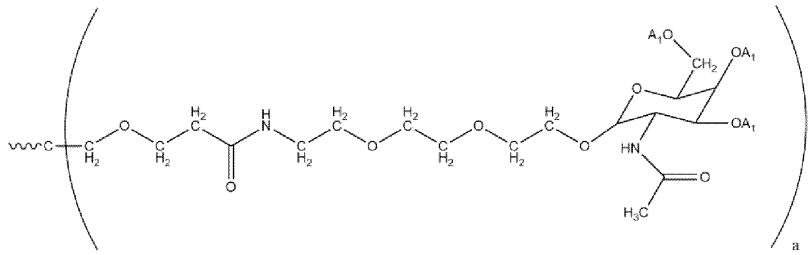
a is 3; and

b is an integer of 3.

[0430] In some embodiments, the moiety:



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



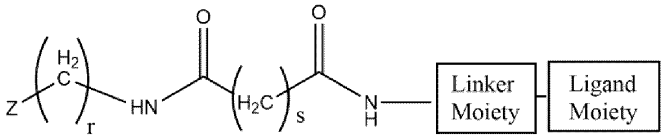
Formula (VII)

wherein:

A_I is hydrogen;

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

[0431] Other exemplary compounds of the invention comprise a 'linker moiety', as depicted in Formula (I*), that is part of an overall 'linker'.



Formula I*

Where:

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

Z is an oligonucleoside moiety.

[0432] 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.

[0433] 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, which 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.

[0434] 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 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.

[0435] 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

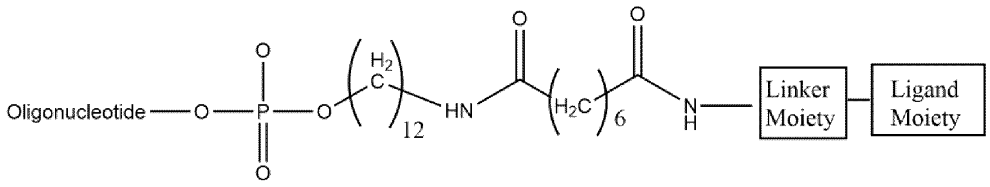
[0436] In relation to Formula (I*), the 'tether moiety' comprises the group of atoms between Z, namely the oligonucleoside moiety, and the linker moiety.

[0437] In some embodiments, s is an integer selected from 4 to 12. In some embodiments, s is 6.

[0438] In some embodiments, r is an integer selected from 4 to 14. In some embodiments, r is 6. In some embodiments, r is 12.

[0439] In some embodiments, r is 12 and s is 6.

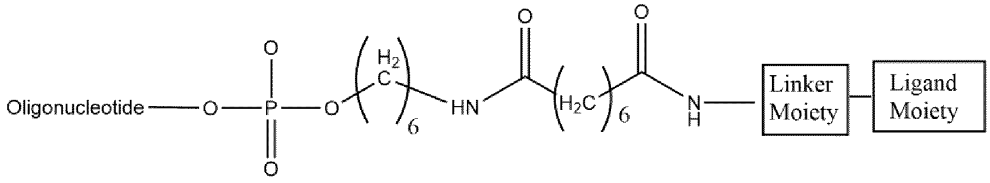
[0440] Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:



Formula (II*)

[0441] In some embodiments, r is 6 and s is 6.

[0442] Thus, in some embodiments, exemplary compounds of the invention comprise the following structure:

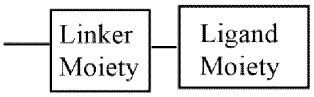


Formula (III*)

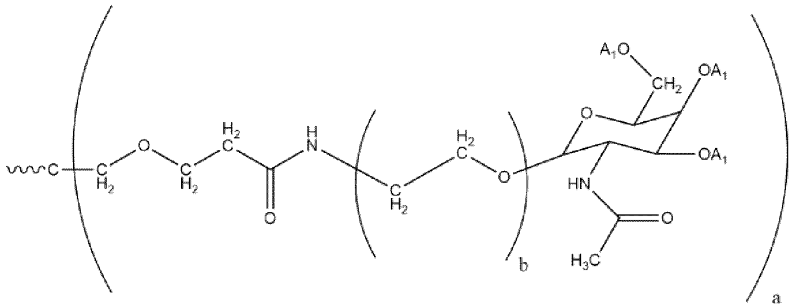
Linker moiety

[0443] 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.

[0444] In some embodiments, the moiety:



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



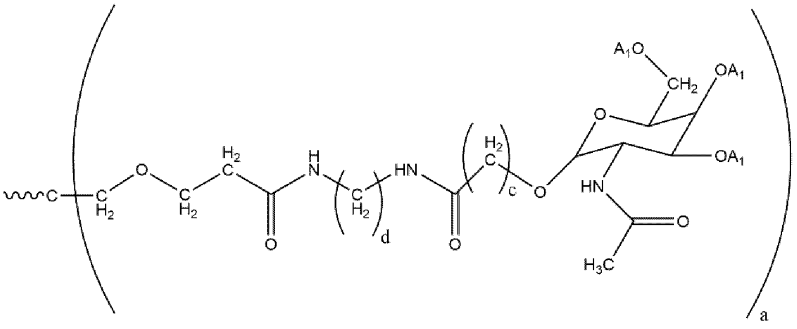
Formula (IV*)

wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

a is an integer of 2 or 3; and

b is an integer of 2 to 5; or



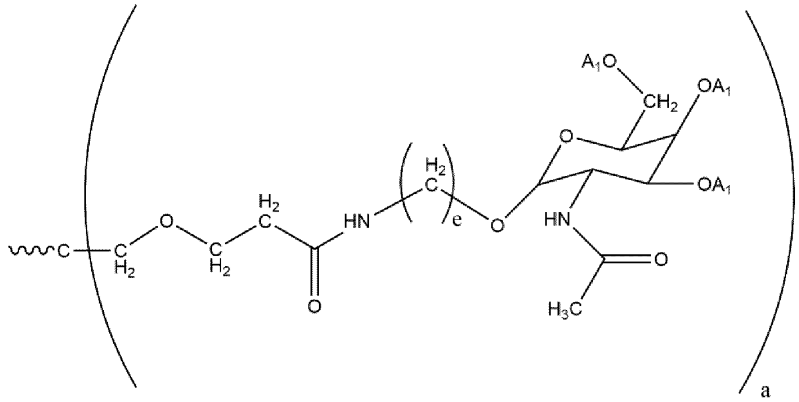
Formula (V*)

wherein:

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 (VI*)

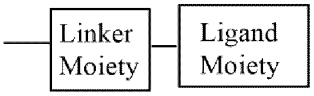
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

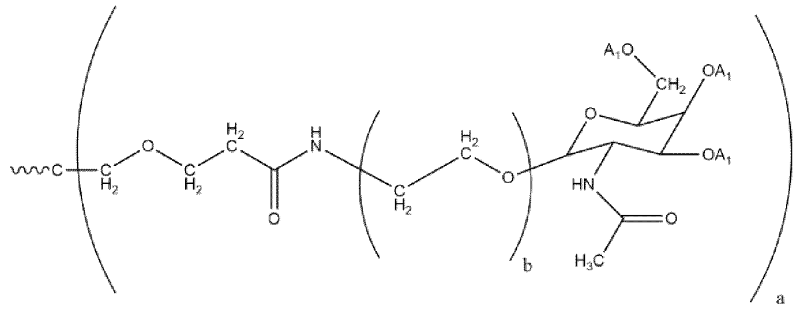
a is an integer of 2 or 3; and

e is an integer of 2 to 10.

[0445] In some embodiments, the moiety:



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



Formula (VIa*)

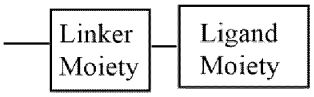
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

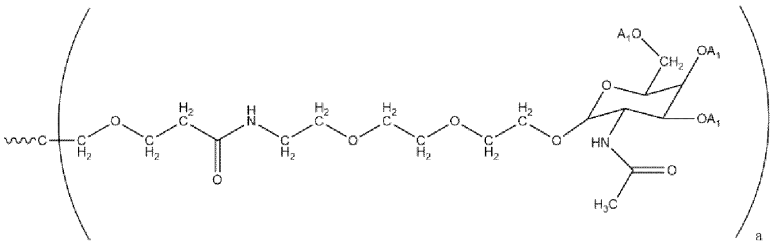
a is 3; and

b is an integer of 3.

[0446] In some embodiments, the moiety:



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



Formula (VII*)

wherein:

A_I is hydrogen;

a is an integer of 2 or 3.

[0447] In some embodiments, a = 2. In some embodiments, a = 3. In some embodiments, b = 3.

VECTOR AND CELL

[0448] In one aspect, the invention provides a cell containing a nucleic acid, such as inhibitory RNA [RNAi] as described herein.

[0449] In one aspect, the invention provides a cell comprising a vector as described herein.

[0450] In one aspect the invention provides a vector comprising an oligonucleotide inhibitor, *e.g.,* an iRNA *e.g.,* siRNA.

PHARMACEUTICALLY ACCEPTABLE COMPOSITIONS

[0451] 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.

[0452] The pharmaceutically acceptable composition may comprise an excipient and or carrier.

[0453] 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.

[0454] 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).

[0455] 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.

[0456] 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.

[0457] 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

[0458] 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.

[0459] 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).

[0460] In the present invention, in particular regarding the treatment of myocardial infarction and/or symptoms thereof, it is preferred that the first administration of the inhibitor is shortly after the myocardial infarction occurred. In particular, the inhibitor of the invention may preferably first be administered at the time a myocardial infarction occurs or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hours after myocardial infarction occurred. It is also provided herein that the inhibitor of the invention is first administered within 1 day, 2, 3, 4, 5, 6, 7, 8, 9 or 10 days after myocardial infarction.

[0461] 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).

[0462] 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.

[0463] 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 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.

[0464] 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 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.

[0465] 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.

[0466] 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. 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 compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection.

[0467] In one embodiment, the nucleic acid *e.g.,* siRNA agent is administered to the subject subcutaneously.

[0468] The inhibitor *e.g.,* nucleic acid *e.g.,* siRNA can be delivered in a manner to target a particular tissue (*e.g.,* in particular heart cells).

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

[0469] The present invention also provides methods of inhibiting expression of a gene in a cell and methods for inhibiting expression and/or function of other target molecules. The methods include contacting a cell with a nucleic acid of the invention *e.g.,* siRNA agent, such as double stranded siRNA in

an amount effective to inhibit expression of the gene in the cell, thereby inhibiting expression of the gene in the cell. In a preferred embodiment, the gene is NR3C2.

[0470] The present invention also provides methods of inhibiting expression of NR3C2 gene in a cell.

[0471] It is to be noted that a nucleic acid "for inhibiting the expression of NR3C2" is a nucleic acid that is capable of inhibiting NR3C2 expression, preferably as described herein below.

[0472] Contacting of a cell with the inhibitor *e.g.,* 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 the inhibitor nucleic acid *e.g.,* siRNA 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.

[0473] The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating", "suppressing", and other similar terms, and includes any level of inhibition.

[0474] In some embodiments of the methods of the invention, expression or activity of a gene or an inhibition target 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. In certain embodiments, the methods include a clinically relevant inhibition of expression of a 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 and/ or activity of the target.

[0475] In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression of the NR3C2 gene with an EC50 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.

[0476] In a preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of the NR3C2 gene with an EC50 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 NR3C2 gene with an EC50 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 NR3C2 gene with an EC50 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 NR3C2 gene with an EC50 value lower than 100 pM.

[0477] 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.

[0478] In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression of the NR3C2 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.

[0479] Alternatively, or in addition, inhibition of expression of the NR3C2 gene may be characterized by a reduction of mean relative expression of the NR3C2 gene.

[0480] In some embodiments, when cells are transfected with 0.1 nM of the nucleic acid of the invention, the mean relative expression of NR3C2 is below 1, 0.9, 0.8, 0.7, 0.6, 0.5, or 0.4, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

[0481] In some embodiments, when cells are transfected with 5 nM of the nucleic acid of the invention, the mean relative expression of NR3C2 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.

[0482] Inhibition of expression of the NR3C2 gene may be quantified by the following method:

[0483] HEK293 cells (human kidney-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 NR3C2 mRNA or a negative control siRNA (siRNA-control; sense strand 5'-GCCTGTACCAAGGCTTTAA-3' (SEQ ID NO:1117), antisense strand 5'-TTAAAGCCTTGGTACAGGC-3' (SEQ ID NO:1118)) in a 6-point, log dose response curve to give final in assay concentrations of 3nM to 0.03pM. Transfection may be carried out by diluting Lipofectamine RNAi MAX (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 RNAi MAX and siRNA mixture may be incubated at room temperature for 15 minutes before 20 µL was added to wells of a 96 well plate. HEK293 cells may be dissociated from flasks using trypsin and resuspended at a density of 300,000 cells/mL. 100 µL of HEK293 cell suspension may be added to each well of the siRNA-containing 96-well plates. Cells may then 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.

[0484] Intracellular RNA may be isolated using a RNeasy kit (Qiagen) according to the manufacturer's instructions. cDNA synthesis may be performed using a HiScript III RT SuperMix kit (Vazyme) according to the manufacturer's instructions. Target cDNA may be quantified by qPCR on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human NR3C2 and human GAPDH (forward:

GAAGGTGAAGGTCGGAGTC (SEQ ID NO:1119), reverse: GAAGATGGTGATGGGATTTC (SEQ ID NO:1120)) using an AceQ Universal U+ Probe Master Mix (Vazyme).

[0485] qPCR may be performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative NR3C2 expression may be calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalized to GAPDH and relative to untreated cells. Maximum percent inhibition of NR3C2 expression and EC50 and/or pEC50 values (-log10 of the EC50) may be calculated using a four parameter (variable slope) model using NumPy (Python).Inhibition of the expression of a gene may be manifested by a reduction of the amount of mRNA of the target gene of interest in comparison to a suitable control. Inhibition of the function of a target may be manifested by a reduction of the activity of the target in comparison to a suitable control.

[0486] In other embodiments, inhibition of the expression of a gene or other target may be assessed in terms of a reduction of a parameter that is functionally linked to gene expression, *e.g.,* protein expression or signalling pathways.

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

[0487] 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 a cell or reduce expression or function of a target. The methods include contacting the cell with a nucleic acid *e.g.,* dsiRNA 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 NR3C2.

[0488] 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 NR3C2 gene expression in a cell.

[0489] 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.

[0490] 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.

[0491] A cell suitable for treatment using the methods of the invention may be any cell that expresses a gene of interest associated with ischaemic heart diseases, in particular myocardial infarction, and/or symptoms thereof.

[0492] A cell suitable for treatment using the methods of the invention may be any cell that expresses a gene of interest associated with HFrEF and/or HFpEF.

[0493] 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.

[0494] 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.

[0495] 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 NR3C2 gene, in a therapeutically effective amount *e.g.,* a nucleic acid such as an siRNA targeting NR3C2 or a pharmaceutical composition comprising the nucleic acid targeting NR3C2. The disease to be treated is related to ischaemic heart diseases, in particular myocardial infarction, and/or symptoms thereof, HFrEF and/or symptoms thereof, and/or HFpEF and/or symptoms thereof.

[0496] As described herein, the invention pertains to treatment of HFrEF and/or HFpEF. Any reference herein to a disease, including ischaemic heart disease, can equally be considered reference to HFrEF and/or HFpEF where allowed by context.

[0497] That is, the nucleic acid according to the invention may be used in the prevention and/or treatment of an ischaemic heart disease. The term, "ischaemic heart disease", as used herein, means any disorder resulting from an imbalance between the myocardial need for oxygen and the adequacy of the oxygen supply. Most cases of ischemic heart disease result from narrowing of the coronary arteries, as occurs in atherosclerosis or other vascular disorders. The nucleic acid of the invention additionally may be useful for treating ischaemic damage to other organs. Non-limiting examples of ischemic heart diseases include ischemic cardiomyopathy, myocardial infarction or ischemic heart failure and chronic ischemic heart disease.

[0498] The patient to be treated may be a patient that already has an ischaemic heart disease or that is at risk of developing an ischaemic heart disease. That is, in certain embodiments, the nucleic acid of the present invention may be used in the treatment of an existing ischaemic heart disease. Treatment of an existing ischaemic heart disease with the nucleic acid of the present invention may prevent worsening of

the ischaemic heart disease and/or ischaemic heart disease. In some instances, treatment of an existing ischaemic heart disease with the nucleic acid of the present invention may even cure the ischaemic heart disease. In certain embodiments, the nucleic acid of the present invention may be used to prevent manifestation of an ischaemic heart disease in a patient that is at risk of developing an ischaemic heart disease.

[0499] The skilled person is capable of diagnosing whether a patient has an ischaemic heart disease or is at risk of developing an ischaemic heart disease. Diagnosing an ischaemic heart disease may include medical history analysis, physical examination, imaging tests (such as ECG or stress test), blood tests (*e.g.,* cardiac enzymes), and/or coronary angiography.

[0500] In certain embodiments, the ischaemic heart disease is myocardial infarction. The term "myocardial infarction", as used herein, means a process by which ischemic disease results in a region of the myocardium being replaced by scar tissue.

[0501] The patient to be treated may be a patient that already has HFrEF and/or HFpEF or that is at risk of developing HFrEF and/or HFpEF. That is, in certain embodiments, the nucleic acid of the present invention may be used in the treatment of existing HFrEF and/or HFpEF. Treatment of existing HFrEF and/or HFpEF with the nucleic acid of the present invention may prevent worsening of the HFrEF and/or HFpEF and/or associated diseases. In some instances, treatment of existing HFrEF and/or HFpEF with the nucleic acid of the present invention may even cure the HFrEF and/or HFpEF. In certain embodiments, the nucleic acid of the present invention may be used to prevent manifestation of HFrEF and/or HFpEF in a patient that is at risk of developing HFrEF and/or HFpEF.

[0502] The skilled person is capable of diagnosing whether a patient has HFrEF and/or HFpEF or is at risk of developing HFrEF and/or HFpEF. Diagnosing HFrEF and/or HFpEF may include medical history analysis, physical examination, imaging tests (such as ECG or stress test), blood tests (*e.g.,* cardiac enzymes), and/or coronary angiography.

[0503] In certain embodiments, the nucleic acid of the invention may be administered to a patient that is at risk of myocardial infarction. Risk factors for myocardial infarction include, without limitation, age, tobacco use, high blood pressure, high cholesterol or triglycerides, obesity, diabetes, metabolic syndrome, family history or heart attacks, lack of exercise, unhealthy diet, stress, drug use, history of preeclampsia and autoimmune conditions.

[0504] In certain embodiments, the nucleic acid of the invention may be administered to a patient after myocardial infarction. That is, the patient to be treated may be a patient that had a history of one or more myocardial infarctions. In such patients, the nucleic acid of the invention may be administered to prevent the occurrence of further myocardial infarctions.

[0505] In certain embodiments, the nucleic acid of the invention may be administered to a patient that is at risk of HFrEF and/or HFpEF. Risk factors for HFrEF and/or HFpEF include, without limitation, age, tobacco use, high blood pressure, high cholesterol or triglycerides, obesity, diabetes, metabolic syndrome, family history or heart attacks, lack of exercise, unhealthy diet, stress, drug use, history of preeclampsia and autoimmune conditions, sex, type 2 diabetes, obesity, sleep apnea, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, iron deficiency, with or without anemia, coronary artery disease, atrial fibrillation, dysrhythmias.

[0506] A person skilled in the art, such as a physician is capable of determining whether a patient is at risk of developing an ischaemic heart disease, in particular a myocardial infarction, HFrEF and/or HFpEF, or whether a person already had an ischaemic heart disease, in particular a myocardial infarction, HFrEF and/or HFpEF.

[0507] 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 osmolarity of the buffer solution can be adjusted such that it is suitable for administering to a subject.

[0508] Alternatively, a nucleic acid *e.g.,* siRNA of the invention may be administered as a pharmaceutical composition, such as a dsiRNA liposomal formulation.

[0509] 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 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.

[0510] 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.

[0511] 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, so as to prevent and/or treat an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, HFrEF and/or symptoms thereof, and/or HFpEF and/or symptoms thereof.

[0512] 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.

[0513] 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.,* s iRNA 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).

[0514] In one aspect the present invention may be applied in the compounds, processes, compositions or uses of the formulae of Figures 5 and 6.

EXAMPLES

[0515] 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.

[0516] Examples 1-5 (Synthesis of tether 1, Duplex Annealing, Synthesis of tether 2, Duplex Annealing, and Alternative synthesis route for the conjugate building block TriGalNAc _Tether2) are specifically disclosed in PCT/EP2023/070919 (WO2024/023262) as Examples 1-5. That disclosure is hereby incorporated by reference.

EXAMPLE 6: SOLID PHASE SYNTHESIS METHOD: SCALE ≤1μMOL

[0517] 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).

[0518] RNA phosphoramidites were purchased from ChemGenes or Hongene.

[0519] 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.

[0520] 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.

[0521] 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.

[0522] 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).

[0523] At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

[0524] The coupling time was 180 seconds. The oxidizer contact time was set to 80 seconds and thiolation time was 2*100 seconds.

[0525] 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.

[0526] 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.

[0527] 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 7: SOLID PHASE SYNTHESIS METHOD: SCALE ≥5 μMOL

[0528] Syntheses of siRNA sense and antisense strands were performed on a MerMade12 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) at 5 μmol scale. Sense strand destined

to 3' conjugation were sytnthesised at 12 μmol on 3'-PT-Amino-Modifier C6 CPG 500 Å solid support with a loading of 86 μmol/g (LGC).

[0529] RNA phosphoramidites were purchased from ChemGenes or Hongene.

[0530] 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.

[0531] 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.

[0532] 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).

[0533] 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.

[0534] At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

[0535] For strands synthesised on universal CPG the coupling was performed with 8 eq. of amidite for 130 seconds. The oxidation time was 47 seconds, the thiolation time was 210 seconds.

[0536] 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.

[0537] 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.

[0538] Oligonucleotide were treated to form the sodium salt by EtOH precipitation from 1M sodium acetate.

[0539] 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.

[0540] 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).

[0541] Sense strands were conjugated as per protocol provided in any of Examples 2, 4, 6.

[0542] Sense and Antisense strands were then annealed in water to form the final duplex siRNA and duplex purity were assessed by size exclusion chromatography.

EXAMPLE 8: NUCLEIC ACID SEQUENCES

[0543] siRNA oligonucleosides according to the present invention target NR3C2. The full DNA sequence of the NR3C2 target gene is SEQ ID NO:1116.

[0544] Following Table 1 provides oligonucleoside mRNA target sequences of NR3C2, together with the corresponding positions in transcript ENST00000358102.8. It is to be understood that SEQ ID NO: 1 to 223 refer to human (Homo sapiens) mRNA sequences.

Table 1

SEQ ID NO	Oligonucleoside mRNA target sequence 5' → 3'	Starting position on ENST00000358102.8
SEQ ID NO: 1	UUAUGGAUGAUAAAGACUAUUAU	1636
SEQ ID NO: 2	UAUGGAUGAUAAAGACUAUUAUU	1637
SEQ ID NO: 3	CCUUUAUGGAUGAUAAAGACUAU	1633
SEQ ID NO: 4	GAAUACACCAUCAUGAAAGUUUU	2859
SEQ ID NO: 5	AAGCUCUACUUUACGAAGUGUUU	2012
SEQ ID NO: 6	AGCUCUACUUUACGAAGUGUUUC	2013
SEQ ID NO: 7	GUUUAUAUAUGGAUUCUGUAAGA	574
SEQ ID NO: 8	GUUGAACAGCUGGUGAAAUUUUA	666
SEQ ID NO: 9	UCCUCUCUCAAGUCCGUUAAGUA	1034
SEQ ID NO: 10	UUGAACAGCUGGUGAAAUUUUAC	667
SEQ ID NO: 11	UAUAUAUGGAUUCUGUAAGAGAU	577
SEQ ID NO: 12	AAAUGUAUCAAGCUCUACUUUAC	2003

SEQ ID NO: 13	GUCACUGCAGUGUAAAAUCUCCA	1087
SEQ ID NO: 14	UAGGAGGAAAUAGCAAAAUAAAU	1489
SEQ ID NO: 15	CUGGAAGAAAUGAUUGCAUCAUU	2176
SEQ ID NO: 16	UGCAGUGUAAAAUCUCCAGUCUC	1092
SEQ ID NO: 17	CUUGCAGACUUCAGAAAUGUCUU	2227
SEQ ID NO: 18	CAGUGUAAAAUCUCCAGUCUCCA	1094
SEQ ID NO: 19	CAGCUGCAAAGUUUUCUUCAAAA	2120
SEQ ID NO: 20	GCAGCUGCAAAGUUUUCUUCAAA	2119
SEQ ID NO: 21	AUGAUAAAGACUAUUAUUCCCUA	1642
SEQ ID NO: 22	UCCAGAAAAUGUAUCAAGCUCUA	1997
SEQ ID NO: 23	CAUUCUCAGUACCAAUAAAGCAA	1522
SEQ ID NO: 24	UUGAUAAGAUUCGACGAAAGAAU	2197
SEQ ID NO: 25	UGGGUUUAUAUAUGGAUUCUGUA	571
SEQ ID NO: 26	CUGCUACUAAGCACAAUUCCAAA	2883
SEQ ID NO: 27	CCCUCCAAGUCACUGCAGUGUAA	1079
SEQ ID NO: 28	UGUUGAACAGCUGGUGAAAUUUU	665
SEQ ID NO: 29	AUCAUGAAAGUUUUGCUGCUACU	2868
SEQ ID NO: 30	UUCCAGAAAAUGUAUCAAGCUCU	1996
SEQ ID NO: 31	CAAGUCACUGCAGUGUAAAAUCU	1084
SEQ ID NO: 32	UCUUAGAAUACAUUCCAGAAAAU	1984
SEQ ID NO: 33	GCUGAGUCCAUGGGUUUAUAUAU	561
SEQ ID NO: 34	CGAUCGGCUAGAGACCAAUCUUU	1866
SEQ ID NO: 35	UUUCCUUUAUGGAUGAUAAAGAC	1630
SEQ ID NO: 36	AUGUUGAACAGCUGGUGAAAUUU	664
SEQ ID NO: 37	AAAAUGUAUCAAGCUCUACUUUA	2002
SEQ ID NO: 38	CUUUAUGGAUGAUAAAGACUAUU	1634
SEQ ID NO: 39	AGGAGGAAAUAGCAAAAUAAAUU	1490
SEQ ID NO: 40	AAUGAUUGCAUCAUUGAUAAGAU	2184
SEQ ID NO: 41	CAUCAUGAAAGUUUUGCUGCUAC	2867
SEQ ID NO: 42	UUUAUGUGCUGGAAGAAAUGAUU	2168
SEQ ID NO: 43	UAAGAGAUGCUGACUAUUCCUAU	592
SEQ ID NO: 44	CCUGCUGGAAUUCUGCUUCUACA	3068
SEQ ID NO: 45	CUGUAAGAGAUGCUGACUAUUCC	589
SEQ ID NO: 46	UCUAGGAGGAAAUAGCAAAAUAA	1487
SEQ ID NO: 47	UACACCAUCAUGAAAGUUUUGCU	2862
SEQ ID NO: 48	GGUAUCCGGUCUUAGAAUACAUU	1975
SEQ ID NO: 49	AAGUCCGUUAAGUAGCAUGAAAU	1043
SEQ ID NO: 50	AGUCACUGCAGUGUAAAAUCUCC	1086
SEQ ID NO: 51	UUCUGUAAGAGAUGCUGACUAUU	587
SEQ ID NO: 52	UCCUUUAUGGAUGAUAAAGACUA	1632
SEQ ID NO: 53	AUGGGUUUAUAUAUGGAUUCUGU	570

SEQ ID NO: 54	UCUCUCAAGUCCGUUAAGUAGCA	1037
SEQ ID NO: 55	AGCCCUCUGAACAUGACAUCUUC	843
SEQ ID NO: 56	CUAAGGAACUUUCAGCAACUGUA	538
SEQ ID NO: 57	AUUCUGUAAGAGAUGCUGACUAU	586
SEQ ID NO: 58	CUGGUGAAAUUUUACAAAGGAAA	675
SEQ ID NO: 59	AAUCUAAGGAACUUUCAGCAACU	535
SEQ ID NO: 60	GAAGAAAUGAGGACAAAUUACAU	2934
SEQ ID NO: 61	AGUACCAAUAAAGCAAGAAUCAA	1529
SEQ ID NO: 62	AUGUCUUCAAGCUGGAAUGAAUU	2243
SEQ ID NO: 63	CAGCUUAAUAUUGUCCAGUACAU	1428
SEQ ID NO: 64	GGGUUUAUAUAUGGAUUCUGUAA	572
SEQ ID NO: 65	CUCCAAGUCACUGCAGUGUAAAA	1081
SEQ ID NO: 66	UGGAUGAUAAAGACUAUUAUUCC	1639
SEQ ID NO: 67	AUGAUUGCAUCAUUGAUAAGAUU	2185
SEQ ID NO: 68	GCUGGUGAAAUUUUACAAAGGAA	674
SEQ ID NO: 69	AGGACAAAUUACAUCAAAGAACU	2943
SEQ ID NO: 70	GCAGUGUAAAAUCUCCAGUCUCC	1093
SEQ ID NO: 71	CAUGAAAGUUUUGCUGCUACUAA	2870
SEQ ID NO: 72	GAUAUUAAAACUGAGCUGGAAUC	516
SEQ ID NO: 73	UUUUCCUUUAUGGAUGAUAAAGA	1629
SEQ ID NO: 74	GAUUCCCAGUGGGUAUUAAACAA	1720
SEQ ID NO: 75	CACCUCUGCUGGAUCCAGUACAU	1298
SEQ ID NO: 76	UGGAUUCUGUAAGAGAUGCUGAC	583
SEQ ID NO: 77	ACUACAUGGAGAUUGUCAACGUA	379
SEQ ID NO: 78	AAGUCACUGCAGUGUAAAAUCUC	1085
SEQ ID NO: 79	AACAGCUGGUGAAAUUUUACAAA	670
SEQ ID NO: 80	UUUAUGGAUGAUAAAGACUAUUA	1635
SEQ ID NO: 81	CCAGCUAAGAUUUAUCAGAAUGU	645
SEQ ID NO: 82	UAGAAUACAUUCCAGAAAAUGUA	1987
SEQ ID NO: 83	UGAUAAGAUUCGACGAAAGAAUU	2198
SEQ ID NO: 84	UUAAGUAGCAUGAAAUCCUCAAU	1050
SEQ ID NO: 85	CACCUGAGUUCCUUUCCUCCUGU	1893
SEQ ID NO: 86	GGCAGCUGCAAAGUUUUCUUCAA	2118
SEQ ID NO: 87	AGUAGCAUGAAAUCCUCAAUUUC	1053
SEQ ID NO: 88	GUCUAGGAGGAAAUAGCAAAAUA	1486
SEQ ID NO: 89	CUGAUAUUAAAACUGAGCUGGAA	514
SEQ ID NO: 90	CUUAAUAUUGUCCAGUACAUAAA	1431
SEQ ID NO: 91	GCUAAGAUUUAUCAGAAUGUUGA	648
SEQ ID NO: 92	UGGUGAAAUUUUACAAAGGAAAU	676
SEQ ID NO: 93	CGUUAAGUAGCAUGAAAUCCUCA	1048
SEQ ID NO: 94	CUGCAGUGUAAAAUCUCCAGUCU	1091

SEQ ID NO: 95	UCAUGAAAGUUUUGCUGCUACUA	2869
SEQ ID NO: 96	UGAUAUUAAAACUGAGCUGGAAU	515
SEQ ID NO: 97	UCCGUUAAGUAGCAUGAAAUCCU	1046
SEQ ID NO: 98	UUGCAGACUUCAGAAAUGUCUUC	2228
SEQ ID NO: 99	AGCUUAAUAUUGUCCAGUACAUA	1429
SEQ ID NO: 100	GUCCAGCUAAGAUUUAUCAGAAU	643
SEQ ID NO: 101	CAAGCUCUACUUUACGAAGUGUU	2011
SEQ ID NO: 102	CAGCUAAGAUUUAUCAGAAUGUU	646
SEQ ID NO: 103	CUCAGUACCAAUAAAGCAAGAAU	1526
SEQ ID NO: 104	CUCCUCUCUCAAGUCCGUUAAGU	1033
SEQ ID NO: 105	UGUAUCAAGCUCUACUUUACGAA	2006
SEQ ID NO: 106	GAAUGUUGAACAGCUGGUGAAAU	662
SEQ ID NO: 107	CUAAGAUUUAUCAGAAUGUUGAA	649
SEQ ID NO: 108	AGUCCAUGGGUUUAUAUAUGGAU	565
SEQ ID NO: 109	UUGAAGAAAUGAGGACAAAUUAC	2932
SEQ ID NO: 110	AUUGAUAAGAUUCGACGAAAGAA	2196
SEQ ID NO: 111	GAUGAUAAAGACUAUUAUUCCCU	1641
SEQ ID NO: 112	GUAGCUGAGUCCAUGGGUUUAUA	558
SEQ ID NO: 113	UUUCCUAAGACUGAGGAAGUAGA	1377
SEQ ID NO: 114	CUUUCCAACACCUGAGUUCCUUU	1885
SEQ ID NO: 115	AUCAUUGAUAAGAUUCGACGAAA	2193
SEQ ID NO: 116	UAGCAUGAAAUCCUCAAUUUCCA	1055
SEQ ID NO: 117	AGAAAAUGUAUCAAGCUCUACUU	2000
SEQ ID NO: 118	GCUGCUACUAAGCACAAUUCCAA	2882
SEQ ID NO: 119	CAGUACUGUGGGAUCUAUCUGUA	1238
SEQ ID NO: 120	CUAGGAGGAAAUAGCAAAAUAAA	1488
SEQ ID NO: 121	AAGAAAUGAUUGCAUCAUUGAUA	2180
SEQ ID NO: 122	UCCAAGUCACUGCAGUGUAAAAU	1082
SEQ ID NO: 123	GAGUCCAGCUAAGAUUUAUCAGA	641
SEQ ID NO: 124	AUUGCAUCAUUGAUAAGAUUCGA	2188
SEQ ID NO: 125	CCGUUAAGUAGCAUGAAAUCCUC	1047
SEQ ID NO: 126	ACUAAUAACAGAUCCACGCUUUC	1203
SEQ ID NO: 127	CAGAAAAUGUAUCAAGCUCUACU	1999
SEQ ID NO: 128	GUCCAUGGGUUUAUAUAUGGAUU	566
SEQ ID NO: 129	GAAAAUGUAUCAAGCUCUACUUU	2001
SEQ ID NO: 130	AGUCCGUUAAGUAGCAUGAAAUC	1044
SEQ ID NO: 131	UGAUAAAGACUAUUAUUCCCUAU	1643
SEQ ID NO: 132	AUGAAAGUUUUGCUGCUACUAAG	2871
SEQ ID NO: 133	CUCUCCUCUCUCAAGUCCGUUAA	1031
SEQ ID NO: 134	AGAGGACCGAUGAGAAUAACUAC	361
SEQ ID NO: 135	AAUACACCAUCAUGAAAGUUUUG	2860

SEQ ID NO: 136	AUUUGAAGAAAUGAGGACAAAUU	2930
SEQ ID NO: 137	AUGGAUGAUAAAGACUAUUAUUC	1638
SEQ ID NO: 138	AUUAAAACUGAGCUGGAAUCUAA	519
SEQ ID NO: 139	GAGAAUAACUACAUGGAGAUUGU	372
SEQ ID NO: 140	UGUAAGAGAUGCUGACUAUUCCU	590
SEQ ID NO: 141	ACCAUCAUGAAAGUUUUGCUGCU	2865
SEQ ID NO: 142	AGUACAUAAAACCAGAACCAGAU	1444
SEQ ID NO: 143	UUUUGCUGCUACUAAGCACAAUU	2878
SEQ ID NO: 144	UUCGACUGCAGCUCACCUUUGAA	2836
SEQ ID NO: 145	UAUUAAAACUGAGCUGGAAUCUA	518
SEQ ID NO: 146	UUUAGUGGAGUCAUGGAAAUCAC	1922
SEQ ID NO: 147	AAAGUUUUGCUGCUACUAAGCAC	2874
SEQ ID NO: 148	UUUGAAGAAAUGAGGACAAAUUA	2931
SEQ ID NO: 149	UACUCAAGGAAGCAGCAAAGAAA	434
SEQ ID NO: 150	UUAUAUAUGGAUUCUGUAAGAGA	576
SEQ ID NO: 151	UGGUAACUAAGUGUCCCAACAAU	2974
SEQ ID NO: 152	UAUCAAGCUCUACUUUACGAAGU	2008
SEQ ID NO: 153	GAGAGGACCGAUGAGAAUAACUA	360
SEQ ID NO: 154	GAGCUUUUAGCAGCUCAUGUCUA	1468
SEQ ID NO: 155	AUUUAUCAGAAUGUUGAACAGCU	654
SEQ ID NO: 156	AAUGUAUCAAGCUCUACUUUACG	2004
SEQ ID NO: 157	CUAUUCCAAACAACAGUACUCAA	418
SEQ ID NO: 158	AUAAAGACUAUUAUUCCCUAUCA	1645
SEQ ID NO: 159	UCUGAACAUGACAUCUUCGGUUU	848
SEQ ID NO: 160	AAUGUUGAACAGCUGGUGAAAUU	663
SEQ ID NO: 161	GGAUGAUAAAGACUAUUAUUCCC	1640
SEQ ID NO: 162	CAUUCCAGAAAAUGUAUCAAGCU	1994
SEQ ID NO: 163	GAAAUGAGGACAAAUUACAUCAA	2937
SEQ ID NO: 164	AUGUCUAGGAGGAAAUAGCAAAA	1484
SEQ ID NO: 165	GCUAUUCCAAACAACAGUACUCA	417
SEQ ID NO: 166	GAUUCUGUAAGAGAUGCUGACUA	585
SEQ ID NO: 167	CUGCAGCUCACCUUUGAAGAAUA	2841
SEQ ID NO: 168	UGAGAUCAUUUAUGUCUGACUCU	739
SEQ ID NO: 169	CUCUGAACAUGACAUCUUCGGUU	847
SEQ ID NO: 170	CUCUCAAGUCCGUUAAGUAGCAU	1038
SEQ ID NO: 171	CCAGUACUGUGGGAUCUAUCUGU	1237
SEQ ID NO: 172	UCAAGCUCUACUUUACGAAGUGU	2010
SEQ ID NO: 173	UUAAAACUGAGCUGGAAUCUAAG	520
SEQ ID NO: 174	UCAGUACCAAUAAAGCAAGAAUC	1527
SEQ ID NO: 175	GUCUUAGAAUACAUUCCAGAAAA	1983
SEQ ID NO: 176	AGAAAUGAUUGCAUCAUUGAUAA	2181

SEQ ID NO: 177	AGCUGGUGAAAUUUUACAAAGGA	673
SEQ ID NO: 178	AAAUGAGGACAAAUUACAUCAAA	2938
SEQ ID NO: 179	UUUCCGGUGCUAUUCCAAACAAC	409
SEQ ID NO: 180	CAACUCAAGGUGCUCUGUUUCCA	1169
SEQ ID NO: 181	UGGAAGAAAUGAUUGCAUCAUUG	2177
SEQ ID NO: 182	AAAGCAAGAAUCAACCAAGCAUU	1538
SEQ ID NO: 183	UGAGCUGGAAUCUAAGGAACUUU	527
SEQ ID NO: 184	CCAGCUUAAUAUUGUCCAGUACA	1427
SEQ ID NO: 185	CCAUGGGUUUAUAUAUGGAUUCU	568
SEQ ID NO: 186	UUAAUAUUGUCCAGUACAUAAAA	1432
SEQ ID NO: 187	AUACAUUCCAGAAAAUGUAUCAA	1991
SEQ ID NO: 188	GGCUCUCCUCUCUCAAGUCCGUU	1029
SEQ ID NO: 189	CUACUAAGCACAAUUCCAAAGGA	2886
SEQ ID NO: 190	CUGAGCUGGAAUCUAAGGAACUU	526
SEQ ID NO: 191	CCAAGUCACUGCAGUGUAAAAUC	1083
SEQ ID NO: 192	GUAUCAAGCUCUACUUUACGAAG	2007
SEQ ID NO: 193	CGGUGCUAUUCCAAACAACAGUA	413
SEQ ID NO: 194	UGCUAUUCCAAACAACAGUACUC	416
SEQ ID NO: 195	CAUGAGUCCAGCUAAGAUUUAUC	638
SEQ ID NO: 196	CCUGCUUGCAGACUUCAGAAAUG	2223
SEQ ID NO: 197	AUGUAUCAAGCUCUACUUUACGA	2005
SEQ ID NO: 198	UCCCAGUGGGUAUUAAACAAGAA	1723
SEQ ID NO: 199	AAUGUCUUCAAGCUGGAAUGAAU	2242
SEQ ID NO: 200	UAAGUAGCAUGAAAUCCUCAAUU	1051
SEQ ID NO: 201	UUCCACUACAGGAUUGGUGCUCA	1824
SEQ ID NO: 202	GUAACUAAGUGUCCCAACAAUUC	2976
SEQ ID NO: 203	GAAGAAAUGAUUGCAUCAUUGAU	2179
SEQ ID NO: 204	CUUGAGAUCAUUUAUGUCUGACU	737
SEQ ID NO: 205	UAAUAUUGUCCAGUACAUAAAAC	1433
SEQ ID NO: 206	GAAGCAUGAGUCCAGCUAAGAUU	634
SEQ ID NO: 207	CAUUUGAAGAAAUGAGGACAAAU	2929
SEQ ID NO: 208	CCUCCAAGUCACUGCAGUGUAAA	1080
SEQ ID NO: 209	UUCUCAGUACCAAUAAAGCAAGA	1524
SEQ ID NO: 210	GGACCGAUGAGAAUAACUACAUG	364
SEQ ID NO: 211	CUAUCUGUAGCCCUGUAAACAAU	1252
SEQ ID NO: 212	GUAGCAUGAAAUCCUCAAUUUCC	1054
SEQ ID NO: 213	GGUGCUAUUCCAAACAACAGUAC	414
SEQ ID NO: 214	CACUGCAGUGUAAAAUCUCCAGU	1089
SEQ ID NO: 215	UAAAGACUAUUAUUCCCUAUCAG	1646
SEQ ID NO: 216	UUUGCUGCUACUAAGCACAAUUC	2879
SEQ ID NO: 217	UCCAACACCUGAGUUCCUUUCCU	1888

SEQ ID NO: 218	UCUGUAAGAGAUGCUGACUAUUC	588
SEQ ID NO: 219	GGAUCUAUCUGUAGCCCUGUAAA	1248
SEQ ID NO: 220	CUGCUUGCAGACUUCAGAAAUGU	2224
SEQ ID NO: 221	UACUUUAGUGGAGUCAUGGAAAU	1919
SEQ ID NO: 222	AAUGAGGACAAAUUACAUCAAAG	2939
SEQ ID NO: 223	GUUUCCGGUGCUAUUCCAAACAA	408

[0545] Table 2 provides the unmodified first (antisense) and corresponding unmodified second (sense) strand sequences for siRNA oligonucleosides according to the present invention, together with the corresponding positions in the overall gene sequence of SEQ ID NO:1116 as follows.

Table 2

SEQ ID NO (AS)	First (Antisense) Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	SEQ ID NO (SS)	Second (Sense) Strand Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	Corresponding positions on ENST00000358102.8
SEQ ID NO: 290	AAUCUUAUCAAUGAUGCAAUCAU	SEQ ID NO: 513	GAUUGCAUCAUUGAUAAGAUU	2185-2207
SEQ ID NO: 270	AGCAAAACUUUCAUGAUGGUGUA	SEQ ID NO: 493	CACCAUCAUGAAAGUUUUGCU	2862-2884
SEQ ID NO: 238	AAUGAUGCAAUCAUUUCUUCCAG	SEQ ID NO: 461	GGAAGAAAUGAUUGCAUCAUU	2176-2198
SEQ ID NO: 245	UAGAGCUUGAUACAUUUUCUGGA	SEQ ID NO: 468	CAGAAAAUGUAUCAAGCUCUA	1997-2019
SEQ ID NO: 283	AUGUAAUUUGUCCUCAUUUCUUC	SEQ ID NO: 506	AGAAAUGAGGACAAAUUACAU	2934-2956
SEQ ID NO: 235	GUAAAGUAGAGCUUGAUACAUUU	SEQ ID NO: 458	AUGUAUCAAGCUCUACUUUAC	2003-2025
SEQ ID NO: 226	AUAGUCUUUAUCAUCCAUAAAGG	SEQ ID NO: 449	UUUAUGGAUGAUAAAGACUAU	1633-1655
SEQ ID NO: 335	UAUAAACCCAUGGACUCAGCUAC	SEQ ID NO: 558	AGCUGAGUCCAUGGGUUUAUA	558-580
SEQ ID NO: 228	AAACACUUCGUAAAGUAGAGCUU	SEQ ID NO: 451	GCUCUACUUUACGAAGUGUUU	2012-2034
SEQ ID NO: 410	UUGAUACAUUUUCUGGAAUGUAU	SEQ ID NO: 633	ACAUUCCAGAAAAUGUAUCAA	1991-2013
SEQ ID NO: 224	AUAAUAGUCUUUAUCAUCCAUAA	SEQ ID NO: 447	AUGGAUGAUAAAGACUAUUAU	1636-1658

SEQ ID NO: 225	AAUAAUAGUCUUUAUCAUCCAUA	SEQ ID NO: 448	UGGAUGAUAAAGACUAUUAUU	1637-1659
SEQ ID NO: 227	AAAACUUUCAUGAUGGUGUAUUC	SEQ ID NO: 450	AUACACCAUCAUGAAAGUUUU	2859-2881
SEQ ID NO: 229	GAAACACUUCGUAAAGUAGAGCU	SEQ ID NO: 452	CUCUACUUUACGAAGUGUUUC	2013-2035
SEQ ID NO: 230	UCUUACAGAAUCCAUAUAUAAAC	SEQ ID NO: 453	UUAUAUAUGGAUUCUGUAAGA	574-596
SEQ ID NO: 231	UAAAAUUUCACCAGCUGUUCAAC	SEQ ID NO: 454	UGAACAGCUGGUGAAAUUUUA	666-688
SEQ ID NO: 232	UACUUAACGGACUUGAGAGAGGA	SEQ ID NO: 455	CUCUCUCAAGUCCGUUAAGUA	1034-1056
SEQ ID NO: 233	GUAAAAUUUCACCAGCUGUUCAA	SEQ ID NO: 456	GAACAGCUGGUGAAAUUUUAC	667-689
SEQ ID NO: 234	AUCUCUUACAGAAUCCAUAUAUA	SEQ ID NO: 457	UAUAUGGAUUCUGUAAGAGAU	577-599
SEQ ID NO: 236	UGGAGAUUUUACACUGCAGUGAC	SEQ ID NO: 459	CACUGCAGUGUAAAAUCUCCA	1087-1109
SEQ ID NO: 237	AUUUAUUUUGCUAUUUCCUCCUA	SEQ ID NO: 460	GGAGGAAAUAGCAAAAUAAAU	1489-1511
SEQ ID NO: 239	GAGACUGGAGAUUUUACACUGCA	SEQ ID NO: 462	CAGUGUAAAAUCUCCAGUCUC	1092-1114
SEQ ID NO: 240	AAGACAUUUCUGAAGUCUGCAAG	SEQ ID NO: 463	UGCAGACUUCAGAAAUGUCUU	2227-2249
SEQ ID NO: 241	UGGAGACUGGAGAUUUUACACUG	SEQ ID NO: 464	GUGUAAAAUCUCCAGUCUCCA	1094-1116
SEQ ID NO: 242	UUUUGAAGAAAACUUUGCAGCUG	SEQ ID NO: 465	GCUGCAAAGUUUUCUUCAAAA	2120-2142
SEQ ID NO: 243	UUUGAAGAAAACUUUGCAGCUGC	SEQ ID NO: 466	AGCUGCAAAGUUUUCUUCAAA	2119-2141
SEQ ID NO: 244	UAGGGAAUAAUAGUCUUUAUCAU	SEQ ID NO: 467	GAUAAAGACUAUUAUUCCCUA	1642-1664
SEQ ID NO: 246	UUGCUUUAUUGGUACUGAGAAUG	SEQ ID NO: 469	UUCUCAGUACCAAUAAAGCAA	1522-1544
SEQ ID NO: 247	AUUCUUUCGUCGAAUCUUAUCAA	SEQ ID NO: 470	GAUAAGAUUCGACGAAAGAAU	2197-2219
SEQ ID NO: 248	UACAGAAUCCAUAUAUAAACCCA	SEQ ID NO: 471	GGUUUAUAUAUGGAUUCUGUA	571-593
SEQ ID NO: 249	UUUGGAAUUGUGCUUAGUAGCAG	SEQ ID NO: 472	GCUACUAAGCACAAUUCCAAA	2883-2905

SEQ ID NO: 250	UUACACUGCAGUGACUUGGAGGG	SEQ ID NO: 473	CUCCAAGUCACUGCAGUGUAA	1079-1101
SEQ ID NO: 251	AAAAUUUCACCAGCUGUUCAACA	SEQ ID NO: 474	UUGAACAGCUGGUGAAAUUUU	665-687
SEQ ID NO: 252	AGUAGCAGCAAAACUUUCAUGAU	SEQ ID NO: 475	CAUGAAAGUUUUGCUGCUACU	2868-2890
SEQ ID NO: 253	AGAGCUUGAUACAUUUUCUGGAA	SEQ ID NO: 476	CCAGAAAAUGUAUCAAGCUCU	1996-2018
SEQ ID NO: 254	AGAUUUUACACUGCAGUGACUUG	SEQ ID NO: 477	AGUCACUGCAGUGUAAAAUCU	1084-1106
SEQ ID NO: 255	AUUUUCUGGAAUGUAUUCUAAGA	SEQ ID NO: 478	UUAGAAUACAUUCCAGAAAAU	1984-2006
SEQ ID NO: 256	AUAUAUAAACCCAUGGACUCAGC	SEQ ID NO: 479	UGAGUCCAUGGGUUUAUAUAU	561-583
SEQ ID NO: 257	AAAGAUUGGUCUCUAGCCGAUCG	SEQ ID NO: 480	AUCGGCUAGAGACCAAUCUUU	1866-1888
SEQ ID NO: 258	GUCUUUAUCAUCCAUAAAGGAAA	SEQ ID NO: 481	UCCUUUAUGGAUGAUAAAGAC	1630-1652
SEQ ID NO: 259	AAAUUUCACCAGCUGUUCAACAU	SEQ ID NO: 482	GUUGAACAGCUGGUGAAAUUU	664-686
SEQ ID NO: 260	UAAAGUAGAGCUUGAUACAUUUU	SEQ ID NO: 483	AAUGUAUCAAGCUCUACUUUA	2002-2024
SEQ ID NO: 261	AAUAGUCUUUAUCAUCCAUAAAG	SEQ ID NO: 484	UUAUGGAUGAUAAAGACUAUU	1634-1656
SEQ ID NO: 262	AAUUUAUUUUGCUAUUUCCUCCU	SEQ ID NO: 485	GAGGAAAUAGCAAAAUAAAUU	1490-1512
SEQ ID NO: 263	AUCUUAUCAAUGAUGCAAUCAUU	SEQ ID NO: 486	UGAUUGCAUCAUUGAUAAGAU	2184-2206
SEQ ID NO: 264	GUAGCAGCAAAACUUUCAUGAUG	SEQ ID NO: 487	UCAUGAAAGUUUUGCUGCUAC	2867-2889
SEQ ID NO: 265	AAUCAUUUCUUCCAGCACAUAAA	SEQ ID NO: 488	UAUGUGCUGGAAGAAAUGAUU	2168-2190
SEQ ID NO: 266	AUAGGAAUAGUCAGCAUCUCUUA	SEQ ID NO: 489	AGAGAUGCUGACUAUUCCUAU	592-614
SEQ ID NO: 267	UGUAGAAGCAGAAUUCCAGCAGG	SEQ ID NO: 490	UGCUGGAAUUCUGCUUCUACA	3068-3090
SEQ ID NO: 268	GGAAUAGUCAGCAUCUCUUACAG	SEQ ID NO: 491	GUAAGAGAUGCUGACUAUUCC	589-611
SEQ ID NO: 269	UUAUUUUGCUAUUUCCUCCUAGA	SEQ ID NO: 492	UAGGAGGAAAUAGCAAAAUAA	1487-1509

SEQ ID NO: 271	AAUGUAUUCUAAGACCGGAUACC	SEQ ID NO: 494	UAUCCGGUCUUAGAAUACAUU	1975-1997
SEQ ID NO: 272	AUUUCAUGCUACUUAACGGACUU	SEQ ID NO: 495	GUCCGUUAAGUAGCAUGAAAU	1043-1065
SEQ ID NO: 273	GGAGAUUUUACACUGCAGUGACU	SEQ ID NO: 496	UCACUGCAGUGUAAAAUCUCC	1086-1108
SEQ ID NO: 274	AAUAGUCAGCAUCUCUUACAGAA	SEQ ID NO: 497	CUGUAAGAGAUGCUGACUAUU	587-609
SEQ ID NO: 275	UAGUCUUUAUCAUCCAUAAAGGA	SEQ ID NO: 498	CUUUAUGGAUGAUAAAGACUA	1632-1654
SEQ ID NO: 276	ACAGAAUCCAUAUAUAAACCCAU	SEQ ID NO: 499	GGGUUUAUAUAUGGAUUCUGU	570-592
SEQ ID NO: 277	UGCUACUUAACGGACUUGAGAGA	SEQ ID NO: 500	UCUCAAGUCCGUUAAGUAGCA	1037-1059
SEQ ID NO: 278	GAAGAUGUCAUGUUCAGAGGGCU	SEQ ID NO: 501	CCCUCUGAACAUGACAUCUUC	843-865
SEQ ID NO: 279	UACAGUUGCUGAAAGUUCCUUAG	SEQ ID NO: 502	AAGGAACUUUCAGCAACUGUA	538-560
SEQ ID NO: 280	AUAGUCAGCAUCUCUUACAGAAU	SEQ ID NO: 503	UCUGUAAGAGAUGCUGACUAU	586-608
SEQ ID NO: 281	UUUCCUUUGUAAAAUUUCACCAG	SEQ ID NO: 504	GGUGAAAUUUUACAAAGGAAA	675-697
SEQ ID NO: 282	AGUUGCUGAAAGUUCCUUAGAUU	SEQ ID NO: 505	UCUAAGGAACUUUCAGCAACU	535-557
SEQ ID NO: 284	UUGAUUCUUGCUUUAUUGGUACU	SEQ ID NO: 507	UACCAAUAAAGCAAGAAUCAA	1529-1551
SEQ ID NO: 285	AAUUCAUUCCAGCUUGAAGACAU	SEQ ID NO: 508	GUCUUCAAGCUGGAAUGAAUU	2243-2265
SEQ ID NO: 286	AUGUACUGGACAAUAUUAAGCUG	SEQ ID NO: 509	GCUUAAUAUUGUCCAGUACAU	1428-1450
SEQ ID NO: 287	UUACAGAAUCCAUAUAUAAACCC	SEQ ID NO: 510	GUUUAUAUAUGGAUUCUGUAA	572-594
SEQ ID NO: 288	UUUUACACUGCAGUGACUUGGAG	SEQ ID NO: 511	CCAAGUCACUGCAGUGUAAAA	1081-1103
SEQ ID NO: 289	GGAAUAAUAGUCUUUAUCAUCCA	SEQ ID NO: 512	GAUGAUAAAGACUAUUAUUCC	1639-1661
SEQ ID NO: 291	UUCCUUUGUAAAAUUUCACCAGC	SEQ ID NO: 514	UGGUGAAAUUUUACAAAGGAA	674-696
SEQ ID NO: 292	AGUUCUUUGAUGUAAUUUGUCCU	SEQ ID NO: 515	GACAAAUUACAUCAAAGAACU	2943-2965

SEQ ID NO: 293	GGAGACUGGAGAUUUUACACUGC	SEQ ID NO: 516	AGUGUAAAAUCUCCAGUCUCC	1093-1115
SEQ ID NO: 294	UUAGUAGCAGCAAAACUUUCAUG	SEQ ID NO: 517	UGAAAGUUUUGCUGCUACUAA	2870-2892
SEQ ID NO: 295	GAUUCCAGCUCAGUUUUAAUAUC	SEQ ID NO: 518	UAUUAAAACUGAGCUGGAAUC	516-538
SEQ ID NO: 296	UCUUUAUCAUCCAUAAAGGAAAA	SEQ ID NO: 519	UUCCUUUAUGGAUGAUAAAGA	1629-1651
SEQ ID NO: 297	UUGUUUAAUACCCACUGGGAAUC	SEQ ID NO: 520	UUCCCAGUGGGUAUUAAACAA	1720-1742
SEQ ID NO: 298	AUGUACUGGAUCCAGCAGAGGUG	SEQ ID NO: 521	CCUCUGCUGGAUCCAGUACAU	1298-1320
SEQ ID NO: 299	GUCAGCAUCUCUUACAGAAUCCA	SEQ ID NO: 522	GAUUCUGUAAGAGAUGCUGAC	583-605
SEQ ID NO: 300	UACGUUGACAAUCUCCAUGUAGU	SEQ ID NO: 523	UACAUGGAGAUUGUCAACGUA	379-401
SEQ ID NO: 301	GAGAUUUUACACUGCAGUGACUU	SEQ ID NO: 524	GUCACUGCAGUGUAAAAUCUC	1085-1107
SEQ ID NO: 302	UUUGUAAAAUUUCACCAGCUGUU	SEQ ID NO: 525	CAGCUGGUGAAAUUUUACAAA	670-692
SEQ ID NO: 303	UAAUAGUCUUUAUCAUCCAUAAA	SEQ ID NO: 526	UAUGGAUGAUAAAGACUAUUA	1635-1657
SEQ ID NO: 304	ACAUUCUGAUAAAUCUUAGCUGG	SEQ ID NO: 527	AGCUAAGAUUUAUCAGAAUGU	645-667
SEQ ID NO: 305	UACAUUUUCUGGAAUGUAUUCUA	SEQ ID NO: 528	GAAUACAUUCCAGAAAAUGUA	1987-2009
SEQ ID NO: 306	AAUUCUUUCGUCGAAUCUUAUCA	SEQ ID NO: 529	AUAAGAUUCGACGAAAGAAUU	2198-2220
SEQ ID NO: 307	AUUGAGGAUUUCAUGCUACUUAA	SEQ ID NO: 530	AAGUAGCAUGAAAUCCUCAAU	1050-1072
SEQ ID NO: 308	ACAGGAGGAAAGGAACUCAGGUG	SEQ ID NO: 531	CCUGAGUUCCUUUCCUCCUGU	1893-1915
SEQ ID NO: 309	UUGAAGAAAACUUUGCAGCUGCC	SEQ ID NO: 532	CAGCUGCAAAGUUUUCUUCAA	2118-2140
SEQ ID NO: 310	GAAAUUGAGGAUUUCAUGCUACU	SEQ ID NO: 533	UAGCAUGAAAUCCUCAAUUUC	1053-1075
SEQ ID NO: 311	UAUUUUGCUAUUUCCUCCUAGAC	SEQ ID NO: 534	CUAGGAGGAAAUAGCAAAAUA	1486-1508
SEQ ID NO: 312	UUCCAGCUCAGUUUUAAUAUCAG	SEQ ID NO: 535	GAUAUUAAAACUGAGCUGGAA	514-536

SEQ ID NO: 313	UUUAUGUACUGGACAAUAUUAAG	SEQ ID NO: 536	UAAUAUUGUCCAGUACAUAAA	1431-1453
SEQ ID NO: 314	UCAACAUUCUGAUAAAUCUUAGC	SEQ ID NO: 537	UAAGAUUUAUCAGAAUGUUGA	648-670
SEQ ID NO: 315	AUUUCCUUUGUAAAAUUUCACCA	SEQ ID NO: 538	GUGAAAUUUUACAAAGGAAAU	676-698
SEQ ID NO: 316	UGAGGAUUUCAUGCUACUUAACG	SEQ ID NO: 539	UUAAGUAGCAUGAAAUCCUCA	1048-1070
SEQ ID NO: 317	AGACUGGAGAUUUUACACUGCAG	SEQ ID NO: 540	GCAGUGUAAAAUCUCCAGUCU	1091-1113
SEQ ID NO: 318	UAGUAGCAGCAAAACUUUCAUGA	SEQ ID NO: 541	AUGAAAGUUUUGCUGCUACUA	2869-2891
SEQ ID NO: 319	AUUCCAGCUCAGUUUUAAUAUCA	SEQ ID NO: 542	AUAUUAAAACUGAGCUGGAAU	515-537
SEQ ID NO: 320	AGGAUUUCAUGCUACUUAACGGA	SEQ ID NO: 543	CGUUAAGUAGCAUGAAAUCCU	1046-1068
SEQ ID NO: 321	GAAGACAUUUCUGAAGUCUGCAA	SEQ ID NO: 544	GCAGACUUCAGAAAUGUCUUC	2228-2250
SEQ ID NO: 322	UAUGUACUGGACAAUAUUAAGCU	SEQ ID NO: 545	CUUAAUAUUGUCCAGUACAUA	1429-1451
SEQ ID NO: 323	AUUCUGAUAAAUCUUAGCUGGAC	SEQ ID NO: 546	CCAGCUAAGAUUUAUCAGAAU	643-665
SEQ ID NO: 324	AACACUUCGUAAAGUAGAGCUUG	SEQ ID NO: 547	AGCUCUACUUUACGAAGUGUU	2011-2033
SEQ ID NO: 325	AACAUUCUGAUAAAUCUUAGCUG	SEQ ID NO: 548	GCUAAGAUUUAUCAGAAUGUU	646-668
SEQ ID NO: 326	AUUCUUGCUUUAUUGGUACUGAG	SEQ ID NO: 549	CAGUACCAAUAAAGCAAGAAU	1526-1548
SEQ ID NO: 327	ACUUAACGGACUUGAGAGAGGAG	SEQ ID NO: 550	CCUCUCUCAAGUCCGUUAAGU	1033-1055
SEQ ID NO: 328	UUCGUAAAGUAGAGCUUGAUACA	SEQ ID NO: 551	UAUCAAGCUCUACUUUACGAA	2006-2028
SEQ ID NO: 329	AUUUCACCAGCUGUUCAACAUUC	SEQ ID NO: 552	AUGUUGAACAGCUGGUGAAAU	662-684
SEQ ID NO: 330	UUCAACAUUCUGAUAAAUCUUAG	SEQ ID NO: 553	AAGAUUUAUCAGAAUGUUGAA	649-671
SEQ ID NO: 331	AUCCAUAUAUAAACCCAUGGACU	SEQ ID NO: 554	UCCAUGGGUUUAUAUAUGGAU	565-587
SEQ ID NO: 332	GUAAUUUGUCCUCAUUUCUUCAA	SEQ ID NO: 555	GAAGAAAUGAGGACAAAUUAC	2932-2954

SEQ ID NO: 333	UUCUUUCGUCGAAUCUUAUCAAU	SEQ ID NO: 556	UGAUAAGAUUCGACGAAAGAA	2196-2218
SEQ ID NO: 334	AGGGAAUAAUAGUCUUUAUCAUC	SEQ ID NO: 557	UGAUAAAGACUAUUAUUCCCU	1641-1663
SEQ ID NO: 336	UCUACUUCCUCAGUCUUAGGAAA	SEQ ID NO: 559	UCCUAAGACUGAGGAAGUAGA	1377-1399
SEQ ID NO: 337	AAAGGAACUCAGGUGUUGGAAAG	SEQ ID NO: 560	UUCCAACACCUGAGUUCCUUU	1885-1907
SEQ ID NO: 338	UUUCGUCGAAUCUUAUCAAUGAU	SEQ ID NO: 561	CAUUGAUAAGAUUCGACGAAA	2193-2215
SEQ ID NO: 339	UGGAAAUUGAGGAUUUCAUGCUA	SEQ ID NO: 562	GCAUGAAAUCCUCAAUUUCCA	1055-1077
SEQ ID NO: 340	AAGUAGAGCUUGAUACAUUUUCU	SEQ ID NO: 563	AAAAUGUAUCAAGCUCUACUU	2000-2022
SEQ ID NO: 341	UUGGAAUUGUGCUUAGUAGCAGC	SEQ ID NO: 564	UGCUACUAAGCACAAUUCCAA	2882-2904
SEQ ID NO: 342	UACAGAUAGAUCCCACAGUACUG	SEQ ID NO: 565	GUACUGUGGGAUCUAUCUGUA	1238-1260
SEQ ID NO: 343	UUUAUUUUGCUAUUUCCUCCUAG	SEQ ID NO: 566	AGGAGGAAAUAGCAAAAUAAA	1488-1510
SEQ ID NO: 344	UAUCAAUGAUGCAAUCAUUUCUU	SEQ ID NO: 567	GAAAUGAUUGCAUCAUUGAUA	2180-2202
SEQ ID NO: 345	AUUUUACACUGCAGUGACUUGGA	SEQ ID NO: 568	CAAGUCACUGCAGUGUAAAAU	1082-1104
SEQ ID NO: 346	UCUGAUAAAUCUUAGCUGGACUC	SEQ ID NO: 569	GUCCAGCUAAGAUUUAUCAGA	641-663
SEQ ID NO: 347	UCGAAUCUUAUCAAUGAUGCAAU	SEQ ID NO: 570	UGCAUCAUUGAUAAGAUUCGA	2188-2210
SEQ ID NO: 348	GAGGAUUUCAUGCUACUUAACGG	SEQ ID NO: 571	GUUAAGUAGCAUGAAAUCCUC	1047-1069
SEQ ID NO: 349	GAAAGCGUGGAUCUGUUAUUAGU	SEQ ID NO: 572	UAAUAACAGAUCCACGCUUUC	1203-1225
SEQ ID NO: 350	AGUAGAGCUUGAUACAUUUUCUG	SEQ ID NO: 573	GAAAAUGUAUCAAGCUCUACU	1999-2021
SEQ ID NO: 351	AAUCCAUAUAUAAACCCAUGGAC	SEQ ID NO: 574	CCAUGGGUUUAUAUAUGGAUU	566-588
SEQ ID NO: 352	AAAGUAGAGCUUGAUACAUUUUC	SEQ ID NO: 575	AAAUGUAUCAAGCUCUACUUU	2001-2023
SEQ ID NO: 353	GAUUUCAUGCUACUUAACGGACU	SEQ ID NO: 576	UCCGUUAAGUAGCAUGAAAUC	1044-1066

SEQ ID NO: 354	AUAGGGAAUAAUAGUCUUUAUCA	SEQ ID NO: 577	AUAAAGACUAUUAUUCCCUAU	1643-1665
SEQ ID NO: 355	CUUAGUAGCAGCAAAACUUUCAU	SEQ ID NO: 578	GAAAGUUUUGCUGCUACUAAG	2871-2893
SEQ ID NO: 356	UUAACGGACUUGAGAGAGGAGAG	SEQ ID NO: 579	CUCCUCUCUCAAGUCCGUUAA	1031-1053
SEQ ID NO: 357	GUAGUUAUUCUCAUCGGUCCUCU	SEQ ID NO: 580	AGGACCGAUGAGAAUAACUAC	361-383
SEQ ID NO: 358	CAAAACUUUCAUGAUGGUGUAUU	SEQ ID NO: 581	UACACCAUCAUGAAAGUUUUG	2860-2882
SEQ ID NO: 359	AAUUUGUCCUCAUUUCUUCAAAU	SEQ ID NO: 582	UUGAAGAAAUGAGGACAAAUU	2930-2952
SEQ ID NO: 360	GAAUAAUAGUCUUUAUCAUCCAU	SEQ ID NO: 583	GGAUGAUAAAGACUAUUAUUC	1638-1660
SEQ ID NO: 361	UUAGAUUCCAGCUCAGUUUUAAU	SEQ ID NO: 584	UAAAACUGAGCUGGAAUCUAA	519-541
SEQ ID NO: 362	ACAAUCUCCAUGUAGUUAUUCUC	SEQ ID NO: 585	GAAUAACUACAUGGAGAUUGU	372-394
SEQ ID NO: 363	AGGAAUAGUCAGCAUCUCUUACA	SEQ ID NO: 586	UAAGAGAUGCUGACUAUUCCU	590-612
SEQ ID NO: 364	AGCAGCAAAACUUUCAUGAUGGU	SEQ ID NO: 587	CAUCAUGAAAGUUUUGCUGCU	2865-2887
SEQ ID NO: 365	AUCUGGUUCUGGUUUUAUGUACU	SEQ ID NO: 588	UACAUAAAACCAGAACCAGAU	1444-1466
SEQ ID NO: 366	AAUUGUGCUUAGUAGCAGCAAAA	SEQ ID NO: 589	UUGCUGCUACUAAGCACAAUU	2878-2900
SEQ ID NO: 367	UUCAAAGGUGAGCUGCAGUCGAA	SEQ ID NO: 590	CGACUGCAGCUCACCUUUGAA	2836-2858
SEQ ID NO: 368	UAGAUUCCAGCUCAGUUUUAAUA	SEQ ID NO: 591	UUAAAACUGAGCUGGAAUCUA	518-540
SEQ ID NO: 369	GUGAUUUCCAUGACUCCACUAAA	SEQ ID NO: 592	UAGUGGAGUCAUGGAAAUCAC	1922-1944
SEQ ID NO: 370	GUGCUUAGUAGCAGCAAAACUUU	SEQ ID NO: 593	AGUUUUGCUGCUACUAAGCAC	2874-2896
SEQ ID NO: 371	UAAUUUGUCCUCAUUUCUUCAAA	SEQ ID NO: 594	UGAAGAAAUGAGGACAAAUUA	2931-2953
SEQ ID NO: 372	UUUCUUUGCUGCUUCCUUGAGUA	SEQ ID NO: 595	CUCAAGGAAGCAGCAAAGAAA	434-456
SEQ ID NO: 373	UCUCUUACAGAAUCCAUAUAUAA	SEQ ID NO: 596	AUAUAUGGAUUCUGUAAGAGA	576-598

SEQ ID NO: 374	AUUGUUGGGACACUUAGUUACCA	SEQ ID NO: 597	GUAACUAAGUGUCCCAACAAU	2974-2996
SEQ ID NO: 375	ACUUCGUAAAGUAGAGCUUGAUA	SEQ ID NO: 598	UCAAGCUCUACUUUACGAAGU	2008-2030
SEQ ID NO: 376	UAGUUAUUCUCAUCGGUCCUCUC	SEQ ID NO: 599	GAGGACCGAUGAGAAUAACUA	360-382
SEQ ID NO: 377	UAGACAUGAGCUGCUAAAAGCUC	SEQ ID NO: 600	GCUUUUAGCAGCUCAUGUCUA	1468-1490
SEQ ID NO: 378	AGCUGUUCAACAUUCUGAUAAAU	SEQ ID NO: 601	UUAUCAGAAUGUUGAACAGCU	654-676
SEQ ID NO: 379	CGUAAAGUAGAGCUUGAUACAUU	SEQ ID NO: 602	UGUAUCAAGCUCUACUUUACG	2004-2026
SEQ ID NO: 380	UUGAGUACUGUUGUUUGGAAUAG	SEQ ID NO: 603	AUUCCAAACAACAGUACUCAA	418-440
SEQ ID NO: 381	UGAUAGGGAAUAAUAGUCUUUAU	SEQ ID NO: 604	AAAGACUAUUAUUCCCUAUCA	1645-1667
SEQ ID NO: 382	AAACCGAAGAUGUCAUGUUCAGA	SEQ ID NO: 605	UGAACAUGACAUCUUCGGUUU	848-870
SEQ ID NO: 383	AAUUUCACCAGCUGUUCAACAUU	SEQ ID NO: 606	UGUUGAACAGCUGGUGAAAUU	663-685
SEQ ID NO: 384	GGGAAUAAUAGUCUUUAUCAUCC	SEQ ID NO: 607	AUGAUAAAGACUAUUAUUCCC	1640-1662
SEQ ID NO: 385	AGCUUGAUACAUUUUCUGGAAUG	SEQ ID NO: 608	UUCCAGAAAAUGUAUCAAGCU	1994-2016
SEQ ID NO: 386	UUGAUGUAAUUUGUCCUCAUUUC	SEQ ID NO: 609	AAUGAGGACAAAUUACAUCAA	2937-2959
SEQ ID NO: 387	UUUUGCUAUUUCCUCCUAGACAU	SEQ ID NO: 610	GUCUAGGAGGAAAUAGCAAAA	1484-1506
SEQ ID NO: 388	UGAGUACUGUUGUUUGGAAUAGC	SEQ ID NO: 611	UAUUCCAAACAACAGUACUCA	417-439
SEQ ID NO: 389	UAGUCAGCAUCUCUUACAGAAUC	SEQ ID NO: 612	UUCUGUAAGAGAUGCUGACUA	585-607
SEQ ID NO: 390	UAUUCUUCAAAGGUGAGCUGCAG	SEQ ID NO: 613	GCAGCUCACCUUUGAAGAAUA	2841-2863
SEQ ID NO: 391	AGAGUCAGACAUAAAUGAUCUCA	SEQ ID NO: 614	AGAUCAUUUAUGUCUGACUCU	739-761
SEQ ID NO: 392	AACCGAAGAUGUCAUGUUCAGAG	SEQ ID NO: 615	CUGAACAUGACAUCUUCGGUU	847-869
SEQ ID NO: 393	AUGCUACUUAACGGACUUGAGAG	SEQ ID NO: 616	CUCAAGUCCGUUAAGUAGCAU	1038-1060

SEQ ID NO: 394	ACAGAUAGAUCCCACAGUACUGG	SEQ ID NO: 617	AGUACUGUGGGAUCUAUCUGU	1237-1259
SEQ ID NO: 395	ACACUUCGUAAAGUAGAGCUUGA	SEQ ID NO: 618	AAGCUCUACUUUACGAAGUGU	2010-2032
SEQ ID NO: 396	CUUAGAUUCCAGCUCAGUUUUAA	SEQ ID NO: 619	AAAACUGAGCUGGAAUCUAAG	520-542
SEQ ID NO: 397	GAUUCUUGCUUUAUUGGUACUGA	SEQ ID NO: 620	AGUACCAAUAAAGCAAGAAUC	1527-1549
SEQ ID NO: 398	UUUUCUGGAAUGUAUUCUAAGAC	SEQ ID NO: 621	CUUAGAAUACAUUCCAGAAAA	1983-2005
SEQ ID NO: 399	UUAUCAAUGAUGCAAUCAUUUCU	SEQ ID NO: 622	AAAUGAUUGCAUCAUUGAUAA	2181-2203
SEQ ID NO: 400	UCCUUUGUAAAAUUUCACCAGCU	SEQ ID NO: 623	CUGGUGAAAUUUUACAAAGGA	673-695
SEQ ID NO: 401	UUUGAUGUAAUUUGUCCUCAUUU	SEQ ID NO: 624	AUGAGGACAAAUUACAUCAAA	2938-2960
SEQ ID NO: 402	GUUGUUUGGAAUAGCACCGGAAA	SEQ ID NO: 625	UCCGGUGCUAUUCCAAACAAC	409-431
SEQ ID NO: 403	UGGAAACAGAGCACCUUGAGUUG	SEQ ID NO: 626	ACUCAAGGUGCUCUGUUUCCA	1169-1191
SEQ ID NO: 404	CAAUGAUGCAAUCAUUUCUUCCA	SEQ ID NO: 627	GAAGAAAUGAUUGCAUCAUUG	2177-2199
SEQ ID NO: 405	AAUGCUUGGUUGAUUCUUGCUUU	SEQ ID NO: 628	AGCAAGAAUCAACCAAGCAUU	1538-1560
SEQ ID NO: 406	AAAGUUCCUUAGAUUCCAGCUCA	SEQ ID NO: 629	AGCUGGAAUCUAAGGAACUUU	527-549
SEQ ID NO: 407	UGUACUGGACAAUAUUAAGCUGG	SEQ ID NO: 630	AGCUUAAUAUUGUCCAGUACA	1427-1449
SEQ ID NO: 408	AGAAUCCAUAUAUAAACCCAUGG	SEQ ID NO: 631	AUGGGUUUAUAUAUGGAUUCU	568-590
SEQ ID NO: 409	UUUUAUGUACUGGACAAUAUUAA	SEQ ID NO: 632	AAUAUUGUCCAGUACAUAAAA	1432-1454
SEQ ID NO: 411	AACGGACUUGAGAGAGGAGAGCC	SEQ ID NO: 634	CUCUCCUCUCUCAAGUCCGUU	1029-1051
SEQ ID NO: 412	UCCUUUGGAAUUGUGCUUAGUAG	SEQ ID NO: 635	ACUAAGCACAAUUCCAAAGGA	2886-2908
SEQ ID NO: 413	AAGUUCCUUAGAUUCCAGCUCAG	SEQ ID NO: 636	GAGCUGGAAUCUAAGGAACUU	526-548
SEQ ID NO: 414	GAUUUUACACUGCAGUGACUUGG	SEQ ID NO: 637	AAGUCACUGCAGUGUAAAAUC	1083-1105

SEQ ID NO: 415	CUUCGUAAAGUAGAGCUUG AUAC	SEQ ID NO: 638	AUCAAGCUCUACUUUAC GAAG	2007-2029
SEQ ID NO: 416	UACUGUUGUUUGGAAUAGC ACCG	SEQ ID NO: 639	GUGCUAUUCCAAACAAC AGUA	413-435
SEQ ID NO: 417	GAGUACUGUUGUUUGGAAU AGCA	SEQ ID NO: 640	CUAUUCCAAACAACAGU ACUC	416-438
SEQ ID NO: 418	GAUAAAUCUUAGCUGGACU CAUG	SEQ ID NO: 641	UGAGUCCAGCUAAGAUU UAUC	638-660
SEQ ID NO: 419	CAUUUCUGAAGUCUGCAAG CAGG	SEQ ID NO: 642	UGCUUGCAGACUUCAGA AAUG	2223-2245
SEQ ID NO: 420	UCGUAAAGUAGAGCUUGAU ACAU	SEQ ID NO: 643	GUAUCAAGCUCUACUUU ACGA	2005-2027
SEQ ID NO: 421	UUCUUGUUUAAUACCCACU GGGA	SEQ ID NO: 644	CCAGUGGGUAUUAAACA AGAA	1723-1745
SEQ ID NO: 422	AUUCAUUCCAGCUUGAAGA CAUU	SEQ ID NO: 645	UGUCUUCAAGCUGGAAU GAAU	2242-2264
SEQ ID NO: 423	AAUUGAGGAUUUCAUGCUA CUUA	SEQ ID NO: 646	AGUAGCAUGAAAUCCUC AAUU	1051-1073
SEQ ID NO: 424	UGAGCACCAAUCCUGUAGU GGAA	SEQ ID NO: 647	CCACUACAGGAUUGGUG CUCA	1824-1846
SEQ ID NO: 425	GAAUUGUUGGGACACUUAG UUAC	SEQ ID NO: 648	AACUAAGUGUCCCAACA AUUC	2976-2998
SEQ ID NO: 426	AUCAAUGAUGCAAUCAUUU CUUC	SEQ ID NO: 649	AGAAAUGAUUGCAUCAU UGAU	2179-2201
SEQ ID NO: 427	AGUCAGACAUAAAUGAUCU CAAG	SEQ ID NO: 650	UGAGAUCAUUUAUGUCU GACU	737-759
SEQ ID NO: 428	GUUUUAUGUACUGGACAAU AUUA	SEQ ID NO: 651	AUAUUGUCCAGUACAUA AAAC	1433-1455
SEQ ID NO: 429	AAUCUUAGCUGGACUCAUG CUUC	SEQ ID NO: 652	AGCAUGAGUCCAGCUAA GAUU	634-656
SEQ ID NO: 430	AUUUGUCCUCAUUUCUUCA AAUG	SEQ ID NO: 653	UUUGAAGAAAUGAGGAC AAAU	2929-2951
SEQ ID NO: 431	UUUACACUGCAGUGACUUG GAGG	SEQ ID NO: 654	UCCAAGUCACUGCAGUG UAAA	1080-1102
SEQ ID NO: 432	UCUUGCUUUAUUGGUACUG AGAA	SEQ ID NO: 655	CUCAGUACCAAUAAAGC AAGA	1524-1546
SEQ ID NO: 433	CAUGUAGUUAUUCUCAUCG GUCC	SEQ ID NO: 656	ACCGAUGAGAAUAACUA CAUG	364-386
SEQ ID NO: 434	AUUGUUUACAGGGCUACAG AUAG	SEQ ID NO: 657	AUCUGUAGCCCUGUAAA CAAU	1252-1274

SEQ ID NO: 435	GGAAAUUGAGGAUUUCAUG CUAC	SEQ ID NO: 658	AGCAUGAAAUCCUCAAU UUCC	1054-1076
SEQ ID NO: 436	GUACUGUUGUUUGGAAUAG CACC	SEQ ID NO: 659	UGCUAUUCCAAACAACA GUAC	414-436
SEQ ID NO: 437	ACUGGAGAUUUUACACUGC AGUG	SEQ ID NO: 660	CUGCAGUGUAAAAUCUC CAGU	1089-1111
SEQ ID NO: 438	CUGAUAGGGAAUAAUAGUC UUUA	SEQ ID NO: 661	AAGACUAUUAUUCCCUA UCAG	1646-1668
SEQ ID NO: 439	GAAUUGUGCUUAGUAGCAG CAAA	SEQ ID NO: 662	UGCUGCUACUAAGCACA AUUC	2879-2901
SEQ ID NO: 440	AGGAAAGGAACUCAGGUGU UGGA	SEQ ID NO: 663	CAACACCUGAGUUCCUU UCCU	1888-1910
SEQ ID NO: 441	GAAUAGUCAGCAUCUCUUA CAGA	SEQ ID NO: 664	UGUAAGAGAUGCUGACU AUUC	588-610
SEQ ID NO: 442	UUUACAGGGCUACAGAUAG AUCC	SEQ ID NO: 665	AUCUAUCUGUAGCCCUG UAAA	1248-1270
SEQ ID NO: 443	ACAUUUCUGAAGUCUGCAA GCAG	SEQ ID NO: 666	GCUUGCAGACUUCAGAA AUGU	2224-2246
SEQ ID NO: 444	AUUUCCAUGACUCCACUAA AGUA	SEQ ID NO: 667	CUUUAGUGGAGUCAUGG AAAU	1919-1941
SEQ ID NO: 445	CUUUGAUGUAAUUUGUCCU CAUU	SEQ ID NO: 668	UGAGGACAAAUUACAUC AAAG	2939-2961
SEQ ID NO: 446	UUGUUUGGAAUAGCACCGG AAAC	SEQ ID NO: 669	UUCCGGUGCUAUUCCAA ACAA	408-430

[0546] Table 3 provides the modified first (antisense) sequences, together with the corresponding unmodified first (antisense) sequences for siRNA oligonucleosides according to the present invention as follows.

Table 3

Antisense strand ID	Modified First (Antisense) Strand 5' → 3'	SEQ ID NO (AS - mod)	Underlying Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	SEQ ID NO (AS - unmod)
ETX-S00006172	AmsAfsUmCmUmUfAmUfCfAmAmUm GmAfUmGfCmAmAmUfCmsAmsUm	SEQ ID NO: 736	AAUCUUAUCAAUGA UGCAAUCAU	SEQ ID NO: 290

ETX-S00006092	AmsGfsCmAmAmAfAmCfUfUmUmCmAmUfGmAfUmGmGmUfGmsUmsAm	SEQ ID NO: 716	AGCAAAACUUUCAUGAUGGUGUA	SEQ ID NO: 270
ETX-S00005964	AmsAfsUmGmAmUfGmCfAfAmUmCmAmUfUmUfCmUmUmCfCmsAmsGm	SEQ ID NO: 684	AAUGAUGCAAUCAUUUCUUCCAG	SEQ ID NO: 238
ETX-S00005992	UmsAfsGmAmGmCfUmUfGfAmUmAmCmAfUmUfUmUmCmUfGmsGmsAm	SEQ ID NO: 691	UAGAGCUUGAUACAUUUUCUGGA	SEQ ID NO: 245
ETX-S00006144	AmsUfsGmUmAmAfUmUfUfGmUmCmCmUfCmAfUmUmUmCfUmsUmsCm	SEQ ID NO: 729	AUGUAAUUUGUCCUCAUUUCUUC	SEQ ID NO: 283
ETX-S00005952	GmsUfsAmAmAmGfUmAfGfAmGmCmUmUfGmAfUmAmCmAfUmsUmsUm	SEQ ID NO: 681	GUAAAGUAGAGCUUGAUACAUUU	SEQ ID NO: 235
ETX-S00005916	AmsUfsAmGmUmCfUmUfUfAmUmCmAmUfCmCfAmUmAmAfAmsGmsGm	SEQ ID NO: 672	AUAGUCUUUAUCAUCCAUAAAGG	SEQ ID NO: 226
ETX-S00006352	UmsAfsUmAmAmAfCmCfCfAmUmGmGmAfCmUfCmAmGmCfUmsAmsCm	SEQ ID NO: 781	UAUAAACCCAUGGACUCAGCUAC	SEQ ID NO: 335
ETX-S00005924	AmsAfsAmCmAmCfUmUfCfGmUmAmAmAfGmUfAmGmAmGfCmsUmsUm	SEQ ID NO: 674	AAACACUUCGUAAAGUAGAGCUU	SEQ ID NO: 228
ETX-S00006652	UmsUfsGmAmUmAfCmAfUfUmUmUmCmUfGmGfAmAmUmGfUmsAmsUm	SEQ ID NO: 856	UUGAUACAUUUUCUGGAAUGUAU	SEQ ID NO: 410
ETX-S00005908	AmsUfsAmAmUmAfGmUfCfUmUmUmAmUfCmAfUmCmCmAfUmsAmsAm	SEQ ID NO: 670	AUAAUAGUCUUUAUCAUCCAUAA	SEQ ID NO: 224
ETX-S00005912	AmsAfsUmAmAmUfAmGfUfCmUmUmUmAfUmCfAmUmCmCfAmsUmsAm	SEQ ID NO: 671	AAUAAUAGUCUUUAUCAUCCAUA	SEQ ID NO: 225
ETX-S00005920	AmsAfsAmAmCmUfUmUfCfAmUmGmAmUfGmGfUmGmUmAfUmsUmsCm	SEQ ID NO: 673	AAAACUUUCAUGAUGGUGUAUUC	SEQ ID NO: 227
ETX-S00005928	GmsAfsAmAmCmAfCmUfUfCmGmUmAmAfAmGfUmAmGmAfGmsCmsUm	SEQ ID NO: 675	GAAACACUUCGUAAAGUAGAGCU	SEQ ID NO: 229
ETX-S00005932	UmsCfsUmUmAmCfAmGfAfAmUmCmCmAfUmAfUmAmUmAfAmsAmsCm	SEQ ID NO: 676	UCUUACAGAAUCCAUAUAUAAAC	SEQ ID NO: 230
ETX-S00005936	UmsAfsAmAmAmUfUmUfCfAmCmCmAmGfCmUfGmUmUmCfAmsAmsCm	SEQ ID NO: 677	UAAAAUUUCACCAGCUGUUCAAC	SEQ ID NO: 231
ETX-S00005940	UmsAfsCmUmUmAfAmCfGfGmAmCmUmUfGmAfGmAmGmAfGmsGmsAm	SEQ ID NO: 678	UACUUAACGGACUUGAGAGAGGA	SEQ ID NO: 232
ETX-S00005944	GmsUfsAmAmAmAfUmUfUfCmAmCmCmAfCmGfCmUfGmUmUfCmsAmsAm	SEQ ID NO: 679	GUAAAAUUUCACCAGCUGUUCAA	SEQ ID NO: 233
ETX-S00005948	AmsUfsCmUmCmUfUmAfCfAmGmAmAmUfAmUfCmCfAmUmAmUfAmsUmsAm	SEQ ID NO: 680	AUCUCUUACAGAAUCCAUAUAUA	SEQ ID NO: 234
ETX-S00005956	UmsGfsGmAmGmAfUmUfUfUmAmCmAmCfUmGfCmAmGmUfGmsAmsCm	SEQ ID NO: 682	UGGAGAUUUUACACUGCAGUGAC	SEQ ID NO: 236
ETX-S00005960	AmsUfsUmUmAmUfUmUfUfGmCmUmAmUfUmUfCmCmUmCfCmsUmsAm	SEQ ID NO: 683	AUUUAUUUUGCUAUUUCCUCCUA	SEQ ID NO: 237

ETX-S00005968	GmsAfsGmAmCmUfGmGfAfGmAmUm UmUfUmAfCmAmCmUfGmsCmsAm	SEQ ID NO: 685	GAGACUGGAGAUUU UACACUGCA	SEQ ID NO: 239
ETX-S00005972	AmsAfsGmAmCmAfUmUfUfCmUmGm AmAfGmUfCmUmGmCfAmsAmsGm	SEQ ID NO: 686	AAGACAUUUCUGAA GUCUGCAAG	SEQ ID NO: 240
ETX-S00005976	UmsGfsGmAmGmAfCmUfGfGmAmGm AmUfUmUfUmAmCmAfCmsUmsGm	SEQ ID NO: 687	UGGAGACUGGAGAU UUUACACUG	SEQ ID NO: 241
ETX-S00005980	UmsUfsUmUmGmAfAmGfAfAmAmAm CmUfUmUfGmCmAmGfCmsUmsGm	SEQ ID NO: 688	UUUUGAAGAAAACU UUGCAGCUG	SEQ ID NO: 242
ETX-S00005984	UmsUfsUmGmAmAfGmAfAfAmAmCm UmUfUmGfCmAmGmCfUmsGmsCm	SEQ ID NO: 689	UUUGAAGAAAACUU UGCAGCUGC	SEQ ID NO: 243
ETX-S00005988	UmsAfsGmGmGmAfAmUfAfAmUmAm GmUfCmUfUmUmAmUfCmsAmsUm	SEQ ID NO: 690	UAGGGAAUAAUAGU CUUUAUCAU	SEQ ID NO: 244
ETX-S00005996	UmsUfsGmCmUmUfUmAfUfUmGmGm UmAfCmUfGmAmGmAfAmsUmsGm	SEQ ID NO: 692	UUGCUUUAUUGGUA CUGAGAAUG	SEQ ID NO: 246
ETX-S00006000	AmsUfsUmCmUmUfUmCfGfUmCmGm AmAfUmCfUmUmAmUfCmsAmsAm	SEQ ID NO: 693	AUUCUUUCGUCGAA UCUUAUCAA	SEQ ID NO: 247
ETX-S00006004	UmsAfsCmAmGmAfAmUfCfCmAmUm AmUfAmUfAmAmAmCfCmsCmsAm	SEQ ID NO: 694	UACAGAAUCCAUAU AUAAACCCA	SEQ ID NO: 248
ETX-S00006008	UmsUfsUmGmGmAfAmUfUfGmUmGm CmUfUmAfGmUmAmGfCmsAmsGm	SEQ ID NO: 695	UUUGGAAUUGUGCU UAGUAGCAG	SEQ ID NO: 249
ETX-S00006012	UmsUfsAmCmAmCfUmGfCfAmGmUm GmAfCmUfUmGmGmAfGmsGmsGm	SEQ ID NO: 696	UUACACUGCAGUGA CUUGGAGGG	SEQ ID NO: 250
ETX-S00006016	AmsAfsAmAmUmUfUmCfAfCmCmAm GmCfUmGfUmUmCmAfAmsCmsAm	SEQ ID NO: 697	AAAAUUUCACCAGC UGUUCAACA	SEQ ID NO: 251
ETX-S00006020	AmsGfsUmAmGmCfAmGfCfAmAmAm AmCfUmUfUmCmAmUfGmsAmsUm	SEQ ID NO: 698	AGUAGCAGCAAAAC UUUCAUGAU	SEQ ID NO: 252
ETX-S00006024	AmsGfsAmGmCmUfUmGfAfUmAmCm AmUfUmUfUmCmUmGfGmsAmsAm	SEQ ID NO: 699	AGAGCUUGAUACAU UUUCUGGAA	SEQ ID NO: 253
ETX-S00006028	AmsGfsAmUmUmUfUmAfCfAmCmUm GmCfAmGfUmGmAmCfUmsUmsGm	SEQ ID NO: 700	AGAUUUUACACUGC AGUGACUUG	SEQ ID NO: 254
ETX-S00006032	AmsUfsUmUmUmCfUmGfGfAmAmUm GmUfAmUfUmCmUmAfAmsGmsAm	SEQ ID NO: 701	AUUUUCUGGAAUGU AUUCUAAGA	SEQ ID NO: 255
ETX-S00006036	AmsUfsAmUmAmUfAmAfAfCmCmCm AmUfGmGfAmCmUmCfAmsGmsCm	SEQ ID NO: 702	AUAUAUAAACCCAU GGACUCAGC	SEQ ID NO: 256
ETX-S00006040	AmsAfsAmGmAmUfUmGfGfUmCmUm CmUfAmGfCmCmGmAfUmsCmsGm	SEQ ID NO: 703	AAAGAUUGGUCUCU AGCCGAUCG	SEQ ID NO: 257
ETX-S00006044	GmsUfsCmUmUmUfAmUfCfAmUmCm CmAfUmAfAmAmGmGfAmsAmsAm	SEQ ID NO: 704	GUCUUUAUCAUCCA UAAAGGAAA	SEQ ID NO: 258
ETX-S00006048	AmsAfsAmUmUmUfCmAfCfCmAmGm CmUfGmUfUmCmAmAfCmsAmsUm	SEQ ID NO: 705	AAAUUUCACCAGCU GUUCAACAU	SEQ ID NO: 259

ETX-S00006052	UmsAfsAmAmGmUfAmGfAfGmCmUmUmGfAmUfAmCmAmUfUmsUmsUm	SEQ ID NO: 706	UAAAGUAGAGCUUGAUACAUUUU	SEQ ID NO: 260
ETX-S00006056	AmsAfsUmAmGmUfCmUfUfUmAmUmCmAfUmCfCmAmUmAfAmsAmsGm	SEQ ID NO: 707	AAUAGUCUUUAUCAUCCAUAAAG	SEQ ID NO: 261
ETX-S00006060	AmsAfsUmUmUmAfUmUfUfUmGmCmUmAfUmUfUmCmCmUfCmsCmsUm	SEQ ID NO: 708	AAUUUAUUUUGCUAUUUCCUCCU	SEQ ID NO: 262
ETX-S00006064	AmsUfsCmUmUmAfUmCfAfAmUmGmAmUfGmCfAmAmUmCfAmsUmsUm	SEQ ID NO: 709	AUCUUAUCAAUGAUGCAAUCAUU	SEQ ID NO: 263
ETX-S00006068	GmsUfsAmGmCmAfGmCfAfAmAmAmCmUfUmUfCmAmUmGfAmsUmsGm	SEQ ID NO: 710	GUAGCAGCAAAACUUUCAUGAUG	SEQ ID NO: 264
ETX-S00006072	AmsAfsUmCmAmUfUmUfCfUmUmCmCmAfGmCfAmCmAmUfAmsAmsAm	SEQ ID NO: 711	AAUCAUUUCUUCCAGCACAUAAA	SEQ ID NO: 265
ETX-S00006076	AmsUfsAmGmGmAfAmUfAfGmUmCmAmGfCmAfUmCmUmCfUmsUmsAm	SEQ ID NO: 712	AUAGGAAUAGUCAGCAUCUCUUA	SEQ ID NO: 266
ETX-S00006080	UmsGfsUmAmGmAfAmGfCfAmGmAmAmUfUmCfCmAmGmCfAmsGmsGm	SEQ ID NO: 713	UGUAGAAGCAGAAUUCCAGCAGG	SEQ ID NO: 267
ETX-S00006084	GmsGfsAmAmUmAfGmUfCfAmGmCmAmUfCmUfCmUmUmAfCmsAmsGm	SEQ ID NO: 714	GGAAUAGUCAGCAUCUCUUACAG	SEQ ID NO: 268
ETX-S00006088	UmsUfsAmUmUmUfUmGfCfUmAmUmUmUfCmCfUmCmCmUfAmsGmsAm	SEQ ID NO: 715	UUAUUUUGCUAUUUCCUCCUAGA	SEQ ID NO: 269
ETX-S00006096	AmsAfsUmGmUmAfUmUfCfUmAmAmGmAfCmCfGmGmAmUfAmsCmsCm	SEQ ID NO: 717	AAUGUAUUCUAAGACCGGAUACC	SEQ ID NO: 271
ETX-S00006100	AmsUfsUmUmCmAfUmGfCfUmAmCmUmUfAmAfCmGmGmAfCmsUmsUm	SEQ ID NO: 718	AUUUCAUGCUACUUAACGGACUU	SEQ ID NO: 272
ETX-S00006104	GmsGfsAmGmAmUfUmUfUfAmCmAmCmUfGmCfAmGmUmGfAmsCmsUm	SEQ ID NO: 719	GGAGAUUUUACACUGCAGUGACU	SEQ ID NO: 273
ETX-S00006108	AmsAfsUmAmGmUfCmAfGfCmAmUmCmUfCmUfCmUfUmAmCmAfGmsAmsAm	SEQ ID NO: 720	AAUAGUCAGCAUCUCUUACAGAA	SEQ ID NO: 274
ETX-S00006112	UmsAfsGmUmCmUfUmUfAfUmCmAmUmCfCmAfUmAmAmAfGmsGmsAm	SEQ ID NO: 721	UAGUCUUUAUCAUCCAUAAAGGA	SEQ ID NO: 275
ETX-S00006116	AmsCfsAmGmAmAfUmCfCfAmUmAmUmAfUmAfUmAfAmAmCmCfCmsAmsUm	SEQ ID NO: 722	ACAGAAUCCAUAUAUAAACCCAU	SEQ ID NO: 276
ETX-S00006120	UmsGfsCmUmAmCfUmUfAfAmCmGmGmAfCmUfUmGmAmGfAmsGmsAm	SEQ ID NO: 723	UGCUACUUAACGGACUUGAGAGA	SEQ ID NO: 277
ETX-S00006124	GmsAfsAmGmAmUfGmUfCfAmUmGmUmUfCmAfGmAmGmGfGmsCmsUm	SEQ ID NO: 724	GAAGAUGUCAUGUUCAGAGGGCU	SEQ ID NO: 278
ETX-S00006128	UmsAfsCmAmGmUfUmGfCfUmGmAmAmAfGmUfUmCmCmUfUmsAmsGm	SEQ ID NO: 725	UACAGUUGCUGAAAGUUCCUUAG	SEQ ID NO: 279
ETX-S00006132	AmsUfsAmGmUmCfAmGfCfAmUmCmUmCfUmCfUmUfAmCmAmGfAmsAmsUm	SEQ ID NO: 726	AUAGUCAGCAUCUCUUACAGAAU	SEQ ID NO: 280

ETX-S00006136	UmsUfsUmCmCmUfUmUfGfUmAmAm AmAfUmUfUmCmAmCfCmsAmsGm	SEQ ID NO: 727	UUUCCUUUGUAAAA UUUCACCAG	SEQ ID NO: 281
ETX-S00006140	AmsGfsUmUmGmCfUmGfAfAmAmGm UmUfCmCfUmUmAmGfAmsUmsUm	SEQ ID NO: 728	AGUUGCUGAAAGUU CCUUAGAUU	SEQ ID NO: 282
ETX-S00006148	UmsUfsGmAmUmUfCmUfUfGmCmUm UmUfAmUfUmGmGmUfAmsCmsUm	SEQ ID NO: 730	UUGAUUCUUGCUUU AUUGGUACU	SEQ ID NO: 284
ETX-S00006152	AmsAfsUmUmCmAfUmUfCfCmAmGm CmUfUmGfAmAmGmAfCmsAmsUm	SEQ ID NO: 731	AAUUCAUUCCAGCU UGAAGACAU	SEQ ID NO: 285
ETX-S00006156	AmsUfsGmUmAmCfUmGfGfAmCmAm AmUfAmUfUmAmAmGfCmsUmsGm	SEQ ID NO: 732	AUGUACUGGACAAU AUUAAGCUG	SEQ ID NO: 286
ETX-S00006160	UmsUfsAmCmAmGfAmAfUfCmCmAm UmAfUmAfUmAmAmAfCmsCmsCm	SEQ ID NO: 733	UUACAGAAUCCAUA UAUAAACCC	SEQ ID NO: 287
ETX-S00006164	UmsUfsUmUmAmCfAmCfUfGmCmAm GmUfGmAfCmUmUmGfGmsAmsGm	SEQ ID NO: 734	UUUUACACUGCAGU GACUUGGAG	SEQ ID NO: 288
ETX-S00006168	GmsGfsAmAmUmAfAmUfAfGmUmCm UmUfUmAfUmCmAmUfCmsCmsAm	SEQ ID NO: 735	GGAAUAAUAGUCUU UAUCAUCCA	SEQ ID NO: 289
ETX-S00006176	UmsUfsCmCmUmUfUmGfUfAmAmAm AmUfUmUfCmAmCmCfAmsGmsCm	SEQ ID NO: 737	UUCCUUUGUAAAAU UUCACCAGC	SEQ ID NO: 291
ETX-S00006180	AmsGfsUmUmCmUfUmUfGfAmUmGm UmAfAmUfUmUmGmUfCmsCmsUm	SEQ ID NO: 738	AGUUCUUUGAUGUA AUUUGUCCU	SEQ ID NO: 292
ETX-S00006184	GmsGfsAmGmAmCfUmGfGfAmGmAm UmUfUmUfAmCmAmCfUmsGmsCm	SEQ ID NO: 739	GGAGACUGGAGAUU UUACACUGC	SEQ ID NO: 293
ETX-S00006188	UmsUfsAmGmUmAfGmCfAfGmCmAm AmAfAmCfUmUmUmCfAmsUmsGm	SEQ ID NO: 740	UUAGUAGCAGCAAA ACUUUCAUG	SEQ ID NO: 294
ETX-S00006192	GmsAfsUmUmCmCfAmGfCfUmCmAm GmUfUmUfUmAmAmUfAmsUmsCm	SEQ ID NO: 741	GAUUCCAGCUCAGU UUUAAUAUC	SEQ ID NO: 295
ETX-S00006196	UmsCfsUmUmUmAfUmCfAfUmCmCm AmUfAmAfAmGmGmAfAmsAmsAm	SEQ ID NO: 742	UCUUUAUCAUCCAU AAAGGAAAA	SEQ ID NO: 296
ETX-S00006200	UmsUfsGmUmUmUfAmAfUfAmCmCm CmAfCmUfGmGmGmAfAmsUmsCm	SEQ ID NO: 743	UUGUUUAAUACCCA CUGGGAAUC	SEQ ID NO: 297
ETX-S00006204	AmsUfsGmUmAmCfUmGfGfAmUmCm CmAfGmCfAmGmAmGfGmsUmsGm	SEQ ID NO: 744	AUGUACUGGAUCCA GCAGAGGUG	SEQ ID NO: 298
ETX-S00006208	GmsUfsCmAmGmCfAmUfCfUmCmUm UmAfCmAfGmAmAmUfCmsCmsAm	SEQ ID NO: 745	GUCAGCAUCUCUUA CAGAAUCCA	SEQ ID NO: 299
ETX-S00006212	UmsAfsCmGmUmUfGmAfCfAmAmUm CmUfCmCfAmUmGmUfAmsGmsUm	SEQ ID NO: 746	UACGUUGACAAUCU CCAUGUAGU	SEQ ID NO: 300
ETX-S00006216	GmsAfsGmAmUmUfUmUfAfCmAmCm UmGfCmAfGmUmGmAfCmsUmsUm	SEQ ID NO: 747	GAGAUUUUACACUG CAGUGACUU	SEQ ID NO: 301
ETX-S00006220	UmsUfsUmGmUmAfAmAfAfUmUmUm CmAfCmCfAmGmCmUfGmsUmsUm	SEQ ID NO: 748	UUUGUAAAAUUUCA CCAGCUGUU	SEQ ID NO: 302

ETX-S00006224	UmsAfsAmUmAmGfUmCfUfUmUmAmUmCfAmUfCmCmAmUfAmsAmsAm	SEQ ID NO: 749	UAAUAGUCUUUAUCAUCCAUAAA	SEQ ID NO: 303
ETX-S00006228	AmsCfsAmUmUmCfUmGfAfUmAmAmAmUfCmUfUmAmGmCfUmsGmsGm	SEQ ID NO: 750	ACAUUCUGAUAAAUCUUAGCUGG	SEQ ID NO: 304
ETX-S00006232	UmsAfsCmAmUmUfUmUfCfUmGmGmAmAfUmGfUmAmUmUfCmsUmsAm	SEQ ID NO: 751	UACAUUUUCUGGAAUGUAUUCUA	SEQ ID NO: 305
ETX-S00006236	AmsAfsUmUmCmUfUmUfCfGmUmCmGmAfAmUfCmUmUmAfUmsCmsAm	SEQ ID NO: 752	AAUUCUUUCGUCGAAUCUUAUCA	SEQ ID NO: 306
ETX-S00006240	AmsUfsUmGmAmGfGmAfUfUmUmCmAmUfGmCfUmAmCmUfUmsAmsAm	SEQ ID NO: 753	AUUGAGGAUUUCAUGCUACUUAA	SEQ ID NO: 307
ETX-S00006244	AmsCfsAmGmGmAfGmGfAfAmAmGmGmAfAmCfUmCmAmGfGmsUmsGm	SEQ ID NO: 754	ACAGGAGGAAAGGAACUCAGGUG	SEQ ID NO: 308
ETX-S00006248	UmsUfsGmAmAmGfAmAfAfAmCmUmUmUfGmCfAmGmCmUfGmsCmsCm	SEQ ID NO: 755	UUGAAGAAAACUUUGCAGCUGCC	SEQ ID NO: 309
ETX-S00006252	GmsAfsAmAmUmUfGmAfGfGmAmUmUmUfCmAfUmGmCmUfAmsCmsUm	SEQ ID NO: 756	GAAAUUGAGGAUUUCAUGCUACU	SEQ ID NO: 310
ETX-S00006256	UmsAfsUmUmUmUfGmCfUfAmUmUmUmCfCmUfCmCmUmAfGmsAmsCm	SEQ ID NO: 757	UAUUUUGCUAUUUCCUCCUAGAC	SEQ ID NO: 311
ETX-S00006260	UmsUfsCmCmAmGfCmUfCfAmGmUmUmUfUmAfUmAfAmUmAmUfCmsAmsGm	SEQ ID NO: 758	UUCCAGCUCAGUUUUAAUAUCAG	SEQ ID NO: 312
ETX-S00006264	UmsUfsUmAmUmGfUmAfCfUmGmGmAmCfAmAfUmAmUmUfAmsAmsGm	SEQ ID NO: 759	UUUAUGUACUGGACAAUAUUAAG	SEQ ID NO: 313
ETX-S00006268	UmsCfsAmAmCmAfUmUfCfUmGmAmUmAfUmAfAmAfUmCmUmUfAmsGmsCm	SEQ ID NO: 760	UCAACAUUCUGAUAAAUCUUAGC	SEQ ID NO: 314
ETX-S00006272	AmsUfsUmUmCmCfUmUfUfGmUmAmAmAfAmAfAmUfUmUmCmAfCmsCmsAm	SEQ ID NO: 761	AUUUCCUUUGUAAAAUUUCACCA	SEQ ID NO: 315
ETX-S00006276	UmsGfsAmGmGmAfUmUfUfCmAmUmGmCfUmAfCmUmUmAfAmsCmsGm	SEQ ID NO: 762	UGAGGAUUUCAUGCUACUUAACG	SEQ ID NO: 316
ETX-S00006280	AmsGfsAmCmUmGfGmAfGfAmUmUmUmUfAmCfAmCmUmGfCmsAmsGm	SEQ ID NO: 763	AGACUGGAGAUUUUACACUGCAG	SEQ ID NO: 317
ETX-S00006284	UmsAfsGmUmAmGfCmAfGfCmAmAmAmAfAmCfUmUfUmUmCmAfUmsGmsAm	SEQ ID NO: 764	UAGUAGCAGCAAAACUUUCAUGA	SEQ ID NO: 318
ETX-S00006288	AmsUfsUmCmCmAfGmCfUfCmAmGmUmUfUmUfAmAmUmAfUmsCmsAm	SEQ ID NO: 765	AUUCCAGCUCAGUUUUAAUAUCA	SEQ ID NO: 319
ETX-S00006292	AmsGfsGmAmUmUfUmCfAfUmGmCmUmAfCmUfUmAmAmCfGmsGmsAm	SEQ ID NO: 766	AGGAUUUCAUGCUACUUAACGGA	SEQ ID NO: 320
ETX-S00006296	GmsAfsAmGmAmCfAmUfUfUmCmUmGmAfGmAfCmUmGfCmsAmsAm	SEQ ID NO: 767	GAAGACAUUUCUGAAGUCUGCAA	SEQ ID NO: 321
ETX-S00006300	UmsAfsUmGmUmAfCmUfGfGmAmCmAmAfUmAfUmAfUmUmAmAfGmsCmsUm	SEQ ID NO: 768	UAUGUACUGGACAAUAUUAAGCU	SEQ ID NO: 322

ETX-S00006304	AmsUfsUmCmUmGfAmUfAfAmAmUmCmUfUmAfGmCmUmGfGmsAmsCm	SEQ ID NO: 769	AUUCUGAUAAAUCUUAGCUGGAC	SEQ ID NO: 323
ETX-S00006308	AmsAfsCmAmCmUfUmCfGfUmAmAmAmGfUmAfGmAmGmCfUmsUmsGm	SEQ ID NO: 770	AACACUUCGUAAAGUAGAGCUUG	SEQ ID NO: 324
ETX-S00006312	AmsAfsCmAmUmUfCmUfGfAmUmAmAmAfUmCfUmUmAmGfCmsUmsGm	SEQ ID NO: 771	AACAUUCUGAUAAAUCUUAGCUG	SEQ ID NO: 325
ETX-S00006316	AmsUfsUmCmUmUfGmCfUfUmUmAmUmUfGmGfUmAmCmUfGmsAmsGm	SEQ ID NO: 772	AUUCUUGCUUUAUUGGUACUGAG	SEQ ID NO: 326
ETX-S00006320	AmsCfsUmUmAmAfCmGfGfAmCmUmUmGfAmGfAmGmAmGfGmsAmsGm	SEQ ID NO: 773	ACUUAACGGACUUGAGAGAGGAG	SEQ ID NO: 327
ETX-S00006324	UmsUfsCmGmUmAfAmAfGfUmAmGmAmGfCmUfUmGmAmUfAmsCmsAm	SEQ ID NO: 774	UUCGUAAAGUAGAGCUUGAUACA	SEQ ID NO: 328
ETX-S00006328	AmsUfsUmUmCmAfCmCfAfGmCmUmGmUfUmCfAmAmCmAfUmsUmsCm	SEQ ID NO: 775	AUUUCACCAGCUGUUCAACAUUC	SEQ ID NO: 329
ETX-S00006332	UmsUfsCmAmAmCfAmUfUfCmUmGmAmUfAmAfAmUmCmUfUmsAmsGm	SEQ ID NO: 776	UUCAACAUUCUGAUAAAUCUUAG	SEQ ID NO: 330
ETX-S00006336	AmsUfsCmCmAmUfAmUfAfUmAmAmAmCfCmCfAmUmGmGfAmsCmsUm	SEQ ID NO: 777	AUCCAUAUAUAAACCCAUGGACU	SEQ ID NO: 331
ETX-S00006340	GmsUfsAmAmUmUfUmGfUfCmCmUmCmAfUmUfUmCmUmUfCmsAmsAm	SEQ ID NO: 778	GUAAUUUGUCCUCAUUUCUUCAA	SEQ ID NO: 332
ETX-S00006344	UmsUfsCmUmUmUfCmGfUfCmGmAmAmUfCmUfUmAmUmCfAmsAmsUm	SEQ ID NO: 779	UUCUUUCGUCGAAUCUUAUCAAU	SEQ ID NO: 333
ETX-S00006348	AmsGfsGmGmAmAfUmAfAfUmAmGmUmCfUmUfUmAmUmCfAmsUmsCm	SEQ ID NO: 780	AGGGAAUAAUAGUCUUUAUCAUC	SEQ ID NO: 334
ETX-S00006356	UmsCfsUmAmCmUfUmCfCfUmCmAmGmUfCmUfUmAmGmGfAmsAmsAm	SEQ ID NO: 782	UCUACUUCCUCAGUCUUAGGAAA	SEQ ID NO: 336
ETX-S00006360	AmsAfsAmGmGmAfAmCfUfCmAmGmGmUfGmUfUmGmGmAfAmsAmsGm	SEQ ID NO: 783	AAAGGAACUCAGGUGUUGGAAAG	SEQ ID NO: 337
ETX-S00006364	UmsUfsUmCmGmUfCmGfAfAmUmCmUmUfAmUfCmAmAmUfGmsAmsUm	SEQ ID NO: 784	UUUCGUCGAAUCUUAUCAAUGAU	SEQ ID NO: 338
ETX-S00006368	UmsGfsGmAmAmAfUmUfGfAmGmGmAmUfUmUfUmCmAmUmGfCmsUmsAm	SEQ ID NO: 785	UGGAAAUUGAGGAUUUCAUGCUA	SEQ ID NO: 339
ETX-S00006372	AmsAfsGmUmAmGfAmGfCfUmUmGmAmUfAmUfAmCfAmUmUmUfUmsCmsUm	SEQ ID NO: 786	AAGUAGAGCUUGAUACAUUUUCU	SEQ ID NO: 340
ETX-S00006376	UmsUfsGmGmAmAfUmUfGfUmGmCmUmUfUmAfAmGfUmAmGmCfAmsGmsCm	SEQ ID NO: 787	UUGGAAUUGUGCUUAGUAGCAGC	SEQ ID NO: 341
ETX-S00006380	UmsAfsCmAmGmAfUmAfGfAmUmCmCmCfAmCfAmCfAmGmUmAfCmsUmsGm	SEQ ID NO: 788	UACAGAUAGAUCCCACAGUACUG	SEQ ID NO: 342
ETX-S00006384	UmsUfsUmAmUmUfUmUfGfCmUmAmUmUfUmCfUmCfCmUmCmCfUmsAmsGm	SEQ ID NO: 789	UUUAUUUUGCUAUUUCCUCCUAG	SEQ ID NO: 343

ETX-S00006388	UmsAfsUmCmAmAfUmGfAfUmGmCmAmAfUmCfAmUmUmUfCmsUmsUm	SEQ ID NO: 790	UAUCAAUGAUGCAAUCAUUUCUU	SEQ ID NO: 344
ETX-S00006392	AmsUfsUmUmUmAfCmAfCfUmGmCmAmGfUmGfAmCmUmUfGmsGmsAm	SEQ ID NO: 791	AUUUUACACUGCAGUGACUUGGA	SEQ ID NO: 345
ETX-S00006396	UmsCfsUmGmAmUfAmAfAfUmCmUmUmAfGmCfUmGmGmAfCmsUmsCm	SEQ ID NO: 792	UCUGAUAAAUCUUAGCUGGACUC	SEQ ID NO: 346
ETX-S00006400	UmsCfsGmAmAmUfCmUfUfAmUmCmAmAfUmGfAmUmGmCfAmsAmsUm	SEQ ID NO: 793	UCGAAUCUUAUCAAUGAUGCAAU	SEQ ID NO: 347
ETX-S00006404	GmsAfsGmGmAmUfUmUfCfAmUmGmCmUfAmCfUmUmAmAfCmsGmsGm	SEQ ID NO: 794	GAGGAUUUCAUGCUACUUAACGG	SEQ ID NO: 348
ETX-S00006408	GmsAfsAmAmGmCfGmUfGfGmAmUmCmUfGmUfUmAmUmUfAmsGmsUm	SEQ ID NO: 795	GAAAGCGUGGAUCUGUUAUUAGU	SEQ ID NO: 349
ETX-S00006412	AmsGfsUmAmGmAfGmCfUfUmGmAmUmAfCmAfUmUmUmUfCmsUmsGm	SEQ ID NO: 796	AGUAGAGCUUGAUACAUUUUCUG	SEQ ID NO: 350
ETX-S00006416	AmsAfsUmCmCmAfUmAfUfAmUmAmAmAfCmCfCmAmUmGfGmsAmsCm	SEQ ID NO: 797	AAUCCAUAUAUAAACCCAUGGAC	SEQ ID NO: 351
ETX-S00006420	AmsAfsAmGmUmAfGmAfGfCmUmUmGmAfUmAfCmAmUmUfUmsUmsCm	SEQ ID NO: 798	AAAGUAGAGCUUGAUACAUUUUC	SEQ ID NO: 352
ETX-S00006424	GmsAfsUmUmUmCfAmUfGfCmUmAmCmUfUmAfAmCmGmGfAmsCmsUm	SEQ ID NO: 799	GAUUUCAUGCUACUUAACGGACU	SEQ ID NO: 353
ETX-S00006428	AmsUfsAmGmGmGfAmAfUfAmAmUmAmGfUmCfUmUmUmAfUmsCmsAm	SEQ ID NO: 800	AUAGGGAAUAAUAGUCUUUAUCA	SEQ ID NO: 354
ETX-S00006432	CmsUfsUmAmGmUfAmGfCfAmGmCmAmAfAmAfAmCmUmUmUfCmsAmsUm	SEQ ID NO: 801	CUUAGUAGCAGCAAAACUUUCAU	SEQ ID NO: 355
ETX-S00006436	UmsUfsAmAmCmGfGmAfCfUmUmGmAmGfAmGfAmGmGmAfGmsAmsGm	SEQ ID NO: 802	UUAACGGACUUGAGAGAGGAGAG	SEQ ID NO: 356
ETX-S00006440	GmsUfsAmGmUmUfAmUfUfCmUmCmAmUfCmGfGmUmCmCfUmsCmsUm	SEQ ID NO: 803	GUAGUUAUUCUCAUCGGUCCUCU	SEQ ID NO: 357
ETX-S00006444	CmsAfsAmAmAmCfUmUfUfCmAmUmGmAfUmGfGmUmGmUfAmsUmsUm	SEQ ID NO: 804	CAAAACUUUCAUGAUGGUGUAUU	SEQ ID NO: 358
ETX-S00006448	AmsAfsUmUmUmGfUmCfCfUmCmAmAmUfUmUfUmCfUmUmCmAfAmsAmsUm	SEQ ID NO: 805	AAUUUGUCCUCAUUUCUUCAAAU	SEQ ID NO: 359
ETX-S00006452	GmsAfsAmUmAmAfUmAfGfUmCmUmUmUfAmUfAmUfCmAmUmCfCmsAmsUm	SEQ ID NO: 806	GAAUAAUAGUCUUUAUCAUCCAU	SEQ ID NO: 360
ETX-S00006456	UmsUfsAmGmAmUfUmCfCfAmGmCmUmCfAmGfUmUmUmUfAmsAmsUm	SEQ ID NO: 807	UUAGAUUCCAGCUCAGUUUUAAU	SEQ ID NO: 361
ETX-S00006460	AmsCfsAmAmUmCfUmCfCfAmUmGmUmAfGmUfUmAmUmUfCmsUmsCm	SEQ ID NO: 808	ACAAUCUCCAUGUAGUUAUUCUC	SEQ ID NO: 362
ETX-S00006464	AmsGfsGmAmAmUfAmGfUfCmAmGmCmAfCmAfUmCfUmCmUmUfAmsCmsAm	SEQ ID NO: 809	AGGAAUAGUCAGCAUCUCUUACA	SEQ ID NO: 363

ETX-S00006468	AmsGfsCmAmGmCfAmAfAfAmCmUmUmUfCmAfUmGmAmUfGmsGmsUm	SEQ ID NO: 810	AGCAGCAAAACUUUCAUGAUGGU	SEQ ID NO: 364
ETX-S00006472	AmsUfsCmUmGmGfUmUfCfUmGmGmUmUfUmUfAmUmGmUfAmsCmsUm	SEQ ID NO: 811	AUCUGGUUCUGGUUUUAUGUACU	SEQ ID NO: 365
ETX-S00006476	AmsAfsUmUmGmUfGmCfUfUmAmGmUmAfGmCfAmGmCmAfAmsAmsAm	SEQ ID NO: 812	AAUUGUGCUUAGUAGCAGCAAAA	SEQ ID NO: 366
ETX-S00006480	UmsUfsCmAmAmAfGmGfUfGmAmGmCmUfGmCfAmGmUmCfGmsAmsAm	SEQ ID NO: 813	UUCAAAGGUGAGCUGCAGUCGAA	SEQ ID NO: 367
ETX-S00006484	UmsAfsGmAmUmUfCmCfAfGmCmUmCmAfGmUfUmUmUmAfAmsUmsAm	SEQ ID NO: 814	UAGAUUCCAGCUCAGUUUUAAUA	SEQ ID NO: 368
ETX-S00006488	GmsUfsGmAmUmUfUmCfCfAmUmGmAmCfUmCfCmAmCmUfAmsAmsAm	SEQ ID NO: 815	GUGAUUUCCAUGACUCCACUAAA	SEQ ID NO: 369
ETX-S00006492	GmsUfsGmCmUmUfAmGfUfAmGmCmAmGfCmAfAmAmAmCfUmsUmsUm	SEQ ID NO: 816	GUGCUUAGUAGCAGCAAAACUUU	SEQ ID NO: 370
ETX-S00006496	UmsAfsAmUmUmUfGmUfCfCmUmCmAmUfUmUfCmUmUmCfAmsAmsAm	SEQ ID NO: 817	UAAUUUGUCCUCAUUUCUUCAAA	SEQ ID NO: 371
ETX-S00006500	UmsUfsUmCmUmUfUmGfCfUmGmCmUmUfCmCfUmGmGmAfGmsUmsAm	SEQ ID NO: 818	UUUCUUUGCUGCUUCCUUGAGUA	SEQ ID NO: 372
ETX-S00006504	UmsCfsUmCmUmUfAmCfAfGmAmAmUmCfCmAfUmAmUmAfUmsAmsAm	SEQ ID NO: 819	UCUCUUACAGAAUCCAUAUAUAA	SEQ ID NO: 373
ETX-S00006508	AmsUfsUmGmUmUfGmGfGfAmCmAmCmUfUmAfGmUmUmAfCmsCmsAm	SEQ ID NO: 820	AUUGUUGGGACACUUAGUUACCA	SEQ ID NO: 374
ETX-S00006512	AmsCfsUmUmCmGfUmAfAfAmGmUmAmGfAmGfCmUmUmGfAmsUmsAm	SEQ ID NO: 821	ACUUCGUAAAGUAGAGCUUGAUA	SEQ ID NO: 375
ETX-S00006516	UmsAfsGmUmUmAfUmUfCfUmCmAmUmCfGmGfUmCmCmUfCmsUmsCm	SEQ ID NO: 822	UAGUUAUUCUCAUCGGUCCUCUC	SEQ ID NO: 376
ETX-S00006520	UmsAfsGmAmCmAfUmGfAfGmCmUmGmCfUmAfAmAmAmGfCmsUmsCm	SEQ ID NO: 823	UAGACAUGAGCUGCUAAAAGCUC	SEQ ID NO: 377
ETX-S00006524	AmsGfsCmUmGmUfUmCfAfAmCmAmUmCfUmGfAmUmAmAfAmsAmsUm	SEQ ID NO: 824	AGCUGUUCAACAUUCUGAUAAAU	SEQ ID NO: 378
ETX-S00006528	CmsGfsUmAmAmAfGmUfAfGmAmGmCmUfGmAfUmAmCmAfUmsUmsUm	SEQ ID NO: 825	CGUAAAGUAGAGCUUGAUACAUU	SEQ ID NO: 379
ETX-S00006532	UmsUfsGmAmGmUfAmCfUfGmUmUmGmUfUmGfGmAmAmAfGmsAmsGm	SEQ ID NO: 826	UUGAGUACUGUUGUUUGGAAUAG	SEQ ID NO: 380
ETX-S00006536	UmsGfsAmUmAmGfGmGfAfAmUmAmAmUfAmGfUmCmUmUfUmsAmsUm	SEQ ID NO: 827	UGAUAGGGAAUAAUAGUCUUUAU	SEQ ID NO: 381
ETX-S00006540	AmsAfsAmCmCmGfAmAfGfAmUmGmUmCfAmGfGmUmUmCfAmsGmsAm	SEQ ID NO: 828	AAACCGAAGAUGUCAUGUUCAGA	SEQ ID NO: 382
ETX-S00006544	AmsAfsUmUmUmCfAmCfCfAmGmCmUmGfUmUfUmCmAmAfCmsAmsUm	SEQ ID NO: 829	AAUUUCACCAGCUGUUCAACAUU	SEQ ID NO: 383

ETX-S00006548	GmsGfsGmAmAmUfAmAfUfAmGmUmCmUfUmUfAmUmCmAfUmsCmsCm	SEQ ID NO: 830	GGGAAUAAUAGUCUUUAUCAUCC	SEQ ID NO: 384
ETX-S00006552	AmsGfsCmUmUmGfAmUfAfCmAmUmUmUfUmCfUmGmGmAfAmsUmsGm	SEQ ID NO: 831	AGCUUGAUACAUUUUCUGGAAUG	SEQ ID NO: 385
ETX-S00006556	UmsUfsGmAmUmGfUmAfAfUmUmUmGmUfCmCfUmCmAmUfUmsUmsCm	SEQ ID NO: 832	UUGAUGUAAUUUGUCCUCAUUUC	SEQ ID NO: 386
ETX-S00006560	UmsUfsUmUmGmCfUmAfUfUmUmCmCmUfCmCfUmAmGmAfCmsAmsUm	SEQ ID NO: 833	UUUUGCUAUUUCCUCCUAGACAU	SEQ ID NO: 387
ETX-S00006564	UmsGfsAmGmUmAfCmUfGfUmUmGmUmUfUmGfGmAmAmUfAmsGmsCm	SEQ ID NO: 834	UGAGUACUGUUGUUUGGAAUAGC	SEQ ID NO: 388
ETX-S00006568	UmsAfsGmUmCmAfGmCfAfUmCmUmCmUfUmAfCmAmGmAfAmsUmsCm	SEQ ID NO: 835	UAGUCAGCAUCUCUUACAGAAUC	SEQ ID NO: 389
ETX-S00006572	UmsAfsUmUmCmUfUmCfAfAmAmGmGmUfGmAfGmCmUmGfCmsAmsGm	SEQ ID NO: 836	UAUUCUUCAAAGGUGAGCUGCAG	SEQ ID NO: 390
ETX-S00006576	AmsGfsAmGmUmCfAmGfAfCmAmUmAmAfAmUfGmAmUmCfUmsCmsAm	SEQ ID NO: 837	AGAGUCAGACAUAAAUGAUCUCA	SEQ ID NO: 391
ETX-S00006580	AmsAfsCmCmGmAfAmGfAfUmGmUmCmAfUmGfUmUmCmAfGmsAmsGm	SEQ ID NO: 838	AACCGAAGAUGUCAUGUUCAGAG	SEQ ID NO: 392
ETX-S00006584	AmsUfsGmCmUmAfCmUfUfAmAmCmGmGfAmCfUmUmGmAfGmsAmsGm	SEQ ID NO: 839	AUGCUACUUAACGGACUUGAGAG	SEQ ID NO: 393
ETX-S00006588	AmsCfsAmGmAmUfAmGfAfUmCmCmCmAfCmAfGmUmAmCfUmsGmsGm	SEQ ID NO: 840	ACAGAUAGAUCCCACAGUACUGG	SEQ ID NO: 394
ETX-S00006592	AmsCfsAmCmUmUfCmGfUfAmAmAmGmUfAmGfAmGmCmUfUmsGmsAm	SEQ ID NO: 841	ACACUUCGUAAAGUAGAGCUUGA	SEQ ID NO: 395
ETX-S00006596	CmsUfsUmAmGmAfUmUfCfCmAmGmCmUfCmAfGmUmUmUfUmsAmsAm	SEQ ID NO: 842	CUUAGAUUCCAGCUCAGUUUUAA	SEQ ID NO: 396
ETX-S00006600	GmsAfsUmUmCmUfUmGfCfUmUmUmAmUfUmGfGmUmAmCfUmsGmsAm	SEQ ID NO: 843	GAUUCUUGCUUUAUUGGUACUGA	SEQ ID NO: 397
ETX-S00006604	UmsUfsUmUmCmUfGmGfAfAmUmGmUmAfUmAfUmUfCmUmAmAfGmsAmsCm	SEQ ID NO: 844	UUUUCUGGAAUGUAUUCUAAGAC	SEQ ID NO: 398
ETX-S00006608	UmsUfsAmUmCmAfAmUfGfAmUmGmCmAfUmAfAmUfCmAmUmUfUmsCmsUm	SEQ ID NO: 845	UUAUCAAUGAUGCAAUCAUUUCU	SEQ ID NO: 399
ETX-S00006612	UmsCfsCmUmUmUfGmUfAfAmAmAmUmUfUmUfUmCfAmCmCmAfGmsCmsUm	SEQ ID NO: 846	UCCUUUGUAAAAUUUCACCAGCU	SEQ ID NO: 400
ETX-S00006616	UmsUfsUmGmAmUfGmUfAfAmUmUmUmGfUmGfUmCfCmUmCmAfUmsUmsUm	SEQ ID NO: 847	UUUGAUGUAAUUUGUCCUCAUUU	SEQ ID NO: 401
ETX-S00006620	GmsUfsUmGmUmUfUmGfGfAmAmUmAmGfAmGfCmAfCmCmGmGfAmsAmsAm	SEQ ID NO: 848	GUUGUUUGGAAUAGCACCGGAAA	SEQ ID NO: 402
ETX-S00006624	UmsGfsGmAmAmAfCmAfGfAmGmCmAmCfUmCfUmUfUmGmAmGfUmsUmsGm	SEQ ID NO: 849	UGGAAACAGAGCACCUUGAGUUG	SEQ ID NO: 403

ETX-S00006628	CmsAfsAmUmGmAfUmGfCfAmAmUm CmAfUmUfUmCmUmUfCmsCmsAm	SEQ ID NO: 850	CAAUGAUGCAAUCA UUUCUUCCA	SEQ ID NO: 404
ETX-S00006632	AmsAfsUmGmCmUfUmGfGfUmUmGm AmUfUmCfUmUmGmCfUmsUmsUm	SEQ ID NO: 851	AAUGCUUGGUUGAU UCUUGCUUU	SEQ ID NO: 405
ETX-S00006636	AmsAfsAmGmUmUfCmCfUfUmAmGm AmUfUmCfCmAmGmCfUmsCmsAm	SEQ ID NO: 852	AAAGUUCCUUAGAU UCCAGCUCA	SEQ ID NO: 406
ETX-S00006640	UmsGfsUmAmCmUfGmGfAfCmAmAm UmAfUmUfAmAmGmCfUmsGmsGm	SEQ ID NO: 853	UGUACUGGACAAUA UUAAGCUGG	SEQ ID NO: 407
ETX-S00006644	AmsGfsAmAmUmCfCmAfUfAmUmAm UmAfAmAfCmCmCmAfUmsGmsGm	SEQ ID NO: 854	AGAAUCCAUAUAUA AACCCAUGG	SEQ ID NO: 408
ETX-S00006648	UmsUfsUmUmAmUfGmUfAfCmUmGm GmAfCmAfAmUmAmUfUmsAmsAm	SEQ ID NO: 855	UUUUAUGUACUGGA CAAUAUUAA	SEQ ID NO: 409
ETX-S00006656	AmsAfsCmGmGmAfCmUfUfGmAmGm AmGfAmGfGmAmGmAfGmsCmsCm	SEQ ID NO: 857	AACGGACUUGAGAG AGGAGAGCC	SEQ ID NO: 411
ETX-S00006660	UmsCfsCmUmUmUfGmGfAfAmUmUm GmUfGmCfUmUmAmGfUmsAmsGm	SEQ ID NO: 858	UCCUUUGGAAUUGU GCUUAGUAG	SEQ ID NO: 412
ETX-S00006664	AmsAfsGmUmUmCfCmUfUfAmGmAm UmUfCmCfAmGmCmUfCmsAmsGm	SEQ ID NO: 859	AAGUUCCUUAGAUU CCAGCUCAG	SEQ ID NO: 413
ETX-S00006668	GmsAfsUmUmUmUfAmCfAfCmUmGm CmAfGmUfGmAmCmUfUmsGmsGm	SEQ ID NO: 860	GAUUUUACACUGCA GUGACUUGG	SEQ ID NO: 414
ETX-S00006672	CmsUfsUmCmGmUfAmAfAfGmUmAm GmAfGmCfUmUmGmAfUmsAmsCm	SEQ ID NO: 861	CUUCGUAAAGUAGA GCUUGAUAC	SEQ ID NO: 415
ETX-S00006676	UmsAfsCmUmGmUfUmGfUfUmUmGm GmAfAmUfAmGmCmAfCmsCmsGm	SEQ ID NO: 862	UACUGUUGUUUGGA AUAGCACCG	SEQ ID NO: 416
ETX-S00006680	GmsAfsGmUmAmCfUmGfUfUmGmUm UmUfGmGfAmAmUmAfGmsCmsAm	SEQ ID NO: 863	GAGUACUGUUGUUU GGAAUAGCA	SEQ ID NO: 417
ETX-S00006684	GmsAfsUmAmAmAfUmCfUfUmAmGm CmUfGmGfAmCmUmCfAmsUmsGm	SEQ ID NO: 864	GAUAAAUCUUAGCU GGACUCAUG	SEQ ID NO: 418
ETX-S00006688	CmsAfsUmUmUmCfUmGfAfAmGmUm CmUfGmCfAmAmGmCfAmsGmsGm	SEQ ID NO: 865	CAUUUCUGAAGUCU GCAAGCAGG	SEQ ID NO: 419
ETX-S00006692	UmsCfsGmUmAmAfAmGfUfAmGmAm GmCfUmUfGmAmUmAfCmsAmsUm	SEQ ID NO: 866	UCGUAAAGUAGAGC UUGAUACAU	SEQ ID NO: 420
ETX-S00006696	UmsUfsCmUmUmGfUmUfUfAmAmUm AmCfCmCfAmCmUmGfGmsGmsAm	SEQ ID NO: 867	UUCUUGUUUAAUAC CCACUGGGA	SEQ ID NO: 421
ETX-S00006700	AmsUfsUmCmAmUfUmCfCfAmGmCm UmUfGmAfAmGmAmCfAmsUmsUm	SEQ ID NO: 868	AUUCAUUCCAGCUU GAAGACAUU	SEQ ID NO: 422
ETX-S00006704	AmsAfsUmUmGmAfGmGfAfUmUmUm CmAfUmGfCmUmAmCfUmsUmsAm	SEQ ID NO: 869	AAUUGAGGAUUUCA UGCUACUUA	SEQ ID NO: 423
ETX-S00006708	UmsGfsAmGmCmAfCmCfAfAmUmCm CmUfGmUfAmGmUmGfGmsAmsAm	SEQ ID NO: 870	UGAGCACCAAUCCU GUAGUGGAA	SEQ ID NO: 424

ETX-S00006712	GmsAfsAmUmUmGfUmUfGfGmGmAm CmAfCmUfUmAmGmUfUmsAmsCm	SEQ ID NO: 871	GAAUUGUUGGGACA CUUAGUUAC	SEQ ID NO: 425
ETX-S00006716	AmsUfsCmAmAmUfGmAfUfGmCmAm AmUfCmAfUmUmUmCfUmsUmsCm	SEQ ID NO: 872	AUCAAUGAUGCAAU CAUUUCUUC	SEQ ID NO: 426
ETX-S00006720	AmsGfsUmCmAmGfAmCfAfUmAmAm AmUfGmAfUmCmUmCfAmsAmsGm	SEQ ID NO: 873	AGUCAGACAUAAAU GAUCUCAAG	SEQ ID NO: 427
ETX-S00006724	GmsUfsUmUmUmAfUmGfUfAmCmUm GmGfAmCfAmAmUmAfUmsUmsAm	SEQ ID NO: 874	GUUUUAUGUACUGG ACAAUAUUA	SEQ ID NO: 428
ETX-S00006728	AmsAfsUmCmUmUfAmGfCfUmGmGm AmCfUmCfAmUmGmCfUmsUmsCm	SEQ ID NO: 875	AAUCUUAGCUGGAC UCAUGCUUC	SEQ ID NO: 429
ETX-S00006732	AmsUfsUmUmGmUfCmCfUfCmAmUm UmUfCmUfUmCmAmAfAmsUmsGm	SEQ ID NO: 876	AUUUGUCCUCAUUU CUUCAAAUG	SEQ ID NO: 430
ETX-S00006736	UmsUfsUmAmCmAfCmUfGfCmAmGm UmGfAmCfUmUmGmGfAmsGmsGm	SEQ ID NO: 877	UUUACACUGCAGUG ACUUGGAGG	SEQ ID NO: 431
ETX-S00006740	UmsCfsUmUmGmCfUmUfUfAmUmUm GmGfUmAfCmUmGmAfGmsAmsAm	SEQ ID NO: 878	UCUUGCUUUAUUGG UACUGAGAA	SEQ ID NO: 432
ETX-S00006744	CmsAfsUmGmUmAfGmUfUfAmUmUm CmUfCmAfUmCmGmGfUmsCmsCm	SEQ ID NO: 879	CAUGUAGUUAUUCU CAUCGGUCC	SEQ ID NO: 433
ETX-S00006748	AmsUfsUmGmUmUfUmAfCfAmGmGm GmCfUmAfCmAmGmAfUmsAmsGm	SEQ ID NO: 880	AUUGUUUACAGGGC UACAGAUAG	SEQ ID NO: 434
ETX-S00006752	GmsGfsAmAmAmUfUmGfAfGmGmAm UmUfUmCfAmUmGmCfUmsAmsCm	SEQ ID NO: 881	GGAAAUUGAGGAUU UCAUGCUAC	SEQ ID NO: 435
ETX-S00006756	GmsUfsAmCmUmGfUmUfGfUmUmUm GmGfAmAfUmAmGmCfAmsCmsCm	SEQ ID NO: 882	GUACUGUUGUUUGG AAUAGCACC	SEQ ID NO: 436
ETX-S00006760	AmsCfsUmGmGmAfGmAfUfUmUmUm AmCfAmCfUmGmCmAfGmsUmsGm	SEQ ID NO: 883	ACUGGAGAUUUUAC ACUGCAGUG	SEQ ID NO: 437
ETX-S00006764	CmsUfsGmAmUmAfGmGfGfAmAmUm AmAfUmAfGmUmCmUfUmsUmsAm	SEQ ID NO: 884	CUGAUAGGGAAUAA UAGUCUUUA	SEQ ID NO: 438
ETX-S00006768	GmsAfsAmUmUmGfUmGfCfUmUmAm GmUfAmGfCmAmGmCfAmsAmsAm	SEQ ID NO: 885	GAAUUGUGCUUAGU AGCAGCAAA	SEQ ID NO: 439
ETX-S00006772	AmsGfsGmAmAmAfGmGfAfAmCmUm CmAfGmGfUmGmUmUfGmsGmsAm	SEQ ID NO: 886	AGGAAAGGAACUCA GGUGUUGGA	SEQ ID NO: 440
ETX-S00006776	GmsAfsAmUmAmGfUmCfAfGmCmAm UmCfUmCfUmUmAmCfAmsGmsAm	SEQ ID NO: 887	GAAUAGUCAGCAUC UCUUACAGA	SEQ ID NO: 441
ETX-S00006780	UmsUfsUmAmCmAfGmGfGfCmUmAm CmAfGmAfUmAmGmAfUmsCmsCm	SEQ ID NO: 888	UUUACAGGGCUACA GAUAGAUCC	SEQ ID NO: 442
ETX-S00006784	AmsCfsAmUmUmUfCmUfGfAmAmGm UmCfUmGfCmAmAmGfCmsAmsGm	SEQ ID NO: 889	ACAUUUCUGAAGUC UGCAAGCAG	SEQ ID NO: 443
ETX-S00006788	AmsUfsUmUmCmCfAmUfGfAmCmUm CmCfAmCfUmAmAmAfGmsUmsAm	SEQ ID NO: 890	AUUUCCAUGACUCC ACUAAAGUA	SEQ ID NO: 444

ETX-S00006792	CmsUfsUmUmGmAfUmGfUfAmAmUmUmUfGmUfCmCmUmCfAmsUmsUm	SEQ ID NO: 891	CUUUGAUGUAAUUUGUCCUCAUU	SEQ ID NO: 445
ETX-S00006796	UmsUfsGmUmUmUfGmGfAfAmUmAmGmCfAmCfCmGmGmAfAmsAmsCm	SEQ ID NO: 892	UUGUUUGGAAUAGCACCGGAAAC	SEQ ID NO: 446

[0547] Table 4 provides the modified second (sense) sequences, together with the corresponding unmodified second (sense) sequences for siRNA oligonucleosides according to the present invention as follows.

Table 4

Sense strand ID	Modified Second (Sense) Strand 5' → 3'	SEQ ID NO (SS - mod)	Underlying Base Sequence 5' → 3' (Shown as an Unmodified Nucleoside Sequence)	SEQ ID NO (SS - unmod)
ETX-S00006171	iaiaGmsAmsUmUmGmCmAmUmCfAfUfUmGmAmUmAmAmGmAmUmUm	SEQ ID NO: 959	GAUUGCAUCAUUGAUAAGAUU	SEQ ID NO: 513
ETX-S00006091	iaiaCmsAmsCmCmAmUmCmAmUfGfAfAmAmGmUmUmUmUmGmCmUm	SEQ ID NO: 939	CACCAUCAUGAAAGUUUUGCU	SEQ ID NO: 493
ETX-S00005963	iaiaGmsGmsAmAmGmAmAmAmUfGfAfUmUmGmCmAmUmCmAmUmUm	SEQ ID NO: 907	GGAAGAAAUGAUUGCAUCAUU	SEQ ID NO: 461
ETX-S00005991	iaiaCmsAmsGmAmAmAmAmUmGfUfAfUmCmAmAmGmCmUmCmUmAm	SEQ ID NO: 914	CAGAAAAUGUAUCAAGCUCUA	SEQ ID NO: 468
ETX-S00006143	iaiaAmsGmsAmAmAmUmGmAmGfGfAfCmAmAmAmUmUmAmCmAmUm	SEQ ID NO: 952	AGAAAUGAGGACAAAUUACAU	SEQ ID NO: 506
ETX-S00005951	iaiaAmsUmsGmUmAmUmCmAmAfGfCfUmCmUmAmCmUmUmUmAmCm	SEQ ID NO: 904	AUGUAUCAAGCUCUACUUUAC	SEQ ID NO: 458
ETX-S00005915	iaiaUmsUmsUmAmUmGmGmAmUfGfAfUmAmAmAmGmAmCmUmAmUm	SEQ ID NO: 895	UUUAUGGAUGAUAAAGACUAU	SEQ ID NO: 449
ETX-S00006351	iaiaAmsGmsCmUmGmAmGmUmCfCfAfUmGmGmGmUmUmUmAmUmAm	SEQ ID NO: 1004	AGCUGAGUCCAUGGGUUUAUA	SEQ ID NO: 558
ETX-S00005923	iaiaGmsCmsUmCmUmAmCmUmUfUfAfCmGmAmAmGmUmGmUmUmUm	SEQ ID NO: 897	GCUCUACUUUACGAAGUGUUU	SEQ ID NO: 451
ETX-S00006651	iaiaAmsCmsAmUmUmCmCmAmGfAfAfAmAmUmGmUmAmUmCmAmAm	SEQ ID NO: 1079	ACAUUCCAGAAAAUGUAUCAA	SEQ ID NO: 633
ETX-S00005907	iaiaAmsUmsGmGmAmUmGmAmUfAfAfAmGmAmCmUmAmUmUmAmUm	SEQ ID NO: 893	AUGGAUGAUAAAGACUAUUAU	SEQ ID NO: 447
ETX-S00005911	iaiaUmsGmsGmAmUmGmAmUmAfAfAfGmAmCmUmAmUmUmAmUmUm	SEQ ID NO: 894	UGGAUGAUAAAGACUAUUAUU	SEQ ID NO: 448

ETX-S00005919	iaiaAmsUmsAmCmAmCmCmAmUfCfAfUmGmAmAmAmGmUmUmUmUm	SEQ ID NO: 896	AUACACCAUCAUGAAAGUUUU	SEQ ID NO: 450
ETX-S00005927	iaiaCmsUmsCmUmAmCmUmUmUfAfCfGmAmAmGmUmGmUmUmUmCm	SEQ ID NO: 898	CUCUACUUUACGAAGUGUUUC	SEQ ID NO: 452
ETX-S00005931	iaiaUmsUmsAmUmAmUmAmUmGfGfAfUmUmCmUmGmUmAmAmGmAm	SEQ ID NO: 899	UUAUAUAUGGAUUCUGUAAGA	SEQ ID NO: 453
ETX-S00005935	iaiaUmsGmsAmAmCmAmGmCmUfGfGfGfUmGmAmAmAmUmUmUmUmAm	SEQ ID NO: 900	UGAACAGCUGGUGAAAUUUUA	SEQ ID NO: 454
ETX-S00005939	iaiaCmsUmsCmUmCmUmCmAmAfGfUfCmCmGmUmUmAmAmGmUmAm	SEQ ID NO: 901	CUCUCUCAAGUCCGUUAAGUA	SEQ ID NO: 455
ETX-S00005943	iaiaGmsAmsAmCmAmGmCmUmGfGfUfGmAmAmAmUmUmUmUmAmCm	SEQ ID NO: 902	GAACAGCUGGUGAAAUUUUAC	SEQ ID NO: 456
ETX-S00005947	iaiaUmsAmsUmAmUmGmGmAmUfUfCfUmGmUmAmAmGmAmGmAmUm	SEQ ID NO: 903	UAUAUGGAUUCUGUAAGAGAU	SEQ ID NO: 457
ETX-S00005955	iaiaCmsAmsCmUmGmCmAmGmUfGfUfAmAmAmAmUmCmUmCmCmAm	SEQ ID NO: 905	CACUGCAGUGUAAAAUCUCCA	SEQ ID NO: 459
ETX-S00005959	iaiaGmsGmsAmGmGmAmAmAmUfAfGfCmAmAmAmAmUmAmAmAmUm	SEQ ID NO: 906	GGAGGAAAUAGCAAAAUAAAU	SEQ ID NO: 460
ETX-S00005967	iaiaCmsAmsGmUmGmUmAmAmAfAfUfCmUmCmCmAmGmUmCmUmCm	SEQ ID NO: 908	CAGUGUAAAAUCUCCAGUCUC	SEQ ID NO: 462
ETX-S00005971	iaiaUmsGmsCmAmGmAmCmUmUfCfAfGmAmAmAmUmGmUmCmUmUm	SEQ ID NO: 909	UGCAGACUUCAGAAAUGUCUU	SEQ ID NO: 463
ETX-S00005975	iaiaGmsUmsGmUmAmAmAmAmUfCfUfCmCmAmGmUmCmUmCmCmAm	SEQ ID NO: 910	GUGUAAAAUCUCCAGUCUCCA	SEQ ID NO: 464
ETX-S00005979	iaiaGmsCmsUmGmCmAmAmAmGfUfUfUmUmCmUmUmCmAmAmAmAm	SEQ ID NO: 911	GCUGCAAAGUUUUCUUCAAAA	SEQ ID NO: 465
ETX-S00005983	iaiaAmsGmsCmUmGmCmAmAmAfGfUfUmUmUmCmUmUmCmAmAmAm	SEQ ID NO: 912	AGCUGCAAAGUUUUCUUCAAA	SEQ ID NO: 466
ETX-S00005987	iaiaGmsAmsUmAmAmAmGmAmCfUfAfUmUmAmAmUmCmCmCmUmAm	SEQ ID NO: 913	GAUAAAGACUAUUAUUCCCUA	SEQ ID NO: 467
ETX-S00005995	iaiaUmsUmsCmUmCmAmGmUmAfCfCfAmAmUmAmAmAmGmCmAmAm	SEQ ID NO: 915	UUCUCAGUACCAAUAAAGCAA	SEQ ID NO: 469
ETX-S00005999	iaiaGmsAmsUmAmAmGmAmUmUfCfGfAmCmGmAmAmAmGmAmAmUm	SEQ ID NO: 916	GAUAAGAUUCGACGAAAGAAU	SEQ ID NO: 470
ETX-S00006003	iaiaGmsGmsUmUmUmAmUmAmUfAfAfUfGmGmAmUmUmCmUmGmUmAm	SEQ ID NO: 917	GGUUUAUAUAUGGAUUCUGUA	SEQ ID NO: 471
ETX-S00006007	iaiaGmsCmsUmAmCmUmAmAmGfCfAfCmAmAmUmUmCmCmAmAmAm	SEQ ID NO: 918	GCUACUAAGCACAAUUCCAAA	SEQ ID NO: 472
ETX-S00006011	iaiaCmsUmsCmCmAmAmGmUmCfAfCfUmGmCmAmGmUmGmUmAmAm	SEQ ID NO: 919	CUCCAAGUCACUGCAGUGUAA	SEQ ID NO: 473

ETX-S00006015	iaiaUmsUmsGmAmAmCmAmGmCfUfGfGmUmGmAmAmAmUmUmUmUm	SEQ ID NO: 920	UUGAACAGCUGGUGAAAUUUU	SEQ ID NO: 474
ETX-S00006019	iaiaCmsAmsUmGmAmAmAmGmUfUfUfUmGmCmUmGmCmUmAmCmUm	SEQ ID NO: 921	CAUGAAAGUUUUGCUGCUACU	SEQ ID NO: 475
ETX-S00006023	iaiaCmsCmsAmGmAmAmAmAmUfGfUfAmUmCmAmAmGmCmUmCmUm	SEQ ID NO: 922	CCAGAAAAUGUAUCAAGCUCU	SEQ ID NO: 476
ETX-S00006027	iaiaAmsGmsUmCmAmCmUmGmCfAfGfUmGmUmAmAmAmAmUmCmUm	SEQ ID NO: 923	AGUCACUGCAGUGUAAAAUCU	SEQ ID NO: 477
ETX-S00006031	iaiaUmsUmsAmGmAmAmUmAmCfAfUfUmCmCmAmGmAmAmAmAmUm	SEQ ID NO: 924	UUAGAAUACAUUCCAGAAAAU	SEQ ID NO: 478
ETX-S00006035	iaiaUmsGmsAmGmUmCmCmAmUfGfGfGmUmUmUmUmAmUmAmUmAmUm	SEQ ID NO: 925	UGAGUCCAUGGGUUUAUAUAU	SEQ ID NO: 479
ETX-S00006039	iaiaAmsUmsCmGmGmCmUmAmGfAfAfGfAmCmCmAmAmUmCmUmUmUm	SEQ ID NO: 926	AUCGGCUAGAGACCAAUCUUU	SEQ ID NO: 480
ETX-S00006043	iaiaUmsCmsCmUmUmUmAmUmGfGfAfUmGmAmUmAmAmGmAmCm	SEQ ID NO: 927	UCCUUUAUGGAUGAUAAAGAC	SEQ ID NO: 481
ETX-S00006047	iaiaGmsUmsUmGmAmAmCmAmGfCfUfGmGmUmGmAmAmUmUmUm	SEQ ID NO: 928	GUUGAACAGCUGGUGAAAUUU	SEQ ID NO: 482
ETX-S00006051	iaiaAmsAmsUmGmUmAmUmCmAfAfGfCmUmCmUmAmCmUmUmUmAm	SEQ ID NO: 929	AAUGUAUCAAGCUCUACUUUA	SEQ ID NO: 483
ETX-S00006055	iaiaUmsUmsAmUmGmGmAmUmGfAfUfAmAmAmGmAmCmUmAmUmUm	SEQ ID NO: 930	UUAUGGAUGAUAAAGACUAUU	SEQ ID NO: 484
ETX-S00006059	iaiaGmsAmsGmGmAmAmAmUmAfGfCfAmAmAmUmAmAmAmUmUm	SEQ ID NO: 931	GAGGAAAUAGCAAAAUAAAUU	SEQ ID NO: 485
ETX-S00006063	iaiaUmsGmsAmUmUmGmCmAmUfCfAfUmUmGmAmUmAmAmGmAmUm	SEQ ID NO: 932	UGAUUGCAUCAUUGAUAAGAU	SEQ ID NO: 486
ETX-S00006067	iaiaUmsCmsAmUmGmAmAmAmGfUfUfUmUmGmCmUmGmCmUmAmCm	SEQ ID NO: 933	UCAUGAAAGUUUUGCUGCUAC	SEQ ID NO: 487
ETX-S00006071	iaiaUmsAmsUmGmUmGmCmUmGfGfAfAmGmAmAmAmUmGmAmUmUm	SEQ ID NO: 934	UAUGUGCUGGAAGAAAUGAUU	SEQ ID NO: 488
ETX-S00006075	iaiaAmsGmsAmGmAmUmGmCmUfGfAfCmUmAmUmUmCmCmUmAmUm	SEQ ID NO: 935	AGAGAUGCUGACUAUUCCUAU	SEQ ID NO: 489
ETX-S00006079	iaiaUmsGmsCmUmGmGmAmAmUfUfCfUmGmCmUmUmCmUmAmCmAm	SEQ ID NO: 936	UGCUGGAAUUCUGCUUCUACA	SEQ ID NO: 490
ETX-S00006083	iaiaGmsUmsAmAmGmAmGmAmUfGfCfUmGmAmCmUmAmUmUmCmCm	SEQ ID NO: 937	GUAAGAGAUGCUGACUAUUCC	SEQ ID NO: 491
ETX-S00006087	iaiaUmsAmsGmGmAmGmGmAmAfAfUfAmGmCmAmAmAmAmUmAmAm	SEQ ID NO: 938	UAGGAGGAAAUAGCAAAAUAA	SEQ ID NO: 492
ETX-S00006095	iaiaUmsAmsUmCmCmGmGmUmCfUfUfAmGmAmAmUmAmCmAmUmUm	SEQ ID NO: 940	UAUCCGGUCUUAGAAUACAUU	SEQ ID NO: 494

ETX-S00006099	iaiaGmsUmsCmCmGmUmUmAmAfGfUfAmGmCmAmUmGmAmAmAmUm	SEQ ID NO: 941	GUCCGUUAAGUAGCAUGAAAU	SEQ ID NO: 495
ETX-S00006103	iaiaUmsCmsAmCmUmGmCmAmGfUfGfUmAmAmAmAmUmCmUmCmCm	SEQ ID NO: 942	UCACUGCAGUGUAAAAUCUCC	SEQ ID NO: 496
ETX-S00006107	iaiaCmsUmsGmUmAmAmGmAmGfAfUfGmCmUmGmAmCmUmAmUmUm	SEQ ID NO: 943	CUGUAAGAGAUGCUGACUAUU	SEQ ID NO: 497
ETX-S00006111	iaiaCmsUmsUmUmAmUmGmGmAfUfGfAmUmAmAmAmGmAmCmUmAm	SEQ ID NO: 944	CUUUAUGGAUGAUAAAGACUA	SEQ ID NO: 498
ETX-S00006115	iaiaGmsGmsGmUmUmUmAmUmAfUfAfUmGmGmAmUmUmCmUmGmUm	SEQ ID NO: 945	GGGUUUAUAUAUGGAUUCUGU	SEQ ID NO: 499
ETX-S00006119	iaiaUmsCmsUmCmAmAmGmUmCfCfGfUmUmAmAmGmUmAmGmCmAm	SEQ ID NO: 946	UCUCAAGUCCGUUAAGUAGCA	SEQ ID NO: 500
ETX-S00006123	iaiaCmsCmsCmUmCmUmGmAmAfCfAfUmGmAmCmAmUmCmUmUmCm	SEQ ID NO: 947	CCCUCUGAACAUGACAUCUUC	SEQ ID NO: 501
ETX-S00006127	iaiaAmsAmsGmGmAmAmCmUmUfUfCfAmGmCmAmAmCmUmGmUmAm	SEQ ID NO: 948	AAGGAACUUUCAGCAACUGUA	SEQ ID NO: 502
ETX-S00006131	iaiaUmsCmsUmGmUmAmAmGmAfGfAfUmGmCmUmGmAmCmUmAmUm	SEQ ID NO: 949	UCUGUAAGAGAUGCUGACUAU	SEQ ID NO: 503
ETX-S00006135	iaiaGmsGmsUmGmAmAmAmUmUfUfUfAmCmAmAmAmGmGmAmAmAm	SEQ ID NO: 950	GGUGAAAUUUUACAAAGGAAA	SEQ ID NO: 504
ETX-S00006139	iaiaUmsCmsUmAmAmGmGmAmAfCfUfUmUmCmAmGmCmAmAmCmUm	SEQ ID NO: 951	UCUAAGGAACUUUCAGCAACU	SEQ ID NO: 505
ETX-S00006147	iaiaUmsAmsCmCmAmAmUmAmAfAfGfCmAmAmGmAmAmUmCmAmAm	SEQ ID NO: 953	UACCAAUAAAGCAAGAAUCAA	SEQ ID NO: 507
ETX-S00006151	iaiaGmsUmsCmUmUmCmAmAmGfCfUfGmGmAmAmUmGmAmAmUmUm	SEQ ID NO: 954	GUCUUCAAGCUGGAAUGAAUU	SEQ ID NO: 508
ETX-S00006155	iaiaGmsCmsUmUmAmAmUmAmUfUfGfUmCmCmAmGmUmAmCmAmUm	SEQ ID NO: 955	GCUUAAUAUUGUCCAGUACAU	SEQ ID NO: 509
ETX-S00006159	iaiaGmsUmsUmUmAmUmAmUmAfUfGfGmAmUmUmCmUmGmUmAmAm	SEQ ID NO: 956	GUUUAUAUAUGGAUUCUGUAA	SEQ ID NO: 510
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ETX-S00006167	iaiaGmsAmsUmGmAmUmAmAmAfGfAfCmUmAmUmUmAmUmUmCmCm	SEQ ID NO: 958	GAUGAUAAAGACUAUUAUUCC	SEQ ID NO: 512
ETX-S00006175	iaiaUmsGmsGmUmGmAmAmAmUfUfUfUmAmCmAmAmAmGmGmAmAm	SEQ ID NO: 960	UGGUGAAAUUUUACAAAGGAA	SEQ ID NO: 514
ETX-S00006179	iaiaGmsAmsCmAmAmAmUmUmAfCfAfUmCmAmAmAmGmAmAmCmUm	SEQ ID NO: 961	GACAAAUUACAUCAAAGAACU	SEQ ID NO: 515
ETX-S00006183	iaiaAmsGmsUmGmUmAmAmAmAfUfCfUmCmCmAmGmUmCmUmCmCm	SEQ ID NO: 962	AGUGUAAAAUCUCCAGUCUCC	SEQ ID NO: 516

ETX-S00006187	iaiaUmsGmsAmAmAmGmUmUmUfUfGfCmUmGmCmUmAmCmUmAmAm	SEQ ID NO: 963	UGAAAGUUUUGCUGCUACUAA	SEQ ID NO: 517
ETX-S00006191	iaiaUmsAmsUmUmAmAmAmAmCfUfGfAmGmCmUmGmGmAmAmUmCm	SEQ ID NO: 964	UAUUAAAACUGAGCUGGAAUC	SEQ ID NO: 518
ETX-S00006195	iaiaUmsUmsCmCmUmUmUmAmUfGfGfAmUmGmAmUmAmAmAmGmAm	SEQ ID NO: 965	UUCCUUUAUGGAUGAUAAAGA	SEQ ID NO: 519
ETX-S00006199	iaiaUmsUmsCmCmCmAmGmUmGfGfGfUmAmUmUmAmAmAmCmAmAm	SEQ ID NO: 966	UUCCCAGUGGGUAUUAAACAA	SEQ ID NO: 520
ETX-S00006203	iaiaCmsCmsUmCmUmGmCmUmGfGfAfUmCmCmAmGmUmAmCmAmUm	SEQ ID NO: 967	CCUCUGCUGGAUCCAGUACAU	SEQ ID NO: 521
ETX-S00006207	iaiaGmsAmsUmUmCmUmGmUmAfAfGfAmGmAmUmGmCmUmGmAmCm	SEQ ID NO: 968	GAUUCUGUAAGAGAUGCUGAC	SEQ ID NO: 522
ETX-S00006211	iaiaUmsAmsCmAmUmGmGmAmGfAfUfUmGmUmCmAmAmCmGmUmAm	SEQ ID NO: 969	UACAUGGAGAUUGUCAACGUA	SEQ ID NO: 523
ETX-S00006215	iaiaGmsUmsCmAmCmUmGmCmAfGfUfGmUmAmAmAmUmCmUmCm	SEQ ID NO: 970	GUCACUGCAGUGUAAAAUCUC	SEQ ID NO: 524
ETX-S00006219	iaiaCmsAmsGmCmUmGmGmUmGfAfAfAmUmUmUmUmAmCmAmAmAm	SEQ ID NO: 971	CAGCUGGUGAAAUUUUACAAA	SEQ ID NO: 525
ETX-S00006223	iaiaUmsAmsUmGmGmAmUmGmAfUfAfAmAmGmAmCmUmAmUmUmAm	SEQ ID NO: 972	UAUGGAUGAUAAAGACUAUUA	SEQ ID NO: 526
ETX-S00006227	iaiaAmsGmsCmUmAmAmGmAmUfUfUfAmUmCmAmGmAmAmUmGmUm	SEQ ID NO: 973	AGCUAAGAUUUAUCAGAAUGU	SEQ ID NO: 527
ETX-S00006231	iaiaGmsAmsAmUmAmCmAmUmUfCfCfAmGmAmAmAmAmUmGmUmAm	SEQ ID NO: 974	GAAUACAUUCCAGAAAAUGUA	SEQ ID NO: 528
ETX-S00006235	iaiaAmsUmsAmAmGmAmUmUmCfGfAfCmGmAmAmAmGmAmAmUmUm	SEQ ID NO: 975	AUAAGAUUCGACGAAAGAAUU	SEQ ID NO: 529
ETX-S00006239	iaiaAmsAmsGmUmAmGmCmAmUfGfAfAmAmUmCmCmUmCmAmAmUm	SEQ ID NO: 976	AAGUAGCAUGAAAUCCUCAAU	SEQ ID NO: 530
ETX-S00006243	iaiaCmsCmsUmGmAmGmUmUmCfCfUfUmUmCmCmUmCmCmUmGmUm	SEQ ID NO: 977	CCUGAGUUCCUUUCCUCCUGU	SEQ ID NO: 531
ETX-S00006247	iaiaCmsAmsGmCmUmGmCmAmAfAfGfUmUmUmUmCmUmUmCmAmAm	SEQ ID NO: 978	CAGCUGCAAAGUUUUCUUCAA	SEQ ID NO: 532
ETX-S00006251	iaiaUmsAmsGmCmAmUmGmAmAfAfUfCmCmUmCmAmAmUmUmUmCm	SEQ ID NO: 979	UAGCAUGAAAUCCUCAAUUUC	SEQ ID NO: 533
ETX-S00006255	iaiaCmsUmsAmGmGmAmGmGmAfAfAfUmAmGmCmAmAmAmUmAm	SEQ ID NO: 980	CUAGGAGGAAAUAGCAAAAUA	SEQ ID NO: 534
ETX-S00006259	iaiaGmsAmsUmAmUmUmAmAmAfAfCfUmGmAmGmCmUmGmGmAmAm	SEQ ID NO: 981	GAUAUUAAAACUGAGCUGGAA	SEQ ID NO: 535
ETX-S00006263	iaiaUmsAmsAmUmAmUmUmGmUfCfCfAmGmUmAmCmAmUmAmAmAm	SEQ ID NO: 982	UAAUAUUGUCCAGUACAUAAA	SEQ ID NO: 536

ETX-S00006267	iaiaUmsAmsAmGmAmUmUmUmAfUfCfAmGmAmAmUmGmUmUmGmAm	SEQ ID NO: 983	UAAGAUUUAUCAGAAUGUUGA	SEQ ID NO: 537
ETX-S00006271	iaiaGmsUmsGmAmAmAmUmUmUfUfAfCmAmAmAmGmGmAmAmAmUm	SEQ ID NO: 984	GUGAAAUUUUACAAAGGAAAU	SEQ ID NO: 538
ETX-S00006275	iaiaUmsUmsAmAmGmUmAmGmCfAfUfGmAmAmAmUmCmCmUmCmAm	SEQ ID NO: 985	UUAAGUAGCAUGAAAUCCUCA	SEQ ID NO: 539
ETX-S00006279	iaiaGmsCmsAmGmUmGmUmAmAfAfAfUmCmUmCmCmAmGmUmCmUm	SEQ ID NO: 986	GCAGUGUAAAAUCUCCAGUCU	SEQ ID NO: 540
ETX-S00006283	iaiaAmsUmsGmAmAmAmGmUmUfUfUfGmCmUmGmCmUmAmCmUmAm	SEQ ID NO: 987	AUGAAAGUUUUGCUGCUACUA	SEQ ID NO: 541
ETX-S00006287	iaiaAmsUmsAmUmUmAmAmAmAfCfUfGmAmGmCmUmGmGmAmAmUm	SEQ ID NO: 988	AUAUUAAAACUGAGCUGGAAU	SEQ ID NO: 542
ETX-S00006291	iaiaCmsGmsUmUmAmAmGmUmAfGfCfAmUmGmAmAmAmUmCmCmUm	SEQ ID NO: 989	CGUUAAGUAGCAUGAAAUCCU	SEQ ID NO: 543
ETX-S00006295	iaiaGmsCmsAmGmAmCmUmUmCfAfGfAmAmAmAmUmGmUmCmUmUmCm	SEQ ID NO: 990	GCAGACUUCAGAAAUGUCUUC	SEQ ID NO: 544
ETX-S00006299	iaiaCmsUmsUmAmAmUmAmUmUfGfUfCmCmAmGmUmAmCmAmUmAm	SEQ ID NO: 991	CUUAAUAUUGUCCAGUACAUA	SEQ ID NO: 545
ETX-S00006303	iaiaCmsCmsAmGmCmUmAmAmGfAfUfUmUmAmUmCmAmGmAmAmUm	SEQ ID NO: 992	CCAGCUAAGAUUUAUCAGAAU	SEQ ID NO: 546
ETX-S00006307	iaiaAmsGmsCmUmCmUmAmCmUfUfUfUfAmCmGmAmAmGmUmGmUmUm	SEQ ID NO: 993	AGCUCUACUUUACGAAGUGUU	SEQ ID NO: 547
ETX-S00006311	iaiaGmsCmsUmAmAmGmAmUmUfUfAfUmCmAmGmAmAmUmGmUmUm	SEQ ID NO: 994	GCUAAGAUUUAUCAGAAUGUU	SEQ ID NO: 548
ETX-S00006315	iaiaCmsAmsGmUmAmCmCmAmAfUfAfAmAmGmCmAmAmGmAmAmUm	SEQ ID NO: 995	CAGUACCAAUAAAGCAAGAAU	SEQ ID NO: 549
ETX-S00006319	iaiaCmsCmsUmCmUmCmUmCmAfAfGfUmCmCmGmUmUmAmAmGmUm	SEQ ID NO: 996	CCUCUCUCAAGUCCGUUAAGU	SEQ ID NO: 550
ETX-S00006323	iaiaUmsAmsUmCmAmAmGmCmUfCfUfAmCmUmUmUmAmCmGmAmAm	SEQ ID NO: 997	UAUCAAGCUCUACUUUACGAA	SEQ ID NO: 551
ETX-S00006327	iaiaAmsUmsGmUmUmGmAmAmCfAfGfCmUmGmGmUmGmAmAmAmUm	SEQ ID NO: 998	AUGUUGAACAGCUGGUGAAAU	SEQ ID NO: 552
ETX-S00006331	iaiaAmsAmsGmAmUmUmUmAmUfCfAfGmAmAmAmUmGmUmUmGmAm	SEQ ID NO: 999	AAGAUUUAUCAGAAUGUUGAA	SEQ ID NO: 553
ETX-S00006335	iaiaUmsCmsCmAmUmGmGmGmUfUfUfAfUmAmUmAmUmAmUmGmGmAmUm	SEQ ID NO: 1000	UCCAUGGGUUUAUAUAUGGAU	SEQ ID NO: 554
ETX-S00006339	iaiaGmsAmsAmGmAmAmAmUmGfAfGfGfAmCmAmAmAmUmUmAmCm	SEQ ID NO: 1001	GAAGAAAUGAGGACAAAUUAC	SEQ ID NO: 555
ETX-S00006343	iaiaUmsGmsAmUmAmAmGmAmUfUfCfGmAmCmGmAmAmGmAmAm	SEQ ID NO: 1002	UGAUAAGAUUCGACGAAAGAA	SEQ ID NO: 556

ETX-S00006347	iaiaUmsGmsAmUmAmAmAmGmAfCfUfAmUmUmAmUmUmCmCmCmUm	SEQ ID NO: 1003	UGAUAAAGACUAUUAUUCCCU	SEQ ID NO: 557
ETX-S00006355	iaiaUmsCmsCmUmAmAmGmAmCfUfGfAmGmGmAmAmGmUmAmGmAm	SEQ ID NO: 1005	UCCUAAGACUGAGGAAGUAGA	SEQ ID NO: 559
ETX-S00006359	iaiaUmsUmsCmCmAmAmCmAmCfCfUfGmAmGmUmUmCmCmUmUmUm	SEQ ID NO: 1006	UUCCAACACCUGAGUUCCUUU	SEQ ID NO: 560
ETX-S00006363	iaiaCmsAmsUmUmGmAmUmAmAfGfAfUmUmCmGmAmCmGmAmAmAm	SEQ ID NO: 1007	CAUUGAUAAGAUUCGACGAAA	SEQ ID NO: 561
ETX-S00006367	iaiaGmsCmsAmUmGmAmAmAmUfCfCfUmCmAmAmUmUmUmCmCmAm	SEQ ID NO: 1008	GCAUGAAAUCCUCAAUUUCCA	SEQ ID NO: 562
ETX-S00006371	iaiaAmsAmsAmAmUmGmUmAmUfCfAfAmGmCmUmCmUmAmCmUmUm	SEQ ID NO: 1009	AAAAUGUAUCAAGCUCUACUU	SEQ ID NO: 563
ETX-S00006375	iaiaUmsGmsCmUmAmCmUmAmAfGfCfAmCmAmAmUmUmCmCmAmAm	SEQ ID NO: 1010	UGCUACUAAGCACAAUUCCAA	SEQ ID NO: 564
ETX-S00006379	iaiaGmsUmsAmCmUmGmUmGmGfGfAfUmCmUmAmUmGmUmAmAm	SEQ ID NO: 1011	GUACUGUGGGAUCUAUCUGUA	SEQ ID NO: 565
ETX-S00006383	iaiaAmsGmsGmAmGmGmAmAmAfUfAfGmCmAmAmAmAmUmAmAmAm	SEQ ID NO: 1012	AGGAGGAAAUAGCAAAAUAAA	SEQ ID NO: 566
ETX-S00006387	iaiaGmsAmsAmAmUmGmAmUmUfGfCfAmUmCmAmUmGmAmUmAm	SEQ ID NO: 1013	GAAAUGAUUGCAUCAUUGAUA	SEQ ID NO: 567
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ETX-S00006395	iaiaGmsUmsCmCmAmGmCmUmAfAfGfAmUmUmUmAmUmCmAmGmAm	SEQ ID NO: 1015	GUCCAGCUAAGAUUUAUCAGA	SEQ ID NO: 569
ETX-S00006399	iaiaUmsGmsCmAmUmCmAmUmUfGfAfUmAmAmGmAmUmUmCmGmAm	SEQ ID NO: 1016	UGCAUCAUUGAUAAGAUUCGA	SEQ ID NO: 570
ETX-S00006403	iaiaGmsUmsUmAmAmGmUmAmGfCfAfUmGmAmAmAmUmCmCmUmCm	SEQ ID NO: 1017	GUUAAGUAGCAUGAAAUCCUC	SEQ ID NO: 571
ETX-S00006407	iaiaUmsAmsAmUmAmAmCmAmGfAfUfCmCmAmCmGmCmUmUmUmCm	SEQ ID NO: 1018	UAAUAACAGAUCCACGCUUUC	SEQ ID NO: 572
ETX-S00006411	iaiaGmsAmsAmAmAmUmGmUmAfUfCfAmAmGmCmUmCmUmAmCmUm	SEQ ID NO: 1019	GAAAAUGUAUCAAGCUCUACU	SEQ ID NO: 573
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ETX-S00006419	iaiaAmsAmsAmUmGmUmAmUmCfAfAfGmCmUmCmUmAmCmUmUmUm	SEQ ID NO: 1021	AAAUGUAUCAAGCUCUACUUU	SEQ ID NO: 575
ETX-S00006423	iaiaUmsCmsCmGmUmUmAmAmGfUfAfGmCmAmUmGmAmAmAmUmCm	SEQ ID NO: 1022	UCCGUUAAGUAGCAUGAAAUC	SEQ ID NO: 576
ETX-S00006427	iaiaAmsUmsAmAmAmGmAmCmUfAfUfUmAmUmUmCmCmCmUmAmUm	SEQ ID NO: 1023	AUAAAGACUAUUAUUCCCUAU	SEQ ID NO: 577

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ETX-S00006435	iaiaCmsUmsCmCmUmCmUmCmUfCfAfAmGmUmCmCmGmUmUmAmAm	SEQ ID NO: 1025	CUCCUCUCUCAAGUCCGUUAA	SEQ ID NO: 579
ETX-S00006439	iaiaAmsGmsGmAmCmCmGmAmUfGfAfGmAmAmUmAmAmCmUmAmCm	SEQ ID NO: 1026	AGGACCGAUGAGAAUAACUAC	SEQ ID NO: 580
ETX-S00006443	iaiaUmsAmsCmAmCmCmAmUmCfAfUfGmAmAmAmGmUmUmUmUmGm	SEQ ID NO: 1027	UACACCAUCAUGAAAGUUUUG	SEQ ID NO: 581
ETX-S00006447	iaiaUmsUmsGmAmAmGmAmAmAfUfGfAmGmGmAmCmAmAmAmUmUm	SEQ ID NO: 1028	UUGAAGAAAUGAGGACAAAUU	SEQ ID NO: 582
ETX-S00006451	iaiaGmsGmsAmUmGmAmUmAmAfAfGfAmCmUmAmUmUmAmUmUmCm	SEQ ID NO: 1029	GGAUGAUAAAGACUAUUAUUC	SEQ ID NO: 583
ETX-S00006455	iaiaUmsAmsAmAmAmCmUmGmAfGfCfUmGmGmAmAmUmCmUmAmAm	SEQ ID NO: 1030	UAAAACUGAGCUGGAAUCUAA	SEQ ID NO: 584
ETX-S00006459	iaiaGmsAmsAmUmAmAmCmUmAfCfAfUmGmGmAmGmAmUmUmGmUm	SEQ ID NO: 1031	GAAUAACUACAUGGAGAUUGU	SEQ ID NO: 585
ETX-S00006463	iaiaUmsAmsAmGmAmGmAmUmGfCfUfGmAmCmUmAmUmUmCmCmUm	SEQ ID NO: 1032	UAAGAGAUGCUGACUAUUCCU	SEQ ID NO: 586
ETX-S00006467	iaiaCmsAmsUmCmAmUmGmAmAfAfGfUfUmUmUmGmGmCmUmGmCmUm	SEQ ID NO: 1033	CAUCAUGAAAGUUUUGCUGCU	SEQ ID NO: 587
ETX-S00006471	iaiaUmsAmsCmAmUmAmAmAmAfCfCfAfGmAmAmCmCmAmGmAmUm	SEQ ID NO: 1034	UACAUAAAACCAGAACCAGAU	SEQ ID NO: 588
ETX-S00006475	iaiaUmsUmsGmCmUmGmCmUmAfCfUfAmAmGmCmAmCmAmAmUmUm	SEQ ID NO: 1035	UUGCUGCUACUAAGCACAAUU	SEQ ID NO: 589
ETX-S00006479	iaiaCmsGmsAmCmUmGmCmAmGfCfUfCmAmCmCmUmUmUmGmAmAm	SEQ ID NO: 1036	CGACUGCAGCUCACCUUUGAA	SEQ ID NO: 590
ETX-S00006483	iaiaUmsUmsAmAmAmAmCmUmGfAfGfCmUmGmGmAmAmUmCmUmAm	SEQ ID NO: 1037	UUAAAACUGAGCUGGAAUCUA	SEQ ID NO: 591
ETX-S00006487	iaiaUmsAmsGmUmGmGmAmGmUfCfAfUmGmGmAmAmAmUmCmAmCm	SEQ ID NO: 1038	UAGUGGAGUCAUGGAAAUCAC	SEQ ID NO: 592
ETX-S00006491	iaiaAmsGmsUmUmUmUmGmCmUfGfCfUmAmCmUmAmGmCmAmCm	SEQ ID NO: 1039	AGUUUUGCUGCUACUAAGCAC	SEQ ID NO: 593
ETX-S00006495	iaiaUmsGmsAmAmGmAmAmAmUfGfAfGmGmAmCmAmAmAmUmUmAm	SEQ ID NO: 1040	UGAAGAAAUGAGGACAAAUUA	SEQ ID NO: 594
ETX-S00006499	iaiaCmsUmsCmAmAmGmGmAmAfGfCfAmGmCmAmAmAmGmAmAmAm	SEQ ID NO: 1041	CUCAAGGAAGCAGCAAAGAAA	SEQ ID NO: 595
ETX-S00006503	iaiaAmsUmsAmUmAmUmGmGmAfUfUfCmUmGmUmAmGmAmGmAm	SEQ ID NO: 1042	AUAUAUGGAUUCUGUAAGAGA	SEQ ID NO: 596
ETX-S00006507	iaiaGmsUmsAmAmCmUmAmAmGfUfGfUmCmCmCmAmCmAmAmUm	SEQ ID NO: 1043	GUAACUAAGUGUCCCAACAAU	SEQ ID NO: 597

ETX-S00006511	iaiaUmsCmsAmAmGmCmUmCmUfAfCfUmUmUmAmCmGmAmAmGmUm	SEQ ID NO: 1044	UCAAGCUCUACUUUACGAAGU	SEQ ID NO: 598
ETX-S00006515	iaiaGmsAmsGmGmAmCmCmGmAfUfGfAmGmAmAmUmAmAmCmUmAm	SEQ ID NO: 1045	GAGGACCGAUGAGAAUAACUA	SEQ ID NO: 599
ETX-S00006519	iaiaGmsCmsUmUmUmUmAmGmCfAfGfCmUmCmAmUmGmUmCmUmAm	SEQ ID NO: 1046	GCUUUUAGCAGCUCAUGUCUA	SEQ ID NO: 600
ETX-S00006523	iaiaUmsUmsAmUmCmAmGmAmAfUfGfUmUmGmAmAmCmAmGmCmUm	SEQ ID NO: 1047	UUAUCAGAAUGUUGAACAGCU	SEQ ID NO: 601
ETX-S00006527	iaiaUmsGmsUmAmUmCmAmAmGfCfUfCmUmAmCmUmUmUmAmCmGm	SEQ ID NO: 1048	UGUAUCAAGCUCUACUUUACG	SEQ ID NO: 602
ETX-S00006531	iaiaAmsUmsUmCmCmAmAmAmCfAfAfCmAmGmUmAmCmUmCmAmAm	SEQ ID NO: 1049	AUUCCAAACAACAGUACUCAA	SEQ ID NO: 603
ETX-S00006535	iaiaAmsAmsAmGmAmCmUmAmUfUfAfUmUmCmCmCmUmAmUmCmAm	SEQ ID NO: 1050	AAAGACUAUUAUUCCCUAUCA	SEQ ID NO: 604
ETX-S00006539	iaiaUmsGmsAmAmCmAmUmGmAfCfAfUmCmUmUmCmGmGmUmUmUm	SEQ ID NO: 1051	UGAACAUGACAUCUUCGGUUU	SEQ ID NO: 605
ETX-S00006543	iaiaUmsGmsUmUmGmAmAmCmAfGfCfUmGmGmUmGmAmAmUmUm	SEQ ID NO: 1052	UGUUGAACAGCUGGUGAAAUU	SEQ ID NO: 606
ETX-S00006547	iaiaAmsUmsGmAmUmAmAmAmGfAfCfUmAmUmUmAmUmUmCmCmCm	SEQ ID NO: 1053	AUGAUAAAGACUAUUAUUCCC	SEQ ID NO: 607
ETX-S00006551	iaiaUmsUmsCmCmAmGmAmAmAfAfUfGmUmAmUmCmAmAmGmCmUm	SEQ ID NO: 1054	UUCCAGAAAAUGUAUCAAGCU	SEQ ID NO: 608
ETX-S00006555	iaiaAmsAmsUmGmAmGmGmAmCfAfAfAmUmUmAmCmAmUmCmAmAm	SEQ ID NO: 1055	AAUGAGGACAAAUUACAUCAA	SEQ ID NO: 609
ETX-S00006559	iaiaGmsUmsCmUmAmGmGmAmGfGfAfAmAmUmAmGmCmAmAmAmAm	SEQ ID NO: 1056	GUCUAGGAGGAAAUAGCAAAA	SEQ ID NO: 610
ETX-S00006563	iaiaUmsAmsUmUmCmCmAmAmAfCfAfAmCmAmGmUmAmCmUmCmAm	SEQ ID NO: 1057	UAUUCCAAACAACAGUACUCA	SEQ ID NO: 611
ETX-S00006567	iaiaUmsUmsCmUmGmUmAmAmGfAfGfAmUmGmCmUmGmAmCmUmAm	SEQ ID NO: 1058	UUCUGUAAGAGAUGCUGACUA	SEQ ID NO: 612
ETX-S00006571	iaiaGmsCmsAmGmCmUmCmAmCfCfUfUmUmGmAmAmGmAmAmUmAm	SEQ ID NO: 1059	GCAGCUCACCUUUGAAGAAUA	SEQ ID NO: 613
ETX-S00006575	iaiaAmsGmsAmUmCmAmUmUmUfAfUfGmUmCmUmGmAmCmUmCmUm	SEQ ID NO: 1060	AGAUCAUUUAUGUCUGACUCU	SEQ ID NO: 614
ETX-S00006579	iaiaCmsUmsGmAmAmCmAmUmGfAfCfAmUmCmUmUmCmGmGmUmUm	SEQ ID NO: 1061	CUGAACAUGACAUCUUCGGUU	SEQ ID NO: 615
ETX-S00006583	iaiaCmsUmsCmAmAmGmUmCmCfGfUfUmAmAmGmUmAmGmCmAmUm	SEQ ID NO: 1062	CUCAAGUCCGUUAAGUAGCAU	SEQ ID NO: 616
ETX-S00006587	iaiaAmsGmsUmAmCmUmGmUmGfGfGfAmUmCmUmAmUmCmUmGmUm	SEQ ID NO: 1063	AGUACUGUGGGAUCUAUCUGU	SEQ ID NO: 617

ETX-S00006591	iaiaAmsAmsGmCmUmCmUmAmCfUfUfUmAmCmGmAmAmGmUmGmUm	SEQ ID NO: 1064	AAGCUCUACUUUACGAAGUGU	SEQ ID NO: 618
ETX-S00006595	iaiaAmsAmsAmAmCmUmGmAmGfCfUfGmGmAmAmUmCmUmAmAmGm	SEQ ID NO: 1065	AAAACUGAGCUGGAAUCUAAG	SEQ ID NO: 619
ETX-S00006599	iaiaAmsGmsUmAmCmCmAmAmUfAfAfAmGmCmAmAmGmAmAmUmCm	SEQ ID NO: 1066	AGUACCAAUAAAGCAAGAAUC	SEQ ID NO: 620
ETX-S00006603	iaiaCmsUmsUmAmGmAmAmUmAfCfAfUmUmCmCmAmGmAmAmAmAm	SEQ ID NO: 1067	CUUAGAAUACAUUCCAGAAAA	SEQ ID NO: 621
ETX-S00006607	iaiaAmsAmsAmUmGmAmUmUmGfCfAfUmCmAmUmUmGmAmUmAmAm	SEQ ID NO: 1068	AAAUGAUUGCAUCAUUGAUAA	SEQ ID NO: 622
ETX-S00006611	iaiaCmsUmsGmGmUmGmAmAmAfUfUfUmUmUmAmCmAmAmAmGmGmAm	SEQ ID NO: 1069	CUGGUGAAAUUUUACAAAGGA	SEQ ID NO: 623
ETX-S00006615	iaiaAmsUmsGmAmGmGmAmCmAfAfAfAfUmUmUmAmCmAmAmAmAm	SEQ ID NO: 1070	AUGAGGACAAAUUACAUCAAA	SEQ ID NO: 624
ETX-S00006619	iaiaUmsCmsCmGmGmUmGmCmUfAfUfUmCmCmAmAmCmAmAmCm	SEQ ID NO: 1071	UCCGGUGCUAUUCCAAACAAC	SEQ ID NO: 625
ETX-S00006623	iaiaAmsCmsUmCmAmAmGmGmUfGfCfUmCmUmGmUmUmUmCmCmAm	SEQ ID NO: 1072	ACUCAAGGUGCUCUGUUUCCA	SEQ ID NO: 626
ETX-S00006627	iaiaGmsAmsAmGmAmAmAmUmGfAfUfUmGmCmAmUmUmGmGm	SEQ ID NO: 1073	GAAGAAAUGAUUGCAUCAUUG	SEQ ID NO: 627
ETX-S00006631	iaiaAmsGmsCmAmAmGmAmAmUfCfAfAfCmCmAmAmGmCmAmUmUm	SEQ ID NO: 1074	AGCAAGAAUCAACCAAGCAUU	SEQ ID NO: 628
ETX-S00006635	iaiaAmsGmsCmUmGmGmAmAmUfCfUfAfAmGmGmAmCmUmUmUm	SEQ ID NO: 1075	AGCUGGAAUCUAAGGAACUUU	SEQ ID NO: 629
ETX-S00006639	iaiaAmsGmsCmUmUmAmAmUmAfUfUfGmUmCmCmAmGmUmAmCmAm	SEQ ID NO: 1076	AGCUUAAUAUUGUCCAGUACA	SEQ ID NO: 630
ETX-S00006643	iaiaAmsUmsGmGmGmUmUmUmAfUfAfUmAmUmGmGmAmUmUmCmUm	SEQ ID NO: 1077	AUGGGUUUAUAUAUGGAUUCU	SEQ ID NO: 631
ETX-S00006647	iaiaAmsAmsUmAmUmUmGmUmCfCfAfGmUmAmCmAmUmAmAmAm	SEQ ID NO: 1078	AAUAUUGUCCAGUACAUAAAA	SEQ ID NO: 632
ETX-S00006655	iaiaCmsUmsCmUmCmCmUmCmUfCfUfCmAmAmGmUmCmCmGmUmUm	SEQ ID NO: 1080	CUCUCCUCUCUCAAGUCCGUU	SEQ ID NO: 634
ETX-S00006659	iaiaAmsCmsUmAmAmGmCmAmCfAfAfUmUmCmCmAmAmGmGmAm	SEQ ID NO: 1081	ACUAAGCACAAUUCCAAAGGA	SEQ ID NO: 635
ETX-S00006663	iaiaGmsAmsGmCmUmGmGmAmAfUfCfUfAmAmGmGmAmAmCmUmUm	SEQ ID NO: 1082	GAGCUGGAAUCUAAGGAACUU	SEQ ID NO: 636
ETX-S00006667	iaiaAmsAmsGmUmCmAmCmUmGfCfAfGmUmGmUmAmAmAmUmCm	SEQ ID NO: 1083	AAGUCACUGCAGUGUAAAAUC	SEQ ID NO: 637
ETX-S00006671	iaiaAmsUmsCmAmAmGmCmUmCfUfAfCmUmUmUmAmCmGmAmAmGm	SEQ ID NO: 1084	AUCAAGCUCUACUUUACGAAG	SEQ ID NO: 638

ETX-S00006675	iaiaGmsUmsGmCmUmAmUmUmCfCfAfAmAmCmAmAmCmAmGmUmAm	SEQ ID NO: 1085	GUGCUAUUCCAAACAACAGUA	SEQ ID NO: 639
ETX-S00006679	iaiaCmsUmsAmUmUmCmCmAmAfAfCfAmAmCmAmGmUmAmCmUmCm	SEQ ID NO: 1086	CUAUUCCAAACAACAGUACUC	SEQ ID NO: 640
ETX-S00006683	iaiaUmsGmsAmGmUmCmCmAmGfCfUfAmAmGmAmUmUmUmAmUmCm	SEQ ID NO: 1087	UGAGUCCAGCUAAGAUUUAUC	SEQ ID NO: 641
ETX-S00006687	iaiaUmsGmsCmUmUmGmCmAmGfAfCfUmUmCmAmGmAmAmAmUmGm	SEQ ID NO: 1088	UGCUUGCAGACUUCAGAAAUG	SEQ ID NO: 642
ETX-S00006691	iaiaGmsUmsAmUmCmAmAmGmCfUfCfUmAmCmUmUmUmAmCmGmAm	SEQ ID NO: 1089	GUAUCAAGCUCUACUUUACGA	SEQ ID NO: 643
ETX-S00006695	iaiaCmsCmsAmGmUmGmGmGmUfAfUfUmAmAmAmCmAmAmGmAmAm	SEQ ID NO: 1090	CCAGUGGGUAUUAAACAAGAA	SEQ ID NO: 644
ETX-S00006699	iaiaUmsGmsUmCmUmUmCmAmAfGfCfUmGmGmAmAmUmGmAmAmUm	SEQ ID NO: 1091	UGUCUUCAAGCUGGAAUGAAU	SEQ ID NO: 645
ETX-S00006703	iaiaAmsGmsUmAmGmCmAmUmGfAfAfAmUmCmCmUmCmAmAmUmUm	SEQ ID NO: 1092	AGUAGCAUGAAAUCCUCAAUU	SEQ ID NO: 646
ETX-S00006707	iaiaCmsCmsAmCmUmAmCmAmGfGfAfUmUmGmGmUmGmCmUmCmAm	SEQ ID NO: 1093	CCACUACAGGAUUGGUGCUCA	SEQ ID NO: 647
ETX-S00006711	iaiaAmsAmsCmUmAmAmGmUmGfUfCfCmCmAmAmCmAmAmUmUmCm	SEQ ID NO: 1094	AACUAAGUGUCCCAACAAUUC	SEQ ID NO: 648
ETX-S00006715	iaiaAmsGmsAmAmAmUmGmAmUfUfGfCmAmUmCmAmUmUmGmAmUm	SEQ ID NO: 1095	AGAAAUGAUUGCAUCAUUGAU	SEQ ID NO: 649
ETX-S00006719	iaiaUmsGmsAmGmAmUmCmAmUfUfUfAmUmGmUmCmUmGmAmCmUm	SEQ ID NO: 1096	UGAGAUCAUUUAUGUCUGACU	SEQ ID NO: 650
ETX-S00006723	iaiaAmsUmsAmUmUmGmUmCmCfAfGfUmAmCmAmUmAmAmAmAmCm	SEQ ID NO: 1097	AUAUUGUCCAGUACAUAAAAC	SEQ ID NO: 651
ETX-S00006727	iaiaAmsGmsCmAmUmGmAmGmUfCfCfAmGmCmUmAmAmGmAmUmUm	SEQ ID NO: 1098	AGCAUGAGUCCAGCUAAGAUU	SEQ ID NO: 652
ETX-S00006731	iaiaUmsUmsUmGmAmAmGmAmAfAfUfGmAmGmGmAmCmAmAmAmUm	SEQ ID NO: 1099	UUUGAAGAAAUGAGGACAAAU	SEQ ID NO: 653
ETX-S00006735	iaiaUmsCmsCmAmAmGmUmCmAfCfUfGmCmAmGmUmGmUmAmAmAm	SEQ ID NO: 1100	UCCAAGUCACUGCAGUGUAAA	SEQ ID NO: 654
ETX-S00006739	iaiaCmsUmsCmAmGmUmAmCmCfAfAfUmAmAmAmGmCmAmAmGmAm	SEQ ID NO: 1101	CUCAGUACCAAUAAAGCAAGA	SEQ ID NO: 655
ETX-S00006743	iaiaAmsCmsCmGmAmUmGmAmGfAfAfUmAmAmCmUmAmCmAmUmGm	SEQ ID NO: 1102	ACCGAUGAGAAUAACUACAUG	SEQ ID NO: 656
ETX-S00006747	iaiaAmsUmsCmUmGmUmAmGmCfCfCfUmGmUmAmAmAmCmAmAmUm	SEQ ID NO: 1103	AUCUGUAGCCCUGUAAACAAU	SEQ ID NO: 657
ETX-S00006751	iaiaAmsGmsCmAmUmGmAmAmAfUfCfCfUmCmAmAmUmUmUmCmCm	SEQ ID NO: 1104	AGCAUGAAAUCCUCAAUUUCC	SEQ ID NO: 658

ETX-S00006755	iaiaUmsGmsCmUmAmUmUmCmCfAfAfAmCmAmAmCmAmGmUmAmCm	SEQ ID NO: 1105	UGCUAUUCCAAACAACAGUAC	SEQ ID NO: 659
ETX-S00006759	iaiaCmsUmsGmCmAmGmUmGmUfAfAfAmAmUmCmUmCmCmAmGmUm	SEQ ID NO: 1106	CUGCAGUGUAAAAUCUCCAGU	SEQ ID NO: 660
ETX-S00006763	iaiaAmsAmsGmAmCmUmAmUmUfAfUfUmCmCmCmUmAmUmCmAmGm	SEQ ID NO: 1107	AAGACUAUUAUUCCCUAUCAG	SEQ ID NO: 661
ETX-S00006767	iaiaUmsGmsCmUmGmCmUmAmCfUfAfAmGmCmAmCmAmAmUmUmCm	SEQ ID NO: 1108	UGCUGCUACUAAGCACAAUUC	SEQ ID NO: 662
ETX-S00006771	iaiaCmsAmsAmCmAmCmCmUmGfAfGfUmUmCmCmUmUmUmCmCmUm	SEQ ID NO: 1109	CAACACCUGAGUUCCUUUCCU	SEQ ID NO: 663
ETX-S00006775	iaiaUmsGmsUmAmAmGmAmGmAfUfGfCmUmGmAmCmUmAmUmUmCm	SEQ ID NO: 1110	UGUAAGAGAUGCUGACUAUUC	SEQ ID NO: 664
ETX-S00006779	iaiaAmsUmsCmUmAmUmCmUmGfUfAfGmCmCmCmUmGmUmAmAmAm	SEQ ID NO: 1111	AUCUAUCUGUAGCCCUGUAAA	SEQ ID NO: 665
ETX-S00006783	iaiaGmsCmsUmUmGmCmAmGmAfCfUfUmCmAmGmAmAmAmUmGmUm	SEQ ID NO: 1112	GCUUGCAGACUUCAGAAAUGU	SEQ ID NO: 666
ETX-S00006787	iaiaCmsUmsUmUmAmGmUmGmGfAfGfUmCmAmUmGmGmAmAmAmUm	SEQ ID NO: 1113	CUUUAGUGGAGUCAUGGAAAU	SEQ ID NO: 667
ETX-S00006791	iaiaUmsGmsAmGmGmAmCmAmAfAfUfUmAmCmAmUmCmAmAmAmGm	SEQ ID NO: 1114	UGAGGACAAAUUACAUCAAAG	SEQ ID NO: 668
ETX-S00006795	iaiaUmsUmsCmCmGmGmUmGmCfUfAfUmUmCmCmAmAmAmCmAmAm	SEQ ID NO: 1115	UUCCGGUGCUAUUCCAAACAA	SEQ ID NO: 669

[0548] Some of the modified second strand sequences as illustrated above in Table 4 include the preferred 5' iaia motif. However, it should also be understood that the scope of these modified second strand sequences additionally includes the Me / F modified second strand in the absence of the 5'iaia motif.

[0549] Table 5 identifies duplexes with Duplex IDs referencing the modified antisense and sense IDs from previous Tables 3 and 4.

Table 5

Duplex ID	First (Antisense) strand ID	Second (Sense) strand ID
ETX-M00001856	ETX-S00005908	ETX-S00005907
ETX-M00001857	ETX-S00005912	ETX-S00005911
ETX-M00001858	ETX-S00005916	ETX-S00005915
ETX-M00001859	ETX-S00005920	ETX-S00005919
ETX-M00001860	ETX-S00005924	ETX-S00005923
ETX-M00001861	ETX-S00005928	ETX-S00005927
ETX-M00001862	ETX-S00005932	ETX-S00005931

ETX-M00001863	ETX-S00005936	ETX-S00005935
ETX-M00001864	ETX-S00005940	ETX-S00005939
ETX-M00001865	ETX-S00005944	ETX-S00005943
ETX-M00001866	ETX-S00005948	ETX-S00005947
ETX-M00001867	ETX-S00005952	ETX-S00005951
ETX-M00001868	ETX-S00005956	ETX-S00005955
ETX-M00001869	ETX-S00005960	ETX-S00005959
ETX-M00001870	ETX-S00005964	ETX-S00005963
ETX-M00001871	ETX-S00005968	ETX-S00005967
ETX-M00001872	ETX-S00005972	ETX-S00005971
ETX-M00001873	ETX-S00005976	ETX-S00005975
ETX-M00001874	ETX-S00005980	ETX-S00005979
ETX-M00001875	ETX-S00005984	ETX-S00005983
ETX-M00001876	ETX-S00005988	ETX-S00005987
ETX-M00001877	ETX-S00005992	ETX-S00005991
ETX-M00001878	ETX-S00005996	ETX-S00005995
ETX-M00001879	ETX-S00006000	ETX-S00005999
ETX-M00001880	ETX-S00006004	ETX-S00006003
ETX-M00001881	ETX-S00006008	ETX-S00006007
ETX-M00001882	ETX-S00006012	ETX-S00006011
ETX-M00001883	ETX-S00006016	ETX-S00006015
ETX-M00001884	ETX-S00006020	ETX-S00006019
ETX-M00001885	ETX-S00006024	ETX-S00006023
ETX-M00001886	ETX-S00006028	ETX-S00006027
ETX-M00001887	ETX-S00006032	ETX-S00006031
ETX-M00001888	ETX-S00006036	ETX-S00006035
ETX-M00001889	ETX-S00006040	ETX-S00006039
ETX-M00001890	ETX-S00006044	ETX-S00006043
ETX-M00001891	ETX-S00006048	ETX-S00006047
ETX-M00001892	ETX-S00006052	ETX-S00006051
ETX-M00001893	ETX-S00006056	ETX-S00006055
ETX-M00001894	ETX-S00006060	ETX-S00006059
ETX-M00001895	ETX-S00006064	ETX-S00006063
ETX-M00001896	ETX-S00006068	ETX-S00006067
ETX-M00001897	ETX-S00006072	ETX-S00006071
ETX-M00001898	ETX-S00006076	ETX-S00006075
ETX-M00001899	ETX-S00006080	ETX-S00006079

ETX-M00001900	ETX-S00006084	ETX-S00006083
ETX-M00001901	ETX-S00006088	ETX-S00006087
ETX-M00001902	ETX-S00006092	ETX-S00006091
ETX-M00001903	ETX-S00006096	ETX-S00006095
ETX-M00001904	ETX-S00006100	ETX-S00006099
ETX-M00001905	ETX-S00006104	ETX-S00006103
ETX-M00001906	ETX-S00006108	ETX-S00006107
ETX-M00001907	ETX-S00006112	ETX-S00006111
ETX-M00001908	ETX-S00006116	ETX-S00006115
ETX-M00001909	ETX-S00006120	ETX-S00006119
ETX-M00001910	ETX-S00006124	ETX-S00006123
ETX-M00001911	ETX-S00006128	ETX-S00006127
ETX-M00001912	ETX-S00006132	ETX-S00006131
ETX-M00001913	ETX-S00006136	ETX-S00006135
ETX-M00001914	ETX-S00006140	ETX-S00006139
ETX-M00001915	ETX-S00006144	ETX-S00006143
ETX-M00001916	ETX-S00006148	ETX-S00006147
ETX-M00001917	ETX-S00006152	ETX-S00006151
ETX-M00001918	ETX-S00006156	ETX-S00006155
ETX-M00001919	ETX-S00006160	ETX-S00006159
ETX-M00001920	ETX-S00006164	ETX-S00006163
ETX-M00001921	ETX-S00006168	ETX-S00006167
ETX-M00001922	ETX-S00006172	ETX-S00006171
ETX-M00001923	ETX-S00006176	ETX-S00006175
ETX-M00001924	ETX-S00006180	ETX-S00006179
ETX-M00001925	ETX-S00006184	ETX-S00006183
ETX-M00001926	ETX-S00006188	ETX-S00006187
ETX-M00001927	ETX-S00006192	ETX-S00006191
ETX-M00001928	ETX-S00006196	ETX-S00006195
ETX-M00001929	ETX-S00006200	ETX-S00006199
ETX-M00001930	ETX-S00006204	ETX-S00006203
ETX-M00001931	ETX-S00006208	ETX-S00006207
ETX-M00001932	ETX-S00006212	ETX-S00006211
ETX-M00001933	ETX-S00006216	ETX-S00006215
ETX-M00001934	ETX-S00006220	ETX-S00006219
ETX-M00001935	ETX-S00006224	ETX-S00006223
ETX-M00001936	ETX-S00006228	ETX-S00006227

ETX-M00001937	ETX-S00006232	ETX-S00006231
ETX-M00001938	ETX-S00006236	ETX-S00006235
ETX-M00001939	ETX-S00006240	ETX-S00006239
ETX-M00001940	ETX-S00006244	ETX-S00006243
ETX-M00001941	ETX-S00006248	ETX-S00006247
ETX-M00001942	ETX-S00006252	ETX-S00006251
ETX-M00001943	ETX-S00006256	ETX-S00006255
ETX-M00001944	ETX-S00006260	ETX-S00006259
ETX-M00001945	ETX-S00006264	ETX-S00006263
ETX-M00001946	ETX-S00006268	ETX-S00006267
ETX-M00001947	ETX-S00006272	ETX-S00006271
ETX-M00001948	ETX-S00006276	ETX-S00006275
ETX-M00001949	ETX-S00006280	ETX-S00006279
ETX-M00001950	ETX-S00006284	ETX-S00006283
ETX-M00001951	ETX-S00006288	ETX-S00006287
ETX-M00001952	ETX-S00006292	ETX-S00006291
ETX-M00001953	ETX-S00006296	ETX-S00006295
ETX-M00001954	ETX-S00006300	ETX-S00006299
ETX-M00001955	ETX-S00006304	ETX-S00006303
ETX-M00001956	ETX-S00006308	ETX-S00006307
ETX-M00001957	ETX-S00006312	ETX-S00006311
ETX-M00001958	ETX-S00006316	ETX-S00006315
ETX-M00001959	ETX-S00006320	ETX-S00006319
ETX-M00001960	ETX-S00006324	ETX-S00006323
ETX-M00001961	ETX-S00006328	ETX-S00006327
ETX-M00001962	ETX-S00006332	ETX-S00006331
ETX-M00001963	ETX-S00006336	ETX-S00006335
ETX-M00001964	ETX-S00006340	ETX-S00006339
ETX-M00001965	ETX-S00006344	ETX-S00006343
ETX-M00001966	ETX-S00006348	ETX-S00006347
ETX-M00001967	ETX-S00006352	ETX-S00006351
ETX-M00001968	ETX-S00006356	ETX-S00006355
ETX-M00001969	ETX-S00006360	ETX-S00006359
ETX-M00001970	ETX-S00006364	ETX-S00006363
ETX-M00001971	ETX-S00006368	ETX-S00006367
ETX-M00001972	ETX-S00006372	ETX-S00006371
ETX-M00001973	ETX-S00006376	ETX-S00006375

ETX-M00001974	ETX-S00006380	ETX-S00006379
ETX-M00001975	ETX-S00006384	ETX-S00006383
ETX-M00001976	ETX-S00006388	ETX-S00006387
ETX-M00001977	ETX-S00006392	ETX-S00006391
ETX-M00001978	ETX-S00006396	ETX-S00006395
ETX-M00001979	ETX-S00006400	ETX-S00006399
ETX-M00001980	ETX-S00006404	ETX-S00006403
ETX-M00001981	ETX-S00006408	ETX-S00006407
ETX-M00001982	ETX-S00006412	ETX-S00006411
ETX-M00001983	ETX-S00006416	ETX-S00006415
ETX-M00001984	ETX-S00006420	ETX-S00006419
ETX-M00001985	ETX-S00006424	ETX-S00006423
ETX-M00001986	ETX-S00006428	ETX-S00006427
ETX-M00001987	ETX-S00006432	ETX-S00006431
ETX-M00001988	ETX-S00006436	ETX-S00006435
ETX-M00001989	ETX-S00006440	ETX-S00006439
ETX-M00001990	ETX-S00006444	ETX-S00006443
ETX-M00001991	ETX-S00006448	ETX-S00006447
ETX-M00001992	ETX-S00006452	ETX-S00006451
ETX-M00001993	ETX-S00006456	ETX-S00006455
ETX-M00001994	ETX-S00006460	ETX-S00006459
ETX-M00001995	ETX-S00006464	ETX-S00006463
ETX-M00001996	ETX-S00006468	ETX-S00006467
ETX-M00001997	ETX-S00006472	ETX-S00006471
ETX-M00001998	ETX-S00006476	ETX-S00006475
ETX-M00001999	ETX-S00006480	ETX-S00006479
ETX-M00002000	ETX-S00006484	ETX-S00006483
ETX-M00002001	ETX-S00006488	ETX-S00006487
ETX-M00002002	ETX-S00006492	ETX-S00006491
ETX-M00002003	ETX-S00006496	ETX-S00006495
ETX-M00002004	ETX-S00006500	ETX-S00006499
ETX-M00002005	ETX-S00006504	ETX-S00006503
ETX-M00002006	ETX-S00006508	ETX-S00006507
ETX-M00002007	ETX-S00006512	ETX-S00006511
ETX-M00002008	ETX-S00006516	ETX-S00006515
ETX-M00002009	ETX-S00006520	ETX-S00006519
ETX-M00002010	ETX-S00006524	ETX-S00006523

ETX-M00002011	ETX-S00006528	ETX-S00006527
ETX-M00002012	ETX-S00006532	ETX-S00006531
ETX-M00002013	ETX-S00006536	ETX-S00006535
ETX-M00002014	ETX-S00006540	ETX-S00006539
ETX-M00002015	ETX-S00006544	ETX-S00006543
ETX-M00002016	ETX-S00006548	ETX-S00006547
ETX-M00002017	ETX-S00006552	ETX-S00006551
ETX-M00002018	ETX-S00006556	ETX-S00006555
ETX-M00002019	ETX-S00006560	ETX-S00006559
ETX-M00002020	ETX-S00006564	ETX-S00006563
ETX-M00002021	ETX-S00006568	ETX-S00006567
ETX-M00002022	ETX-S00006572	ETX-S00006571
ETX-M00002023	ETX-S00006576	ETX-S00006575
ETX-M00002024	ETX-S00006580	ETX-S00006579
ETX-M00002025	ETX-S00006584	ETX-S00006583
ETX-M00002026	ETX-S00006588	ETX-S00006587
ETX-M00002027	ETX-S00006592	ETX-S00006591
ETX-M00002028	ETX-S00006596	ETX-S00006595
ETX-M00002029	ETX-S00006600	ETX-S00006599
ETX-M00002030	ETX-S00006604	ETX-S00006603
ETX-M00002031	ETX-S00006608	ETX-S00006607
ETX-M00002032	ETX-S00006612	ETX-S00006611
ETX-M00002033	ETX-S00006616	ETX-S00006615
ETX-M00002034	ETX-S00006620	ETX-S00006619
ETX-M00002035	ETX-S00006624	ETX-S00006623
ETX-M00002036	ETX-S00006628	ETX-S00006627
ETX-M00002037	ETX-S00006632	ETX-S00006631
ETX-M00002038	ETX-S00006636	ETX-S00006635
ETX-M00002039	ETX-S00006640	ETX-S00006639
ETX-M00002040	ETX-S00006644	ETX-S00006643
ETX-M00002041	ETX-S00006648	ETX-S00006647
ETX-M00002042	ETX-S00006652	ETX-S00006651
ETX-M00002043	ETX-S00006656	ETX-S00006655
ETX-M00002044	ETX-S00006660	ETX-S00006659
ETX-M00002045	ETX-S00006664	ETX-S00006663
ETX-M00002046	ETX-S00006668	ETX-S00006667
ETX-M00002047	ETX-S00006672	ETX-S00006671

ETX-M00002048	ETX-S00006676	ETX-S00006675
ETX-M00002049	ETX-S00006680	ETX-S00006679
ETX-M00002050	ETX-S00006684	ETX-S00006683
ETX-M00002051	ETX-S00006688	ETX-S00006687
ETX-M00002052	ETX-S00006692	ETX-S00006691
ETX-M00002053	ETX-S00006696	ETX-S00006695
ETX-M00002054	ETX-S00006700	ETX-S00006699
ETX-M00002055	ETX-S00006704	ETX-S00006703
ETX-M00002056	ETX-S00006708	ETX-S00006707
ETX-M00002057	ETX-S00006712	ETX-S00006711
ETX-M00002058	ETX-S00006716	ETX-S00006715
ETX-M00002059	ETX-S00006720	ETX-S00006719
ETX-M00002060	ETX-S00006724	ETX-S00006723
ETX-M00002061	ETX-S00006728	ETX-S00006727
ETX-M00002062	ETX-S00006732	ETX-S00006731
ETX-M00002063	ETX-S00006736	ETX-S00006735
ETX-M00002064	ETX-S00006740	ETX-S00006739
ETX-M00002065	ETX-S00006744	ETX-S00006743
ETX-M00002066	ETX-S00006748	ETX-S00006747
ETX-M00002067	ETX-S00006752	ETX-S00006751
ETX-M00002068	ETX-S00006756	ETX-S00006755
ETX-M00002069	ETX-S00006760	ETX-S00006759
ETX-M00002070	ETX-S00006764	ETX-S00006763
ETX-M00002071	ETX-S00006768	ETX-S00006767
ETX-M00002072	ETX-S00006772	ETX-S00006771
ETX-M00002073	ETX-S00006776	ETX-S00006775
ETX-M00002074	ETX-S00006780	ETX-S00006779
ETX-M00002075	ETX-S00006784	ETX-S00006783
ETX-M00002076	ETX-S00006788	ETX-S00006787
ETX-M00002077	ETX-S00006792	ETX-S00006791
ETX-M00002078	ETX-S00006796	ETX-S00006795

[0550] For duplexes of Table 5:

ETX-M00001856 – ETX-M00002078 have a duplex structure according to Figure 7b.

[0551] Definitions as provided in the above Tables:

A – adenosine

C – cytidine

G – guanosine

T – thymidine

m – 2'-O-methyl

f – 2'fluro

s – phosphorothioate bond

o - thermally destabilised nucleoside

ia - inverted abasic nucleoside

[0552] 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-M00001860	ETX-S00005924 (SEQ ID NO: 674)	ETX-S00005923 (SEQ ID NO: 897)
ETX-M00001870	ETX-S00005964 (SEQ ID NO: 684)	ETX-S00005963 (SEQ ID NO: 907)
ETX-M00001875	ETX-S00005984 (SEQ ID NO: 689)	ETX-S00005983 (SEQ ID NO: 912)
ETX-M00001867	ETX-S00005952 (SEQ ID NO: 681)	ETX-S00005951 (SEQ ID NO: 904)
ETX-M00001877	ETX-S00005992 (SEQ ID NO: 691)	ETX-S00005991 (SEQ ID NO: 914)
ETX-M00001882	ETX-S00006012 (SEQ ID NO: 696)	ETX-S00006011 (SEQ ID NO: 919)

[0553] 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-M00001870	ETX-S00005964 (SEQ ID NO: 684)	ETX-S00005963 (SEQ ID NO: 907)

[0554] In another 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-M00001877	ETX-S00005992 (SEQ ID NO: 691)	ETX-S00005991 (SEQ ID NO: 914)

[0555] In a further, 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-M00001922 (ETX-M00003139)	ETX-S00006172 (SEQ ID NO: 736)	ETX-S00006171 (SEQ ID NO: 959)
ETX-M00001902 (ETX-M00003137)	ETX-S00006092 (SEQ ID NO: 716)	ETX-S00006091 (SEQ ID NO: 939)
ETX-M00001870 (ETX-M00002655)	ETX-S00005964 (SEQ ID NO: 684)	ETX-S00005963 (SEQ ID NO: 907)
ETX-M00001877 (ETX-M00002664)	ETX-S00005992 (SEQ ID NO: 691)	ETX-S00005991 (SEQ ID NO: 914)
ETX-M00001915 (ETX-M00003134)	ETX-S00006144 (SEQ ID NO: 729)	ETX-S00006143 (SEQ ID NO: 952)
ETX-M00001867 (ETX-M00002659)	ETX-S00005952 (SEQ ID NO: 681)	ETX-S00005951 (SEQ ID NO: 904)
ETX-M00001858 (ETX-M00003135)	ETX-S00005916 (SEQ ID NO: 672)	ETX-S00005915 (SEQ ID NO:)895
ETX-M00001967 (ETX-M00003177)	ETX-S00006352 (SEQ ID NO: 781)	ETX-S00006351 (SEQ ID NO: 1004)
ETX-M00001860 (ETX-M00002592)	ETX-S00005924 (SEQ ID NO: 674)	ETX-S00005923 (SEQ ID NO: 897)
ETX-M00002042 (ETX-M00003170)	ETX-S00006652 (SEQ ID NO: 856)	ETX-S00006651 (SEQ ID NO: 1079)

[0556] In a further, more 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-M00001922 (ETX-M00003139)	ETX-S00006172 (SEQ ID NO: 736)	ETX-S00006171 (SEQ ID NO: 959)
ETX-M00001902 (ETX-M00003137)	ETX-S00006092 (SEQ ID NO: 716)	ETX-S00006091 (SEQ ID NO: 939)
ETX-M00001870 (ETX-M00002655)	ETX-S00005964 (SEQ ID NO: 684)	ETX-S00005963 (SEQ ID NO: 907)
ETX-M00001877 (ETX-M00002664)	ETX-S00005992 (SEQ ID NO: 691)	ETX-S00005991 (SEQ ID NO: 914)
ETX-M00001915 (ETX-M00003134)	ETX-S00006144 (SEQ ID NO: 729)	ETX-S00006143 (SEQ ID NO: 952)

[0557] In a further, 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-M00001922 (ETX-M00003139)	ETX-S00006172 (SEQ ID NO: 736)	ETX-S00006171 (SEQ ID NO: 959)

[0558] In a further, 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-M00001902 (ETX-M00003137)	ETX-S00006092 (SEQ ID NO: 716)	ETX-S00006091 (SEQ ID NO: 939)

EXAMPLE 9: DOSE-RESPONSE FOR INHIBITION OF NR3C2 EXPRESSION IN HUMAN HEK293 CELLS

[0559] HEK293 cells (human kidney-derived cell line, obtained from JCRB Cell Bank) were 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 were transfected with siRNA duplexes targeting either NR3C2 mRNA or a negative control siRNA (siRNA-control; sense strand 5'- GCCTGTACCAAGGCTTTAA-3' (SEQ ID NO:1117), antisense strand 5'- TTAAAGCCTTGGTACAGGC-3' (SEQ ID NO:1118)) in a 6-point, log dose response curve to give final in assay concentrations of 3nM to 0.03pM. Transfection was carried out by diluting Lipofectamine RNAiMAX (ThermoFisher) in Opti-MEM (ThermoFisher) medium at a ratio of 48.5:1.5. This solution was added to an equal volume of siRNA, diluted to the required concentration in phosphate buffered saline. The lipofectamine RNAiMAX and siRNA mixture was incubated at room temperature for 15 minutes before 20 µL was added to wells of a 96 well plate. HEK293 cells were dissociated from flasks using trypsin and resuspended at a density of 300,000 cells/mL. 100 µL of HEK293 cell suspension were added to each well of the siRNA-containing 96-well plates. Cells were then incubated for 24 hours at 37°C, 5% CO2,95% humidity. Each siRNA was tested in triplicate wells and on two separate days for a total of six replicates.

[0560] Intracellular RNA was isolated using a RNeasy kit (Qiagen) according to the manufacturer's instructions. cDNA synthesis was performed using a HiScript III RT SuperMix kit (Vazyme) according to the manufacturer's instructions. Target cDNA was quantified by qPCR on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human NR3C2 and human GAPDH (forward: GAAGGTGAAGGTCGGAGTC (SEQ ID NO:1119), reverse: GAAGATGGTGATGGGATTTC (SEQ ID NO:1120)) using an AceQ Universal U+ Probe Master Mix (Vazyme).

[0561] qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative NR3C2 expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalized to GAPDH and relative to untreated cells. Maximum percent inhibition of NR3C2 expression and pEC50 values (-log10 of the EC50) are calculated using a four parameter (variable slope) model using NumPy (Python). Results are shown in Table 6. Sequences of RNAi molecules are depicted in the relevant Tables herein.

[0562] **Table 6** – Results of dose-response experiments for inhibition of NR3C2 mRNA expression in human HEK293 cells. Observed pEC50s are reported along with the minimum relative expression value (relative to medium control) for two experimental replicates (repeated on separate days with three repeats per day).

ETXM-ID	pEC50 R1	pEC50 R2	Average pEC50	Observed Min R1	Observed Min R2	Average Observed Min
ETX-M00001856	10.26	10.22	10.24	0.14	0.14	0.14
ETX-M00001857	9.74	9.84	9.79	0.22	0.19	0.21
ETX-M00001858	10.04	9.93	9.98	0.18	0.22	0.20
ETX-M00001859	10.14	10.13	10.13	0.17	0.17	0.17
ETX-M00001860	10.04	10.04	10.04	0.15	0.15	0.15
ETX-M00001861	9.39	9.64	9.51	0.2	0.2	0.20
ETX-M00001862	9.44	9.42	9.43	0.39	0.43	0.41
ETX-M00001863	9.56	9.79	9.67	0.22	0.22	0.22
ETX-M00001864	9.43	9.46	9.44	0.28	0.39	0.34
ETX-M00001865	9.51	9.38	9.44	0.31	0.35	0.33
ETX-M00001866	9.1	9.48	9.29	0.26	0.3	0.28
ETX-M00001867	10.29	10.26	10.27	0.15	0.2	0.18
ETX-M00001868	9.43	8.7	9.06	0.31	0.41	0.36
ETX-M00001869	10.12	10.23	10.17	0.22	0.21	0.22
ETX-M00001870	10.76	10.62	10.69	0.17	0.17	0.17
ETX-M00001871	10.33	9.61	9.96	0.33	0.32	0.33
ETX-M00001872	9.23	9.49	9.36	0.28	0.39	0.34
ETX-M00001873	10.41	9.46	9.92	0.23	0.34	0.29
ETX-M00001874	12.01	10.32	11.13	0.16	0.23	0.20
ETX-M00001875	10.59	10.28	10.43	0.16	0.21	0.19
ETX-M00001876	9.5	8.82	9.15	0.25	0.31	0.28
ETX-M00001877	10.07	10.43	10.25	0.15	0.21	0.18
ETX-M00001878	8.9	8.56	8.73	0.35	0.45	0.40
ETX-M00001879	10.28	10.18	10.23	0.17	0.22	0.20
ETX-M00001880	9.39	9.34	9.36	0.37	0.45	0.41
ETX-M00001881	9.73	9.47	9.60	0.18	0.24	0.21
ETX-M00001882	10.44	9.73	10.08	0.21	0.2	0.21
ETX-M00001883	9.71	9.19	9.45	0.24	0.28	0.26
ETX-M00001884	9.55	9.29	9.42	0.22	0.33	0.28
ETX-M00001885	10.24	9.9	10.07	0.26	0.33	0.30

ETX-M00001886	10.05	9.84	9.94	0.25	0.28	0.27
ETX-M00001887	10.41	10.11	10.26	0.17	0.21	0.19
ETX-M00001888	8.82	9.49	9.15	0.36	0.33	0.35
ETX-M00001889	9.79	9.99	9.89	0.22	0.22	0.22
ETX-M00001890	10.57	7.36	8.82	0.75	0.72	0.74
ETX-M00001891	10.15	10.4	10.27	0.2	0.21	0.21
ETX-M00001892	8.81	8.91	8.86	0.45	0.32	0.39
ETX-M00001893	9.46	9.87	9.66	0.28	0.19	0.24
ETX-M00001894	9.68	10.25	9.96	0.24	0.18	0.21
ETX-M00001895	9.64	10.12	9.88	0.24	0.18	0.21
ETX-M00001896	8.84	9.48	9.15	0.35	0.23	0.29
ETX-M00001897	10.07	10.3	10.18	0.18	0.15	0.17
ETX-M00001898	8.91	9.59	9.24	0.32	0.24	0.28
ETX-M00001899	9.38	9.98	9.68	0.19	0.13	0.16
ETX-M00001900	8.64	9.08	8.86	0.44	0.38	0.41
ETX-M00001901	10.44	10.55	10.49	0.22	0.21	0.22
ETX-M00001902	8.84	8.98	8.91	0.33	0.32	0.33
ETX-M00001903	9.74	10.08	9.91	0.27	0.24	0.26
ETX-M00001904	10.19	10.23	10.21	0.29	0.26	0.28
ETX-M00001905	9.6	9.81	9.70	0.29	0.22	0.26
ETX-M00001906	9.5	9.64	9.57	0.33	0.29	0.31
ETX-M00001907	9.47	9.38	9.42	0.47	0.35	0.41
ETX-M00001908	9.47	8.41	8.92	0.36	0.52	0.44
ETX-M00001909	9.66	8.85	9.25	0.3	0.32	0.31
ETX-M00001910	8.56	9.15	8.85	0.3	0.48	0.39
ETX-M00001911	8.55	9.31	8.92	0.44	0.59	0.52
ETX-M00001912	9.63	9.26	9.44	0.25	0.51	0.38
ETX-M00001913	8.66	8.64	8.65	0.29	0.28	0.29
ETX-M00001914	11.98	8.5	10.09	0.55	0.44	0.50
ETX-M00001915	10.24	8.22	9.17	0.12	0.62	0.37
ETX-M00001916	9.21	8.74	8.97	0.32	0.42	0.37
ETX-M00001917	9.19	8.55	8.86	0.29	0.37	0.33
ETX-M00001918	9.86	9.08	9.46	0.16	0.26	0.21
ETX-M00001919	8.41	6.92	7.63	0.61	0.78	0.70
ETX-M00001920	10	8.84	9.40	0.21	0.33	0.27
ETX-M00001921	8.82	9.48	9.14	0.38	0.46	0.42
ETX-M00001922	11.91	9.91	10.86	0.11	0.18	0.15
ETX-M00001923	9.9	9.4	9.65	0.18	0.25	0.22
ETX-M00001924	9.66	9.59	9.62	0.16	0.24	0.20
ETX-M00001925	9.65	9.47	9.56	0.17	0.24	0.21
ETX-M00001926	10.61	NA	10.61	0.24	0	0.12
ETX-M00001927	NA	8.38	8.38	0	0.65	0.33
ETX-M00001928	9.53	9.12	9.32	0.55	0.32	0.44
ETX-M00001929	9.96	9.35	9.65	0.24	0.22	0.23
ETX-M00001930	9.49	9.14	9.31	0.22	0.32	0.27
ETX-M00001931	7.55	7.49	7.52	0.57	0.53	0.55
ETX-M00001932	9.67	9.57	9.62	0.26	0.3	0.28

ETX-M00001933	11.99	10.04	10.97	0.58	0.71	0.65
ETX-M00001934	10.09	9.41	9.74	0.22	0.23	0.23
ETX-M00001935	8.26	9.43	8.83	0.6	0.6	0.60
ETX-M00001936	9.29	9.14	9.21	0.2	0.29	0.25
ETX-M00001937	>13.52	8.62	10.80	0.39	0.39	0.39
ETX-M00001938	9.2	10.02	9.60	0.18	0.17	0.18
ETX-M00001939	10.39	10.06	10.22	0.24	0.21	0.23
ETX-M00001940	9.44	8.86	9.15	0.37	0.28	0.33
ETX-M00001941	9.7	11.11	10.38	0.29	0.18	0.24
ETX-M00001942	9.72	7.42	8.49	0.4	0.42	0.41
ETX-M00001943	9.52	10.18	9.84	0.25	0.24	0.25
ETX-M00001944	9.12	8.99	9.05	0.27	0.36	0.32
ETX-M00001945	8.77	8.83	8.80	0.34	0.32	0.33
ETX-M00001946	9.28	8.8	9.04	0.3	0.37	0.34
ETX-M00001947	9.87	9.65	9.76	0.18	0.19	0.19
ETX-M00001948	9.51	9.55	9.53	0.25	0.29	0.27
ETX-M00001949	8.88	9.19	9.03	0.35	0.36	0.36
ETX-M00001950	12	0.18	1.47	0.51	0.32	0.42
ETX-M00001951	8.11	8.52	8.31	0.44	0.58	0.51
ETX-M00001952	9.35	9.38	9.36	0.4	0.35	0.38
ETX-M00001953	0	8.47	NA	0.67	0.58	0.63
ETX-M00001954	9.53	9.67	9.60	0.26	0.31	0.29
ETX-M00001955	9.52	9.58	9.55	0.22	0.25	0.24

EXAMPLE 10: PREDICTION OF NR3C2 INHIBITION BY NUCLEIC ACIDS OF THE INVENTION

[0563] siRNAdesignR is a computational tool developed by e-therapeutics for the engineering, selection, and optimisation of features for the prediction of siRNA efficacy. In the first step of the process siRNAdesignR identified all possible siRNA target sequences in a gene (consensus regions found in all transcripts) and then filtered out sequences with undesirable characteristics (sequences that match any other human gene with 0 or 1 mismatches, sequences that are commonly mutated (in >1% of the population), sequences that encode immunostimulatory motifs or have degenerate bases and sequences in the 5' untranslated region.

[0564] For the remaining sequences we then derived over 400 features describing the nucleotide sequence of an siRNA target sequence and how these nucleotides interacted with each other and other nucleotides on the messenger RNA at a distance from the target sequence. These nucleotide interactions were predicted using a large language model trained on messenger RNA sequences. The most informative features were then selected with a regression analysis and used to train a machine learning model, which learnt how individual, and combinations of, features encode information on whether an siRNA is likely to be efficacious *in vitro* i.e. cause a significant reduction in mRNA levels.

[0565] For the development of the machine learning model a database of siRNA sequences was built and their corresponding efficacy determined by screening hundreds of siRNAs in *in vitro* (cell line) models. This data was split into training (90% of the data) and test (10% of the data) sets. These datasets were used to train and test different machine learning models with optimised model hyperparameters. Over 10,000 models were evaluated with this method using an automated pipeline that tracked the hyperparameters and model performance. Performance was evaluated using five metrics; the Spearman correlation coefficient (see Figure 9), the root mean squared error, precision@10, precision@20 and the rank of the best performing siRNA (determined experimentally).

[0566] The best performing model (ranked over all five metrics) was then validated using a previously unseen dataset (Figure 10). Models were considered accurate if precision@20 was greater than 0.5, and if the most efficacious siRNA (determined experimentally) was in the top 20 predictions.

[0567] As a final selection step, siRNAdesignR checked for cross species reactivity of the ranked siRNA sequences. This was not applied as a hard filter, but rather siRNA sequences would be preferred if they had cross species reactivity with Macaca fascicularis, Mus musculus and Rattus norvegicus but accepted if they had high efficacy predictions and Macaca fascicularis cross reactivity.

[0568] The outcome of the prediction is shown in Table 7.

[0569] **Table 7** – siRNAdesignR predictions for efficacious antisense sequences of siRNAs targeting NR3C2.

sequence	prediction	predicted_rank
AUAAUAGUCUUUAUCAUCCAUAA	0.93080792	1
AAUAAUAGUCUUUAUCAUCCAUA	0.9187498	2
AUAGUCUUUAUCAUCCAUAAAGG	0.91493609	3
AAAACUUUCAUGAUGGUGUAUUC	0.90869496	4
AAACACUUCGUAAAGUAGAGCUU	0.90530773	5
GAAACACUUCGUAAAGUAGAGCU	0.9042025	6
UCUUACAGAAUCCAUAUAUAAAC	0.89368663	7
UAAAAUUUCACCAGCUGUUCAAC	0.87712427	8
UACUUAACGGACUUGAGAGAGGA	0.87572166	9
GUAAAAUUUCACCAGCUGUUCAA	0.87248272	10
AUCUCUUACAGAAUCCAUAUAUA	0.86436318	11
GUAAAGUAGAGCUUGAUACAUUU	0.85502941	12
UGGAGAUUUUACACUGCAGUGAC	0.85259541	13
AUUUAUUUUGCUAUUUCCUCCUA	0.85011891	14
AAUGAUGCAAUCAUUUCUUCCAG	0.84994891	15
GAGACUGGAGAUUUUACACUGCA	0.8494771	16
AAGACAUUUCUGAAGUCUGCAAG	0.84854162	17
UGGAGACUGGAGAUUUUACACUG	0.84594905	18
UUUUGAAGAAAACUUUGCAGCUG	0.84065826	19

UUUGAAGAAAACUUUGCAGCUGC	0.83856085	20
UAGGGAAUAAUAGUCUUUAUCAU	0.8367488	21
UAGAGCUUGAUACAUUUUCUGGA	0.8365073	22
UUGCUUUAUUGGUACUGAGAAUG	0.8360377	23
AUUCUUUCGUCGAAUCUUAUCAA	0.83564573	24
UACAGAAUCCAUAUAUAAACCCA	0.83442723	25
UUUGGAAUUGUGCUUAGUAGCAG	0.82920705	26
UUACACUGCAGUGACUUGGAGGG	0.82502689	27
AAAAUUUCACCAGCUGUUCAACA	0.82415466	28
AGUAGCAGCAAAACUUUCAUGAU	0.82395703	29
AGAGCUUGAUACAUUUUCUGGAA	0.82378426	30
AGAUUUUACACUGCAGUGACUUG	0.82315638	31
AUUUUCUGGAAUGUAUUCUAAGA	0.82314623	32
AUAUAUAAACCCAUGGACUCAGC	0.82155851	33
AAAGAUUGGUCUCUAGCCGAUCG	0.81872262	34
GUCUUUAUCAUCCAUAAAGGAAA	0.81801319	35
AAAUUUCACCAGCUGUUCAACAU	0.8176866	36
UAAAGUAGAGCUUGAUACAUUUU	0.81710846	37
AAUAGUCUUUAUCAUCCAUAAAG	0.81601251	38
AAUUUAUUUUGCUAUUUCCUCCU	0.81437503	39
AUCUUAUCAAUGAUGCAAUCAUU	0.81391647	40
GUAGCAGCAAAACUUUCAUGAUG	0.81148703	41
AAUCAUUUCUUCCAGCACAUAAA	0.81146517	42
AUAGGAAUAGUCAGCAUCUCUUA	0.81039136	43
UGUAGAAGCAGAAUUCCAGCAGG	0.80965973	44
GGAAUAGUCAGCAUCUCUUACAG	0.80892336	45
UUAUUUUGCUAUUUCCUCCUAGA	0.8069342	46
AGCAAAACUUUCAUGAUGGUGUA	0.806332	47
AAUGUAUUCUAAGACCGGAUACC	0.80544934	48
AUUUCAUGCUACUUAACGGACUU	0.80396434	49
GGAGAUUUUACACUGCAGUGACU	0.80299748	50
AAUAGUCAGCAUCUCUUACAGAA	0.8025755	51
UAGUCUUUAUCAUCCAUAAAGGA	0.80221002	52
ACAGAAUCCAUAUAUAAACCCAU	0.80078759	53
UGCUACUUAACGGACUUGAGAGA	0.79985552	54
GAAGAUGUCAUGUUCAGAGGGCU	0.79871964	55
UACAGUUGCUGAAAGUUCCUUAG	0.79822651	56
AUAGUCAGCAUCUCUUACAGAAU	0.79795294	57
UUUCCUUUGUAAAAUUUCACCAG	0.79720899	58
AGUUGCUGAAAGUUCCUUAGAUU	0.79645837	59
AUGUAAUUUGUCCUCAUUUCUUC	0.79645592	60
UUGAUUCUUGCUUUAUUGGUACU	0.79423957	61
AAUUCAUUCCAGCUUGAAGACAU	0.79412435	62
AUGUACUGGACAAUAUUAAGCUG	0.79376581	63

UUACAGAAUCCAUAUAUAAACCC	0.79369456	64
UUUUACACUGCAGUGACUUGGAG	0.79287269	65
GGAAUAAUAGUCUUUAUCAUCCA	0.79242118	66
AAUCUUAUCAAUGAUGCAAUCAU	0.79193103	67
UUCCUUUGUAAAAUUUCACCAGC	0.78971795	68
AGUUCUUUGAUGUAAUUUGUCCU	0.78957675	69
GGAGACUGGAGAUUUUACACUGC	0.78785118	70
UUAGUAGCAGCAAAACUUUCAUG	0.78762668	71
GAUUCCAGCUCAGUUUUAAUAUC	0.78601686	72
UCUUUAUCAUCCAUAAAGGAAAA	0.78509384	73
UUGUUUAAUACCCACUGGGAAUC	0.78192006	74
AUGUACUGGAUCCAGCAGAGGUG	0.78118709	75
GUCAGCAUCUCUUACAGAAUCCA	0.78102622	76
UACGUUGACAAUCUCCAUGUAGU	0.78098592	77
GAGAUUUUACACUGCAGUGACUU	0.78004064	78
UUUGUAAAAUUUCACCAGCUGUU	0.7792156	79
UAAUAGUCUUUAUCAUCCAUAAA	0.77798884	80
ACAUUCUGAUAAAUCUUAGCUGG	0.77669864	81
UACAUUUUCUGGAAUGUAUUCUA	0.7766573	82
AAUUCUUUCGUCGAAUCUUAUCA	0.77585269	83
AUUGAGGAUUUCAUGCUACUUAA	0.77562964	84
ACAGGAGGAAAGGAACUCAGGUG	0.77513108	85
UUGAAGAAAACUUUGCAGCUGCC	0.77470264	86
GAAAUUGAGGAUUUCAUGCUACU	0.77462018	87
UAUUUUGCUAUUUCCUCCUAGAC	0.77432905	88
UUCCAGCUCAGUUUUAAUAUCAG	0.77391337	89
UUUAUGUACUGGACAAUAUUAAG	0.77370548	90
UCAACAUUCUGAUAAAUCUUAGC	0.77204473	91
AUUUCCUUUGUAAAAUUUCACCA	0.77183623	92
UGAGGAUUUCAUGCUACUUAACG	0.77150154	93
AGACUGGAGAUUUUACACUGCAG	0.77013266	94
UAGUAGCAGCAAAACUUUCAUGA	0.77012195	95
AUUCCAGCUCAGUUUUAAUAUCA	0.7699468	96
AGGAUUUCAUGCUACUUAACGGA	0.76992472	97
GAAGACAUUUCUGAAGUCUGCAA	0.76734641	98
UAUGUACUGGACAAUAUUAAGCU	0.76729151	99
AUUCUGAUAAAUCUUAGCUGGAC	0.76662098	100
AACACUUCGUAAAGUAGAGCUUG	0.76633372	101
AACAUUCUGAUAAAUCUUAGCUG	0.76582919	102
AUUCUUGCUUUAUUGGUACUGAG	0.76580476	103
ACUUAACGGACUUGAGAGAGGAG	0.76521912	104
UUCGUAAAGUAGAGCUUGAUACA	0.76291947	105
AUUUCACCAGCUGUUCAACAUUC	0.76197386	106
UUCAACAUUCUGAUAAAUCUUAG	0.76192044	107

AUCCAUAUAUAAACCCAUGGACU	0.7609392	108
GUAAUUUGUCCUCAUUUCUUCAA	0.76050622	109
UUCUUUCGUCGAAUCUUAUCAAU	0.76046167	110
AGGGAAUAAUAGUCUUUAUCAUC	0.75997338	111
UAUAAACCCAUGGACUCAGCUAC	0.75930769	112
UCUACUUCCUCAGUCUUAGGAAA	0.75845417	113
AAAGGAACUCAGGUGUUGGAAAG	0.75839615	114
UUUCGUCGAAUCUUAUCAAUGAU	0.75751681	115
UGGAAAUUGAGGAUUUCAUGCUA	0.75569469	116
AAGUAGAGCUUGAUACAUUUUCU	0.75486115	117
UUGGAAUUGUGCUUAGUAGCAGC	0.75442988	118
UACAGAUAGAUCCCACAGUACUG	0.75421433	119
UUUAUUUUGCUAUUUCCUCCUAG	0.75340285	120
UAUCAAUGAUGCAAUCAUUUCUU	0.75308371	121
AUUUUACACUGCAGUGACUUGGA	0.75244439	122
UCUGAUAAAUCUUAGCUGGACUC	0.75219724	123
UCGAAUCUUAUCAAUGAUGCAAU	0.75210885	124
GAGGAUUUCAUGCUACUUAACGG	0.75108129	125
GAAAGCGUGGAUCUGUUAUUAGU	0.75064536	126
AGUAGAGCUUGAUACAUUUUCUG	0.74960925	127
AAUCCAUAUAUAAACCCAUGGAC	0.7489822	128
AAAGUAGAGCUUGAUACAUUUUC	0.74829375	129
GAUUUCAUGCUACUUAACGGACU	0.74779256	130
AUAGGGAAUAAUAGUCUUUAUCA	0.74766895	131
CUUAGUAGCAGCAAAACUUUCAU	0.74617939	132
UUAACGGACUUGAGAGAGGAGAG	0.74589063	133
GUAGUUAUUCUCAUCGGUCCUCU	0.74465891	134
CAAAACUUUCAUGAUGGUGUAUU	0.74408032	135
AAUUUGUCCUCAUUUCUUCAAAU	0.74351972	136
GAAUAAUAGUCUUUAUCAUCCAU	0.74219306	137
UUAGAUUCCAGCUCAGUUUUAAU	0.74142971	138
ACAAUCUCCAUGUAGUUAUUCUC	0.74087412	139
AGGAAUAGUCAGCAUCUCUUACA	0.74078972	140
AGCAGCAAAACUUUCAUGAUGGU	0.74038324	141
AUCUGGUUCUGGUUUUAUGUACU	0.73980681	142
AAUUGUGCUUAGUAGCAGCAAAA	0.73966993	143
UUCAAAGGUGAGCUGCAGUCGAA	0.7393098	144
UAGAUUCCAGCUCAGUUUUAAUA	0.73837999	145
GUGAUUUCCAUGACUCCACUAAA	0.73834823	146
GUGCUUAGUAGCAGCAAAACUUU	0.7375378	147
UAAUUUGUCCUCAUUUCUUCAAA	0.73728789	148
UUUCUUUGCUGCUUCCUUGAGUA	0.73701478	149
UCUCUUACAGAAUCCAUAUAUAA	0.73623879	150
AUUGUUGGGACACUUAGUUACCA	0.73591594	151

ACUUCGUAAAGUAGAGCUUGAUA	0.73539601	152
UAGUUAUUCUCAUCGGUCCUCUC	0.73435332	153
UAGACAUGAGCUGCUAAAAGCUC	0.73340335	154
AGCUGUUCAACAUUCUGAUAAAU	0.73240542	155
CGUAAAGUAGAGCUUGAUACAUU	0.73188306	156
UUGAGUACUGUUGUUUGGAAUAG	0.73041348	157
UGAUAGGGAAUAAUAGUCUUUAU	0.7294934	158
AAACCGAAGAUGUCAUGUUCAGA	0.72935979	159
AAUUUCACCAGCUGUUCAACAUU	0.7286419	160
GGGAAUAAUAGUCUUUAUCAUCC	0.72859377	161
AGCUUGAUACAUUUUCUGGAAUG	0.72687817	162
UUGAUGUAAUUUGUCCUCAUUUC	0.72619256	163
UUUUGCUAUUUCCUCCUAGACAU	0.72491909	164
UGAGUACUGUUGUUUGGAAUAGC	0.72458679	165
UAGUCAGCAUCUCUUACAGAAUC	0.72447192	166
UAUUCUUCAAAGGUGAGCUGCAG	0.72423646	167
AGAGUCAGACAUAAAUGAUCUCA	0.72368524	168
AACCGAAGAUGUCAUGUUCAGAG	0.72347072	169
AUGCUACUUAACGGACUUGAGAG	0.7232032	170
ACAGAUAGAUCCCACAGUACUGG	0.72279644	171
ACACUUCGUAAAGUAGAGCUUGA	0.72215382	172
CUUAGAUUCCAGCUCAGUUUUAA	0.72184176	173
GAUUCUUGCUUUAUUGGUACUGA	0.72159732	174
UUUUCUGGAAUGUAUUCUAAGAC	0.72150947	175
UUAUCAAUGAUGCAAUCAUUUCU	0.72143048	176
UCCUUUGUAAAAUUUCACCAGCU	0.7213032	177
UUUGAUGUAAUUUGUCCUCAUUU	0.72045407	178
GUUGUUUGGAAUAGCACCGGAAA	0.72044023	179
UGGAAACAGAGCACCUUGAGUUG	0.72017866	180
CAAUGAUGCAAUCAUUUCUUCCA	0.71843173	181
AAUGCUUGGUUGAUUCUUGCUUU	0.71842802	182
AAAGUUCCUUAGAUUCCAGCUCA	0.71736476	183
UGUACUGGACAAUAUUAAGCUGG	0.71700197	184
AGAAUCCAUAUAUAAACCCAUGG	0.71660262	185
UUUUAUGUACUGGACAAUAUUAA	0.71595725	186
UUGAUACAUUUUCUGGAAUGUAU	0.71400847	187
AACGGACUUGAGAGAGGAGAGCC	0.71351023	188
UCCUUUGGAAUUGUGCUUAGUAG	0.71314221	189
AAGUUCCUUAGAUUCCAGCUCAG	0.71309193	190
GAUUUUACACUGCAGUGACUUGG	0.71262817	191
CUUCGUAAAGUAGAGCUUGAUAC	0.71260761	192
UACUGUUGUUUGGAAUAGCACCG	0.71237975	193
GAGUACUGUUGUUUGGAAUAGCA	0.71042503	194
GAUAAAUCUUAGCUGGACUCAUG	0.71016412	195

CAUUUCUGAAGUCUGCAAGCAGG	0.70986221	196
UCGUAAAGUAGAGCUUGAUACAU	0.70966079	197
UUCUUGUUUAAUACCCACUGGGA	0.7085608	198
AUUCAUUCCAGCUUGAAGACAUU	0.70843457	199
AAUUGAGGAUUUCAUGCUACUUA	0.70832493	200
UGAGCACCAAUCCUGUAGUGGAA	0.70830388	201
GAAUUGUUGGGACACUUAGUUAC	0.70802647	202
AUCAAUGAUGCAAUCAUUUCUUC	0.70777982	203
AGUCAGACAUAAAUGAUCUCAAG	0.70736583	204
GUUUUAUGUACUGGACAAUAUUA	0.70723969	205
AAUCUUAGCUGGACUCAUGCUUC	0.70639465	206
AUUUGUCCUCAUUUCUUCAAAUG	0.70628542	207
UUUACACUGCAGUGACUUGGAGG	0.70599219	208
UCUUGCUUUAUUGGUACUGAGAA	0.70538282	209
CAUGUAGUUAUUCUCAUCGGUCC	0.70530805	210
AUUGUUUACAGGGCUACAGAUAG	0.70469379	211
GGAAAUUGAGGAUUUCAUGCUAC	0.70466775	212
GUACUGUUGUUUGGAAUAGCACC	0.70408242	213
ACUGGAGAUUUUACACUGCAGUG	0.70380376	214
CUGAUAGGGAAUAAUAGUCUUUA	0.70314439	215
GAAUUGUGCUUAGUAGCAGCAAA	0.70308742	216
AGGAAAGGAACUCAGGUGUUGGA	0.7025084	217
GAAUAGUCAGCAUCUCUUACAGA	0.70207851	218
UUUACAGGGCUACAGAUAGAUCC	0.70174165	219
ACAUUUCUGAAGUCUGCAAGCAG	0.70151892	220
AUUUCCAUGACUCCACUAAAGUA	0.7009477	221
CUUUGAUGUAAUUUGUCCUCAUU	0.70088572	222
UUGUUUGGAAUAGCACCGGAAAC	0.70056282	223

[0570] To demonstrate that siRNAdesignR could be used to find lead sequences for clinical projects, the inventors validated predictions for a different target, SLC25A5, in relevant preclinical models (Figures 11-14).

[0571] Highlighted in Figure 11 is an siRNA sequence that ranked within the top 20 predictions by siRNAdesignR for the target SLC25A5. This sequence was subsequently tested in dose response *in vitro* (in a Huh7 cell line), measuring the amount of mRNA knockdown (Figure 12), and *in vivo* (in C57BL/6 mice), measuring mRNA and protein knockdown (Figures 13 and 14).

EXAMPLE 11: PHARMACODYNAMIC STUDY IN HEALTHY MICE

Methods

[0572] To test the activity of 4 selected GalNAc-siRNAs against the murine Nr3c2 transcript, male C57BL/6 mice were injected subcutaneously with either 1 or 3 mg/kg of GalNAc-siRNA constructs (ETX-

M2590 (ETX-M00001882), ETX-M2591 (ETX-M00001856), ETX-M2592 (ETX-M00001860) or ETX-M2593 (ETX-M00001924)). Control animals received 0.9% saline injections, and negative control animals were injected with 3 mg/kg of a negative control GalNAc-siRNA (ETX-M2594 (sense strand CACGUACGCGGAAUACUUCGA – SEQ ID NO: 1124; antisense strand UCGAAGUAUUCCGCGUACGUGAU – SEQ ID NO: 1125)) that has no mRNA target in mice. Each group contained n=4 mice. At various time-points post dosing, a subset of mice was sacrificed, livers and serum were harvested and analysed. For the analysis of liver target mRNA expression, liver samples were homogenized, RNA was extracted using the MagMAX™ mirVana™ Total RNA Isolation Kit (Thermo-A27828), cDNA was prepared using HiScript® III RT SuperMix for qPCR (+gDNA wiper)(Vazyme-R323), and gene expression of Nr3c2 and the housekeeper Gapdh were measured by RT-qPCR on a Q7 Fast Real-time PCR system (Applied biosystem). The levels of Nr3c2 were measured using in-house designed primers (Fwd: TCTGGCTTCTGCTTCTTC (SEQ ID NO: 1121); Rev: CTTCCAAGAGCAAGTTCTG (SEQ ID NO: 1122); Probe: AAGGACAGCACTCTCAGGACC (SEQ ID NO: 1123)) and Gapdh levels were measured using a commercial Taqman assay (Thermo, Mm99999915_g1). The Expression levels were calculated using the 2-ddCt method whereby Nr3c2 levels were normalised to Gapdh levels and then normalised to the expression levels of vehicle control animals at each timepoint. The results are shown in Figure 20. Serum samples were analysed for levels of liver markers ALT, AST, and ALP on an Automatic biochemical analyzer (AU480, Beckman) using commercial kits (Beckman-OSR6107, Beckman-OSR6104, Beckman-OSR6109). The results are shown in Figure 21.

Results

Pharmacodynamic Study in Healthy Mice- Knockdown of hepatic Nr3c2 mRNA in mice treated with GalNAc-siRNA constructs.

[0573] To test the knockdown efficacy of 4 selected GalNAc-siRNAs with predicted activity against human, monkey, and mouse NR3C2, mice were injected with 2 doses (1 and 3 mg/kg) of GalNAc-siRNA and liver samples were analysed up to 4 weeks post GalNAc-siRNA dosing. All 4 GalNAc-siRNAs tested resulted in knockdown up to 40% at day 7 at 3 mg/kg which was sustained until day 14 (Figure 1B). ETX-M2590 exhibited knockdown at the 1 mg/kg dose level (Figure 20A).

[0574] Regarding Figure 20, Mice were injected with saline, a negative control GalNAc-siRNA with no target mRNA in mouse, as well as 4 different anti-NR3C2 GalNAc-siRNAs on day 0. Mice were sacrificed, livers were collected 7-, 14-, 21- and 28-days post dosing and Nr3c2 target mRNA levels were analysed by qPCR and normalised to the housekeeper Gapdh. **A**: Hepatic target mRNA levels following injection with 1 mg/kg GalNAc-siRNA, 3 mg/kg negative control GalNAc-siRNA or saline. **B**: Hepatic target mRNA levels following injection with 3 mg/kg GalNAc-siRNA or saline.

[0575] Note that saline levels are plotted in both graphs for comparison. Mean ± SEM. N=4 per timepoint/treatment.

Pharmacodynamic Study in Healthy Mice - No treatment-related effect on markers of liver health in mice treated with GalNAc-siRNAs.

[0576] To examine the effects of the tested GalNAc-siRNAs on liver health, serum levels of the liver markers ALP (alkaline phosphatase), ALT (alanine transaminase) and AST (aspartate transaminase) were measured throughout the time course. No changes in the serum levels of these markers of liver health were observed with either 1 mg/kg (Figure 21 A-C) or 3 mg/kg (Figure 21 D-F) of the 4 tested GalNAc-siRNA constructs. These data indicate that the GalNAc-siRNAs displayed a favourable safety profile in this study. Regarding Figure 21, mice were injected with saline, a negative control GalNAc-siRNA with no target mRNA in mouse, as well as 4 different anti-Nr3c2 GalNAc-siRNAs on day 0. Mice were sacrificed and serum was collected 7-, 14-, 21- and 28-days post dosing for biochemical assessment of ALP, ALT, and AST levels. **A-C**: Levels of ALP (**A**), ALT (**B**) or AST (**C**) following injection of 1 mg/kg GalNAc-siRNA, 3 mg/kg negative control GalNAc-siRNA or saline. **D-F**: Levels of ALP (**D**), ALT (**E**) or AST (**F**) following injection of 3 mg/kg GalNAc-siRNA or saline.

[0577] Note that saline levels are plotted in both graphs for comparison. Mean ± SEM. N=4 per timepoint/treatment.

EXAMPLE 12: DISEASE MODEL PROOF-OF-CONCEPT (PoC) STUDY

Methods

[0578] To model heart failure with reduced ejection fraction (HFrEF) in mice, male C57BL/6 mice underwent myocardial infarction (MI) induction by left anterior descending artery (LAD) ligation. Mice were injected subcutaneously 7 days before MI, or at the time of MI, with 10 mg/kg of GalNAc-siRNA (ETX-M2590). The mice subsequently received GalNAc-siRNA (ETX-M2590) injections once per week over the course of 6 weeks post-MI. Control groups included sham-operated animals and MI-animals injected with vehicle (0.9% saline, subcutaneous, 1x/week) as well as animals receiving the mineralocorticoid receptor antagonist eplerenone by food at a dose of 1 g/kg diet as positive control. A combination group received siRNA on the day of MI induction, followed by weekly siRNA injections and eplerenone by food for the first 7 days. Survival, body weight and food intake were recorded weekly and are shown in Figure 23.

[0579] On days 14, 21 and 42 post-MI, Echocardiography was performed (group size n=14-19) using a Vevo 1100 High-Resolution Imaging System (VisualSonics) and a 30 mHz probe. During the procedure, the mice were anesthetized using Isoflurane (1%). Parameters assessed by Echocardiography were LVEF, FS, ESD, EDD, CO, SV, LVPWTs, LVPWTd, LV mass and HR. The results for day 42 ECHO are shown in Figure 24.

[0580] Afterwards, the animals were sacrificed, and livers and hearts were collected. Livers and hearts were frozen for subsequent molecular analysis, and heart samples were also prepared for histological assessment. Serum was harvested for terminal biochemical analysis and ELISA measurements.

[0581] For the analysis of mRNA expression, liver or heart samples were homogenized, RNA was extracted using the MagMAX™ mirVana™ Total RNA Isolation Kit (Thermo-A27828), cDNA was prepared using HiScript® III RT SuperMix for qPCR (+gDNA wiper)(Vazyme-R323), and gene expression of *Nr3c2* (Liver) or *Anp* and *Bnp* (heart) and the housekeeper *Gapdh* were measured by RT-qPCR on a Q7 Fast Real-time PCR system (Applied biosystem). The levels of *Nr3c2* were measured using in-house designed primers (Fwd: TCTGGCTTCTGCTTCTTC (SEQ ID NO: 1121); Rev: CTTCCAAGAGCAAGTTCTG (SEQ ID NO: 1122); Probe: AAGGACAGCACTCTCAGGACC (SEQ ID NO: 1123)) and *Gapdh*, *Anp* and *Bnp* levels were measured using commercial Taqman assays: *Gapdh* (Thermo, Mm99999915_g1), *Anp* (Thermo, Mm01255747_g1) and *Bnp* (Thermo, Mm01255770_g1).

[0582] For histological analysis, 3 sections of the heart, taken at equal spacing between apex and base, were stained using hematoxylin/eosin (H&E) and picrosirius red (PSR) to assess general morphology and fibrosis, respectively.

[0583] For serum analysis, a biochemical analyzer was used to measure the levels of circulating ALT/AST/ALP, Albumin, Bilirubin, Creatinine, BUN, Ca, Phos, total protein, Cl, Na and K.

[0584] ELISA analysis was performed to measure the circulating levels of FGF21 (abcam; ab212160), ANP (Novus; NBP2-66733) and NT-proBNP (Novus; NBP2-76775), according to the manufacturer's instructions.

[0585] Two additional groups of mice were subjected to MI induction by LAD ligation. The mice in groups of n=10 were injected with 0.9% saline or 10 mg/kg GalNAc-siRNA (ETX-M2590) 6 days prior to MI induction by LAD ligation. One day post MI, mice were sacrificed, livers and serum were harvested, and *Nr3C2* mRNA expression was assessed by qPCR. For the analysis of liver target mRNA expression, liver samples were homogenized, RNA was extracted using the MagMAX™ mirVana™ Total RNA Isolation Kit (Thermo-A27828), cDNA was prepared using HiScript® III RT SuperMix for qPCR (+gDNA wiper)(Vazyme-R323), and gene expression of *Nr3c2* and the housekeeper *Gapdh* were measured by RT-qPCR on a Q7 Fast Real-time PCR system (Applied biosystem). The levels of *Nr3c2* were measured using in-house designed primers (Fwd: TCTGGCTTCTGCTTCTTC (SEQ ID NO: 1121); Rev: CTTCCAAGAGCAAGTTCTG (SEQ ID NO: 1122); Probe: AAGGACAGCACTCTCAGGACC (SEQ ID NO: 1123)) and *Gapdh* levels were measured using a commercial Taqman assay (Thermo, Mm99999915_g1). Expression levels were calculated using the 2^{-ddCt} method whereby *Nr3c2* levels were normalised to *Gapdh* levels and then normalised to the expression levels of the vehicle control group. The results are shown in Figure 22A.

[0586] Serum FGF21 levels were measured using a commercial ELISA kit (abcam ab212160), according to the manufacturer's instructions. The results are shown in Figure 22B.

Results

Disease Model PoC Study – Knockdown efficiency and FGF21 levels in mice treated with GalNAc-siRNA to reduce hepatic NR3C2 expression prior to myocardial infarction.

[0587] To assess the effect of hepatic *Nr3c2* knockdown in the MI disease model, mice were pre-injected with saline or 10 mg/kg of ETX-M2590 six days before induction of myocardial infarction (MI). Mice then underwent MI-induction by left anterior descending artery (LAD) ligation and were sacrificed one day post-MI. Measurement of hepatic *Nr3c2* target mRNA expression revealed a more than 70% target mRNA knockdown. Analysis of serum fibroblast growth factor 21 (FGF21) levels one day post-MI in control and ETX-M2590 treated animals revealed a trend towards increased FGF21 in ETX-M2590 treated mice (Figure 22B).

[0588] Regarding Figure 22, mice were injected with saline or GalNAc-siRNA (ETX-M2590) on day -6 before MI. Mice then underwent MI-induction on day 0 and were sacrificed one day post-MI and liver and serum were collected. A – Hepatic *Nr3c2* levels normalised to the housekeeper *Gapdh*. B – Serum FGF21 levels.

[0589] Mean ± SEM. N=10 per group.

Disease Model PoC Study – No treatment-related effects on survival, body weight or food intake

[0590] To examine the effects of reducing hepatic Nr3c2 expression using GalNAc-siRNA on post-MI cardiac remodeling, male C57BL/6 mice were injected subcutaneously with 10 mg/kg ETX-M2590 GalNAc-siRNA either 7 days before or on the day of MI induction and were then injected weekly with ETX-M2590. Control groups included saline injected, sham-operated, or MI-operated animals as well as animals treated with the positive control mineralocorticoid receptor antagonist (MRA) Eplerenone by food at 1 g/kg diet starting on the day of MI. An additional group was injected weekly with ETX-M2590 at 10 mg/kg starting on the day of MI and received MRA by food for the first 7 days post MI.

[0591] All MI groups exhibited a certain, expected, degree of mortality within the first 2 weeks post-surgery which was not affected by treatment (Figure 23A). One additional death was observed in the MRA+siRNA group on day 41. Body weight (Figure 23B) and food intake (Figure 23C) were unaffected by treatment, and all MI animals gained weight and consumed the same amount of food as sham operated controls.

[0592] Regarding Figure 23, mice were injected weekly with saline or GalNAc-siRNA (ETX-M2590) starting on day -7 or day 0 (day of MI). A positive control group received an MRA (Eplerenone) by food starting on day 0. An additional group received weekly GalNAc-siRNA injections starting on day 0,

combined with MRA treatment for the first 7 days post-MI. Mice underwent MI-induction on day 0 and survival, body weights and food intake were recorded throughout the study. **A** – Survival rates; **B** – Body weights; **C** – Food intake.

[0593] Mean ± SEM. N=14-19 per group.

Disease Model PoC Study – Improved cardiac function post-MI in mice treated with ETX-M2590.

[0594] To assess the effects of reducing hepatic *Nr3c2* mRNA expression on cardiac parameters in mice following myocardial infarction (MI), echocardiography (ECHO) was performed 42 days post MI in ETX-M2590 treated mice.

[0595] Myocardial infarction resulted in the expected decreases in ejection fraction and fractional shortening, indicative of a HFrEF phenotype (Figure 24A, B). Treatment with ETX-M2590 either pre- or post-MI resulted in significant improvements of these parameters of cardiac function to a similar extend as the positive control MRA, alone or in combination ETX-M2590+MRA (Figure 24A, B). Stroke volume and the resulting cardiac output were reduced by MI and significantly improved with ETX-M2590 pre- and post-MI treatment as well as by the positive control MRA and by combination treatment of ETX-M2590+MRA (Figure 24C, D). The dimensional parameters end-systolic and end-diastolic left ventricular (LV) diameter were increased by MI, indicative of the expected cardiac dilation (Figure 24 E, F). Treatment with ETX-M2590 pre-MI as well as MRA treatment, alone or in combination ETX-M2590+MRA, significantly improved the end systolic LV diameter (Figure 24E), indicative of reduced cardiac dilation. Systolic posterior wall thinning was observed in the MI group which was significantly improved with ETX-M2590 treatment pre- and post-MI as well as combination of ETX-M2590+MRA and by the positive control MRA alone (Figure 24G), indicating a potentially improved cardiac structural remodelling with ETX-M2590 treatment to reduce hepatic *Nr3c2* expression. Diastolic posterior wall thickness was unaffected (Figure 24H). Left ventricular mass was increased by MI, as expected, and not affected by treatment (Figure 5I) and heart rate was not affected by any intervention (Figure 24J).

[0596] Regarding Figure 24, mice were injected weekly with saline or GalNAc-siRNA (ETX-M2590) starting on day -7 or day 0 (day of MI). A positive control group received an MRA (Eplerenone) by food starting on day 0. An additional group received weekly GalNAc-siRNA injections starting on day 0, combined with MRA treatment for the first 7 days post-MI. Mice underwent MI-induction on day 0 and echocardiography measurements were performed on day 42 post-MI. **A** – Left ventricular ejection fraction (LVEF); **B** – Fractional shortening (FS); **C** – Stroke volume (SV); **D** – Cardiac output (CO); **E** – End-systolic diameter (ESD); **F** – End-diastolic diameter (EDD); **G** – Left ventricular posterior wall thickness systolic (LVPWs); **H** – Left ventricular posterior wall thickness diastolic (LVPWd); **I** – Left ventricular mass (LV mass); **J** – Heartrate (HR).

[0597] Mean ± SEM. N=14-19 per group. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 versus MI+Vehicle.

[0598] Overall, these data indicate a positive effect of reducing hepatic *Nr3c2* mRNA expression using the GalNAc-siRNA ETX-M2590 on cardiac function and remodelling post-MI.

EXAMPLE 13: HDI (HYDRODYNAMIC INJECTION) STUDY

Methods

[0599] To test the activity of 15 selected GalNAc-siRNAs against the human *NR3C2* sequence in mice, female Balb/c mice, in groups of n=5, were injected subcutaneously with 3 mg/kg of GalNAc-siRNA (ETX-M2590, ETX-M2591, ETX-M2592, ETX-M2593, ETX-M2655 (ETX-M00001870), ETX-M2656 (ETX-M00001875), ETX-M2657 (ETX-M00001901), ETX-M2658 (ETX-M00001887), ETX-M2659 (ETX-M00001867), ETX-M2660 (ETX-M00001879), ETX-M2661 (ETX-M00001891), ETX-M2662 (ETX-M00001859), ETX-M2663 (ETX-M00001869), ETX-M2664 (ETX-M00001877) or ETX-M2665 (ETX-M00001897)), a negative control GalNAc-siRNA (ETX-M2594) with no mRNA target in mice or human, or with 0.9% saline vehicle. 6 days after GalNAc-siRNA injection, the mice received 30 µg/mouse of a plasmid (pcDNA3.1) encoding the human *NR3C2* cDNA by hydrodynamic injection. One day after plasmid injection, the animals were sacrificed, and livers were harvested. For the analysis of human target mRNA expression in mouse livers, liver samples were homogenized, RNA was extracted using the MagMAX™ mirVana™ Total RNA Isolation Kit (Thermo-A27828), cDNA was prepared using HiScript® III RT SuperMix for qPCR (+gDNA wiper)(Vazyme-R323), and gene expression of *NR3C2* and the housekeeper *NEO* were measured by RT-qPCR on a Q7 Fast Real-time PCR system (Applied biosystem). In-house designed primers were used to detect the expression levels of *NR3C2* (Fwd: TGTATGAACTATGCCAGGGGA – SEQ ID NO: 1126; Rev: TGGAATTGTGCTTAGTAGCAGC – SEQ ID NO: 1127; Probe: CACCAAATCAGCCTTCAGTTCGTTCG – SEQ ID NO: 1128) and *NEO* (Fwd: GATGGATTGCACGCAGGTTCTC – SEQ ID NO: 1128; Rev: GAACACGGCGGCATCAGAGC – SEQ ID NO: 1130; Probe: CGCTTGGGTGGAGAGGCTATTCGGCTATGA – SEQ ID NO: 1131). Expression levels were calculated using the 2^{-ddCt} method whereby *NR3C2* levels were normalised to *NEO* levels and then normalised to the expression levels in saline-injected controls.

Results

[0600] The 4 GalNAc-siRNAs against *NR3C2* tested in the pharmacodynamic study (Figures 20 and 21) also target the human and monkey *NR3C2* transcript. *In vitro* screening identified additional 11 sequences with *in vitro* high efficacy that were predicted to only be active against the human and monkey *NR3C2* transcript but not the murine. To test the activity of these sequences, as well as the 4 sequences already tested against the murine transcript in the pharmacodynamic study, against the human *NR3C2* transcript, a hydrodynamic injection (HDI) model was used. In this model, hepatic expression of the human *NR3C2*

transcript in mice was achieved by injecting 30 μg of a plasmid (pcDNA3.1) encoding the human *NR3C2* cDNA into mice *via* hydrodynamic injection. Mice were injected with 3 mg/kg of the respective GalNAc-siRNAs six days before HDI and were sacrificed one day post-HDI to assess hepatic expression of human *NR3C2* and the internal expression control neomycin resistance (*NEO*).

[0601] HDI resulted in the expression of the human *NR3C2* transcript in mouse livers (Figure 25). Pre-treatment with siRNA resulted in >70% reduction in hepatic *NR3C2* expression with all GalNAc-siRNAs tested (Figure 25). ETX-M2655 and ETX-M2664 were identified as top sequences (>85% knockdown) with multiple additional sequences defined as second tier: ETX-M2590 used in the mouse disease model study above as well as ETX-M2592, ETX-M2656 and ETX-M2659.

[0602] Regarding Figure 25, Mice were injected with saline, a negative control GalNAc-siRNA with no target mRNA in mouse, as well as 15 different anti-NR3C2 GalNAc-siRNAs on day -6. Mice were injected by hydrodynamic injection (HDI) with an NR3C2 encoding plasmid on day 0 and sacrificed on day 1. Livers were collected and human *NR3C2* target mRNA levels were analysed by qPCR and normalised to the expression control *NEO*. **A**: Hepatic target mRNA levels following injection with 3 mg/kg GalNAc-siRNA, negative control GalNAc-siRNA or saline.

[0603] Mean ± SEM. N=4-5 per group. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 versus Saline.

EXAMPLE 14: Confirmation of siRNA Activity against NR3C2 in Primary Human Hepatocytes (PHH)

Methods

[0604] The activity of 54 siRNAs against NR3C2 mRNA in Primary Human Hepatocytes (PHH) was carried out. PHH cells from BioIVT & Elevating Science™ were cultured in InvitroGRO CP Medium (BioreclamationIVT-S03316, 225 mL) supplemented with Fetal bovine serum (Gbico-10091148, 25.3 mL) and Penicillin-Streptomycin Solution (Gibco-15070-063, 2.5 mL). GalNAc-siRNA were transfected using Lipofectamine®RNAiMAX Reagent (ThermoFisher) at 0.01nM and 1.0nM for 48 hours. RNA was isolated using EZ-Press 96 RNA Purification Kit (EZBioscience-EZ4001-L). cDNA was prepared using 5× HiScript III qRT SuperMix (+gDNA wiper) and gene expression of NR3C2 and the housekeeping gene, B-actin were measured by RT-qPCR on a Q7 Fast Real-time PCR system (Applied Biosystem). Relative NR3C2 expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalized to b-actin.

Results

[0605] The siRNAs tested in this study are shown in Table 8 below along with their Mean Relative Expression. Activity of all tested siRNAs is shown in Figure 26. All tested siRNAs displayed activity in PHH. Results were evaluated with the HDI results (Example 15) to select lead siRNAs.

Table 8

ETX ID	Alternative ETX ID	Concentration (nM)	Mean Relative Expression	SEM
ETX-M00002590	ETX-M00001882	0.01	0.67	0.01
ETX-M00002591	ETX-M00001856	0.01	0.65	0.02
ETX-M00002592	ETX-M00001860	0.01	0.59	0.04
ETX-M00002655	ETX-M00001870	0.01	0.55	0.04
ETX-M00002659	ETX-M00001867	0.01	0.83	0.01
ETX-M00002660	ETX-M00001879	0.01	0.6	0.02
ETX-M00002661	ETX-M00001891	0.01	0.7	0.01
ETX-M00002662	ETX-M00001859	0.01	0.62	0.02
ETX-M00002664	ETX-M00001877	0.01	0.46	0.01
ETX-M00002665	ETX-M00001897	0.01	0.67	0.03
ETX-M00003134	ETX-M00001915	0.01	0.53	0.03
ETX-M00003135	ETX-M00001858	0.01	0.74	0.01
ETX-M00003136	ETX-M00001865	0.01	0.94	0.02
ETX-M00003137	ETX-M00001902	0.01	0.74	0.03
ETX-M00003138	ETX-M00001895	0.01	0.91	0.03
ETX-M00003139	ETX-M00001922	0.01	0.66	0.02
ETX-M00003140	ETX-M00001863	0.01	0.72	0.02
ETX-M00003141	ETX-M00001935	0.01	0.89	0.03
ETX-M00003142	ETX-M00001954	0.01	0.75	0.03
ETX-M00003143	ETX-M00001857	0.01	0.8	0.05
ETX-M00003144	ETX-M00002058	0.01	0.98	0.01
ETX-M00003145	ETX-M00001937	0.01	0.9	0.01
ETX-M00003146	ETX-M00001893	0.01	0.76	0.02
ETX-M00003147	ETX-M00001918	0.01	0.72	0.03
ETX-M00003148	ETX-M00001903	0.01	0.76	0.02
ETX-M00003149	ETX-M00001976	0.01	0.72	0.03
ETX-M00003150	ETX-M00001866	0.01	0.87	0.02
ETX-M00003151	ETX-M00001889	0.01	0.67	0.03
ETX-M00003152	ETX-M00001947	0.01	0.58	0.04
ETX-M00003153	ETX-M00001960	0.01	0.77	0.02
ETX-M00003154	ETX-M00001945	0.01	0.94	0.05
ETX-M00003155	ETX-M00001945	0.01	0.9	0.02
ETX-M00003156	ETX-M00001992	0.01	1.08	0.03
ETX-M00003157	ETX-M00001864	0.01	0.91	0.02
ETX-M00003158	ETX-M00001876	0.01	0.78	0.04
ETX-M00003159	ETX-M00002047	0.01	0.75	0.02
ETX-M00003160	ETX-M00002018	0.01	0.78	0.01
ETX-M00003161	ETX-M00001892	0.01	0.64	0.02
ETX-M00003162	ETX-M00001921	0.01	0.84	0.07
ETX-M00003163	ETX-M00001861	0.01	0.75	0.03
ETX-M00003164	ETX-M00001890	0.01	0.82	0.02
ETX-M00003165	ETX-M00001907	0.01	0.84	0.06
ETX-M00003166	ETX-M00001971	0.01	0.95	0.06
ETX-M00003167	ETX-M00001898	0.01	0.99	< 0.005
ETX-M00003168	ETX-M00001878	0.01	0.92	0.02
ETX-M00003169	ETX-M00001942	0.01	0.89	0.03

ETX-M00003170	ETX-M00002042	0.01	0.61	0.04
ETX-M00003171	ETX-M00001881	0.01	0.54	0.07
ETX-M00003172	ETX-M00001972	0.01	0.47	0.06
ETX-M00003173	ETX-M00002052	0.01	0.64	0.05
ETX-M00003174	ETX-M00001884	0.01	0.7	0.02
ETX-M00003175	ETX-M00001990	0.01	0.72	0.04
ETX-M00003176	ETX-M00002031	0.01	0.62	0.01
ETX-M00003177	ETX-M00001967	0.01	0.83	0.05
ETX-M00002590	ETX M00001882	1	0.16	0.01
ETX-M00002591	ETX-M00001856	1	0.14	0.01
ETX-M00002592	ETX-M00001860	1	0.12	< 0.005
ETX-M00002655	ETX-M00001870	1	0.16	0.01
ETX-M00002659	ETX-M00001867	1	0.2	< 0.005
ETX-M00002660	ETX-M00001879	1	0.18	N/A
ETX-M00002661	ETX-M00001891	1	0.2	0.02
ETX-M00002662	ETX-M00001859	1	0.09	0.01
ETX-M00002664	ETX-M00001877	1	0.14	< 0.005
ETX-M00002665	ETX-M00001897	1	0.15	0.01
ETX-M00003134	ETX-M00001915	1	0.07	< 0.005
ETX-M00003135	ETX-M00001858	1	0.19	0.02
ETX-M00003136	ETX-M00001865	1	0.27	0.02
ETX-M00003137	ETX-M00001902	1	0.23	0.02
ETX-M00003138	ETX-M00001895	1	0.19	0.01
ETX-M00003139	ETX-M00001922	1	0.21	< 0.005
ETX-M00003140	ETX-M00001863	1	0.22	0.01
ETX-M00003141	ETX-M00001935	1	0.37	0.04
ETX-M00003142	ETX-M00001954	1	0.22	< 0.005
ETX-M00003143	ETX-M00001857	1	0.18	0.02
ETX-M00003144	ETX-M00002058	1	0.6	0.04
ETX-M00003145	ETX-M00001937	1	0.24	0.03
ETX-M00003146	ETX-M00001893	1	0.17	0.01
ETX-M00003147	ETX-M00001918	1	0.25	0.01
ETX-M00003148	ETX-M00001903	1	0.19	0.02
ETX-M00003149	ETX-M00001976	1	0.15	0.02
ETX-M00003150	ETX-M00001866	1	0.3	0.03
ETX-M00003151	ETX-M00001889	1	0.21	0.01
ETX-M00003152	ETX-M00001947	1	0.19	0.02
ETX-M00003153	ETX-M00001960	1	0.17	0.01
ETX-M00003154	ETX-M00001945	1	0.27	0.01
ETX-M00003155	ETX-M00001945	1	0.19	0.02
ETX-M00003156	ETX-M00001992	1	0.57	< 0.005
ETX-M00003157	ETX-M00001864	1	0.34	0.01
ETX-M00003158	ETX-M00001876	1	0.23	< 0.005
ETX-M00003159	ETX-M00002047	1	0.23	0.01
ETX-M00003160	ETX-M00002018	1	0.11	< 0.005
ETX-M00003161	ETX-M00001892	1	0.25	< 0.005
ETX-M00003162	ETX-M00001921	1	0.3	0.02
ETX-M00003163	ETX-M00001861	1	0.18	0.02
ETX-M00003164	ETX-M00001890	1	0.62	0.01

ETX-M00003165	ETX-M00001907	1	0.21	0.01
ETX-M00003166	ETX-M00001971	1	0.37	0.02
ETX-M00003167	ETX-M00001898	1	0.21	0.06
ETX-M00003168	ETX-M00001878	1	0.24	0.03
ETX-M00003169	ETX-M00001942	1	0.24	0.02
ETX-M00003170	ETX-M00002042	1	0.23	0.02
ETX-M00003171	ETX-M00001881	1	0.09	0.01
ETX-M00003172	ETX-M00001972	1	0.18	0.01
ETX-M00003173	ETX-M00002052	1	0.2	< 0.005
ETX-M00003174	ETX-M00001884	1	0.11	N/A
ETX-M00003175	ETX-M00001990	1	0.29	0.02
ETX-M00003176	ETX-M00002031	1	0.16	0.01
ETX-M00003177	ETX-M00001967	1	0.23	< 0.005

EXAMPLE 15: Confirmation of siRNA Activity in a Human hydrodynamic injection (HDI) Mouse Model

Methods

[0606] Transient expression of human mRNA in mice was used to assess the activity of siRNAs against human mRNA sequences. A single subcutaneous dose of siRNAs (0.5 mg/kg) was administered on Day -6. Hydrodynamic injection (HDI) of a plasmid expressing human NR3C2 mRNA was performed on Day 0. The study was terminated, and mRNA expression was analyzed on Day 1. As a negative control, saline was injected in place of an siRNA in the vehicle control group. An overview of the study is shown in Figure 27.

[0607] Female BALB/c mice (n=5) were injected subcutaneously with 0.5 mg/kg of GalNAc-siRNA or with 0.9% saline vehicle. Six days after GalNAc-siRNA injection, the mice received 30 μg/mouse of a plasmid (pcDNA3.1) encoding the human NR3C2 cDNA by hydrodynamic injection. One day after plasmid injection, the animals were sacrificed, and livers were harvested. For the analysis of human target mRNA expression in mouse livers, liver samples were homogenized, RNA was extracted using the MagMAX™ mirVana™ Total RNA Isolation Kit (Thermo-A27828), cDNA was prepared using HiScript® III RT SuperMix for qPCR (+gDNA wiper)(Vazyme-R323), and gene expression of NR3C2 and the plasmid control gene, NEO were measured by RT-qPCR on a Q7 Fast Real-time PCR system (Applied biosystem). Expression levels were calculated using the 2-ΔΔCt method whereby NR3C2 levels were normalised to NEO levels and then normalised to the expression levels in saline-injected controls. qPCR was performed in triplicate on cDNA derived from each well and the mean Ct calculated. Relative NR3C2 expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to NEO and relative to vehicle-injected.

Results

[0608] The siRNAs tested in this study are shown in Table 9 below along with their mean relative expression in the experiment. Activity of all tested siRNAs was in the human HDI mouse model is shown

in Figure 28. As can be seen from Figure 28 and Table 9, a number of siRNAs tested displayed high activity against the human NR3C2 mRNA sequence. Particularly preferred siRNAs for use in the invention are ETX-M00003139 and ETX-M00003137, and these are specifically contemplated through this disclosure, even when not singled out in a specific passage of this disclosure.

Table 9

ETX ID	Alternative Sequence ID	Mean Relative Expression	SEM
ETX-M00002590	ETX M00001882	0.81	0.04
ETX-M00002591	ETX-M00001856	0.76	0.05
ETX-M00002592	ETX-M00001860	0.6	0.07
ETX-M00002655	ETX-M00001870	0.42	0.06
ETX-M00002659	ETX-M00001867	0.55	0.04
ETX-M00002660	ETX-M00001879	0.6	0.06
ETX-M00002661	ETX-M00001891	0.82	0.08
ETX-M00002662	ETX-M00001859	0.85	0.03
ETX-M00002664	ETX-M00001877	0.46	0.06
ETX-M00002665	ETX-M00001897	0.67	0.05
ETX-M00003134	ETX-M00001915	0.52	0.04
ETX-M00003135	ETX-M00001858	0.56	0.05
ETX-M00003136	ETX-M00001865	0.61	0.03
ETX-M00003137	ETX-M00001902	0.38	0.03
ETX-M00003138	ETX-M00001895	0.67	0.06
ETX-M00003139	ETX-M00001922	0.36	0.04
ETX-M00003140	ETX-M00001863	0.86	0.05
ETX-M00003141	ETX-M00001935	0.79	0.05
ETX-M00003142	ETX-M00001954	0.62	0.06
ETX-M00003143	ETX-M00001857	0.83	0.06
ETX-M00003144	ETX-M00002058	0.89	0.03
ETX-M00003145	ETX-M00001937	0.62	0.05
ETX-M00003146	ETX-M00001893	0.81	0.11
ETX-M00003147	ETX-M00001918	0.76	0.04
ETX-M00003148	ETX-M00001903	0.81	0.04
ETX-M00003149	ETX-M00001976	0.6	0.04
ETX-M00003150	ETX-M00001866	0.97	0.07
ETX-M00003151	ETX-M00001889	0.98	0.08
ETX-M00003152	ETX-M00001947	0.89	0.17
ETX-M00003153	ETX-M00001960	0.87	0.07
ETX-M00003154	ETX-M00001945	0.74	0.07
ETX-M00003155	ETX-M00001945	1.03	0.06
ETX-M00003156	ETX-M00001992	0.91	0.05
ETX-M00003157	ETX-M00001864	0.68	0.02
ETX-M00003158	ETX-M00001876	0.62	0.07
ETX-M00003159	ETX-M00002047	1.04	0.12
ETX-M00003160	ETX-M00002018	0.67	0.05
ETX-M00003161	ETX-M00001892	0.84	0.04

ETX-M00003162	ETX-M00001921	0.89	0.07
ETX-M00003163	ETX-M00001861	0.8	0.03
ETX-M00003164	ETX-M00001890	1.1	0.04
ETX-M00003165	ETX-M00001907	1.01	0.08
ETX-M00003166	ETX-M00001971	1.19	0.06
ETX-M00003167	ETX-M00001898	0.99	0.05
ETX-M00003168	ETX-M00001878	0.94	0.04
ETX-M00003169	ETX-M00001942	1.1	0.17
ETX-M00003170	ETX-M00002042	0.6	0.05
ETX-M00003171	ETX-M00001881	0.95	0.06
ETX-M00003172	ETX-M00001972	0.74	0.08
ETX-M00003173	ETX-M00002052	0.74	0.04
ETX-M00003174	ETX-M00001884	1.11	0.08
ETX-M00003175	ETX-M00001990	0.61	0.02
ETX-M00003176	ETX-M00002031	1.18	0.15
ETX-M00003177	ETX-M00001967	0.57	0.08

EXAMPLE 16: DISEASE MODEL PROOF-OF-CONCEPT (PoC) STUDY – HFpEF

Methods

[0609] HFpEF was induced in C57B6N mice fed a high-fat diet (60% kcal from fat) and water containing L-NAME (0.5 g/L) over 11 weeks. Mice were randomized into homogenous treatment groups, according to their echocardiography parameters obtained at week 10 (E/A ratio, E'/A' ratio and ejection fraction confirming HFpEF phenotype) after the induction phase. One group of mice was treated with 10 mg/kg ETX-M00002590 weekly for 6 weeks by subcutaneous injection. Control animals received weekly subcutaneous saline injections. Positive control groups received either eplerenone in their diet (1g/kg diet) or 10 mg/kg empagliflozin by daily oral gavage for a period of 6 weeks (until end of study). All groups remained on a high fat diet and L-NAME drinking water for the duration of the study.

[0610] In week 10 and 17, left ventricular function and dimensions was assessed using two-dimensional echocardiograph (VF16-5 probe, Siemens, Acuson NX3 Elite). Numeric images of the heart were obtained in parasternal long and short-axis views using or not time motion for systolic function. Heart rate left ventricular end-diastolic and end-systolic diameters and volumes, as well as posterior and anterior wall thicknesses in diastole and systole were measured. Left ventricular ejection fraction and fractional shortening were calculated. Diastolic function was assessed using pulse-wave doppler imaging from apical four chambers view of the mitral flow and the mitral annulus. Early (E) and late (A) peak transmitral flow velocity and, the isovolumic relaxation time (IVRT) and annular tissue velocity of the mitral valve (E' and A' peaks) were measured and E/A, as well as E'/A' and E/E' ratios were calculated.

[0611] After the final echocardiography on week 17, arterial and left ventricle pressure were measured. Animals were anesthetized and a 2-cm incision was performed to the right of the trachea to visualize the right carotid artery. The artery was dissected free, and an ultraminiature conductance catheter (Millar probe)

was inserted and advanced into the ascending aorta to measure blood pressure. Thereafter, the catheter was further advanced into the left ventricle to record internal pressure. Systolic, diastolic, and mean arterial pressure were obtained from arterial trace. Left ventricle end-diastolic, end-systolic, and pulsed pressure, as well as tau (relaxation index), dP/dt min and max (relaxation and contractile indices) were measured.

[0612] Data were fitted to a linear model with a single categorical covariate representing the mean effect of the treatment, relative to the Vehicle Control. Treatment groups were compared to the Vehicle Control with one or two-tailed t-tests on their respective covariate (testing for a distinct effect versus the Vehicle Control). P-values were subsequently adjusted for multiple comparisons *via* the FDR-method.

[0613] After 5 weeks of treatment period (week 16), an exercise tolerance test, consisting in gradual increase in running speed until exhaustion was performed on a computerized treadmill (Harvard apparatus). Exercise capacity was evaluated using test duration and distance covered.

[0614] For serum analysis, a biochemical analyzer was used to measure the levels of circulating ALT/AST/ALP, Albumin, Bilirubin, Creatinine, BUN, Ca, Phos, total protein, Cl, Na and K using commercial assays at IDEXX laboratories. ELISA analysis was performed for FGF21 (abcam, ab212160) according to the manufacturer's instructions. Treatment groups were compared to the Vehicle Control with pairwise one or two-tailed Wilcoxon tests. P-values were subsequently adjusted for multiple comparisons *via* the FDR-method.

Results

Disease Model PoC Study – FGF21 levels in mice treated with GalNAc-siRNA to reduce hepatic NR3C2 expression.

[0615] Analysis of serum fibroblast growth factor 21 (FGF21) levels revealed a trend towards increased FGF21 in ETX-M00002590 treated mice (Figure 29).

Disease Model PoC Study – Improved cardiac remodelling in mice treated with ETX-M00002590

[0616] Echocardiography examination in week 17 showed a cardiac remodelling in HFD/L-NAME vehicle mice, with an increase in Left Ventricle (LV) wall thickness, as assessed by anterior and posterior wall thickness in diastole and systole. LV anterior and posterior wall thickness in diastole and systole were improved by treatment with ETX-M00002590 (Figure 30). Eplerenone also led to statistically significant improvements in all four parameters.

Disease Model PoC Study – Improved cardiac function in mice treated with ETX-M00002590

[0617] The HFD/L-NAME model results in mild diastolic dysfunction, and treatment with ETX-M00002590 improved the diastolic function with an increased E'/A' and a decreased E/E' ratios (Figure 31A, B). Eplerenone and Empaglifizon also improved diastolic dysfunction. Arterial blood pressure was

increased by HFD/L-NAME diet and ETX-M00002590 treatment led to significant decrease in blood pressure (Figure 31C, D, E). siRNA treatment led to a statistically significant reduction in LV end-diastolic pressure (Figure 31F) as well as trending improvements in contractility indices (Figure 31G, H) confirming beneficial outcome on cardiac function.

Disease Model PoC Study – No Hyperkalaemia and decreased glucose observed in mice treated with ETX-M00002590

[0618] At termination of HFD/L-NAME model, plasma was collected, and panels of biochemistry parameters were examined. No change in plasma concentration of potassium was observed with any of the treatments (Figure 32A). A decrease in plasma glucose was detected with ETX-M00002590 and empagliflozin (Figure 32B).

Disease Model PoC Study - Mice treated with ETX-M00002590 showed no change in heart weight and a decrease in liver weight.

[0619] At termination of HFD/L-NAME model, organs were collected and a decrease in liver weight was detected with ETX-M00002590 and empagliflozin (Figure 33).

[0620] Overall, ETX-M00002590 treatment achieved beneficial effects on improved diastolic function, while reducing cardiac hypertrophy, arterial pressure, and LV end-diastolic pressure in HFD / L-NAME induced model of HFpEF.

[0621] The present invention is not intended to be limited in scope to the 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.

[0622] 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.

[0623] While the disclosure has been described with reference to the specific embodiments set forth in the following Examples, it should be understood by those skilled in the art that various changes may be made, and equivalents may be substituted without departing from the true spirit and scope of the disclosure. Further, the following Examples are offered by way of illustration and are not intended to limit the scope of the disclosure in any manner. In addition, modifications may be made to adapt to a situation, material, composition of matter, process, process step or steps, to the objective, spirit, and scope of the disclosure.

All such modifications are intended to be within the scope of the disclosure. Standard techniques well known in the art or the techniques specifically described below were utilized.

[0624] The invention also relates to the following numbered clauses:

1. An inhibitor of expression and / or function of NR3C2, wherein said inhibitor is conjugated to one or more ligand moieties.

2. An inhibitor according to clause 1, wherein said inhibitor is an siRNA oligomer.

3. An inhibitor of expression and / or function of NR3C2, wherein said inhibitor is an siRNA oligomer.

4. An inhibitor according to clause 3, wherein said inhibitor comprises an siRNA oligomer conjugated to one or more ligand moieties.

5. An inhibitor of expression and / or function of NR3C2, such as the inhibitor of clauses 1-4, for use in treatment of HFrEF, such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or for use in the treatment of HFpEF.

6. An inhibitor according to clause 1, 2 or 4, wherein said one or more ligand moieties comprise one or more GalNAc ligands or comprise one more GalNAc ligand derivatives.

7. An inhibitor for use according to clause 1, 2 or 4 wherein said one or more ligand moieties comprise one or more GalNAc ligand derivatives.

8. An inhibitor or an inhibitor for use according to one or more preceding clauses, wherein the target of the inhibitor is NR3C2.

9. An inhibitor, or inhibitor for use, according to one or more preceding clauses, 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.

10. An inhibitor, or inhibitor for use, according to clause 9, 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.

11. An inhibitor, or inhibitor for use, according to clause 10, 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

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

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

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; and / or

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; and / or

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; and / or

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

(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.

12. An inhibitor, or inhibitor for use, according to clause 10 or 11, 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.

13. An inhibitor, or inhibitor for use, according to any one of clauses 10 to 12, wherein the reversed internucleoside linkage is a 3'3 reversed linkage.

14. An inhibitor, or inhibitor for use, according to any one of clauses 10 to 12, wherein the reversed internucleoside linkage is a 5'5 reversed linkage.

15. An inhibitor, or inhibitor for use, according to any one of clauses 9 to 14, wherein one or more nucleosides on the first strand and / or the second strand is / are modified, to form modified nucleosides.

16. An inhibitor, or inhibitor for use, according to clause 15, wherein the modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

17. An inhibitor, or inhibitor for use, according to clause 15 or 16, 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.

18. An inhibitor, or inhibitor for use, according to any one of clauses 15 to 17, 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.

19. An inhibitor, or inhibitor for use, according to any one of clauses 15 to 18, wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

20. An inhibitor, or inhibitor for use, according to any one of clauses 15 to 19, 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 (IMUNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid.

21. An inhibitor, or inhibitor for use, according to clause 20, 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.

22. An inhibitor, or inhibitor for use, according to any one of clauses 15 to 21, 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

23. An inhibitor, or inhibitor for use, according to any one of clauses 15 to 22, which 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.

24. An inhibitor, or inhibitor for use, according to any one of clauses 15 to 23, 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.

25. An inhibitor, or inhibitor for use, according to any one of clauses 15 to 24, 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.

26. An inhibitor, or inhibitor for use, according to any one of clauses 15 to 25, wherein the siRNA oligomer further comprises one or more phosphorothioate internucleoside linkages.

27. An inhibitor, or inhibitor for use, according to clause 26, 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 clause 10.

28. An inhibitor, or inhibitor for use, according to clause 26 or 27, 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.

29. An inhibitor, or inhibitor for use according to any one of clauses 9 to 28, 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.

30. An inhibitor, or inhibitor for use according to clause 29, wherein the ligand moiety comprises

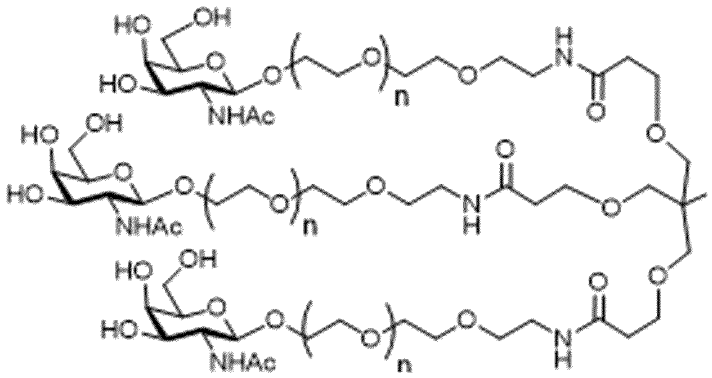
i) one or more GalNAc ligands; and / or

ii) one or more GalNAc ligand derivatives; and / or

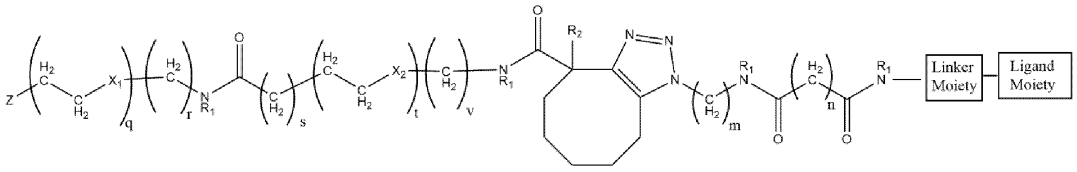
iii) one or more GalNAc ligands and / or GalNAc ligand derivatives conjugated to said SiRNA through a linker.

31. An inhibitor, or inhibitor for use according to clause 30, 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.

32. An inhibitor, or inhibitor for use according to clause 30 or 31, wherein the ligand moiety comprises:



33. An inhibitor, or inhibitor for use according to clause 30 or 31, 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;

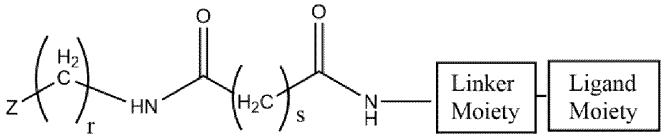
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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.

34. An inhibitor, or inhibitor for use according to clause 30 or 31, having the structure:



wherein:

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

Z is an oligomer.

35. An inhibitor, or inhibitor for use according to one or more preceding clauses, formulated as a pharmaceutical composition with an excipient and / or carrier.

36. A pharmaceutical composition comprising an inhibitor according to one or more preceding clauses, in combination with a pharmaceutically acceptable excipient or carrier.

37. A pharmaceutical composition comprising an inhibitor according to one or more preceding clauses, in combination with a pharmaceutically acceptable excipient or carrier, for use in the treatment of HFrEF, such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or for use in the treatment of HFpEF and/or symptoms thereof.

38. Use of NR3C2 as a target for identifying one or more therapeutic agents for the treatment of HFrEF, such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or for the treatment of HFrEF and/or symptoms thereof.

39. A method of treating HFrEF, such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or for treating HFpEF and/or symptoms thereof, which comprises administering to a patient an inhibitor of NR3C2, such as an inhibitor as defined according to one or more preceding clauses.

40. NR3C2 for use as a biomarker of HFrEF and associated conditions such as ischaemic heart diseases, in particular myocardial infarction, and/or symptoms thereof, and/or a biomarker of HFpEF and/or symptoms thereof.

41. NR3C2 for use in an *in vivo* method of predicting susceptibility to HFrEF, such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or susceptibility to HFpEF and/or symptoms thereof typically by monitoring the sequence and/ or level of expression and / or function of NR3C2 in a sample obtained from a patient.

42. A method of predicting susceptibility to HFrEF, such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or predicting susceptibility to HFpEF and/or symptoms thereof, and optionally treating a disease related to HFrEF, such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or a disease related to HFpEF and/or symptoms thereof in a patient, said method comprising:

(a) obtaining a sample from the patient,

(b) detecting the sequence and / or expression and / or function of NR3C2 in said sample obtained from the patient,

(c) predicting susceptibility to a disease related to HFrEF, such as ischaemic heart disease, or a disease related to HFpEF, based on the sequence and / or expression and / or function of NR3C2 in said sample obtained from the patient,

(d) preferably administering to the diagnosed patient an effective amount of an inhibitor of NR3C2.

43. An inhibitor or composition according to any preceding clause, in the preparation of a medicament for use in the treatment of HFrEF, an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, and/or the treatment of HFpEF and/or symptoms thereof.

44. The inhibitor for use or the composition for use according to any of the preceding clauses, wherein the inhibitor or the composition is administered after myocardial infarction.

45. A nucleic acid for inhibiting expression of NR3C2, comprising 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 NR3C2 gene, and

(ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

46. A nucleic acid for inhibiting expression of NR3C2, comprising 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 NR3C2 gene, and

(ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand modified sequences as listed in Table 3.

47. A nucleic acid according to clause 45 or 46, wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in clause 45 or 46, in particular wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in Tables 2 or 3.

48. A nucleic acid according to clause 45, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

49. A nucleic acid according to clause 46, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

50. A nucleic acid according to clause 45, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

51. A nucleic acid according to clause 46, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.

52. A nucleic acid according to clause 48, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

53. A nucleic acid according to clause 49, wherein the second strand comprises any one of the second strand modified sequences as listed in Table 4.

54. A nucleic acid according to any one of clauses 45-53, wherein the first strand has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 23 nucleosides.

55. A nucleic acid according to any one of clauses 45-54, wherein the second strand has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 21 or 23 nucleosides.

56. A nucleic acid according to any one of clauses 45-55, wherein the duplex region of the nucleic acid is between 17 and 30 nucleosides in length, more preferably is 19 or 21 or 23 nucleosides in length.

57. A nucleic acid according to any one of clauses 45-56, wherein the region of complementarity between the first strand and the portion of RNA transcribed from the NR3C2 gene is between 17 and 30 nucleosides in length.

58. A nucleic acid according to any one of clauses 45-57, wherein the nucleic acid further comprises one or more single-stranded nucleoside overhangs, optionally wherein the overhang is present on the first or second strand, preferably at the 3' terminus of the first or second strand, and/or wherein the overhang comprises 1 to 4 nucleosides, more preferably 2 nucleosides.

59. A nucleic acid according to any one of clauses 45-58, wherein the nucleic acid is an siRNA oligonucleoside.

60. A nucleic acid according to any of clauses 49 or 53, wherein 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 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.

61. A nucleic acid according to clause 50, wherein

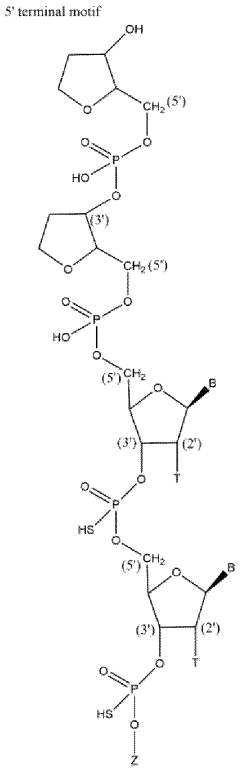
(i) the first strand and the second strand each has a length of 23 nucleosides;

(ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 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 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.

62. A nucleic acid according to clause 50 or 51, wherein the 2 consecutive inverted abasic nucleosides in the 5' terminal region of the second strand present as the following 5' terminal motif



wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of the second strand, and

Z represents the remaining 19 contiguous basic nucleosides of said second strand.

63. A nucleic acid according to any one of clauses 45-62, wherein the nucleic acid is conjugated directly or indirectly to one or more ligand moieties, optionally wherein said ligand moiety is present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

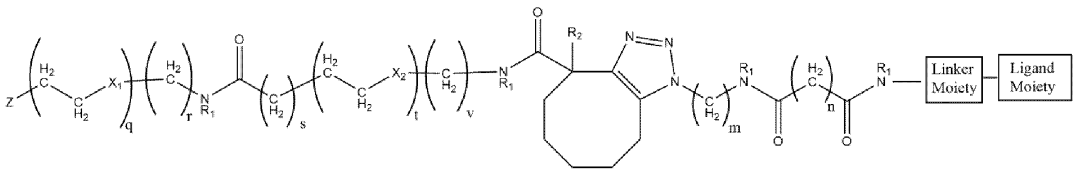
64. A nucleic acid according to clause 63, wherein the ligand moiety comprises:

(i) one or more N-acetyl galactosamine (GalNAc) ligands, and / or

(ii) one or more N-acetyl galactosamine (GalNAc) ligand derivatives.

65. A nucleic acid according to clause 64, 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 nucleic acid, preferably at the 3' terminal region thereof.

66. A nucleic acid according to any one of clauses 63 to 65, comprising the structure:



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;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

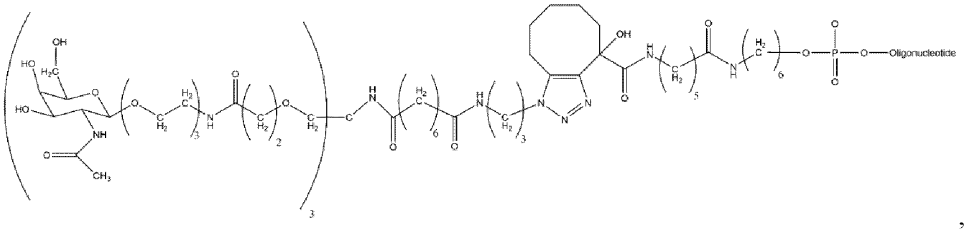
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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;

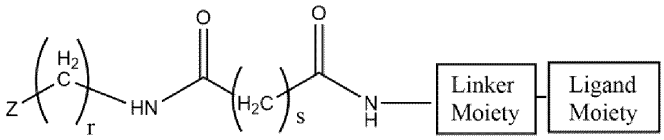
Z is an oligonucleoside moiety.

67. A nucleic acid according to clause 66, comprising the structure:



wherein oligonucleotide represents the contiguous nucleosides of the second strand.

68. A nucleic acid according to any one of clauses 63 to 65, comprising the structure:

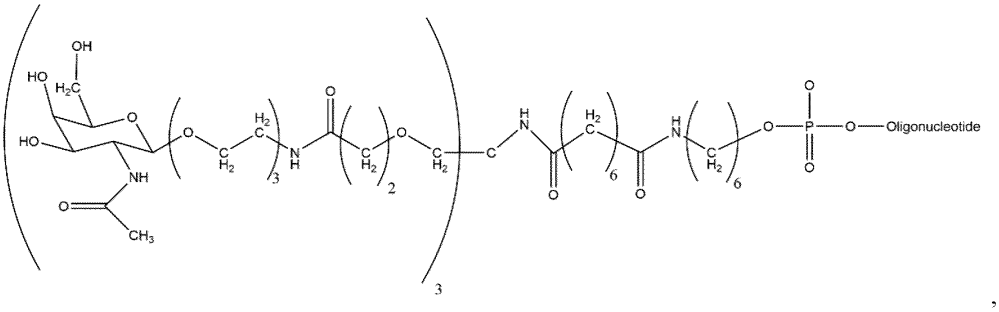


wherein:

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

Z is an oligonucleoside moiety.

69. A nucleic acid according to clause 68, comprising the structure:



wherein oligonucleotide represents the contiguous nucleosides of the second strand.

70. A nucleic acid according to clause 67 or 69, wherein the structure is conjugated to the 3' terminal region of the second strand.

71. A nucleic acid as defined in clauses 62, 67 and 70.

72. A nucleic acid as defined in clauses 62, 69 and 70.

73. A pharmaceutical composition comprising a nucleic acid according to any one of clauses 45-72, in combination with a pharmaceutically acceptable excipient or carrier.

74. A nucleic acid or pharmaceutical composition according to any one of clauses 45-73, for use in therapy.

75. A nucleic acid or pharmaceutical composition according to any one of clauses 45-74, for use in the treatment of HFrEF, such as an ischaemic heart disease, in particular myocardial infarction and/or symptoms thereof, or for use in the treatment of HFpEF and/or symptoms thereof.

76. A nucleic acid or pharmaceutical composition according to clause 75, wherein the nucleic acid or the pharmaceutical composition is administered after myocardial infarction.

77. A nucleic acid according to clause 50, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 228, SEQ ID NO: 238, SEQ ID NO: 243, SEQ ID NO: 235, SEQ ID NO: 245 and SEQ ID NO: 250, preferably SEQ ID NO: 238 or SEQ ID NO: 245.

78. An nucleic according to clause 51, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 674, SEQ ID NO: 684, SEQ ID NO: 689, SEQ ID NO: 681, SEQ ID NO: 691 and SEQ ID NO: 696, Preferably SEQ ID NO: 684 or SEQ ID NO: 691.

79. A nucleic according to clause 52, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 451, SEQ ID NO: 461, SEQ ID NO: 466, SEQ ID NO: 458, SEQ ID NO: 468 and SEQ ID NO: 473, preferably SEQ ID NO: 461 or SEQ ID NO: 468.

80. A nucleic acid according to clause 53, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 897, SEQ ID NO: 907, SEQ ID NO: 912, SEQ ID NO: 904, SEQ ID NO: 914, and SEQ ID NO: 919, preferably SEQ ID NO: 907 or SEQ ID NO: 914.

81. A nucleic acid according to clause 45 or clause 48, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 228	SEQ ID NO: 451
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 243	SEQ ID NO: 466
SEQ ID NO: 235	SEQ ID NO: 458
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 250	SEQ ID NO: 473

, preferably

Unmodified first strand	Unmodified second strand
SEQ ID NO: 238	SEQ ID NO: 461

or

Unmodified first strand	Unmodified second strand
SEQ ID NO: 245	SEQ ID NO: 468

82. A nucleic acid according to clause 46 or clause 49, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 674	SEQ ID NO: 897
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 689	SEQ ID NO: 912
SEQ ID NO: 681	SEQ ID NO: 904
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 696	SEQ ID NO: 919

, preferably

Modified first strand	Modified second strand
SEQ ID NO: 684	SEQ ID NO: 907

or

Modified first strand	Modified second strand
SEQ ID NO: 691	SEQ ID NO: 914

CLAIMS

1. An inhibitor of expression and / or function of NR3C2, for use in the treatment of heart failure with preserved ejection fraction (HFpEF).

2. An inhibitor for use according to claim 1, wherein said inhibitor is conjugated to one or more ligand moieties.

3. An inhibitor for use according to claim 1 or claim 2, wherein said inhibitor is an siRNA oligomer.

4. An inhibitor for use according to claim 3, wherein said one or more ligand moieties comprise one or more GalNAc ligands or comprise one more GalNAc ligand derivatives.

5. An inhibitor for use according to one or more preceding claims, wherein the target of the inhibitor is NR3C2.

6. An inhibitor for use according to one or more preceding claims, 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.

7. An inhibitor for use according to claim 6, 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.

8. An inhibitor for use according to claim 7, 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

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

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

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; and / or

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; and / or

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; and / or

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,

(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.

9. An inhibitor for use according claim 7 or 8, 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. An inhibitor for use according to any one of claims 7 to 9, wherein the reversed internucleoside linkage is a 3'3 reversed linkage.

11. An inhibitor for use according to any one of claims 7 to 9, wherein the reversed internucleoside linkage is a 5’5 reversed linkage.

12. An inhibitor for use according to any one of claims 6 to 11, wherein one or more nucleosides on the first strand and / or the second strand is / are modified, to form modified nucleosides.

13. An inhibitor for use according to claim 12, wherein the modification is a modification at the 2’-OH group of the ribose sugar, optionally selected from 2'-Me or 2’-F modifications.

14. An inhibitor for use according to claim 12 or 13, 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.

15. An inhibitor for use according to any one of claims 12 to 14, 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.

16. An inhibitor for use according to any one of claims 12 to 15, wherein the first and second strand each comprise 2'-Me and 2’-F modifications.

17. An inhibitor for use according to any one of claims 12 to 16, 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 (IMUNA) and a glycol nucleic acid (GNA), preferably a glycol nucleic acid.

18. An inhibitor for use according to claim 17, 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.

19. An inhibitor for use according to any one of claims 12 to 18, 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.

20. An inhibitor for use according to any one of claims 12 to 19, which 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.

21. An inhibitor for use according to any one of claims 12 to 20, 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.

22. An inhibitor for use according to any one of claims 12 to 21, 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.

23. An inhibitor for use according to any one of claims 12 to 22, wherein the siRNA oligomer further comprises one or more phosphorothioate internucleoside linkages.

24. An inhibitor for use according to claim 23, 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 to said terminal region.

25. An inhibitor for use according to claim 23 or 24, 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.

26. An inhibitor for use according to any one of claims 6 to 25, 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.

27. An inhibitor for use according to claim 26, wherein the ligand moiety comprises

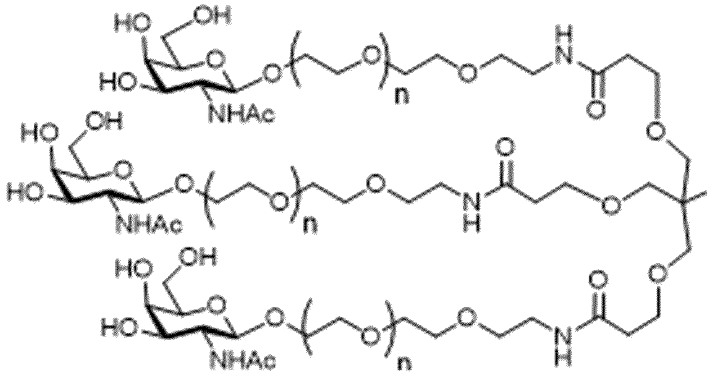
i) one or more GalNAc ligands; and / or

ii) one or more GalNAc ligand derivatives; and / or

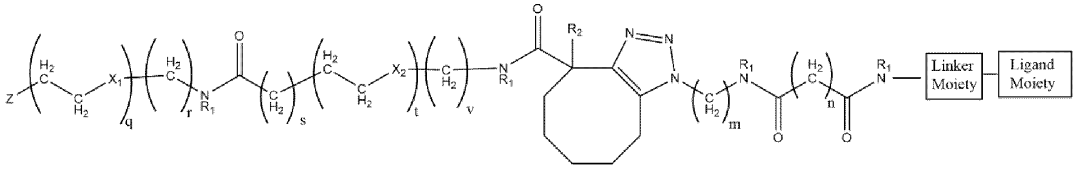
iii) one or more GalNAc ligands and / or GalNAc ligand derivatives conjugated to said siRNA through a linker.

28. An inhibitor for use according to claim 27, 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.

29. An inhibitor for use according to claim 27 or 28, wherein the ligand moiety comprises:



30. An inhibitor for use according to claim 27 or 28, 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;

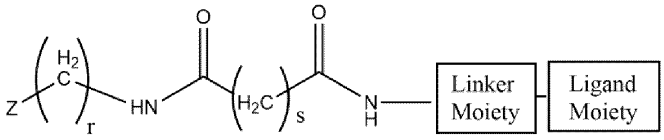
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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.

31. An inhibitor for use according to claim 27 or 28, having the structure:



wherein:

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

Z is an oligomer.

32. An inhibitor for use according to one or more preceding claims, formulated as a pharmaceutical composition with an excipient and / or carrier.

33. A pharmaceutical composition comprising an inhibitor according to any one of the preceding claims, in combination with a pharmaceutically acceptable excipient or carrier, for use in the treatment of HFpEF.

34. Use of NR3C2 as a target for identifying one or more therapeutic agents for the treatment of HFpEF, and/or associated disorders and/or symptoms thereof.

35. A method of treating HFpEF, and/or associated disorders and/or symptoms thereof, which comprises administering to a patient an inhibitor of NR3C2, such as an inhibitor as defined according to one or more preceding claims.

36. NR3C2 for use as a biomarker of HFpEF and/or associated conditions and/or symptoms thereof.

37. NR3C2 for use in an *in vivo* method of predicting susceptibility to HFpEF, and/or associated disorders and/or symptoms thereof, typically by monitoring the sequence and/ or level of expression and / or function of NR3C2 in a sample obtained from a patient.

38. A method of predicting susceptibility to HFpEF, and optionally treating a disease related to HFpEF, in a patient, said method comprising:

(a) obtaining a sample from the patient,

(b) detecting the sequence and / or expression and / or function of NR3C2 in said sample obtained from the patient,

(c) predicting susceptibility to a disease related to HFpEF, based on the sequence and / or expression and / or function of NR3C2 in said sample obtained from the patient,

(d) preferably administering to the diagnosed patient an effective amount of an inhibitor of NR3C2.

39. An inhibitor or composition according to any preceding claim, in the preparation of a medicament for use in the treatment of HFpEF.

40. A nucleic acid for inhibiting expression of NR3C2, comprising 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 NR3C2 gene, and

(ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

41. A nucleic acid for inhibiting expression of NR3C2, comprising 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 NR3C2 gene, and

(ii) comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand modified sequences as listed in Table 3.

42. A nucleic acid according to claim 40 or 41, wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in claim 40 or 41, in particular wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in Tables 2 or 3.

43. A nucleic acid according to claim 40, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 2, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

44. A nucleic acid according to claim 41, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand modified sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

45. A nucleic acid according to claim 40, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

46. A nucleic acid according to claim 41, wherein the first strand comprises any one of the first strand modified sequences as listed in Table 3.

47. A nucleic acid according to claim 43, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

48. A nucleic acid according to claim 44, wherein the second strand comprises any one of the second strand modified sequences as listed in Table 4.

49. A nucleic acid according to any one of claims 40-48, wherein the first strand has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 23 nucleosides.

50. A nucleic acid according to any one of claims 40-49, wherein the second strand has a length in the range of 17 to 30 nucleosides, preferably 19 to 25 nucleosides, more preferably 19 or 21 or 23 nucleosides.

51. A nucleic acid according to any one of claims 40-50, wherein the duplex region of the nucleic acid is between 17 and 30 nucleosides in length, more preferably is 19 or 21 or 23 nucleosides in length.

52. A nucleic acid according to any one of claims 40-51, wherein the region of complementarity between the first strand and the portion of RNA transcribed from the NR3C2 gene is between 17 and 30 nucleosides in length.

53. A nucleic acid according to any one of claims 40-52, wherein the nucleic acid further comprises one or more single-stranded nucleoside overhangs, optionally wherein the overhang is present on the first or second strand, preferably at the 3' terminus of the first or second strand, and/or wherein the overhang comprises 1 to 4 nucleosides, more preferably 2 nucleosides.

54. A nucleic acid according to any one of claims 40-53, wherein the nucleic acid is an siRNA oligonucleoside.

55. A nucleic acid according to any of claims 44 or 48, wherein 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 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.

56. A nucleic acid according to claim 45, wherein

(i) the first strand and the second strand each has a length of 23 nucleosides;

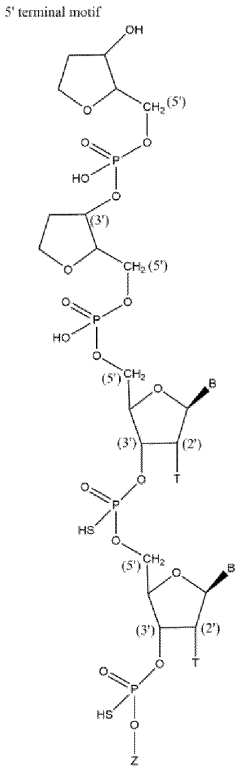
(ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 5' near terminal region of the second strand, wherein a first phosphorothioate internucleoside linkage

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 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.

57. A nucleic acid according to claim 45 or claim 46, wherein the 2 consecutive inverted abasic nucleosides in the 5' terminal region of the second strand present as the following 5' terminal motif:



wherein:

T represents a 2'Me ribose modification,

B represents the nucleoside bases of the first two basic nucleosides in the 5' terminal region of the second strand, and

Z represents the remaining 19 contiguous basic nucleosides of said second strand.

58. A nucleic acid according to any one of claims 40-57, wherein the nucleic acid is conjugated directly or indirectly to one or more ligand moieties, optionally wherein said ligand moiety is present at a terminal region of the second strand, preferably at the 3' terminal region thereof.

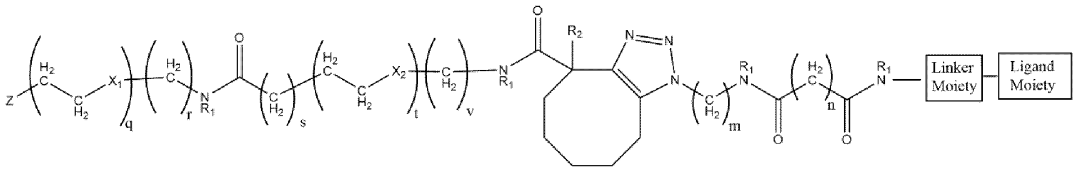
59. A nucleic acid according to claim 58, wherein the ligand moiety comprises:

(i) one or more N-acetyl galactosamine (GalNAc) ligands, and / or

(ii) one or more N-acetyl galactosamine (GalNAc) ligand derivatives.

60. A nucleic acid according to claim 59, 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 nucleic acid, preferably at the 3' terminal region thereof.

61. A nucleic acid according to any one of claims 58 to 60, comprising the structure:



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;

m is an integer of from 1 to 6;

n is an integer of from 1 to 10;

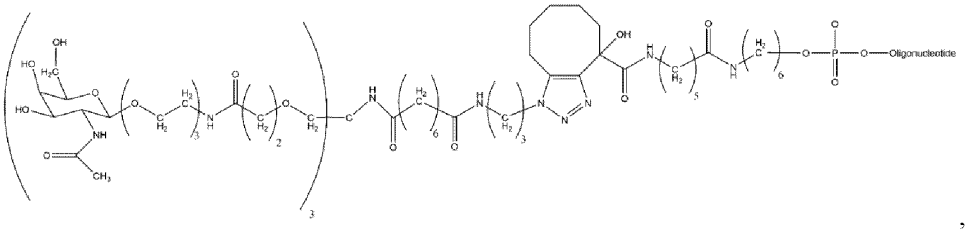
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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;

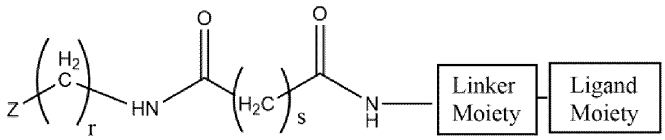
Z is an oligonucleoside moiety.

62. A nucleic acid according to claim 61, comprising the structure:



wherein oligonucleotide represents the contiguous nucleosides of the second strand.

63. A nucleic acid according to any one of claims 58 to 60, comprising the structure:

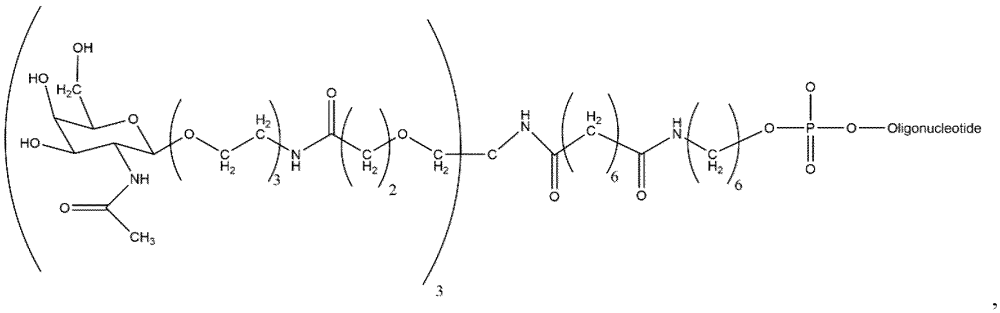


wherein:

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

Z is an oligonucleoside moiety.

64. A nucleic acid according to claim 63, comprising the structure:



wherein oligonucleotide represents the contiguous nucleosides of the second strand.

65. A nucleic acid according to claim 62 or claim 64, wherein the structure is conjugated to the 3' terminal region of the second strand.

66. A nucleic acid as defined in claims 57, 62 and 65.

67. A nucleic acid as defined in claims 57, 64 and 65.

68. A nucleic acid according to claim 45, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 290, SEQ ID NO: 270, SEQ ID NO: 238, SEQ ID NO: 245, SEQ ID NO: 283, SEQ ID NO: 235, SEQ ID NO: 226, SEQ ID NO: 335, SEQ ID NO: 228 or SEQ ID NO: 410, preferably SEQ ID NO: 290, SEQ ID NO: 270, SEQ ID NO: 238, SEQ ID NO: 245 or SEQ ID NO: 283, more preferably SEQ ID NO: 290 or SEQ ID NO: 270.

69. A nucleic according to claim 46, wherein the first strand comprises any one of the following sequences: SEQ ID NO: 736, SEQ ID NO: 716, SEQ ID NO: 684, SEQ ID NO: 691, SEQ ID NO: 729, SEQ ID NO: 681, SEQ ID NO: 672, SEQ ID NO: 781, SEQ ID NO: 674 or SEQ ID NO: 856, preferably SEQ ID NO: 736, SEQ ID NO: 716, SEQ ID NO: 684, SEQ ID NO: 691 or SEQ ID NO: 729, more preferably SEQ ID NO: 736 or SEQ ID NO: 716.

70. A nucleic according to claim 47, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 513, SEQ ID NO: 493, SEQ ID NO: 461, SEQ ID NO: 468, SEQ ID NO: 506, SEQ ID NO: 458, SEQ ID NO: 449, SEQ ID NO: 558, SEQ ID NO: 451 or SEQ ID NO: 633, preferably SEQ ID NO: 513, SEQ ID NO: 493, SEQ ID NO: 461, SEQ ID NO: 468 or SEQ ID NO: 506, more preferably SEQ ID NO: 513 or SEQ ID NO: 493.

71. A nucleic acid according to claim 48, wherein the second strand comprises any one of the following sequences: SEQ ID NO: 959, SEQ ID NO: 939, SEQ ID NO: 907, SEQ ID NO: 914, SEQ ID NO: 952, SEQ ID NO: 904, SEQ ID NO: 895, SEQ ID NO: 1004, SEQ ID NO: 897, SEQ ID NO: 897 or SEQ ID NO: 1079, preferably SEQ ID NO: 959, SEQ ID NO: 939, SEQ ID NO: 907, SEQ ID NO: 914 or SEQ ID NO: 952, more preferably SEQ ID NO: 959 or SEQ ID NO: 939.

72. A nucleic acid according to claim 40 or claim 43, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513
SEQ ID NO: 270	SEQ ID NO: 493
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 283	SEQ ID NO: 506
SEQ ID NO: 235	SEQ ID NO: 458
SEQ ID NO: 226	SEQ ID NO: 449
SEQ ID NO: 335	SEQ ID NO: 558
SEQ ID NO: 228	SEQ ID NO: 451

SEQ ID NO: 410	SEQ ID NO: 633

73. A nucleic acid according to claim 45 or claim 48, 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 combinations of first and second sequences:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513
SEQ ID NO: 270	SEQ ID NO: 493
SEQ ID NO: 238	SEQ ID NO: 461
SEQ ID NO: 245	SEQ ID NO: 468
SEQ ID NO: 283	SEQ ID NO: 506

74. A nucleic acid according to claim 45 or claim 48, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 290	SEQ ID NO: 513

75. A nucleic acid according to claim 45 or claim 48, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 270	SEQ ID NO: 493

76. A nucleic acid according to claim 41 or claim 44, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 736	SEQ ID NO: 959
SEQ ID NO: 716	SEQ ID NO: 939
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 729	SEQ ID NO: 952
SEQ ID NO: 681	SEQ ID NO: 904
SEQ ID NO: 672	SEQ ID NO: 895
SEQ ID NO: 781	SEQ ID NO: 1004

SEQ ID NO: 674	SEQ ID NO: 897
SEQ ID NO: 856	SEQ ID NO: 1079

77. A nucleic acid according to claim 41 or claim 44, 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 combinations of first and second sequences:

Modified first strand	Modified second strand
SEQ ID NO: 736	SEQ ID NO: 959
SEQ ID NO: 716	SEQ ID NO: 939
SEQ ID NO: 684	SEQ ID NO: 907
SEQ ID NO: 691	SEQ ID NO: 914
SEQ ID NO: 729	SEQ ID NO: 952

78. A nucleic acid according to claim 41 or claim 44, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 736	SEQ ID NO: 959

79. A nucleic acid according to claim 41 or claim 44, comprising first and second strands that comprise, consist of, or consist essentially of a nucleoside sequence differing by 0 or 1 nucleosides from the following first and second sequence:

Unmodified first strand	Unmodified second strand
SEQ ID NO: 716	SEQ ID NO: 939

80. A pharmaceutical composition comprising a nucleic acid according to any one of claims 40-79, in combination with a pharmaceutically acceptable excipient or carrier.

81. A nucleic acid or pharmaceutical composition according to any one of claims 40-80, for use in therapy.

82. A nucleic acid or pharmaceutical composition according to any one of claims 40-80, for use in the treatment of HFrEF, such as an ischaemic heart disease, in particular myocardial infarction, and/or symptoms thereof.

83. A nucleic acid or pharmaceutical composition according to claim 81 or claim 82, wherein the nucleic acid or the pharmaceutical composition is administered after myocardial infarction.

84. A nucleic acid or pharmaceutical composition according to any one of claims 40-80, for use in the treatment of HFpEF and/or symptoms thereof.