Claims

1. A nucleic acid for inhibiting expression of *LPA* in a cell, comprising at least one duplex region that comprises at least a portion of a first strand and at least a portion of a second strand that is at least partially complementary to the first strand, wherein said first strand is at least partially complementary to at least a portion of RNA transcribed from the *LPA* gene, wherein said first strand comprises a nucleotide sequence selected from the following sequences: SEQ ID NO: 9, 5, 1, 3, 7, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 or 43.

2. The nucleic acid of claim 1, wherein said first strand comprises a nucleotide sequence of SEQ ID NO: 9, and optionally wherein said second strand comprises a nucleotide sequence of SEQ ID NO: 10; or wherein said first strand comprises a nucleotide sequence of SEQ ID NO: 5, and optionally wherein said second strand comprises a nucleotide sequence of SEQ ID NO: 6.

3. A nucleic acid for inhibiting expression of *LPA* in a cell, comprising at least one duplex region that comprises at least a portion of a first strand and at least a portion of a second strand that is at least partially complementary to the first strand, wherein said first strand is at least partially complementary to at least a portion of RNA transcribed from the *LPA* gene, wherein said first strand comprises a nucleotide sequence selected from the following sequences: SEQ ID NO: 63, 65, 67, 69, 71 or 73.

4. The nucleic acid of any of the preceding claims, wherein said first strand and/or said second strand are each from 17-35 nucleotides in length.

5. The nucleic acid of any of the preceding claims, wherein the at least one duplex region consists of 17-25, preferably 19-25, consecutive nucleotide base pairs.

6. The nucleic acid of any of the preceding claims, wherein the nucleic acid:

   a) is blunt ended at both ends; or
   b) has an overhang at one end and a blunt end at the other; or
   c) has an overhang at both ends.

7. The nucleic acid of any of the preceding claims, wherein one or more nucleotides on the first and/or second strand are modified, to form modified nucleotides.

8. The nucleic acid of any of the preceding claims, wherein the nucleic acid comprises a phosphorothioate linkage between the terminal one, two or three 3' nucleotides and/or 5' nucleotides of one or both ends of the first and/or the second strand.

9. The nucleic acid of any of the preceding claims, wherein the nucleic acid is conjugated to a ligand.

10. The nucleic acid of claim 9, wherein the ligand comprises (i) one or more N-acetyl galactosamine (GalNAc) moieties or derivatives thereof, and (ii) a linker, wherein the linker conjugates the at least one GalNAc moiety or derivative thereof to the nucleic acid.

11. The nucleic acid of any of claims 9-10, wherein the nucleic acid is conjugated to a ligand comprising a compound of formula (I):

$$[S\text{-}X^1\text{-}P\text{-}X^2]_3\text{-}A\text{-}X^3 \qquad \text{(I)}$$

wherein:

S represents a saccharide, preferably wherein the saccharide is N-acetyl galactosamine;

X^1 represents C_3-C_6 alkylene or $(\text{-}CH_2\text{-}CH_2\text{-}O)_m(\text{-}CH_2)_2$- wherein m is 1, 2, or 3;

P is a phosphate or modified phosphate, preferably a thiophosphate;

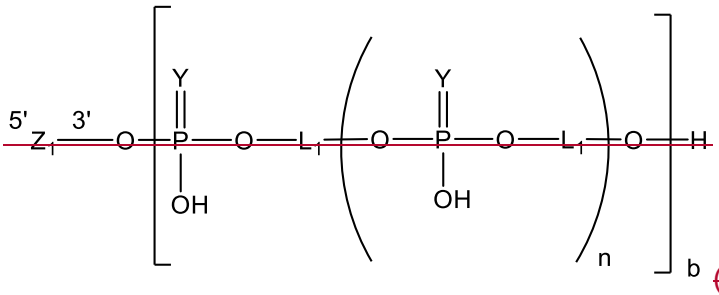
X^2 is alkylene or an alkylene ether of the formula $(\text{-}CH_2)_n\text{-}O\text{-}CH_2$- where n = 1-6;

A is a branching unit;

X^3 represents a bridging unit;

wherein a nucleic acid as defined in any of claims 1 to 8 is conjugated to X^3 via a phosphate or modified phosphate, preferably a thiophosphate.

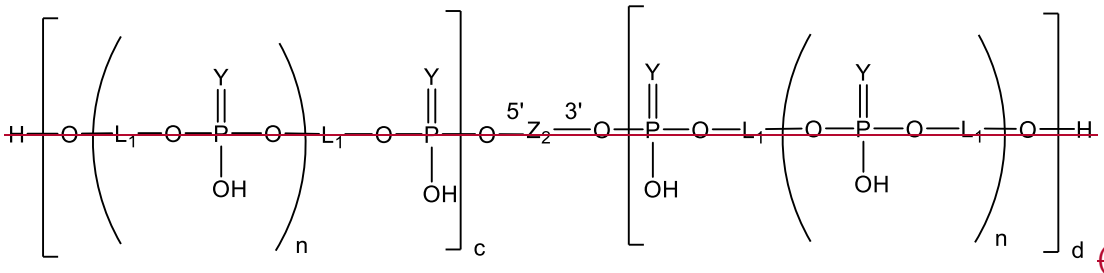
12. The nucleic acid of any of claims 9-10, wherein the first RNA strand is a compound of formula (X):



(X)

wherein b is 0 or 1; and

the second RNA strand is a compound of formula (XI):



(XI);

wherein:

c and d are independently 0 or 1;

Z_1 and Z_2 are the RNA portions of the first and second RNA strands respectively;

Y is O or S;

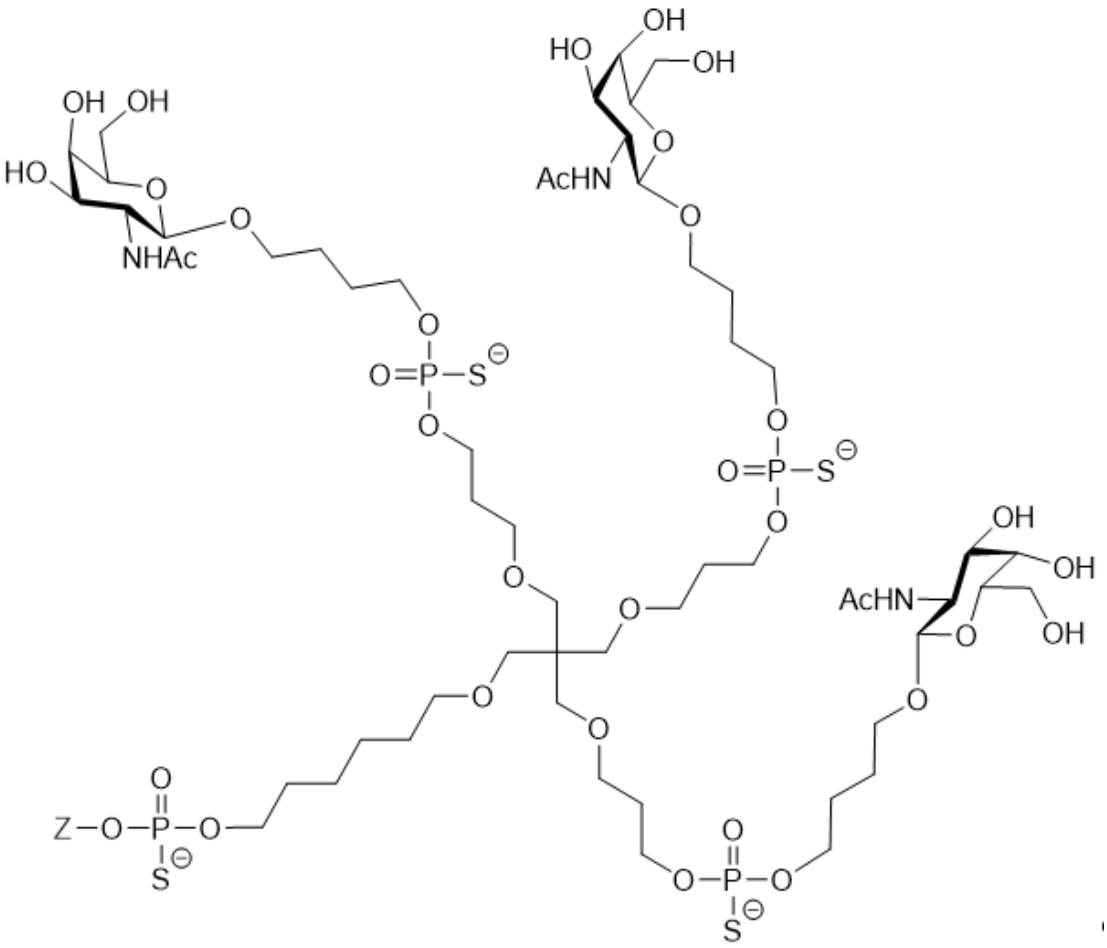
n is 0, 1, 2 or 3; and

L_1 is a linker to which a ligand is attached; and

wherein b + c + d is 2 or 3.

13. A nucleic acid for inhibiting expression of *LPA* in a cell, comprising at least one duplex region that comprises at least a portion of a first strand and at least a portion of a second strand that is at least partially complementary to the first strand, wherein said first strand is at least partially complementary to at least a portion of RNA transcribed from the *LPA* gene, wherein said first strand comprises, and preferably consists of, the nucleotide sequence of SEQ ID NO: 9 and optionally, wherein said second strand comprises, and preferably consists of, the nucleotide sequence of SEQ ID NO. 10.

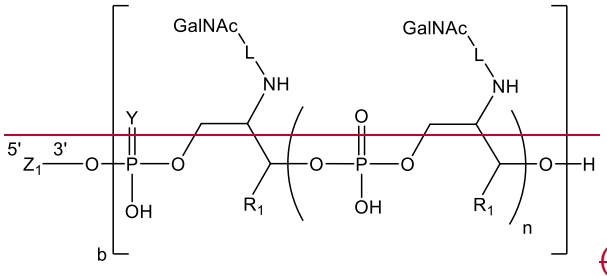
14. The nucleic acid of claim 13, wherein the nucleic acid is conjugated to a ligand and has the following structure



wherein Z is a nucleic acid according ot claim 13.

15. The nucleic acid of claim 14, wherein the nucleic acid comprises two phosphorothioate linkages between each of the three terminal 3' and between each of the three terminal 5' nucleotides on the first strand, and two phosphorothioate linkages between the three terminal nucleotides of the 3' end of the second strand and wherein the ligand is conjugated to the 5' end of the second strand.

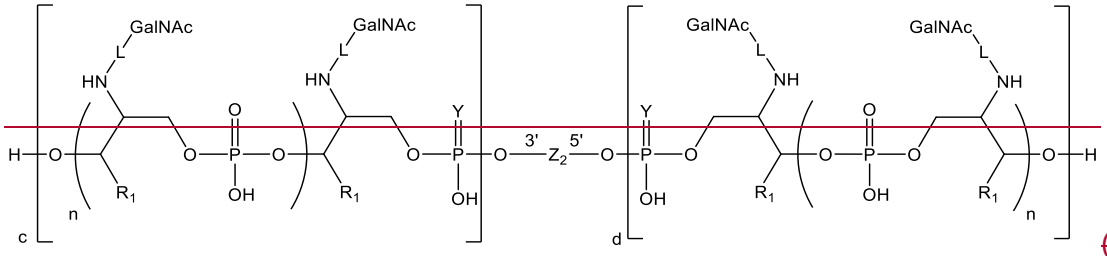
16. The nucleic acid of claim 13, wherein the nucleic acid is conjugated to a ligand, wherein the first RNA strand is a compound of formula (XV):



(XV)

wherein b is 0 or 1; and

the second RNA strand is a compound of formula (XVI):



(XVI);

wherein c and d are independently 0 or 1;

wherein:

Z_1 and Z_2 are the RNA portions of the first and second RNA strands respectively;

Y is O or S;

R_1 is H or methyl;

n is 0, 1, 2 or 3; and

L is the same or different in formulae (XV) and (XVI) and is selected from the group consisting of:

- $-(CH_2)_q-$, wherein q = 2-12;
- $-(CH_2)_r-C(O)-$, wherein r = 2-12;
- $-(CH_2-CH_2-O)_s-CH_2-C(O)-$, wherein s = 1-5;
- $-(CH_2)_t-CO-NH-(CH_2)_t-NH-C(O)-$, wherein t is independently is 1-5;
- $-(CH_2)_u-CO-NH-(CH_2)_u-C(O)-$, wherein u is independently is 1-5; and
- $-(CH_2)_v-NH-C(O)-$, wherein v is 2-12; and

wherein the terminal C(O), if present, is attached to the NH group;

and wherein b + c + d is 2 or 3.

17. The nucleic acid of any of claims 13-16, comprising a sequence and modifications as shown below:

SEQ ID NO:	sequence	modifications
9	5' AUAACUCUGUCCAUUACCG 3	61627171817361527 38
10	5' CGGUAAUGGACAGAGUUAU 3'	38452618463646451 61

wherein, the specific modifications are depicted by numbers

1=2´F-dU,

2=2'F-dA,

3=2´F-dC,

4=2´F-dG,

5=2'-OMe-rU;

6=2'-OMe-rA;

~~7=2'-OMe-rC;~~
~~8=2'-OMe-rG.~~

~~18. The nucleic acid of any of claims 13-16, wherein the nucleotides at positions 2 and 14 from the 5' end of the first strand are modified with a 2' fluoro modification, and the nucleotides on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand are modified with a 2' fluoro modification.~~

~~19. A composition comprising a nucleic acid of any of claims 1-18 and optionally a delivery vehicle and/or a physiologically acceptable excipient and/or a carrier and/or a diluent and/or a buffer and/or a preservative, for use as a medicament, preferably for the prevention or treatment or risk reduction of a disease or pathology, wherein the disease or pathology preferably is a cardiovascular disease, wherein the cardiovascular disease preferably is a stroke, atherosclerosis, thrombosis, a coronary heart disease or aortic stenosis and/or any other disease or pathology associated to elevated levels of Lp(a)-containing particles.~~

~~20. A pharmaceutical composition comprising a nucleic acid of any of claims 1-18 and further comprising a delivery vehicle, preferably liposomes and/or a physiologically acceptable excipient and/or a carrier and/or a diluent.~~

~~21. Use of a nucleic acid of any of claims 1-18 or a pharmaceutical composition of claim 20 for the prevention or treatment or risk reduction of a disease or pathology, wherein the disease or pathology preferably is a cardiovascular disease, wherein the cardiovascular disease preferably is a stroke, atherosclerosis, thrombosis, a coronary heart disease or aortic stenosis and any other disease or pathology associated to elevated levels of Lp(a)-containing particles.~~

~~22. A method of preventing or treating a disease, disorder or syndrome comprising administering a composition comprising a nucleic acid of any of claims 1-18 or a composition according to claims 19-20 to an individual in need of treatment, preferably wherein the nucleic acid or composition is administered to the subject subcutaneously, intravenously or using any other application routes such as oral, rectal or intraperitoneal.~~

Claims

1. A nucleic acid for inhibiting expression of *LPA* in a cell, comprising at least one duplex region that comprises at least a portion of a first strand and at least a portion of a second strand that is at least partially complementary to the first strand, wherein said first strand is at least partially complementary to at least a portion of RNA transcribed from the *LPA* gene, wherein said first strand comprises a nucleotide sequence of SEQ ID NO: 9 and optionally wherein said second strand comprises a nucleotide sequence of SEQ ID NO: 10.

2. The nucleic acid of claim 1, wherein said first strand is 19-35 nucleotides in length and/or said second strand is 17-35 nucleotides in length, optionally wherein the at least one duplex region consists of 17-25, preferably 19-25, consecutive nucleotide base pairs, and further optionally wherein the nucleic acid:

   a) is blunt ended at both ends; or
   b) has an overhang at one end and a blunt end at the other; or
   c) has an overhang at both ends.

3. The nucleic acid of any of the preceding claims, wherein one or more nucleotides on the first and/or second strand are modified, to form modified nucleotides.

4. The nucleic acid of any of the preceding claims, wherein the nucleic acid comprises a phosphorothioate linkage between the terminal two or three 3' nucleotides and/or 5' nucleotides of one or both ends of the first and/or the second strand.

5. The nucleic acid of any of the preceding claims, wherein the nucleic acid is conjugated to a ligand.

6. The nucleic acid of claim 5, wherein the ligand comprises (i) one or more N-acetyl galactosamine (GalNAc) moieties or derivatives thereof, and (ii) a linker, wherein the linker conjugates the at least one GalNAc moiety or derivative thereof to the nucleic acid.

7. The nucleic acid of any of claims 5-6, wherein the nucleic acid is conjugated to a ligand comprising a compound of formula (I):

$$[S\text{-}X^1\text{-}P\text{-}X^2]_3\text{-}A\text{-}X^3\text{-} \quad (I)$$

wherein:

S represents a saccharide, preferably wherein the saccharide is N-acetyl galactosamine;

X^1 represents C_3-C_6 alkylene or $(\text{-}CH_2\text{-}CH_2\text{-}O)_m(\text{-}CH_2)_2\text{-}$ wherein m is 1, 2, or 3;

P is a phosphate or modified phosphate, preferably a thiophosphate;

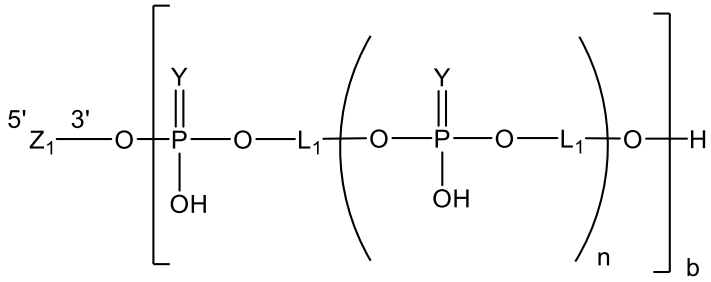
X^2 is alkylene or an alkylene ether of the formula $(\text{-}CH_2)_n\text{-}O\text{-}CH_2\text{-}$ where n = 1-6;

A is a branching unit;

X^3 represents a bridging unit;

wherein a nucleic acid as defined in any of claims 1 to 3 is conjugated to X^3 via a phosphate or modified phosphate, preferably a thiophosphate.

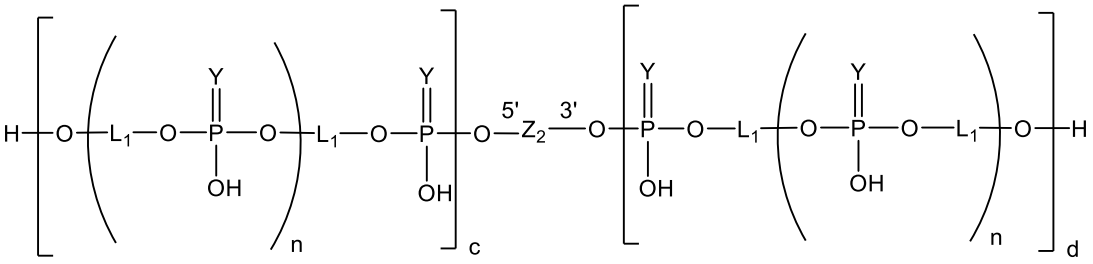
8. The nucleic acid of any of claims 5-6, wherein the first RNA strand is a compound of formula (X):



(X)

wherein b is 0 or 1; and

the second RNA strand is a compound of formula (XI):



(XI);

wherein:

c and d are independently 0 or 1;

Z_1 and Z_2 are the RNA portions of the first and second RNA strands respectively;

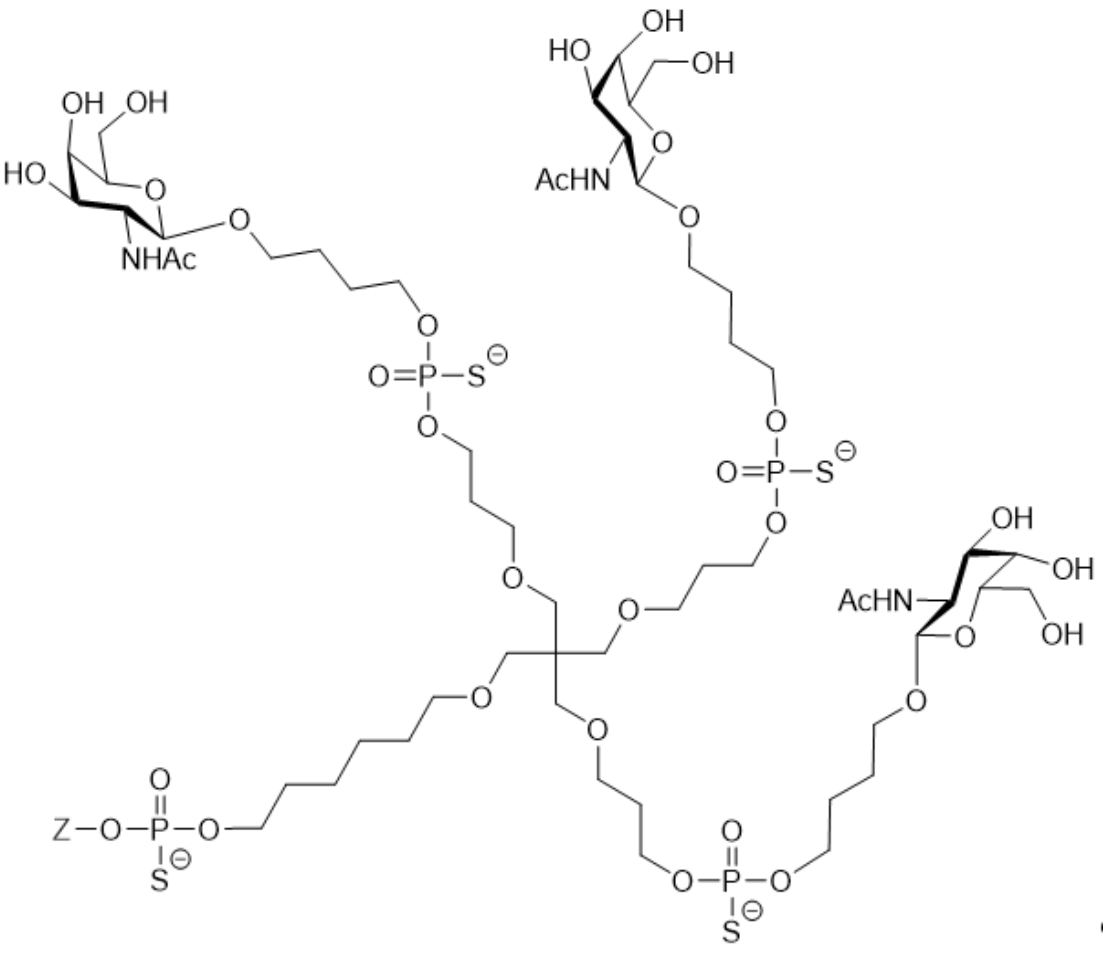
Y is O or S;

n is 0, 1, 2 or 3; and

L_1 is a linker to which a ligand is attached; and

wherein b + c + d is 2 or 3.

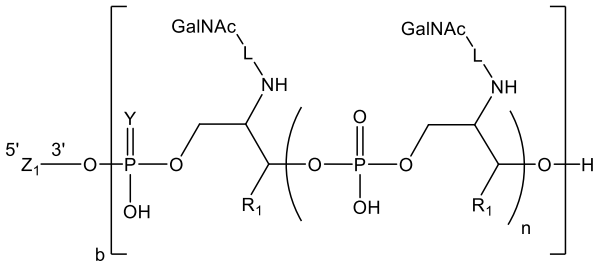
9. The nucleic acid of claim 1, wherein the nucleic acid is conjugated to a ligand and has the following structure



wherein Z is a nucleic acid according to claim 1.

10. The nucleic acid of claim 9, wherein the nucleic acid comprises two phosphorothioate linkages between each of the three terminal 3' and between each of the three terminal 5' nucleotides on the first strand, and two phosphorothioate linkages between the three terminal nucleotides of the 3' end of the second strand and wherein the ligand is conjugated to the 5' end of the second strand.

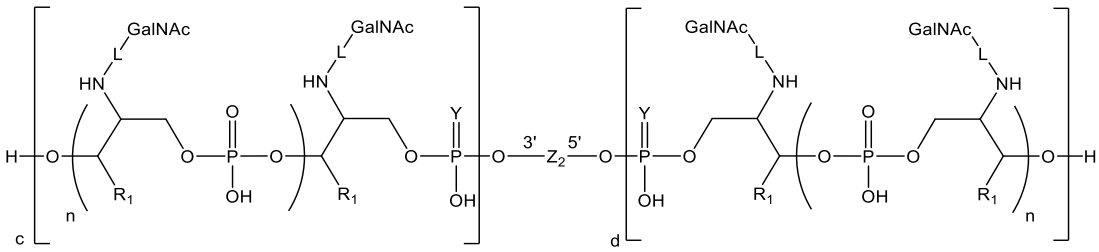
11. The nucleic acid of claim 1, wherein the nucleic acid is conjugated to a ligand, wherein the first RNA strand is a compound of formula (XV):



(XV)

wherein b is 0 or 1; and

the second RNA strand is a compound of formula (XVI):



(XVI)

;

wherein c and d are independently 0 or 1;

wherein:

Z_1 and Z_2 are the RNA portions of the first and second RNA strands respectively;

Y is O or S;

R_1 is H or methyl;

n is 0, 1, 2 or 3; and

L is the same or different in formulae (XV) and (XVI) and is selected from the group consisting of:

$-(CH_2)_q$, wherein q = 2-12;

$-(CH_2)_r-C(O)-$, wherein r = 2-12;

$-(CH_2-CH_2-O)_s-CH_2-C(O)-$, wherein s = 1-5;

$-(CH_2)_t-CO-NH-(CH_2)_t-NH-C(O)-$, wherein t is independently is 1-5;

$-(CH_2)_u-CO-NH-(CH_2)_u-C(O)-$, wherein u is independently is 1-5; and

$-(CH_2)_v-NH-C(O)-$, wherein v is 2-12; and

wherein the terminal C(O), if present, is attached to the NH group;

and wherein b + c + d is 2 or 3.

12. The nucleic acid of any of claims 1 or 9-11, comprising a sequence and modifications as shown below:

SEQ ID NO:	sequence	modifications
9	5’ AUAACUCUGUCCAUUACCG 3	6162717181736152738
10	5’ CGGUAAUGGACAGAGUUAU 3’	3845261846364645161

wherein, the specific modifications are depicted by numbers
1=2´F-dU,
2=2‘F-dA,
3=2´F-dC,
4=2´F-dG,
5=2'-OMe-rU;
6=2'-OMe-rA;
7=2'-OMe-rC;
8=2'-OMe-rG.

13. The nucleic acid of any of claims 1 or 9-11, wherein the nucleotides at positions 2 and 14 from the 5’ end of the first strand are modified with a 2' fluoro modification, and the nucleotides on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand are modified with a 2' fluoro modification.

14. A composition comprising a nucleic acid of any of claims 1-13 and optionally a delivery vehicle and/or a physiologically acceptable excipient and/or a carrier and/or a diluent and/or a buffer and/or a preservative, for use as a medicament, preferably for the prevention or treatment or risk reduction of a disease or pathology, wherein the disease or pathology preferably is a cardiovascular disease, wherein the cardiovascular disease preferably is a stroke, atherosclerosis, thrombosis, a coronary heart disease or aortic stenosis and/or any other disease or pathology associated to elevated levels of Lp(a)-containing particles.

15. A pharmaceutical composition comprising a nucleic acid of any of claims 1-13 and further comprising a delivery vehicle, preferably liposomes and/or a physiologically acceptable excipient and/or a carrier and/or a diluent.

16. The nucleic acid of any of claims 1-13 for use in medicine.

17. Use of a nucleic acid of any of claims 1-13 and optionally a delivery vehicle and/or a physiologically acceptable excipient and/or a carrier and/or a diluent and/or a buffer and/or a preservative, in the manufacture of a medicament for the prevention or treatment or risk reduction of a cardiovascular disease.

18. The use of claim 17, wherein the cardiovascular disease is selected from the group consisting of stroke, atherosclerosis, thrombosis, a coronary heart disease and aortic stenosis.