Claims

1. A nucleic acid for inhibiting expression of a target gene 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 said target gene,
wherein the nucleic acid comprises a phosphorodithioate linkage between the two terminal nucleotides at the 3' end of the first strand,
wherein the nucleic acid comprises a phosphorodithioate linkage between the two terminal nucleotides at the 3' end and between the two terminal nucleotides at the 5' end of the second strand, and
wherein the first strand comprise a linkage other than a phosphorodithioate between the two, three or four terminal nucleotides at the 5' end.

2. The nucleic acid of claim 1, wherein the nucleic acid is conjugated to a ligand comprising a compound of formula (I):

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

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 an unsubstituted phosphate;

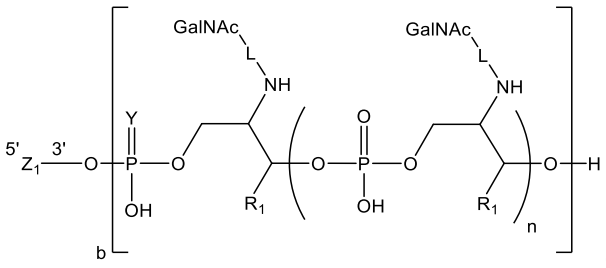
X^2 is alkylene or an alkylene ether of the formula $(\text{-}CH_2)_n\text{-}O\text{-}CH_2\text{-}$ where n = 1-6;

A is a branching unit;

X^3 represents a bridging unit;

wherein a nucleic acid as defined in claim 1 is conjugated to X^3 via a phosphate or modified phosphate.

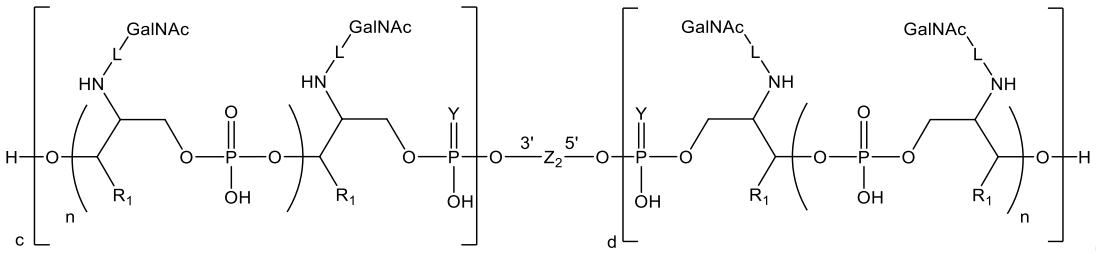
3. The nucleic acid of claim 1, wherein the nucleic acid is conjugated to a ligand, wherein the first RNA strand is a compound of formula (XV):



(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, preferably O;

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.

4. The nucleic acid of any of claims 1-3, wherein the first RNA strand has a terminal 5' (E)-vinylphosphonate nucleotide at its 5' end and wherein the terminal 5' (E)-vinylphosphonate nucleotide is preferably linked to the second nucleotide in the first strand by a phosphodiester linkage.

5. The nucleic acid of any of claims 1-4, wherein the nucleotides of the first strand are modified by a first modification on the odd numbered nucleotides, and modified with

a second modification on the even numbered nucleotides, and the nucleotides of the second strand are modified on the odd numbered nucleotides with the second modification and modified with the first modification on the even numbered nucleotides, wherein the first strand is numbered 5’ to 3’, the 5’-most nucleotide being nucleotide number 1 of the first strand and the second strand is numbered 3' to 5', the 3’-most nucleotide being nucleotide number 1 of the second strand, wherein the first modification is preferably 2’OMe, wherein the second modification is preferably 2’ fluoro, and wherein the nucleic acid is preferably blunt ended at both ends.

6. The nucleic acid of any of claims 1-4, 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 and preferably wherein the remaining nucleotides are modified with a 2’OMe modification.

7 The nucleic acid of any of claims 1-6, wherein all the linkages between the nucleotides of both strands other than the linkage between the two terminal nucleotides at the 3’ end of the first strand and the linkages between the two terminal nucleotides at the 3’ end and at the 5’ end of the second strand are unsubstituted phosphate linkages.

8. A composition comprising a nucleic acid of any of claims 1-7 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.

9. A pharmaceutical composition comprising a nucleic acid of any of claims 1-7 and further comprising a delivery vehicle, preferably liposomes and/or a physiologically acceptable excipient and/or a carrier and/or a diluent.

10. A nucleic acid of any of claims 1-7 or a pharmaceutical composition of claim 9 for use in the prevention or treatment of a disease, disorder or syndrome.

11. The nucleic acid or pharmaceutical composition for use according to claim 10, wherein the nucleic acid or composition is to be administered subcutaneously or intravenously.