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(54) **PHARMACEUTICAL COMPOSITION**

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(2), (4) Date: **Sep. 10, 2009**

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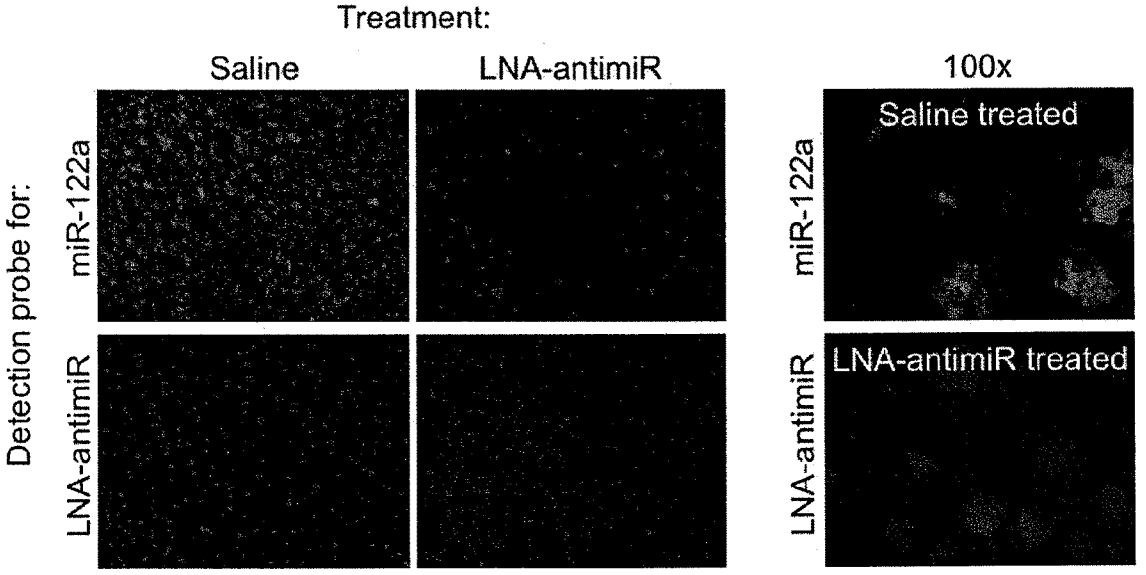
A61P 43/00 (2006.01)

(52) **U.S. Cl.** ..... **514/44 R**

(57) **ABSTRACT**

The invention provides pharmaceutical compositions comprising short single stranded oligonucleotides, of length of between 8 and 17 nucleobases which are complementary to human microRNAs. The short oligonucleotides are particularly effective at alleviating miRNA repression in vivo. It is found that the incorporation of high affinity nucleotide analogues into the oligonucleotides results in highly effective anti-microRNA molecules which appear to function via the formation of almost irreversible duplexes with the miRNA target, rather than RNA cleavage based mechanisms, such as mechanisms associated with RNaseH or RISC.



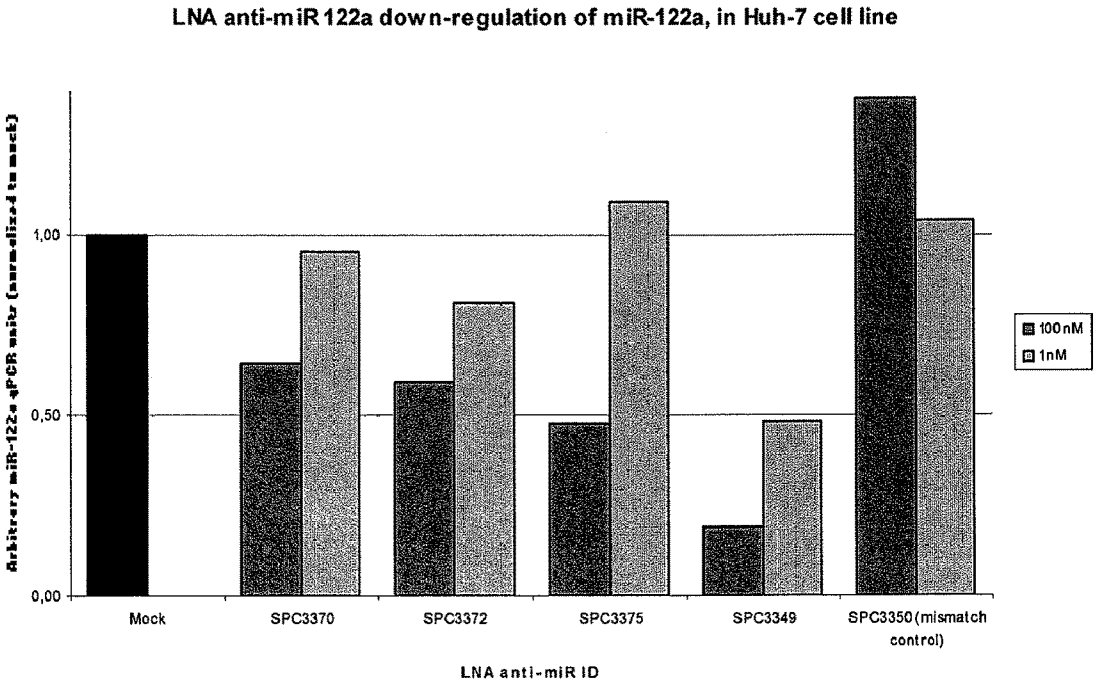

LNA anti-miR122a down-regulation of miR-122a, in Huh-7 cell line
Arbitrary miR-122a qPCR units (normalized to mock)
1,00
0,50
0,00
Mock
SPC3370
SPC3372
SPC3375
SPC3349
SPC3350 (mismatch control)
LNA anti-miR ID
100nM
1nM

Figure 1

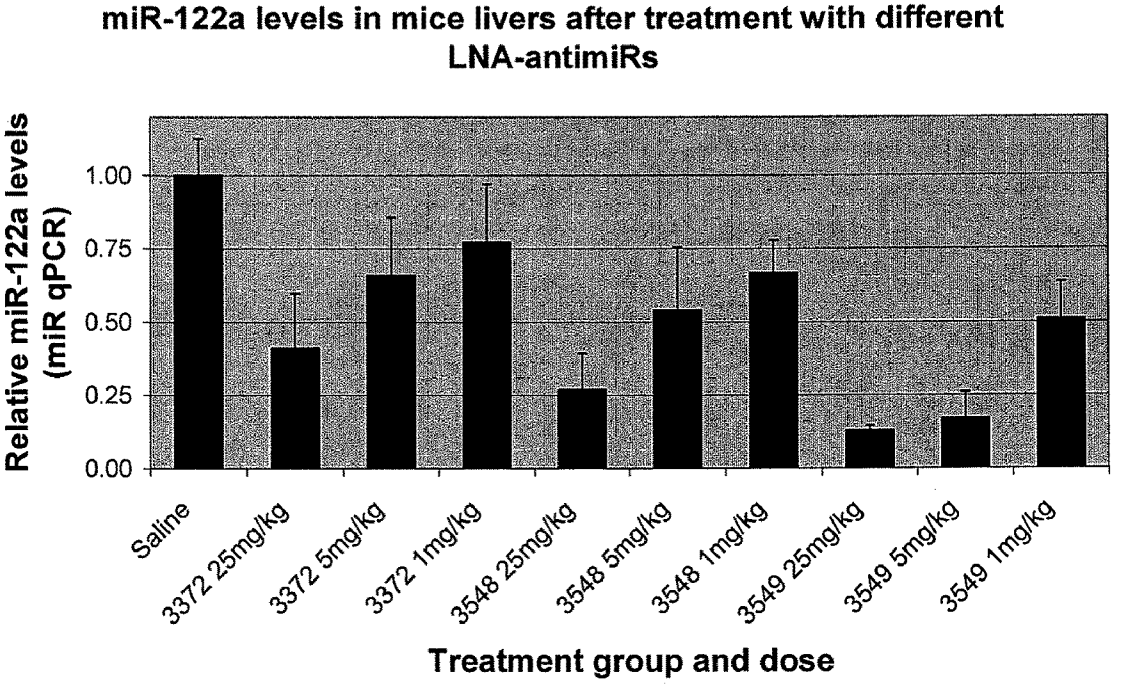


Figure 2

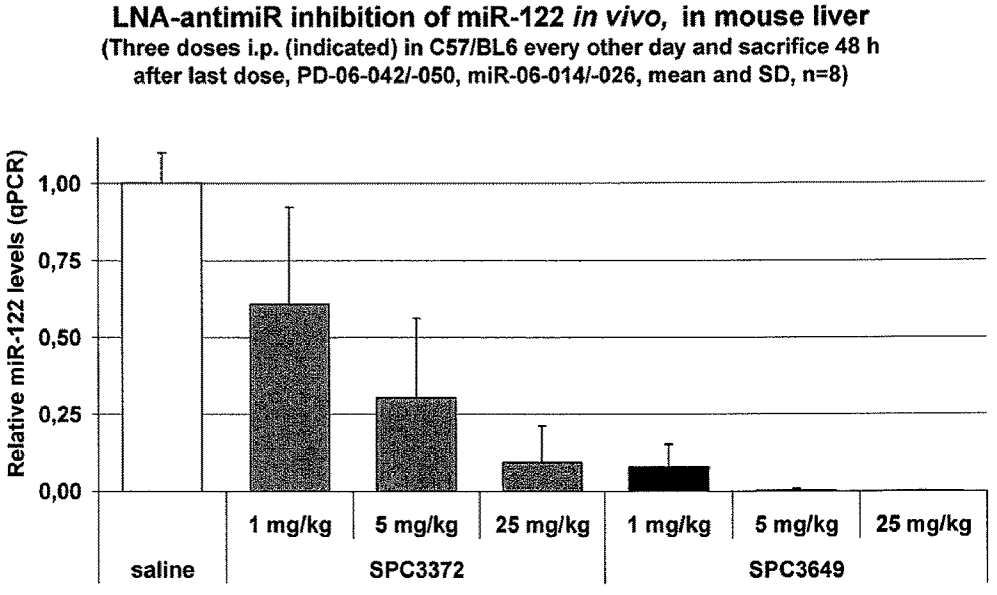
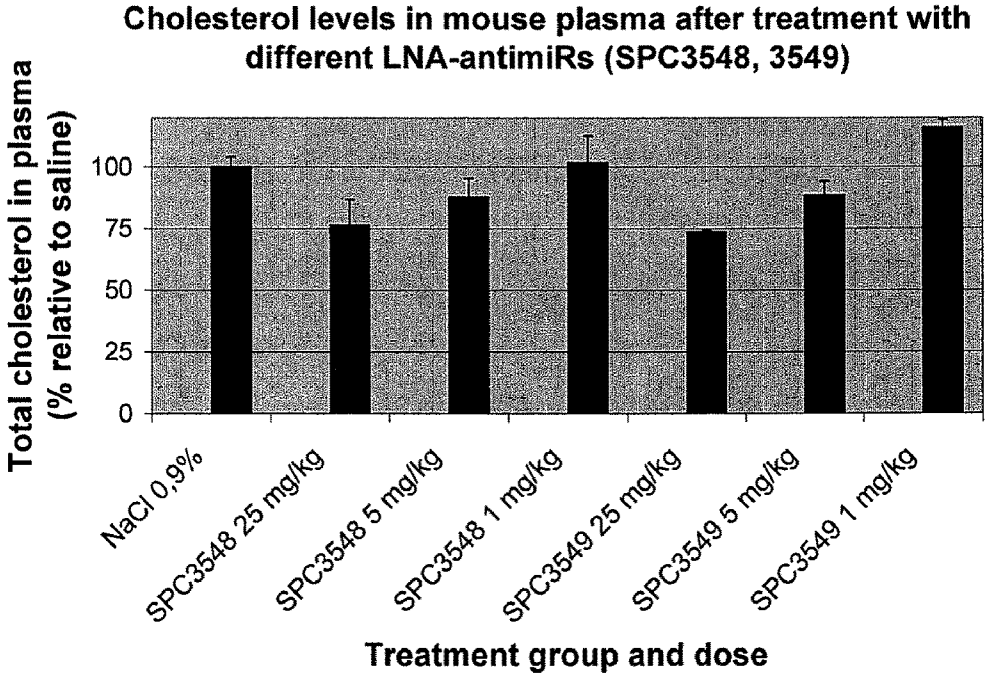


Figure 2b.



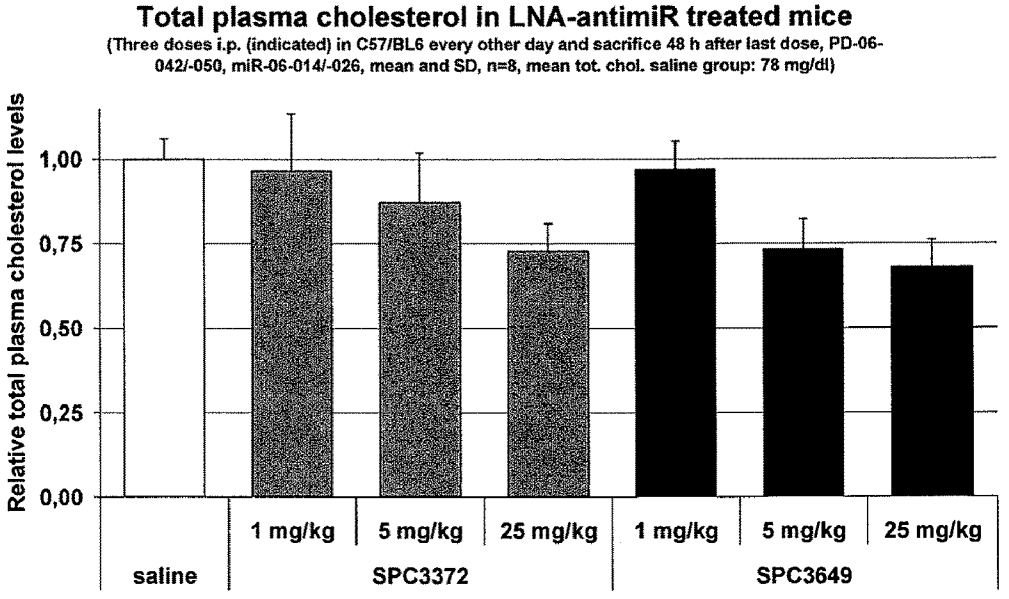


Figure 3 (A and B)

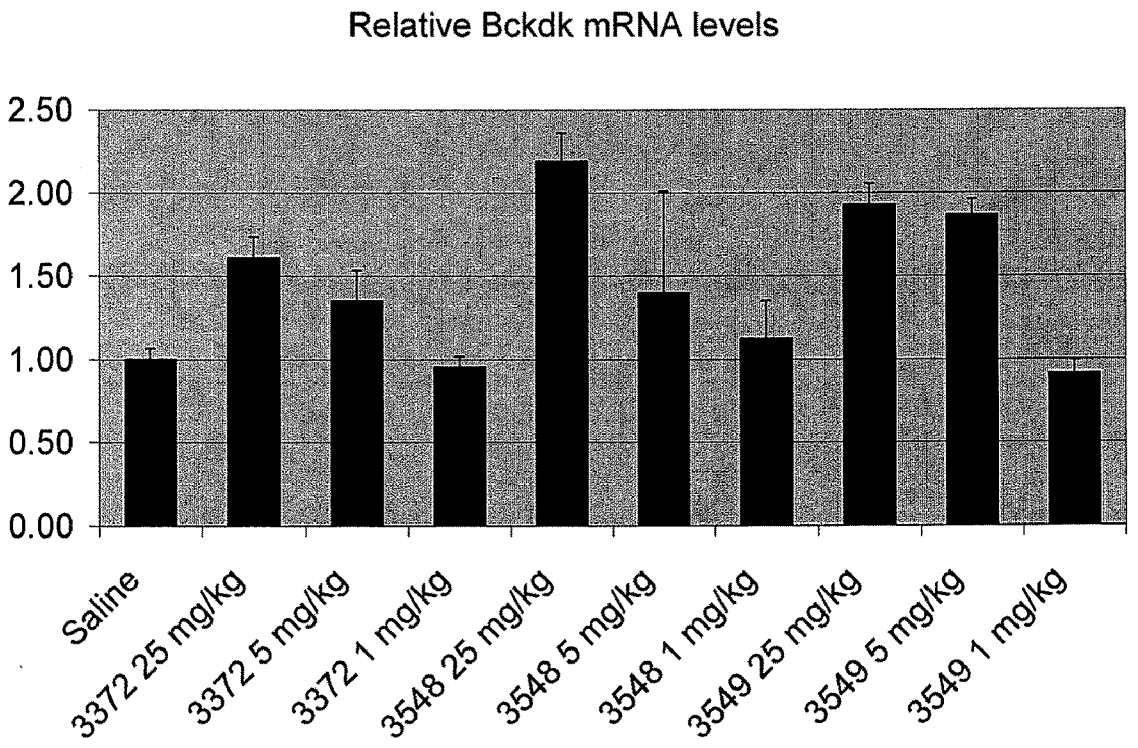

Relative Bckdk mRNA levels
2.50
2.00
1.50
1.00
0.50
0.00
Saline
3372 25 mg/kg
3372 5 mg/kg
3372 1 mg/kg
3548 25 mg/kg
3548 5 mg/kg
3548 1 mg/kg
3549 25 mg/kg
3549 5 mg/kg
3549 1 mg/kg

Figure 4a

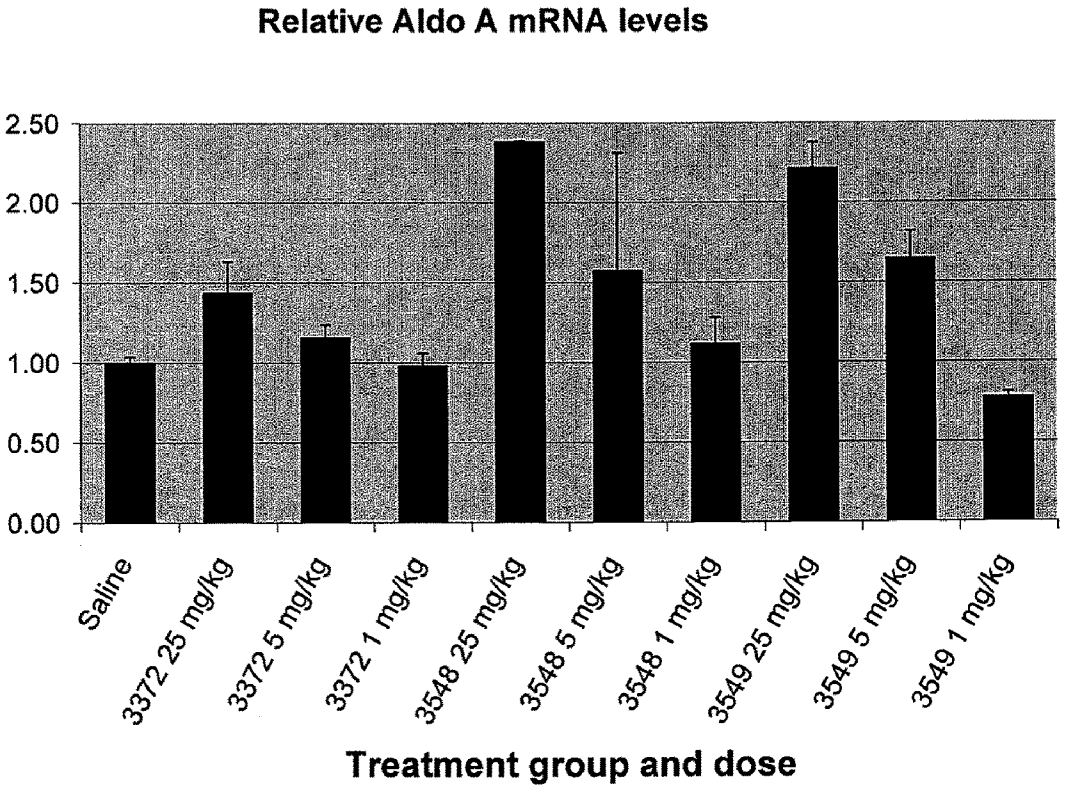

Relative Aldo A mRNA levels
2.50
2.00
1.50
1.00
0.50
0.00
Saline
3372 25 mg/kg
3372 5 mg/kg
3372 1 mg/kg
3548 25 mg/kg
3548 5 mg/kg
3548 1 mg/kg
3549 25 mg/kg
3549 5 mg/kg
3549 1 mg/kg
Treatment group and dose

Figure 4b

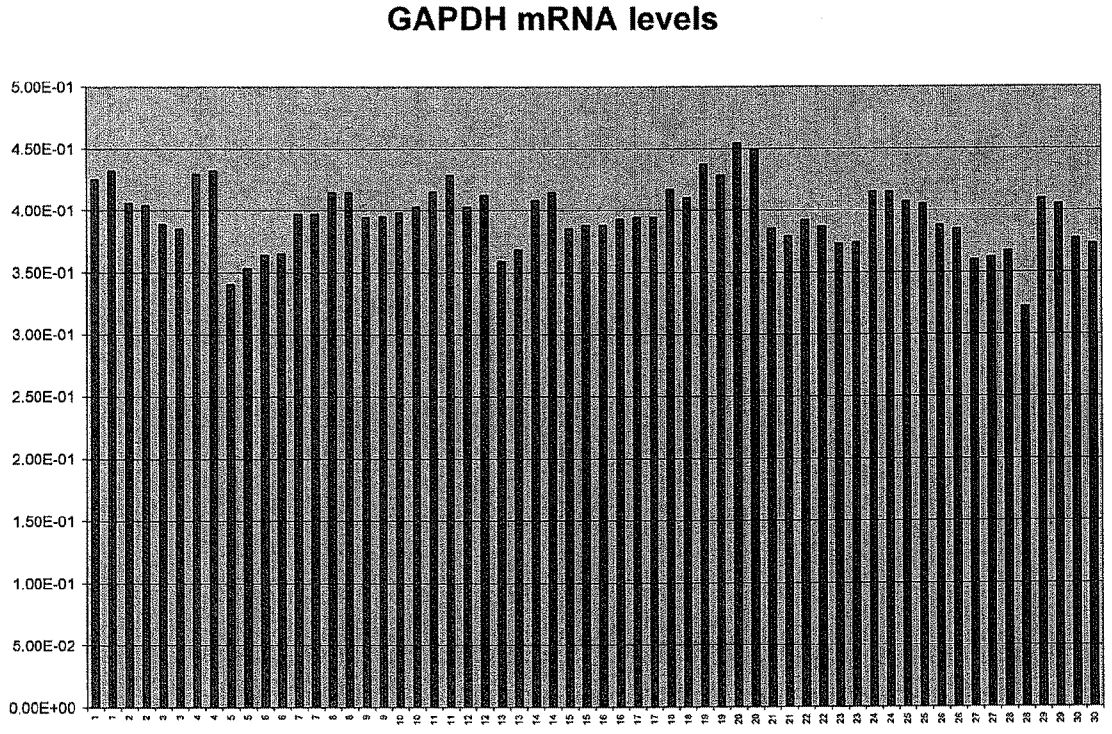

GAPDH mRNA levels
5.00E-01
4.50E-01
4.00E-01
3.50E-01
3.00E-01
2.50E-01
2.00E-01
1.50E-01
1.00E-01
5.00E-02
0.00E+00

Figure 4c

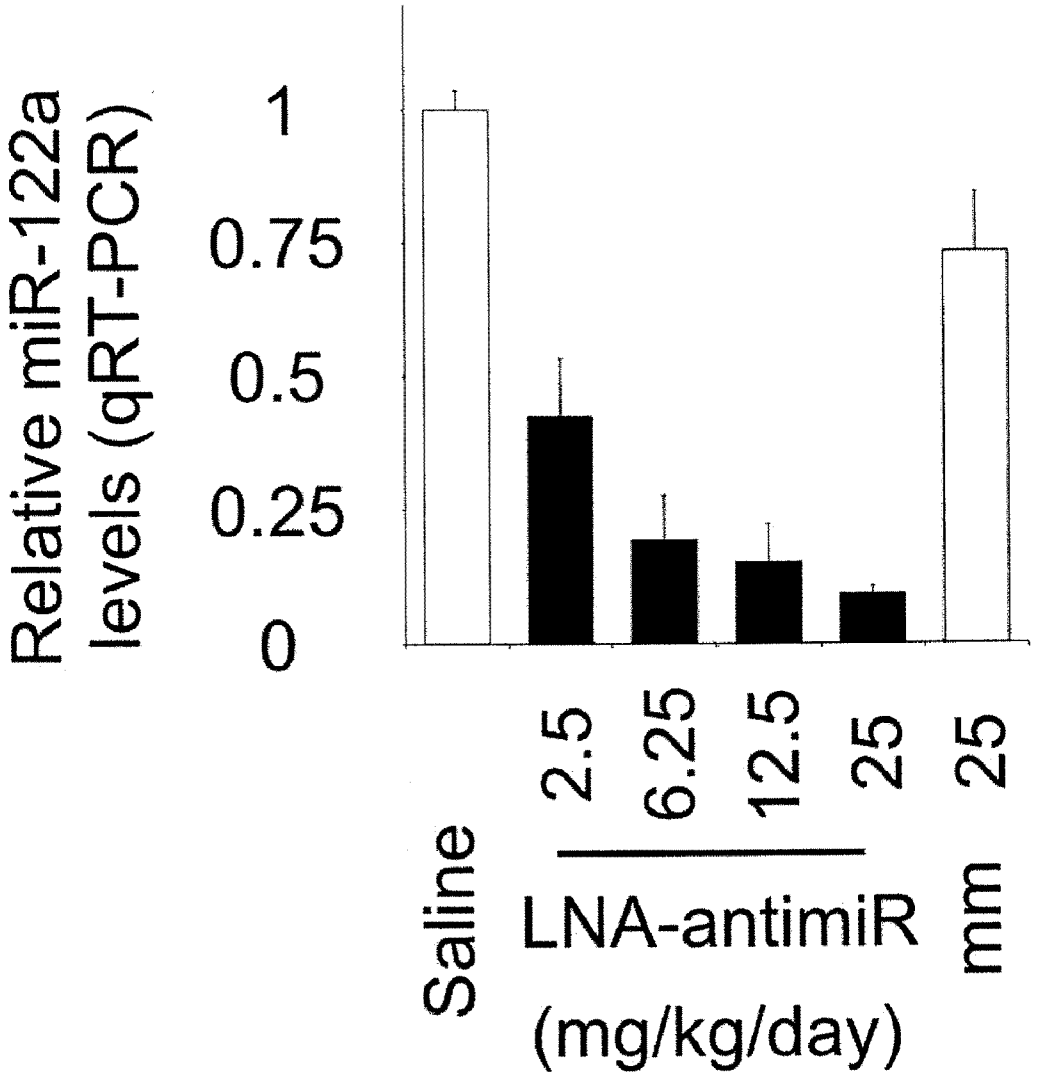


Figure 5

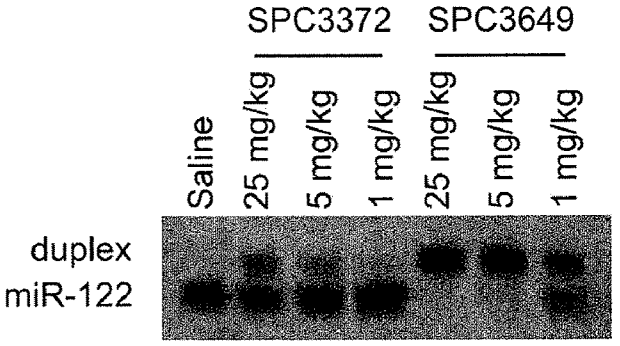


Figure 6

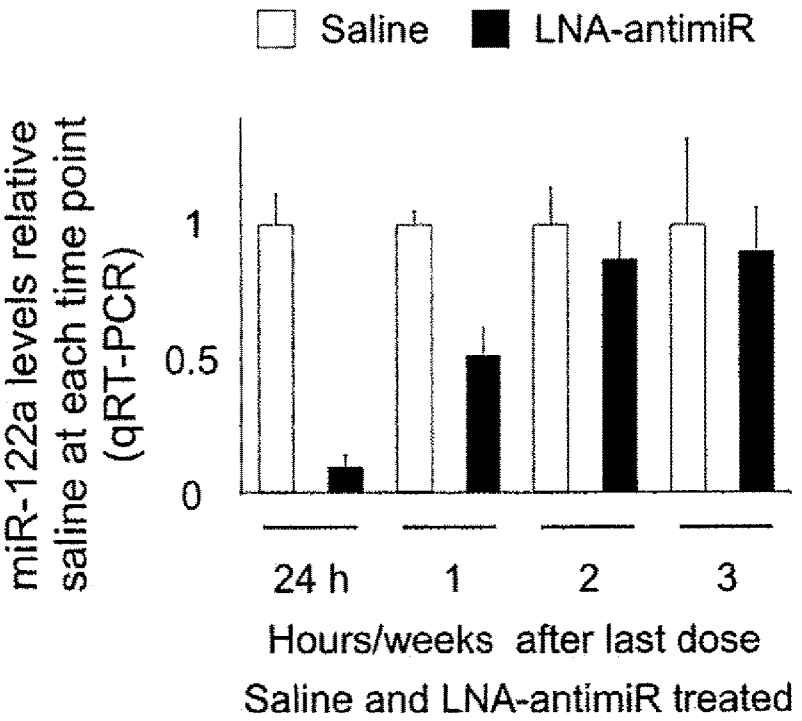


Figure 7

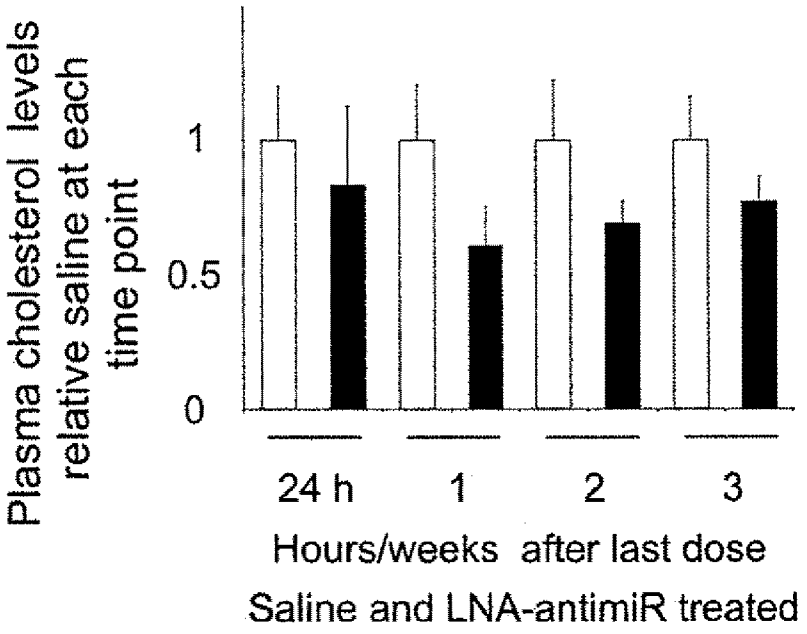


Figure 8

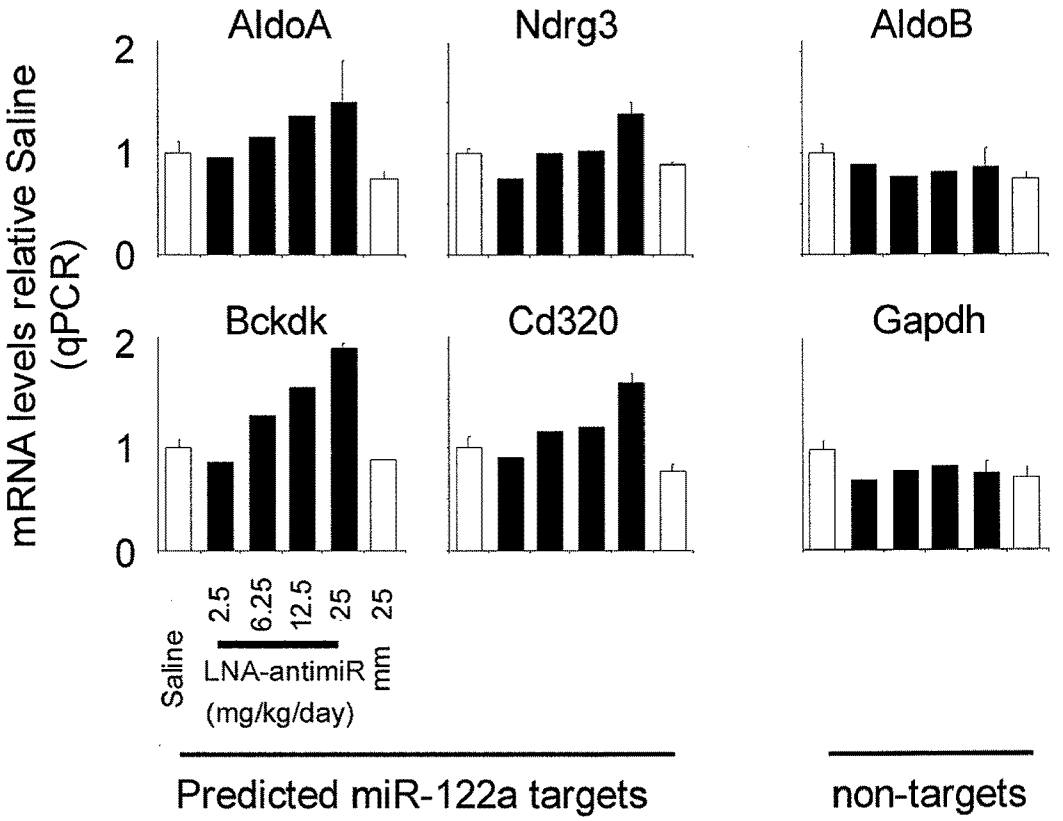


Figure 9

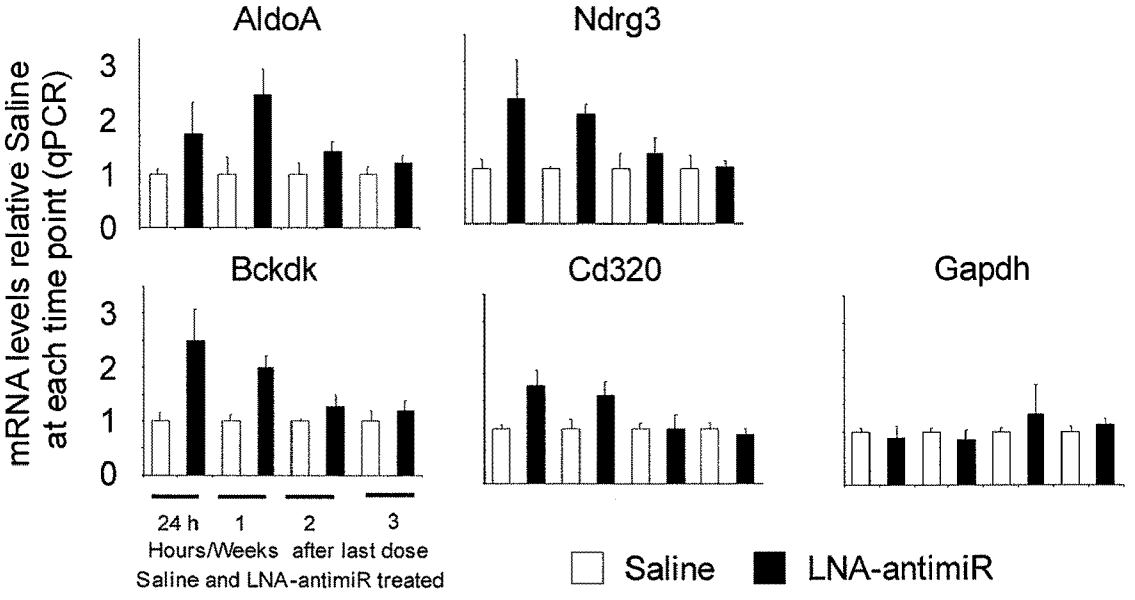


Figure 10

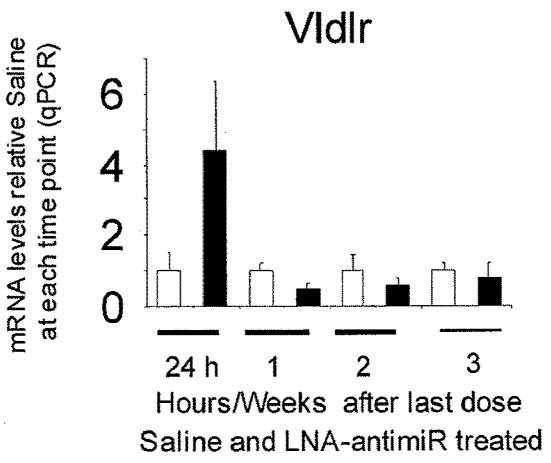


Figure 11

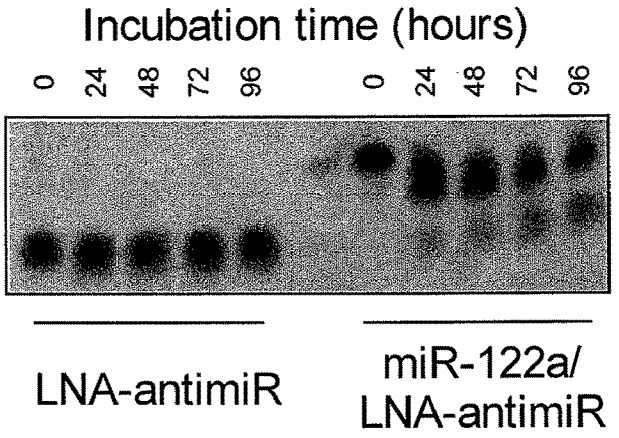


Figure 12

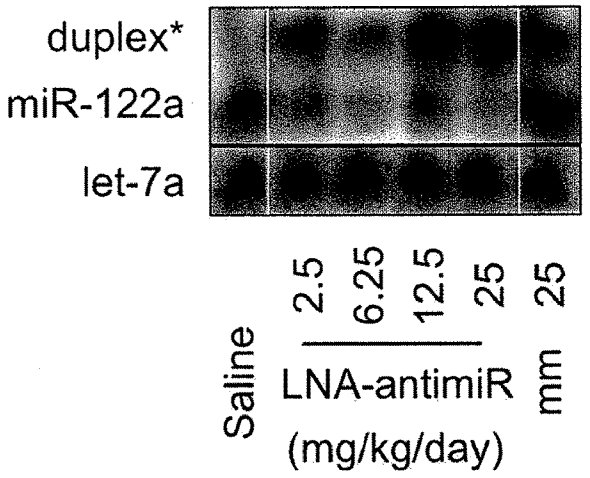


Figure 13

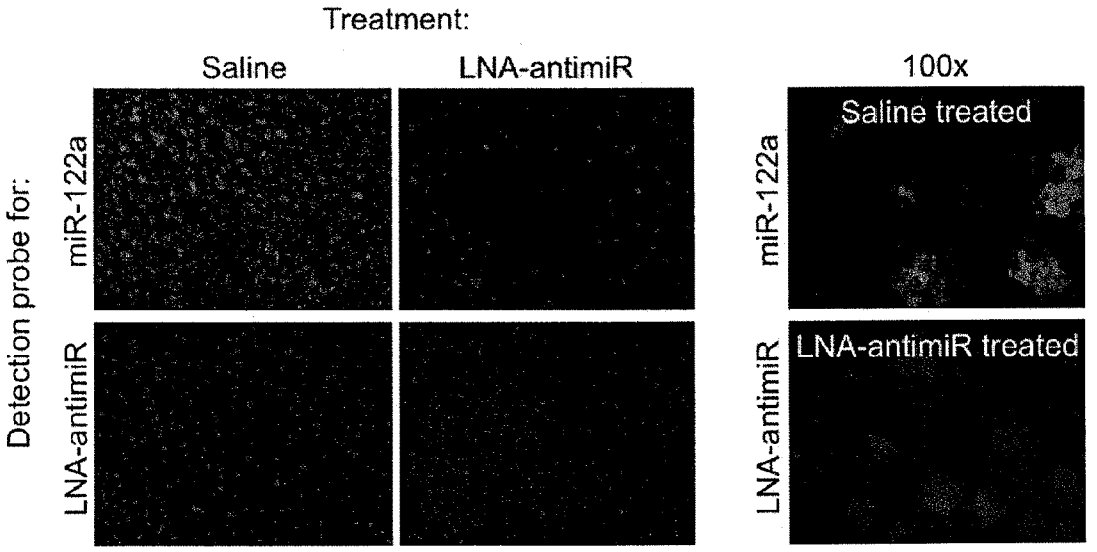

Treatment:
Saline
LNA-antimiR
Detection probe for:
miR-122a
LNA-antimiR
100x
Saline treated
LNA-antimiR treated

Figure 14

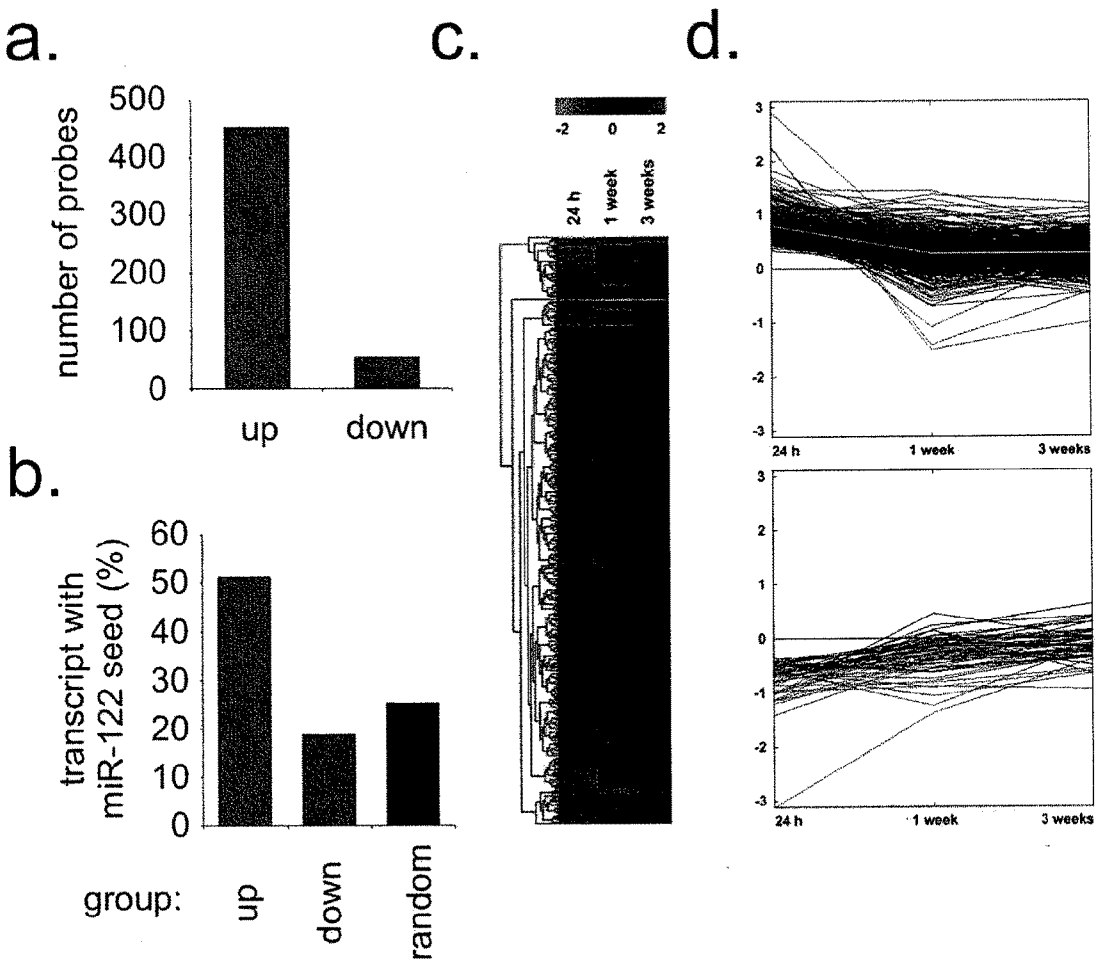

a.
number of probes
500
400
300
200
100
0
up
down
b.
transcript with miR-122 seed (%)
60
50
40
30
20
10
0
group:
up
down
random
c.
-2
0
2
24 h
1 week
3 weeks
d.
3
2
1
0
-1
-2
-3
24 h
1 week
3 weeks

Figure 15

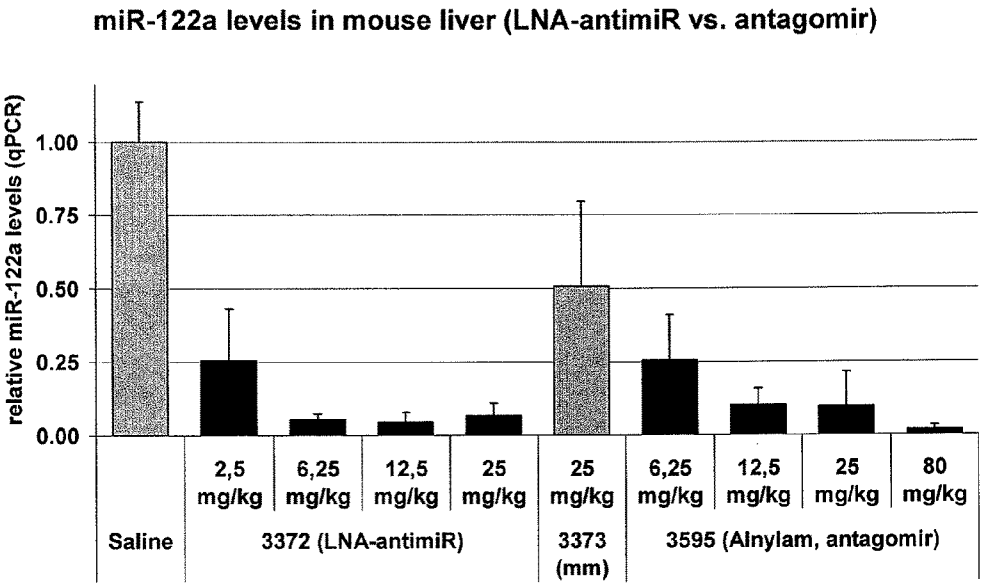


Figure 16

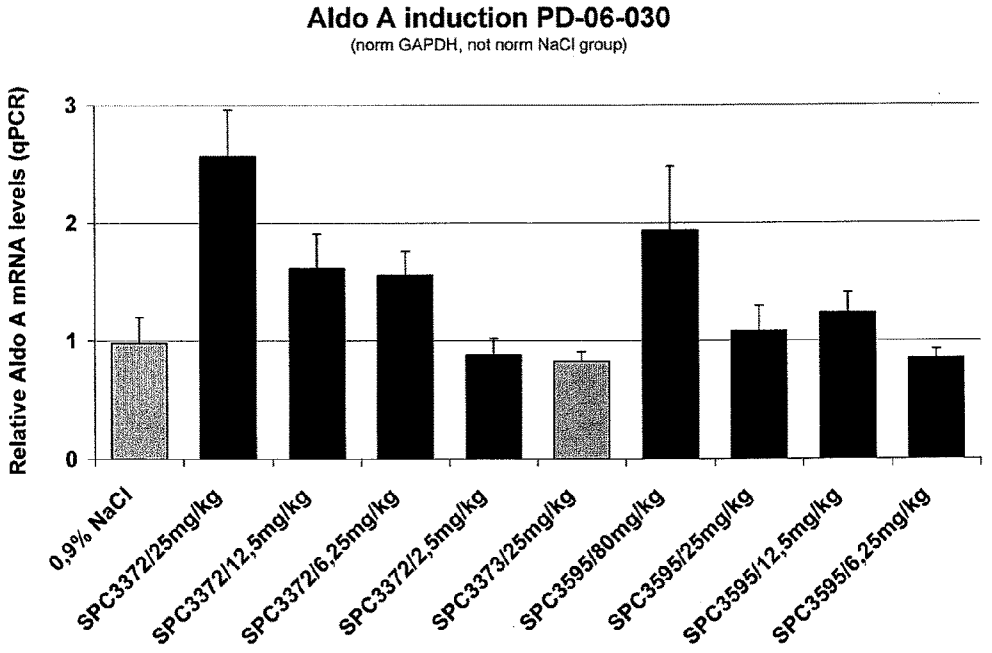


Figure 17

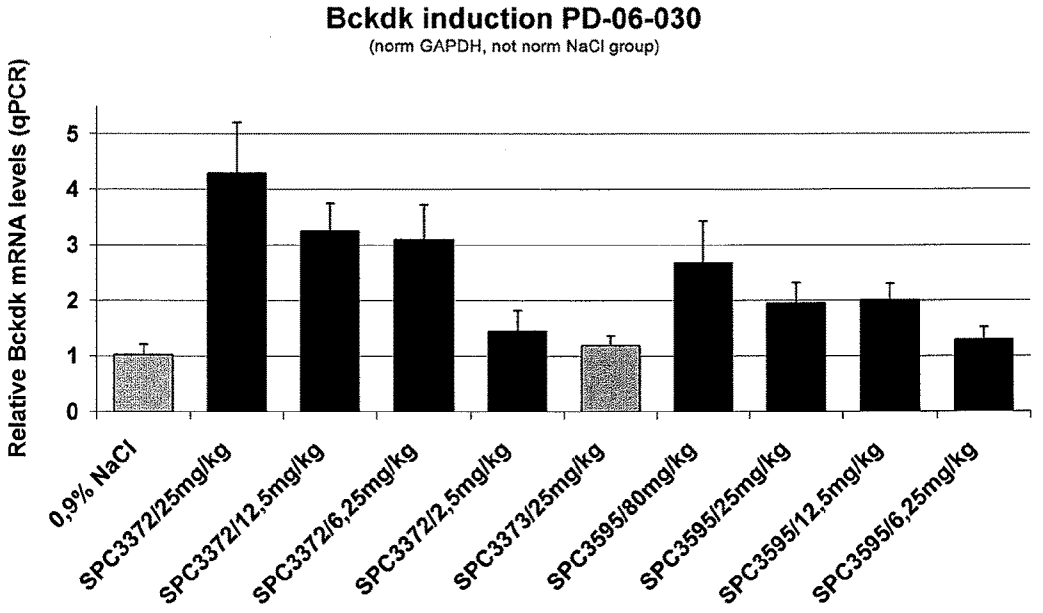


Figure 18

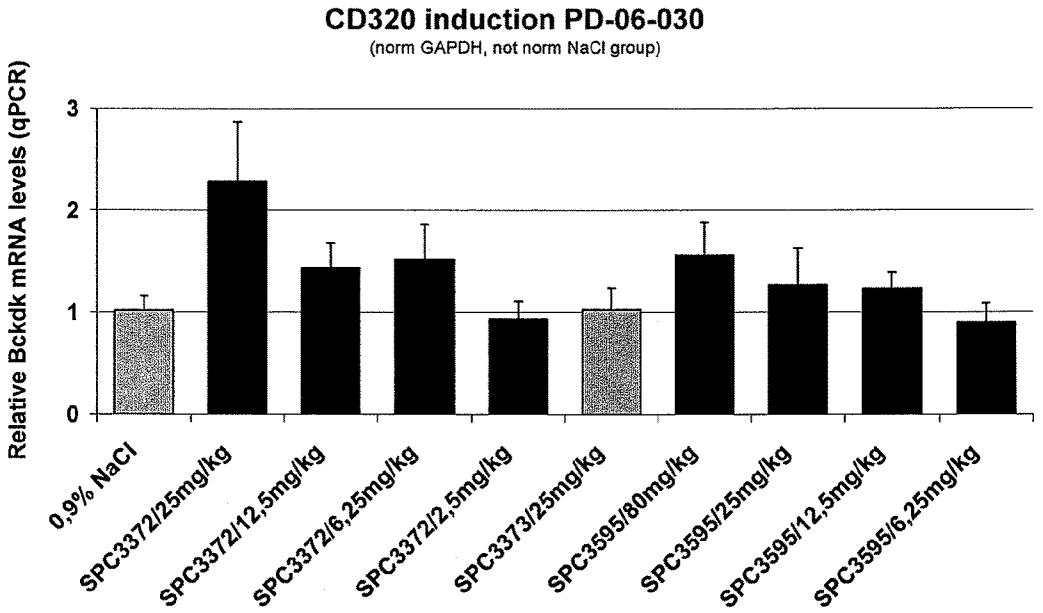


Figure 19

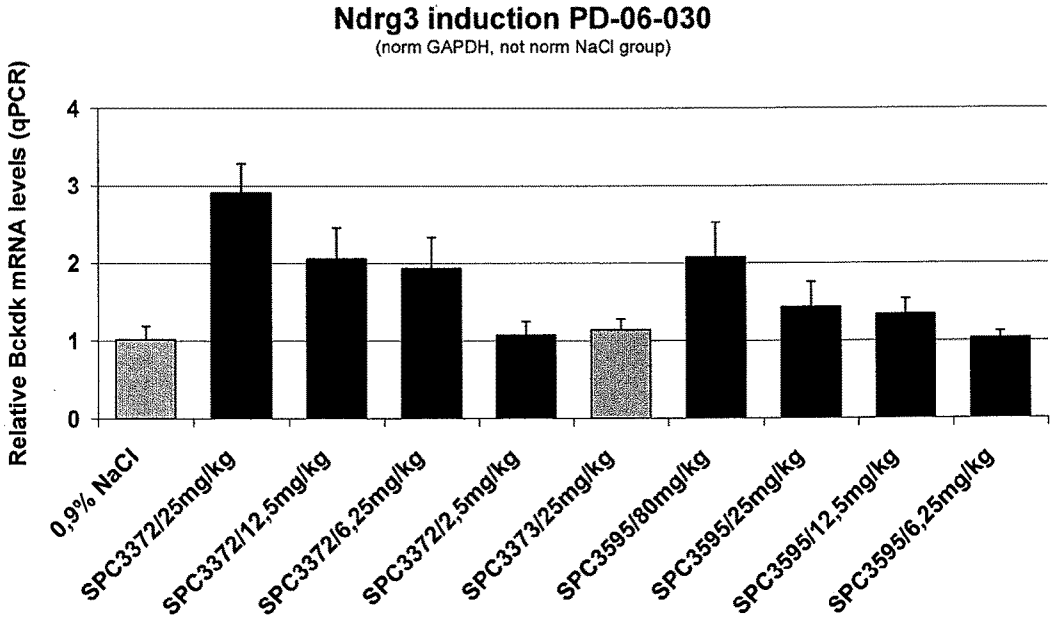


Figure 20

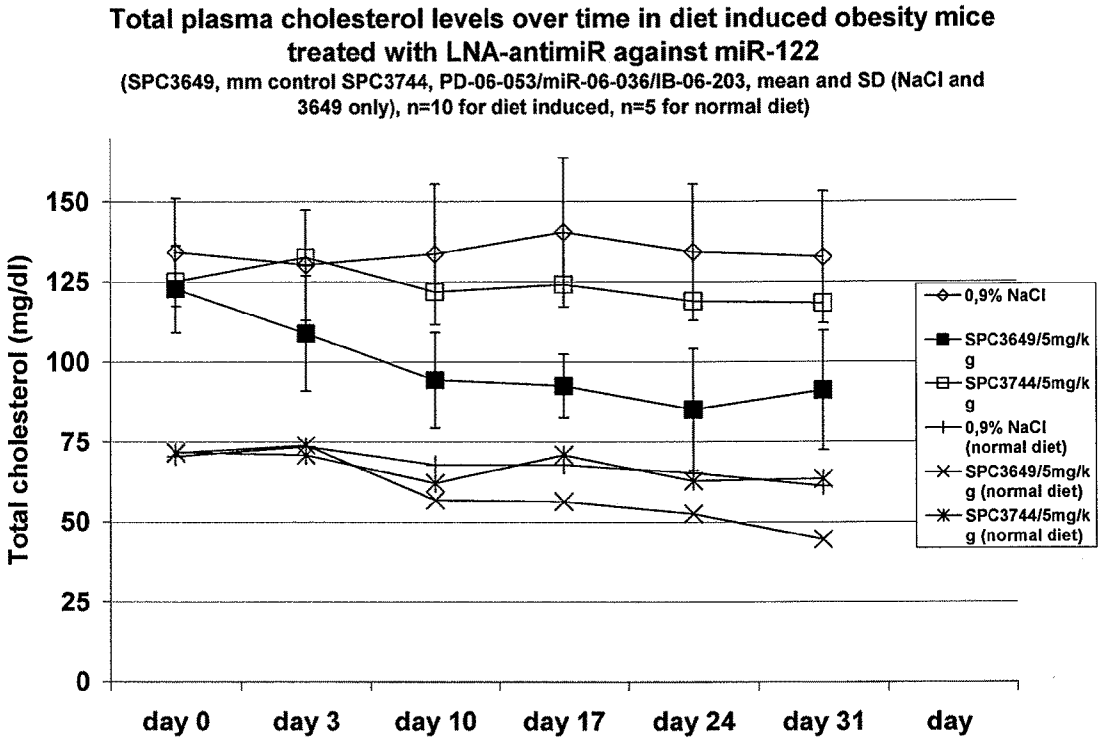


Figure 21

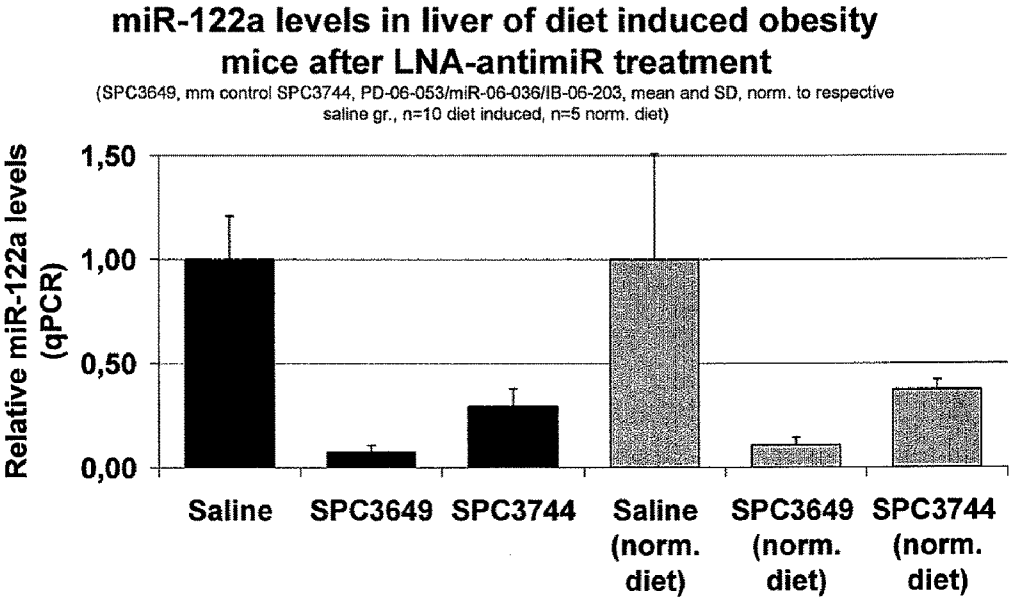


Figure 22

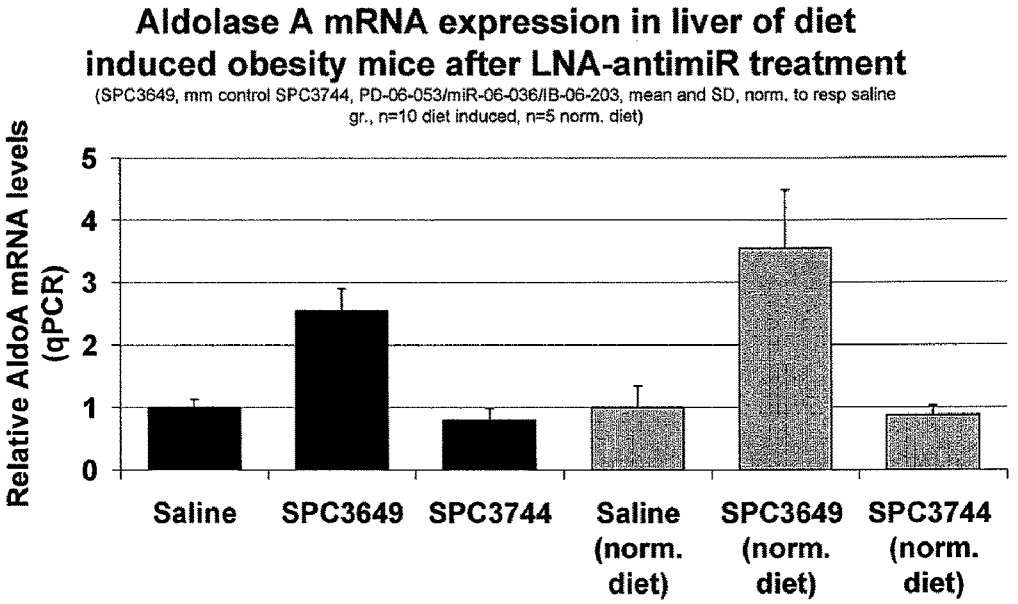


Figure 23

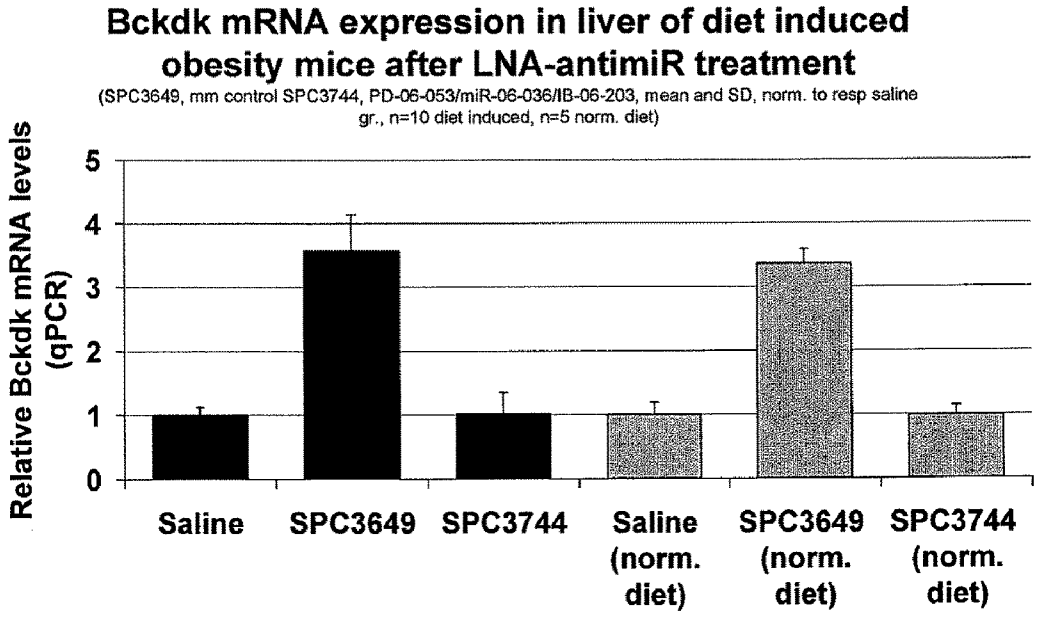


Figure 24

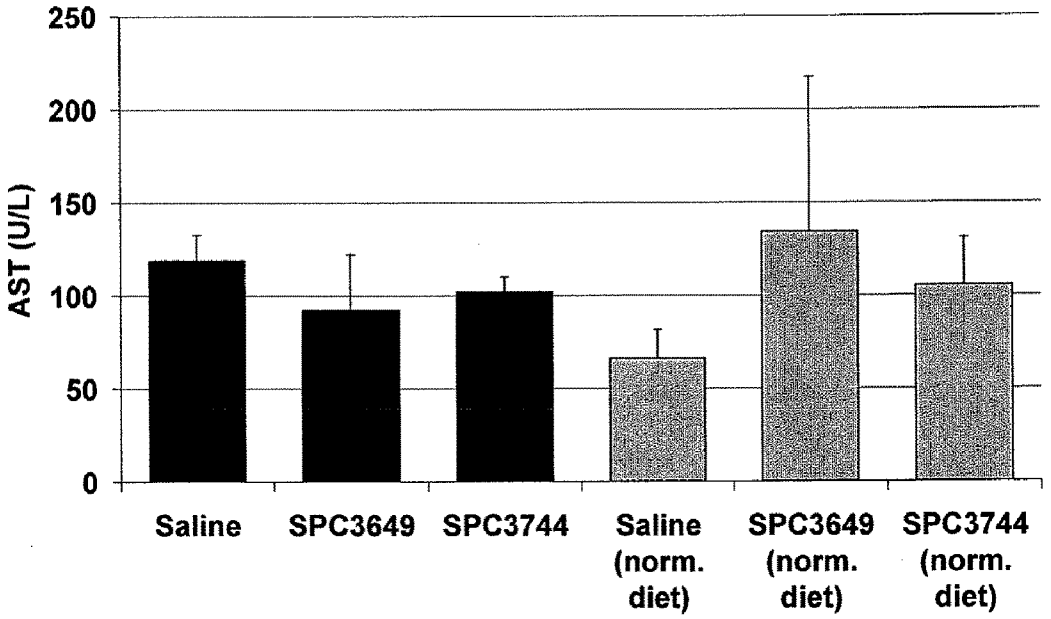


Figure 25

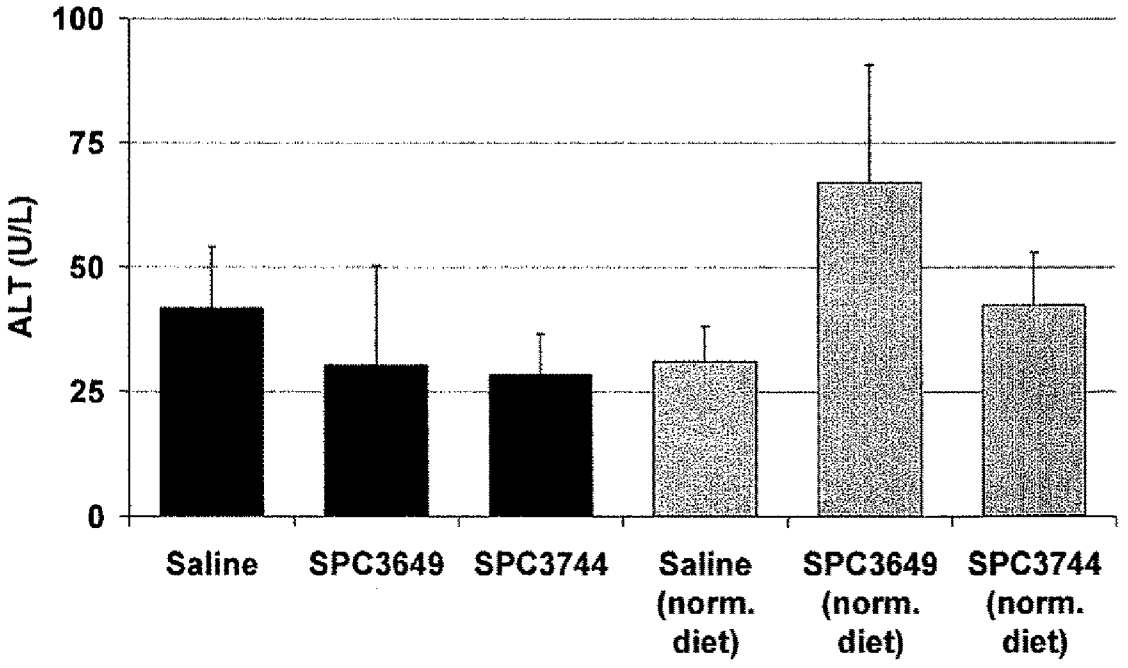

100
75
50
25
0
ALT (U/L)
Saline
SPC3649
SPC3744
Saline (norm. diet)
SPC3649 (norm. diet)
SPC3744 (norm. diet)

Figure 26

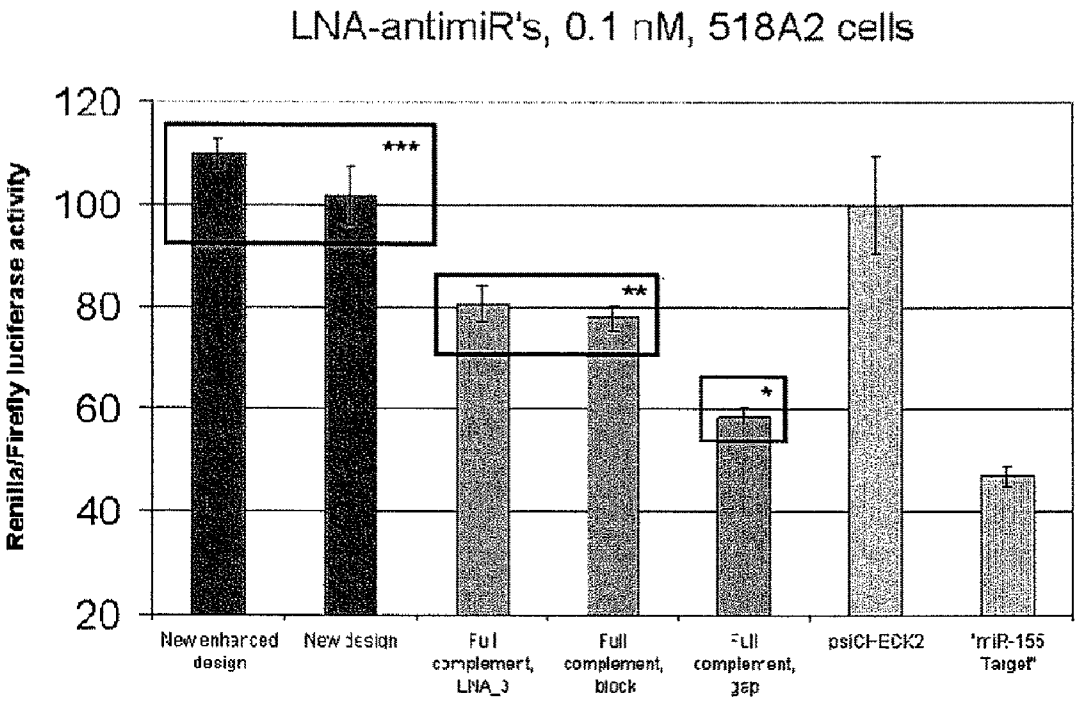


Figure 27

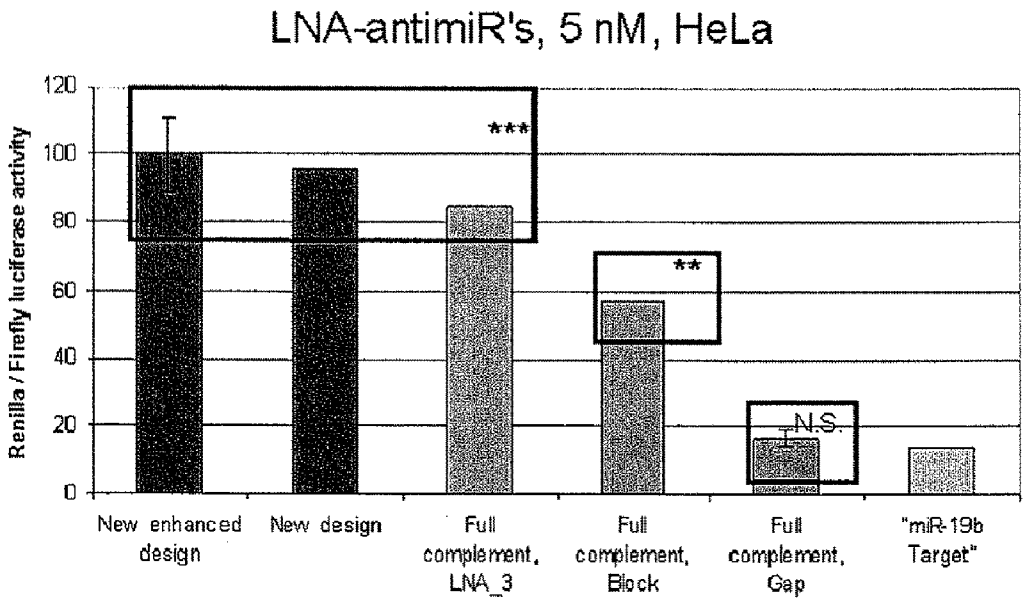


Figure 28

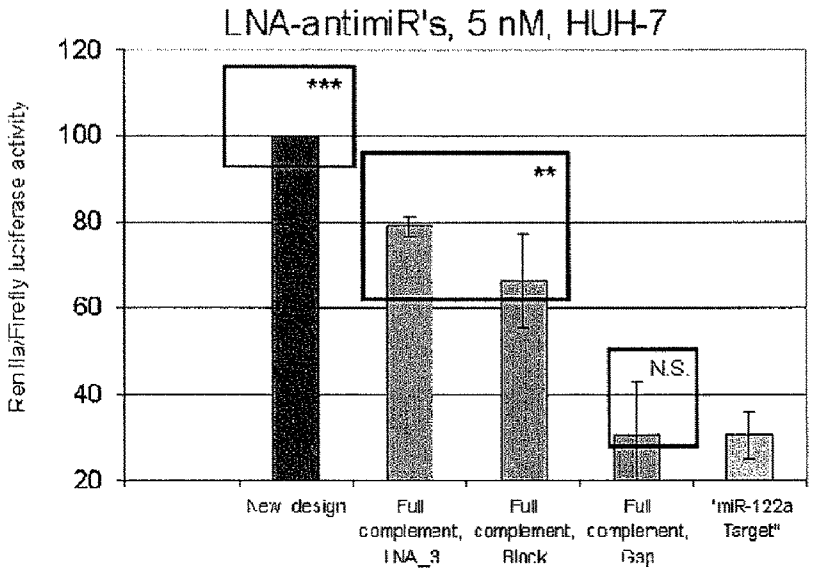


Figure 29

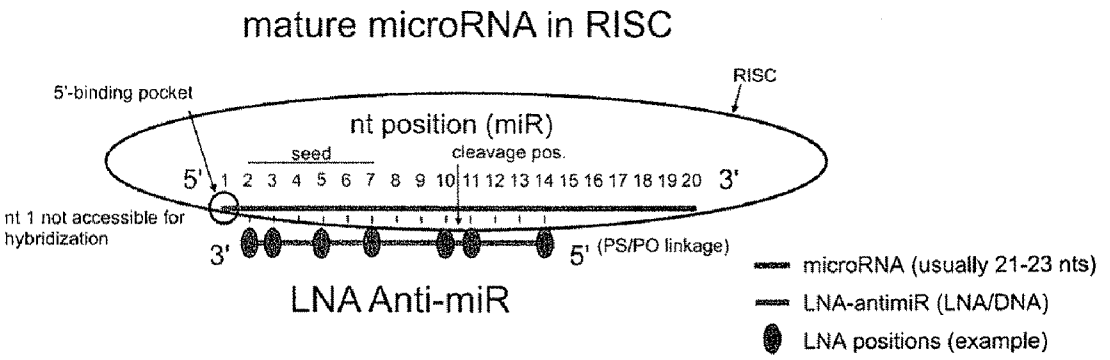


Figure 30

PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION

[0001] The present invention concerns pharmaceutical compositions comprising LNA-containing single stranded oligonucleotides capable of inhibiting disease-inducing microRNAs.

BACKGROUND OF THE INVENTION

[0002] MicroRNAs—Novel Regulators of Gene Expression

[0003] MicroRNAs (miRNAs) are an abundant class of short endogenous RNAs that act as post-transcriptional regulators of gene expression by base-pairing with their target mRNAs. The mature miRNAs are processed sequentially from longer hairpin transcripts by the RNAse III ribonucleases Drosha (Lee et al. 2003) and Dicer (Hutvagner et al. 2001, Ketting et al. 2001). To date more than 3400 miRNAs have been annotated in vertebrates, invertebrates and plants according to the miRBase microRNA database release 7.1 in October 2005 (Griffith-Jones 2004, Griffith-Jones et al. 2006), and many miRNAs that correspond to putative genes have also been identified.

[0004] Most animal miRNAs recognize their target sites located in 3'-UTRs by incomplete base-pairing, resulting in translational repression of the target genes (Bartel 2004). An increasing body of research shows that animal miRNAs play fundamental biological roles in cell growth and apoptosis (Brennecke et al. 2003), hematopoietic lineage differentiation (Chen et al. 2004), life-span regulation (Boehm and Slack 2005), photoreceptor differentiation (Li and Carthew 2005), homeobox gene regulation (Yekta et al. 2004, Hornstein et al. 2005), neuronal asymmetry (Johnston et al. 2004), insulin secretion (Poy et al. 2004), brain morphogenesis (Giraldez et al. 2005), muscle proliferation and differentiation (Chen, Mandel et al. 2005, Kwon et al. 2005, Sokol and Ambros 2005), cardiogenesis (Zhao et al. 2005) and late embryonic development in vertebrates (Wienholds et al. 2005).

[0005] MicroRNAs in Human Diseases

[0006] miRNAs are involved in a wide variety of human diseases. One is spinal muscular atrophy (SMA), a paediatric neurodegenerative disease caused by reduced protein levels or loss-of-function mutations of the survival of motor neurons (SMN) gene (Paushkin et al. 2002). A mutation in the target site of miR-189 in the human SLITRK1 gene was recently shown to be associated with Tourette's syndrome (Abelson et al. 2005), while another recent study reported that the hepatitis C virus (HCV) RNA genome interacts with a host-cell microRNA, the liver-specific miR-122a, to facilitate its replication in the host (Jopling et al. 2005). Other diseases in which miRNAs or their processing machinery have been implicated, include frag-ile X mental retardation (FXMR) caused by absence of the fragile X mental retardation protein (FMRP) (Nelson et al. 2003, Jin et al. 2004) and DiGeorge syndrome (Landthaler et al. 2004).

[0007] In addition, perturbed miRNA expression patterns have been reported in many human cancers. For example, the human miRNA genes miR15a and miR16-1 are deleted or down-regulated in the majority of B-cell chronic lymphocytic leukemia (CLL) cases, where a unique signature of 13 miRNA genes was recently shown to associate with prognosis and progression (Calin et al. 2002, Calin et al. 2005). The role of miRNAs in cancer is further supported by the fact that more than 50% of the human miRNA genes are located in cancer-associated genomic regions or at fragile sites (Calin et al. 2004). Recently, systematic expression analysis of a diversity of human cancers revealed a general down-regulation of miRNAs in tumors compared to normal tissues (Lu et al. 2005). Interestingly, miRNA-based classification of poorly differentiated tumors was successful, whereas mRNA profiles were highly inaccurate when applied to the same samples. miRNAs have also been shown to be deregulated in breast cancer (Iorio et al. 2005), lung cancer (Johnson et al. 2005) and colon cancer (Michael et al. 2004), while the miR-17-92 cluster, which is amplified in human B-cell lymphomas and miR-155 which is upregulated in Burkitt's lymphoma have been reported as the first human miRNA oncogenes (Eis et al. 2005, He et al. 2005). Thus, human miRNAs would not only be highly useful as biomarkers for future cancer diagnostics, but are rapidly emerging as attractive targets for disease intervention by oligonucleotide technologies.

[0008] Inhibition of MicroRNAs Using Single Stranded oligonucleotides

[0009] Several oligonucleotide approaches have been reported for inhibition of miRNAs.

[0010] WO03/029459 (Tuschl) claims oligonucleotides which encode microRNAs and their complements of between 18-25 nucleotides in length which may comprise nucleotide analogues. LNA is suggested as a possible nucleotide analogue, although no LNA containing oligonucleotides are disclosed. Tuschl claims that miRNA oligonucleotides may be used in therapy.

[0011] US2005/0182005 discloses a 24mer 2'OMe RNA oligoribonucleotide complementary to the longest form of miR 21 which was found to reduce miR 21 induced repression, whereas an equivalent DNA containing oligonucleotide did not. The term 2'OMe-RNA refers to an RNA analogue where there is a substitution to methyl at the 2' position (2'OMethyl).

[0012] US2005/0227934 (Tuschl) refers to antimir molecules with upto 50% DNA residues. It also reports that antimirs containing 2' OMe RNA were used against pancreatic microRNAs but it appears that no actual oligonucleotide structures are disclosed.

[0013] US20050261218 (ISIS) claims an oligomeric compound comprising a first region and a second region, wherein at least one region comprises a modification and a portion of the oligomeric compound is targeted to a small non-coding RNA target nucleic acid, wherein the small non-coding RNA target nucleic acid is a miRNA. Oligomeric compounds of between 17 and 25 nucleotides in length are claimed. The examples refer to entirely 2' OMe PS compounds, 21mers and 20mer and 2'OMe gapmer oligonucleotides targeted against a range of pre-miRNA and mature miRNA targets.

[0014] Boutla et al. 2003 (Nucleic Acids Research 31: 4973-4980) describe the use of DNA antisense oligonucleotides complementary to 11 different miRNAs in *Drosophila* as well as their use to inactivate the miRNAs by injecting the DNA oligonucleotides into fly embryos. Of the 11 DNA antisense oligonucleotides, only 4 constructs showed severe interference with normal development, while the remaining 7 oligonucleotides didn't show any phenotypes presumably due to their inability to inhibit the miRNA in question.

[0015] An alternative approach to this has been reported by Hutvagner et al. (2004) and Leaman et al. (2005), in which 2'-O-methyl antisense oligonucleotides, complementary to

the mature miRNA could be used as potent and irreversible inhibitors of short interfering RNA (siRNA) and miRNA function in vitro and in vivo in *Drosophila* and *C. elegans,* thereby inducing a loss-of-function phenotype. A drawback of this method is the need of high 2'-O-methyl oligonucleotide concentrations (100 micromolar) in transfection and injection experiments, which may be toxic to the animal. This method was recently applied to mice studies, by conjugating 2'-O-methyl antisense oligonucleotides complementary to four different miRNAs with cholesterol for silencing miRNAs in vivo (Krützfedt et al. 2005). These so-called antagomirs were administered to mice by intravenous injections. Although these experiments resulted in effective silencing of endogenous miRNAs in vivo, which was found to be specific, efficient and long-lasting, a major drawback was the need of high dosage (80 mg/kg) of 2'-O-Me antagomir for efficient silencing.

[0016] Inhibition of microRNAs using LNA-modified oligonucleotides have previously been described by Chan et al. *Cancer Research* 2005, 65 (14) 6029-6033, Lecellier et al. *Science* 2005, 308, 557-560, Naguibneva et al. *Nature Cell Biology* 2006 8 (3), 278-84 and Ørum et al. *Gene* 2006, (Available online 24 Feb. 2006). In all cases, the LNA-modified anti-mir oligonucleotides were complementary to the entire mature microRNA, i.e. 20-23 nucleotides in length, which hampers efficient in vivo uptake and wide biodistribution of the molecules.

[0017] Naguibneva (Naguibneva et al. Nature Cell Biology 2006 8 describes the use of mixmer DNA-LNA-DNA antisense oligonucleotide anti-mir to inhibit microRNA miR-181 function in vitro, in which a block of 8 LNA nucleotides is located at the center of the molecule flanked by 6 DNA nucleotides at the 5' end, and 9 DNA nucleotides at the 3' end, respectively. A major drawback of this antisense design is low in vivo stability due to low nuclease resistance of the flanking DNA ends.

[0018] While Chan et al. (Chan et al. *Cancer Research* 2005, 65 (14) 6029-6033), and Ørum et al. (Ørum et al. *Gene* 2006, (Available online 24 Feb. 2006) do not disclose the design of the LNA-modified anti-mir molecules used in their study, Lecellier et al. (Lecellier et al. *Science* 2005, 308, 557-560) describes the use of gapmer LNA-DNA-LNA antisense oligonucleotide anti-mir to inhibit microRNA function, in which a block of 4 LNA nucleotides is located both at the 5' end, and at the 3' end, respectively, with a window of 13 DNA nucleotides at the center of the molecule. A major drawback of this antisense design is low in vivo uptake, as well as low in vivo stability due to the 13 nucleotide DNA stretch in the anti-mir oligonucleotide.

[0019] Thus, there is a need in the field for improved oligonucleotides capable of inhibiting microRNAs.

SUMMARY OF THE INVENTION

[0020] The present invention is based upon the discovery that the use of short oligonucleotides designed to bind with high affinity to miRNA targets are highly effective in alleviating the repression of mRNA by microRNAs in vivo.

[0021] Whilst not wishing to be bound to any specific theory, the evidence disclosed herein indicates that the highly efficient targeting of miRNAs in vivo is achieved by designing oligonucleotides with the aim of forming a highly stable duplex with the miRNA target in vivo. This is achieved by the use of high affinity nucleotide analogues such as at least one LNA units and suitably further high affinity nucleotide analogues, such as LNA, 2'-MOE RNA of 2'-Fluoro nucleotide analogues, in a short, such as 10-17 or 10-16 nucleobase oligonucleotides. In one aspect the aim is to generate an oligonucleotide of a length which is unlikely to form a siRNA complex (i.e. a short oligonucleotide), and with sufficient loading of high affinity nucleotide analogues that the oligonucleotide sticks almost permanently to its miRNA target, effectively forming a stable and non-functional duplex with the miRNA target. We have found that such designs are considerably more effective than the prior art oligonucleotides, particularly gapmer and blockmer designs and oligonucleotides which have a long length, e.g. 20-23mers. The term 2'fluor-DNA refers to an DNA analogue where the is a substitution to fluor at the 2' position (2'F).

[0022] The invention provides a pharmaceutical composition comprising a single stranded oligonucleotide having a length of between 8 and 17, such as 10 and 17, such as 8-16 or 10-16 nucleobase units, a pharmaceutically acceptable diluent, carrier, or adjuvant, wherein at least one of the nucleobase units of the single stranded oligonucleotide is a high affinity nucleotide analogue, such as a Locked Nucleic Acid (LNA) nucleobase unit, and wherein the single stranded oligonucleotide is complementary to a human microRNA sequence.

[0023] The high affinity nucleotide analogues are nucleotide analogues which result in oligonucleotide which has a higher thermal duplex stability with a complementary RNA nucleotide than the binding affinity of an equivalent DNA nucleotide. This is typically determined by measuring the T_m.

[0024] We have not identified any significant off-target effects when using these short, high affinity oligonucleotides targeted against specific miRNAs. Indeed, the evidence provided herein indicates the effects on mRNA expression are either due to the presence of a complementary sequence to the targeted miRNA (primary mRNA targets) within the mRNA or secondary effects on mRNAs which are regulated by primary mRNA targets (secondary mRNA targets). No toxicity effects were identified indicating no significant detrimental off-target effects.

[0025] The invention further provides a pharmaceutical composition comprising a single stranded oligonucleotide having a length of between 8 and 17 nucleobase units, such as between 10 and 17 nucleobase units, such as between 10 and 16 nucleobase units, and a pharmaceutically acceptable diluent, carrier, or adjuvant, wherein at least one of the nucleobase units of the single stranded oligonucleotide is a Locked Nucleic Acid (LNA) nucleobase unit, and wherein the single stranded oligonucleotide is complementary to a human microRNA sequence.

[0026] The invention further provides for the use of an oligonucleotide according to the invention, such as those which may form part of the pharmaceutical composition, for the manufacture of a medicament for the treatment of a disease or medical disorder associated with the presence or over-expression (upregulation) of the microRNA.

[0027] The invention further provides for a method for the treatment of a disease or medical disorder associated with the presence or over-expression of the microRNA, comprising the step of administering a composition (such as the pharmaceutical composition) according to the invention to a person in need of treatment.

[0028] The invention further provides for a method for reducing the effective amount of a miRNA in a cell or an organism, comprising administering a composition (such as

the pharmaceutical composition) according to the invention or a single stranded oligonucleotide according to the invention to the cell or the organism. Reducing the effective amount in this context refers to the reduction of functional miRNA present in the cell or organism. It is recognised that the preferred oligonucleotides according to the invention may not always significantly reduce the actual amount of miRNA in the cell or organism as they typically form very stable duplexes with their miRNA targets.

[0029] The invention further provides for a method for de-repression of a target mRNA of a miRNA in a cell or an organism, comprising administering a composition (such as the pharmaceutical composition) or a single stranded oligonucleotide according to the invention to the cell or the organism.

[0030] The invention further provides for the use of a single stranded oligonucleotide of between 8-16 such as 10-16 nucleobases in length, for the manufacture of a medicament for the treatment of a disease or medical disorder associated with the presence or over-expression of the microRNA.

[0031] The invention further provides for a method for the treatment of a disease or medical disorder associated with the presence or over-expression of the microRNA, comprising the step of administering a composition (such as the pharmaceutical composition) comprising a single stranded oligonucleotide of between between 8-16 such as between 10-16 nucleobases in length to a person in need of treatment.

[0032] The invention further provides for a method for reducing the effective amount of a miRNA target (i.e. 'available' miRNA) in a cell or an organism, comprising administering a composition (such as the pharmaceutical composition) comprising a single stranded oligonucleotide of between 8-16 such as between 10-16 nucleobases to the cell or the organism.

[0033] The invention further provides for a method for de-repression of a target mRNA of a miRNA in a cell or an organism, comprising a single stranded oligonucleotide of between 8-16 such as between 10-16 nucleobases or (or a composition comprising said oligonucleotide) to the cell or the organism.

[0034] The invention further provides for a method for the synthesis of a single stranded oligonucleotide targeted against a human microRNA, such as a single stranded oligonucleotide described herein, said method comprising the steps of:

[0035] a. Optionally selecting a first nucleobase, counting from the 3' end, which is a nucleotide analogue, such as an LNA nucleobase.

[0036] b. Optionally selecting a second nucleobase, counting from the 3' end, which is an nucleotide analogue, such as an LNA nucleobase.

[0037] c. Selecting a region of the single stranded oligonucleotide which corresponds to the miRNA seed region, wherein said region is as defined herein.

[0038] d. Optionally selecting a seventh and eight nucleobase is as defined herein.

[0039] e. Optionally selecting a 5' region of the single stranded oligonucleotide is as defined herein.

[0040] f. Optionally selecting a 5' terminal of the single stranded oligonucleotide is as defined herein.

[0041] Wherein the synthesis is performed by sequential synthesis of the regions defined in steps a-f, wherein said synthesis may be performed in either the 3'-5' (a to f) or 5'-3' (f to a) direction, and wherein said single stranded oligonucleotide is complementary to a sequence of the miRNA target.

[0042] In one embodiment the oligonucleotide of the invention is designed not to be recruited by RISC or to mediate RISC directed cleavage of the miRNA target. It has been considered that by using long oligonucleotides, e.g. 21 or 22mers, particularly RNA oligonucleotides, or RNA 'analogue' oligonucleotide which are complementary to the miRNA target, the oligonucleotide can compete against the target mRNA in terms of RISC complex association, and thereby alleviate miRNA repression of miRNA target mRNAs via the introduction of an oligonucleotide which competes as a substrate for the miRNA.

[0043] However, the present invention seeks to prevent such undesirable target mRNA cleavage or translational inhibition by providing oligonucleotides capable of complementary, and apparently in some cases almost irreversible binding to the mature microRNA. This appears to result in a form of protection against degradation or cleavage (e.g. by RISC or RNAseH or other endo or exo-nucleases), which may not result in substantial or even significant reduction of the miRNA (e.g. as detected by northern blot using LNA probes) within a cell, but ensures that the effective amount of the miRNA, as measured by de-repression analysis is reduced considerably. Therefore, in one aspect, the invention provides oligonucleotides which are purposefully designed not to be compatible with the RISC complex, but to remove miRNA by titration by the oligonucleotide. Although not wishing to be bound to a specific theory of why the oligonucleotides of the present invention are so effective, in analogy with the RNA based oligonucleotides (or complete 2'OMe oligonucleotides), it appears that the oligonucleotides according to the present invention work through non-competitive inhibition of miRNA function as they effectively remove the available miRNA from the cytoplasm, where as the prior art oligonucleotides provide an alternative miRNA substrate, which may act as a competitor inhibitor, the effectiveness of which would be far more dependant upon the concentration of the oligonucleotide in the cytoplasm, as well as the concentration of the target mRNA and miRNA.

[0044] Again, whilst not wishing to be bound to any specific theory, one further possibility that may exist with the use of oligonucleotides of approximately similar length to the miRNA targets, is that the oligonucleotides could form a siRNA like duplex with the miRNA target, a situation which would reduce the effectiveness of the oligonucleotide. It is also possible that the oligonucleotides themselves could be used as the guiding strand within the RISC complex, thereby generating the possibility of RISC directed degradation of non-specific targets which just happen to have sufficient complementarity to the oligonucleotide guide.

[0045] By selecting short oligonucleotides for targeting miRNA sequences, such problems are avoided.

[0046] Short oligonucleotides which incorporate LNA are known from the reagents area, such as the LNA (see for example WO2005/098029 and WO 2006/069584). However the molecules designed for diagnostic or reagent use are very different in design than those for pharmaceutical use. For example, the terminal nucleobases of the reagent oligos are typically not LNA, but DNA, and the internucleoside linkages are typically other than phosphorothioate, the preferred linkage for use in the oligonucleotides of the present invention. The invention therefore provides for a novel class of oligonucleotide per se.

[0047] The invention further provides for a (single stranded) oligonucleotide as described in the context of the pharmaceutical composition of the invention, wherein said oligonucleotide comprises either

[0048] i) at least one phosphorothioate linkage and/or

[0049] ii) at least one 3' terminal LNA unit, and/or

[0050] iii) at least one 5' terminal LNA unit.

[0051] It is preferable for most therapeutic uses that the oligonucleotide is fully phosphorothiolated—the exception being for therapeutic oligonucleotides for use in the CNS, such as in the brain or spine where phosphorothioation can be toxic, and due to the absence of nucleases, phosphodieater bonds may be used, even between consecutive DNA units. As referred to herein, other preferred aspects of the oligonucleotide according to the invention is that the second 3' nucleobase, and/or the 9^{th} and 10^{th} (from the 3' end), may also be LNA.

[0052] The inventors have found that other methods of avoiding RNA cleavage (such as exo-nuclease degradation in blood serum, or RISC associated cleavage of the oligonucleotide according to the invention are possible, and as such the invention also provides for a single stranded oligonucleotide which comprises of either:

[0053] a. an LNA unit at position 1 and 2 counting from the 3' end and/or

[0054] b. an LNA unit at position 9 and/or 10, also counting from the 3' end, and/or

[0055] c. either one or two 5' LNA units.

[0056] Whilst the benefits of these other aspects may be seen with longer oligonucleotides, such as nucleotide of up to 26 nucleobase units in length, it is considered these features may also be used with the shorter oligonucleotides referred to herein, such as the oligonucleotides of between 10-17 or 10-16 nucleobases described herein. It is highly preferably that the oligonucleotides comprise high affinity nucleotide analogues, such as those referred to herein, most preferably LNA units.

[0057] The inventors have therefore surprisingly found that carefully designed single stranded oligonucleotides comprising locked nucleic acid (LNA) units in a particular order show significant silencing of microRNAs, resulting in reduced microRNA levels. It was found that tight binding of said oligonucleotides to the so-called seed sequence, nucleotides 2 to 8 or 2-7, counting from the 5' end, of the target microRNAs was important. Nucleotide 1 of the target microRNAs is a non-pairing base and is most likely hidden in a binding pocket in the Ago 2 protein. Whilst not wishing to be bound to a specific theory, the present inventors consider that by selecting the seed region sequences, particularly with oligonucleotides that comprise LNA, preferably LNA units in the region which is complementary to the seed region, the duplex between miRNA and oligonucleotide is particularly effective in targeting miRNAs, avoiding off target effects, and possibly providing a further feature which prevents RISC directed miRNA function.

[0058] The inventors have surprisingly found that microRNA silencing is even more enhanced when LNA-modified single stranded oligonucleotides do not contain a nucleotide at the 3' end corresponding to this non-paired nucleotide 1. It was further found that two LNA units in the 3' end of the oligonucleotides according to the present invention made said oligonucleotides highly nuclease resistant.

[0059] It was further found that the oligonucleotides of the invention which have at least one nucleotide analogue, such as an LNA nucleotide in the positions corresponding to positions 10 and 11, counting from the 5' end, of the target microRNA may prevent cleavage of the oligonucleotides of the invention

[0060] Accordingly, in one aspect of the invention relates to an oligonucleotide having a length of from 12 to 26 nucleotides, wherein

[0061] i) the first nucleotide, counting from the 3' end, is a locked nucleic acid (LNA) unit;

[0062] ii) the second nucleotide, counting from the 3' end, is an LNA unit; and

[0063] iii) the ninth and/or the tenth nucleotide, counting from the 3' end, is an LNA unit.

[0064] The invention further provides for the oligonucleotides as defined herein for use as a medicament.

[0065] The invention further relates to compositions comprising the oligonucleotides defined herein and a pharmaceutically acceptable carrier.

[0066] As mentioned above, microRNAs are related to a number of diseases. Hence, a fourth aspect of the invention relates to the use of an oligonucleotide as defined herein for the manufacture of a medicament for the treatment of a disease associated with the expression of microRNAs selected from the group consisting of spinal muscular atrophy, Tourette's syndrome, hepatitis C virus, fragile X mental retardation, DiGeorge syndrome and cancer, such as chronic lymphocytic leukemia, breast cancer, lung cancer and colon cancer, in particular cancer.

[0067] A further aspect of the invention is a method to reduce the levels of target microRNA by contacting the target microRNA to an oligonucleotide as defined herein, wherein the oligonucleotide

[0068] 1. is complementary to the target microRNA

[0069] 2. does not contain a nucleotide at the 3' end that corresponds to the first 5' end nucleotide of the target microRNA.

[0070] The invention further provides for an oligonucleotide comprising a nucleobase sequence selected from the group consisting of SEQ IDs NO 1-534, SEQ ID NOs 539-544, SEQ ID NOs 549-554, SEQ ID NOs 559-564, SEQ ID NOs 569-574 and SEQ ID NOs 594-598, and SEQ ID NOs 579-584, or a pharmaceutical composition comprising said oligonucleotide. In one embodiment, the oligonucleotide may have a nucleobase sequence of between 1-17 nucleobases, such as 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 nucleobases, and as such the oligonucleobase in such an embodiment may be a contiguous subsequence within the oligonucleotides disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0071] FIG. **1**. The effect of treatment with different LNA anti-miR oligonucleotides on target nucleic acid expression in the miR-122a expressing cell line Huh-7. Shown are amounts of miR-122a (arbitrary units) derived from miR-122a specific qRT-PCR as compared to untreated cells (mock). The LNA anti-miR oligonucleotides were used at two concentrations, 1 and 100 nM, respectively. Included is also a mismatch control (SPC3350) to SPC3349 (also referred to herein as SPC3549).

[0072] FIG. **2**. Assessment of LNA anti-miR-122a knockdown dose-response for SPC3548 and SPC3549 in comparison with SPC3372 in vivo in mice livers using miR-122a real-time RT-PCR.

[0073] FIG. **2***b* miR-122 levels in the mouse liver after treatment with different LNA-antimiRs. The LNA-antimiR molecules SPC3372 and SPC3649 were administered into normal mice by three i.p. injections on every second day over a six-day-period at indicated doses and sacrificed 48 hours after last dose. Total RNA was extracted from the mice livers and miR-122 was measured by miR-122 specific qPCR.

[0074] FIG. **3**. Assessment of plasma cholesterol levels in LNA-antimiR-122a treated mice compared to the control mice that received saline.

[0075] FIG. **4***a*. Assessment of relative Bckdk mRNA levels in LNA antimiR-122a treated mice in comparison with saline control mice using real-time quantitative RT-PCR.

[0076] FIG. **4***b*. Assessment of relative aldolase A mRNA levels in LNA antimiR-122a treated mice in comparison with saline control mice using real-time quantitative RT-PCR.

[0077] FIG. **4***c*. Assessment of GAPDH mRNA levels in LNA antimiR-122a treated mice (animals 4-30) in comparison with saline control mice (animals 1-3) using real-time quantitative RT-PCR.

[0078] FIG. **5**. Assessment of LNA-antimiR™-122a knock-down dose-response in vivo in mice livers using miR-122a real-time RT-PCR. Six groups of animals (5 mice per group) were treated in the following manner. Group 1 animals were injected with 0.2ml saline by i.v. on 3 successive days, Group 2 received 2.5mg/kg SPC3372, Group 3 received 6.25 mg/kg, Group 4 received 12.5 mg/kg and Group 5 received 25 mg/kg, while Group 6 received 25 mg/kg SPC 3373 (mismatch LNA-antimiR™ oligonucleotide), all in the same manner. The experiment was repeated (therefore n=10) and the combined results are shown.

[0079] FIG. **6**. Northern blot comparing SPC3649 with SPC3372. Total RNA from one mouse in each group were subjected to miR-122 specific northern blot. Mature miR-122 and the duplex (blocked microRNA) formed between the LNA-antimiR and miR-122 is indicated.

[0080] FIG. **7**. Mice were treated with 25 mg/kg/day LNA-antimiR or saline for three consecutive days and sacrificed 1, 2 or 3 weeks after last dose. Included are also the values from the animals sacrificed 24 hours after last dose (example 11 "old design"). miR-122 levels were assessed by qPCR and normalized to the mean of the saline group at each individual time point. Included are also the values from the animals sacrificed 24 hours after last dose (shown mean and SD, n=7, 24 h n=10). Sacrifice day 9, 16 or 23 corresponds to sacrifice 1, 2 or 3 weeks after last dose.).

[0081] FIG. **8**. Mice were treated with 25 mg/kg/day LNA-antimiR or saline for three consecutive days and sacrificed 1, 2 or 3 weeks after last dose. Included are also the values from the animals sacrificed 24 hours after last dose (example 11 "old design"). Plasma cholesterol was measured and normalized to the saline group at each time point (shown mean and SD, n=7, 24 h n=10).

[0082] FIG. **9**. Dose dependent miR-122a target mRNA induction by SPC3372 inhibition of miR-122a. Mice were treated with different SPC3372 doses for three consecutive days, as described above and sacrificed 24 hours after last dose. Total RNA extracted from liver was subjected to qPCR. Genes with predicted miR-122 target site and observed to be upregulated by microarray analysis were investigated for dose-dependent induction by increasing SPC3372 doses using qPCR. Total liver RNA from 2 to 3 mice per group sacrificed 24 hours after last dose were subjected to qPCR for the indicated genes. Shown in FIG. **9** is mRNA levels relative to Saline group, n=2-3 (2.5-12.5 mg/kg/day: n=2, no SD). Shown is also the mismatch control (mm, SPC3373)

[0083] FIG. **10**. Transient induction of miR-122a target mRNAs following SPC3372 treatment. NMRI female mice were treated with 25 mg/kg/day SPC3372 along with saline control for three consecutive days and sacrificed 1, 2 or 3 weeks after last dose, respectively. RNA was extracted from livers and mRNA levels of predicted miR-122a target mRNAs, selected by microarray data were investigated by qPCR. Three animals from each group were analysed.

[0084] FIG. **11**. Induction of Vldlr in liver by SPC3372 treatment. The same liver RNA samples as in previous example (FIG. **10**) were investigated for Vldlr induction.

[0085] FIG. **12**. Stability of miR-122a/SPC3372 duplex in mouse plasma. Stability of SPC3372 and SPC3372/miR-122a duplex were tested in mouse plasma at 37° C. over 96 hours. Shown in FIG. **12** is a SYBR-Gold stained PAGE.

[0086] FIG. **13**. Sequestering of mature miR-122a by SPC3372 leads to duplex formation. Shown in FIG. **13** is a membrane probed with a miR-122a specific probe (upper panel) and re-probed with a Let-7 specific probe (lower panel). With the miR-122 probe, two bands could be detected, one corresponding to mature miR-122 and one corresponding to a duplex between SPC3372 and miR-122.

[0087] FIG. **14**. miR-122a sequestering by SPC3372 along with SPC3372 distribution assessed by in situ hybridization of liver sections. Liver cryo-sections from treated animals were

[0088] FIG. **15**. Liver gene expression in miR-122 LNA-antimiR treated mice.

[0089] Saline and LNA-antimiR treated mice were compared by genome-wide expression profiling using Affymetrix Mouse Genome 430 2.0 arrays. (a,1) Shown is number of probes displaying differentially expression in liver samples of LNA-antimiR-122 treated and saline treated mice 24 hours post treatment. (b,2) The occurrence of miR-122 seed sequence in differentially expressed genes. The plot shows the percentage of transcripts with at least one miR-122 seed recognition sequence in their 3' UTR. Random: Random sequences were generated and searched for miR-122 seed recognition sequences.

[0090] Temporal liver gene expression profiles in LNA-antimiR treated mice. Mice were treated with 25 mg/kg/day LNA-antimiR or saline for three consecutive days and sacrificed 1, 2 or 3 weeks after last dose. Included are also the values from the animals sacrificed 24 hours after last dose. (c,3) RNA samples from different time points were also subjected to expression profiling. Hierarchical cluster analysis of expression profiles of genes identified as differentially expressed between LNA-antimiR and saline treated mice 24 hours, one week or three weeks post treatment. (d,4) Expression profiles of genes identified as differentially expressed between LNA-antimiR and saline treated mice 24 hours post treatment were followed over time. The expression ratios of up- and down-regulated genes in LNA-antimiR treated mice approach 1 over the time-course, indicating a reversible effect of the LNA-antimiR treatment.

[0091] FIG. **16**. The effect of treatment with SPC3372 and 3595 on miR-122 levels in mice livers.

[0092] FIG. **17**. The effect of treatment with SPC3372 and 3595 on Aldolase A levels in mice livers.

[0093] FIG. **18**. The effect of treatment with SPC3372 and 3595 on Bckdk levels in mice livers.

[0094] FIG. **19**. The effect of treatment with SPC3372 and 3595 on CD320 levels in mice livers.

[0095] FIG. **20**. The effect of treatment with SPC3372 and 3595 on Ndrg3 levels in mice livers.

[0096] FIG. **21**. The effect of long-term treatment with SPC3649 on total plasma cholesterol in hypercholesterolemic and normal mice. Weekly samples of blood plasma were obtained from the SPC3649 treated and saline control mice once weekly followed by assessment of total plasma cholesterol. The mice were treated with 5 mg/kg SPC3649, SPC3744 or saline twice weekly. Normal mice given were treated in parallel.

[0097] FIG. **22**. The effect of long-term treatment with SPC3649 on miR-122 levels in hypercholesterolemic and normal mice.

[0098] FIG. **23**. The effect of long-term treatment with SPC3649 on Aldolase A levels in hypercholesterolemic and normal mice.

[0099] FIG. **24**. The effect of long-term treatment with SPC3649 on Bckdk levels in hypercholesterolemic and normal mice.

[0100] FIG. **25**. The effect of long-term treatment with SPC3649 on AST levels in hypercholesterolemic and normal mice.

[0101] FIG. **26**. The effect of long-term treatment with SPC3649 on ALT levels in hypercholesterolemic and normal mice.

[0102] FIG. **27**. Functional de-repression of renilla luciferase with miR-155 target by miR-155 blocking oligonucleotides in an endogenously miR-155 expressing cell line, 518A2. "psiCheck2" is the plasmid without miR-155 target, i.e. full expression and "miR-155 target" is the corresponding plasmid with miR-155 target but not co-transfected with oligo blocking miR-155 and hence represent fully miR-155 repressed renilla luciferace expression.

[0103] FIG. **28**. Functional de-repression of renilla luciferase with miR-19b target by miR-19b blocking oligonucleotides in an endogenously miR-19b expressing cell line, HeLa. "miR-19b target" is the plasmid with miR-19b target but not co-transfected with oligo blocking miR-19b and hence represent fully miR-19b repressed renilla luciferace expression.

[0104] FIG. **29**. Functional de-repression of renilla luciferase with miR-122 target by miR-122 blocking oligonucleotides in an endogenously miR-122 expressing cell line, Huh-7. "miR-122 target" is the corresponding plasmid with miR-122 target but not co-transfected with oligo blocking miR-122 and hence represent fully miR-122 repressed renilla luciferace expression.

[0105] FIG. **30**. Diagram illustrating the alignment of an oligonucleotide according to the invention and a microRNA target.

DETAILED DESCRIPTION OF THE INVENTION

[0106] The invention provides pharmaceutical compositions comprising short single stranded oligonucleotides, of length of between 8 and 17 such as between 10 and 17 nucleobases which are complementary to human microRNAs. The short oligonucleotides are particularly effective at alleviating miRNA repression in vivo. It is found that the incorporation of high affinity nucleotide analogues into the oligonucleotides results in highly effective anti-microRNA molecules which appear to function via the formation of almost irreversible duplexes with the miRNA target, rather than RNA cleavage based mechanisms, such as mechanisms associated with RNaseH or RISC.

[0107] It is highly preferable that the single stranded oligonucleotide according to the invention comprises a region of contiguous nucleobase sequence which is 100% complementary to the human microRNA seed region.

[0108] It is preferable that single stranded oligonucleotide according to the invention is complementary to the mature human microRNA sequence.

[0109] In one embodiment the single stranded oligonucleotide according to the invention is complementary to a microRNA sequence, such as a microRNA sequence selected from the group consisting of: hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-miR-15a, hsa-miR-16, hsa-miR-17-5p, hsa-miR-17-3p, hsa-miR-18a, hsa-miR-19a, hsa-miR-19b, hsa-miR-20a, hsa-miR-21, hsa-miR-22, hsa-miR-23a, hsa-miR-189, hsa-miR-24, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27a, hsa-miR-28, hsa-miR-29a, hsa-miR-30a-5p, hsa-miR-30a-3p, hsa-miR-31, hsa-miR-32, hsa-miR-33, hsa-miR-92, hsa-miR-93, hsa-miR-95, hsa-miR-96, hsa-miR-98, hsa-miR-99a, hsa-miR-100, hsa-miR-101, hsa-miR-29b, hsa-miR-103, hsa-miR-105, hsa-miR-106a, hsa-miR-107, hsa-miR-192, hsa-miR-196a, hsa-miR-197, hsa-miR-198, hsa-miR-199a, hsa-miR-199a*, hsa-miR-208, hsa-miR-129, hsa-miR-148a, hsa-miR-30c, hsa-miR-30d, hsa-miR-139, hsa-miR-147, hsa-miR-7, hsa-miR-10a, hsa-miR-10b, hsa-miR-34a, hsa-miR-181a, hsa-miR-181b, hsa-miR-181c, hsa-miR-182, hsa-miR-182*, hsa-miR-183, hsa-miR-187, hsa-miR-199b, hsa-miR-203, hsa-miR-204, hsa-miR-205, hsa-miR-210, hsa-miR-211, hsa-miR-212, hsa-miR-181a*, hsa-miR-214, hsa-miR-215, hsa-miR-216, hsa-miR-217, hsa-miR-218, hsa-miR-219, hsa-miR-220, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-200b, hsa-let-7g, hsa-let-7i, hsa-miR-1, hsa-miR-15b, hsa-miR-23b, hsa-miR-27b, hsa-miR-30b, hsa-miR-122a, hsa-miR-124a, hsa-miR-125b, hsa-miR-128a, hsa-miR-130a, hsa-miR-132, hsa-miR-133a, hsa-miR-135a, hsa-miR-137, hsa-miR-138, hsa-miR-140, hsa-miR-141, hsa-miR-142-5p, hsa-miR-142-3p, hsa-miR-143, hsa-miR-144, hsa-miR-145, hsa-miR-152, hsa-miR-153, hsa-miR-191, hsa-miR-9, hsa-miR-9*, hsa-miR-125a, hsa-miR-126*, hsa-miR-126, hsa-miR-127, hsa-miR-134, hsa-miR-136, hsa-miR-146a, hsa-miR-149, hsa-miR-150, hsa-miR-154, hsa-miR-154*, hsa-miR-184, hsa-miR-185, hsa-miR-186, hsa-miR-188, hsa-miR-190, hsa-miR-193a, hsa-miR-194, hsa-miR-195, hsa-miR-206, hsa-miR-320, hsa-miR-200c, hsa-miR-155, hsa-miR-128b, hsa-miR-106b, hsa-miR-29c, hsa-miR-200a, hsa-miR-302a*, hsa-miR-302a, hsa-miR-34b, hsa-miR-34c, hsa-miR-299-3p, hsa-miR-301, hsa-miR-99b, hsa-miR-296, hsa-miR-130b, hsa-miR-30e-5p, hsa-miR-30e-3p, hsa-miR-361, hsa-miR-362, hsa-miR-363, hsa-miR-365, hsa-mir-302b*, hsa-miR-302b, hsa-miR-302c*, hsa-miR-302c, hsa-miR-302d, hsa-miR-367, hsa-miR-368, hsa-miR-369-3p, hsa-miR-370, hsa-miR-371, hsa-miR-372, hsa-miR-373*, hsa-miR-373, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377, hsa-miR-378, hsa-miR-422b, hsa-miR-379, hsa-miR-380-5p, hsa-miR-380-3p, hsa-miR-381, hsa-miR-382, hsa-miR-383, hsa-miR-340, hsa-miR-330, hsa-miR-328, hsa-miR-342, hsa-miR-337, hsa-miR-323, hsa-miR-326, hsa-miR-151, hsa-miR-135b, hsa-miR-148b, hsa-miR-331, hsa-miR-324-5p, hsa-miR-324-3p, hsa-miR-338, hsa-miR-339, hsa-miR-335, hsa-miR-133b, hsa-miR-325, hsa-miR-345, hsa-miR-346, ebv-miR-BHRF1-1,

ebv-miR-BHRF1-2*, ebv-miR-BHRF1-2, ebv-miR-BHRF1-3, ebv-miR-BART1-5p, ebv-miR-BART2, hsa-miR-384, hsa-miR-196b, hsa-miR-422a, hsa-miR-423, hsa-miR-424, hsa-miR-425-3p, hsa-miR-18b, hsa-miR-20b, hsa-miR-448, hsa-miR-429, hsa-miR-449, hsa-miR-450, hcmv-miR-UL22A, hcmv-miR-UL22A*, hcmv-miR-UL36, hcmv-miR-UL112, hcmv-miR-UL148D, hcmv-miR-US5-1, hcmv-miR-US5-2, hcmv-miR-US25-1, hcmv-miR-US25-2-5p, hcmv-miR-US25-2-3p, hcmv-miR-US33, hsa-miR-191*, hsa-miR-200a*, hsa-miR-369-5p, hsa-miR-431, hsa-miR-433, hsa-miR-329, hsa-miR-453, hsa-miR-451, hsa-miR-452, hsa-miR-452*, hsa-miR-409-5p, hsa-miR-409-3p, hsa-miR-412, hsa-miR-410, hsa-miR-376b, hsa-miR-483, hsa-miR-484, hsa-miR-485-5p, hsa-miR-485-3p, hsa-miR-486, hsa-miR-487a, kshv-miR-K12-10a, kshv-miR-K12-10b, kshv-miR-K12-11, kshv-miR-K12-1, kshv-miR-K12-2, kshv-miR-K12-9*, kshv-miR-K12-9, kshv-miR-K12-8, kshv-miR-K12-7, kshv-miR-K12-6-5p, kshv-miR-K12-6-3p, kshv-miR-K12-5, kshv-miR-K12-4-5p, kshv-miR-K12-4-3p, kshv-miR-K12-3, kshv-miR-K12-3*, hsa-miR-488, hsa-miR-489, hsa-miR-490, hsa-miR-491, hsa-miR-511, hsa-miR-146b, hsa-miR-202*, hsa-miR-202, hsa-miR-492, hsa-miR-493-5p, hsa-miR-432, hsa-miR-432*, hsa-miR-494, hsa-miR-495, hsa-miR-496, hsa-miR-193b, hsa-miR-497, hsa-miR-181d, hsa-miR-512-5p, hsa-miR-512-3p, hsa-miR-498, hsa-miR-520e, hsa-miR-515-5p, hsa-miR-515-3p, hsa-miR-519e*, hsa-miR-519e, hsa-miR-520f, hsa-miR-526c, hsa-miR-519c, hsa-miR-520a*, hsa-miR-520a, hsa-miR-526b, hsa-miR-526b*, hsa-miR-519b, hsa-miR-525, hsa-miR-525*, hsa-miR-523, hsa-miR-518f*, hsa-miR-518f, hsa-miR-520b, hsa-miR-518b, hsa-miR-526a, hsa-miR-520c, hsa-miR-518c*, hsa-miR-518c, hsa-miR-524*, hsa-miR-524, hsa-miR-517*, hsa-miR-517a, hsa-miR-519d, hsa-miR-521, hsa-miR-520d*, hsa-miR-520d, hsa-miR-517b, hsa-miR-520g, hsa-miR-516-5p, hsa-miR-516-3p, hsa-miR-518e, hsa-miR-527, hsa-miR-518a, hsa-miR-518d, hsa-miR-517c, hsa-miR-520h, hsa-miR-522, hsa-miR-519a, hsa-miR-499, hsa-miR-500, hsa-miR-501, hsa-miR-502, hsa-miR-503, hsa-miR-504, hsa-miR-505, hsa-miR-513, hsa-miR-506, hsa-miR-507, hsa-miR-508, hsa-miR-509, hsa-miR-510, hsa-miR-514, hsa-miR-532, hsa-miR-299-5p, hsa-miR-18a*, hsa-miR-455, hsa-miR-493-3p, hsa-miR-539, hsa-miR-544, hsa-miR-545, hsa-miR-487b, hsa-miR-551a, hsa-miR-552, hsa-miR-553, hsa-miR-554, hsa-miR-92b, hsa-miR-555, hsa-miR-556, hsa-miR-557, hsa-miR-558, hsa-miR-559, hsa-miR-560, hsa-miR-561, hsa-miR-562, hsa-miR-563, hsa-miR-564, hsa-miR-565, hsa-miR-566, hsa-miR-567, hsa-miR-568, hsa-miR-551b, hsa-miR-569, hsa-miR-570, hsa-miR-571, hsa-miR-572, hsa-miR-573, hsa-miR-574, hsa-miR-575, hsa-miR-576, hsa-miR-577, hsa-miR-578, hsa-miR-579, hsa-miR-580, hsa-miR-581, hsa-miR-582, hsa-miR-583, hsa-miR-584, hsa-miR-585, hsa-miR-548a, hsa-miR-586, hsa-miR-587, hsa-miR-548b, hsa-miR-588, hsa-miR-589, hsa-miR-550, hsa-miR-590, hsa-miR-591, hsa-miR-592, hsa-miR-593, hsa-miR-595, hsa-miR-596, hsa-miR-597, hsa-miR-598, hsa-miR-599, hsa-miR-600, hsa-miR-601, hsa-miR-602, hsa-miR-603, hsa-miR-604, hsa-miR-605, hsa-miR-606, hsa-miR-607, hsa-miR-608, hsa-miR-609, hsa-miR-610, hsa-miR-611, hsa-miR-612, hsa-miR-613, hsa-miR-614, hsa-miR-615, hsa-miR-616, hsa-miR-548c, hsa-miR-617, hsa-miR-618, hsa-miR-619, hsa-miR-620, hsa-miR-621, hsa-miR-622, hsa-miR-623, hsa-miR-624, hsa-miR-625, hsa-miR-626, hsa-miR-627, hsa-miR-628, hsa-miR-629, hsa-miR-630, hsa-miR-631, hsa-miR-33b, hsa-miR-632, hsa-miR-633, hsa-miR-634, hsa-miR-635, hsa-miR-636, hsa-miR-637, hsa-miR-638, hsa-miR-639, hsa-miR-640, hsa-miR-641, hsa-miR-642, hsa-miR-643, hsa-miR-644, hsa-miR-645, hsa-miR-646, hsa-miR-647, hsa-miR-648, hsa-miR-649, hsa-miR-650, hsa-miR-651, hsa-miR-652, hsa-miR-548d, hsa-miR-661, hsa-miR-662, hsa-miR-663, hsa-miR-449b, hsa-miR-653, hsa-miR-411, hsa-miR-654, hsa-miR-655, hsa-miR-656, hsa-miR-549, hsa-miR-657, hsa-miR-658, hsa-miR-659, hsa-miR-660, hsa-miR-421, hsa-miR-542-5p, hcmv-miR-US4, hcmv-miR-UL70-5p, hcmv-miR-UL70-3p, hsa-miR-363*, hsa-miR-376a*, hsa-miR-542-3p, ebv-miR-BART1-3p, hsa-miR-425-5p, ebv-miR-BART3-5p, ebv-miR-BART3-3p, ebv-miR-BART4, ebv-miR-BART5, ebv-miR-BART6-5p, ebv-miR-BART6-3p, ebv-miR-BART7, ebv-miR-BART8-5p, ebv-miR-BART8-3p, ebv-miR-BART9, ebv-miR-BART10, ebv-miR-BART11-5p, ebv-miR-BART11-3p, ebv-miR-BART12, ebv-miR-BART13, ebv-miR-BART14-5p, ebv-miR-BART14-3p, kshv-miR-K12-12, ebv-miR-BART15, ebv-miR-BART16, ebv-miR-BART17-5p, ebv-miR-BART17-3p, ebv-miR-BART18, ebv-miR-BART19, ebv-miR-BART20-5p, ebv-miR-BART20-3p, hsv1-miR-H1, hsa-miR-758, hsa-miR-671, hsa-miR-668, hsa-miR-767-5p, hsa-miR-767-3p, hsa-miR-454-5p, hsa-miR-454-3p, hsa-miR-769-5p, hsa-miR-769-3p, hsa-miR-766, hsa-miR-765, hsa-miR-768-5p, hsa-miR-768-3p, hsa-miR-770-5p, hsa-miR-802, hsa-miR-801, hsa-miR-675.

[0110] In one embodiment the single stranded oligonucleotide according to the invention is complementary to a microRNA sequence, such as a microRNA sequence selected from the group consisting of: hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-miR-15a, hsa-miR-16, hsa-miR-17-5p, hsa-miR-17-3p, hsa-miR-18a, hsa-miR-19a, hsa-miR-20a, hsa-miR-22, hsa-miR-23a, hsa-miR-189, hsa-miR-24, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27a, hsa-miR-28, hsa-miR-29a, hsa-miR-30a-5p, hsa-miR-30a-3p, hsa-miR-31, hsa-miR-32, hsa-miR-33, hsa-miR-92, hsa-miR-93, hsa-miR-95, hsa-miR-96, hsa-miR-98, hsa-miR-99a, hsa-miR-100, hsa-miR-101, hsa-miR-29b, hsa-miR-103, hsa-miR-105, hsa-miR-106a, hsa-miR-107, hsa-miR-192, hsa-miR-196a, hsa-miR-197, hsa-miR-198, hsa-miR-199a, hsa-miR-199a*, hsa-miR-208, hsa-miR-129, hsa-miR-148a, hsa-miR-30c, hsa-miR-30d, hsa-miR-139, hsa-miR-147, hsa-miR-7, hsa-miR-10a, hsa-miR-10b, hsa-miR-34a, hsa-miR-181a, hsa-miR-181b, hsa-miR-181c, hsa-miR-182, hsa-miR-182*, hsa-miR-183, hsa-miR-187, hsa-miR-199b, hsa-miR-203, hsa-miR-204, hsa-miR-205, hsa-miR-210, hsa-miR-211, hsa-miR-212, hsa-miR-181a*, hsa-miR-214, hsa-miR-215, hsa-miR-216, hsa-miR-217, hsa-miR-218, hsa-miR-219, hsa-miR-220, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-200b, hsa-let-7g, hsa-let-7i, hsa-miR-1, hsa-miR-15b, hsa-miR-23b, hsa-miR-27b, hsa-miR-30b, hsa-miR-124a, hsa-miR-125b, hsa-miR-128a, hsa-miR-130a, hsa-miR-132, hsa-miR-133a, hsa-miR-135a, hsa-miR-137, hsa-miR-138, hsa-miR-140, hsa-miR-141, hsa-miR-142-5p, hsa-miR-142-3p, hsa-miR-143, hsa-miR-144, hsa-miR-145, hsa-miR-152, hsa-miR-153, hsa-miR-191, hsa-miR-9, hsa-miR-9*, hsa-miR-125a, hsa-miR-126*, hsa-miR-126, hsa-miR-127, hsa-miR-134, hsa-miR-136, hsa-miR-146a, hsa-miR-149, hsa-miR-150, hsa-miR-154, hsa-miR-154*, hsa-miR-184, hsa-miR-185, hsa-miR-186, hsa-miR-188, hsa-miR-190, hsa-miR-193a, hsa-miR-194, hsa-miR-195, hsa-miR-206, hsa-miR-320, hsa-miR-200c, hsa-miR-128b, hsa-miR-106b, hsa-miR-29c,

hsa-miR-200a, hsa-miR-302a*, hsa-miR-302a, hsa-miR-34b, hsa-miR-34c, hsa-miR-299-3p, hsa-miR-301, hsa-miR-99b, hsa-miR-296, hsa-miR-130b, hsa-miR-30e-5p, hsa-miR-30e-3p, hsa-miR-361, hsa-miR-362, hsa-miR-363, hsa-miR-365, hsa-miR-302b*, hsa-miR-302b, hsa-miR-302c*, hsa-miR-302c, hsa-miR-302d, hsa-miR-367, hsa-miR-368, hsa-miR-369-3p, hsa-miR-370, hsa-miR-371, hsa-miR-372, hsa-miR-373*, hsa-miR-373, hsa-miR-374, hsa-miR-376a, hsa-miR-377, hsa-miR-378, hsa-miR-422b, hsa-miR-379, hsa-miR-380-5p, hsa-miR-380-3p, hsa-miR-381, hsa-miR-382, hsa-miR-383, hsa-miR-340, hsa-miR-330, hsa-miR-328, hsa-miR-342, hsa-miR-337, hsa-miR-323, hsa-miR-326, hsa-miR-151, hsa-miR-135b, hsa-miR-148b, hsa-miR-331, hsa-miR-324-5p, hsa-miR-324-3p, hsa-miR-338, hsa-miR-339, hsa-miR-335, hsa-miR-133b, hsa-miR-325, hsa-miR-345, hsa-miR-346, ebv-miR-BHRF1-1, ebv-miR-BHRF1-2*, ebv-miR-BHRF1-2, ebv-miR-BHRF1-3, ebv-miR-BART1-5p, ebv-miR-BART2, hsa-miR-384, hsa-miR-196b, hsa-miR-422a, hsa-miR-423, hsa-miR-424, hsa-miR-425-3p, hsa-miR-18b, hsa-miR-20b, hsa-miR-448, hsa-miR-429, hsa-miR-449, hsa-miR-450, hcmv-miR-UL22A, hcmv-miR-UL22A*, hcmv-miR-UL36, hcmv-miR-UL112, hcmv-miR-UL148D, hcmv-miR-US5-1, hcmv-miR-US5-2, hcmv-miR-US25-1, hcmv-miR-US25-2-5p, hcmv-miR-US25-2-3p, hcmv-miR-US33, hsa-miR-191*, hsa-miR-200a*, hsa-miR-369-5p, hsa-miR-431, hsa-miR-433, hsa-miR-329, hsa-miR-453, hsa-miR-451, hsa-miR-452, hsa-miR-452*, hsa-miR-409-5p, hsa-miR-409-3p, hsa-miR-412, hsa-miR-410, hsa-miR-376b, hsa-miR-483, hsa-miR-484, hsa-miR-485-5p, hsa-miR-485-3p, hsa-miR-486, hsa-miR-487a, kshv-miR-K12-10a, kshv-miR-K12-10b, kshv-miR-K12-11, kshv-miR-K12-1, kshv-miR-K12-2, kshv-miR-K12-9*, kshv-miR-K12-9, kshv-miR-K12-8, kshv-miR-K12-7, kshv-miR-K12-6-5p, kshv-miR-K12-6-3p, kshv-miR-K12-5, kshv-miR-K12-4-5p, kshv-miR-K12-4-3p, kshv-miR-K12-3, kshv-miR-K12-3*, hsa-miR-488, hsa-miR-489, hsa-miR-490, hsa-miR-491, hsa-miR-511, hsa-miR-146b, hsa-miR-202*, hsa-miR-202, hsa-miR-492, hsa-miR-493-5p, hsa-miR-432, hsa-miR-432*, hsa-miR-494, hsa-miR-495, hsa-miR-496, hsa-miR-193b, hsa-miR-497, hsa-miR-181d, hsa-miR-512-5p, hsa-miR-512-3p, hsa-miR-498, hsa-miR-520e, hsa-miR-515-5p, hsa-miR-515-3p, hsa-miR-519e*, hsa-miR-519e, hsa-miR-520f, hsa-miR-526c, hsa-miR-519c, hsa-miR-520a*, hsa-miR-520a, hsa-miR-526b, hsa-miR-526b*, hsa-miR-519b, hsa-miR-525, hsa-miR-525*, hsa-miR-523, hsa-miR-518f*, hsa-miR-518f, hsa-miR-520b, hsa-miR-518b, hsa-miR-526a, hsa-miR-520c, hsa-miR-518c*, hsa-miR-518c, hsa-miR-524*, hsa-miR-524, hsa-miR-517*, hsa-miR-517a, hsa-miR-519d, hsa-miR-521, hsa-miR-520d*, hsa-miR-520d, hsa-miR-517b, hsa-miR-520g, hsa-miR-516-5p, hsa-miR-516-3p, hsa-miR-518e, hsa-miR-527, hsa-miR-518a, hsa-miR-518d, hsa-miR-517c, hsa-miR-520h, hsa-miR-522, hsa-miR-519a, hsa-miR-499, hsa-miR-500, hsa-miR-501, hsa-miR-502, hsa-miR-503, hsa-miR-504, hsa-miR-505, hsa-miR-513, hsa-miR-506, hsa-miR-507, hsa-miR-508, hsa-miR-509, hsa-miR-510, hsa-miR-514, hsa-miR-532, hsa-miR-299-5p, hsa-miR-18a*, hsa-miR-455, hsa-miR-493-3p, hsa-miR-539, hsa-miR-544, hsa-miR-545, hsa-miR-487b, hsa-miR-551a, hsa-miR-552, hsa-miR-553, hsa-miR-554, hsa-miR-92b, hsa-miR-555, hsa-miR-556, hsa-miR-557, hsa-miR-558, hsa-miR-559, hsa-miR-560, hsa-miR-561, hsa-miR-562, hsa-miR-563, hsa-miR-564, hsa-miR-565, hsa-miR-566, hsa-miR-567, hsa-miR-568, hsa-miR-551b, hsa-miR-569, hsa-miR-570, hsa-miR-571, hsa-miR-572, hsa-miR-573, hsa-miR-574, hsa-miR-575, hsa-miR-576, hsa-miR-577, hsa-miR-578, hsa-miR-579, hsa-miR-580, hsa-miR-581, hsa-miR-582, hsa-miR-583, hsa-miR-584, hsa-miR-585, hsa-miR-548a, hsa-miR-586, hsa-miR-587, hsa-miR-548b, hsa-miR-588, hsa-miR-589, hsa-miR-550, hsa-miR-590, hsa-miR-591, hsa-miR-592, hsa-miR-593, hsa-miR-595, hsa-miR-596, hsa-miR-597, hsa-miR-598, hsa-miR-599, hsa-miR-600, hsa-miR-601, hsa-miR-602, hsa-miR-603, hsa-miR-604, hsa-miR-605, hsa-miR-606, hsa-miR-607, hsa-miR-608, hsa-miR-609, hsa-miR-610, hsa-miR-611, hsa-miR-612, hsa-miR-613, hsa-miR-614, hsa-miR-615, hsa-miR-616, hsa-miR-548c, hsa-miR-617, hsa-miR-618, hsa-miR-619, hsa-miR-620, hsa-miR-621, hsa-miR-622, hsa-miR-623, hsa-miR-624, hsa-miR-625, hsa-miR-626, hsa-miR-627, hsa-miR-628, hsa-miR-629, hsa-miR-630, hsa-miR-631, hsa-miR-33b, hsa-miR-632, hsa-miR-633, hsa-miR-634, hsa-miR-635, hsa-miR-636, hsa-miR-637, hsa-miR-638, hsa-miR-639, hsa-miR-640, hsa-miR-641, hsa-miR-642, hsa-miR-643, hsa-miR-644, hsa-miR-645, hsa-miR-646, hsa-miR-647, hsa-miR-648, hsa-miR-649, hsa-miR-650, hsa-miR-651, hsa-miR-652, hsa-miR-548d, hsa-miR-661, hsa-miR-662, hsa-miR-663, hsa-miR-449b, hsa-miR-653, hsa-miR-411, hsa-miR-654, hsa-miR-655, hsa-miR-656, hsa-miR-549, hsa-miR-657, hsa-miR-658, hsa-miR-659, hsa-miR-660, hsa-miR-421, hsa-miR-542-5p, hcmv-miR-US4, hcmv-miR-UL70-5p, hcmv-miR-UL70-3p, hsa-miR-363*, hsa-miR-376a*, hsa-miR-542-3p, ebv-miR-BART1-3p, hsa-miR-425-5p, ebv-miR-BART3-5p, ebv-miR-BART3-3p, ebv-miR-BART4, ebv-miR-BART5, ebv-miR-BART6-5p, ebv-miR-BART6-3p, ebv-miR-BART7, ebv-miR-BART8-5p, ebv-miR-BART8-3p, ebv-miR-BART9, ebv-miR-BART10, ebv-miR-BART11-5p, ebv-miR-BART11-3p, ebv-miR-BART12, ebv-miR-BART13, ebv-miR-BART14-5p, ebv-miR-BART14-3p, kshv-miR-K12-12, ebv-miR-BART15, ebv-miR-BART16, ebv-miR-BART17-5p, ebv-miR-BART17-3p, ebv-miR-BART18, ebv-miR-BART19, ebv-miR-BART20-5p, ebv-miR-BART20-3p, hsv1-miR-H1, hsa-miR-758, hsa-miR-671, hsa-miR-668, hsa-miR-767-5p, hsa-miR-767-3p, hsa-miR-454-5p, hsa-miR-454-3p, hsa-miR-769-5p, hsa-miR-769-3p, hsa-miR-766, hsa-miR-765, hsa-miR-768-5p, hsa-miR-768-3p, hsa-miR-770-5p, hsa-miR-802, hsa-miR-801, hsa-miR-675

[0111] Preferred single stranded oligonucleotide according to the invention are complementary to a microRNA sequence selected from the group consisting of has-miR19b, hsa-miR21, hsa-miR 122, hsa-miR 142 a7b, hsa-miR 155, hsa-miR 375.

[0112] Preferred single stranded oligonucleotide according to the invention are complementary to a microRNA sequence selected from the group consisting of hsa-miR196b and has-181a.

[0113] In one embodiment, the oligonucleotide according to the invention does not comprise a nucleobase at the 3' end that corresponds to the first 5' end nucleotide of the target microRNA.

[0114] In one embodiment, the first nucleobase of the single stranded oligonucleotide according to the invention, counting from the 3' end, is a nucleotide analogue, such as an LNA unit.

[0115] In one embodiment, the second nucleobase of the single stranded oligonucleotide according to the invention, counting from the 3' end, is a nucleotide analogue, such as an LNA unit.

[0116] In one embodiment, the ninth and/or the tenth nucleotide of the single stranded oligonucleotide according to the invention, counting from the 3' end, is a nucleotide analogue, such as an LNA unit.

[0117] In one embodiment, the ninth nucleobase of the single stranded oligonucleotide according to the invention, counting from the 3' end is a nucleotide analogue, such as an LNA unit.

[0118] In one embodiment, the tenth nucleobase of the single stranded oligonucleotide according to the invention, counting from the 3' end is a nucleotide analogue, such as an LNA unit.

[0119] In one embodiment, both the ninth and the tenth nucleobase of the single stranded oligonucleotide according to the invention, calculated from the 3' end is a nucleotide analogue, such as an LNA unit.

[0120] In one embodiment, the single stranded oligonucleotide according to the invention does not comprise a region of more than 5 consecutive DNA nucleotide units. In one embodiment, the single stranded oligonucleotide according to the invention does not comprise a region of more than 6 consecutive DNA nucleotide units. In one embodiment, the single stranded oligonucleotide according to the invention does not comprise a region of more than 7 consecutive DNA nucleotide units. In one embodiment, the single stranded oligonucleotide according to the invention does not comprise a region of more than 8 consecutive DNA nucleotide units. In one embodiment, the single stranded oligonucleotide according to the invention does not comprise a region of more than 3 consecutive DNA nucleotide units. In one embodiment, the single stranded oligonucleotide according to the invention does not comprise a region of more than 2 consecutive DNA nucleotide units.

[0121] In one embodiment, the single stranded oligonucleotide comprises at least region consisting of at least two consecutive nucleotide analogue units, such as at least two consecutive LNA units.

[0122] In one embodiment, the single stranded oligonucleotide comprises at least region consisting of at least three consecutive nucleotide analogue units, such as at least three consecutive LNA units.

[0123] In one embodiment, the single stranded oligonucleotide of the invention does not comprise a region of more than 7 consecutive nucleotide analogue units, such as LNA units. In one embodiment, the single stranded oligonucleotide of the invention does not comprise a region of more than 6 consecutive nucleotide analogue units, such as LNA units. In one embodiment, the single stranded oligonucleotide of the invention does not comprise a region of more than 5 consecutive nucleotide analogue units, such as LNA units. In one embodiment, the single stranded oligonucleotide of the invention does not comprise a region of more than 4 consecutive nucleotide analogue units, such as LNA units. In one embodiment, the single stranded oligonucleotide of the invention does not comprise a region of more than 3 consecutive nucleotide analogue units, such as LNA units. In one embodiment, the single stranded oligonucleotide of the invention does not comprise a region of more than 2 consecutive nucleotide analogue units, such as LNA units.

[0124] In one embodiment, the first or second 3' nucleobase of the single stranded oligonucleotide corresponds to the second 5' nucleotide of the microRNA sequence.

[0125] In one embodiment, nucleobase units 1 to 6 (inclusive) of the single stranded oligonucleotide as measured from the 3' end the region of the single stranded oligonucleotide are complementary to the microRNA seed region sequence.

[0126] In one embodiment, nucleobase units 1 to 7 (inclusive) of the single stranded oligonucleotide as measured from the 3' end the region of the single stranded oligonucleotide are complementary to the microRNA seed region sequence.

[0127] In one embodiment, nucleobase units 2 to 7 (inclusive) of the single stranded oligonucleotide as measured from the 3' end the region of the single stranded oligonucleotide are complementary to the microRNA seed region sequence.

[0128] In one embodiment, the single stranded oligonucleotide comprises at least one nucleotide analogue unit, such as at least one LNA unit, in a position which is within the region complementary to the miRNA seed region. The single stranded oligonucleotide may, in one embodiment comprise at between one and 6 or between 1 and 7 nucleotide analogue units, such as between 1 and 6 and 1 and 7 LNA units, in a position which is within the region complementary to the miRNA seed region.

[0129] In one embodiment, the nucleobase sequence of the single stranded oligonucleotide which is complementary to the sequence of the microRNA seed region, is selected from the group consisting of (X)Xxxxxx, (X)xXxxxx, (X)xxXxxx, (X)xxxXxx, (X)xxxxXx and (X)xxxxxX, as read in a 3'-5'direction, wherein "X" denotes a nucleotide analogue, (X) denotes an optional nucleotide analogue, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0130] In one embodiment, the single stranded oligonucleotide comprises at least two nucleotide analogue units, such as at least two LNA units, in positions which are complementary to the miRNA seed region.

[0131] In one embodiment, the nucleobase sequence of the single stranded oligonucleotide which is complementary to the sequence of the microRNA seed region, is selected from the group consisting of (X)XXxxxx, (X)XxXxxx, (X)XxxXxx, (X)XxxxXx, (X)XxxxxX, (X)xXXxxx, (X)xXxXxx, (X)xXxxXx, (X)xXxxxX, (X)xxXXxx, (X)xxXxXx, (X)xxXxxX, (X)xxxXXx, (X)xxxXxX and (X)xxxxXX, wherein "X" denotes a nucleotide analogue, such as an LNA unit, (X) denotes an optional nucleotide analogue, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0132] In one embodiment, the single stranded oligonucleotide comprises at least three nucleotide analogue units, such as at least three LNA units, in positions which are complementary to the miRNA seed region.

[0133] In one embodiment, the nucleobase sequence of the single stranded oligonucleotide which is complementary to the sequence of the microRNA seed region, is selected from the group consisting of (X)XXXxxx, (X)xXXXxx, (X)xxXXXx, (X)xxxXXX, (X)XXxXxx, (X)XXxxXx, (X)XXxxxX, (X)xXXxXx, (X)xXXxxX, (X)xxXXxX, (X)XxXXxx, (X)XxxXXx, (X)XxxxXX, (X)xXxXXx, (X)xXxxXX, (X)xxXxXX, (X)xXxXxX and (X)XxXxXx, wherein "X" denotes a nucleotide analogue, such as an LNA unit, (X) denotes an optional nucleotide analogue, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0134] In one embodiment, the single stranded oligonucleotide comprises at least four nucleotide analogue units, such as at least four LNA units, in positions which are complementary to the miRNA seed region.

[0135] In one embodiment the nucleobase sequence of the single stranded oligonucleotide which is complementary to the sequence of the microRNA seed region, is selected from

the group consisting of (X)xxXXX, (X)xXxXXX, (X)xXXxXX, (X))xXXXxX, (X))xXXXXx, (X)XxxXXXX, (X)XxXxXX, (X)XxXXxX, (X)XxXXx, (X)XXxxXX, (X)XXxXxX, (X)XXxXXx, (X)XXXxxX, (X)XXXxXx, and (X)XXXXxx, wherein "X" denotes a nucleotide analogue, such as an LNA unit, (X) denotes an optional nucleotide analogue, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0136] In one embodiment, the single stranded oligonucleotide comprises at least five nucleotide analogue units, such as at least five LNA units, in positions which are complementary to the miRNA seed region.

[0137] In one embodiment, the nucleobase sequence of the single stranded oligonucleotide which is complementary to the sequence of the microRNA seed region, is selected from the group consisting of (X)xXXXXX, (X)XxXXXX, (X)XXxXXX, (X)XXXxXX, (X)XXXXxX and (X)XXXXXx, wherein "X" denotes a nucleotide analogue, such as an LNA unit, (X) denotes an optional nucleotide analogue, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0138] In one embodiment, the single stranded oligonucleotide comprises six or seven nucleotide analogue units, such as six or seven LNA units, in positions which are complementary to the miRNA seed region.

[0139] In one embodiment, the nucleobase sequence of the single stranded oligonucleotide which is complementary to the sequence of the microRNA seed region, is selected from the group consisting of XXXXXX, XxXXXXX, XXxXXXX, XXXxXXX, XXXXxXX, XXXXXxX and XXXXXXx, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0140] In one embodiment, the two nucleobase motif at position 7 to 8, counting from the 3' end of the single stranded oligonucleotide is selected from the group consisting of xx, XX, xX and Xx, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0141] In one embodiment, the two nucleobase motif at position 7 to 8, counting from the 3' end of the single stranded oligonucleotide is selected from the group consisting of XX, xX and Xx, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0142] In one embodiment, the single stranded oligonucleotide comprises at least 12 nucleobases and wherein the two nucleobase motif at position 11 to 12, counting from the 3' end of the single stranded oligonucleotide is selected from the group consisting of xx, XX, xX and Xx, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0143] In one embodiment, the single stranded oligonucleotide comprises at least 12 nucleobases and wherein the two nucleobase motif at position 11 to 12, counting from the 3' end of the single stranded oligonucleotide is selected from the group consisting of XX, xX and Xx, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0144] In one embodiment, the single stranded oligonucleotide comprises at least 13 nucleobases and wherein the three nucleobase motif at position 11 to 13, counting from the 3' end, is selected from the group consisting of xxx, Xxx, xXx, xxX, XXx, XxX, xXX and XXX, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0145] In one embodiment, the three nucleobase motif at position 11 to 13, counting from the 3' end of the single stranded oligonucleotide, is selected from the group consisting of Xxx, xXx, xxX, XXx, XxX, xXX and XXX, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0146] In one embodiment, the single stranded oligonucleotide comprises at least 14 nucleobases and wherein the four nucleobase motif at positions 11 to 14, counting from the 3' end, is selected from the group consisting of xxxx, Xxxx, xXxx, xxXx, xxxX, XXxx, XxXx, XxxX, xXXx, xXxX, xxXX, XXXx, XxXX, xXXX, XXxX and XXXX wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0147] In one embodiment, the four nucleobase motif at position 11 to 14 of the single stranded oligonucleotide, counting from the 3' end, is selected from the group consisting of Xxxx, xXxx, xxXx, xxxX, XXxx, XxXx, XxxX, xXXx, xXxX, xxXX, XXXx, XxXX, xXXX, XXxX and XXXX, wherein "X" denotes a nucleotide analogue, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0148] In one embodiment, the single stranded oligonucleotide comprises 15 nucleobases and the five nucleobase motif at position 11 to 15, counting from the 3' end, is selected from the group consisting of Xxxxx, xXxxx, xxXxx, xxxXx, xxxxX, XXxxx, XxXxx, XxxXx, XxxxX, xXXxx, xXxXx, xXxxX, xxXXx, xxXxX, xxxXX, XXXxx, XXxxX, XxxXX, xXXXx, xxXXX, XXxXX, XxXxX, XXXXx, XXXxX, XXxXX, XxXXXX, xXXXX, and XXXXX wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0149] In one embodiment, the single stranded oligonucleotide comprises 16 nucleobases and the six nucleobase motif at positions 11 to 16, counting from the 3' end, is selected from the group consisting of Xxxxxx, xXxxxx, xxXxxx, xxxXxx, xxxxXx, xxxxxX, XXxxxx, XxXxxx, XxxXxx, XxxxXx, XxxxxX, xXXxxx, xXxXxx, xXxxXx, xXxxxX, xxXXxx, xxXxXx, xxXxxX, xxxXXx, xxxXxX, xxxxXX, XXXxxx, XXxXxx, XXxxXx, XXxxxX, XxXXxx, XxXxXx, XxXxxX, XxxXXx, XxxXxX, XxxxXX, xXXXxx, xXXxXx, xXXxxX, xXxXXx, xXxXxX, xXxxXX, xxXXXx, xxXXxX, xxXxXX, xxxXXX, XXXXxx, XXXxxX, XXxxXX, XxxXXX, xxXXXX, xXxXXX, XxXxXX, XXxXxX, XXXxXx, xXXxXX, XxXXXxX, XXxXXx, xXXXxX, XxXXXx, xXXXXx, xXXXXX, XxXXXX, XXxXXX, XXXxXX, XXXXxX, XXXXXx, and XXXXXX wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0150] In one embodiment, the six nucleobase motif at positions 11 to 16 of the single stranded oligonucleotide, counting from the 3' end, is xxXxxX, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit.

[0151] In one embodiment, the three 5' most nucleobases, is selected from the group consisting of Xxx, xXx, xxX, XXx, XxX, xXX and XXX, wherein "X" denotes a nucleotide analogue, such as an LNA unit, such as an LNA unit, and "x" denotes a DNA or RNA nucleotide unit. In one embodiment, x" denotes a DNA unit.

[0152] In one embodiment, the single stranded oligonucleotide comprises a nucleotide analogue unit, such as an LNA unit, at the 5' end.

[0153] In one embodiment, the nucleotide analogue units, such as X, are independently selected form the group consisting of: 2'-O-alkyl-RNA unit, 2'-OMe-RNA unit, 2'-amino-DNA unit, 2'-fluoro-DNA unit, LNA unit, PNA unit, HNA unit, INA unit.

[0154] In one embodiment, all the nucleobases of the single stranded oligonucleotide of the invention are nucleotide analogue units.

[0155] In one embodiment, the nucleotide analogue units, such as X, are independently selected form the group consisting of: 2'-OMe-RNA units, 2'-fluoro-DNA units, and LNA units,

[0156] In one embodiment, the single stranded oligonucleotide comprises said at least one LNA analogue unit and at least one further nucleotide analogue unit other than LNA.

[0157] In one embodiment, the non-LNA nucleotide analogue unit or units are independently selected from 2'-OMe RNA units and 2'-fluoro DNA units.

[0158] In one embodiment, the single stranded oligonucleotide consists of at least one sequence XYX or YXY, wherein X is LNA and Y is either a 2'-OMe RNA unit and 2'-fluoro DNA unit.

[0159] In one embodiment, the sequence of nucleobases of the single stranded oligonucleotide consists of alternative X and Y units.

[0160] In one embodiment, the single stranded oligonucleotide comprises alternating LNA and DNA units (Xx) or (xX).

[0161] In one embodiment, the single stranded oligonucleotide comprises a motif of alternating LNA followed by 2 DNA units (Xxx), xXx or xxX.

[0162] In one embodiment, at least one of the DNA or non-LNA nucleotide analogue units are replaced with a LNA nucleobase in a position selected from the positions identified as LNA nucleobase units in any one of the embodiments referred to above.

[0163] In one embodiment, "X" donates an LNA unit.

[0164] In one embodiment, the single stranded oligonucleotide comprises at least 2 nucleotide analogue units, such as at least 3 nucleotide analogue units, such as at least 4 nucleotide analogue units, such as at least 5 nucleotide analogue units, such as at least 6 nucleotide analogue units, such as at least 7 nucleotide analogue units, such as at least 8 nucleotide analogue units, such as at least 9 nucleotide analogue units, such as at least 10 nucleotide analogue units.

[0165] In one embodiment, the single stranded oligonucleotide comprises at least 2 LNA units, such as at least 3 LNA units, such as at least 4 LNA units, such as at least 5 LNA units, such as at least 6 LNA units, such as at least 7 LNA units, such as at least 8 LNA units, such as at least 9 LNA units, such as at least 10 LNA units.

[0166] In one embodiment wherein at least one of the nucleotide analogues, such as LNA units, is either cytosine or guanine, such as between 1-10 of the of the nucleotide analogues, such as LNA units, is either cytosine or guanine, such as 2, 3, 4, 5, 6, 7, 8, or 9 of the of the nucleotide analogues, such as LNA units, is either cytosine or guanine.

[0167] In one embodiment at least two of the nucleotide analogues such as LNA units is either cytosine or guanine. In one embodiment at least three of the nucleotide analogues such as LNA units is either cytosine or guanine. In one embodiment at least four of the nucleotide analogues such as LNA units is either cytosine or guanine. In one embodiment at least five of the nucleotide analogues such as LNA units is either cytosine or guanine. In one embodiment at least six of the nucleotide analogues such as LNA units is either cytosine or guanine. In one embodiment at least seven of the nucleotide analogues such as LNA units is either cytosine or guanine. In one embodiment at least eight of the nucleotide analogues such as LNA units is either cytosine or guanine.

[0168] In a preferred embodiment the nucleotide analogues have a higher thermal duplex stability a complementary RNA nucleotide than the binding affinity of an equivalent DNA nucleotide to said complementary RNA nucleotide.

[0169] In one embodiment, the nucleotide analogues confer enhanced serum stability to the single stranded oligonucleotide.

[0170] In one embodiment, the single stranded oligonucleotide forms an A-helix conformation with a complementary single stranded RNA molecule.

[0171] A duplex between two RNA molecules typically exists in an A-form conformation, where as a duplex between two DNA molecules typically exits in a B-form conformation. A duplex between a DNA and RNA molecule typically exists in a intermediate conformation (A/B form). The use of nucleotide analogues, such as beta-D-oxy LNA can be used to promote a more A form like conformation. Standard circular dichromisms (CD) or NMR analysis is used to determine the form of duplexes between the oligonucleotides of the invention and complementary RNA molecules.

[0172] As recruitment by the RISC complex is thought to be dependant upon the specific structural conformation of the miRNA/mRNA target, the oligonucleotides according to the present invention may, in one embodiment form a A/B-form duplex with a complementary RNA molecule.

[0173] However, we have also determined that the use of nucleotide analogues which promote the A-form structure can also be effective, such as the alpha-L isomer of LNA.

[0174] In one embodiment, the single stranded oligonucleotide forms an A/B-form conformation with a complementary single stranded RNA molecule.

[0175] In one embodiment, the single stranded oligonucleotide forms an A-form conformation with a complementary single stranded RNA molecule.

[0176] In one embodiment, the single stranded oligonucleotide according to the invention does not mediate RNAseH based cleavage of a complementary single stranded RNA molecule. Typically a stretch of at least 5 (typically not effective for RNAse H recruitment), more preferably at least 6, more preferably at least 7 or 8 consecutive DNA nucleobases (or alternative nucleobases which can recruit RNAseH, such as alpha L-amino LNA) are required in order for an oligonucleotide to be effective in recruitment of RNAseH.

[0177] EP 1 222 309 provides in vitro methods for determining RNaseH activity, which may be used to determine the ability to recruit RNaseH. A compound is deemed capable of recruiting RNase H if, when provided with the complementary RNA target, it has an initial rate, as measured in pmol/l/min, of at least 1%, such as at least 5%, such as at least 10% or less than 20% of the equivalent DNA only oligonucleotide, with no 2' substitutions, with phosphorothiote linkage groups between all nucleotides in the oligonucleotide, using the methodology provided by Example 91-95 of EP 1 222 309.

[0178] A compound is deemed essentially incapable of recruiting RNaseH if, when provided with the complemen-

tary RNA target, and RNaseH, the RNaseH initial rate, as measured in pmol/l/min, is less than 1%, such as less than 5%, such as less than 10% or less than 20% of the initial rate determined using the equivalent DNA only oligonucleotide, with no 2' substitutions, with phosphiothiote linkage groups between all nucleotides in the oligonucleotide, using the methodology provided by Example 91-95 of EP 1 222 309.

[0179] In a highly preferred embodiment, the single stranded oligonucleotide of the invention is capable of forming a duplex with a complementary single stranded RNA nucleic acid molecule (typically of about the same length of said single stranded oligonucleotide) with phosphodiester internucleoside linkages, wherein the duplex has a T_m of at least about 60° C., indeed it is preferred that the single stranded oligonucleotide is capable of forming a duplex with a complementary single stranded RNA nucleic acid molecule with phosphodiester internucleoside linkages, wherein the duplex has a T_m of between about 70° C. to about 95° C., such as a T_m of between about 70° C. to about 90° C., such as between about 70° C. and about 85° C.

[0180] In one embodiment, the single stranded oligonucleotide is capable of forming a duplex with a complementary single stranded DNA nucleic acid molecule with phosphodiester internucleoside linkages, wherein the duplex has a T_m of between about 50° C. to about 95° C., such as between about 50° C. to about 90° C., such as at least about 55° C., such as at least about 60° C., or no more than about 95° C.

[0181] The single stranded oligonucleotide may, in one embodiment have a length of between 14-16 nucleobases, including 15 nucleobases.

[0182] In one embodiment, the LNA unit or units are independently selected from the group consisting of oxy-LNA, thio-LNA, and amino-LNA, in either of the D-β and L-α configurations or combinations thereof.

[0183] In one specific embodiment the LNA units may be an ENA nucleobase.

[0184] In one the embodiment the LNA units are beta D oxy-LNA.

[0185] In one embodiment the LNA units are in alpha-L amino LNA.

[0186] In a preferable embodiment, the single stranded oligonucleotide comprises between 3 and 17 LNA units.

[0187] In one embodiment, the single stranded oligonucleotide comprises at least one internucleoside linkage group which differs from phosphate.

[0188] In one embodiment, the single stranded oligonucleotide comprises at least one phosphorothioate internucleoside linkage.

[0189] In one embodiment, the single stranded oligonucleotide comprises phosphodiester and phosphorothioate linkages.

[0190] In one embodiment, the all the internucleoside linkages are phosphorothioate linkages.

[0191] In one embodiment, the single stranded oligonucleotide comprises at least one phosphodiester internucleoside linkage.

[0192] In one embodiment, all the internucleoside linkages of the single stranded oligonucleotide of the invention are phosphodiester linkages.

[0193] In one embodiment, pharmaceutical composition according to the invention comprises a carrier such as saline or buffered saline.

[0194] In one embodiment, the method for the synthesis of a single stranded oligonucleotide targeted against a human microRNA, is performed in the 3' to 5' direction a-f.

[0195] The method for the synthesis of the single stranded oligonucleotide according to the invention may be performed using standard solid phase oligonucleotide synthesis.

[0196] Definitions

[0197] The term 'nucleobase' refers to nucleotides, such as DNA and RNA, and nucleotide analogues.

[0198] The term "oligonucleotide" (or simply "oligo") refers, in the context of the present invention, to a molecule formed by covalent linkage of two or more nucleobases. When used in the context of the oligonucleotide of the invention (also referred to the single stranded oligonucleotide), the term "oligonucleotide" may have, in one embodiment, for example between 8-26 nucleobases, such as between 10 to 26 nucleobases such between 12 to 26 nucleobases. In a preferable embodiment, as detailed herein, the oligonucleotide of the invention has a length of between 8-17 nucleobases, such as between 20-27 nucleobases such as between 8-16 nucleobases, such as between 12-15 nucleobases,

[0199] In such an embodiment, the oligonucleotide of the invention may have a length of 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 nucleobases.

[0200] It will be recognised that for shorter oligonucleotides it may be necessary to increase the proportion of (high affinity) nucleotide analogues, such as LNA. Therefore in one embodiment at least about 30% of the nucleobases are nucleotide analogues, such as at least about 33%, such as at least about 40%, or at least about 50% or at least about 60%, such as at least about 66%, such as at least about 70%, such as at least about 80%, or at least about 90%. It will also be apparent that the oligonucleotide may comprise of a nucleobase sequence which consists of only nucleotide analogue sequences.

[0201] Herein, the term "nitrogenous base" is intended to cover purines and pyrimidines, such as the DNA nucleobases A, C, T and G, the RNA nucleobases A, C, U and G, as well as non-DNA/RNA nucleobases, such as 5-methylcytosine (^{Me}C), isocytosine, pseudoisocytosine, 5-bromouracil, 5-propynyluracil, 5-propyny-6-fluoroluracil, 5-methylthiazoleuracil, 6-aminopurine, 2-aminopurine, inosine, 2,6-diaminopurine, 7-propyne-7-deazaadenine, 7-propyne-7-deazaguanine and 2-chloro-6-aminopurine, in particular ^{Me}C. It will be understood that the actual selection of the non-DNA/RNA nucleobase will depend on the corresponding (or matching) nucleotide present in the microRNA strand which the oligonucleotide is intended to target. For example, in case the corresponding nucleotide is G it will normally be necessary to select a non-DNA/RNA nucleobase which is capable of establishing hydrogen bonds to G. In this specific case, where the corresponding nucleotide is G, a typical example of a preferred non-DNA/RNA nucleobase is ^{Me}C.

[0202] The term "internucleoside linkage group" is intended to mean a group capable of covalently coupling together two nucleobases, such as between DNA units, between DNA units and nucleotide analogues, between two non-LNA units, between a non-LNA unit and an LNA unit, and between two LNA units, etc. Preferred examples include phosphate, phosphodiester groups and phosphorothioate groups.

[0203] The internucleoside linkage may be selected form the group consisting of: —O—$P(O)_2$—O—, —O—P(O,S)—O—, —O—$P(S)_2$—O—, —S—$P(O)_2$—O—, —S—P(O,

S)—O—, —S—P(S)$_2$—O—, —O—P(O)$_2$—S—, —O—P(O,S)—S—, —S—P(O)$_2$—S—, —O—PO(R^H)—O—, O—PO(OCH$_3$)—O—, —O—PO(NR^H)—O—, —O—PO(OCH$_2$CH$_2$S—R)—O—, —O—PO(BH$_3$)—O—, —O—PO(NHR^H)—O—, —O—P(O)$_2$—NR^H—, —NR^H—P(O)$_2$—O—, —NR^H—CO—O—, —NR^H—CO—NR^H, and/or the internucleoside linkage may be selected form the group consisting of: —O—CO—O—, —O—CO—NR^H—, —NR^H—CO—CH$_2$—, —O—CH$_2$—CO—NR^H—, —O—CH$_2$—CH$_2$—NR^H—, —CO—NR^H—CH$_2$—, —CH$_2$—NR^H—CO—, —O—CH$_2$—CH$_2$—S—, —S—CH$_2$—CH$_2$—O—, —S—CH$_2$—CH$_2$—S—, —CH$_2$—SO$_2$—CH$_2$—, —CH$_2$—CO—NR^H—, —O—CH$_2$—CH$_2$—NR^H—CO—, —CH$_2$—NCH$_3$—O—CH$_2$—, where R^H is selected from hydrogen and C$_{1-4}$-alkyl. Suitably, in some embodiments, sulphur (S) containing internucleoside linkages as provided above may be preferred

[0204] The terms "corresponding to" and "corresponds to" as used in the context of oligonucleotides refers to the comparison between either a nucleobase sequence of the compound of the invention, and the reverse complement thereof, or in one embodiment between a nucleobase sequence and an equivalent (identical) nucleobase sequence which may for example comprise other nucleobases but retains the same base sequence, or complement thereof. Nucleotide analogues are compared directly to their equivalent or corresponding natural nucleotides. Sequences which form the reverse complement of a sequence are referred to as the complement sequence of the sequence.

[0205] When referring to the length of a nucleotide molecule as referred to herein, the length corresponds to the number of monomer units, i.e. nucleobases, irrespective as to whether those monomer units are nucleotides or nucleotide analogues. With respect to nucleobases, the terms monomer and unit are used interchangeably herein.

[0206] It should be understood that when the term "about" is used in the context of specific values or ranges of values, the disclosure should be read as to include the specific value or range referred to.

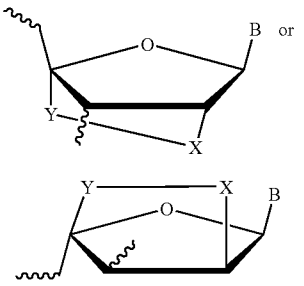
[0207] Preferred DNA analogues includes DNA analogues where the 2'-H group is substituted with a substitution other than —OH (RNA) e.g. by substitution with —O—CH$_3$, —O—CH$_2$—CH$_2$—O—CH$_3$, —O—CH$_2$—CH$_2$—CH$_2$—NH$_2$, —O—CH$_2$—CH$_2$—CH$_2$—OH or —F.

[0208] Preferred RNA analogues includes RNA analogues which have been modified in its 2'-OH group, e.g. by substitution with a group other than —H (DNA), for example —O—CH$_3$, —O—CH$_2$—CH$_2$—O—CH$_3$, —O—CH$_2$—CH$_2$—CH$_2$—NH$_2$, —O—CH$_2$—CH$_2$—CH$_2$—OH or —F.

[0209] In one embodiment the nucleotide analogue is "ENA".

[0210] When used in the present context, the terms "LNA unit", "LNA monomer", "LNA residue", "locked nucleic acid unit", "locked nucleic acid monomer" or "locked nucleic acid residue", refer to a bicyclic nucleoside analogue. LNA units are described in inter alia WO 99/14226, WO 00/56746, WO 00/56748, WO 01/25248, WO 02/28875, WO 03/006475 and WO 03/095467. The LNA unit may also be defined with respect to its chemical formula. Thus, an "LNA unit", as used herein, has the chemical structure shown in Scheme 1 below:

Scheme 1



[0211] wherein

[0212] X is selected from the group consisting of O, S and NR^H, where R^H is H or C$_{1-4}$-alkyl;

[0213] Y is (—CH$_2$)$_r$, where r is an integer of 1-4; and

[0214] B is a nitrogenous base.

[0215] When referring to substituting a DNA unit by its corresponding LNA unit in the context of the present invention, the term "corresponding LNA unit" is intended to mean that the DNA unit has been replaced by an LNA unit containing the same nitrogenous base as the DNA unit that it has replaced, e.g. the corresponding LNA unit of a DNA unit containing the nitrogenous base A also contains the nitrogenous base A. The exception is that when a DNA unit contains the base C, the corresponding LNA unit may contain the base C or the base ^{Me}C, preferably ^{Me}C.

[0216] Herein, the term "non-LNA unit" refers to a nucleoside different from an LNA-unit, i.e. the term "non-LNA unit" includes a DNA unit as well as an RNA unit. A preferred non-LNA unit is a DNA unit.

[0217] The terms "unit", "residue" and "monomer" are used interchangeably herein.

[0218] The term "at least one" encompasses an integer larger than or equal to 1, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 and so forth.

[0219] The terms "a" and "an" as used about a nucleotide, an agent, an LNA unit, etc., is intended to mean one or more. In particular, the expression "a component (such as a nucleotide, an agent, an LNA unit, or the like) selected from the group consisting of . . . " is intended to mean that one or more of the cited components may be selected. Thus, expressions like "a component selected from the group consisting of A, B and C" is intended to include all combinations of A, B and C, i.e. A, B, C, A+B, A+C, B+C and A+B+C.

[0220] The term "thio-LNA unit" refers to an LNA unit in which X in Scheme 1 is S. A thio-LNA unit can be in both the beta-D form and in the alpha-L form. Generally, the beta-D form of the thio-LNA unit is preferred. The beta-D-form and alpha-L-form of a thio-LNA unit are shown in Scheme 3 as compounds 3A and 3B, respectively.

[0221] The term "amino-LNA unit" refers to an LNA unit in which X in Scheme 1 is NH or NR^H, where R^H is hydrogen or C$_{1-4}$-alkyl. An amino-LNA unit can be in both the beta-D form and in the alpha-L form. Generally, the beta-D form of the amino-LNA unit is preferred. The beta-D-form and alpha-L-form of an amino-LNA unit are shown in Scheme 4 as compounds 4A and 4B, respectively.

[0222] The term "oxy-LNA unit" refers to an LNA unit in which X in Scheme 1 is O. An Oxy-LNA unit can be in both

the beta-D form and in the alpha-L form. Generally, the beta-D form of the oxy-LNA unit is preferred. The beta-D form and the alpha-L form of an oxy-LNA unit are shown in Scheme 5 as compounds 5A and 5B, respectively.

[0223] In the present context, the term "C_{1-6}-alkyl" is intended to mean a linear or branched saturated hydrocarbon chain wherein the longest chains has from one to six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl and hexyl. A branched hydrocarbon chain is intended to mean a C_{1-6}-alkyl substituted at any carbon with a hydrocarbon chain.

[0224] In the present context, the term "C_{1-4}-alkyl" is intended to mean a linear or branched saturated hydrocarbon chain wherein the longest chains has from one to four carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. A branched hydrocarbon chain is intended to mean a C_{1-4}-alkyl substituted at any carbon with a hydrocarbon chain.

[0225] When used herein the term "C_{1-6}-alkoxy" is intended to mean C_{1-6}-alkyl-oxy, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy and hexoxy.

[0226] In the present context, the term "C_{2-6}-alkenyl" is intended to mean a linear or branched hydrocarbon group having from two to six carbon atoms and containing one or more double bonds. Illustrative examples of C_{2-6}-alkenyl groups include allyl, homo-allyl, vinyl, crotyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl and hexadienyl. The position of the unsaturation (the double bond) may be at any position along the carbon chain.

[0227] In the present context the term "C_{2-6}-alkynyl" is intended to mean linear or branched hydrocarbon groups containing from two to six carbon atoms and containing one or more triple bonds. Illustrative examples of C_{2-6}-alkynyl groups include acetylene, propynyl, butynyl, pentynyl and hexynyl. The position of unsaturation (the triple bond) may be at any position along the carbon chain. More than one bond may be unsaturated such that the "C_{2-6}-alkynyl" is a di-yne or enedi-yne as is known to the person skilled in the art.

[0228] As used herein, "hybridisation" means hydrogen bonding, which may be Watson-Crick, Hoogsteen, reversed Hoogsteen hydrogen bonding, etc., between complementary nucleoside or nucleotide bases. The four nucleobases commonly found in DNA are G, A, T and C of which G pairs with C, and A pairs with T. In RNA T is replaced with uracil (U), which then pairs with A. The chemical groups in the nucleobases that participate in standard duplex formation constitute the Watson-Crick face. Hoogsteen showed a couple of years later that the purine nucleobases (G and A) in addition to their Watson-Crick face have a Hoogsteen face that can be recognised from the outside of a duplex, and used to bind pyrimidine oligonucleotides via hydrogen bonding, thereby forming a triple helix structure.

[0229] In the context of the present invention "complementary" refers to the capacity for precise pairing between two nucleotides sequences with one another. For example, if a nucleotide at a certain position of an oligonucleotide is capable of hydrogen bonding with a nucleotide at the corresponding position of a DNA or RNA molecule, then the oligonucleotide and the DNA or RNA are considered to be complementary to each other at that position. The DNA or RNA strand are considered complementary to each other when a sufficient number of nucleotides in the oligonucleotide can form hydrogen bonds with corresponding nucleotides in the target DNA or RNA to enable the formation of a stable complex. To be stable in vitro or in vivo the sequence of an oligonucleotide need not be 100% complementary to its target microRNA. The terms "complementary" and "specifically hybridisable" thus imply that the oligonucleotide binds sufficiently strong and specific to the target molecule to provide the desired interference with the normal function of the target whilst leaving the function of non-target RNAs unaffected.

[0230] In a preferred example the oligonucleotide of the invention is 100% complementary to a human microRNA sequence, such as one of the microRNA sequences referred to herein.

[0231] In a preferred example, the oligonucleotide of the invention comprises a contiguous sequence which is 100% complementary to the seed region of the human microRNA sequence.

[0232] MicroRNAs are short, non-coding RNAs derived from endogenous genes that act as post-transcriptional regulators of gene expression. They are processed from longer (ca 70-80 nt) hairpin-like precursors termed pre-miRNAs by the RNAse III enzyme Dicer. MicroRNAs assemble in ribonucleoprotein complexes termed miRNPs and recognize their target sites by antisense complementarity thereby mediating down-regulation of their target genes. Near-perfect or perfect complementarity between the miRNA and its target site results in target mRNA cleavage, whereas limited complementarity between the microRNA and the target site results in translational inhibition of the target gene.

[0233] The term "microRNA" or "miRNA", in the context of the present invention, means an RNA oligonucleotide consisting of between 18 to 25 nucleotides in length. In functional terms miRNAs are typically regulatory endogenous RNA molecules.

[0234] The terms "target microRNA" or "target miRNA" refer to a microRNA with a biological role in human disease, e.g. an upregulated, oncogenic miRNA or a tumor suppressor miRNA in cancer, thereby being a target for therapeutic intervention of the disease in question.

[0235] The terms "target gene" or "target mRNA" refer to regulatory mRNA targets of microRNAs, in which said "target gene" or "target mRNA" is regulated post-transcriptionally by the microRNA based on near-perfect or perfect complementarity between the miRNA and its target site resulting in target mRNA cleavage; or limited complementarity, often conferred to complementarity between the so-called seed sequence (nucleotides 2-7 of the miRNA) and the target site resulting in translational inhibition of the target mRNA.

[0236] In the context of the present invention the oligonucleotide is single stranded, this refers to the situation where the oligonucleotide is in the absence of a complementary oligonucleotide—i.e. it is not a double stranded oligonucleotide complex, such as an siRNA. In one embodiment, the composition according to the invention does not comprise a further oligonucleotide which has a region of complementarity with the single stranded oligonucleotide of five or more consecutive nucleobases, such as eight or more, or 12 or more of more consecutive nucleobases. It is considered that the further oligonucleotide is not covalently linked to the single stranded oligonucleotide.

[0237] Modification of Nucleotides in Positions 3 to 8, Counting from the 3' End

[0238] In the following embodiments which refer to the modification of nucleotides in positions 3 to 8, counting from

the 3' end, the LNA units may be replaced with other nucleotide analogues, such as those referred to herein. "X" may, therefore be selected from the group consisting of 2'-O-alkyl-RNA unit, 2'-OMe-RNA unit, 2'-amino-DNA unit, 2'-fluoro-DNA unit, LNA unit, PNA unit, HNA unit, INA unit. "x" is preferably DNA or RNA, most preferably DNA.

[0239] In an interesting embodiment of the invention, the oligonucleotides of the invention are modified in positions 3 to 8, counting from the 3' end. The design of this sequence may be defined by the number of non-LNA units present or by the number of LNA units present. In a preferred embodiment of the former, at least one, such as one, of the nucleotides in positions three to eight, counting from the 3' end, is a non-LNA unit. In another embodiment, at least two, such as two, of the nucleotides in positions three to eight, counting from the 3' end, are non-LNA units. In yet another embodiment, at least three, such as three, of the nucleotides in positions three to eight, counting from the 3' end, are non-LNA units. In still another embodiment, at least four, such as four, of the nucleotides in positions three to eight, counting from the 3' end, are non-LNA units. In a further embodiment, at least five, such as five, of the nucleotides in positions three to eight, counting from the 3' end, are non-LNA units. In yet a further embodiment, all six nucleotides in positions three to eight, counting from the 3' end, are non-LNA units. In a preferred embodiment, said non-LNA unit is a DNA unit.

[0240] Alternatively defined, in a preferred embodiment, the oligonucleotide according to the invention comprises at least one LNA unit in positions three to eight, counting from the 3' end. In an embodiment thereof, the oligonucleotide according to the present invention comprises one LNA unit in positions three to eight, counting from the 3' end. The substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, may be selected from the group consisting of Xxxxxx, xXxxxx, xxXxxx, xxxXxx, xxxxXx and xxxxxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0241] In another embodiment, the oligonucleotide according to the present invention comprises at least two LNA units in positions three to eight, counting from the 3' end. In an embodiment thereof, the oligonucleotide according to the present invention comprises two LNA units in positions three to eight, counting from the 3' end. The substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, may be selected from the group consisting of XXxxxx, XxXxxx, XxxXxx, XxxxXx, XxxxxX, xXXxxx, xXxXxx, xXxxXx, xXxxxX, xxXXxx, xxXxXx, xxXxxX, xxxXXx, xxxXxX and xxxxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a preferred embodiment, the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of XxXxxx, XxxXxx, XxxxXx, XxxxxX, xXxXxx, xXxxXx, xXxxxX, xxXxXx, xxXxxX and xxxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a more preferred embodiment, the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of xXxXxx, xXxxXx, xXxxxX, xxXxXx, xxXxxX and xxxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In an even more preferred embodiment, the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of xXxXxx, xXxxXx, xXxxxX, xxXxXx, xxXxxX and xxxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a most preferred embodiment, the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is xXxXxx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0242] In yet another embodiment, the oligonucleotide according to the present invention comprises at least three LNA units in positions three to eight, counting from the 3' end. In an embodiment thereof, the oligonucleotide according to the present invention comprises three LNA units in positions three to eight, counting from the 3' end. The substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, may be selected from the group consisting of XXXxxx, xXXXxx, xxXXXx, xxxXXX, XXxXxx, XXxxXx, XXxxxX, xXXxXx, xXXxxX, xxXXxX, XxXXxx, XxxXXx, XxxxXX, xXxXXx, xXxxXX, xxXxXX, xXxXxX and XxXxXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a preferred embodiment, the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of XXxXxx, XXxxXx, XXxxxX, xXXxXx, xXXxxX, xxXXxX, XxXXxx, XxxXXx, XxxxXX, xXxXXx, xXxxXX, xxXxXX, xXxXxX and XxXxXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a more preferred embodiment, the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of xXXxXx, xXXxxX, xxXXxX, xXxXXx, xXxxXX, xxXxXX and xXxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In an even more preferred embodiment, the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is xXxXxX or XxXxXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a most preferred embodiment, the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is xXxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0243] In a further embodiment, the oligonucleotide according to the present invention comprises at least four LNA units in positions three to eight, counting from the 3' end. In an embodiment thereof, the oligonucleotide according to the present invention comprises four LNA units in positions three to eight, counting from the 3' end. The substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, may be selected from the group consisting of xxXXXX, xXxXXX, xXXxXX, xXXXxX, xXXXXx, XxxXXX, XxXxXX, XxXXxX, XxXXXx, XXxxXX, XXxXxX, XXxXXx, XXXxxX, XXXxXx and XXXXxx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0244] In yet a further embodiment, the oligonucleotide according to the present invention comprises at least five LNA units in positions three to eight, counting from the 3' end. In an embodiment thereof, the oligonucleotide according to the present invention comprises five LNA units in positions three to eight, counting from the 3' end. The substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, may be selected from the group consisting of xXXXXX, XxXXXX, XXxXXX, XXXxXX, XXXXxX and XXXXXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0245] Preferably, the oligonucleotide according to the present invention comprises one or two LNA units in posi-

tions three to eight, counting from the 3' end. This is considered advantageous for the stability of the A-helix formed by the oligo:microRNA duplex, a duplex resembling an RNA: RNA duplex in structure.

[0246] In a preferred embodiment, said non-LNA unit is a DNA unit.

[0247] Variation of the Length of the Oligonucleotides

[0248] The length of the oligonucleotides of the invention need not match the length of the target microRNAs exactly. Accordingly, the length of the oligonucleotides of the invention may vary. Indeed it is considered advantageous to have short oligonucleotides, such as between 10-17 or 10-16 nucleobases.

[0249] In one embodiment, the oligonucleotide according to the present has a length of from 8 to 24 nucleotides, such as 10 to 24, between 12 to 24 nucleotides, such as a length of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 nucleotides, preferably a length of from 10-22, such as between 12 to 22 nucleotides, such as a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22 nucleotides, more preferably a length of from 10-20, such as between 12 to 20 nucleotides, such as a length of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 nucleotides, even more preferably a length of from 10 to 19, such as between 12 to 19 nucleotides, such as a length of 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 nucleotides, e.g. a length of from 10 to 18, such as between 12 to 18 nucleotides, such as a length of 10, 11, 12, 13, 14, 15, 16, 17 or 18 nucleotides, more preferably a length of from 10-17, such as from 12 to 17 nucleotides, such as a length of 10, 11, 12, 13, 14, 15, 16 or 17 nucleotides, most preferably a length of from 10 to 16, such as between 12 to 16 nucleotides, such as a length of 10, 11, 12, 13, 14, 15 or 16 nucleotides.

[0250] Modification of Nucleotides from Position 11, Counting from the 3' End, to the 5' End

[0251] The substitution pattern for the nucleotides from position 11, counting from the 3' end, to the 5' end may include nucleotide analogue units (such as LNA) or it may not. In a preferred embodiment, the oligonucleotide according to the present invention comprises at least one nucleotide analogue unit (such as LNA), such as one nucleotide analogue unit, from position 11, counting from the 3' end, to the 5' end. In another preferred embodiment, the oligonucleotide according to the present invention comprises at least two nucleotide analogue units, such as LNA units, such as two nucleotide analogue units, from position 11, counting from the 3' end, to the 5' end.

[0252] In the following embodiments which refer to the modification of nucleotides in the nucleobases from position 11 to the 5' end of the oligonucleotide, the LNA units may be replaced with other nucleotide analogues, such as those referred to herein. "X" may, therefore be selected from the group consisting of 2'-O-alkyl-RNA unit, 2'-OMe-RNA unit, 2'-amino-DNA unit, 2'-fluoro-DNA unit, LNA unit, PNA unit, HNA unit, INA unit. "x" is preferably DNA or RNA, most preferably DNA.

[0253] In one embodiment, the oligonucleotide according to the present invention has the following substitution pattern, which is repeated from nucleotide eleven, counting from the 3' end, to the 5' end: xXxX or XxXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In another embodiment, the oligonucleotide according to the present invention has the following substitution pattern, which is repeated from nucleotide eleven, counting from the 3' end, to the 5' end: XxxXxx, xXxxXx or xxXxxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In yet another embodiment, the oligonucleotide according to the present invention has the following substitution pattern, which is repeated from nucleotide eleven, counting from the 3' end, to the 5' end: XxxxXxxx, xXxxxXxx, xxXxxxXx or xxxXxxxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0254] The specific substitution pattern for the nucleotides from position 11, counting from the 3' end, to the 5' end depends on the number of nucleotides in the oligonucleotides according to the present invention. In a preferred embodiment, the oligonucleotide according to the present invention contains 12 nucleotides and the substitution pattern for positions 11 to 12, counting from the 3' end, is selected from the group consisting of xX and Xx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a more preferred embodiment thereof, the substitution pattern for positions 11 to 12, counting from the 3' end, is xX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. Alternatively, no LNA units are present in positions 11 to 12, counting from the 3' end, i.e. the substitution pattern is xx.

[0255] In another preferred embodiment, the oligonucleotide according to the present invention contains 13 nucleotides and the substitution pattern for positions 11 to 13, counting from the 3' end, is selected from the group consisting of Xxx, xXx, xxX, XXx, XxX, xXX and XXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a more preferred embodiment thereof, the substitution pattern for positions 11 to 13, counting from the 3' end, is selected from the group consisting of xXx, xxX and xXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a most preferred embodiment thereof, the substitution pattern for positions 11 to 13, counting from the 3' end, is xxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. Alternatively, no LNA units are present in positions 11 to 13, counting from the 3' end, i.e. the substitution pattern is xxx.

[0256] In yet another preferred embodiment, the oligonucleotide according to the present invention contains 14 nucleotides and the substitution pattern for positions 11 to 14, counting from the 3' end, is selected from the group consisting of Xxxx, xXxx, xxXx, xxxX, XXxx, XxXx, XxxX, xXXx, xXxX and xxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a preferred embodiment thereof, the substitution pattern for positions 11 to 14, counting from the 3' end, is selected from the group consisting of xXxx, xxXx, xxxX, xXxX and xxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a more preferred embodiment thereof, the substitution pattern for positions 11 to 14, counting from the 3' end, is xXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. Alternatively, no LNA units are present in positions 11 to 14, counting from the 3' end, i.e. the substitution pattern is xxxx

[0257] In a further preferred embodiment, the oligonucleotide according to the present invention contains 15 nucleotides and the substitution pattern for positions 11 to 15, counting from the 3' end, is selected from the group consisting of Xxxxx, xXxxx, xxXxx, xxxXx, xxxxX, XXxxx, XxXxx, XxxXx, XxxxX, xXXxx, xXxXx, xXxxX, xxXXx, xxXxX, xxxXX and XxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a preferred embodiment thereof, the substitution pattern for positions 11 to 15, counting from the 3' end, is selected from the group consisting of xxXxx, XxXxx, XxxXx, xXxXx, xXxxX and xxXxX,

wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a more preferred embodiment thereof, the substitution pattern for positions 11 to 15, counting from the 3' end, is selected from the group consisting of xxXxx, xXxXx, xXxxX and xxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In an even more preferred embodiment thereof, the substitution pattern for positions 11 to 15, counting from the 3' end, is selected from the group consisting of xXxxX and xxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a most preferred embodiment, the substitution pattern for positions 11 to 15, counting from the 3' end, is xxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. Alternatively, no LNA units are present in positions 11 to 15, counting from the 3' end, i.e. the substitution pattern is xxxxx

[0258] In yet a further preferred embodiment, the oligonucleotide according to the present invention contains 16 nucleotides and the substitution pattern for positions 11 to 16, counting from the 3' end, is selected from the group consisting of Xxxxxx, xXxxxx, xxXxxx, xxxXxx, xxxxXx, xxxxxX, XXxxxx, XxXxxx, XxxXxx, XxxxXx, XxxxxX, xXXxxx, xXxXxx, xXxxXx, xXxxxX, xxXXxx, xxXxXx, xxXxxX, xxxXXx, xxxXxX, xxxxXX, XXXxxx, XXxXxx, XXxxXx, XXxxxX, XxXXxx, XxXxXx, XxXxxX, XxxXXx, XxxXxX, XxxxXX, xXXXxx, xXXxXx, xXXxxX, xXxXXx, xXxXxX, xXxxXX, xxXXXx, xxXXxX, xxXxXX and xxxXXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a preferred embodiment thereof, the substitution pattern for positions 11 to 16, counting from the 3' end, is selected from the group consisting of XxxXxx, xXxXxx, xXxxXx, xxXxXx, xxXxxX, XxXxXx, XxXxxX, XxxXxX, xXxXxX, xXxxXX and xxXxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a more preferred embodiment thereof, the substitution pattern for positions 11 to 16, counting from the 3' end, is selected from the group consisting of xXxXxx, xXxxXx, xxXxXx, xxXxxX, xXxXxX, xXxxXX and xxXxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In an even more preferred embodiment thereof, the substitution pattern for positions 11 to 16, counting from the 3' end, is selected from the group consisting of xxXxxX, xXxXxX, xXxxXX and xxXxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a still more preferred embodiment thereof, the substitution pattern for positions 11 to 16, counting from the 3' end, is selected from the group consisting of xxXxxX and xXxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. In a most preferred embodiment thereof, the substitution pattern for positions 11 to 16, counting from the 3' end, is xxXxxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. Alternatively, no LNA units are present in positions 11 to 16, counting from the 3' end, i.e. the substitution pattern is xxxxxx

[0259] In a preferred embodiment of the invention, the oligonucleotide according to the present invention contains an LNA unit at the 5' end. In another preferred embodiment, the oligonucleotide according to the present invention contains an LNA unit at the first two positions, counting from the 5' end.

[0260] In a particularly preferred embodiment, the oligonucleotide according to the present invention contains 13 nucleotides and the substitution pattern, starting from the 3' end, is XXxXxXxxXXxxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. The preferred sequence for this embodiment, starting from the 3' end, is CCtCaCacT-GttA, wherein a capital letter denotes a nitrogenous base in an LNA-unit and a small letter denotes a nitrogenous base in a non-LNA unit.

[0261] In another particularly preferred embodiment, the oligonucleotide according to the present invention contains 15 nucleotides and the substitution pattern, starting from the 3' end, is XXxXxXxxXXxxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit. The preferred sequence for this embodiment, starting from the 3' end, is CCtCaCacTGttAcC, wherein a capital letter denotes a nitrogenous base in an LNA-unit and a small letter denotes a nitrogenous base in a non-LNA unit.

[0262] Modification of the Internucleoside Linkage Group

[0263] Typical internucleoside linkage groups in oligonucleotides are phosphate groups, but these may be replaced by internucleoside linkage groups differing from phosphate. In a further interesting embodiment of the invention, the oligonucleotide of the invention is modified in its internucleoside linkage group structure, i.e. the modified oligonucleotide comprises an internucleoside linkage group which differs from phosphate. Accordingly, in a preferred embodiment, the oligonucleotide according to the present invention comprises at least one internucleoside linkage group which differs from phosphate.

[0264] Specific examples of internucleoside linkage groups which differ from phosphate (—O—P(O)$_2$—O—) include —O—P(O,S)—O—, —O—P(S)$_2$—O—, —S—P(O)$_2$—O—, —S—P(O,S)—O—, —S—P(S)$_2$—O—, —O—P(O)$_2$—S—, —O—P(O,S)—S—, —S—P(O)$_2$—S—, —O—PO(R^H)—O—, O—PO(OCH$_3$)—O—, —O—PO(NR^H)—O—, —O—PO(OCH$_2$CH$_2$S—R)—O—, —O—PO(BH$_3$)—O—, —O—PO(NHR^H)—O—, —O—P(O)$_2$—NR^H—, —NR^H—P(O)$_2$—O—, —NR^H—CO—O—, —NR^H—CO—NR^H—, —O—CO—O—, —O—CO—NR^H—, —NR^H—CO—CH$_2$—, —O—CH$_2$—CO—NR^H—, —O—CH$_2$—CH$_2$—NR^H—, —CO—NR^H—CH$_2$—, —CH$_2$—NR^H—CO—, —O—CH$_2$—CH$_2$—S—, —S—CH$_2$—CH$_2$—O—, —S—CH$_2$—CH$_2$—S—, —CH$_2$—SO$_2$—CH$_2$—, —CH$_2$—CO—NR^H—, —O—CH$_2$—CH$_2$—NR^H—CO—, —CH$_2$NCH$_3$—O—CH$_2$—, where R^H is hydrogen or C$_{1-4}$-alkyl.

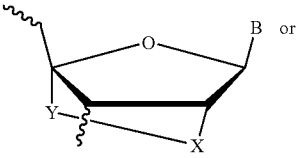
[0265] When the internucleoside linkage group is modified, the internucleoside linkage group is preferably a phosphorothioate group (—O—P(O,S)—O—). In a preferred embodiment, all internucleoside linkage groups of the oligonucleotides according to the present invention are phosphorothioate.

[0266] The LNA Unit

[0267] In a preferred embodiment, the LNA unit has the general chemical structure shown in Scheme 1 below:

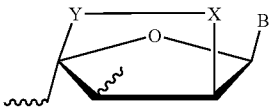
Scheme 1

1A



-continued

1B



[0268] wherein

[0269] X is selected from the group consisting of O, S and NR^H, where R^H is H or C_{1-4}-alkyl;

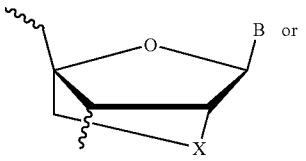
[0270] Y is $(—CH_2)_r$, where r is an integer of 1-4; and

[0271] B is a nitrogenous base.

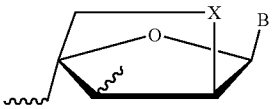
[0272] In a preferred embodiment of the invention, r is 1 or 2, in particular 1, i.e. a preferred LNA unit has the chemical structure shown in Scheme 2 below:

Scheme 2

2A



2B



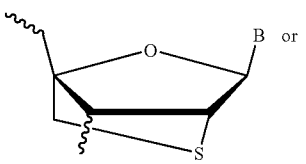
[0273] wherein X and B are as defined above.

[0274] In an interesting embodiment, the LNA units incorporated in the oligonucleotides of the invention are independently selected from the group consisting of thio-LNA units, amino-LNA units and oxy-LNA units.

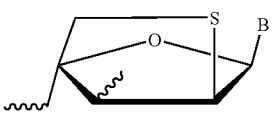
[0275] Thus, the thio-LNA unit may have the chemical structure shown in Scheme 3 below:

Scheme 3

3A



3B



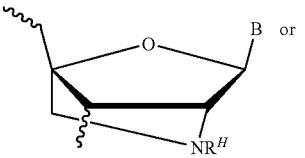
[0276] wherein B is as defined above.

[0277] Preferably, the thio-LNA unit is in its beta-D-form, i.e. having the structure shown in 3A above.

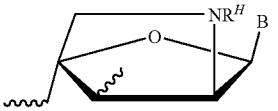
[0278] likewise, the amino-LNA unit may have the chemical structure shown in Scheme 4 below:

Scheme 4

4A



4B



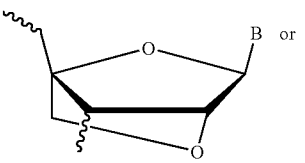
[0279] wherein B and R^H are as defined above.

[0280] Preferably, the amino-LNA unit is in its beta-D-form, i.e. having the structure shown in 4A above.

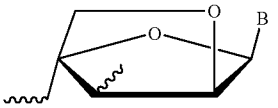
[0281] The oxy-LNA unit may have the chemical structure shown in Scheme 5 below:

Scheme 5

5A



5B



[0282] wherein B is as defined above.

[0283] Preferably, the oxy-LNA unit is in its beta-D-form, i.e. having the structure shown in 5A above.

[0284] As indicated above, B is a nitrogenous base which may be of natural or non-natural origin. Specific examples of nitrogenous bases include adenine (A), cytosine (C), 5-methylcytosine (^{Me}C), isocytosine, pseudoisocytosine, guanine (G), thymine (T), uracil (U), 5-bromouracil, 5-propynyluracil, 5-propyny-6, 5-methylthiazoleuracil, 6-aminopurine, 2-aminopurine, inosine, 2,6-diaminopurine, 7-propyne-7-deazaadenine, 7-propyne-7-deazaguanine and 2-chloro-6-aminopurine.

[0285] Terminal Groups

[0286] Specific examples of terminal groups include terminal groups selected from the group consisting of hydrogen, azido, halogen, cyano, nitro, hydroxy, Prot-O—, mercapto, Prot-S—, C_{1-6}-alkylthio, amino, Prot-N(R^H)—, mono- or di(C_{1-6}-alkyl)amino, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{2-6}-alkenyloxy, optionally substituted C_{2-6}-alkynyl, optionally substituted C_{2-6}-alkynyloxy, monophosphate including protected monophosphate, monothiophosphate including protected monothiophosphate, diphosphate including protected diphosphate, dithiophosphate including protected dithiophosphate, triphosphate including protected triphosphate, trithiophosphate including

protected trithiophosphate, where Prot is a protection group for —OH, —SH and —NH(R^H), and R^H is hydrogen or C_{1-6}-alkyl.

[0287] Examples of phosphate protection groups include S-acetylthioethyl (SATE) and S-pivaloylthioethyl (t-butyl-SATE).

[0288] Still further examples of terminal groups include DNA intercalators, photochemically active groups, thermochemically active groups, chelating groups, reporter groups, ligands, carboxy, sulphono, hydroxymethyl, Prot-O—CH_2—, Act-O—CH_2—, aminomethyl, Prot-N(R^H)—CH_2—, Act-N(R^H)—CH_2—, carboxymethyl, sulphonomethyl, where Prot is a protection group for —OH, —SH and —NH(R^H), and Act is an activation group for —OH, —SH, and —NH(R^H), and R^H is hydrogen or C_{1-6}-alkyl.

[0289] Examples of protection groups for —OH and —SH groups include substituted trityl, such as 4,4'-dimethoxytrityloxy (DMT), 4-monomethoxytrityloxy (MMT); trityloxy, optionally substituted 9-(9-phenyl)xanthenyloxy (pixyl), optionally substituted methoxytetrahydro-pyranyloxy (mthp); silyloxy, such as trimethylsilyloxy (TMS), triisopropylsilyloxy (TIPS), tert-butyldimethylsilyloxy (TBDMS), triethylsilyloxy, phenyldimethylsilyloxy; tert-butylethers; acetals (including two hydroxy groups); acyloxy, such as acetyl or halogen-substituted acetyls, e.g. chloroacetyloxy or fluoroacetyloxy, isobutyryloxy, pivaloyloxy, benzoyloxy and substituted benzoyls, methoxymethyloxy (MOM), benzyl ethers or substituted benzyl ethers such as 2,6-dichlorobenzyloxy (2,6-Cl_2Bzl). Moreover, when Z or Z* is hydroxyl they may be protected by attachment to a solid support, optionally through a linker.

[0290] Examples of amine protection groups include fluorenylmethoxycarbonylamino (Fmoc), tert-butyloxycarbonylamino (BOC), trifluoroacetylamino, allyloxycarbonylamino (alloc, AOC), Z-benzyloxycarbonylamino (Cbz), substituted benzyloxycarbonylamino, such as 2-chloro benzyloxycarbonylamino (2-ClZ), monomethoxytritylamino (MMT), dimethoxytritylamino (DMT), phthaloylamino, and 9-(9-phenyl)xanthenylamino (pixyl).

[0291] In the present context, the term "phosphoramidite" means a group of the formula —P(OR^x)—N(R^y)$_2$, wherein R^x designates an optionally substituted alkyl group, e.g. methyl, 2-cyanoethyl, or benzyl, and each of R^y designates optionally substituted alkyl groups, e.g. 5 ethyl or isopropyl, or the group —N(R^y)$_2$ forms a morpholino group (—N(CH_2CH_2)$_2$O). R^x preferably designates 2-cyanoethyl and the two R^y are preferably identical and designates isopropyl. Accordingly, a particularly preferred phosphoramidite is N,N-diisopropyl-O-(2-cyanoethyl)phosphoramidite.

[0292] The most preferred terminal groups are hydroxy, mercapto and amino, in particular hydroxy.

[0293] Designs for Specific MicroRNAs

[0294] The following table provides examples of oligonucleotide according to the present invention, such as those used in pharmaceutical compositions, as compared to prior art type of molecules.

Oligo #, target microRNA, oligo sequence	Design	SEQ ID
target: hsa-miR-122a MIMAT0000421		
uggagugugacaaugguguuugu		SEQ ID NO 535
screened in HUH-7 cell line expressing miR-122		
3962: miR-122 5'-ACAAacaccattgtcacacTCCA-3'	Full complement, gap	SEQ ID NO 536
3965: miR-122 5'-acaaacACCATTGTcacactcca-3'	Full complement, block	SEQ ID NO 537
3972: miR-122 5'-acAaaCacCatTgtCacActCca-3'	Full complement, LNA_3	SEQ ID NO 538
3549 (3649): miR-122 5'-CcAttGTcaCaCtCC-3'	New design	SEQ ID NO 539
3975: miR-122 5'-CcAtTGTcaCACtCC-3'	Enhanced new design	SEQ ID NO 540
3975': miR-122 5'-ATTGTcACACtCC-3'	ED - 13mer	SEQ ID NO 541
3975": miR-122 5'-TGTcACACtCC-3'	ED - 11mer	SEQ ID NO 542
3549'C3649): miR-122 5' $CC^MAT^MT^MGTC^MA^MCA^MCT^MCC$-3'	New design - 2'MOE	SEQ ID NO 543
3549" (3649): miR-122 5' $CC^FAT^FT^FGTC^FA^FCA^FCT^FCC$-3'	New design - 2'Fluoro	SEQ ID NO 544
target: hsa-miR-19b MIMAT0000074		
ugugcaaauccaugcaaaacuga		SEQ ID NO 545
screened HeLa cell line expressing miR-19b		
3963: miR-19b 5'-TCAGttttgcatggatttgCACA-3'	Full complement, gap	SEQ ID NO 546
3967: miR-19b 5'-tcagttTTGCATGGatttgcaca-3'	Full complement, block	SEQ ID NO 547
3973: miR-19b 5'-tcAgtTttGcaTggAttTgcAca-3'	Full complement, LNA_3	SEQ ID NO 548
3560: miR-19b 5'-TgCatGGatTtGcAC-3'	New design	SEQ ID NO 549
3976: miR-19b 5'-TgCaTGGatTTGcAC-3'	Enhanced new design	SEQ ID NO 550
3976': miR-19b 5'-CaTGGaTTTGcAC-3'	ED - 13mer	SEQ ID NO 551
3976": miR-19b 5'-TGGaTTTGcAC-3'	ED - 11mer	SEQ ID NO 552
3560': miR-19b 5' $TG^MCA^MT^MGGA^MT^MTT^MGC^MAC$-3'	New design - 2'MOE	SEQ ID NO 553
3560": miR-19b 5'-$TG^FCA^FT^FGGA^FT^FTT^FGC^FAC$-3'	New design - 2'MOE	SEQ ID NO 554
target: hsa-miR-155 MIMAT0000646		
uuaaugcuaaucgugauagggg		SEQ ID NO 555
screen in 518A2 cell line expressing miR-155		
3964: miR-155 5'-CCCCtatcacgattagcaTTAA-3'	Full complement, gap	SEQ ID NO 556
3968: miR-155 5'-cccctaTCACGATTagcattaa-3'	Full complement, block	SEQ ID NO 557
3974: miR-155 5'-cCccTatCacGatTagCatTaa-3'	Full complement, LNA_3	SEQ ID NO 558
3758: miR-155 5'-TcAcgATtaGcAtTA-3'	New design	SEQ ID NO 559

-continued

Oligo #, target microRNA, oligo sequence	Design	SEQ ID
3818: miR-155 5'-TcAcGATtaGCAtTA-3'	Enhanced new design	SEQ ID NO 560
3818': miR-155 5'-ACGATtAGCAtTA-3'	ED - 13mer	SEQ ID NO 561
3818": miR-155 5'-GATtAGCaTTA-3'	ED - 11mer	SEQ ID NO 562
3758': miR-155 5'-TC^{M}AC^{M}G^{M}ATTA^{M}GC^{M}AT^{M}TA-3'	New design - 2'MOE	SEQ ID NO 563
3758": miR-155 5'-TC^{F}AC^{F}G^{F}ATT^{F}A^{F}GC^{F}AT^{F}TA-3'	New design - 2'Fluoro	SEQ ID NO 564
target: hsa-miR-21 MIMAT0000076		
uagcuuaucagacugauguuga		SEQ ID NO 565
miR-21 5'- TCAAcatcagtctgataaGCTA -3'	Full complement, gap	SEQ ID NO 566
miR-21 5'- tcaacaTCAGTCTGataagcta -3'	Full complement, block	SEQ ID NO 567
miR-21 5'- tcAtcAtcAgtCtgAtaAGcTta -3'	Full complement, LNA_3	SEQ ID NO 568
miR-21 5'- TcAgtCTgaTaAgCT -3'	New design	SEQ ID NO 569
miR-21 5'- TcAgTCTgaTAAgCT -3'-	Enhanced new design	SEQ ID NO 570
miR-21 5'- AGTCTgATAAgCT -3'-	ED - 13mer	SEQ ID NO 571
miR-21 5'- TCTgAtAAGCT -3'-	ED - 11mer	SEQ ID NO 572
miR-21 5'- TC^{M}AG^{M}T^{M}CTG^{M}A^{M}TA^{M}AG^{M}CT - 3'	New design - 2'MOE	SEQ ID NO 573
miR-21 5'- TC^{F}AG^{F}T^{F}CTG^{F}A^{F}TA^{F}AG^{F}CT-3'	New design - 2'Fluoro	SEQ ID NO 574
target: hsa-miR-375 MIMAT0000728		
uuuguucguucggcucgcguga		SEQ ID NO 575
miR- 375 5'- TCTCgcgtgccgttcgttCTTT -3'	Full complement, gap	SEQ ID NO 576
miR- 375 5'- tctcgcGTGCCGTTcgttcttt -3'	Full complement, block	SEQ ID NO 577
miR- 375 5'- tcTcgCgtGccGttCgtTctTt -3'	Full complement, LNA_3	SEQ ID NO 578
miR- 375 5'- GtGccGTtcGtTcTT 3'	New design	SEQ ID NO 579
miR- 375 5'- GtGcCGTtcGTTcTT 3'	Enhanced new design	SEQ ID NO 580
miR- 375 5'- GCCGTtCgTTCTT 3'	ED - 13mer	SEQ ID NO 581
miR- 375 5'- CGTTcGTTCTT 3'	ED - 11mer	SEQ ID NO 582
miR- 375 5'- GT^{M}GC^{M}C^{M}GTT^{M}C^{M}GT^{M}TC^{M}TT 3'	New design - 2'MOE	SEQ ID NO 583
miR- 375 5'- GT^{F}GC^{F}C^{F}GTT^{F}C^{F}GT^{F}TC^{F}TT 3'	New design - 2'Fluoro	SEQ ID NO 584

[0295] Capital Letters without a superscript M or F, refer to LNA units. Lower case=DNA, except for lower case in bold=RNA. The LNA cytosines may optionally be methylated). Capital letters followed by a superscript M refer to 2'OME RNA units, Capital letters followed by a superscript F refer to 2'fluoro DNA units, lowercase letter refer to DNA. The above oligos may in one embodiment be entirely phosphorothioate, but other nucleobase linkages as herein described bay be used. In one embodiment the nucleobase linkages are all phosphodiester. It is considered that for use within the brain/spinal cord it is preferable to use phosphodiester linkages, for example for the use of antimiRs targeting miR21.

[0296] Table 2 below provides non-limiting examples of oligonucleotide designs against known human microRNA sequences in miRBase microRNA database version 8.1.

[0297] The oligonucleotides according to the invention, such as those disclosed in table 2 may, in one embodiment, have a sequence of nucleobases 5'-3' selected form the group consisting of:

[0298] LdLddLLddLdLdLL (New design)

[0299] LdLdLLLddLLLdLL (Enhanced new design)

[0300] LMLMMLLMMLMLMLL (New design—2'MOE)

[0301] LMLMLLLMMLLLMLL (Enhanced new design—2'MOE)

[0302] LFLFFLLFFLFLFLL (New design—2' Fluoro)

[0303] LFLFLLLFFLLLFLL (Enhanced new design—2' Fluoro)

[0304] LddLddLddL(d)(d)(L)(d)(d)(L)(d) 'Every third'

[0305] dLddLddLdd(L)(d)(d)(L)(d)(d)(L) 'Every third'

[0306] ddLddLddLd(d)(L)(d)(d)(L)(d)(d) 'Every third'

[0307] LMMLMMLMML(M)(M)(L)(M)(M)(L)(M) 'Every third'

[0308] MLMMLMMLMM(L)(M)(M)(L)(M)(M)(L) 'Every third'

[0309] MMLMMLMMLM(M)(L)(M)(M)(L)(M)(M) 'Every third'

[0310] LFFLFFLFFL(F)(F)(L)(F)(F)(L)(F) 'Every third'

[0311] FLFFLFFLFF(L)(F)(F)(L)(F)(F)(L) 'Every third'

[0312] FFLFFLFFLF(F)(L)(F)(F)(L)(F)(F) 'Every third'

[0313] dLdLdLdLdL(d)(L)(d)(L)(d)(L)(d) 'Every second'

[0314] LdLdLdLdL(d)(L)(d)(L)(d)(L)(d)(L) 'Every second'

[0315] MLMLMLMLML(M)(L)(M)(L)(M)(L)(M) 'Every second'

[0316] LMLMLMLML(M)(L)(M)(L)(M)(L)(M)(L) 'Every second'

[0317] FLFLFLFLFL(F)(L)(F)(L)(F)(L)(F) 'Every second'

[0318] LFLFLFLFL(F)(L)(F)(L)(F)(L)(F)(L) 'Every second'

[0319] Wherein L=LNA unit, d=DNA units, M=2'MOE RNA, F=2'Fluoro and residues in brackets are optional

[0320] Conjugates

[0321] The invention also provides for conjugates comprising the oligonucleotide according to the invention.

[0322] In one embodiment of the invention the oligomeric compound is linked to ligands/conjugates, which may be used, e.g. to increase the cellular uptake of antisense oligonucleotides. This conjugation can take place at the terminal positions 5'/3'-OH but the ligands may also take place at the sugars and/or the bases. In particular, the growth factor to which the antisense oligonucleotide may be conjugated, may comprise transferrin or folate. Transferrin-polylysine-oligo-

nucleotide complexes or folate-polylysine-oligonucleotide complexes may be prepared for uptake by cells expressing high levels of transferrin or folate receptor. Other examples of conjugates/ligands are cholesterol moieties, duplex intercalators such as acridine, poly-L-lysine, "end-capping" with one or more nuclease-resistant linkage groups such as phosphoromonothioate, and the like. The invention also provides for a conjugate comprising the compound according to the invention as herein described, and at least one non-nucleotide or non-polynucleotide moiety covalently attached to said compound. Therefore, in one embodiment where the compound of the invention consists of s specified nucleic acid, as herein disclosed, the compound may also comprise at least one non-nucleotide or non-polynucleotide moiety (e.g. not comprising one or more nucleotides or nucleotide analogues) covalently attached to said compound. The non-nucleobase moiety may for instance be or comprise a sterol such as cholesterol.

[0323] Therefore, it will be recognised that the oligonucleotide of the invention, such as the oligonucleotide used in pharmaceutical (therapeutic) formulations may comprise further non-nucleobase components, such as the conjugates herein defined.

[0324] Therapy and Pharmaceutical Compositions

[0325] As explained initially, the oligonucleotides of the invention will constitute suitable drugs with improved properties. The design of a potent and safe drug requires the fine-tuning of various parameters such as affinity/specificity, stability in biological fluids, cellular uptake, mode of action, pharmacokinetic properties and toxicity.

[0326] Accordingly, in a further aspect the present invention relates to a pharmaceutical composition comprising an oligonucleotide according to the invention and a pharmaceutically acceptable diluent, carrier or adjuvant. Preferably said carrier is saline of buffered saline.

[0327] In a still further aspect the present invention relates to an oligonucleotide according to the present invention for use as a medicament.

[0328] As will be understood, dosing is dependent on severity and responsiveness of the disease state to be treated, and the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Optimum dosages may vary depending on the relative potency of individual oligonucleotides. Generally it can be estimated based on EC50s found to be effective in in vitro and in vivo animal models. In general, dosage is from 0.01 μg to 1 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 10 years or by continuous infusion for hours up to several months. The repetition rates for dosing can be estimated based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state.

[0329] Pharmaceutical Compositions

[0330] As indicated above, the invention also relates to a pharmaceutical composition, which comprises at least one oligonucleotide of the invention as an active ingredient. It should be understood that the pharmaceutical composition according to the invention optionally comprises a pharmaceutical carrier, and that the pharmaceutical composition optionally comprises further compounds, such as chemotherapeutic compounds, anti-inflammatory compounds, antiviral compounds and/or immuno-modulating compounds.

[0331] The oligonucleotides of the invention can be used "as is" or in form of a variety of pharmaceutically acceptable salts. As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the herein-identified oligonucleotides and exhibit minimal undesired toxicological effects. Non-limiting examples of such salts can be formed with organic amino acid and base addition salts formed with metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, sodium, potassium, and the like, or with a cation formed from ammonia, N,N-dibenzylethylenediamine, D-glucosamine, tetraethylammonium, or ethylenediamine.

[0332] In one embodiment of the invention, the oligonucleotide may be in the form of a pro-drug. Oligonucleotides are by virtue negatively charged ions. Due to the lipophilic nature of cell membranes the cellular uptake of oligonucleotides are reduced compared to neutral or lipophilic equivalents. This polarity "hindrance" can be avoided by using the pro-drug approach (see e.g. Crooke, R. M. (1998) in Crooke, S. T. *Antisense research and Application.* Springer-Verlag, Berlin, Germany, vol. 131, pp. 103-140). Pharmaceutically acceptable binding agents and adjuvants may comprise part of the formulated drug.

[0333] Examples of delivery methods for delivery of the therapeutic agents described herein, as well as details of pharmaceutical formulations, salts, may are well described elsewhere for example in U.S. provisional application 60/838,710 and 60/788,995, which are hereby incorporated by reference, and Danish applications, PA 2006 00615 which is also hereby incorporated by reference.

[0334] Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Delivery of drug to tumour tissue may be enhanced by carrier-mediated delivery including, but not limited to, cationic liposomes, cyclodextrins, porphyrin derivatives, branched chain dendrimers, polyethylen-imine polymers, nanoparticles and microspheres (Dass C R. J Pharm Pharmacol 2002; 54(1):3-27). The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product. The compositions of the present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels and suppositories. The compositions of the present invention may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethyl-cellulose, sorbitol and/or dextran. The suspension may also contain stabilizers. The compounds of the invention may

also be conjugated to active drug substances, for example, aspirin, ibuprofen, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

[0335] In another embodiment, compositions of the invention may contain one or more oligonucleotide compounds, targeted to a first microRNA and one or more additional oligonucleotide compounds targeted to a second microRNA target. Two or more combined compounds may be used together or sequentially.

[0336] The compounds disclosed herein are useful for a number of therapeutic applications as indicated above. In general, therapeutic methods of the invention include administration of a therapeutically effective amount of an oligonucleotide to a mammal, particularly a human. In a certain embodiment, the present invention provides pharmaceutical compositions containing (a) one or more compounds of the invention, and (b) one or more chemotherapeutic agents. When used with the compounds of the invention, such chemotherapeutic agents may be used individually, sequentially, or in combination with one or more other such chemotherapeutic agents or in combination with radiotherapy. All chemotherapeutic agents known to a person skilled in the art are here incorporated as combination treatments with compound according to the invention. Other active agents, such as anti-inflammatory drugs, including but not limited to nonsteroidal anti-inflammatory drugs and corticosteroids, antiviral drugs, and immuno-modulating drugs may also be combined in compositions of the invention. Two or more combined compounds may be used together or sequentially.

[0337] Examples of therapeutic indications which may be treated by the pharmaceutical compositions of the invention:

microRNA	Possible medical indications
miR-21	Glioblastoma, breast cancer
miR-122	hypercholesterolemia, hepatitis C, hemochromatosis
miR-19b	lymphoma and other tumour types
miR-155	lymphoma, breast and lung cancer
miR-375	diabetes, metabolic disorders
miR-181	myoblast differentiation, auto immune disorders

[0338] Tumor suppressor gene tropomysin 1 (TPM1) mRNA has been indicated as a target of miR-21. Myotrophin (mtpn) mRNA has been indicated as a target of miR 375.

[0339] In an even further aspect, the present invention relates to the use of an oligonucleotide according to the invention for the manufacture of a medicament for the treatment of a disease selected from the group consisting of: atherosclerosis, hypercholesterolemia and hyperlipidemia; cancer, glioblastoma, breast cancer, lymphoma, lung cancer; diabetes, metabolic disorders; myoblast differentiation; immune disorders.

[0340] The invention further refers to an oligonucleotides according to the invention for the use in the treatment of from a disease selected from the group consisting of: atherosclerosis, hypercholesterolemia and hyperlipidemia; cancer, glioblastoma, breast cancer, lymphoma, lung cancer; diabetes, metabolic disorders; myoblast differentiation; immune disorders.

[0341] The invention provides for a method of treating a subject suffering from a disease or condition selected from from the group consisting of: atherosclerosis, hypercholesterolemia and hyperlipidemia; cancer, glioblastoma, breast cancer, lymphoma, lung cancer; diabetes, metabolic disorders; myoblast differentiation; immune disorders, the method comprising the step of administering an oligonucleotide or pharmaceutical composition of the invention to the subject in need thereof.

[0342] Cancer

[0343] In an even further aspect, the present invention relates to the use of an oligonucleotide according to the invention for the manufacture of a medicament for the treatment of cancer. In another aspect, the present invention concerns a method for treatment of, or prophylaxis against, cancer, said method comprising administering an oligonucleotide of the invention or a pharmaceutical composition of the invention to a patient in need thereof.

[0344] Such cancers may include lymphoreticular neoplasia, lymphoblastic leukemia, brain tumors, gastric tumors, plasmacytomas, multiple myeloma, leukemia, connective tissue tumors, lymphomas, and solid tumors.

[0345] In the use of a compound of the invention for the manufacture of a medicament for the treatment of cancer, said cancer may suitably be in the form of a solid tumor. Analogously, in the method for treating cancer disclosed herein said cancer may suitably be in the form of a solid tumor.

[0346] Furthermore, said cancer is also suitably a carcinoma. The carcinoma is typically selected from the group consisting of malignant melanoma, basal cell carcinoma, ovarian carcinoma, breast carcinoma, non-small cell lung cancer, renal cell carcinoma, bladder carcinoma, recurrent superficial bladder cancer, stomach carcinoma, prostatic carcinoma, pancreatic carcinoma, lung carcinoma, cervical carcinoma, cervical dysplasia, laryngeal papillomatosis, colon carcinoma, colorectal carcinoma and carcinoid tumors. More typically, said carcinoma is selected from the group consisting of malignant melanoma, non-small cell lung cancer, breast carcinoma, colon carcinoma and renal cell carcinoma. The malignant melanoma is typically selected from the group consisting of superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral melagnoma, amelanotic melanoma and desmoplastic melanoma.

[0347] Alternatively, the cancer may suitably be a sarcoma. The sarcoma is typically in the form selected from the group consisting of osteosarcoma, Ewing's sarcoma, chondrosarcoma, malignant fibrous histiocytoma, fibrosarcoma and Kaposi's sarcoma.

[0348] Alternatively, the cancer may suitably be a glioma.

[0349] A further embodiment is directed to the use of an oligonucleotide according to the invention for the manufacture of a medicament for the treatment of cancer, wherein said medicament further comprises a chemotherapeutic agent selected from the group consisting of adrenocorticosteroids, such as prednisone, dexamethasone or decadron; altretamine (hexalen, hexamethylmelamine (HMM)); amifostine (ethyol); aminoglutethimide (cytadren); amsacrine (M-AMSA); anastrozole (arimidex); androgens, such as testosterone; asparaginase (elspar); *bacillus* calmette-gurin; bicalutamide (casodex); bleomycin (blenoxane); busulfan (myleran); carboplatin (paraplatin); carmustine (BCNU, BiCNU); chlorambucil (leukeran); chlorodeoxyadenosine (2-CDA, cladribine, leustatin); cisplatin (platinol); cytosine arabinoside (cytarabine); dacarbazine (DTIC); dactinomycin (actinomycin-D, cosmegen); daunorubicin (cerubidine); docetaxel (taxotere); doxorubicin (adriomycin); epirubicin; estramustine (emcyt); estrogens, such as diethylstilbestrol (DES); etopside (VP-16, VePesid, etopophos); fludarabine (fludara); flutamide (eulexin); 5-FUDR (floxuridine); 5-fluo-

rouracil (5-FU); gemcitabine (gemzar); goserelin (zodalex); herceptin (trastuzumab); hydroxyurea (hydrea); idarubicin (idamycin); ifosfamide; IL-2 (proleukin, aldesleukin); interferon alpha (intron A, roferon A); irinotecan (camptosar); leuprolide (lupron); levamisole (ergamisole); lomustine (CCNU); mechlorathamine (mustargen, nitrogen mustard); melphalan (alkeran); mercaptopurine (purinethol, 6-MP); methotrexate (mexate); mitomycin-C (mutamucin); mitoxantrone (novantrone); octreotide (sandostatin); pentostatin (2-deoxycoformycin, nipent); plicamycin (mithramycin, mithracin); prorocarbazine (matulane); streptozocin; tamoxifin (nolvadex); taxol (paclitaxel); teniposide (vumon, VM-26); thiotepa; topotecan (hycamtin); tretinoin (vesanoid, all-trans retinoic acid); vinblastine (valban); vincristine (oncovin) and vinorelbine (navelbine). Suitably, the further chemotherapeutic agent is selected from taxanes such as Taxol, Paclitaxel or Docetaxel.

[0350] Similarly, the invention is further directed to the use of an oligonucleotide according to the invention for the manufacture of a medicament for the treatment of cancer, wherein said treatment further comprises the administration of a further chemotherapeutic agent selected from the group consisting of adrenocorticosteroids, such as prednisone, dexamethasone or decadron; altretamine (hexalen, hexamethylmelamine (HMM)); amifostine (ethyol); aminoglutethimide (cytadren); amsacrine (M-AMSA); anastrozole (arimidex); androgens, such as testosterone; asparaginase (elspar); *bacillus* calmette-gurin; bicalutamide (casodex); bleomycin (blenoxane); busulfan (myleran); carboplatin (paraplatin); carmustine (BCNU, BiCNU); chlorambucil (leukeran); chlorodeoxyadenosine (2-CDA, cladribine, leustatin); cisplatin (platinol); cytosine arabinoside (cytarabine); dacarbazine (DTIC); dactinomycin (actinomycin-D, cosmegen); daunorubicin (cerubidine); docetaxel (taxotere); doxorubicin (adriomycin); epirubicin; estramustine (emcyt); estrogens, such as diethylstilbestrol (DES); etopside (VP-16, VePesid, etopophos); fludarabine (fludara); flutamide (eulexin); 5-FUDR (floxuridine); 5-fluorouracil (5-FU); gemcitabine (gemzar); goserelin (zodalex); herceptin (trastuzumab); hydroxyurea (hydrea); idarubicin (idamycin); ifosfamide; IL-2 (proleukin, aldesleukin); interferon alpha (intron A, roferon A); irinotecan (camptosar); leuprolide (lupron); levamisole (ergamisole); lomustine (CCNU); mechlorathamine (mustargen, nitrogen mustard); melphalan (alkeran); mercaptopurine (purinethol, 6-MP); methotrexate (mexate); mitomycin-C (mutamucin); mitoxantrone (novantrone); octreotide (sandostatin); pentostatin (2-deoxycoformycin, nipent); plicamycin (mithramycin, mithracin); prorocarbazine (matulane); streptozocin; tamoxifin (nolvadex); taxol (paclitaxel); teniposide (vumon, VM-26); thiotepa; topotecan (hycamtin); tretinoin (vesanoid, all-trans retinoic acid); vinblastine (valban); vincristine (oncovin) and vinorelbine (navelbine). Suitably, said treatment further comprises the administration of a further chemotherapeutic agent selected from taxanes, such as Taxol, Paclitaxel or Docetaxel.

[0351] Alternatively stated, the invention is furthermore directed to a method for treating cancer, said method comprising administering an oligonucleotide of the invention or a pharmaceutical composition according to the invention to a patient in need thereof and further comprising the administration of a further chemotherapeutic agent. Said further administration may be such that the further chemotherapeutic agent is conjugated to the compound of the invention, is present in the pharmaceutical composition, or is administered in a separate formulation.

[0352] Infectious Diseases

[0353] It is contemplated that the compounds of the invention may be broadly applicable to a broad range of infectious diseases, such as diphtheria, tetanus, pertussis, polio, hepatitis B, hepatitis C, hemophilus influenza, measles, mumps, and rubella.

[0354] Hsa-miR122 is indicated in hepatitis C infection and as such oligonucleotides according to the invention which target miR-122 may be used to treat Hepatitis C infection.

[0355] Accordingly, in yet another aspect the present invention relates the use of an oligonucleotide according to the invention for the manufacture of a medicament for the treatment of an infectious disease, as well as to a method for treating an infectious disease, said method comprising administering an oligonucleotide according to the invention or a pharmaceutical composition according to the invention to a patient in need thereof.

[0356] Inflammatory Diseases

[0357] The inflammatory response is an essential mechanism of defense of the organism against the attack of infectious agents, and it is also implicated in the pathogenesis of many acute and chronic diseases, including autoimmune disorders. In spite of being needed to fight pathogens, the effects of an inflammatory burst can be devastating. It is therefore often necessary to restrict the symptomatology of inflammation with the use of anti-inflammatory drugs. Inflammation is a complex process normally triggered by tissue injury that includes activation of a large array of enzymes, the increase in vascular permeability and extravasation of blood fluids, cell migration and release of chemical mediators, all aimed to both destroy and repair the injured tissue.

[0358] In yet another aspect, the present invention relates to the use of an oligonucleotide according to the invention for the manufacture of a medicament for the treatment of an inflammatory disease, as well as to a method for treating an inflammatory disease, said method comprising administering an oligonucleotide according to the invention or a pharmaceutical composition according to the invention to a patient in need thereof.

[0359] In one preferred embodiment of the invention, the inflammatory disease is a rheumatic disease and/or a connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematous (SLE) or Lupus, scleroderma, polymyositis, inflammatory bowel disease, dermatomyositis, ulcerative colitis, Crohn's disease, vasculitis, psoriatic arthritis, exfoliative psoriatic dermatitis, pemphigus vulgaris and Sjorgren's syndrome, in particular inflammatory bowel disease and Crohn's disease.

[0360] Alternatively, the inflammatory disease may be a non-rheumatic inflammation, like bursitis, synovitis, capsulitis, tendinitis and/or other inflammatory lesions of traumatic and/or sportive origin.

[0361] Metabolic Diseases

[0362] A metabolic disease is a disorder caused by the accumulation of chemicals produced naturally in the body. These diseases are usually serious, some even life threatening. Others may slow physical development or cause mental retardation. Most infants with these disorders, at first, show no obvious signs of disease. Proper screening at birth can often discover these problems. With early diagnosis and treatment, metabolic diseases can often be managed effectively.

[0363] In yet another aspect, the present invention relates to the use of an oligonucleotide according to the invention or a conjugate thereof for the manufacture of a medicament for the treatment of a metabolic disease, as well as to a method for treating a metabolic disease, said method comprising administering an oligonucleotide according to the invention or a conjugate thereof, or a pharmaceutical composition according to the invention to a patient in need thereof.

[0364] In one preferred embodiment of the invention, the metabolic disease is selected from the group consisting of Amyloidosis, Biotinidase, OMIM (Online Mendelian Inheritance in Man), Crigler Najjar Syndrome, Diabetes, Fabry Support & Information Group, Fatty acid Oxidation Disorders, Galactosemia, Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, Glutaric aciduria, International Organization of Glutaric Acidemia, Glutaric Acidemia Type I, Glutaric Acidemia, Type II, Glutaric Acidemia Type I, Glutaric Acidemia Type-II, F-HYPDRR-Familial Hypophosphatemia, Vitamin D Resistant Rickets, Krabbe Disease, Long chain 3 hydroxyacyl CoA dehydrogenase deficiency (LCHAD), Mannosidosis Group, Maple Syrup Urine Disease, Mitochondrial disorders, Mucopolysaccharidosis Syndromes: Niemann Pick, Organic acidemias, PKU, Pompe disease, Porphyria, Metabolic Syndrome, Hyperlipidemia and inherited lipid disorders, Trimethylaminuria: the fish malodor syndrome, and Urea cycle disorders.

[0365] Liver Disorders

[0366] In yet another aspect, the present invention relates to the use of an oligonucleotide according to the invention or a conjugate thereof for the manufacture of a medicament for the treatment of a liver disorder, as well as to a method for treating a liver disorder, said method comprising administering an oligonucleotide according to the invention or a conjugate thereof, or a pharmaceutical composition according to the invention to a patient in need thereof.

[0367] In one preferred embodiment of the invention, the liver disorder is selected from the group consisting of Biliary Atresia, Alagille Syndrome, Alpha-1 Antitrypsin, Tyrosinemia, Neonatal Hepatitis, and Wilson Disease.

[0368] Other Uses

[0369] The oligonucleotides of the present invention can be utilized for as research reagents for diagnostics, therapeutics and prophylaxis. In research, the oligonucleotide may be used to specifically inhibit the synthesis of target genes in cells and experimental animals thereby facilitating functional analysis of the target or an appraisal of its usefulness as a target for therapeutic intervention. In diagnostics the oligonucleotides may be used to detect and quantitate target expression in cell and tissues by Northern blotting, in-situ hybridisation or similar techniques. For therapeutics, an animal or a human, suspected of having a disease or disorder, which can be treated by modulating the expression of target is treated by administering the oligonucleotide compounds in accordance with this invention. Further provided are methods of treating an animal particular mouse and rat and treating a human, suspected of having or being prone to a disease or condition, associated with expression of target by administering a therapeutically or prophylactically effective amount of one or more of the oligonucleotide compounds or compositions of the invention.

[0370] Therapeutic Use of Oligonucleotides Targeting miR-122a

[0371] In the examples section, it is demonstrated that a LNA-antimiR™, such as SPC3372, targeting miR-122a reduces plasma cholesterol levels. Therefore, another aspect of the invention is use of the above described oligonucleotides targeting miR-122a as medicine. Still another aspect of the invention is use of the above described oligonucleotides targeting miR-122a for the preparation of a medicament for treatment of increased plasma cholesterol levels. The skilled man will appreciate that increased plasma cholesterol levels is undesirable as it increases the risk of various conditions, e.g. atherosclerosis. Still another aspect of the invention is use of the above described oligonucleotides targeting miR-122a for upregulating the mRNA levels of Nrdg3, Aldo A, Bckdk or CD320.

Further Embodiments

[0372] The following embodiments may be combined with the other embodiments as described herein:

[0373] 1. An oligonucleotide having a length of from 12 to 26 nucleotides, wherein

[0374] i) the first nucleotide, counting from the 3' end, is a locked nucleic acid (LNA) unit;

[0375] ii) the second nucleotide, counting from the 3' end, is an LNA unit; and

[0376] iii) the ninth and/or the tenth nucleotide, counting from the 3' end, is an LNA unit.

[0377] 2. The oligonucleotide according to claim **1**, wherein the ninth nucleotide, counting from the 3' end, is an LNA unit.

[0378] 3. The oligonucleotide according to embodiment 1, wherein the tenth nucleotide, counting from the 3' end, is an LNA unit.

[0379] 4. The oligonucleotide according to embodiment 1, wherein both the ninth and the tenth nucleotide, calculated from the 3' end, are LNA units.

[0380] 5. The oligonucleotide according to any of embodiments 1-4, wherein said oligonucleotide comprises at least one LNA unit in positions three to eight, counting from the 3' end.

[0381] 6. The oligonucleotide according to embodiment 5, wherein said oligonucleotide comprises one LNA unit in positions three to eight, counting from the 3' end.

[0382] 7. The oligonucleotide according to embodiment 6, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of Xxxxxx, xXxxxx, xxXxxx, xxxXxx, xxxxXx and xxxxxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0383] 8. The oligonucleotide according to embodiment 5, wherein said oligonucleotide comprises at least two LNA units in positions three to eight, counting from the 3' end.

[0384] 9. The oligonucleotide according to embodiment 8, wherein said oligonucleotide comprises two LNA units in positions three to eight, counting from the 3' end.

[0385] 10. The oligonucleotide according to embodiment 9, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of XXxxxx, XxXxxx, XxxXxx, XxxxXx, XxxxxX, xXXxxx, xXxXxx, xXxxXx, xXxxxX, xxXXxx, xxXxXx, xxXxxX, xxxXXx, xxxXxX and xxxxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0386] 11. The oligonucleotide according to embodiment 10, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of XxXxxx, XxxXxx, XxxxXx,

XxxxxX, xXxXxx, xXxxXx, xXxxxX, xxXxXx, xxXxxX and xxxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0387] 12. The oligonucleotide according to embodiment 11, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of xXxXxx, xXxxXx, xXxxxX, xxXxXx, xxXxxX and xxxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0388] 13. The oligonucleotide according to embodiment 12, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of xXxXxx, xXxxXx and xxXxXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0389] 14. The oligonucleotide according to embodiment 13, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is xXxXxx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0390] 15. The oligonucleotide according to embodiment 5, wherein said oligonucleotide comprises at least three LNA units in positions three to eight, counting from the 3' end.

[0391] 16. The oligonucleotide according to embodiment 15, wherein said oligonucleotide comprises three LNA units in positions three to eight, counting from the 3' end.

[0392] 17. The oligonucleotide according to embodiment 16, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of XXXxxx, xXXXxx, xxXXXx, xxxXXX, XXxXxx, XXxxXx, XXxxxX, xXXxXx, xXXxxX, xxXXxX, XxXXxx, XxxXXx, XxxxXX, xXxXXx, xXxxXX, xxXxXX, xXxXxX and XxXxXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0393] 18. The oligonucleotide according to embodiment 17, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of XXxXxx, XXxxXx, XXxxxX, xXXxXx, xXXxxX, xxXXxX, XxXXxx, XxxXXx, XxxxXX, xXxXXx, xXxxXX, xxXxXX, xXxXxX and XxXxXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0394] 19. The oligonucleotide according to embodiment 18, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is selected from the group consisting of xXXxXx, xXXxxX, xxXXxX, xXxXXx, xXxxXX, xxXxXX and xXxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0395] 20. The oligonucleotide according to embodiment 18, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is xXxXxX or XxXxXx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0396] 21. The oligonucleotide according to embodiment 20, wherein the substitution pattern for the nucleotides in positions three to eight, counting from the 3' end, is xXxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0397] 22. The oligonucleotide according to any of embodiment 7-21, wherein said non-LNA unit is a DNA unit.

[0398] 23. The oligonucleotide according to any of the preceding embodiments, wherein said nucleotide has a length of from 12 to 24 nucleotides, such as a length of from 12 to 22 nucleotides, preferably a length of from 12 to 20 nucleotides, such as a length of from 12 to 19 nucleotides, more preferably a length of from 12 to 18 nucleotides, such as a length of from 12 to 17 nucleotides, even more preferably a length of from 12 to 16 nucleotides.

[0399] 24. The oligonucleotide according to any of the preceding embodiments, wherein said oligonucleotide comprises at least one LNA unit, such as one LNA unit, from position 11, counting from the 3' end, to the 5' end.

[0400] 25. The oligonucleotide according to any of the preceding embodiments, wherein said oligonucleotide comprises at least two LNA units, such as two LNA units, from position 11, counting from the 3' end, to the 5' end.

[0401] 26. The oligonucleotide according to embodiment 24 or 25, wherein said oligonucleotide comprises 12 nucleotides and the substitution pattern for positions 11 to 12, counting from the 3' end, is selected from the group consisting of xX and Xx, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0402] 27. The oligonucleotide according to embodiment 26, wherein the substitution pattern for positions 11 to 12, counting from the 3' end, is xX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0403] 28. The oligonucleotide according to embodiment 24 or 25, wherein said oligonucleotide comprises 13 nucleotides and the substitution pattern for positions 11 to 13, counting from the 3' end, is selected from the group consisting of Xxx, xXx, xxX, XXx, XxX, xXX and XXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0404] 29. The oligonucleotide according to embodiment 28, wherein the substitution pattern for positions 11 to 13, counting from the 3' end, is xxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0405] 30. The oligonucleotide according to embodiment 24 or 25, wherein said oligonucleotide comprises 14 nucleotides and the substitution pattern for positions 11 to 14, counting from the 3' end, is selected from the group consisting of Xxxx, xXxx, xxXx, xxxX, XXxx, XxXx, XxxX, xXXx, xXxX and xxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0406] 31. The oligonucleotide according to embodiment 30, wherein the substitution pattern for positions 11 to 14, counting from the 3' end, is xXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0407] 32. The oligonucleotide according to embodiment 24 or 25, wherein said oligonucleotide comprises 15 nucleotides and the substitution pattern for positions 11 to 15, counting from the 3' end, is selected from the group consisting of Xxxxx, xXxxx, xxXxx, xxxXx, xxxxX, XXxxx, XxXxx, XxxXx, XxxxX, xXXxx, xXxXx, xXxxX, xxXXx, xxXxX and xxxXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0408] 33. The oligonucleotide according to embodiment 32, wherein the substitution pattern for positions 11 to 15, counting from the 3' end, is xxXxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0409] 34. The oligonucleotide according to embodiment 24 or 25, wherein said oligonucleotide comprises 16 nucleotides and the substitution pattern for positions 11 to 16, counting from the 3' end, is selected from the group consisting of Xxxxxx, xXxxxx, xxXxxx, xxxXxx, xxxxXx, xxxxxX, XXxxxx, XxXxxx, XxxXxx, XxxxXx, XxxxxX, xXXxxx, xXxXxx, xXxxXx, xXxxxX, xxXXxx, xxXxXx, xxXxxX, xxxXXx, xxxXxX, xxxxXX, XXXxxx, XXxXxx, XXxxXx,

XXxxxX, XxXXxx, XxXxXx, XxXxxX, XxxXXx, XxxXxX, XxxxXX, xXXXxx, xXXxX, xXXxxX, xXxXXx, xXxXxX, xXxxXX, xxXXXx, xxXXxX, xxXxXX and xxxXXX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0410] 35. The oligonucleotide according to embodiment 34, wherein the substitution pattern for positions 11 to 16, counting from the 3' end, is xxXxxX, wherein "X" denotes an LNA unit and "x" denotes a non-LNA unit.

[0411] 36. The oligonucleotide according to embodiment 24 or 25, wherein said oligonucleotide comprises an LNA unit at the 5' end.

[0412] 37. The oligonucleotide according to embodiment 36 containing an LNA unit at the first two positions, counting from the 5' end.

[0413] 38. The oligonucleotide according to any of the preceding embodiments, wherein the oligonucleotide comprises at least one internucleoside linkage group which differs from phosphate.

[0414] 39. The oligonucleotide according to embodiment 38, wherein said internucleoside linkage group, which differs from phosphate, is phosphorothioate.

[0415] 40. The oligonucleotide according to embodiment 39, wherein all internucleoside linkage groups are phosphorothioate.

[0416] 41. The oligonucleotide according to any of the preceding embodiments, wherein said LNA units are independently selected from the group consisting of thio-LNA units, amino-LNA units and oxy-LNA units.

[0417] 42. The oligonucleotide according to embodiment 41, wherein said LNA units are in the beta-D-form.

[0418] 43. The oligonucleotide according to embodiment 41, wherein said LNA units are oxy-LNA units in the beta-D-form.

[0419] 44. The oligonucleotide according to any of the preceding embodiments for use as a medicament.

[0420] 45. A pharmaceutical composition comprising an oligonucleotide according to any of embodiments 1-43 and a pharmaceutically acceptable carrier.

[0421] 46. The composition according to embodiment 45, wherein said carrier is saline or buffered saline.

[0422] 47. Use of an oligonucleotide according to any of embodiments 1-43 for the manufacture of a medicament for the treatment of cancer.

[0423] 48. A method for the treatment of cancer, comprising the step of administering an oligonucleotide according to any of embodiments 1-43 or a composition according to embodiment 45.

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Experimental

Example 1

Monomer Synthesis

[0460] The LNA monomer building blocks and derivatives thereof were prepared following published procedures and references cited therein, see, e.g. WO 03/095467 A1 and D. S. Pedersen, C. Rosenbohm, T. Koch (2002) Preparation of LNA Phosphoramidites, Synthesis 6, 802-808.

Example 2

Oligonucleotide Synthesis

[0461] Oligonucleotides were synthesized using the phosphoramidite approach on an Expedite 8900/MOSS synthesizer (Multiple Oligonucleotide Synthesis System) at 1 μmol or 15 μmol scale. For larger scale synthesis an Äkta Oligo Pilot (GE Healthcare) was used. At the end of the synthesis (DMT-on), the oligonucleotides were cleaved from the solid support using aqueous ammonia for 1-2 hours at room temperature, and further deprotected for 4 hours at 65° C. The oligonucleotides were purified by reverse phase HPLC (RP-HPLC). After the removal of the DMT-group, the oligonucleotides were characterized by AE-HPLC, RP-HPLC, and CGE and the molecular mass was further confirmed by ESI-MS. See below for more details.

[0462] Preparation of the LNA-Solid Support:

[0463] Preparation of the LNA succinyl hemiester

[0464] 5'-O-Dmt-3'-hydroxy-LNA monomer (500 mg), succinic anhydride (1.2 eq.) and DMAP (1.2 eq.) were dissolved in DCM (35 mL). The reaction was stirred at room temperature overnight. After extractions with NaH_2PO_4 0.1 M pH 5.5 (2×) and brine (1×), the organic layer was further dried with anhydrous Na_2SO_4 filtered and evaporated. The hemiester derivative was obtained in 95% yield and was used without any further purification.

[0465] Preparation of the LNA-Support

[0466] The above prepared hemiester derivative (90 μmol) was dissolved in a minimum amount of DMF, DIEA and pyBOP (90 μmol) were added and mixed together for 1 min. This pre-activated mixture was combined with LCAA-CPG (500 Å, 80-120 mesh size, 300 mg) in a manual synthesizer and stirred. After 1.5 hours at room temperature, the support was filtered off and washed with DMF, DCM and MeOH. After drying, the loading was determined to be 57 μmol/g (see Tom Brown, Dorcas J. S. Brown. Modern machine-aided methods of oligodeoxyribonucleotide synthesis. In: F. Eckstein, editor. Oligonucleotides and Analogues A Practical Approach. Oxford: IRL Press, 1991: 13-14).

[0469] Purification by RP-HPLC:

[0470] Column: Xterra RP_{18}

[0471] Flow rate: 3 mL/min

[0472] Buffers: 0.1 M ammonium acetate pH 8 and acetonitrile

[0473] Abbreviations:

[0474] DMT: Dimethoxytrityl

[0475] DCI: 4,5-Dicyanoimidazole

[0476] DMAP: 4-Dimethylaminopyridine

[0477] DCM: Dichloromethane

[0478] DMF: Dimethylformamide

[0479] THF: Tetrahydrofurane

[0480] DIEA: N,N-diisopropylethylamine

[0481] PyBOP:Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate

[0482] Bz: Benzoyl

[0483] Ibu: Isobutyryl

Example 3

Design of the LNA Anti-miR Oligonucleotides and Melting Temperatures

[0484]

Target microRNA:
miR-122a: 5'-uggagugugacaaugguguuugu-3' SEQ ID NO: 535

miR-122a 3' to 5': 3'-uguuuguggguaacagugugaggu-5' (SEQ ID NO: 535 reverse orientation)

TABLE 1

LNA anti-miR oligonucleotide sequences and T_m:

SEQ ID NO:	Oligo ID		SED ID	Sequence:		Tm (° C.)
2	SPC3370	XxxX design	SEQ ID 585	5'-cCatTgtCacActCca-3'	PS backbone	75
3	SPC3372	XxxX design	SEQ ID 586	5'-ccAttGtcAcaCtcCa-3'	PS backbone	69
4	SPC3375	Gapmer	SEQ ID 587	5'-CCAttgtcacacTCCa-3'	PS backbone	69
5	SPC3549	15-mer	SEQ ID 588	5'-CcAttGTcaCaCtCC-3'	PS backbone	78
6	SPC3550	mismatch control	SEQ ID 589	5'-CcAttCTgaCcCtAC-3'	PS backbone	32
7	SPC3373	mismatch control	SEQ ID 590	5'-ccAttGtcTcaAtcCa-3'	PS backbone	46
8	SPC3548	13-mer	SEQ ID 591	5'-AttGTcaCaCtCC-3'	PS backbone	

[0467] Elongation of the Oligonucleotide

[0468] The coupling of phosphoramidites (A(bz), G(lbu), 5-methyl-C(bz)) or T-β-cyanoethyl-phosphoramidite) is performed by using a solution of 0.1 M of the 5'-O-DMT-protected amidite in acetonitrile and DCI (4,5-dicyanoimidazole) in acetonitrile (0.25 M) as activator. The thiolation is carried out by using xanthane chloride (0.01 M in acetonitrile: pyridine 10%). The rest of the reagents are the ones typically used for oligonucleotide synthesis.

lower case: DNA, uppercase: LNA (all LNA C were methylated), underlined: mismatch

[0485] The melting temperatures were assessed towards the mature miR-122a sequence, using a synthetic miR-122a RNA oligonucleotide with phosphorothioate linkaged.

[0486] The LNA anti-miR/miR-122a oligo duplex was diluted to 3 μM in 500 μl RNase free H_20, which was then mixed with 500 μl 2× dimerization buffer (final oligo/duplex

conc. 1.5 μM, 2× Tm buffer: 200 mM NaCl, 0.2 mM EDTA, 20 mM NaP, pH 7.0, DEPC treated to remove RNases). The mix was first heated to 95 degrees for 3 minutes, then allowed to cool at room temperature (RT) for 30 minutes.

[0487] Following RT incubation T_m was measured on Lambda 40 UV/VIS Spectrophotometer with peltier temperature programmer PTP6 using PE Templab software (Perkin Elmer). The Temperature was ramped up from 20° C. to 95° C. and then down again to 20° C., continuously recording absorption at 260 nm. First derivative and local maximums of both the melting and annealing was used to assess melting/annealing point (T_m), both should give similar/same T_m values. For the first derivative 91 points was used to calculate the slope.

[0488] By substituting the antimir oligonucleotide and the complementary RNA molecule, the above assay can be used to determine the T_m of other oligonucleotides such as the oligonucleotides according to the invention.

[0489] However, in one embodiment the T_m may be made with a complementary DNA (phosphorothioate linkages) molecule. Typically the T_m measured against a DNA complementary molecule is about 10° C. lower than the T_m with an equivalent RNA complement. The T_m measured using the DNA complement may therefore be used in cases where the duplex has a very high T_m.

[0490] Melting Temperature (T_m) Measurements:

	T_m
oligo to miR-122 RNA complement	
SPC3372 + miR-122a, RNA	69° C.
SPC3648 + miR-122a, RNA	74° C.
SPC3649 + miR-122a, RNA	79° C.
oligo to DNA complement	
SPC3372 + 122R, DNA	57° C.
SPC3649 + 122R, DNA	66° C.

[0491] It is recognised that for oligonucleotides with very high T_m, the above T_m assays may be insufficient to determine the T_m. In such an instance the use of a phosphorothioated DNA complementary molecule may further lower the T_m.

[0492] The use of formamide is routine in the analysis of oligonucleotide hybridisation (see Hutton 1977, NAR 4 (10) 3537-3555). In the above assay the inclusion of 15% formamide typically lowers the T_m by about 9° C., and the inclusion of 50% formamide typically lowers the T_m by about 30° C. Using these ratios, it is therefore possible to determine the comparative T_m of an oligonucleotide against its complementary RNA (phosphodiester) molecule, even when the T_m of the duplex is, for example higher than 95° C. (in the absence of formamide).

[0493] For oligonucleotides with a very high T_m, an alternative method of determining the T_m, is to make titrations and run it out on a gel to see single strand versus duplex and by those concentrations and ratios determine Kd (the dissociation constant) which is related to deltaG and also T_m.

Example 4

Stability of LNA Oligonucleotides in Human or Rat Plasma

[0494] LNA oligonucleotide stability was tested in plasma from human or rats (it could also be mouse, monkey or dog plasma). In 45 μl plasma, 5 μl LNA oligonucleotide is added (at a final concentration of 20 μM). The LNA oligonucleotides are incubated in plasma for times ranging from 0 to 96 hours at 37° C. (the plasma is tested for nuclease activity up to 96 hours and shows no difference in nuclease cleavage-pattern).

[0495] At the indicated time the sample were snap frozen in liquid nitrogen. 2 μL (equals 40 pmol) LNA oligonucleotide in plasma was diluted by adding 15 μL of water and 3 μL 6× loading dye (Invitrogen). As marker a 10 bp ladder (Invitrogen, USA 10821-015) is used. To 1 μl ladder, 1 μl 6× loading and 4 μl water is added. The samples are mixed, heated to 65° C. for 10 min and loaded to a pre-run gel (16% acrylamide, 7 M UREA, 1×TBE, pre-run at 50 Watt for 1 h) and run at 50-60 Watt for 2½ hours. Subsequently, the gel is stained with 1× SyBR gold (molecular probes) in 1× TBE for 15 min. The bands were visualised using a phosphoimager from BioRad.

Example 5

In Vitro Model: Cell Culture

[0496] The effect of LNA oligonucleotides on target nucleic acid expression (amount) can be tested in any of a variety of cell types provided that the target nucleic acid is present at measurable levels. Target can be expressed endogenously or by transient or stable transfection of a nucleic acid encoding said nucleic acid.

[0497] The expression level of target nucleic acid can be routinely determined using, for example, Northern blot analysis (including microRNA northern), Quantitative PCR (including microRNA qPCR), Ribonuclease protection assays. The following cell types are provided for illustrative purposes, but other cell types can be routinely used, provided that the target is expressed in the cell type chosen.

[0498] Cells were cultured in the appropriate medium as described below and maintained at 37° C. at 95-98% humidity and 5% CO_2. Cells were routinely passaged 2-3 times weekly.

[0499] 15PC3: The human prostate cancer cell line 15PC3 was kindly donated by Dr. F. Baas, Neurozintuigen Laboratory, AMC, The Netherlands and was cultured in DMEM (Sigma)+10% fetal bovine serum (FBS)+Glutamax I+gentamicin.

[0500] PC3: The human prostate cancer cell line PC3 was purchased from ATCC and was cultured in F12 Coon's with glutamine (Gibco)+10% FBS+gentamicin.

[0501] 518A2: The human melanoma cancer cell line 518A2 was kindly donated by Dr. B. Jansen, Section of experimental Oncology, Molecular Pharmacology, Department of Clinical Pharmacology, University of Vienna and was cultured in DMEM (Sigma)+10% fetal bovine serum (FBS)+Glutamax I+gentamicin.

[0502] HeLa: The cervical carcinoma cell line HeLa was cultured in MEM (Sigma) containing 10% fetal bovine serum gentamicin at 37° C., 95% humidity and 5% CO_2.

[0503] MPC-11: The murine multiple myeloma cell line MPC-11 was purchased from ATCC and maintained in DMEM with 4 mM Glutamax+10% Horse Serum.

[0504] DU-145: The human prostate cancer cell line DU-145 was purchased from ATCC and maintained in RPMI with Glutamax+10% FBS.

[0505] RCC-4±VHL: The human renal cancer cell line RCC4 stably transfected with plasmid expressing VHL or

empty plasmid was purchased from ECACC and maintained according to manufacturers instructions.

[0506] 786-0: The human renal cell carcinoma cell line 786-0 was purchased from ATCC and maintained according to manufacturers instructions

[0507] HUVEC: The human umbilical vein endothelial cell line HUVEC was purchased from Camcrex and maintained in EGM-2 medium.

[0508] K562: The human chronic myelogenous leukaemia cell line K562 was purchased from ECACC and maintained in RPMI with Glutamax+10% FBS. U87MG: The human glioblastoma cell line U87MG was purchased from ATCC and maintained according to the manufacturers instructions.

[0509] B16: The murine melanoma cell line B16 was purchased from ATCC and maintained according to the manufacturers instructions.

[0510] LNCap: The human prostate cancer cell line LNCap was purchased from ATCC and maintained in RPMI with Glutamax+10% FBS

[0511] Huh-7: Human liver, epithelial like cultivated in Eagles MEM with 10% FBS, 2 mM Glutamax I, 1× non-essential amino acids, Gentamicin 25 μg/ml

[0512] L428: (Deutsche Sammlung für Mikroorganismen (DSM, Braunschweig, Germany)): Human B cell lymphoma maintained in RPMI 1640 supplemented with 10% FCS, L-glutamine and antibiotics.

[0513] L1236: (Deutsche Sammlung für Mikroorganismen (DSM, Braunschweig, Germany)): Human B cell lymphoma maintained in RPMI 1640 supplemented with 10% FCS, L-glutamine and antibiotics.

Example 6

In Vitro Model: Treatment with LNA Anti-miR Antisense Oligonucleotide

[0514] The miR-122a expressing cell line Huh-7 was transfected with LNA anti-miRs at 1 and 100 nM concentrations according to optimized lipofectamine 2000 (LF2000, Invitrogen) protocol (as follows).

[0515] Huh-7 cells were cultivated in Eagles MEM with 10% FBS, 2mM Glutamax I, 1× non-essential amino acids, Gentamicin 25 μg/ml. The cells were seeded in 6-well plates (300000 cells per well), in a total vol. of 2.5 ml the day before transfection. At the day of transfection a solution containing LF2000 diluted in Optimem (Invitrogen) was prepared (1.2 ml optimem+3.75 μl LF2000 per well, final 2.5 pg LF2000/ml, final tot vol 1.5 ml).

[0516] LNA Oligonucleotides (LNA anti-miRs) were also diluted in optimem. 285 μl optimem+15 μl LNA oligonucleotide (10 μM oligonucleotide stock for final concentration 100 nM and 0.1 μM for final concentration 1 nM) Cells were washed once in optimem then the 1.2 ml optimem/LF2000 mix were added to each well. Cells were incubated 7 min at room temperature in the LF2000 mix where after the 300 μl oligonucleotide optimem solution was added.

[0517] Cell were further incubated for four hours with oligonucleotide and lipofectamine2000 (in regular cell incubator at 37° C., 5% CO2). After these four hours the medium/mix was removed and regular complete medium was added. Cells were allowed to grow for another 20 hours. Cells were harvested in Trizol (Invitrogen) 24 hours after transfection. RNA was extracted according to a standard Trizol protocol according to the manufacturer's instructions (Invitrogen), especially to retain the microRNA in the total RNA extraction.

Example 7

In Vitro and In Vivo Model: Analysis of Oligonucleotide Inhibition of miR Expression by microRNA Specific Quantitative PCR

[0518] miR-122a levels in the RNA samples were assessed on an ABI 7500 Fast real-time PCR instrument (Applied Biosystems, USA) using a miR-122a specific qRT-PCR kit, mirVana (Ambion, USA) and miR-122a primers (Ambion, USA). The procedure was conducted according to the manufacturers protocol.

[0519] Results:

[0520] The miR-122a -specific new LNA anti-miR oligonucleotide design (ie SPC3349 (also referred to as SPC 3549)), was more efficient in inhibiting miR-122a at 1 nM compared to previous design models, including "every-third" and "gap-mer" (SPC3370, SPC3372, SPC3375) motifs were at 100 nM. The mismatch control was not found to inhibit miR-122a (SPC3350). Results are shown in FIG. **1**.

Example 8

Assessment of LNA antago-mir Knock-Down Specificity Using miRNA Microarray Expression Profiling

[0521] A) RNA Labeling for miRNA Microarray Profiling

[0522] Total RNA was extracted using Trizol reagent (Invitrogen) and 3'end labeled using T4 RNA ligase and Cy3- or Cy5-labeled RNA linker (5'-PO4-rUrUrU-Cy3/dT-3' or 5'-PO4-rUrUrU-Cy5/dT-3'). The labeling reactions contained 2-5 μg total RNA, 15 μM RNA linker, 50 mM Tris-HCl (pH 7.8), 10 mM MgCl2, 10 mM DTT, 1 mM ATP, 16% polyethylene glycol and 5 unit T4 RNA ligase (Ambion, USA) and were incubated at 30° C. for 2 hours followed by heat inactivation of the T4 RNA ligase at 80° C. for 5 minutes.

[0523] B) Microarray Hybridization and Post-Hybridization Washes

[0524] LNA-modified oligonucleotide capture probes comprising probes for all annotated miRNAs annotated from mouse (*Mus musculus*) and human (*Homo sapiens*) in the miRBase MicroRNA database Release 7.1 including a set of positive and negative control probes were purchased from Exiqon (Exiqon, Denmark) and used to print the microarrays for miRNA profiling. The capture probes contain a 5'-terminal C6-amino modified linker and were designed to have a Tm of 72° C. against complementary target miRNAs by adjustment of the LNA content and length of the capture probes. The capture probes were diluted to a final concentration of 10 μM in 150 mM sodium phosphate buffer (pH 8.5) and spotted in quadruplicate onto Codelink slides (Amersham Biosciences) using the MicroGrid II arrayer from BioRobotics at 45% humidity and at room temperature. Spotted slides were post-processed as recommended by the manufacturer.

[0525] Labeled RNA was hybridized to the LNA microarrays overnight at 65° C. in a hybridization mixture containing 4×SSC, 0.1% SDS, 1 μg/μl Herring Sperm DNA and 38% formamide. The hybridized slides were washed three times in 2×SSC, 0.025% SDS at 65° C., followed by three times in 0.08×SSC and finally three times in 0.4×SSC at room temperature.

[0526] C) Array Scanning, Image Analysis and Data Processing

[0527] The microarrays were scanned using the ArrayWorx scanner (Applied Precision, USA) according to the manufacturer's recommendations. The scanned images were imported into TIGR Spotfinder version 3.1 (Saeed et al., 2003) for the extraction of mean spot intensities and median local background intensities, excluding spots with intensities below median local background+4× standard deviations. Background-correlated intensities were normalized using variance stabilizing normalization package version 1.8.0 (Huber et al., 2002) for R (www.r-project.org). Intensities of replicate spots were averaged using Microsoft Excel. Probes displaying a coefficient of variance>100% were excluded from further data analysis.

Example 9

Detection of MicroRNAs by In Situ Hybridization Detection of MicroRNAs in Formalin-Fixed Paraffin-Embedded Tissue Sections by In Situ Hybridization

[0528] A) Preparation of the formalin-fixed, paraffin-embedded sections for in situ hybridization Archival paraffin-embedded samples are retrieved and sectioned at 5 to 10 mm sections and mounted in positively-charged slides using floatation technique. Slides are stored at 4° C. until the in situ experiments are conducted.

[0529] B) In Situ Hybridization

[0530] Sections on slides are deparaffinized in xylene and then rehydrated through an ethanol dilution series (from 100% to 25%). Slides are submerged in DEPC-treated water and subject to HCl and 0.2% Glycine treatment, re-fixed in 4% paraformaldehyde and treated with acetic anhydride/triethanolamine; slides are rinsed in several washes of 1×PBS in-between treatments. Slides are pre-hybridized in hyb solution (50% formamide, 5×SSC, 500 mg/mL yeast tRNA, 1× Denhardt) at 50° C. for 30 min. Then, 3 pmol of a FITC-labeled LNA probe (Exiqon, Denmark) complementary to each selected miRNA is added to the hyb. solution and hybridized for one hour at a temperature 20-25° C. below the predicted Tm of the probe (typically between 45-55° C. depending on the miRNA sequence). After washes in 0.1× and 0.5×SCC at 65° C., a tyramide signal amplification reaction was carried out using the Genpoint Fluorescein (FITC) kit (DakoCytomation, Denmark) following the vendor's recommendations. Finally, slides are mounted with Prolong Gold solution. Fluorescence reaction is allowed to develop for 16-24 hr before documenting expression of the selected miRNA using an epifluorescence microscope.

[0531] Detection of MicroRNAs by Whole-Mount In Situ Hybridization of Zebrafish, *Xenopus* and Mouse Embryos.

[0532] All washing and incubation steps are performed in 2 ml eppendorf tubes. Embryos are fixed overnight at 4° C. in 4% paraformaldehyde in PBS and subsequently transferred through a graded series (25% MeOH in PBST (PBS containing 0.1% Tween-20), 50% MeOH in PBST, 75% MeOH in PBST) to 100% methanol and stored at −20° C. up to several months. At the first day of the in situ hybridization embryos are rehydrated by successive incubations for 5 min in 75% MeOH in PBST, 50% MeOH in PBST, 25% MeOH in PBST and 100% PBST (4×5 min).

[0533] Fish, mouse and Xenopus embryos are treated with proteinaseK (10 μg/ml in PBST) for 45 min at 37° C., refixed for 20 min in 4% paraformaldehyde in PBS and washed 3×5 min with PBST. After a short wash in water, endogenous alkaline phosphatase activity is blocked by incubation of the embryos in 0.1 M tri-ethanolamine and 2.5% acetic anhydride for 10 min, followed by a short wash in water and 5×5 min washing in PBST. The embryos are then transferred to hybridization buffer (50% Formamide, 5×SSC, 0.1% Tween, 9.2 mM citric acid, 50 ug/ml heparin, 500 ug/ml yeast RNA) for 2-3 hour at the hybridization temperature. Hybridization is performed in fresh pre-heated hybridization buffer containing 10 nM of 3' DIG-labeled LNA probe (Roche Diagnostics) complementary to each selected miRNA. Post-hybridization washes are done at the hybridization temperature by successive incubations for 15 min in HM-(hybridization buffer without heparin and yeast RNA), 75% HM-/25% 2×SSCT (SSC containing 0.1% Tween-20), 50% HM-/50% 2×SSCT, 25% HM-/75% 2×SSCT, 100% 2×SSCT and 2×30 min in 0.2× SSCT.

[0534] Subsequently, embryos are transferred to PBST through successive incubations for 10 min in 75% 0.2×SSCT/25% PBST, 50% 0.2×SSCT/50% PBST, 25% 0.2×SSCT/75% PBST and 100% PBST. After blocking for 1 hour in blocking buffer (2% sheep serum/2 mg:ml BSA in PBST), the embryos are incubated overnight at 4° C. in blocking buffer containing anti-DIG-AP FAB fragments (Roche, 1/2000). The next day, zebrafish embryos are washed 6×15 min in PBST, mouse and X. tropicalis embryos are washed 6×1 hour in TBST containing 2 mM levamisole and then for 2 days at 4° C. with regular refreshment of the wash buffer.

[0535] After the post-antibody washes, the embryos are washed 3×5 min in staining buffer (100 mM tris HCl pH9.5, 50 mM MgCl2, 100 mM NaCl, 0.1% tween 20). Staining was done in buffer supplied with 4.5 μl/ml NBT (Roche, 50 mg/ml stock) and 3.5 μl/ml BCIP (Roche, 50 mg/ml stock). The reaction is stopped with 1 mM EDTA in PBST and the embryos are stored at 4° C. The embryos are mounted in Murray's solution (2:1 benzylbenzoate:benzylalcohol) via an increasing methanol series (25% MeOH in PBST, 50% MeOH in PBST, 75% MeOH in PBST, 100% MeOH) prior to imaging.

Example 10

In Vitro Model: Isolation and Analysis of mRNA Expression (Total RNA Isolation and cDNA Synthesis for mRNA Analysis)

[0536] Total RNA was isolated either using RNeasy mini kit (Qiagen) or using the Trizol reagent (Invitrogen). For total RNA isolation using RNeasy mini kit (Qiagen), cells were washed with PBS, and Cell Lysis Buffer (RTL, Qiagen) supplemented with 1% mercaptoethanol was added directly to the wells. After a few minutes, the samples were processed according to manufacturer's instructions.

[0537] For in vivo analysis of mRNA expression tissue samples were first homogenised using a Retsch 300MM homogeniser and total RNA was isolated using the Trizol reagent or the RNeasy mini kit as described by the manufacturer.

[0538] First strand synthesis (cDNA from mRNA) was performed using either OmniScript Reverse Transcriptase kit or M-MLV Reverse transcriptase (essentially described by manufacturer (Ambion)) according to the manufacturer's instructions (Qiagen). When using OmniScript Reverse Transcriptase 0.5 μg total RNA each sample, was adjusted to 12 μl

and mixed with 0.2 μl poly $(dT)_{12-18}$ (0.5 μg/μl) (Life Technologies), 2 μl dNTP mix (5 mM each), 2 μl 10× RT buffer, 0.5 μl RNAguard™ RNase Inhibitor (33 units/ml, Amersham) and 1 μl OmniScript Reverse Transcriptase followed by incubation at 37° C. for 60 min. and heat inactivation at 93° C. for 5 min.

[0539] When first strand synthesis was performed using random decamers and M-MLV-Reverse Transcriptase (essentially as described by manufacturer (Ambion)) 0.25 μg total RNA of each sample was adjusted to 10.8 μl in H_2O. 2 μl decamers and 2 μl dNTP mix (2.5 mM each) was added. Samples were heated to 70° C. for 3 min. and cooled immediately in ice water and added 3.25 μl of a mix containing (2 μl 10× RT buffer; 1 μl M-MLV Reverse Transcriptase; 0.25 μl RNAase inhibitor). cDNA is synthesized at 42° C. for 60 min followed by heating inactivation step at 95° C. for 10 min and finally cooled to 4° C. The cDNA can further be used for mRNA quantification by for example Real-time quantitative PCR.

[0540] mRNA expression can be assayed in a variety of ways known in the art. For example, mRNA levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), Ribonuclease protection assay (RPA) or real-time PCR. Real-time quantitative PCR is presently preferred. RNA analysis can be performed on total cellular RNA or mRNA.

[0541] Methods of RNA isolation and RNA analysis such as Northern blot analysis are routine in the art and is taught in, for example, Current Protocols in Molecular Biology, John Wiley and Sons.

[0542] Real-time quantitative (PCR) can be conveniently accomplished using the commercially available iQ Multi-Color Real Time PCR Detection System available from Bio-RAD. Real-time Quantitative PCR is a technique well-known in the art and is taught in for example Heid et al. Real time quantitative PCR, Genome Research (1996), 6: 986-994.

Example 11

LNA Oligonucleotide Uptake and Efficacy In Vivo

[0543] In vivo study: Six groups of animals (5 mice per group) were treated in the following manner. Group 1 animals were injected with 0.2 ml saline by i.v. on 3 successive days, Group 2 received 2.5 mg/kg SPC3372, Group 3 received 6.25 mg/kg, Group 4 received 12.5 mg/kg and Group 5 received 25 mg/kg, while Group 6 received 25 mg/kg SPC 3373 (mismatch LNA-antimiR™ oligonucleotide), all in the same manner. All doses were calculated from the Day 0 body weights of each animal.

[0544] Before dosing (Day 0) and 24 hour after last dose (Day 3), retro-orbital blood was collected in tubes containing EDTA and the plasma fraction harvested and stored frozen −80° C. for cholesterol analysis. At sacrifice livers were dissected and one portion was cut into 5 mm cubes and immersed in 5 volumes of ice-cold RNAlater. A second portion was snap frozen in liquid nitrogen and stored for cryo-sectioning.

[0545] Total RNA was extracted from liver samples as described above and analysed for miR-122a levels by microRNA specific QPCR. FIG. **5** demonstrates a clear dose-response obtained with SPC3372 with an IC50 at ca 3-5 mg/kg, whereas no miR-122a inhibition was detected using the mismatch LNA antago-mir SPC 3373 for miR-122a.

Example 12

LNA-AntimiR-122a Dose-Response In Vivo in C57/BL/3 Female Mice

[0546] In vivo study: Ten groups of animals (female C57/BL6; 3 mice per group) were treated in the following manner. Group 1 animals were injected with 0.2 ml saline by i.p. on day 0, day 2 and day 4. Groups 2-10 were dosed by i.p. with three different conc. (25 mg/kg, 5 mg/kg and 1 mg/kg) of either LNA antimiR-122a/SPC3372 (group 2-4), LNA antimir-122a/SPC3548 (group 5-7) or LNA antimir-122a/SPC3549 (group 8-10); the LNA antimir-122a sequences are given in the Table 1. All three LNA antimiR-122a oligonucleotides target the liver-specific miR-122a. The doses were calculated from the Day 0 body weights of each animal.

[0547] The animals were sacrificed 48 hours after last dose (Day 6), retro-orbital blood was collected in tubes containing EDTA and the plasma fraction harvested and stored frozen −80° C. for cholesterol analysis. At sacrifice livers were dissected and one portion was cut into 5 mm cubes and immersed in 5 volumes of ice-cold RNAlater. A second portion was snap frozen in liquid nitrogen and stored for cryo-sectioning.

[0548] Total RNA was extracted from liver samples using Trizol reagent according to the manufacturer's recommendations (Invitrogen, USA) and analysed for miR-122a levels by microRNA-specific QPCR according to the manufacturer's recommendations (Ambion, USA). FIG. **2** demonstrates a clear dose-response obtained with all three LNA antimir-122a molecules (SPC3372, SPC3548, SPC3549). Both SPC3548 and SPC3549 show significantly improved efficacy in vivo in miR-122a silencing (as seen from the reduced miR-122a levels) compared to SPC3372, with SPC3549 being most potent (IC_{50} ca 1 mg/kg).

[0549] The above example was repeated using SPC3372 and SPC 3649 using 5 mice per group and the data combined (total of eight mice per group) is shown in FIG. **2***b*.

Example 12a

Northern Blot

[0550] MicroRNA specific northern blot showing enhanced miR-122 blocking by SPC3649 compared to SPC3372 in LNA-antimiR treated mouse livers.

[0551] Oligos Used in This Example:

SPC3649: 5'-CcAttGTcaCaCtCC-3'	(SEQ ID 539)	New design
SPC3372: 5'-CcAttGtcAcaCtcCa-3'	(SEQ ID 586)	Old design

[0552] We decided to assess the effect of SPC3649 on miR-122 miRNA levels in the livers of SPC3649-treated mice. The LNA-antimiRs SPC3649 and SPC3372 were administered into mice by three i.p. injections on every second day over a six-day-period at indicated doses followed by sacrificing the animals 48 hours after the last dose. Total RNA was extracted from the livers. miR-122 levels were assessed by microRNA specific northern blot (FIG. **6**)

[0553] Treatment of normal mice with SPC3649 resulted in dramatically improved, dose-dependent reduction of miR-122. MicroRNA specific northern blot comparing SPC3649

with SPC3372 was performed (FIG. **6**). SPC3649 completely blocked miR-122 at both 5 and 25 mg/kg as seen by the absence of mature single stranded miR-122 and only the presence of the duplex band between the LNA-antimiR and miR-122. Comparing duplex versus mature band on the northern blot SPC3649 seem equally efficient at 1 mg/kg as SPC3372 at 25 mg/kg.

Example 13

Assessment of Cholesterol Levels in Plasma in LNA Anti-miR122 Treated Mice

[0554] Total cholesterol level was measured in plasma using a colometric assay Cholesterol CP from ABX Pentra. Cholesterol was measured following enzymatic hydrolysis and oxidation (2.3). 21.5 μl water was added to 1.5 μl plasma. 250 μl reagent was added and within 5 min the cholesterol content measured at a wavelength of 540 nM. Measurements on each animal were made in duplicate. The sensitivity and linearity was tested with 2-fold diluted control compound (ABX Pentra N control). The cholesterol level was determined by subtraction of the background and presented relative to the cholesterol levels in plasma of saline treated mice.

[0555] FIG. **3** demonstrates a markedly lowered level of plasma cholesterol in the mice that received SPC3548 and SPC3549 compared to the saline control at Day 6.

Example 14

Assessment of miR-122a Target mRNA Levels in LNA AntimiR-122a Treated Mice

[0556] The saline control and different LNA-antimiR-122a treated animals were sacrificed 48 hours after last dose (Day 6), and total RNA was extracted from liver samples as using Trizol reagent according to the manufacturer's recommendations (Invitrogen, USA). The mRNA levels were assessed by real-time quantitative RT-PCR for two miR-122a target genes, Bckdk (branched chain ketoacid dehydrogenase kinase, ENSMUSG0000030802) and aldolase A (aldoA, ENSMUSG00000030695), respectively, as well as for GAPDH as control, using Taqman assays according to the manufacturer's instructions (Applied biosystems, USA). FIGS. **4***a* and **4***b* demonstrate a clear dose-dependent upregulation of the two miR-122a target genes, Bckdk and AldoA, respectively, as a response to treatment with all three LNA antimiR-122a molecules (SPC3372, SPC3548, SPC3549). In contrast, the qPCR assays for GAPDH control did not reveal any differences in the GAPD mRNA levels in the LNA-antimiR-122a treated mice compared to the saline control animals (FIG. **4***c*). The Bckdk and AldoA mRNA levels were significantly higher in the SPC3548 and SPC3549 treated mice compared to the SPC3372 treated mice (FIGS. **4***a* and **4***b*), thereby demonstrating their improved in vivo efficacy.

Example 15

LNA Oligonucleotide Duration of Action In Vivo

[0557] In vivo study: Two groups of animals (21 mice per group) were treated in the following manner. Group 1 animals were injected with 0.2 ml saline by i.v. on 3 successive days, Group 2 received 25mg/kg SPC3372 in the same manner. All doses were calculated from the Day 0 body weights of each animal.

[0558] After last dose (Day 3), 7 animals from each group were sacrificed on Day 9, Day 16 and Day 23, respectively. Prior to this, on each day, retro-orbital blood was collected in tubes containing EDTA and the plasma fraction harvested and stored frozen −80° C. for cholesterol analysis from each day. At sacrifice livers were dissected and one portion was cut into 5 mm cubes and immersed in 5 volumes of ice-cold RNAlater. A second portion was snap frozen in liquid nitrogen and stored for cryo-sectioning.

[0559] Total RNA was extracted from liver samples as described above and analysed for miR-122a levels by microRNA specific QPCR. FIG. **7** (Sacrifice day 9, 16 or 23 correspond to sacrifice 1, 2 or 3 weeks after last dose) demonstrates a two-fold inhibition in the mice that received SPC3372 compared to the saline control, and this inhibition could still be detected at Day 16, while by Day 23 the mi122a levels approached those of the saline group.

Example 16

LNA Oligonucleotide Duration of Action In Vivo

[0560] In vivo study: Two groups of animals (21 mice per group) were treated in the following manner. Group 1 animals were injected with 0.2 ml saline by i.v. on 3 successive days, Group 2 received 25 mg/kg SPC3372 in the same manner. All doses were calculated from the Day 0 body weights of each animal.

[0561] After last dose (Day 3), 7 animals from each group were sacrificed on Day 9, Day 16 and Day 23, respectively. Prior to this, on each day, retro-orbital blood was collected in tubes containing EDTA and the plasma fraction harvested and stored frozen −80° C. for cholesterol analysis from each day. At sacrifice livers were dissected and one portion was cut into 5 mm cubes and immersed in 5 volumes of ice-cold RNAlater. A second portion was snap frozen in liquid nitrogen and stored for cryo-sectioning.

[0562] Total RNA was extracted from liver samples as described above and analysed for miR-122a levels by microRNA specific QPCR. FIG. **8** demonstrates a two-fold inhibition in the mice that received SPC3372 compared to the saline control, and this inhibition could still be detected at Day 16, while by Day23 the miR-122a levels approached those of the saline group.

As to Examples 17-22, the Following Procedures Apply

[0563] NMRI mice were administered intravenously with SPC3372 using daily doses ranging from 2.5 to 25 mg/kg for three consecutive days. Animals were sacrificed 24 hours, 1, 2 or 3 weeks after last dose. Livers were harvested divided into pieces and submerged in RNAlater (Ambion) or snap-frozen. RNA was extracted with Trizol reagent according to the manufacturer's instructions (Invitrogen) from the RNAlater tissue, except that the precipitated RNA was washed in 80% ethanol and not vortexed. The RNA was used for mRNA TaqMan qPCR according to manufacturer (Applied biosystems) or northern blot (see below). The snap-frozen pieces were cryo-sectioned for in situ hybridizations.

[0564] Further, as to FIGS. **9-14**, SPC3372 is designated LNA-antimiR and SPC3373 (the mismatch control) is designated "mm" instead of using the SPC number.

Example 17

Dose Dependent miR-122a Target mRNA Induction by SPC3372 Inhibition of miR-122a

[0565] Mice were treated with different SPC3372 doses for three consecutive days, as described above and sacrificed 24

hours after last dose. Total RNA extracted from liver was subjected to qPCR. Genes with predicted miR-122 target site and observed to be upregulated by microarray analysis were investigated for dose-dependent induction by increasing SPC3372 doses using qPCR. Total liver RNA from 2 to 3 mice per group sacrificed 24 hours after last dose were subjected to qPCR for the indicated genes. Shown in FIG. **9** is mRNA levels relative to Saline group, n=2-3 (2.5-12.5 mg/kg/day: n=2, no SD). Shown is also the mismatch control (mm, SPC3373).

[0566] Assayed genes: Nrdg3 Aldo A, Bckdk, CD320 with predicted miR-122 target site. Aldo B and Gapdh do not have a predicted miR-122a target site.

[0567] A clear dose-dependent induction was seen of the miR-122a target genes after treatment with different doses of SPC3372.

Example 18

Transient Induction of miR-122a Target mRNAs Following SPC3372 Treatment

[0568] NMRI female mice were treated with 25 mg/kg/day SPC3372 along with saline control for three consecutive days and sacrificed 1, 2 or 3 weeks after last dose, respectively. RNA was extracted from livers and mRNA levels of predicted miR-122a target mRNAs, selected by microarray data were investigated by qPCR. Three animals from each group were analysed.

[0569] Assayed genes: Nrdg3 Aldo A, Bckdk, CD320 with predicted miR-122 target site. Gapdh does not have a predicted miR-122a target site.

[0570] A transient induction followed by a restoration of normal expression levels in analogy with the restoration of normal miR-122a levels was seen (FIG. **10**).

[0571] mRNA levels are normalized to the individual GAPDH levels and to the mean of the Saline treated group at each individual time point. Included are also the values from the animals sacrificed 24 hours after last dose. Shown is mean and standard deviation, n=3 (24 h n=3)

Example 19

Induction of Vldlr in Liver by SPC3372 Treatment

[0572] The same liver RNA samples as in previous example were investigated for Vldlr induction.

[0573] A transient up-regulation was seen after SPC3372 treatment, as with the other predicted miR-122a target mRNAs (FIG. **11**)

Example 20

Stability of miR-122a/SPC3372 Duplex in Mouse Plasma

[0574] Stability of SPC3372 and SPC3372/miR-122a duplex were tested in mouse plasma at 37° C. over 96 hours. Shown in FIG. **12** is a SYBR-Gold stained PAGE.

[0575] SPC3372 was completely stable over 96 hours. The SPC3372/miR-122a duplex was immediately truncated (degradation of the single stranded miR-122a region not covered by SPC3372) but thereafter almost completely stable over 96 hours.

[0576] The fact that a preformed SPC3372/miR-122 duplex showed stability in serum over 96 hours together with the high thermal duplex stability of SPC3372 molecule supported our notion that inhibition of miR-122a by SPC3372 was due to stable duplex formation between the two molecules, which has also been reported in cell culture (Naguibneva et al. 2006).

Example 21

Sequestering of Mature miR-122a by SPC3372 Leads to Duplex Formation

[0577] The liver RNA was also subjected to microRNA Northern blot. Shown in FIG. **13** is a membrane probed with a miR-122a specific probe (upper panel) and re-probed with a Let-7 specific probe (lower panel). With the miR-122 probe, two bands could be detected, one corresponding to mature miR-122 and one corresponding to a duplex between SPC3372 and miR-122.

[0578] To confirm silencing of miR-122, liver RNA samples were subjected to small RNA northern blot analysis, which showed significantly reduced levels of detectable mature miR-122, in accordance with our real-time RT-PCR results. By comparison, the levels of the let-7a control were not altered. Interestingly, we observed dose-dependent accumulation of a shifted miR-122/SPC3372 heteroduplex band, suggesting that SPC3372 does not target miR-122 for degradation, but rather binds to the microRNA, thereby sterically hindering its function.

[0579] Northern Blot Analysis was Performed as Follows:

[0580] Preparation of northern membranes was done as described in Sempere et al. 2002, except for the following changes: Total RNA, 10 μg per lane, in formamide loading buffer (47.5% formamide, 9 mM EDTA, 0.0125% Bromophenol Blue, 0.0125% Xylene Cyanol, 0.0125% SDS) was loaded onto a 15% denaturing Novex TBE-Urea polyacrylamide gel (Invitrogen) without preheating the RNA. The RNA was electrophoretically transferred to a GeneScreen plus Hybridization Transfer Membrane (PerkinElmer) at 200 mA for 35 min. Membranes were probed with 32P-labelled LNA-modified oligonucleotides complimentary to the mature microRNAs*. The LNA oligonucleotides were labelled and hybridized to the membrane as described in (Válóczi et al. 2004) except for the following changes: The prehybridization and hybridization solutions contained 50% formamide, 0.5% SDS, 5×SSC, 5× Denhardt's solution and 20 μg/ml sheared denatured herring sperm DNA. Hybridizations were performed at 45° C. The blots were visualized by scanning in a Storm 860 scanner. The signal of the background membrane was subtracted from the radioactive signals originating from the miRNA bands. The values of the miR-122 signals were corrected for loading differences based on the let-7a signal. To determine the size of the radioactive signals the Decade Marker System (Ambion) was used according to the suppliers' recommendations.

Example 22

miR-122a Sequestering by SPC3372 Along with SPC3372 Distribution Assessed by In Situ Hybridization of Liver Sections

[0581] Liver cryo-sections from treated animals were subjected to in situ hybridizations for detection and localization of miR-122 and SPC3372 (FIG. **14**). A probe complementary to miR-122 could detect miR-122a. A second probe was complementary to SPC3372. Shown in FIG. **14** is an overlay, in green is distribution and apparent amounts of miR-122a

and SPC3372 and blue is DAPI nuclear stain, at 10× magnification. 100× magnifications reveal the intracellular distribution of miR-122a and SPC3372 inside the mouse liver cells. The liver sections from saline control animals showed a strong miR-122 staining pattern over the entire liver section, whereas the sections from SPC3372 treated mice showed a significantly reduced patchy staining pattern. In contrast, SPC3372 molecule was readily detected in SPC3372 treated liver, but not in the untreated saline control liver. Higher magnification localized miR-122a to the cytoplasm in the hepatocytes, where the miR-122 in situ pattern was clearly compartmentalized, while SPC3372 molecule was evenly distributed in the entire cytoplasm.

Example 23

Micro Array Analysis

[0582] We carried out genome-wide expression profiling of total RNA samples from saline LNA-antimiR-122 treated and LNA mismatch control treated mice livers 24 hours after the last dose using Affymetrix Mouse Genome 430 2.0 arrays. Analysis of the array data revealed 455 transcripts that were upregulated in the LNA-antimiR treated mice livers compared to saline and LNA mismatch controls, while 54 transcripts were downregulated (FIG. **15***a*). A total of 415 of the upregulated and 53 downregulated transcripts could be identified in the Ensembl database. We subsequently examined the 3' untranslated regions (UTRs) of the differentially expressed mRNAs for the presence of the 6 nt sequence CACTCC, corresponding to the reverse complement of the nucleotide 2-7 seed region in mature miR-122. The number of transcripts having at least one miR-122 recognition sequence was 213 (51%) among the upregulated transcripts, and 10 (19%) within the downregulated transcripts, while the frequency in a random sequence population was 25%, implying that a significant pool of the upregulated mRNAs represent direct miR-122 targets in the liver (FIG. **15***b*).

[0583] The LNA-antimiR treatment showed maximal reduction of miR-122 levels at 24 hours, 50% reduction at one week and matched saline controls at three weeks after last LNA dose (Example 12 "old design"). This coincided with a markedly reduced number of differentially expressed genes between the two mice groups at the later time points. Compared to the 509 mRNAs 24 hours after the last LNA dose we identified 251 differentially expressed genes after one week, but only 18 genes after three weeks post treatment (FIGS. **15***c* and **15***d*). In general genes upregulated 24 hours after LNA-antimiR treatment then reverted towards control levels over the next two weeks (FIG. **15***d*).

[0584] In conclusion, a large portion of up-regulated/de-repressed genes after LNA-antimiR treatment are miR-122 targets, indicating a very specific effect for blocking miR-122. Also genes up-regulated/de-repressed approach normal levels 3 weeks after end of treatment, suggest a relative long therapeutic effect, but however not cause a permanent alteration, ie the effect is reversible.

[0585] Methods:

[0586] Gene Expression Profiling of LNA-AntimiR Treated Mice.

[0587] Expression profiles of livers of saline and LNA-antimiR treated mice were compared. NMRI female mice were treated with 25 mg/kg/day of LNA-antimiR along with saline control for three consecutive days and sacrificed 24 h, 1, 2 or 3 weeks after last dose. Additionally, expression profiles of livers of mice treated with the mismatch LNA control oligonucleotide 24 h after last dose were obtained. Three mice from each group were analyzed, yielding a total of 21 expression profiles. RNA quality and concentration was measured using an Agilent 2100 Bioanalyzer and Nanodrop ND-1000, respectively. Total RNA was processed following the GeneChip Expression 3'-Amplification Reagents One-cycle cDNA synthesis kit instructions (Affymetrix Inc, Santa Clara, Calif., USA) to produce double-stranded cDNA. This was used as a template to generate biotin-labeled cRNA following manufacturer's specifications. Fifteen micrograms of biotin-labeled cRNA was fragmented to strands between 35 and 200 bases in length, of which 10 micrograms were hybridised onto Affymetrix Mouse Genome 430 2.0 arrays overnight in the GeneChip Hybridisation oven 6400 using standard procedures. The arrays were washed and stained in a GeneChip Fluidics Station 450. Scanning was carried out using the GeneChip Scanner 3000 and image analysis was performed using GeneChip Operating Software. Normalization and statistical analysis were done using the LIMMA software package for the R programming environment27. Probes reported as absent by GCOS software in all hybridizations were removed from the dataset. Additionally, an intensity filter was applied to the dataset to remove probes displaying background-corrected intensities below 16. Data were normalized using quantile normalization28. Differential expression was assessed using a linear model method. P values were adjusted for multiple testing using the Benjamini and Hochberg. Tests were considered to be significant if the adjusted p values were $p<0.05$. Clustering and visualization of Affymetrix array data were done using the MultiExperiment Viewer software29.

[0588] Target Site Prediction

[0589] Transcripts with annotated 3' UTRs were extracted from the Ensembl database (Release 41) using the EnsMart data mining tool30 and searched for the presence of the CACTCC sequence which is the reverse complement of the nucleotide 2-7 seed in the mature miR-122 sequence. As a background control, a set of 1000 sequences with a length of 1200 nt, corresponding to the mean 3' UTR length of the up- and downregulated transcripts at 24 h after last LNA-antimiR dose, were searched for the 6 nucleotide miR-122 seed matches. This was carried out 500 times and the mean count was used for comparison

Example 24

Dose-Dependent Inhibition of miR-122 in Mouse Liver by LNA-AntimiR is Enhanced as Compared to antagomir Inhibition of miR-122

[0590] NMRI female mice were treated with indicated doses of LNA-antimiR (SPC3372) along with a mismatch control (mm, SPC3373), saline and antagomir (SPC3595) for three consecutive days and sacrificed 24 hours after last dose (as in example 11 "old design", n=5). miR-122 levels were analyzed by qPCR and normalized to the saline treated group. Genes with predicted miR-122 target site and up regulated in the expression profiling (AldoA, Nrdg3, Bckdk and CD320) showed dose-dependent de-repression by increasing LNA-antimiR doses measured by qPCR.

[0591] The de-repression was consistently higher on all tested miR-122 target mRNAs (AldoA, Bckdk, CD320 and Nrdg3 FIG. **17**, **18**, **19**, **20**) in LNA-antimiR treated mice compared to antagomir treated mice. This was also indicated

when analysing the inhibition of miR-122 by miR-122 specific qPCR (FIG. **16**). Hence LNA-antimiRs give a more potent functional inhibition of miR-122 than corresponding dose antagomir.

Example 25

Inhibition of miR-122 by LNA-AntimiR in Hypercholesterolemic Mice Along with Cholesterol Reduction and miR-122 Target mRNA De-Repression

[0592] C57BL/6J female mice were fed on high fat diet for 13 weeks before the initiation of the SPC3649 treatment. This resulted in increased weight to 30-35 g compared to the weight of normal mice, which was just under 20 g, as weighed at the start of the LNA-antimiR treatment. The high fat diet mice lead to significantly increased total plasma cholesterol level of about 130 mg/dl, thus rendering the mice hypercholesterolemic compared to the normal level of about 70 mg/dl. Both hypercholesterolemic and normal mice were treated i.p. twice weekly with 5 mg/kg SPC3649 and the corresponding mismatch control SPC3744 for a study period of 5½ weeks. Blood samples were collected weekly and total plasma cholesterol was measured during the entire course of the study. Upon sacrificing the mice, liver and blood samples were prepared for total RNA extraction, miRNA and mRNA quantification, assessment of the serum transaminase levels, and liver histology.

[0593] Treatment of hypercholesterolemic mice with SPC3649 resulted in reduction of total plasma cholesterol of about 30% compared to saline control mice already after 10 days and sustained at this level during the entire study (FIG. **21**). The effect was not as pronounced in the normal diet mice. By contrast, the mismatch control SPC3744 did not affect the plasma cholesterol levels in neither hypercholesterolemic nor normal mice.

[0594] Quantification of miR-122 inhibition and miR-122 target gene mRNA de-repression (AldoA and Bckdk) after the long-term treatment with SPC3649 revealed a comparable profile in both hypercholesterolemic and normal mice (FIG. **22**, **23**, **24**), thereby demonstrating the potency of SPC3649 in miR-122 antagonism in both animal groups. The miR-122 qPCR assay indicated that also the mismatch control SPC3744 had an effect on miR-122 levels in the treated mice livers, albeit to a lesser extent compared to SPC3649. This might be a reduction associated with the stem-loop qPCR. Consistent with this notion, treatment of mice with the mismatch control SPC3744 did not result in any functional derepression of the direct miR-122 target genes (FIGS. **23** and **24**) nor reduction of plasma cholesterol (FIG. **21**), implying that SPC3649-mediated antagonism of miR-122 is highly specific in vivo.

[0595] Liver enzymes in hypercholesterolemic and normal mice livers were assessed after long term SPC3649 treatment. No changes in the alanine and aspartate aminotransferase (ALT and AST) levels were detected in the SPC3649 treated hypercholesterolemic mice compared to saline control mice (FIGS. **25** and **26**). A possibly elevated ALT level was observed in the normal mice after long-term treatment with SPC3649 (FIG. **26**).

Example 26

Methods for Performing the LNA-AntimiR/Hypercholesterolemic Experiment and Analysis

[0596] Mice and Dosing.

[0597] C57BL/6J female mice (Taconic M&B Laboratory Animals, Ejby, Denmark) were used. All substances were formulated in physiological saline (0.9% NaCl) to final concentration allowing the mice to receive an intraperitoneal injection volume of 10 ml/kg.

[0598] In the diet induced obesity study, the mice received a high fat (60EN %) diet (D12492, Research Diets) for 13 weeks to increase their blood cholesterol level before the dosing started. The dose regimen was stretched out to 5½ weeks of 5 mg/kg LNA-antimiR™ twice weekly. Blood plasma was collected once a week during the entire dosing period. After completion of the experiment the mice were sacrificed and RNA extracted from the livers for further analysis. Serum was also collected for analysis of liver enzymes.

[0599] Total RNA Extraction.

[0600] The dissected livers from sacrificed mice were immediately stored in RNA later (Ambion). Total RNA was extracted with Trizol reagent according to the manufacturer's instructions (Invitrogen), except that the precipitated RNA pellet was washed in 80% ethanol and not vortexed.

[0601] MicroRNA-Specific Quantitative RT-PCR.

[0602] The miR-122 and let-7a microRNA levels were quantified with TaqMan microRNA Assay (Applied Biosystems) following the manufacturer's instructions. The RT reaction was diluted ten times in water and subsequently used for real time PCR amplification according to the manufacturer's instructions. A two-fold cDNA dilution series from liver total RNA of a saline-treated animal or mock transfected cells cDNA reaction (using 2.5 times more total RNA than in samples) served as standard to ensure a linear range (Ct versus relative copy number) of the amplification. Applied Biosystems 7500 or 7900 real-time PCR instrument was used for amplification.

[0603] Quantitative RT-PCR

[0604] mRNA quantification of selected genes was done using standard TaqMan assays (Applied Biosystems). The reverse transcription reaction was carried out with random decamers, 0.5 μg total RNA, and the M-MLV RT enzyme from Ambion according to a standard protocol. First strand cDNA was subsequently diluted 10 times in nuclease-free water before addition to the RT-PCR reaction mixture. A two-fold cDNA dilution series from liver total RNA of a saline-treated animal or mock transfected cells cDNA reaction (using 2.5 times more total RNA than in samples) served as standard to ensure a linear range (Ct versus relative copy number) of the amplification. Applied Biosystems 7500 or 7900 real-time PCR instrument was used for amplification.

[0605] Metabolic Measurements.

[0606] Immediately before sacrifice retro-orbital sinus blood was collected in EDTA-coated tubes followed by isolation of the plasma fraction. Total plasma cholesterol was analysed using ABX Pentra Cholesterol CP (Horiba Group, Horiba ABX Diagnostics) according to the manufacturer's instructions.

[0607] Liver Enzymes (ALT and AST) Measurement

[0608] Serum from each individual mouse was prepared as follows: Blood samples were stored at room temperature for 2 h before centrifugation (10 min, 3000 rpm at room temperature). After centrifugation, serum was harvested and frozen at −20° C.

[0609] ALT and AST measurement was performed in 96-well plates using ALT and AST reagents from ABX Pentra according to the manufacturer's instructions. In short, serum samples were diluted 2.5 fold with H_2O and each sample was assayed in duplicate. After addition of 50 μl diluted sample or standard (multical from ABX Pentra) to each well, 200 μl of 37° C. AST or ALT reagent mix was added to each well. Kinetic measurements were performed for 5 min with an interval of 30 s at 340 nm and 37° C. using a spectrophotometer.

Example 27

Modulation of Hepatitis C Replication by LNA-AntimiR (SPC3649)

[0610] Oligos used in this example (uppercase: LNA, lowercase DNA, LNA Cs are methyl-^{m}c, and LNAs are preferably B-D-oxy (o subscript after LNA residue e.g. $C_s{}^o$):

SPC3649 (LNA-antimiR targeting miR-122, was in the initial small scale synthesis designated SPC3549) SEQ ID 558

5'-$^{m}C_s^{o}c_sA_s^{o}t_st_sG_s^{o}T_s^{o}c_sa_s^{m}C_s^{o}a_s^{m}C_s^{o}t_s^{m}C_s^{o}{}^{m}C^{o}$-3'

SPC3648 (LNA-antimiR targeting miR-122, was in the initial small scale synthesis designated SPC3548)

5'-A_s^{o} t_s t_s G_s^{o} T_s^{o} c_s a_s $^{m}C_s^{o}$ a_s $^{m}C_s^{o}$ t_s $^{m}C_s^{o}$ $^{m}C^{o}$-3'

SPC3550 (4 nt mismatch control to SPC3649) SEQ ID 592

5'-$^{m}C_s^{o}$ c_s A_s^{o} t_s t_s $^{m}C_s^{o}$ T_s^{o} g_s a_s $^{m}C_s^{o}$ c_s $^{m}C_s^{o}$ t_s A_s^{o} $^{m}C^{o}$-3'

2'OMe anti-122: full length (23 nt) 2'OMe modified oligo complementary to miR-122

2'OMe Ctrl: scrambled 2'OMe modified control

[0611] Hepatitis C (HCV) replication has been shown to be facilitated by miR-122 and consequently, antagonizing miR-122 has been demonstrated to affect HCV replication in a hepatoma cell model in vitro. We assess the efficacy of SPC3649 reducing HCV replication in the Huh-7 based cell model. The different LNA-antimiR molecules along with a 2' OMe antisense and scramble oligonucleotide are transfected into Huh-7 cells, HCV is allowed to replicate for 48 hours. Total RNA samples extracted from the Huh-7 cells are subjected to Northern blot analysis.

[0612] A significant reduction of HCV RNA was observed in cells treated with SPC3649 as compared to the mock and SPC3550 mismatch control. The inhibition was clearly dose-dependent with both SPC3649 and SPC3648. Interestingly, using a 2'OMe oligonucleotide fully complementary to miR-122 at 50 nM was much less efficient than SPC3649 at the same final concentration. Notably, the 13 nt SPC3648 LNA-antimiR showed comparable efficacy with SPC3649.

Example 28

Enhanced LNA-AntimiR™ Antisense Oligonucleotide Targeting miR-21

[0613] Mature miR-21 Sequence from Sanger Institute miRBase:

>hsa-miR-21 MIMAT0000076
UAGCUUAUCAGACUGAUGUUGA (SEQ ID NO 565)

>mmu-miR-21 MIMAT0000530
UAGCUUAUCAGACUGAUGUUGA (SEQ ID NO 593)

[0614] Sequence of Compounds:

SPC3521 miR-21 5'-FAM TCAgtctgataaGCTa-3' (SEQ ID NO 594) (gap-mer design)

SPC3870 miR-21(mm) 5'-FAM TCCgtcttagaaGATa-3' (SEQ ID NO 595)

SPC3825 miR-21 5'-FAM TcTgtCAgaTaCgAT-3' (SEQ ID NO 596) (new design)

SPC3826 miR-21(mm) 5'-FAM TcAgtCTgaTaAgCT-3' (SEQ ID NO 597)

SPC3827 miR-21 5'-FAM TcAGtCTGaTaAgCT-3' (SEQ ID NO 598) (new, enhanced design)

[0615] All compounds preferably have a fully or almost fully thiolated backbone (preferably fully) and have here also a FAM label in the 5' end (optional).

[0616] miR-21 has been show to be up-regulated in both glioblastoma (Chan et al. Cancer Research 2005, 65 (14), p6029) and breast cancer (Iorio et al. Cancer Research 2005, 65 (16), p7065) and hence has been considered a potential 'oncogenic' microRNA. Chan et al. also show induction of apoptosis in glioblastoma cells by antagonising miR-21 with 2'OMe or LNA modified antisense oligonucleotides. Hence, agents antagonising miR-21 have the potential to become therapeutics for treatment of glioblastoma and other solid tumours, such as breast cancer. We present an enhanced LNA modified oligonucleotide targeting miR-21, an LNA-antimiR™, with surprisingly good properties to inhibit miR-21 suited for the abovementioned therapeutic purposes.

[0617] Suitable therapeutic administration routes are, for example, intracranial injections in glioblastomas, intratumoural injections in glioblastoma and breast cancer, as well as systemic delivery in breast cancer

[0618] Inhibition of miR-21 in U373 Glioblastoma Cell Line and MCF-7 Breast Cancer Cell Line.

[0619] Efficacy of current LNA-antimiR™ is assessed by transfection at different concentrations, along with control oligonucleotides, into U373 and MCF-7 cell lines known to express miR-21 (or others miR-21 expressing cell lines as well). Transfection is performed using standard Lipofectamine2000 protocol (Invitrogen). 24 hours post transfection, the cells are harvested and total RNA extracted using the Trizol protocol (Invitrogen). Assessment of miR-21 levels, depending on treatment and concentration used is done by miR-21 specific, stem-loop real-time RT-PCR (Applied Bio-

systems), or alternatively by miR-21 specific non-radioactive northern blot analyses. The detected miR-21 levels compared to vehicle control reflects the inhibitory potential of the LNA-antimiR™.

[0620] Functional Inhibition of miR-21 by Assessment of miR-21 Target Gene Up-Regulation.

[0621] The effect of miR-21 antagonism is investigated through cloning of the perfect match miR-21 target sequence behind a standard Renilla luciferase reporter system (between coding sequence and 3' UTR, psiCHECK-2, Promega)—see Example 29. The reporter construct and LNA-antimiR™ will be co-transfected into miR-21 expressing cell lines (f. ex. U373, MCF-7). The cells are harvested 24 hours post transfection in passive lysis buffer and the luciferase activity is measured according to a standard protocol (Promega, Dual Luciferase Reporter Assay System). The induction of luciferase activity is used to demonstrate the functional effect of LNA-antimiR™ antagonising miR-21.

Example 29

Luciferase Reporter Assay for Assessing Functional Inhibition of MicroRNA by LNA-AntimiRs and Other MicroRNA Targeting Oligos: Generalisation of New and Enhanced New Design as Preferred Design for Blocking MicroRNA Function

[0622] Oligos used in this example (uppercase: LNA, lowercase: DNA) to assess LNA-antimiR de-repressing effect on luciferase reporter with microRNA target sequence cloned by blocking respective microRNA:

[0623] A reporter plasmid (psiCheck-2 Promega) encoding both the Renilla and the Firefly variants of luciferase was engineered so that the 3'UTR of the Renilla luciferase includes a single copy of a sequence fully complementary to the miRNA under investigation.

[0624] Cells endogenously expressing the investigated miRNAs (HuH-7 for miR-122a, HeLa for miR-19b, 518A2 for miR-155) were co-transfected with LNA-antimiRs or other miR binding oligonucleotides (the full complementary ie full length) and the corresponding microRNA target reporter plasmid using Lipofectamine 2000 (Invitrogen). The transfection and measurement of luciferase activity were carried out according to the manufacturer's instructions (Invitrogen Lipofectamine 2000/Promega Dual-luciferase kit) using 150 000 to 300 000 cells per well in 6-well plates. To compensate for varying cell densities and transfection efficiencies the Renilla luciferase signal was normalized with the Firefly luciferase signal. All experiments were done in triplicate.

[0625] Surprisingly, new design and new enhanced design were the best functional inhibitors for all three microRNA targets, miR-155, miR-19b and miR-122 (FIG. **27**, **28**, **29**). The results are summarized in following table 3.

Oligo #, target microRNA, oligo sequence	Design
target: hsa-miR- 122a MIMAT0000421 uggagugugacaaugguguuugu screened in HUH-7 cell line expressing miR-122	
3962: miR-122 5'-ACAAacaccattgtcacacTCCA-3'	Full complement, gap
3965: miR-122 5'-acaaacACCATTGTcacactcca-3'	Full complement, block
3972: miR-122 5'-acAaaCacCatTgtCacActCca-3'	Full complement, LNA_3
3549 (3649): miR-122 5'-CcAttGTcaCaCtCC-3'	New design
3975: miR-122 5'-CcAtTGTcaCACtCC-3'	Enhanced new design
target: hsa-miR-19b MIMAT0000074 ugugcaaauccaugcaaaacuga screened HeLa cell line expressing miR-19b	
3963: miR-19b 5'-TCAGttttgcatggatttgCACA-3'	Full complement, gap
3967: miR-19b 5'-tcagttTTGCATGGatttgcaca-3'	Full complement, block
3973: miR-19b 5'-tcAgtTttGcaTggAttTgcAca-3'	Full complement, LNA_3
3560: miR-19b 5'-TgCatGGatTtGcAC-3'	New design
3976: miR-19b 5'-TgCaTGGatTTGcAC-3'	Enhanced new design
target: hsa-miR-155 MIMAT0000646 uuaaugcuaaucgugauagggg screen in 518A2 cell line expressing miR-155	
3964: miR-155 5'-CCCCtatcacgattagcaTTAA-3'	Full complement, gap
3968: miR-155 5'-cccctaTCACGATTagcattaa-3'	Full complement, block
3974: miR-155 5'-cCccTatCacGatTagCatTaa-3'	Full complement, LNA_3
3758: miR-155 5'-TcAcgATtaGcAtTA-3'	New design
3818: miR-155 5'-TcAcGATtaGCAtTA-3'	Enhanced new design

SEQ ID NOs as before.

[0626] Result Summary:

TABLE 3

Degree of de-repression of endogenous miR-155, miR-19b and miR-122a function by various designs of LNA-antimiR's.

Design	miR-155	miR-19b	miR-122a
New enhanced design	***	***	no data
New design	***	***	***
Full complement, LNA_3	**	***	**
Full complement, block	**	**	**
Full complement, gap	*	not signif.	not signif.

Example 30

Design of a LNA AntimiR Library for All Human MicroRNA Sequences in miRBase MicroRNA Database Version 8.1, Griffiths-Jones, S., Grocock, R. J., Van Dongen, S., Bateman, A., Enright, A. J. 2006. miRBase: MicroRNA Sequences, Targets and Gene Nomenclature. Nucleic Acids Res. 34: D140-4 (http://microrna.sanger.ac.uk/sequences/index.shtml).

[0627] LNA nucleotides are shown in uppercase letters, DNA nucleotides in lowercase letters, LNA C nucleotides denote LNA methyl-C (mC). The LNA-antimiR oligonucleotides can be conjugated with a variety of haptens or fluorochromes for monitoring uptake into cells and tissues using standard methods.

TABLE 2

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-let-7a	MIMAT0000062	SEQ ID NO 1	AcAacCTacTaCcTC
hsa-let-7b	MIMAT0000063	SEQ ID NO 2	AcAaCCTacTaCcTC
hsa-let-7c	MIMAT0000064	SEQ ID NO 2	AcAacCTacTaCcTC
hsa-let-7d	MIMAT0000065	SEQ ID NO 4	GcAacCTacTaCcTC
hsa-let-7e	MIMAT0000066	SEQ ID NO 5	AcAacCTccTaCcTC
hsa-let-7f	MIMAT0000067	SEQ ID NO 6	AcAatCTacTaCcTC
hsa-miR-15a	MIMAT0000068	SEQ ID NO 7	CcAttATgtGcTgCT
hsa-miR-16	MIMAT0000069	SEQ ID NO 8	TaTttACgtGcTgCT
hsa-miR-17-5p	MIMAT0000070	SEQ ID NO 9	CaCtgTAagCaCtTT
hsa-miR-17-3p	MIMAT0000071	1EQ ID NO 10	GtGccTTcaCtGcAG
hsa-miR-18a	MIMAT0000072	SEQ ID NO 11	CaCtaGAtgCaCcTT
hsa-miR-19a	MIMAT0000073	SEQ ID NO 12	TgCatAGatTtGcAC
hsa-miR-19b	MIMAT0000074	SEQ ID NO 13	TgCatGGatTtGcAC
hsa-miR-20a	MIMAT0000075	SEQ ID NO 14	CaCtaTAagCaCtTT
hsa-miR-21	MIMAT0000076	SEQ ID NO 15	TcAgtCTgaTaAgCT
hsa-miR-22	MIMAT0000077	SEQ ID NO 16	CtTcaACtgGcAgCT
hsa-miR-23a	MIMAT0000078	SEQ ID NO 17	TcCctGCcaAtGtGA
hsa-miR-189	MIMAT0000079	SEQ ID NO 18	TcAgcTCagTaGgCA
hsa-miR-24	MIMAT0000080	SEQ ID NO 19	CtGctGAacTgAgCC
hsa-miR-25	MIMAT0000081	SEQ ID NO 20	CgAgaCAagTgCaAT
hsa-miR-26a	MIMAT0000082	SEQ ID NO 21	TcCtgGAttAcTtGA
hsa-miR-26b	MIMAT0000083	SEQ ID NO 22	TcCtgAAttAcTtGA
hsa-miR-27a	MIMAT0000084	SEQ ID NO 23	AcTtaGCcaCtGtGA
hsa-miR-28	MIMAT0000085	SEQ ID NO 24	AgActGTgaGcTcCT
hsa-miR-29a	MIMAT0000086	SEQ ID NO 25	AtTtcAGatGgTgCT
hsa-miR-30a-5p	MIMAT0000087	SEQ ID NO 26	GtCgaGGatGtTtAC

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-30a-3p	MIMAT0000088	SEQ ID NO 27	AaCatCCgaCtGaAA
hsa-miR-31	MIMAT0000089	SEQ ID NO 28	AtGccAGcaTcTtGC
hsa-miR-32	MIMAT0000090	SEQ ID NO 29	TtAgtAAtgTgCaAT
hsa-miR-33	MIMAT0000091	SEQ ID NO 30	TgCaaCTacAaTgCA
hsa-miR-92	MIMAT0000092	SEQ ID NO 31	CgGgaCAagTgCaAT
hsa-miR-93	MIMAT0000093	SEQ ID NO 32	GcAcgAAcaGcAcTT
hsa-miR-95	MIMAT0000094	SEQ ID NO 33	AtAaaTAccCgTtGA
hsa-miR-96	MIMAT0000095	SEQ ID NO 34	AtGtgCTagTgCcAA
hsa-miR-98	MIMAT0000096	SEQ ID NO 35	AcAacTTacTaCcTC
hsa-miR-99a	MIMAT0000097	SEQ ID NO 36	AtCggATctAcGgGT
hsa-miR-100	MIMAT0000098	SEQ ID NO 37	TtCggATctAcGgCT
hsa-miR-101	MIMAT0000099	SEQ ID NO 38	TtAtcACagTaCtGT
hsa-miR-29b	MIMAT0000100	SEQ ID NO 39	AtTtcAAatGgTgCT
hsa-miR-103	MIMAT0000101	SEQ ID NO 40	CcTgtACaaTgCtGC
hsa-miR-105	MIMAT0000102	SEQ ID NO 41	GaGtcTGagCaTtTG
hsa-miR-106a	MIMAT0000103	SEQ ID NO 42	CaCtgTAagCaCtTT
hsa-miR-107	MIMAT0000104	SEQ ID NO 43	CcTgtACaaTgCtGC
hsa-miR-192	MIMAT0000222	SEQ ID NO 44	TcAatTCatAgGtCA
hsa-miR-196a	MIMAT0000226	SEQ ID NO 45	AaCatGAaaCtAcCT
hsa-miR-197	MIMAT0000227	SEQ ID NO 46	TgGagAAggTgGtGA
hsa-miR-198	MIMAT0000228	SEQ ID NO 47	AtCtcCCctCtGgAC
hsa-miR-199a	MIMAT0000231	SEQ ID NO 48	TaGtcTGaaCaCtGG
hsa-miR-199a*	MIMAT0000232	SEQ ID NO 49	TgTgcAGacTaCtGT
hsa-miR-208	MIMAT0000241	SEQ ID NO 50	TtTttGCtcGtCtTA
hsa-miR-129	MIMAT0000242	SEQ ID NO 51	CcCagACcgCaAaAA
hsa-miR-148a	MIMAT0000243	SEQ ID NO 52	TtCtgTAgtGcAcTG
hsa-miR-30c	MIMAT0000244	SEQ ID NO 53	GtGtaGGatGtTtAC
hsa-miR-30d	MIMAT0000245	SEQ ID NO 54	GtCggGGatGtTtAC
hsa-miR-139	MIMAT0000250	SEQ ID NO 55	AcAcgTGcaCtGtAG
hsa-miR-147	MIMAT0000251	SEQ ID NO 56	AaGcaTTtcCaCaCA
hsa-miR-7	MIMAT0000252	SEQ ID NO 57	AaTcaCTagTcTtCC
hsa-miR-10a	MIMAT0000253	SEQ ID NO 58	TcGgaTCtaCaGgGT
hsa-miR-10b	MIMAT0000254	SEQ ID NO 59	TcGgtTCtaCaGgGT
hsa-miR-34a	MIMAT0000255	SEQ ID NO 60	AgCtaAGacAcTgCC
hsa-miR-181a	MIMAT0000256	SEQ ID NO 61	GaCagCGttGaAtGT

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-181b	MIMAT0000257	SEQ ID NO 62	GaCagCAatGaAtGT
hsa-miR-181c	MIMAT0000258	SEQ ID NO 63	CgAcaGGttGaAtGT
hsa-miR-182	MIMAT0000259	SEQ ID NO 64	TtCtaCCatTgCcAA
hsa-miR-182*	MIMAT0000260	SEQ ID NO 65	GgCaaGTctAgAaCC
hsa-miR-183	MIMAT0000261	SEQ ID NO 66	TtCtaCCagTgCcAT
hsa-miR-187	MIMAT0000262	SEQ ID NO 67	GcAacACaaGaCaCG
hsa-miR-199b	MIMAT0000263	SEQ ID NO 68	TaGtcTAaaCaCtGG
hsa-miR-203	MIMAT0000264	SEQ ID NO 69	GtCctAAacAtTtCA
hsa-miR-204	MIMAT0000265	SEQ ID NO 70	AgGatGAcaAaGgGA
hsa-miR-205	MIMAT0000266	SEQ ID NO 71	CcGgtGGaaTgAaGG
hsa-miR-210	MIMAT0000267	SEQ ID NO 72	GcTgtCAcaCgCaCA
hsa-miR-211	MIMAT0000268	SEQ ID NO 73	AgGatGAcaAaGgGA
hsa-miR-212	MIMAT0000269	SEQ ID NO 74	TgActGGagAcTgTT
hsa-miR-181a*	MIMAT0000270	SEQ ID NO 75	AtCaaCGgtCgAtGG
hsa-miR-214	MIMAT0000271	SEQ ID NO 76	TgTctGTgcCtGcTG
hsa-miR-215	MIMAT0000272	SEQ ID NO 77	TcAatTCatAgGtCA
hsa-miR-216	MIMAT0000273	SEQ ID NO 78	TtGccAGctGaGaTT
hsa-miR-217	MIMAT0000274	SEQ ID NO 79	AgTtcCTgaTgCaGT
hsa-miR-218	MIMAT0000275	SEQ ID NO 80	GtTagATcaAgCaCA
hsa-miR-219	MIMAT0000276	SEQ ID NO 81	TgCgtTTggAcAaTC
hsa-miR-220	MIMAT0000277	SEQ ID NO 82	GtCagATacGgTgTG
hsa-miR-221	MIMAT0000278	SEQ ID NO 83	AgCagACaaTgTaGC
hsa-miR-222	MIMAT0000279	SEQ ID NO 84	GtAgcCAgaTgTaGC
hsa-miR-223	MIMAT0000280	SEQ ID NO 85	AtTtgACaaAcTgAC
hsa-miR-224	MIMAT0000281	SEQ ID NO 86	AaCcaCTagTgAcTT
hsa-miR-200b	MIMAT0000318	SEQ ID NO 87	TtAccAGgcAgTaTT
hsa-let-7g	MIMAT0000414	SEQ ID NO 88	AcAaaCTacTaCcTC
hsa-let-7i	MIMAT0000415	SEQ ID NO 89	AcAaaCTacTaCcTC
hsa-miR-1	MIMAT0000416	SEQ ID NO 90	AcTtcTTtaCaTtCC
hsa-miR-15b	MIMAT0000417	SEQ ID NO 91	CcAtgATgtGcTgCT
hsa-miR-23b	NIMAT0000418	SEQ ID NO 92	TcCctGGcaAtGtGA
hsa-miR-27b	MIMAT0000419	SEQ ID NO 93	AcTtaGCcaCtGtGA
hsa-miR-30b	MIMAT0000420	SEQ ID NO 94	GtGtaGGatGtTtAC
hsa-miR-122a	MIMAT0000421	SEQ ID NO 95	CcAttGTcaCaCtCC
hsa-miR-124a	MIMAT0000422	SEQ ID NO 96	TcAccGCgtGcCtTA
hsa-miR-125b	MIMAT0000423	SEQ ID NO 97	GtTagGGtcTcAgGG

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-128a	MIMAT0000424	SEQ ID NO 98	GaCcgGTtcAcTgTG
hsa-miR-130a	MIMAT0000425	SEQ ID NO 99	TtTtaACatTgCaCT
hsa-miR-132	MIMAT0000426	SEQ ID NO 100	TgGctGTagAcTgTT
hsa-miR-133a	MIMAT0000427	SEQ ID NO 101	GgTtgAAggGgAcCA
hsa-miR-135a	MIMAT0000428	SEQ ID NO 102	GgAatAAaaAgCcAT
hsa-miR-137	MIMAT0000429	SEQ ID NO 103	GtAttCTtaAgCaAT
hsa-miR-138	MIMAT0000430	SEQ ID NO 104	AtTcaCAacAcCaGC
hsa-miR-140	MIMAT0000431	SEQ ID NO 105	AtAggGTaaAaCcAC
hsa-miR-141	MIMAT0000432	SEQ ID NO 106	TtAccAGacAgTgTT
hsa-miR-142-5p	MIMAT0000433	SEQ ID NO 107	TgCttTCtaCtTtAT
hsa-miR-142-3p	MIMAT0000434	SEQ ID NO 108	AgTagGAaaCaCtAC
hsa-miR-143	MIMAT0000435	SEQ ID NO 109	AcAgtGCttCaTcTC
hsa-miR-144	MIMAT0000436	SEQ ID NO 110	CaTcaTCtaTaCtGT
hsa-miR-145	MIMAT0000437	SEQ ID NO 111	CcTggGAaaAcTgGA
hsa-miR-152	MIMAT0000438	SEQ ID NO 112	TtCtgTCatGcAcTG
hsa-miR-153	MIMAT0000439	SEQ ID NO 113	TtTtgTGacTaTgCA
hsa-miR-191	MIMAT0000440	SEQ ID NO 114	TtTtgGGatTcCgTT
hsa-miR-9	MIMAT0000441	SEQ ID NO 115	GcTagATaaCcAaAG
hsa-miR-9*	MIMAT0000442	SEQ ID NO 116	CgGttATctAgCtTT
hsa-miR-125a	MIMAT0000443	SEQ ID NO 117	TaAagGGtcTcAgGG
hsa~miR-126*	MIMAT0000444	SEQ ID NO 118	AcCaaAAgtAaTaAT
hsa-miR-126	MIMAT0000445	SEQ ID NO 119	AtTacTCacGgTaCG
hsa-miR-127	MIMAT0000446	SEQ ID NO 120	GcTcaCAcgGaTcCG
hsa-miR-134	MIMAT0000447	SEQ ID NO 121	TgGtcAAccAgTcAC
hsa-miR-136	MIMAT0000448	SEQ ID NO 122	TcAaaACaaAtGgAG
hsa-miR-146a	MIMAT0000449	SEQ ID NO 123	TgGaaTTcaGtTcTC
hsa-miR-149	MIMAT0000450	SEQ ID NO 124	AaGacACggAgCcAG
hsa-miR-150	MIMAT0000451	SEQ ID NO 125	TaCaaGGgtTgGgAG
hsa-miR-154	MIMAT0000452	SEQ ID NO 126	CaAcaCGgaTaAcCT
hsa-miR-154*	MIMAT0000453	SEQ ID NO 127	TcAacCGtgTaTgAT
hsa-miR-184	MIMAT0000454	SEQ ID NO 128	AtCagTTctCcGtCC
hsa-miR-185	MIMAT0000455	SEQ ID NO 129	AcTgcCTttCtCtCC
hsa-miR-186	MIMAT0000456	SEQ ID NO 130	AaAggAGaaTtCtTT
hsa-miR-188	MIMAT0000457	SEQ ID NO 131	CaCcaTCcaAgGgAT
hsa-miR-190	MIMAT0000458	SEQ ID NO 132	TaTatCAaaCaTaTC

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-193a	MIMAT0000459	SEQ ID NO 133	AcTttGTagGcCaGT
hsa-miR-194	MIMAT0000460	SEQ ID NO 134	TgGagTTgcTgTtAC
hsa-miR-195	MIMAT0000461	SEQ ID NO 135	TaTttCTgtGcTgCT
hsa-miR-206	MIMAT0000462	SEQ ID NO 136	AcTtcCTtaCaTtCC
hsa-miR-320	MIMAT0000510	SEQ ID NO 137	TcTcaACccAgCtTT
hsa-miR-200c	MIMAT0000617	SEQ ID NO 138	TtAccCGgcAgTaTT
hsa-miR-155	MIMAT0000646	SEQ ID NO 139	TcAcgATtaGcAtTA
hsa-miR-128b	MIMAT0000676	SEQ ID NO 140	GaCcgGTtcAcTgTG
hsa-miR-106b	MIMAT0000680	SEQ ID NO 141	CaCtgTCagCaCtTT
hsa-miR-29c	MIMAT0000681	SEQ ID NO 142	AtTtcAAatGgTgCT
hsa-miR-200a	MIMAT0000682	SEQ ID NO 143	TtAccAGacAgTgTT
hsa-miR-302a*	MIMAT0000683	SEQ ID NO 144	AgTacATccAcGtTT
hsa-miR-302a	MIMAT0000684	SEQ ID NO 145	AaCatGGaaGcAcTT
hsa-miR-34b	MIMAT0000685	SEQ ID NO 146	CtAatGAcaCtGcCT
hsa-miR-34c	MIMAT0000686	SEQ ID NO 147	GcTaaCTacAcTgCC
hsa-miR-299-3p	MIMAT0000687	SEQ ID NO 148	TtTacCAtcCcAcAT
hsa-miR-301	MIMAT0000688	SEQ ID NO 149	CaAtaCTatTgCaCT
hsa-miR-99b	MIMAT0000689	SEQ ID NO 150	GtCggTTctAcGgGT
hsa-miR-296	MIMAT0000690	SEQ ID NO 151	AtTgaGGggGgGcCC
hsa-miR-130b	MIMAT0000691	SEQ ID NO 152	TtTcaTCatTgCaCT
hsa-miR-30e-5p	MIMAT0000692	SEQ ID NO 153	GtCaaGGatGtTtAC
hsa-miR-30e-3p	MIMA10000693	SEQ ID NO 154	AaCatCCgaCtGaAA
hsa-miR-361	MIMAT0000703	SEQ ID NO 155	CtGgaGAttCtGaTA
hsa-miR-362	MIMAT0000705	SEQ ID NO 156	CtAggTTccAaGgAT
hsa-miR-363	MIMAT0000707	SEQ ID NO 157	TgGatACcgTgCaAT
hsa-miR-365	MIMAT0000710	SEQ ID NO 158	AtTttTAggGgCaTT
hsa-miR-302b*	MIMAT0000714	SEQ ID NO 159	AcTtcCAtgTtAaAG
hsa-miR-302b	MIMAT0000715	SEQ ID NO 160	AaCatGGaaGcAcTT
hsa-miR-302c*	MIMAT0000716	SEQ ID NO 161	GtAccCCcaTgTtAA
hsa-miR-302c	MIMAT0000717	SEQ ID NO 162	AaCatGGaaGcAcTT
hsa-miR-302d	MIMAT0000718	SEQ ID NO 163	AaCatGGaaGcAcTT
hsa-miR-367	MIMAT0000719	SEQ ID NO 164	TtGctAAagTgCaAT
hsa-miR-368	MIMAT0000720	SEQ ID NO 165	GgAatTTccTcTaTG
hsa-miR-369-3p	MIMAT0000721	SEQ ID NO 166	TcAacCAtgTaTtAT
hsa-miR-370	MIMAT0000722	SEQ ID NO 167	TtCcaCCccAgCaGG
hsa-miR-371	MIMAT0000723	SEQ ID NO 168	CaAaaGAtgGcGgCA

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-372	MIMAT0000724	SEQ ID NO 169	AaTgtCGcaGcAcTT
hsa-miR-373*	MIMAT0000725	SEQ ID NO 170	CgCccCCatTtTgAG
hsa-miR-373	MIMAT0000726	SEQ ID NO 171	AaAatCGaaGcAcTT
hsa-miR-374	MIMAT0000727	SEQ ID NO 172	TcAggTTgtAtTaTA
hsa-miR-375	MIMAT0000728	SEQ ID NO 173	GaGccGAacGaAcAA
hsa-miR-376a	MIMAT0000729	SEQ ID NO 174	GaTttTCctCtAtGA
hsa-miR-377	MIMAT0000730	SEQ ID NO 175	GtTgcCTttCtGtCA
hsa-miR-378	MIMAT0000731	SEQ ID NO 176	GaCctGGagTcAgGA
hsa-miR-422b	MIMAT0000732	SEQ ID NO 177	CtGacTCcaAgTcCA
hsa-miR-379	MIMAT0000733	SEQ ID NO 178	GtTccATagTcTaCC
hsa-miR-380-5p	MIMAT0000734	SEQ ID NO 179	GtTctATggTcAaCC
hsa-miR-380-3p	MIMAT0000735	SEQ ID NO 180	TgGacCAtaTtAcAT
hsa-miR-381	MIMAT0000736	SEQ ID NO 181	AgCttGCccTtGtAT
hsa-miR-382	MIMAT0000737	SEQ ID NO 182	CaCcaCGaaCaAcTT
hsa-miR-383	MIMAT0000738	SEQ ID NO 183	AaTcaCCttCtGaTC
hsa-miR-340	MIMAT0000750	SEQ ID NO 184	AaGtaACtgAgAcGG
hsa-miR-330	MIMAT0000751	SEQ ID NO 185	AgGccGTgtGcTtTG
hsa-miR-328	MIMAT0000752	SEQ ID NO 186	GgGcaGAgaGgGcCA
hsa-miR-342	MTMAT0000753	SEQ ID NO 187	CgAttTCtgTgTgAG
hsa-miR-337	MIMAT0000754	SEQ ID NO 188	TcAtaTAggAgCtGG
hsa-miR-323	MIMAT0000755	SEQ ID NO 189	CgAccGTgtAaTgTG
hsa-miR-326	MTMAT0000756	SEQ ID NO 190	AgGaaGGgcCcAgAG
hsa-miR-151	MIMAT0000757	SEQ ID NO 191	GgAgcTTcaGtCtAG
hsa-miR-135b	MIMAT0000758	SEQ ID NO 192	GgAatGAaaAgCcAT
hsa-miR-148b	MIMAT0000759	SEQ ID NO 193	TtCtgTGatGcAcTG
hsa-miR-331	MIMAT0000760	SEQ ID NO 194	GgAtaGGccCaGgGG
hsa-miR-324-5p	MIMAT0000761	SEQ ID NO 195	TgCccTAggGgAtGC
hsa-miR-324-3p	MIMAT0000762	SEQ ID NO 196	GcAccTGggGcAgTG
hsa-miR-338	MIMAT0000763	SEQ ID NO 197	AaTcaCTgaTgCtGG
hsa-miR-339	MTMAT0000764	SEQ ID NO 198	TcCtgGAggAcAgCG
hsa-miR-335	MIMAT0000765	SEQ ID NO 199	TcGttATtgCtCtTG
hsa-miR-133b	MIMAT0000770	SEQ ID NO 200	GgTtgAAggGgAcCA
hsa-miR-325	MIMAT0000771	SEQ ID NO 201	CtGgaCAccTaCtAG
hsa-miR-345	MIMAT0000772	SEQ ID NO 202	GgActAGgaGtCaGC
hsa-miR-346	MIMAT0000773	SEQ ID NO 203	GgCatGCggGcAgAC

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
ebv-miR-BHRF1-1	MIMAT0000995	SEQ ID NO 204	GgGgcTGatCaGgTT
ebv-miR-BHRF1-2*	MIMAT0000996	SEQ ID NO 205	TgCtgCAacAgAaTT
ebv-miR-BHRF1-2	MIMAT0000997	SEQ ID NO 206	TcTgcCGcaAaAgAT
ebv-miR-BHRF1-3	MIMAT0000998	SEQ ID NO 207	TaCacACttCcCgTT
ebv-miR-BART1-5p	MIMAT0000999	SEQ ID NO 208	GtCacTTccAcTaAG
ebv-miR-BART2	MIMAT0001000	SEQ ID NO 209	GcGaaTGcaGaAaAT
hsa-miR-384	MIMAT0001075	SEQ ID NO 210	AaCaaTTtcTaGgAA
hsa-miR-196b	MIMAT0001080	SEQ ID NO 211	AaCagGAaaCtAcCT
hsa-miR-422a	MIMAT0001339	SEQ ID NO 212	CtGacCCtaAgTcCA
hsa-miR-423	MIMAT0001340	SEQ ID NO 213	GgCctCAgaCcGaGC
hsa-miR-424	MIMAT0001341	SEQ ID NO 214	AcAtgAAttGcTgCT
hsa-miR-425-3p	MIMAT0001343	SEQ ID NO 215	AcAcgACatTcCcGA
hsa-miR-18b	MIMAT0001412	SEQ ID NO 216	CaCtaGAtgCaCcTT
hsa-miR-20b	MIMAT0001413	SEQ ID NO 217	CaCtaTGagCaCtTT
hsa-miR-448	MIMAT0001532	SEQ ID NO 218	CaTccTAcaTaTgCA
hsa-miR-429	MIMAT0001536	SEQ ID NO 219	TtAccAGacAgTaTT
hsa-miR-449	MIMAT0001541	SEQ ID NO 220	TaAcaATacAcTgCC
hsa-miR-450	MIMAT0001545	SEQ ID NO 221	GaAcaCAtcGcAaAA
hcmv-miR-UL22A	MIMAT0001574	SEQ ID NO 222	AcGggAAggCtAgTT
hcmv-miR-UL22A*	MIMAT0001575	SEQ ID NO 223	AcTagCAttCtGgTG
hcmv-miR-UL36	MIMAT0001576	SEQ ID NO 224	CaGgtGTctTcAaCG
hcmv-miR-UL112	MIMAT0001577	SEQ ID NO 225	GaTctCAccGtCaCT
hcmv-miR-DL148D	MIMAT0001578	SEQ ID NO 226	AaGaaGGggAgGaCG
hcmv-miR-US5-1	MIMAT0001579	SEQ ID NO 227	CtCgtCAggCtTgTC
hcmv-miR-US5-2	MIMAT0001580	SEQ ID NO 228	GtCacACctAtCaTA
hcmv-miR-US25-1	MIMAT0001581	SEQ ID NO 229	GaGccACtgAgCgGT
hcmv-miR-US25-2-5p	MIMAT0001582	SEQ ID NO 230	AcCtgAAcaGaCcGC
hcmv-miR-US25-2-3p	MIMAT0001583	SEQ ID NO 231	AgCtcTCcaAgTgGA
hcmv-miR-US33	MIMAT0001584	SEQ ID NO 232	CgGtcCGggCaCaAT
hsa-miR-191*	MIMAT0001618	SEQ ID NO 233	GaAatCCaaGcGcAG
hsa-miR-200a*	MIMAT0001620	SEQ ID NO 234	AcTgtCCggTaAgAT
hsa-miR-369-5p	MIMAT0001621	SEQ ID NO 235	AtAacACggTcGaTC
hsa-miR-431	MIMAT0001625	SEQ ID NO 236	GaCggCCtgCaAgAC
hsa-miR-433	MIMAT0001627	SEQ ID NO 237	AgGagCCcaTcAtGA
hsa-miR-329	MIMAT0001629	SEQ ID NO 238	GtTaaCCagGtGtGT
hsa-miR-453	MIMAT0001630	SEQ ID NO 239	CaCcaCGgaCaAcCT

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-451	MIMAT0001631	SEQ ID ND 240	GtAatGGtaAcGgTT
hsa-miR-452	MIMAT0001635	SEQ ID NO 241	GtTtcCTctGcAaAC
hsa-miR-452*	MIMAT0001636	SEQ ID NO 242	TtGcaGAtgAgAcTG
hsa-miR-409-5p	MIMAT0001638	SEQ ID NO 243	GtTgcTCggGtAaCC
hsa-miR-409-3p	MIMAT0001639	SEQ ID NO 244	CaCcgAGcaAcAtTC
hsa-miR-412	MIMAT0002170	SEQ ID NO 245	GtGgaCCagGtGaAG
hsa-miR-410	MIMAT0002171	SEQ ID NO 246	CcAtcTGtgTtAtAT
hsa-miR-376b	MIMAT0002172	SEQ ID NO 247	GaTttTCctCtAtGA
hsa-miR-483	MIMAT0002173	SEQ ID NO 248	GgGagGAgaGgAgTG
hsa-miR-484	MIMAT0002174	SEQ ID ND 249	AgGggACtgAgCcTG
hsa-miR-485-5p	MIMAT0002175	SEQ ID NO 250	AtCacGGccAgCcTC
hsa-miR-485-3p	MIMAT0002176	SEQ ID ND 251	GaGagCCgtGtAtGA
hsa-miR-486	MIMAT0002177	SEQ ID NO 252	GcAgcTCagTaCaCG
hsa-miR-487a	MIMAT0002178	SEQ ID NO 253	AtGtcCCtgTaTgAT
kshv-miR-K12-10a	MIMAT0002179	SEQ ID NO 254	CgGggGGacAaCaCT
kshv-miR-K12-10b	MIMAT0002180	SEQ ID NO 255	CgGggGGacAaCaCC
kshv-miR-K12-11	MIMAT0002181	SEQ ID NO 256	AcAggCTaaGcAtTA
kshv-miR-K12-1	MIMAT0002182	SEQ ID NO 257	CcCagTTtcCtGtAA
kshv-miR-K12-2	MIMAT0002183	SEQ ID NO 258	GaCccGGaCTaCaGT
kshv-miR-K12-9*	MIMAT0002184	SEQ ID NO 259	GtTtaCGcaGcTgGG
kshv-miR-K12-9	MIMAT0002185	SEQ ID NO 260	AgCtgCGtaTaCcCA
kshv-miR-K12-8	MIMAT0002186	SEQ ID NO 261	CtCtcAGtcGcGcCT
kshv-miR-K12-7	MIMAT0002187	SEQ ID NO 262	CaGcaACatGgGaTC
kshv-miR-K12-6-5p	MIMAT0002188	SEQ ID NO 263	GaTtaGGtgCtGcTG
kshv-miR-K12-6-3p	MIMAT0002189	SEQ ID NO 264	AgCccGAaaAcCaTC
kshv-miR-K12-5	MIMAT0002190	SEQ ID NO 265	AgTtcCAggCaTcCT
kshv-miR-K12-4-5p	MIMAT0002191	SEQ ID NO 266	GtActGCggTtTaGC
kshv-miR-K12-4-3p	MIMAT0002192	SEQ ID NO 267	AgGccTCagTaTtCT
kshv-miR-K12-3	MIMAT0002193	SEQ ID NO 268	CgTccTCagAaTgTG
kshv-miR-K12-3*	MIMAT0002194	SEQ ID NO 269	CaTtcTGtgAcCgCG
hsa-miR-488	MIMAT0002804	SEQ ID NO 270	AgTgcCAttAtCtGG
hsa-miR-489	MIMAT0002805	SEQ ID NO 271	TaTatGTgaTgTcAC
hsa-miR-490	MIMAT0002806	SEQ ID NO 272	GgAgtCCtcCaGgTT
hsa-miR-491	MIMAT0002807	SEQ ID NO 273	GgAagGGttCcCcAC
hsa-miR-511	MIMAT0002808	SEQ ID NO 274	GcAgaGCaaAaGaCA

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-146b	NIMAT0002809	SEQ ID NO 275	TgGaaTTcaGtTcTC
hsa-miR-202*	MIMAT0002810	SEQ ID NO 276	GtAtaTGcaTaGgAA
hsa-miR-202	MIMAT0002811	SEQ ID NO 277	CaTgcCCtaTaCcTC
hsa-miR-492	MIMAT0002812	SEQ ID NO 278	TtGtcCCgcAgGtCC
hsa-miR-493-5p	MIMAT0002813	SEQ ID NO 279	AgCctACcaTgTaCA
hsa-miR-432	MIMAT0002814	SEQ ID NO 280	AtGacCTacTcCaAG
hsa-miR-432*	MIMAT0002815	SEQ ID NO 281	TgGagGAgcCaTcCA
hsa-miR-494	MIMAT0002816	SEQ ID NO 282	TcCcgTGtaTgTtTC
hsa-miR-495	MIMAT0002817	SEQ ID NO 283	TgCacCAtgTtTgTT
hsa-miR-496	MIMAT0002818	SEQ ID NO 284	AgAttGGccAtGtAA
hsa-miR-193b	MIMAT0002819	SEQ ID NO 285	AcTttGAggGcCaGT
hsa-miR-497	MIMAT0002820	SEQ ID NO 286	CcAcaGTgtGcTgCT
hsa-miR-181d	MIMAT0002821	SEQ ID NO 287	GaCaaCAatGaAtGT
hsa-miR-512-5p	MIMAT0002822	SEQ ID NO 288	CcCtcAAggCtGaGT
hsa-miR-512-3p	MIMAT0002823	SEQ ID NO 289	AgCtaTGacAgCaCT
hsa-miR-498	MIMAT0002824	SEQ ID NO 290	GcCccCTggCtTgAA
hsa-miR-520e	MIMAT0002825	SEQ ID NO 291	AaAaaGGaaGcAcTT
hsa-miR-515-5p	MIMAT0002826	SEQ ID NO 292	GcTttCTttTgGaGA
hsa-miR-515-3p	MIMAT0002827	SEQ ID NO 293	CcAaaAGaaGgCaCT
hsa-miR-519e*	MIMAT0002828	SEQ ID NO 294	GcTccCTttTgGaGA
hsa-miR-519e	MIMAT0002829	SEQ ID NO 295	TaAaaGGagGcAcTT
hsa-miR-520f	MIMAT0002830	SEQ ID NO 296	CtAaaAGgaAgCaCT
hsa-miR-526c	MIMAT0002831	SEQ ID NO 297	GcGctTCccTcTaGA
hsa-miR-519c	MIMAT0002832	SEQ ID NO 298	TaAaaAGatGcAcTT
hsa-miR-520a*	MIMAT0002833	SEQ ID NO 299	GtActTCccTcTgGA
hsa-miR-520a	MIMAT0002834	SEQ ID NO 300	CaAagGGaaGcAcTT
hsa-miR-526b	MIMAT0002835	SEQ ID NO 301	GtGctTCCcTcAaGA
hsa-miR-526b*	MIMAT0002836	SEQ ID NO 302	TaAaaGGaaGcAcTT
hsa-miR-519b	MIMAT0002837	SEQ ID NO 303	TaAaaGGatGcAcTT
hsa-miR-525	MIMAT0002838	SEQ ID NO 304	GtGcaTCccTcTgGA
hsa-miR-525*	MIMAT0002839	SEQ ID NO 305	AaAggGAagCgCcTT
hsa-miR-523	MIMAT0002840	SEQ ID NO 306	TaTagGGaaGcGcGT
hsa-miR-518f*	MIMAT0002841	SEQ ID NO 307	GtGctTCccTcTaGA
hsa-miR-518f	MIMAT0002842	SEQ ID NO 308	TaAagAGaaGcGcTT
hsa-miR-520b	MIMAT0002843	SEQ ID NO 309	TaAaaGGaaGcAcTT
hsa-miR-518b	MIMAT0002844	SEQ ID NO 310	AaAggGGagCgCtTT

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-526a	MIMAT0002845	SEQ ID NO 311	GtGctTCccTcTaGA
hsa-miR-520c	MIMAT0002846	SEQ ID NO 312	TaAaaGGaaGcAcTT
hsa-miR-518c*	MIMAT0002847	SEQ ID NO 313	TgCttCCctCcAgAG
hsa-miR-518c	MIMAT0002848	SEQ ID NO 314	AaAgaGAagCgCtTT
hsa-miR-524*	MIMAT0002849	SEQ ID NO 315	GtGctTCccTtTgTA
hsa-miR-524	MIMAT0002850	SEQ ID NO 316	AaAggGAagCgCcTT
hsa-miR-517*	MIMAT0002851	SEQ ID NO 317	TgCttCCatCtAgAG
hsa-miR-517a	MIMAT0002852	SEQ ID NO 318	TaAagGGatGcAcCA
hsa-miR-519d	MIMAT0002853	SEQ ID NO 319	AaAggGAggCaCtTT
hsa-miR-521	MIMAT0002854	SEQ ID NO 320	TaAagGGaaGtGcGT
hsa-miR-520d*	MIMAT0002855	SEQ ID NO 321	GgCttCCctTtGtAG
hsa-miR-520d	MIMAT0002856	SEQ ID NO 322	CaAagAGaaGcAcTT
hsa-miR-517b	MIMAT0002857	SEQ ID NO 323	CtAaaGGgaTgCaCG
hsa-miR-520g	MIMAT0002858	SEQ ID NO 324	AaGggAAgcAcTtTG
hsa-miR-516-5p	MIMAT0002859	SEQ ID NO 325	TtCttACctCcAgAT
hsa-miR-516-3p	MIMAT0002860	SEQ ID NO 326	CcTctGAaaGgAaGC
hsa-miR-518e	MIMAT0002861	SEQ ID NO 327	TgAagGGaaGcGcTT
hsa-miR-527	MIMAT0002862	SEQ ID NO 328	GgGctTCccTtTgCA
hsa-miR-518a	MIMAT0002863	SEQ ID NO 329	CaAagGGaaGcGcTT
hsa-miR-518d	MIMAT0002864	SEQ ID NO 330	AaAggGAagCgCtTT
hsa-miR-517c	MIMAT0002866	SEQ ID NO 331	TaAaaGGatGcAcGA
hsa-miR-520h	MIMAT0002867	SEQ ID NO 332	AaGggAAgcAcTtTG
hsa-miR-522	MIMAT0002868	SEQ ID NO 333	TaAagGGaaCcAtTT
hsa-miR-519a	MIMAT0002869	SEQ ID NO 334	TaAaaGGatGcAcTT
hsa-miR-499	MIMAT0002870	SEQ ID NO 335	TcActGCaaGtCtTA
hsa-miR-500	MIMAT0002871	SEQ ID NO 336	CcTtgCCcaGgTgCA
hsa-miR-501	MIMAT0002872	SEQ ID NO 337	CcAggGAcaAaGgAT
hsa-miR-502	MIMAT0002873	SEQ ID NO 338	CcCagATagCaAgGA
hsa-miR-503	MIMAT0002874	SEQ ID NO 339	AcTgtTCccGcTgCT
hsa-miR-504	MIMAT0002875	SEQ ID NO 340	GtGcaGAccAgGgTC
hsa-miR-505	MIMAT0002876	SEQ ID NO 341	AcCagCAagTgTtGA
hsa-miR-513	MIMAT0002877	SEQ ID NO 342	GaCacCTccCtGtGA
hsa-miR-506	MIMAT0002878	SEQ ID NO 343	TcAgaAGggTgCcTT
hsa-miR-507	MIMAT0002879	SEQ ID NO 344	TcCaaAAggTgCaAA
hsa-miR-508	MIMAT0002880	SEQ ID NO 345	CaAaaGGctAcAaTC

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-509	MIMAT0002881	SEQ ID NO 346	AcAgaCGtaCcAaTC
hsa-miR-510	MIMAT0002882	SEQ ID NO 347	GcCacTCtcCtGaGT
hsa-miR-514	MIMAT0002883	SEQ ID NO 348	TCAcaGAagTgTcAA
hsa-miR-532	MIMAT0002888	SEQ ID NO 349	CtACaCTcaAgGcAT
hsa-miR-299-5p	MIMAT0002890	SEQ ID NO 350	GtGggACggTaAaCC
hsa-miR-18a*	MIMAT0002891	SEQ ID NO 351	GaGcaCTtaGgGcAG
hsa-miR-455	MIMAT0003150	SEQ ID NO 352	AgTccAAagGcAcAT
hsa-miR-493-3p	MIMAT0003161	SEQ ID NO 353	AcAcaGTagAcCtTC
hsa-miR-539	MIMAT0003163	SEQ ID NO 354	CaAggATaaTtTcTC
hsa-miR-544	MIMAT0003164	SEQ ID NO 355	GcTaaAAatGcAgAA
hsa-miR-545	MTMAT0003165	SEQ ID NO 356	AtAaaTGttTgCtGA
hsa-miR-487b	MIMAT0003180	SEQ ID NO 357	AtGacCCtgTaCgAT
hsa-miR-551a	MIMAT0003214	SEQ ID NO 358	AcCaaGAgtGgGtCG
hsa-miR-552	MIMAT0003215	SEQ ID NO 359	TaAccAGtcAcCtGT
hsa-miR-553	MIMAT0003216	SEQ ID NO 360	AaAatCTcaCcGtTT
hsa-miR-554	MIMAT0003217	SEQ ID NO 361	CtGagTCagGaCtAG
hsa-miR-92b	MIMAT0003218	SEQ ID NO 362	CgGgaCGagTgCaAT
hsa-miR-555	MIMAT0003219	SEQ ID NO 363	AgGttCAgcTtAcCC
hsa-miR-556	MIMAT0003220	SEQ ID NO 364	TtAcaATgaGcTcAT
hsa-miR-557	MIMAT0003221	SEQ ID NO 365	GcCcaCCcgTgCaAA
hsa-miR-558	MIMAT0003222	SEQ ID NO 366	TtGgtACagCaGcTC
hsa-miR-559	MIMAT0003223	SEQ ID NO 367	GtGcaTAttTaCtTT
hsa-miR-560	MIMAT0003224	SEQ ID NO 368	GcCggCCggCgCaCG
hsa-miR-561	MIMAT0003225	SEQ ID NO 369	AgGatCTtaAaCtTT
hsa-miR-562	MIMAT0003226	SEQ ID NO 370	AtGgtACagCtAcTT
hsa-miR-563	MIMAT0003227	SEQ ID NO 371	AaAcgTAtgTcAaCC
hsa-miR-564	MIMAT0003228	SEQ ID NO 372	TgCtgACacCgTgCC
hsa-miR-565	MIMAT0003229	SEQ ID NO 373	AcAtcGCgaGcCaGC
hsa-miR-566	MIMAT0003230	SEQ ID NO 374	GgGatCAcaGgCgCC
hsa-miR-567	MIMAT0003231	SEQ ID NO 375	CcTggAAgaAcAtAC
hsa-miR-568	MIMAT0003232	SEQ ID NO 376	GtAtaCAttTaTaCA
hsa-miR-551b	MIMAT0003233	SEQ ID NO 377	AcCaaGTatGgGtCG
hsa-miR-569	MIMAT0003234	SEQ ID NO 378	CcAggATtcAtTaAC
hsa-miR-570	MIMAT0003235	SEQ ID NO 379	GgTaaTTgcTgTtTT
hsa-miR-571	MIMAT0003236	SEQ ID NO 380	TcAgaTGgcCaAcTC
hsa-miR-572	MIMAT0003237	SEQ ID NO 381	CcAccGCcgAgCgGA

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-573	MIMAT0003238	SEQ ID NO 382	TtAcaCAtcAcTtCA
hsa-miR-574	MIMAT0003239	SEQ ID NO 383	TgTgtCGatGaGcGT
hsa-miR-575	MIMAT0003240	SEQ ID NO 384	CcTgtCCaaCtGgCT
hsa-miR-576	MIMAT0003241	SEQ ID NO 385	GtGgaGAaaTtAgAA
hsa-miR-577	MIMAT0003242	SEQ ID NO 386	AcCaaTAttTtAtCT
hsa-miR-578	MIMAT0003243	SEQ ID NO 387	CcTagAGcaCaAgAA
hsa-miR-579	MIMAT0003244	SEQ ID NO 388	TtTatACcaAaTgAA
hsa-miR-580	MIMAT0003245	SEQ ID NO 389	GaTtcATcaTtCtCA
hsa-miR-581	MIMAT0003246	SEQ ID NO 390	TcTagAGaaCaCaAG
hsa-miR-582	MIMAT0003247	SEQ ID NO 391	GgTtgAAcaAcTgTA
hsa-miR-583	MIMAT0003248	SEQ ID NO 392	GgGacCTtcCtCtTT
hsa-miR-584	MIMAT0003249	SEQ ID NO 393	CcCagGCaaAcCaTA
hsa-miR-585	MIMAT0003250	SEQ ID NO 394	CaTacAGatAcGcCC
hsa-miR-548a	MIMAT0003251	SEQ ID NO 395	GtAatTGccAgTtTT
hsa-miR-586	MIMAT0003252	SEQ ID NO 396	AaAaaTAcaAtGcAT
hsa-miR-587	MIMAT0003253	SEQ ID NO 397	TcAtcACctAtGgAA
hsa-miR-548b	MIMAT0003254	SEQ ID NO 398	GcAacTGagGtTcTT
hsa-miR-588	MIMAT0003255	SEQ ID NO 399	AaCccATtgTgGcCA
hsa-miR-589	MIMAT0003256	SEQ ID NO 400	CcGgcATttGtTcTG
hsa-miR-550	MIMAT0003257	SEQ ID NO 401	CtGagGGagTaAgAC
hsa-miR-590	MIMAT0003258	SEQ ID NO 402	TtTtaTGaaTaAgCT
hsa-miR-591	MIMAT0003259	SEQ ID NO 403	TgAgaACccAtGgTC
hsa-miR-592	MIMAT0003260	SEQ ID NO 404	TcGcaTAttGaCaCA
hsa-miR-593	MIMAT0003261	SEQ ID NO 405	TgCctGGctGgTgCC
hsa-miR-595	MIMAT0003263	SEQ ID NO 406	CaCcaCGgcAcAcTT
hsa-miR-596	MIMAT0003264	SEQ ID NO 407	GgAgcCGggCaGgCT
hsa-miR-597	MIMAT0003265	SEQ ID NO 408	GtCatCGagTgAcAC
hsa-miR-598	MIMAT0003266	SEQ ID NO 409	TgAcaACgaTgAcGT
hsa-miR-599	MIMAT0003267	SEQ ID NO 410	GaTaaACtgAcAcAA
hsa-miR-600	MIMAT0003268	SEQ ID NO 411	GcTctTGtcTgTaAG
hsa-miR-601	MIMAT0003269	SEQ ID NO 412	CaAcaATccTaGaCC
hsa-miR-602	MIMAT0003270	SEQ ID NO 413	AgCtgTCgcCcGtGT
hsa-miR-603	MIMAT0003271	SEQ ID NO 414	GtAatTGcaGtGtGT
hsa-miR-604	MIMAT0003272	SEQ ID NO 415	CtGaaTTccGcAgCC
hsa-miR-605	MIMAT0003273	SEQ ID NO 416	GgCacCAtgGgAtTT

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-606	MIMAT0003274	SEQ ID NO 417	TgAttTTcaGtAgTT
hsa-miR-607	MIMAT0003275	SEQ ID NO 418	AgAtcTGgaTtTgAA
hsa-miR-608	MIMAT0003276	SEQ ID NO 419	TcCcaACacCaCcCC
hsa-miR-609	MIMAT0003277	SEQ ID NO 420	AtGagAGaaAcAcCC
hsa-miR-610	MIMAT0003278	SEQ ID NO 421	GcAcaCAttTaGcTC
hsa-miR-611	MIMAT0003279	SEQ ID NO 422	CcCgaGGggTcCtCG
hsa-miR-612	MIMAT0003280	SEQ ID NO 423	AgAagCCctGcCcAG
hsa-miR-613	MIMAT0003281	SEQ ID NO 424	AaGaaGGaaCaTtCC
hsa-miR-614	MIMAT0003282	SEQ ID NO 425	GcAagAAcaGgCgTT
hsa-miR-615	MIMAT0003283	SEQ ID NO 426	GaGacCCagGcTcGG
hsa-miR-616	MIMAT0003284	SEQ ID NO 427	CtGaaGGgtTtTgAG
hsa-miR-548c	MIMAT0003285	SEQ ID NO 428	GtAatTGagAtTtTT
hsa-miR-617	MIMAT0003286	SEQ ID NO 429	TtCaaATggGaAgTC
hsa-miR-618	MIMAT0003287	SEQ ID NO 430	AgGacAAgtAgAgTT
hsa-miR-619	MIMAT0003288	SEQ ID NO 431	CaAacATgtCcAgGT
hsa-miR-620	MIMAT0003289	SEQ ID NO 432	CtAtaTCtaTcTcCA
hsa-miR-621	MIMAT0003290	SEQ ID NO 433	AgCgcTGttGcTaGC
hsa-miR-622	MIMAT0003291	SEQ ID NO 434	AaCctCAgcAgAcTG
hsa-miR-623	MIMAT0003292	SEQ ID NO 435	AgCccCTgcAaGgGA
hsa-miR-624	MIMAT0003293	SEQ ID NO 436	CaAggTACtGgTaCT
hsa-miR-625	MIMAT0003294	SEQ ID NO 437	AtAgaACttTcCcCC
hsa-miR-626	MIMAT0003295	SEQ ID NO 438	AcAttTTcaGaCaGC
hsa-miR-627	MIMAT0003296	SEQ ID NO 439	TtTctTAgaGaCtCA
hsa-miR-628	MIMAT0003297	SEQ ID NO 440	TgCcaCTctTaCtAG
hsa-miR-629	MIMAT0003298	SEQ ID NO 441	CtTacGTtgGgAgAA
hsa-miR-630	MIMAT0003299	SEQ ID NO 442	CcTggTAcaGaAtAC
hsa-miR-631	MIMAT0003300	SEQ ID NO 443	GgTctGGgcCaGgTC
hsa-miR-33b	MIMAT0003301	SEQ ID NO 444	TgCaaCAgcAaTgCA
hsa-miR-632	MIMAT0003302	SEQ ID NO 445	CaCagGAagCaGaCA
hsa-miR-633	MIMAT0003303	SEQ ID NO 446	TgGtaGAtaCtAtTA
hsa-miR-634	MIMAT0003304	SEQ ID NO 447	AgTtgGGgtGcTgGT
hsa-miR-635	MIMAT0003305	SEQ ID NO 448	GtTtcAGtgCcCaAG
hsa-miR-636	MIMAT0003306	SEQ ID NO 449	GgGacGAgcAaGcAC
hsa-miR-637	MIMAT0003307	SEQ ID NO 450	CcCgaAAgcCcCcAG
hsa-miR-638	MIMAT0003308	SEQ ID NO 451	CcCgcCCgcGaTcCC
hsa-miR-639	MIMAT0003309	SEQ ID NO 452	TcGcaACcgCaGcGA

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-640	MIMAT0003310	SEQ ID NO 453	CaGgtTCctGgAtCA
hsa-miR-641	MIMAT0003311	SEQ ID NO 454	TcTatCCtaTgTcTT
hsa-miR-642	MIMAT0003312	SEQ ID NO 455	AcAttTGgaGaGgGA
hsa-miR-643	MIMAT0003313	SEQ ID NO 456	GaGctAGcaTaCaAG
hsa-miR-644	MIMAT0003314	SEQ ID NO 457	CtAagAAagCcAcAC
hsa-miR-645	MIMAT0003315	SEQ ID NO 458	GcAgtACcaGcCtAG
hsa-miR-646	MIMAT0003316	SEQ ID NO 459	TcAgaGGcaGcTgCT
hsa-miR-647	MIMAT0003317	SEQ ID NO 460	AaGtgAGtgCaGcCA
hsa-miR-648	MIMAT0003318	SEQ ID NO 461	AgTgcCCtgCaCaCT
hsa-miR-649	MIMAT0003319	SEQ ID NO 462	TgAacAAcaCaGgTT
hsa-miR-650	MIMAT0003320	SEQ ID NO 463	GaGagCGctGcCtCC
hsa-miR-651	MIMAT0003321	SEQ ID NO 464	TcAagCTtaTcCtAA
hsa-miR-652	MIMAT0003322	SEQ ID NO 465	CcCtaGTggCgCcAT
hsa-miR-548d	MIMAT0003323	SEQ ID NO 466	GaAacTGtgGtTtTT
hsa-miR-661	MIMAT0003324	SEQ ID NO 467	GcCagAGacCcAgGC
hsa-miR-662	MIMAT0003325	SEQ ID NO 468	GgGccACaaCgTgGG
hsa-miR-663	MIMAT0003326	SEQ ID NO 469	CcGcgGCgcCcCgCC
hsa-miR-449b	MIMAT0003327	SEQ ID NO 470	TaAcaATacAcTgCC
hsa-miR-653	MIMAT0003328	SEQ ID NO 471	GtAgaGAttGtTtCA
hsa-miR-411	MIMAT0003329	SEQ ID NO 472	GcTatACggTcTaCT
hsa-miR-654	MIMAT0003330	SEQ ID NO 473	GtTctGCggCcCaCC
hsa-miR-655	MIMAT0003331	SEQ ID NO 474	GtTaaCCatGtAtTA
hsa-miR-656	MIMAT0003332	SEQ ID NO 475	TtGacTGtaTaAtAT
hsa-miR-549	MIMAT0003333	SEQ ID NO 476	TcAtcCAtaGtTgTC
hsa-miR-657	MIMAT0003335	SEQ ID NO 477	AgGgtGAgaAcCtGC
hsa-miR-658	MIMAT0003336	SEQ ID NO 478	CcTacTTccCtCcGC
hsa-miR-659	MIMAT0003337	SEQ ID NO 479	CcCtcCCtgAaCcAA
hsa-miR-660	MIMAT0003338	SEQ ID NO 480	CgAtaTGcaAtGgGT
hsa-miR-421	MIMAT0003339	SEQ ID NO 481	AtTaaTGtcTgTtGA
hsa-miR-542-5p	MIMAT0003340	SEQ ID NO 482	AcAtgATgaTcCcCG
hcmv-miR-US4	MIMAT0003341	SEQ ID NO 483	CtGcaCGtcCaTgTC
hcmv-miR-UL70-5p	MIMAT0003342	SEQ ID NO 484	AcGagGCcgAgAcGC
hcmv-miR-UL70-3p	MIMAT0003343	SEQ ID NO 485	GcGccAGccCaTcCC
hsa-miR-363*	MIMAT0003385	SEQ ID NO 486	CaTcgTGatCcAcCC
hsa-miR-376a*	MIMAT0003386	SEQ ID NO 487	AgAagGAgaAtCtAC

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-542-3p	MIMAT0003389	SEQ ID NO 488	TtAtcAAtcTgTcAC
ebv-miR-BART1-3p	MIMAT0003390	SEQ ID NO 489	GtGgaTAgcGgTgCT
hsa-miR-425-5p	MIMAT0003393	SEQ ID NO 490	GaGtgATcgTgTcAT
ebv-miR-BART3-5p	MIMAT0003410	SEQ ID NO 491	AcActAAcaCtAgGT
ebv-miR-BART3-3p	MIMAT0003411	SEQ ID NO 492	GgTgaCTagTgGtGC
ebv-miR-BART4	MIMAT0003412	SEQ ID NO 493	CcAgcAGcaTcAgGT
ebv-miR-BART5	MIMAT0003413	SEQ ID NO 494	AgCtaTAttCaCcTT
ebv-miR-BART6-5p	MIMAT0003414	SEQ ID NO 495	AtGgaTTggAcCaAC
ebv-miR-BART6-3p	MIMAT0003415	SEQ ID NO 496	GcTagTCcgAtCcCC
ebv-miR-BART7	MIMAT0003416	SEQ ID NO 497	AcActGGacTaTgAT
ebv-miR-BART8-5p	MIMAT0003417	SEQ ID NO 498	AaTctAGgaAaCcGT
ebv-miR-BART8-3p	MIMAT0003418	SEQ ID NO 499	CcCcaTAgaTtGtGA
ebv-miR-BART9	MIMAT0003419	SEQ ID NO 500	GaCccATgaAgTgTT
ebv-miR-BART10	MIMAT0003420	SEQ ID NO 501	AaCtCCAtgGtTaTG
ebv-miR-BART11-5p	MIMAT0003421	SEQ ID NO 502	AgCgcACcaAaCtGT
ebv-miR-BART11-3p	MIMAT0003422	SEQ ID NO 503	TcAgcCTggTgTgCG
ebv-miR-BART12	MIMAT0003423	SEQ ID NO 504	AcCaaACacCaCaGG
ebv-miR-BART13	MIMAT0003424	SEQ ID NO 505	TcCctGGcaAgTtAC
ebv-miR-BART14-5p	MIMAT0003425	SEQ ID NO 506	TcGgcAGcgTaCgGT
ebv-miR-BART14-3p	MIMAT0003426	SEQ ID NO 507	AcTacTGcaGcAtTT
kshv-miR-K12-12	MIMAT0003712	SEQ ID NO 508	GgAatGGtgGcCtGG
ebv-miR-BART15	MIMAT0003713	SEQ ID NO 509	AgGaaACaaAaCcAC
ebv-miR-BART16	MIMAT0003714	SEQ ID NO 510	CaCacACcCAcTcTA
ebv-miR-BART17-5p	MIMAT0003715	SEQ ID NO 511	AtGccTGcgTcCtCT
ebv-miR-BART17-3p	MIMAT0003716	SEQ ID NO 512	GaCacCAggCaTaCA
ebv-miR-BART18	MIMAT0003717	SEQ ID NO 513	AgGaaGTgcGaAcTT
ebv-miR-BART19	MIMAT0003718	SEQ ID NO 514	CcAagCAaaCaAaAC
ebv-miR-BART20-5p	MIMAT0003719	SEQ ID NO 515	AaGacATgcCtGcTA
ebv-miR-BART20-3p	MIMAT0003720	SEQ ID NO 516	AgGctGTgcCtTcAT
hsvl-miR-H1	MIMAT0003744	SEQ ID NO 517	AcTtcCCgtCcTtCC
hsa-miR-758	MIMAT0003879	SEQ ID NO 518	TgGacCAggTcAcAA
hsa-miR-671	MIMAT0003880	SEQ ID NO 519	CcCtcCAggGcTtCC
hsa-miR-668	MIMAT0003881	SEQ ID NO 520	GcCgaGCcgAgTgAC
hsa-miR-767-5p	MIMAT0003882	SEQ ID NO 521	AgAcaACcaTgGtGC
hsa-miR-767-3p	MIMAT0003883	SEQ ID NO 522	AtGggGTatGaGcAG
hsa-miR-454-5p	MIMAT0003884	SEQ ID NO 523	AcAatATtgAtAgGG

TABLE 2-continued

(SEQ ID refers to Example antimiR)

microRNA	Accession nr.	SEQ ID NO	Example LNA antimiR 5'-3'
hsa-miR-454-3p	MIMAT0003885	SEQ ID NO 524	AaGcaATatTgCaCT
hsa-miR-769-5p	MIMAT0003886	SEQ ID NO 525	GaAccCAgaGgTcTC
hsa-miR-769-3p	MIMAT0003887	SEQ ID NO 526	AcCccGGagAtCcCA
hsa-miR-766	MIMAT0003888	SEQ ID NO 527	GcTgtGGggCtGgAG
hsa-miR-765	MIMAT0003945	SEQ ID NO 528	CcTtcCTtcTcCtCC
hsa-miR-768-5p	MIMAT0003946	SEQ ID NO 529	AcTttCAtcCtCcAA
hsa-miR-768-3p	MIMAT0003947	SEQ ID NO 530	AgTgtCAgcAtTgTG
hsa-miR-770-5p	MIMAT0003948	SEQ ID NO 531	GaCacGTggTaCtGG
hsa-miR-802	MIMAT0004185	SEQ ID NO 532	TgAatCTttGtTaCT
hsa-miR-801	MIMAT0004209	SEQ ID NO 533	CgCacGCagAgCaAT
hsa-miR-675	MIMAT0004284	SEQ ID NO 534	GgCccTCtcCgCaCC

SEQUENCE LISTING

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aacatccgac tgaaa 15

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gcacgaacag cactt 15

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gagtctgagc atttg 15

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aacatgaaac tacct 15

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tggagaaggt ggtga 15

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gtcggggatg tttac 15

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acacgtgcac tgtag 15

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aagcatttcc acaca 15

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agctaagaca ctgcc 15

<210> SEQ ID NO 61
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gacagcaatg aatgt 15

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ggcaagtcta gaacc 15

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gcaacacaag acacg 15

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tagtctaaac actgg 15

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gtcctaaaca tttca 15

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aggatgacaa aggga 15

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ccggtggaat gaagg 15

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gctgtcacac gcaca 15

<210> SEQ ID NO 73
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aggatgacaa aggga 15

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<400> SEQUENCE: 77

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ttgccagctg agatt 15

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agttcctgat gcagt 15

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gttagatcaa gcaca 15

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tgcgtttgga caatc 15

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gtcagatacg gtgtg 15

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ccatgatgtg ctgct 15

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gttagggtct caggg 15

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gaccggttca ctgtg 15

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acagtgcttc atctc 15

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cctgggaaaa ctgga 15

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ttctgtcatg cactg 15

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ttttgtgact atgca 15

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gctagataac caaag 15

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cggttatcta gcttt 15

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gctcagacgg atccg 15

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tggaattcag ttctc 15

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aagacacgga gccag 15

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tacaagggtt gggag 15

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tcaaccgtgt atgat 15

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atcagttctc cgtcc 15

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aaaggagaat tcttt 15

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caccatgcaa gggat 15

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tatatcaaac atatc 15

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tctcaaccca gcttt 15

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tcacgattag catta 15

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gaccggttca ctgtg 15

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cactgtcagc acttt 15

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<210> SEQ ID NO 143
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<400> SEQUENCE: 145

aacatggaag cactt 15

<210> SEQ ID NO 146
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gctaactaca ctgcc 15

<210> SEQ ID NO 148
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caatactatt gcact 15

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gtcggttcta cgggt 15

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gtcaaggatg tttac 15

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aacatccgac tgaaa 15

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<400> SEQUENCE: 155

ctggagattc tgata 15

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ctaggttcca aggat 15

<210> SEQ ID NO 157
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<400> SEQUENCE: 157

tggataccgt gcaat 15

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<400> SEQUENCE: 163

aacatggaag cactt 15

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<400> SEQUENCE: 164

ttgctaaagt gcaat 15

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ggaatttcct ctatg 15

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<400> SEQUENCE: 166

tcaaccatgt attat 15

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<400> SEQUENCE: 167

ttccacccca gcagg 15

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caaaagatgg cggca 15

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aatgtcgcag cactt 15

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cgcccccatt ttgag 15

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aaaatcgaag cactt 15

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tcaggttgta ttata 15

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<400> SEQUENCE: 173

gagccgaacg aacaa 15

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gattttcctc tatga 15

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ctgactccaa gtcca 15

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gttctatggt caacc 15

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aatcaccttc tgatc 15

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cgatttctgt gtgag 15

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ttctgtgatg cactg 15

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ggactaggag tcagc 15

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tgctgcaaca gaatt 15

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tctgccgcaa aagat 15

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tacacacttc ccgtt 15

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gcgaatgcag aaaat 15

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aacaatttct aggaa 15

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aacaggaaac tacct 15

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ctgaccctaa gtcca 15

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ggcctcagac cgagc 15

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acatgaattg ctgct 15

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acacgacatt cccga 15

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cactatgagc acttt 15

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catcctacat atgca 15

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gaacacatcg caaaa 15

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caggtgtctt caacg 15

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gatctcaccg tcact 15

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aagaagggga ggacg 15

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ctcgtcaggc ttgtc 15

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gtcacaccta tcata 15

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<400> SEQUENCE: 229

gagccactga gcggt 15

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acctgaacag accgc 15

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agctctccaa gtgga 15

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cggtccgggc acaat 15

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gaaatccaag cgcag 15

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ataacacggt cgatc 15

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gacggcctgc aagac 15

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aggagcccat catga 15

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caccacggac aacct 15

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gtaatggtaa cggtt 15

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gtttcctctg caaac 15

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ttgcagatga gactg 15

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gttgctcggg taacc 15

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caccgagcaa cattc 15

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gtggaccagg tgaag 15

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ccatctgtgt tatat 15

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<400> SEQUENCE: 247

gattttcctc tatga 15

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gggaggagag gagtg 15

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<400> SEQUENCE: 249

aggggactga gcctg 15

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atcacggcca gcctc 15

<210> SEQ ID NO 251
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gagagccgtg tatga 15

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<400> SEQUENCE: 252

gcagctcagt acagg 15

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atgtccctgt atgat 15

<210> SEQ ID NO 254
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<400> SEQUENCE: 254

cgggggggaca acact 15

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<400> SEQUENCE: 255

cgggggggaca acacc 15

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<400> SEQUENCE: 256

acaggctaag catta 15

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cccagtttcc tgtaa 15

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gacccggact acagt 15

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gtttacgcag ctggg 15

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agctgcgtat accca 15

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ctctcagtcg cgcct 15

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<400> SEQUENCE: 262

cagcaacatg ggatc 15

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gattaggtgc tgctg 15

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agcccgaaaa ccatc 15

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agttccaggc atcct 15

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<400> SEQUENCE: 266

gtactgcggt ttagc 15

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<400> SEQUENCE: 267

aggcctcagt attct 15

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<400> SEQUENCE: 268

cgtcctcaga atgtg 15

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cattctgtga ccgcg 15

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agtgccatta tctgg 15

<210> SEQ ID NO 271
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gtaattgcca gtttt 15

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aacctcagca gactg 15

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tcgcaaccgc agcga 15

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caggttcctg gatca 15

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gagctagcat acaag 15

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ctaagaaagc cacac 15

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aagtgagtgc agcca 15

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agtgccctgc acact 15

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gagagcgctg cctcc 15

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<400> SEQUENCE: 464

tcaagcttat cctaa 15

<210> SEQ ID NO 465
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 465

ccctagtggc gccat 15

<210> SEQ ID NO 466
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

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<400> SEQUENCE: 466

gaaactgtgg ttttt 15

<210> SEQ ID NO 467
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 467

gccagagacc caggc 15

<210> SEQ ID NO 468
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 468

gggccacaac gtggg 15

<210> SEQ ID NO 469
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 469

ccgcggcgcc ccgcc 15

<210> SEQ ID NO 470
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 470

taacaataca ctgcc 15

<210> SEQ ID NO 471
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 471

gtagagattg tttca 15

<210> SEQ ID NO 472
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 472

gctatacggt ctact 15

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<210> SEQ ID NO 473
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 473

gttctgcggc ccacc 15

<210> SEQ ID NO 474
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<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 474

gttaaccatg tatta 15

<210> SEQ ID NO 475
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<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 475

ttgactgtat aatat 15

<210> SEQ ID NO 476
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 476

tcatccatag ttgtc 15

<210> SEQ ID NO 477
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<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 477

agggtgagaa cctgc 15

<210> SEQ ID NO 478
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 478

cctacttccc tccgc 15

<210> SEQ ID NO 479
<211> LENGTH: 15

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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 479

ccctccctga accaa 15

<210> SEQ ID NO 480
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 480

cgatatgcaa tgggt 15

<210> SEQ ID NO 481
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 481

attaatgtct gttga 15

<210> SEQ ID NO 482
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 482

acatgatgat ccccg 15

<210> SEQ ID NO 483
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 483

ctgcacgtcc atgtc 15

<210> SEQ ID NO 484
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 484

acgaggccga gacgc 15

<210> SEQ ID NO 485
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

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<400> SEQUENCE: 485

gcgccagccc atccc 15

<210> SEQ ID NO 486
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 486

catcgtgatc caccc 15

<210> SEQ ID NO 487
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 487

agaaggagaa tctac 15

<210> SEQ ID NO 488
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 488

ttatcaatct gtcac 15

<210> SEQ ID NO 489
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 489

gtggatagcg gtgct 15

<210> SEQ ID NO 490
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 490

gagtgatcgt gtcat 15

<210> SEQ ID NO 491
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 491

acactaacac taggt 15

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<210> SEQ ID NO 492
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<212> TYPE: DNA
<213> ORGANISM: artificial
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<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 492

ggtgactagt ggtgc 15

<210> SEQ ID NO 493
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 493

ccagcagcat caggt 15

<210> SEQ ID NO 494
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 494

agctatattc acctt 15

<210> SEQ ID NO 495
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 495

atggattgga ccaac 15

<210> SEQ ID NO 496
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 496

gctagtccga tcccc 15

<210> SEQ ID NO 497
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 497

acactggact atgat 15

<210> SEQ ID NO 498
<211> LENGTH: 15

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<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 498

aatctaggaa accgt 15

<210> SEQ ID NO 499
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 499

ccccatagat tgtga 15

<210> SEQ ID NO 500
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 500

gacccatgaa gtgtt 15

<210> SEQ ID NO 501
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 501

aactccatgg ttatg 15

<210> SEQ ID NO 502
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 502

agcgcaccaa actgt 15

<210> SEQ ID NO 503
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 503

tcagcctggt gtgcg 15

<210> SEQ ID NO 504
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

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<400> SEQUENCE: 504

accaaacacc acagg 15

<210> SEQ ID NO 505
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 505

tccctggcaa gttac 15

<210> SEQ ID NO 506
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 506

tcggcagcgt agggt 15

<210> SEQ ID NO 507
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 507

actactgcag cattt 15

<210> SEQ ID NO 508
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 508

ggaatggtgg cctgg 15

<210> SEQ ID NO 509
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 509

aggaaacaaa accac 15

<210> SEQ ID NO 510
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 510

cacacaccca ctcta 15

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<210> SEQ ID NO 511
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 511

atgcctgcgt cctct 15

<210> SEQ ID NO 512
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 512

gacaccaggc ataca 15

<210> SEQ ID NO 513
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 513

aggaagtgcg aactt 15

<210> SEQ ID NO 514
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 514

ccaagcaaac aaaac 15

<210> SEQ ID NO 515
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 515

aagacatgcc tgcta 15

<210> SEQ ID NO 516
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 516

aggctgtgcc ttcat 15

<210> SEQ ID NO 517
<211> LENGTH: 15

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<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 517

acttcccgtc cttcc 15

<210> SEQ ID NO 518
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 518

tggaccaggt cacaa 15

<210> SEQ ID NO 519
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 519

ccctccaggg cttcc 15

<210> SEQ ID NO 520
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 520

gccgagccga gtgac 15

<210> SEQ ID NO 521
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 521

agacaaccat ggtgc 15

<210> SEQ ID NO 522
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 522

atggggtatg agcag 15

<210> SEQ ID NO 523
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

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<400> SEQUENCE: 523

acaatattga taggg 15

<210> SEQ ID NO 524
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 524

aagcaatatt gcact 15

<210> SEQ ID NO 525
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 525

gaacccagag gtctc 15

<210> SEQ ID NO 526
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 526

accccggaga tccca 15

<210> SEQ ID NO 527
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 527

gctgtggggc tggag 15

<210> SEQ ID NO 528
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 528

ccttccttct cctcc 15

<210> SEQ ID NO 529
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 529

actttcatcc tccaa 15

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<210> SEQ ID NO 530
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 530

agtgtcagca ttgtg 15

<210> SEQ ID NO 531
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 531

gacacgtggt actgg 15

<210> SEQ ID NO 532
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 532

tgaatctttg ttact 15

<210> SEQ ID NO 533
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 533

cgcacgcaga gcaat 15

<210> SEQ ID NO 534
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: miRNA Antimir oligonucleotide seqeunce

<400> SEQUENCE: 534

ggccctctcc gcacc 15

<210> SEQ ID NO 535
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 535

uggaguguga caaugguguu ugu 23

<210> SEQ ID NO 536
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial

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<220> FEATURE:
<223> OTHER INFORMATION: Full complement gapmer, LNA at positions 1-4 and 20-23

<400> SEQUENCE: 536

acaaacacca ttgtcacact cca 23

<210> SEQ ID NO 537
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement blockmer, LNA at positions 7-14

<400> SEQUENCE: 537

acaaacacca ttgtcacact cca 23

<210> SEQ ID NO 538
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement LNA mixmer- LNA at third position and every third position thereafter

<400> SEQUENCE: 538

acaaacacca ttgtcacact cca 23

<210> SEQ ID NO 539
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA units at position 1, 3, 6, 7, 10, 12, 14 and 15

<400> SEQUENCE: 539

ccattgtcac actcc 15

<210> SEQ ID NO 540
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1, 3, 5, 6, 7, 10, 11, 12, 14, 15

<400> SEQUENCE: 540

ccattgtcac actcc 15

<210> SEQ ID NO 541
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1-5, 7-10, 12 & 13.

<400> SEQUENCE: 541

attgtcacac tcc 13

<210> SEQ ID NO 542
<211> LENGTH: 11
<212> TYPE: DNA
<213> ORGANISM: artificial

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<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1-3, 5-8, 10 & 11.

<400> SEQUENCE: 542

tgtcacactc c 11

<210> SEQ ID NO 543
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'OME

<400> SEQUENCE: 543

ccattgtcac actcc 15

<210> SEQ ID NO 544
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'fluoro

<400> SEQUENCE: 544

ccattgtcac actcc 15

<210> SEQ ID NO 545
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 545

ugugcaaauc caugcaaaac uga 23

<210> SEQ ID NO 546
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement gapmer, LNA at positions 1-4 and 20-23

<400> SEQUENCE: 546

tcagttttgc atggatttgc aca 23

<210> SEQ ID NO 547
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement blockmer, LNA at positions 7-14

<400> SEQUENCE: 547

tcagttttgc atggatttgc aca 23

<210> SEQ ID NO 548
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement LNA mixmer- LNA at third position and every third position thereafter

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<400> SEQUENCE: 548

tcagttttgc atggatttgc aca 23

<210> SEQ ID NO 549
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA units at position 1, 3, 6, 7, 10, 12, 14 and 15

<400> SEQUENCE: 549

tgcatggatt tgcac 15

<210> SEQ ID NO 550
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1, 3, 5, 6, 7, 10, 11, 12, 14, 15

<400> SEQUENCE: 550

tgcatggatt tgcac 15

<210> SEQ ID NO 551
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1, 3-5, 7-10, 12 & 13.

<400> SEQUENCE: 551

catggatttg cac 13

<210> SEQ ID NO 552
<211> LENGTH: 11
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1-3, 5-8, 10 & 11.

<400> SEQUENCE: 552

tggatttgca c 11

<210> SEQ ID NO 553
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'OME

<400> SEQUENCE: 553

tgcatggatt tgcac 15

<210> SEQ ID NO 554
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'fluoro

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<400> SEQUENCE: 554

tgcatggatt tgcac 15

<210> SEQ ID NO 555
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homos sapiens

<400> SEQUENCE: 555

uuaaugcuaa ucgugauagg gg 22

<210> SEQ ID NO 556
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement gapmer, LNA at positions 1-4 and 20-23

<400> SEQUENCE: 556

cccctatcac gattagcatt aa 22

<210> SEQ ID NO 557
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement blockmer, LNA at positions 7-14

<400> SEQUENCE: 557

cccctatcac gattagcatt aa 22

<210> SEQ ID NO 558
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement LNA mixmer- LNA at third position and every third position thereafter

<400> SEQUENCE: 558

cccctatcac gattagcatt aa 22

<210> SEQ ID NO 559
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1, 3, 6, 7, 10, 12, 14, 15

<400> SEQUENCE: 559

tcacgattag catta 15

<210> SEQ ID NO 560
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1, 3, 5, 6, 7, 10, 11, 12, 14, 15

<400> SEQUENCE: 560

-continued

tcacgattag catta 15

<210> SEQ ID NO 561
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1-5, 8-11, 12 & 13.

<400> SEQUENCE: 561

acgattagca tta 13

<210> SEQ ID NO 562
<211> LENGTH: 11
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1-3, 5-7, and 9-11

<400> SEQUENCE: 562

gattagcatt a 11

<210> SEQ ID NO 563
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'OME

<400> SEQUENCE: 563

tcacgattag catta 15

<210> SEQ ID NO 564
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'fluoro

<400> SEQUENCE: 564

tcacgattag catta 15

<210> SEQ ID NO 565
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 565

uagcuuauca gacugauguu ga 22

<210> SEQ ID NO 566
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement gapmer, LNA at positions 1-4 and 20-23

<400> SEQUENCE: 566

tcatcatcag tctgataagc tta 23

-continued

<210> SEQ ID NO 567
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement blockmer, LNA at positions 7-14

<400> SEQUENCE: 567

tcatcatcag tctgataagc tta 23

<210> SEQ ID NO 568
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement LNA mixmer- LNA at third position and every third position thereafter

<400> SEQUENCE: 568

tcatcatcag tctgataagc tta 23

<210> SEQ ID NO 569
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA units at position 1, 3, 6, 7, 10, 12, 14 and 15

<400> SEQUENCE: 569

tcagtctgat aagct 15

<210> SEQ ID NO 570
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1, 3, 5, 6, 7, 10, 11, 12, 14, 15

<400> SEQUENCE: 570

tcagtctgat aagct 15

<210> SEQ ID NO 571
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1-5, 7-10, 12 & 13.

<400> SEQUENCE: 571

agtctgataa gct 13

<210> SEQ ID NO 572
<211> LENGTH: 11
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA untis at positions 1-3, 5, 7-11

<400> SEQUENCE: 572

tctgataagc t 11

-continued

<210> SEQ ID NO 573
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'OME

<400> SEQUENCE: 573

tcagtctgat aagct 15

<210> SEQ ID NO 574
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'fluoro

<400> SEQUENCE: 574

tcagtctgat aagct 15

<210> SEQ ID NO 575
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 575

uuuguucguu cggcucgcgu ga 22

<210> SEQ ID NO 576
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement gapmer, LNA at positions 1-4 and 20-23

<400> SEQUENCE: 576

tctcgcgtgc cgttcgttct tt 22

<210> SEQ ID NO 577
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Blockmer, LNA at positions 7-14

<400> SEQUENCE: 577

tctcgcgtgc cgttcgttct tt 22

<210> SEQ ID NO 578
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Full complement LNA mixmer- LNA at third position and every third position thereafter

<400> SEQUENCE: 578

tctcgcgtgc cgttcgttct tt 22

<210> SEQ ID NO 579
<211> LENGTH: 15

-continued

<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA at positions 1, 3, 6, 7, 10, 12, 14, 15

<400> SEQUENCE: 579

gtgccgttcg ttctt 15

<210> SEQ ID NO 580
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA at positions 1, 3, 5-7, 10-12, 14 & 15

<400> SEQUENCE: 580

gtgccgttcg ttctt 15

<210> SEQ ID NO 581
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA at positions 1-5, 7, 9-13

<400> SEQUENCE: 581

gccgttcgtt ctt 13

<210> SEQ ID NO 582
<211> LENGTH: 11
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: LNA at positions 1-4, 6-11

<400> SEQUENCE: 582

cgttcgttct t 11

<210> SEQ ID NO 583
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'OME

<400> SEQUENCE: 583

gtgccgttcg ttctt 15

<210> SEQ ID NO 584
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: All residues LNA except at positions 2, 4, 5, 8, 9, 11, 13 which are 2'fluoro

<400> SEQUENCE: 584

gtgccgttcg ttctt 15

<210> SEQ ID NO 585
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: artificial

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Phosphorothioate backbone, LNA at positions 2 and every thirdtherafter.

<400> SEQUENCE: 585

ccattgtcac actcca 16

<210> SEQ ID NO 586
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Phosphorothioate backbone, LNA at position 3 and every thirdtherafter.

<400> SEQUENCE: 586

ccattgtcac actcca 16

<210> SEQ ID NO 587
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Phosphorothioate backbone - Gapmer design with LNA at positions1-3, & 13-15

<400> SEQUENCE: 587

ccattgtcac actcca 16

<210> SEQ ID NO 588
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Phosphorothioate backbone, LNA at positions 1, 3, 6, 7, 10, 12, 14 &15

<400> SEQUENCE: 588

ccattgtcac actcc 15

<210> SEQ ID NO 589
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Phosphorothioate backbone, LNA at positions 1, 3, 6, 7, 10, 12, 14 &15, LNA cytosines are methylated

<400> SEQUENCE: 589

ccattctgac cctac 15

<210> SEQ ID NO 590
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Phosphorothioate backbone, LNA at positions 3 and every thirdthereafter

<400> SEQUENCE: 590

ccattgtctc aatcca 16

<210> SEQ ID NO 591
<211> LENGTH: 13

-continued

<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Phosphorothioate backbone, LNA at position 1, 4, 5, 8, 10, 12 & 13

<400> SEQUENCE: 591

attgtcacac tcc 13

<210> SEQ ID NO 592
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Fully phosphorothioate, LNA at positions 1, 3, 6, 7, 10, 12, 14 &16, all C LNAs are methylated. LNA is preferably Beta-D-oxy LNA.

<400> SEQUENCE: 592

ccattctgac cctac 15

<210> SEQ ID NO 593
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 593

uagcuuauca gacugauguu ga 22

<210> SEQ ID NO 594
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Gapmer design, Optional FAM label at 5' end, LNA at positions 1-3 and 13-15.

<400> SEQUENCE: 594

tcagtctgat aagcta 16

<210> SEQ ID NO 595
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Gapmer design, Optional FAM label at 5' end, LNA at positions 1-3 and 13-15.

<400> SEQUENCE: 595

tccgtcttag aagata 16

<210> SEQ ID NO 596
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Optional FAM label at 5' end, LNA at positions 1, 3, 6, 7, 10, 12, 13 & 15

<400> SEQUENCE: 596

tctgtcagat acgat 15

<210> SEQ ID NO 597
<211> LENGTH: 15

-continued

<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Optional FAM label at 5' end, LNA at positions 1, 3, 6, 7, 10, 12, 13 & 15

<400> SEQUENCE: 597

tcagtctgat aagct 15

<210> SEQ ID NO 598
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: Optional FAM label at 5' end, LNA at positions 1, 3, 4 6, 7, 8, 10, 12, 14 & 15

<400> SEQUENCE: 598

tcagtctgat aagct 15

1. A pharmaceutical composition comprising a single stranded oligonucleotide, or a conjugate of said oligonucleotide, having a length of between 8 and 17 nucleobase units, and a pharmaceutically acceptable diluent, carrier, or adjuvant; wherein said oligonucleotide, or conjugate thereof, comprises a Locked Nucleic Acid nucleobase unit, and wherein said oligonucleotide, or conjugate thereof, is complementary to a human microRNA sequence.

2-3. (canceled)

4. A pharmaceutical composition according to claim **1**, wherein the single stranded oligonucleotide is complementary to a microRNA sequence selected from the group consisting of: hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7d, hsa-let-7e, hsa-let-7f, hsa-miR-15a, hsa-miR-16, hsa-miR-17-5p, hsa-miR-17-3p, hsa-miR-18a, hsa-miR-19a, hsa-miR-19b, hsa-miR-20a, hsa-miR-21, hsa-miR-22, hsa-miR-23a, hsa-miR-189, hsa-miR-24, hsa-miR-25, hsa-miR-26a, hsa-miR-26b, hsa-miR-27a, hsa-miR-28, hsa-miR-29a, hsa-miR-30a-5p, hsa-miR-30a-3p, hsa-miR-31, hsa-miR-32, hsa-miR-33, hsa-miR-92, hsa-miR-93, hsa-miR-95, hsa-miR-96, hsa-miR-98, hsa-miR-99a, hsa-miR-100, hsa-miR-101, hsa-miR-29b, hsa-miR-103, hsa-miR-105, hsa-miR-106a, hsa-miR-107, hsa-miR-192, hsa-miR-196a, hsa-miR-197, hsa-miR-198, hsa-miR-199a, hsa-miR-199a*, hsa-miR-208, hsa-miR-129, hsa-miR-148a, hsa-miR-30c, hsa-miR-30d, hsa-miR-139, hsa-miR-147, hsa-miR-7, hsa-miR-10a, hsa-miR-10b, hsa-miR-34a, hsa-miR-181a, hsa-miR-181b, hsa-miR-181c, hsa-miR-182, hsa-miR-182*, hsa-miR-183, hsa-miR-187, hsa-miR-199b, hsa-miR-203, hsa-miR-204, hsa-miR-205, hsa-miR-210, hsa-miR-211, hsa-miR-212, hsa-miR-181a*, hsa-miR-214, hsa-miR-215, hsa-miR-216, hsa-miR-217, hsa-miR-218, hsa-miR-219, hsa-miR-220, hsa-miR-221, hsa-miR-222, hsa-miR-223, hsa-miR-224, hsa-miR-200b, hsa-let-7g, hsa-let-7i, hsa-miR-1, hsa-miR-15b, hsa-miR-23b, hsa-miR-27b, hsa-miR-30b, hsa-miR-122a, hsa-miR-124a, hsa-miR-125b, hsa-miR-128a, hsa-miR-130a, hsa-miR-132, hsa-miR-133a, hsa-miR-135a, hsa-miR-137, hsa-miR-138, hsa-miR-140, hsa-miR-141, hsa-miR-142-5p, hsa-miR-142-3p, hsa-miR-143, hsa-miR-144, hsa-miR-145, hsa-miR-152, hsa-miR-153, hsa-miR-191, hsa-miR-9, hsa-miR-9*, hsa-miR-125a, hsa-miR-126*, hsa-miR-126, hsa-miR-127, hsa-miR-134, hsa-miR-136, hsa-miR-146a, hsa-miR-149, hsa-miR-150, hsa-miR-154, hsa-miR-154*, hsa-miR-184, hsa-miR-185, hsa-miR-186, hsa-miR-188, hsa-miR-190, hsa-miR-193a, hsa-miR-194, hsa-miR-195, hsa-miR-206, hsa-miR-320, hsa-miR-200c, hsa-miR-155, hsa-miR-128b, hsa-miR-106b, hsa-miR-29c, hsa-miR-200a, hsa-miR-302a*, hsa-miR-302a, hsa-miR-34b, hsa-miR-34c, hsa-miR-299-3p, hsa-miR-301, hsa-miR-99b, hsa-miR-296, hsa-miR-130b, hsa-miR-30e-5p, hsa-miR-30e-3p, hsa-miR-361, hsa-miR-362, hsa-miR-363, hsa-miR-365, hsa-miR-302b*, hsa-miR-302b, hsa-miR-302c*, hsa-miR-302c, hsa-miR-302d, hsa-miR-367, hsa-miR-368, hsa-miR-369-3p, hsa-miR-370, hsa-miR-371, hsa-miR-372, hsa-miR-373*, hsa-miR-373, hsa-miR-374, hsa-miR-375, hsa-miR-376a, hsa-miR-377, hsa-miR-378, hsa-miR-422b, hsa-miR-379, hsa-miR-380-5p, hsa-miR-380-3p, hsa-miR-381, hsa-miR-382, hsa-miR-383, hsa-miR-340, hsa-miR-330, hsa-miR-328, hsa-miR-342, hsa-miR-337, hsa-miR-323, hsa-miR-326, hsa-miR-151, hsa-miR-135b, hsa-miR-148b, hsa-miR-331, hsa-miR-324-5p, hsa-miR-324-3p, hsa-miR-338, hsa-miR-339, hsa-miR-335, hsa-miR-133b, hsa-miR-325, hsa-miR-345, hsa-miR-346, ebv-miR-BHRF1-1, ebv-miR-BHRF1-2*, ebv-miR-BHRF1-2, ebv-miR-BHRF1-3, ebv-miR-BART1-5p, ebv-miR-BART2, hsa-miR-384, hsa-miR-196b, hsa-miR-422a, hsa-miR-423, hsa-miR-424, hsa-miR-425-3p, hsa-miR-18b, hsa-miR-20b, hsa-miR-448, hsa-miR-429, hsa-miR-449, hsa-miR-450, hcmv-miR-UL22A, hcmv-miR-UL22A*, hcmv-miR-UL36, hcmv-miR-UL 112, hcmv-miR-UL148D, hcmv-miR-US5-1, hcmv-miR-US5-2, hcmv-miR-US25-1, hcmv-miR-US25-2-5p, hcmv-miR-US25-2-3p, hcmv-miR-US33, hsa-miR-191*, hsa-miR-200a*, hsa-miR-369-5p, hsa-miR-431, hsa-miR-433, hsa-miR-329, hsa-miR-453, hsa-miR-451, hsa-miR-452, hsa-miR-452*, hsa-miR-409-5p, hsa-miR-409-3p, hsa-miR-412, hsa-miR-410, hsa-miR-376b, hsa-miR-483, hsa-miR-484, hsa-miR-485-5p, hsa-miR-485-3p, hsa-miR-486, hsa-miR-487a, kshv-miR-K12-10a, kshv-miR-K12-10b, kshv-miR-K12-11, kshv-miR-K12-1, kshv-miR-K12-2, kshv-miR-K12-9*, kshv-miR-K12-9, kshv-miR-K12-8, kshv-miR-K12-7, kshv-miR-K12-6-5p, kshv-miR-K12-6-3p, kshv-miR-K12-5, kshv-

miR-K12-4-5p, kshv-miR-K12-4-3p, kshv-miR-K12-3, kshv-miR-K12-3*, hsa-miR-488, hsa-miR-489, hsa-miR-490, hsa-miR-491, hsa-miR-51 1, hsa-miR-146b, hsa-miR-202*, hsa-miR-202, hsa-miR-492, hsa-miR-493-5p, hsa-miR-432, hsa-miR-432*, hsa-miR-494, hsa-miR-495, hsa-miR-496, hsa-miR-193b, hsa-miR-497, hsa-miR-181d, hsa-miR-512-5p, hsa-miR-512-3p, hsa-miR-498, hsa-miR-520e, hsa-miR-515-5p, hsa-miR-515-3p, hsa-miR-519e*, hsa-miR-519e, hsa-miR-520f, hsa-miR-526c, hsa-miR-519c, hsa-miR-520a*, hsa-miR-520a, hsa-miR-526b, hsa-miR-526b*, hsa-miR-519b, hsa-miR-525, hsa-miR-525*, hsa-miR-523, hsa-miR-518f*, hsa-miR-518f, hsa-miR-520b, hsa-miR-518b, hsa-miR-526a, hsa-miR-520c, hsa-miR-518c*, hsa-miR-518c, hsa-miR-524*, hsa-miR-524, hsa-miR-517*, hsa-miR-517a, hsa-miR-519d, hsa-miR-521, hsa-miR-520d*, hsa-miR-520d, hsa-miR-517b, hsa-miR-520g, hsa-miR-516-5p, hsa-miR-516-3p, hsa-miR-518e, hsa-miR-527, hsa-miR-518a, hsa-miR-518d, hsa-miR-517c, hsa-miR-520h, hsa-miR-522, hsa-miR-519a, hsa-miR-499, hsa-miR-500, hsa-miR-501, hsa-miR-502, hsa-miR-503, hsa-miR-504, hsa-miR-505, hsa-miR-513, hsa-miR-506, hsa-miR-507, hsa-miR-508, hsa-miR-509, hsa-miR-510, hsa-miR-514, hsa-miR-532, hsa-miR-299-5p, hsa-miR-18a*, hsa-miR-455, hsa-miR-493-3p, hsa-miR-539, hsa-miR-544, hsa-miR-545, hsa-miR-487b, hsa-miR-551a, hsa-miR-552, hsa-miR-553, hsa-miR-554, hsa-miR-92b, hsa-miR-555, hsa-miR-556, hsa-miR-557, hsa-miR-558, hsa-miR-559, hsa-miR-560, hsa-miR-561, hsa-miR-562, hsa-miR-563, hsa-miR-564, hsa-miR-565, hsa-miR-566, hsa-miR-567, hsa-miR-568, hsa-miR-551b, hsa-miR-569, hsa-miR-570, hsa-miR-571, hsa-miR-572, hsa-miR-573, hsa-miR-574, hsa-miR-575, hsa-miR-576, hsa-miR-577, hsa-miR-578, hsa-miR-579, hsa-miR-580, hsa-miR-581, hsa-miR-582, hsa-miR-583, hsa-miR-584, hsa-miR-585, hsa-miR-548a, hsa-miR-586, hsa-miR-587, hsa-miR-548b, hsa-miR-588, hsa-miR-589, hsa-miR-550, hsa-miR-590, hsa-miR-591, hsa-miR-592, hsa-miR-593, hsa-miR-595, hsa-miR-596, hsa-miR-597, hsa-miR-598, hsa-miR-599, hsa-miR-600, hsa-miR-601, hsa-miR-602, hsa-miR-603, hsa-miR-604, hsa-miR-605, hsa-miR-606, hsa-miR-607, hsa-miR-608, hsa-miR-609, hsa-miR-610, hsa-miR-611, hsa-miR-612, hsa-miR-613, hsa-miR-614, hsa-miR-615, hsa-miR-616, hsa-miR-548c, hsa-miR-617, hsa-tniR-618, hsa-miR-619, hsa-miR-620, hsa-miR-621, hsa-miR-622, hsa-miR-623, hsa-miR-624, hsa-miR-625, hsa-miR-626, hsa-miR-627, hsa-miR-628, hsa-miR-629, hsa-miR-630, hsa-miR-631, hsa-miR-33b, hsa-miR-632, hsa-miR-633, hsa-miR-634, hsa-miR-635, hsa-miR-636, hsa-miR-637, hsa-miR-638, hsa-miR-639, hsa-miR-640, hsa-miR-641, hsa-miR-642, hsa-miR-643, hsa-miR-644, hsa-miR-645, hsa-miR-646, hsa-miR-647, hsa-miR-648, hsa-miR-649, hsa-miR-650, hsa-miR-651, hsa-miR-652, hsa-miR-548d, hsa-miR-661, hsa-miR-662, hsa-miR-663, hsa-miR-449b, hsa-miR-653, hsa-miR-411, hsa-miR-654, hsa-miR-655, hsa-miR-656, hsa-miR-549, hsa-miR-657, hsa-miR-658, hsa-miR-659, hsa-miR-660, hsa-miR-421, hsa-miR-542-5p, hcmv-miR-US4, hcmv-miR-UL70-5p, hcmv-miR-UL70-3p, hsa-miR-363*, hsa-miR-376a*, hsa-miR-542-3p, ebv-miR-BART1-3p, hsa-miR-425-5p, ebv-miR-BART3-5p, ebv-miR-BART3-3p, ebv-miR-BART4, ebv-miR-BART5, ebv-miR-BART6-5p, ebv-miR-BART6-3p, ebv-miR-BART7, ebv-miR-BART8-5p, ebv-miR-BART8-3p, ebv-miR-BART9, ebv-miR-BART10, ebv-miR-BART11-5p, ebv-miR-BART11-3p, ebv-miR-BART12, ebv-miR-BART13, ebv-miR-BART14-5p, ebv-miR-BART14-3p, kshv-miR-K12-12, ebv-miR-BART15, ebv-miR-BART16, ebv-miR-BART17-5p, ebv-miR-BART17-3p, ebv-miR-BART18, ebv-miR-BART19, ebv-miR-BART20-5p, ebv-miR-BART20-3p, hsv1-miR-H1, hsa-miR-758, hsa-miR-671, hsa-miR-668, hsa-miR-767-5p, hsa-miR-767-3p, hsa-miR-454-5p, hsa-miR-454-3p, hsa-miR-769-5p, hsa-miR-769-3p, hsa-miR-766, hsa-miR-765, hsa-miR-768-5p, hsa-miR-768-3p, hsa-miR-770-5p, hsa-miR-802, hsa-miR-801, hsa-miR-675,

5. A pharmaceutical composition according to claim **1** wherein said oligonucleotide or said conjugate thereof comprises a nucleotide analog at a position selected from the following; the first nucleobase, counting from the 3' end, the second nucleobase, counting from the 3' end, the ninth based, counting from the 3' end, and the tenth base, counting from the 3' end.

6-18. (canceled)

19. A pharmaceutical composition according to claim **1**, wherein the single stranded oligonucleotide comprises at least one nucleotide analogue unit, in a position which is within the region complementary to the miRNA seed region.

20. A pharmaceutical composition according to claim **19**, wherein the nucleobase sequence of the single stranded oligonucleotide which is complementary to the sequence of the microRNA seed region, is selected from the group consisting of

(a) (X)Xxxxxx, (X)xXxxxx, (X)xxXxxx, (X)xxxXxx, (X)xxxxXx and (X)xxxxxX,

(b) (X)XXxxxx, (X)XxXxxx, (X)XxxXxx, (X)XxxxXx, (X)XxxxxX, (X)xXXxxx, (X)xXxXxx, (X)xXxxXx, (X)xXxxxX, (X)xxXXxx, (X)xxXxXx, (X)xxXxxX, (X)xxxXXx, (X)xxxXxX and (X)xxxxXX,

(c) (X)XXXxxx, (X)xXXXxx, (X)xxXXXx, (X)xxxXXX, (X)XXxXxx, (X)XXxxXx, (X)XXxxxX, (X)xXXxXx, (X)xXXxxX, (X)xxXXxX, (X)XxXXxx, (X)XxxXXx (X)XxxxXX, (X)xXxXXx, (X)xXxxXX, (X)xxXxXX, (X)xXxXxX and (X)XxXxXx,

(d) (X)xxXXX, (X)xXxXXX, (X)xXXxXX, (X)xXXXχX, (X)xXXXXx, (X)XxxXXXX, (X)XxXxXX, (X)XxXXxX, (X)XxXXxx, (X)XXxxXX, (X)XXxXxX, (X)XXxXXx, (X)XXXxxX, (X)XXXxXx, and (X)XXXXxx,

(e) (X)xXXXXX, (X)XxXXXX, (X)XXxXXX, (X)XXXxXX, (X)XXXXxX and (X)XXXXXx, and

(f) XXXXXX, XxXXXXX, XXxXXXX, XXXxXXX, XXXXxXX, XXXXXxX and XXXXXXx,

as read in a 3'-5' direction, wherein "X" denotes a nucleotide analogue, (X) denotes an optional nucleotide analogue, and "x" denotes a DNA or RNA nucleotide unit,

21-44. (canceled)

45. A pharmaceutical composition according to claim **20**, wherein the nucleotide analogue units are independently selected form the group consisting of: 2'-O-alkyl-RNA unit, 2'-OMe-RNA unit, 2'-amino-DNA unit, 2'-fluoro-DNA unit, LNA unit, PNA unit, HNA unit, INA unit.

46-59. (canceled)

60. A pharmaceutical composition according to claim **1**, wherein the nucleotide analogues have a higher thermal duplex stability to a complementary RNA nucleotide than the thermal duplex stability of an equivalent DNA nucleotide to said complementary RNA nucleotide.

61. A pharmaceutical composition according to claim **1**, wherein the nucleotide analogues confer enhanced serum stability to the single stranded oligonucleotide.

62. A pharmaceutical composition according to claim **1**, wherein the single stranded oligonucleotide forms an A-helix conformation with a complementary single stranded RNA molecule.

63. A pharmaceutical composition according to claim **1**, wherein the oligonucleotide does not mediate RNAseH based cleavage of a complementary single stranded RNA molecule.

64-66. (canceled)

67. The pharmaceutical composition according to any one of claims **1-66** wherein the single stranded oligonucleotide is capable of forming a duplex with a complementary single stranded DNA nucleic acid molecule with phosphodiester internucleoside linkages, wherein the duplex has a Tm of between about 50° C. to about 95° C.

68-69. (canceled)

70. A pharmaceutical composition according to claim **1**, wherein the LNA unit are independently selected from the group consisting of oxy-LNA, thio-LNA, and amino-LNA, in either of the D-β and L-α configurations or combinations thereof.

71-73. (canceled)

74. A pharmaceutical composition according to claim **1**, wherein the oligonucleotide comprises at least one internucleoside linkage group which differs from phosphate.

75-82. (canceled)

83. A method for the treatment of a disease or medical disorder associated with the presence or over-expression of the microRNA, comprising the step of administering a composition comprising a single stranded oligonucleotide, or a conjugate of said oligonucleotide, having a length of between 8 and 17 nucleobase units, and a pharmaceutically acceptable diluent, carrier, or adjuvant; wherein said oligonucleotide, or conjugate thereof, comprises a Locked Nucleic Acid nucleobase unit, and wherein said oligonucleotide, or conjugate thereof, is complementary to a human microRNA sequence.

84. A method for reducing the effective amount of a miRNA target in a cell or an organism, comprising administering a composition comprising a single stranded oligonucleotide, or a conjugate of said oligonucleotide, having a length of between 8 and 17 nucleobase units, and a pharmaceutically acceptable diluent, carrier, or adjuvant; wherein said oligonucleotide, or conjugate thereof, comprises a Locked Nucleic Acid nucleobase unit, and wherein said oligonucleotide, or conjugate thereof, is complementary to a human microRNA sequence.

85-88. (canceled)

89. The method according to claim **87**, wherein the miRNA target is selected from the group consisting of the miRNA targets shown in table 2.

90-95. (canceled)

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