

Nucleic acids for inhibiting expression of complement factor B (CFB) in a cell**Field of the invention**

5 The invention relates to nucleic acid products that interfere with or inhibit complement factor B (CFB) gene expression. It further relates to therapeutic uses of such inhibition such as for the treatment of diseases and disorders associated with complement pathway deregulation, (particularly of the alternative pathway), and/or with over-activation or with ectopic expression or localisation or accumulation, of CFB in the body.

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Background

Double-stranded RNAs (dsRNA) able to bind through complementary base pairing to expressed mRNAs have been shown to block gene expression (Fire et al., 1998, Nature. 1998 Feb 19;391(6669):806-11 and Elbashir et al., 2001, Nature. 2001 May 24;411(6836):494-8) by
15 a mechanism that has been termed "RNA interference (RNAi)". Short dsRNAs direct gene specific, post transcriptional silencing in many organisms, including vertebrates, and have become a useful tool for studying gene function. RNAi is mediated by the RNA induced silencing complex (RISC), a sequence specific, multi component nuclease that degrades
20 messenger RNAs having sufficient complementary or homology to the silencing trigger loaded into the RISC complex. Interfering RNAs such as siRNAs, antisense RNAs, and micro RNAs, are oligonucleotides that prevent the formation of proteins by gene silencing, i.e., inhibiting gene translation of the protein through degradation of mRNA molecules. Gene silencing agents are becoming increasingly important for therapeutic applications in medicine.

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According to Watts and Corey in the Journal of Pathology (2012; Vol 226, p 365-379), there are algorithms that can be used to design nucleic acid silencing triggers, but all of these have severe limitations. It may take various experimental methods to identify potent siRNAs, as algorithms do not take into account factors such as tertiary structure of the target mRNA or the
30 involvement of RNA binding proteins. Therefore, the discovery of a potent nucleic acid silencing trigger with minimal off-target effects is a complex process. For the pharmaceutical development of these highly charged molecules, it is necessary that they can be synthesised economically, distributed to target tissues, enter cells and function within acceptable limits of toxicity.

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The complement system or pathway is part of the innate immune system of host defence against invading pathogens. It mainly consists of a number of proteins that circulate in the

bloodstream in the form of precursors. Most of the proteins that form the complement system, including the complement component protein C3 (also referred to herein simply as C3), are largely synthesised and secreted into the bloodstream by hepatocytes in the liver. Activation of the system leads to inflammatory responses resulting in phagocyte attraction and opsonization and consequently clearance of pathogens, immune complexes and cellular debris (Janeway's Immunobiology 9th Edition). The complement system consists of 3 pathways (Classical, Leptin and Alternative pathways), which all converge at the formation of so-called complement component 3 convertase enzyme complexes. These enzyme complexes cleave the complement component C3 protein into C3a and C3b. Once cleaved, C3b forms part of a complex that in turn cleaves C5 into C5a and C5b. After cleavage, C5b is one of the key components of the main complement pathway effectors, the membrane attack complex. C3 is therefore a key component of the complement system activation pathway.

Complement Factor B (CFB or "factor B") is involved in activation of the alternative pathway. Binding of CFB to C3b (e.g., on a cell surface) renders CFB susceptible to cleavage by Factor D, forming the serine protease C3Bb, which is itself a C3 convertase, leading to an amplification loop for C3 activation. CFB is primarily synthesised in the liver, as well as in low levels at several extrahepatic sites.

Several diseases are associated with aberrant acquired or genetic activation of the complement pathway as well as with aberrant or over-expression of C3. Among others, these are C3 glomerulopathy (CFBG), atypical hemolytic uremic syndrome (aHUS), immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), systemic lupus erythematosus, lupus nephritis (LN; a renal complication of SLE), ischemia/reperfusion injury and IgA nephropathy (IgA N; reviewed in Ricklin et al., Nephrology, 2016 and others). Most of these diseases are associated with the kidney, as this organ is uniquely sensitive to complement-induced damage. However, diseases of other organs are also known to be related to complement dysfunction, such as, e.g., age-related macular degeneration (AMD), rheumatoid arthritis (RA), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), dysbiotic periodontal disease, malarial anaemia, paroxysmal nocturnal hemoglobinuria (PNH) and sepsis.

There are currently only few treatments for complement system mediated diseases, disorders and syndromes. The monoclonal humanized antibody Eculizumab is one of them. It is known to bind complement protein C5, thereby blocking the membrane attack complex at the end of the complement cascade (Hillmen et al., 2006 NEJM). However, only a subset of patients suffering from the above listed diseases respond to Eculizumab therapy. There is thus a high

unmet need for medical treatments of complement mediated or associated diseases. C3 is a pivotal factor in the complement pathway activation. Inhibiting expression of factors such as CFB which are involved in C3 activation therefore presents a promising therapeutic strategy for many complement-mediated diseases. Targeting of CFB expression or activity, e.g., via antisense oligonucleotides or small molecule inhibitors, has been proposed as a potential therapeutic strategy for various complement-mediated conditions including AMD (Grossman et al., Molecular Vision 2017; 23:561-571) and lupus nephritis (Grossman et al., Immunobiology 2016; 221:701-708).

WO200404554, WO2007089375, WO2015089368, WO2019027015, WO2019089922 and WO2021222549 describe double-stranded siRNAs, WO2015038939, WO2015168635 describe single stranded antisense oligonucleotides (=ASO) targeted to CFB.

Summary of the invention

One aspect of the invention is a double-stranded nucleic acid for inhibiting expression of component factor B (CFB), wherein the nucleic acid comprises a first strand and a second strand, wherein the unmodified equivalent of the first strand sequence comprises a sequence of at least 15 nucleotides differing by no more than 3 nucleotides from any one of the first strand sequences shown in Table 5a.

The unmodified equivalent of the first strand sequence may, for example, comprise a sequence of at least 15 nucleotides differing by no more than 3 nucleotides from any one of the first strand sequences listed in Table 1.

The nucleic acids described herein are thus double-stranded nucleic acids capable of inhibiting expression of CFB, preferably in a cell, and may find use as a therapeutic agent or diagnostic agent, e.g., in associated diagnostic or therapeutic methods. The nucleic acid comprises or consists of a first strand and a second strand, and the first strand typically comprises sequences sufficiently complementary to CFB mRNA so as to mediate RNA interference.

One aspect relates to a composition comprising a nucleic acid as disclosed herein and a solvent (preferably water) and/or a delivery vehicle and/or a physiologically acceptable excipient and/or a carrier and/or a salt and/or a diluent and/or a buffer and/or a preservative.

One aspect relates to a composition comprising a nucleic acid as disclosed herein and a further therapeutic agent selected from e.g., an oligonucleotide, a small molecule, a monoclonal antibody, a polyclonal antibody and a peptide.

- 5 One aspect relates to a nucleic acid or a composition comprising it as disclosed herein for use as a therapeutic agent or diagnostic agent, e.g., in associated methods.

One aspect relates to a nucleic acid or a composition comprising it as disclosed herein for use in the prophylaxis or treatment of a disease, disorder or syndrome.

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One aspect relates to the use of a nucleic acid or a composition comprising it as disclosed herein in the prophylaxis or treatment of a disease, disorder or syndrome.

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One aspect relates to the use of a nucleic acid or a composition comprising it as disclosed herein in the preparation of a medicament for the prophylaxis or treatment of a disease, disorder or syndrome.

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One aspect relates to a method of prophylaxis or treatment of a disease, disorder or syndrome comprising administering a pharmaceutically effective dose or amount of a nucleic acid or composition comprising it as disclosed herein to an individual in need of treatment, preferably wherein the nucleic acid or composition is administered to the subject subcutaneously, intravenously or by oral, rectal, pulmonary, intramuscular or intraperitoneal administration.

Detailed description of the invention

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The present invention relates to a nucleic acid which is double-stranded and which comprises a sequence homologous to an expressed RNA transcript of CFB, and compositions thereof. These nucleic acids, conjugates thereof, and compositions comprising them, may be used in the prophylaxis and treatment of a variety of diseases, disorders and syndromes in which
30 reduced expression of the CFB gene product is desirable.

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A first aspect of the invention is a double-stranded nucleic acid for inhibiting expression of CFB, preferably in a cell, wherein the nucleic acid comprises a first strand and a second strand, wherein the unmodified equivalent of the first strand sequence comprises a sequence of at least 15 nucleotides differing by no more than 3 nucleotides from any one of the first strand sequences shown in Table 5a. These nucleic acids among others have the advantage of being active in various species that are relevant for pre-clinical and clinical development and/or of

having few relevant off-target effects. Having few relevant off-target effects means that a nucleic acid specifically inhibits the intended target and does not significantly inhibit other genes or inhibits only one or few other genes at a therapeutically acceptable level.

- 5 For example, the unmodified equivalent of the first strand sequence may comprise a sequence of at least 15 nucleotides differing by no more than 3 nucleotides from any one of the first strand sequences listed in Table 1.

10 Preferably, the unmodified equivalent of the first strand sequence comprises a sequence of at least 16, more preferably at least 17, yet more preferably at least 18 and most preferably all 19 nucleotides differing by no more than 3 nucleotides, preferably by no more than 2 nucleotides, more preferably by no more than 1 nucleotide, and most preferably not differing by any nucleotide from any one of the first strand sequences shown in Table 5a.

- 15 For example, the unmodified equivalent of the first strand sequence may comprise a sequence of at least 16, more preferably at least 17, yet more preferably at least 18 and most preferably all 19 nucleotides differing by no more than 3 nucleotides, preferably by no more than 2 nucleotides, more preferably by no more than 1 nucleotide, and most preferably not differing by any nucleotide from any one of the first strand sequences listed in Table 1.

20 Preferably, the unmodified equivalent of the first strand sequence of the nucleic acid consists of one of the first strand sequences shown in Table 5a. The sequence may however be modified by a number of nucleic acid modifications that do not change the identity of the nucleotide. For example, modifications of the backbone or sugar residues of the nucleic acid
25 do not change the identity of the nucleotide because the base itself remains the same as in the reference sequence.

For example, the unmodified equivalent of the first strand sequence of the nucleic acid may consist of one of the first strand sequences shown in Table 1, optionally modified by one or
30 more of said nucleic acid modifications.

A nucleic acid that comprises a sequence according to a reference sequence herein means that the nucleic acid comprises a sequence of contiguous nucleotides in the order as defined in the reference sequence.

35 When reference is made herein to a reference sequence comprising or consisting of nucleotides, this reference is not limited to the sequence with unmodified nucleotides. The

same reference also encompasses the same nucleotide sequence in which one, several, such as two, three, four, five, six, seven or more, including all, nucleotides are modified by modifications such as 2'-OMe, 2'-F, a ligand, a linker, a 3' end or 5' end modification or any other modification. It also refers to sequences in which two or more nucleotides are linked to each other by the natural phosphodiester linkage or by any other linkage such as a phosphorothioate or a phosphorodithioate linkage.

A double-stranded nucleic acid is a nucleic acid in which the first strand and the second strand hybridise to each other over at least part of their lengths and are therefore capable of forming a duplex region under physiological conditions, such as in PBS at 37°C at a concentration of 1 µM of each strand. The first and second strand are preferably able to hybridise to each other and therefore to form a duplex region over a region of at least 15 nucleotides, preferably 16, 17, 18 or 19 nucleotides. This duplex region comprises nucleotide base pairings between the two strands, preferably based on Watson-Crick base pairing and/or wobble base pairing (such as GU base pairing). All the nucleotides of the two strands within a duplex region do not have to base pair to each other to form a duplex region. A certain number of mismatches, deletions or insertions between the nucleotide sequences of the two strands are acceptable. Overhangs on either end of the first or second strand or unpaired nucleotides at either end of the double-stranded nucleic acid are also possible. The double-stranded nucleic acid is preferably a stable double-stranded nucleic acid under physiological conditions, and preferably has a melting temperature (T_m) of 45°C or more, preferably 50°C or more, and more preferably 55°C or more for example in PBS at a concentration of 1 µM of each strand.

A stable double-stranded nucleic acid under physiological conditions is a double-stranded nucleic acid that has a T_m of 45°C or more, preferably 50°C or more, and more preferably 55°C or more, for example in PBS at a concentration of 1 µM of each strand.

The first strand and the second strand are preferably capable of forming a duplex region (i.e., are complementary to each other) over i) at least a portion of their lengths, preferably over at least 15 nucleotides of both of their lengths, ii) over the entire length of the first strand, iii) over the entire length of the second strand or iv) over the entire length of both the first and the second strand. Strands being complementary to each other over a certain length means that the strands are able to base pair to each other, either via Watson-Crick or wobble base pairing, over that length. Each nucleotide of the length does not necessarily have to be able to base pair with its counterpart in the other strand over the entire given length as long as a stable double-stranded nucleotide under physiological conditions can be formed. It is however,

preferred, in certain embodiments, if each nucleotide of the length can base pair with its counterpart in the other strand over the entire given length.

5 A certain number of mismatches, deletions or insertions between the first strand and the target sequence, or between the first strand and the second strand can be tolerated in the context of the siRNA and even have the potential in certain cases to increase RNA interference (e.g., inhibition) activity.

10 The inhibition activity of the nucleic acids according to the present invention relies on the formation of a duplex region between all or a portion of the first strand and a portion of a target nucleic acid. The portion of the target nucleic acid that forms a duplex region with the first strand, defined as beginning with the first base pair formed between the first strand and the target sequence and ending with the last base pair formed between the first strand and the target sequence, inclusive, is the target nucleic acid sequence or simply, target sequence. The
15 duplex region formed between the first strand and the second strand need not be the same as the duplex region formed between the first strand and the target sequence. That is, the second strand may have a sequence different from the target sequence; however, the first strand must be able to form a duplex structure with both the second strand and the target sequence, at least under physiological conditions.

20 The complementarity between the first strand and the target sequence may be perfect (i.e., 100% identity with no nucleotide mismatches or insertions or deletions in the first strand as compared to the target sequence).

25 The complementarity between the first strand and the target sequence may not be perfect. The complementarity may be from about 70% to about 100%. More specifically, the complementarity may be at least 70%, 80%, 85%, 90% or 95% and intermediate values.

30 The identity between the first strand and the complementary sequence of the target sequence may range from about 75% to about 100%. More specifically, the complementarity may be at least 75%, 80%, 85%, 90% or 95% and intermediate values, provided a nucleic acid is capable of reducing or inhibiting the expression of CFB.

35 A nucleic acid having less than 100% complementarity between the first strand and the target sequence may be able to reduce the expression of CFB to the same level as a nucleic acid having perfect complementarity between the first strand and target sequence. Alternatively, it may be able to reduce expression of CFB to a level that is 15%, 20%, 25%, 30%, 35%, 40%,

45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% of the level of reduction achieved by the nucleic acid with perfect complementarity.

A nucleic acid of the present disclosure may be a nucleic acid wherein:

- 5 (a) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 3 nucleotides from any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence differing by no more than 3 nucleotides from the corresponding second strand sequence;
- 10 (b) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 2 nucleotides from any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence differing by no more than 2 nucleotides from the corresponding second strand sequence;
- 15 (c) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 1 nucleotide from any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence differing by no more than 1 nucleotide from the corresponding second strand sequence;
- 20 (d) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of the corresponding second strand sequence;
- 25 (e) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of the corresponding second strand sequence;
- 30 (f) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of the corresponding second strand sequence;
- 35 (g) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second

strand sequence comprises a sequence corresponding to nucleotides 1 to 18 from the 5' end of the corresponding second strand sequence;

- 5 (h) the unmodified equivalent of the first strand sequence comprises a sequence of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence of the corresponding second strand sequence;
- 10 (i) the unmodified equivalent of the first strand sequence consists of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence consists of the sequence of the corresponding second strand sequence;
- 15 (j) the unmodified equivalent of the first strand sequence consists essentially of any one of the first strand sequences with a given SEQ ID No. shown in Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence consists essentially of the sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 5a;
- 20 (k) the unmodified equivalent of the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 5a, wherein said unmodified equivalent of the first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown Table 5a;
- 25 (l) the unmodified equivalent of the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 5a, wherein said unmodified equivalent of the first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 5a, and wherein said unmodified equivalent of the first strand sequence consists of a contiguous region of from 17-25 nucleotides in length, preferably of from 18-24 nucleotides in length, complementary to the CFB transcript of SEQ ID NO. 758; and
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optionally wherein the unmodified equivalent of the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 5a;

- 5 (m) unmodified equivalent of the first strand and the unmodified equivalent of the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are present on a single strand wherein the unmodified equivalent of the first strand and the unmodified equivalent of the second strand are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length; or
- 10 (n) the unmodified equivalent of the first strand and the unmodified equivalent of the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are on two separate strands that are able to hybridise to each other and to thereby form a double stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length.

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For example, a nucleic acid of the present disclosure may be a nucleic acid wherein:

- (a) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 3 nucleotides from any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises
- 20 a sequence differing by no more than 3 nucleotides from the corresponding second strand sequence;
- (b) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 2 nucleotides from any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises
- 25 a sequence differing by no more than 2 nucleotides from the corresponding second strand sequence;
- (c) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 1 nucleotide from any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises
- 30 a sequence differing by no more than 1 nucleotide from the corresponding second strand sequence;
- (d) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second
- 35 strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of the corresponding second strand sequence;

- (e) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of the corresponding second strand sequence;
- (f) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of the corresponding second strand sequence;
- (g) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 1 to 18 from the 5' end of the corresponding second strand sequence;
- (h) the unmodified equivalent of the first strand sequence comprises a sequence of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence of the corresponding second strand sequence;
- (i) the unmodified equivalent of the first strand sequence consists of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence consists of the sequence of the corresponding second strand sequence;
- (j) the unmodified equivalent of the first strand sequence consists essentially of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, and optionally wherein the unmodified equivalent of the second strand sequence consists essentially of the sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 1;
- (k) the unmodified equivalent of the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, wherein said unmodified equivalent of the first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 1,

and optionally wherein the unmodified equivalent of the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown Table 1;

- 5 (l) the unmodified equivalent of the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, wherein said unmodified equivalent of the first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6
10 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, and wherein said unmodified equivalent of the first strand sequence consists of a contiguous region of from 17-25 nucleotides in length, preferably of from 18-24 nucleotides in length, complementary to the CFB transcript of SEQ ID NO. 758; and
15 optionally wherein the unmodified equivalent of the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 1;
- (m) unmodified equivalent of the first strand and the unmodified equivalent of the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are present
20 on a single strand wherein the unmodified equivalent of the first strand and the unmodified equivalent of the second strand are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length; or
- (n) the unmodified equivalent of the first strand and the unmodified equivalent of the second
25 strand of any one of the nucleic acid molecules of subsections (a) to (l) above are on two separate strands that are able to hybridise to each other and to thereby form a double stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length.

30 By a "corresponding" second strand is meant a second strand present in the same duplex as a given first strand in Table 5a, 5b or 5c, or listed as a corresponding second strand sequence in Table 1 or Table 2, as the case may be. That is to say, a first strand and its corresponding second strand are designated as the "A" and "B" strands respectively of a duplex having a given Duplex ID in Table 5a, 5b or 5c, or are described as such in Tables 1 and 2.

Table 1:

First strand sequence (SEQ ID No.)	Corresponding second strand sequence (SEQ ID No.)
57	58
71	72
295	296
201	202
47	48
319	320
249	250
721	48
295	296
722	202
723	72
724	58

In one aspect, if the 5'-most nucleotide of the first strand is a nucleotide other than A or U, this nucleotide is replaced by an A or U. Preferably, if the 5'-most nucleotide of the first strand is a nucleotide other than U, this nucleotide is replaced by U, and more preferably by U with a 5' vinylphosphonate.

When a nucleic acid of the invention does not comprise the entire sequence of a reference first strand and/or second strand sequence (as for example given in Tables 1, 2, 5a, 5b or 5c), or one or both strands differ from the corresponding reference sequence by one, two or three nucleotides, this nucleic acid preferably retains at least 30%, more preferably at least 50%, more preferably at least 70%, more preferably at least 80%, even more preferably at least 90%, yet more preferably at least 95% and most preferably at least 100% of the CFB inhibition activity compared to the inhibition activity of the corresponding nucleic acid that comprises the entire first strand and second strand reference sequences in a comparable experiment.

Nucleic acids that are capable of hybridising under physiological conditions are nucleic acids that are capable of forming base pairs, preferably Watson-Crick or wobble base-pairs, between at least a portion of the opposed nucleotides in the strands so as to form at least a duplex region. Such a double-stranded nucleic acid is preferably a stable double-stranded nucleic acid under physiological conditions (for example in PBS at 37°C at a concentration of 1 µM of each strand), meaning that under such conditions, the two strands stay hybridised to each other. The T_m of the double-stranded nucleotide is preferably 45°C or more, preferably 50°C or more and more preferably 55°C or more.

One aspect of the present invention relates to a nucleic acid for inhibiting expression of CFB, wherein the nucleic acid comprises a first sequence of at least 15, preferably at least 16, more preferably at least 17, yet more preferably at least 18 and most preferably all nucleotides differing by no more than 3 nucleotides, preferably no more than 2 nucleotides, more preferably
5 no more than 1 nucleotide and most preferably not differing by any nucleotide from any of the first strand unmodified equivalent sequences of Table 5a, or of Table 1, the first sequence being able to hybridise to a target gene transcript (such as an mRNA) under physiological conditions. Preferably, the nucleic acid further comprises a second sequence of at least 15, preferably at least 16, more preferably at least 17, yet more preferably at least 18 and most
10 preferably all nucleotides differing by no more than 3 nucleotides, preferably no more than 2 nucleotides, more preferably no more than 1 nucleotide and most preferably not differing by any nucleotide from any of the corresponding second strand unmodified equivalent sequences of Table 5a, or of Table 1, the second sequence being able to hybridise to the first sequence under physiological conditions and preferably the nucleic acid being an siRNA that is capable
15 of inhibiting CFB expression via the RNAi pathway.

One aspect relates to any double-stranded nucleic acid as disclosed in Tables 5a, 5b or 5c, each of which may be referred to by a given Duplex ID, preferably for inhibiting expression of CFB, provided that the double-stranded nucleic acid is able to inhibit expression of CFB. These
20 nucleic acids are all siRNAs. Some (Table 5a) are composed of unmodified nucleotide sequences. Others (Table 5b) comprise various nucleotide and/or backbone modifications. Still others (Table 5c) are conjugates comprising GalNAc moieties that can be specifically targeted to cells with GalNAc receptors, such as hepatocytes.

25 One aspect relates to a double-stranded nucleic acid that is capable of inhibiting expression of CFB, preferably in a cell, for use as a therapeutic or diagnostic agent, e.g., in associated therapeutic or diagnostic methods, wherein the nucleic acid preferably comprises or consists of a first strand and a second strand and preferably wherein the first strand comprises sequences sufficiently complementary to a CFB mRNA so as to mediate RNA interference.

30 The nucleic acids described herein may be capable of inhibiting the expression of CFB. Inhibition may be complete, i.e., 0% remaining expression. Inhibition of CFB expression may be partial, i.e., it may be 15%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more, or intermediate values of inhibition of the level of CFB expression in the absence of
35 a nucleic acid of the invention. The level of inhibition may be measured by comparing a treated sample with an untreated sample or with a sample treated with a control such as for example a siRNA that does not target CFB. Inhibition may be measured by measuring CFB mRNA

and/or protein levels or levels of a biomarker or indicator that correlates with CFB presence or activity. It may be measured in cells that may have been treated *in vitro* with a nucleic acid described herein. Alternatively, or in addition, inhibition may be measured in cells, such as hepatocytes, or tissue, such as liver tissue, or an organ, such as the liver, or in a body fluid
5 such as blood, serum, lymph or any other body part or fluid that has been taken from a subject previously treated with a nucleic acid disclosed herein. Preferably, inhibition of CFB expression is determined by comparing the CFB mRNA level measured in CFB-expressing cells after 24 or 48 hours *in vitro* treatment with a double-stranded RNA disclosed herein under ideal conditions (see the examples for appropriate concentrations and conditions) to the CFB mRNA
10 level measured in control cells that were untreated or mock treated or treated with a control double-stranded RNA under the same conditions.

One aspect of the present invention relates to a nucleic acid, wherein the first strand and the second strand are present on a single strand of a nucleic acid that loops around so that the
15 first strand and the second strand are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region.

Preferably, the first strand and the second strand of the nucleic acid are separate strands. The two separate strands are preferably each 17-25 nucleotides in length, more preferably 18-25
20 nucleotides in length. The two strands may be of the same or different lengths. The first strand may be 17-25 nucleotides in length, preferably it may be 18-24 nucleotides in length, it may be 18, 19, 20, 21, 22, 23 or 24 nucleotides in length. Most preferably, the first strand is 19 nucleotides in length. The second strand may independently be 17-25 nucleotides in length, preferably it may be 18-24 nucleotides in length, it may be 18, 19, 20, 21, 22, 23 or 24
25 nucleotides in length. More preferably, the second strand is 18 or 19 or 20 nucleotides in length, and most preferably it is 19 nucleotides in length.

Preferably, the first strand and the second strand of the nucleic acid form a duplex region of 17-25 nucleotides in length. More preferably, the duplex region is 18-24 nucleotides in length.
30 The duplex region may be 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length. In the most preferred embodiment, the duplex region is 18 or 19 nucleotides in length. The duplex region is defined here as the region between and including the 5'-most nucleotide of the first strand that is base paired to a nucleotide of the second strand to the 3'-most nucleotide of the first strand that is base paired to a nucleotide of the second strand. The duplex region may
35 comprise nucleotides in either or both strands that are not base-paired to a nucleotide in the other strand. It may comprise one, two, three or four such nucleotides on the first strand and/or on the second strand. However, preferably, the duplex region consists of 17-25 consecutive

nucleotide base pairs. That is to say that it preferably comprises 17-25 consecutive nucleotides on both of the strands that all base pair to a nucleotide in the other strand. More preferably, the duplex region consists of 18 or 19 consecutive nucleotide base pairs, most preferably 18.

- 5 In each of the embodiments disclosed herein, the nucleic acid may be blunt ended at both ends; have an overhang at one end and a blunt end at the other end; or have an overhang at both ends.

- 10 The nucleic acid may have an overhang at one end and a blunt end at the other end. The nucleic acid may have an overhang at both ends. The nucleic acid may be blunt ended at both ends. The nucleic acid may be blunt ended at the end with the 5' end of the first strand and the 3' end of the second strand or at the 3' end of the first strand and the 5' end of the second strand.

- 15 The nucleic acid may comprise an overhang at a 3' or 5' end. The nucleic acid may have a 3' overhang on the first strand. The nucleic acid may have a 3' overhang on the second strand. The nucleic acid may have a 5' overhang on the first strand. The nucleic acid may have a 5' overhang on the second strand. The nucleic acid may have an overhang at both the 5' end and 3' end of the first strand. The nucleic acid may have an overhang at both the 5' end and 3' end of the second strand. The nucleic acid may have a 5' overhang on the first strand and a 3' overhang on the second strand. The nucleic acid may have a 3' overhang on the first strand and a 5' overhang on the second strand. The nucleic acid may have a 3' overhang on the first strand and a 3' overhang on the second strand. The nucleic acid may have a 5' overhang on the first strand and a 5' overhang on the second strand.

- 25 An overhang at the 3' end or 5' end of the second strand or the first strand may consist of 1, 2, 3, 4 and 5 nucleotides in length. Optionally, an overhang may consist of 1 or 2 nucleotides, which may or may not be modified.

- 30 In one embodiment, the 5' end of the first strand is a single-stranded overhang of one, two or three nucleotides, preferably of one nucleotide.

- 35 Preferably, the nucleic acid is an siRNA. siRNAs are short interfering or short silencing RNAs that are able to inhibit the expression of a target gene through the RNA interference (RNAi) pathway. Inhibition occurs through targeted degradation of mRNA transcripts of the target gene after transcription. The siRNA forms part of the RISC complex. The RISC complex specifically

targets the target RNA by sequence complementarity of the first (antisense) strand with the target sequence.

Preferably, the nucleic acid mediates RNA interference (RNAi). Preferably, the nucleic acid
5 mediates RNA interference with an efficacy of at least 50% inhibition, more preferably at least 70%, more preferably at least 80%, even more preferably at least 90%, yet more preferably at least 95% and most preferably 100% inhibition. The inhibition efficacy is preferably measured by comparing the CFB mRNA level in cells, such as hepatocytes, treated with a CFB specific siRNA to the CFB mRNA level in cells treated with a control in a comparable experiment. The
10 control can be a treatment with a non-CFB targeting siRNA or without a siRNA. The nucleic acid, or at least the first strand of the nucleic acid, is therefore preferably able to be incorporated into the RISC complex. As a result, the nucleic acid, or at least the first strand of the nucleic acid, is therefore able to guide the RISC complex to a specific target RNA with which the nucleic acid, or at least the first strand of the nucleic acid, is at least partially
15 complementary. The RISC complex then specifically cleaves this target RNA and as a result leads to inhibition of the expression of the gene from which the RNA stems.

Nucleic acid modifications

20 Nucleic acids discussed herein include unmodified RNA as well as RNA which has been modified, e.g., to improve efficacy or stability. Unmodified RNA refers to a molecule in which the components of the nucleic acid, namely sugars, bases, and phosphate moieties, are the same or essentially the same as those which occur in nature, for example as occur naturally in the human body. The term "modified nucleotide" as used herein refers to a nucleotide in
25 which one or more of the components of the nucleotide, namely the sugar, base, and phosphate moiety, is/are different from those which occur in nature. The term "modified nucleotide" also refers in certain cases to molecules that are not nucleotides in the strict sense of the term because they lack, or have a substitute of, an essential component of a nucleotide, such as the sugar, base or phosphate moiety. A nucleic acid comprising such modified
30 nucleotides is still to be understood as being a nucleic acid, even if one or more of the nucleotides of the nucleic acid has been replaced by a modified nucleotide that lacks, or has a substitution of, an essential component of a nucleotide.

Modifications of the nucleic acid of the present invention generally provide a powerful tool in
35 overcoming potential limitations including, but not limited to, *in vitro* and *in vivo* stability and bioavailability inherent to native RNA molecules. The nucleic acids according to the invention may be modified by chemical modifications. Modified nucleic acids can also minimise the

possibility of inducing interferon activity in humans. Modifications can further enhance the functional delivery of a nucleic acid to a target cell. The modified nucleic acids of the present invention may comprise one or more chemically modified ribonucleotides of either or both of the first strand or the second strand. A ribonucleotide may comprise a chemical modification
5 of the base, sugar or phosphate moieties. The ribonucleic acid may be modified by substitution with or insertion of analogues of nucleic acids or bases.

Throughout the description of the invention, "same or common modification" means the same modification to any nucleotide, be that A, G, C or U modified with a group such as a methyl
10 group (2'-OMe) or a fluoro group (2'-F). For example, 2'-F-dU, 2'-F-dA, 2'-F-dC, 2'-F-dG are all considered to be the same or common modification, as are 2'-OMe-rU, 2'-OMe-rA; 2'-OMe-rC; 2'-OMe-rG. In contrast, a 2'-F modification is a different modification compared to a 2'-OMe modification.

15 Preferably, at least one nucleotide of the first and/or second strand of the nucleic acid is a modified nucleotide, preferably a non-naturally occurring nucleotide such as preferably a 2'-F modified nucleotide.

A modified nucleotide can be a nucleotide with a modification of the sugar group. The 2'
20 hydroxyl group (OH) can be modified or replaced with a number of different "oxy" or "deoxy" substituents.

Examples of "oxy"-2' hydroxyl group modifications include alkoxy or aryloxy (OR, e.g., R=H, alkyl (such as methyl), cycloalkyl, aryl, aralkyl, heteroaryl or sugar); polyethyleneglycols (PEG),
25 $O(CH_2CH_2O)_nCH_2CH_2OR$; "locked" nucleic acids (LNA) in which the 2' hydroxyl is connected, e.g., by a methylene bridge, to the 4' carbon of the same ribose sugar; O-AMINE (AMINE= NH_2 , alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino, ethylene diamine, or polyamino) and aminoalkoxy, $O(CH_2)_nAMINE$, (e.g., AMINE= NH_2 , alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl
30 amino, or diheteroaryl amino, ethylene diamine, or polyamino).

"Deoxy" modifications include hydrogen, halogen, amino (e.g., NH_2 , alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino, or amino acid);
35 $NH(CH_2CH_2NH)_nCH_2CH_2-AMINE$ (AMINE= NH_2 , alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino), $-NHC(O)R$ (R=alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar), cyano; mercapto; alkyl-thio-alkyl; thioalkoxy; and alkyl, cycloalkyl, aryl, alkenyl and alkynyl, which may be optionally substituted with e.g., an

amino functionality. Other substituents of certain embodiments include 2'-methoxyethyl, 2'-OCH₃, 2'-O-allyl, 2'-C-allyl, and 2'-fluoro.

5 The sugar group can also contain one or more carbons that possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, a modified nucleotide may contain a sugar such as arabinose.

Modified nucleotides can also include "abasic" sugars, which lack a nucleobase at C - 1'. These abasic sugars can further contain modifications at one or more of the constituent sugar atoms.

10

The 2' modifications may be used in combination with one or more phosphate internucleoside linker modifications (e.g., phosphorothioate or phosphorodithioate).

One or more nucleotides of a nucleic acid of the present invention may be modified. The nucleic acid may comprise at least one modified nucleotide. The modified nucleotide may be in the first strand. The modified nucleotide may be in the second strand. The modified nucleotide may be in the duplex region. The modified nucleotide may be outside the duplex region, i.e., in a single-stranded region. The modified nucleotide may be on the first strand and may be outside the duplex region. The modified nucleotide may be on the second strand and may be outside the duplex region. The 3'-terminal nucleotide of the first strand may be a modified nucleotide. The 3'-terminal nucleotide of the second strand may be a modified nucleotide. The 5'-terminal nucleotide of the first strand may be a modified nucleotide. The 5'-terminal nucleotide of the second strand may be a modified nucleotide.

15

20

25 A nucleic acid of the invention may have 1 modified nucleotide or a nucleic acid of the invention may have about 2-4 modified nucleotides, or a nucleic acid may have about 4-6 modified nucleotides, about 6-8 modified nucleotides, about 8-10 modified nucleotides, about 10-12 modified nucleotides, about 12-14 modified nucleotides, about 14-16 modified nucleotides about 16-18 modified nucleotides, about 18-20 modified nucleotides, about 20-22 modified nucleotides, about 22-24 modified nucleotides, about 24-26 modified nucleotides or about 26-28 modified nucleotides. In each case the nucleic acid comprising said modified nucleotides retains at least 50% of its activity as compared to the same nucleic acid but without said modified nucleotides or vice versa. The nucleic acid may retain 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% and intermediate values of its activity as compared to the same nucleic acid but without said modified nucleotides, or may have more than 100% of the activity of the same nucleic acid without said modified nucleotides.

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The modified nucleotide may be a purine or a pyrimidine. At least half of the purines may be modified. At least half of the pyrimidines may be modified. All of the purines may be modified. All of the pyrimidines may be modified. The modified nucleotides may be selected from the group consisting of a 3' terminal deoxy thymine (dT) nucleotide, a 2'-O-methyl (2'-OMe) modified nucleotide, a 2' modified nucleotide, a 2' deoxy modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2' amino modified nucleotide, a 2' alkyl modified nucleotide, a 2'-deoxy-2'-fluoro (2'-F) modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic and a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group.

The nucleic acid may comprise a nucleotide comprising a modified base, wherein the base is selected from 2-aminoadenosine, 2,6-diaminopurine, inosine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidine (e.g., 5-methylcytidine), 5-alkyluridine (e.g., ribothymidine), 5-halouridine (e.g., 5-bromouridine), 6-azapyrimidine, 6-alkylpyrimidine (e.g. 6-methyluridine), propyne, quesosine, 2-thiouridine, 4-thiouridine, wybutosine, wybutoxosine, 4-acetylcytidine, 5-(carboxyhydroxymethyl)uridine, 5'-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluridine, beta-D-galactosylqueosine, 1-methyladenosine, 1-methylinosine, 2,2-dimethylguanosine, 3-methylcytidine, 2-methyladenosine, 2-methylguanosine, N6-methyladenosine, 7-methylguanosine, 5-methoxyaminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylcarbonylmethyluridine, 5-methoxyuridine, 5-methyl-2-thiouridine, 2-methylthio-N6-isopentenyladenosine, beta-D-mannosylqueosine, uridine-5-oxyacetic acid and 2-thiocytidine.

Many of the modifications described herein and that occur within a nucleic acid will be repeated within a polynucleotide molecule, such as a modification of a base, or a phosphate moiety, or a non-linking O of a phosphate moiety. In some cases, the modification will occur at all of the possible positions/nucleotides in the polynucleotide but in many cases it will not. A modification may only occur at a 3' or 5' terminal position, may only occur in a terminal region, such as at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double-strand region, a single-strand region, or in both. A modification may occur only in the double-strand region of a nucleic acid of the invention or may only occur in a single-strand region of a nucleic acid of the invention. A phosphorothioate or phosphorodithioate modification at a non-linking O position may only occur at one or both termini, may only occur in a terminal region, e.g., at a position on a terminal nucleotide or in

the last 2, 3, 4 or 5 nucleotides of a strand, or may occur in duplex and/or in single-strand regions, particularly at termini. The 5' end and/or 3' end may be phosphorylated.

5 Stability of a nucleic acid of the invention may be increased by including particular bases in overhangs, or by including modified nucleotides, in single-strand overhangs, e.g., in a 5' or 3' overhang, or in both. Purine nucleotides may be included in overhangs. All or some of the bases in a 3' or 5' overhang may be modified. Modifications can include the use of
10 modifications at the 2' OH group of the ribose sugar, the use of deoxyribonucleotides, instead of ribonucleotides, and modifications in the phosphate group, such as phosphorothioate or phosphorodithioate modifications. Overhangs need not be homologous with the target sequence.

Nucleases can hydrolyse nucleic acid phosphodiester bonds. However, chemical
15 modifications to nucleic acids can confer improved properties, and, can render oligoribonucleotides more stable to nucleases.

Modified nucleic acids, as used herein, can include one or more of:

- (i) alteration, e.g., replacement, of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens (referred to as linking even if at the 5' and 3' terminus of the nucleic acid of the invention);
20
- (ii) alteration, e.g., replacement, of a constituent of the ribose sugar, e.g., of the 2' hydroxyl on the ribose sugar;
- (iii) replacement of the phosphate moiety with "dephospho" linkers;
- (iv) modification or replacement of a naturally occurring base;
- 25 (v) replacement or modification of the ribose-phosphate backbone; and
- (vi) modification of the 3' end or 5' end of the first strand and/or the second strand, e.g., removal, modification or replacement of a terminal phosphate group or conjugation of a moiety, e.g., a fluorescently labelled moiety, to either the 3' or 5' end of one or both strands.

30

The terms "replacement", "modification" and "alteration" indicate a difference from a naturally occurring molecule.

Specific modifications are discussed in more detail below.

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The nucleic acid may comprise one or more nucleotides on the second and/or first strands that are modified. Alternating nucleotides may be modified, to form modified nucleotides.

“Alternating” as described herein means to occur one after another in a regular way. In other words, alternating means to occur in turn repeatedly. For example, if one nucleotide is modified, the next contiguous nucleotide is not modified and the following contiguous nucleotide is modified and so on. One nucleotide may be modified with a first modification, the next contiguous nucleotide may be modified with a second modification and the following contiguous nucleotide is modified with the first modification and so on, where the first and second modifications are different.

Some representative modified nucleic acid sequences of the present invention are shown in the examples. These examples are meant to be representative and not limiting.

In one aspect of the nucleic acid, at least nucleotides 2 and 14 of the first strand are modified, preferably by a first common modification, the nucleotides being numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand. The first modification is preferably 2'-F.

In one aspect, at least one, several or preferably all the even-numbered nucleotides of the first strand are modified, preferably by a first common modification, the nucleotides being numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand. The first modification is preferably 2'-F.

In one aspect, at least one, several or preferably all the odd-numbered nucleotides of the first strand are modified, the nucleotides being numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand. Preferably, they are modified by a second modification. This second modification is preferably different from the first modification if the nucleic acid also comprises a first modification, for example of nucleotides 2 and 14 or of all the even-numbered nucleotides of the first strand. The first modification is preferably any 2' ribose modification that is of the same size or smaller in volume than a 2'-OH group, or a locked nucleic acid (LNA), or an unlocked nucleic acid (UNA), or a 2'-Fluoroarabino Nucleic Acid (FANA) modification. A 2' ribose modification that is of the same size or smaller in volume than a 2'-OH group can for example be a 2'-F, 2'-H, 2'-halo, or 2'-NH₂. The second modification is preferably any 2' ribose modification that is larger in volume than a 2'-OH group. A 2' ribose modification that is larger in volume than a 2'-OH group can for example be a 2'-OMe, 2'-O-MOE (2'-O-methoxyethyl), 2'-O-allyl or 2'-O-alkyl, with the proviso that the nucleic acid is capable of reducing the expression of the target gene to at least the same extent as the same nucleic acid without the modification(s) under comparable conditions. The first modification is preferably 2'-F and/or the second modification is preferably 2'-OMe.

In the context of this disclosure, the size or volume of a substituent, such as a 2' ribose modification, is preferably measured as the van der Waals volume.

In one aspect, at least one, several or preferably all the nucleotides of the second strand in a position corresponding to an even-numbered nucleotide of the first strand are modified, preferably by a third modification. Preferably in the same nucleic acid nucleotides 2 and 14 or all the even numbered nucleotides of the first strand are modified with a first modification. In addition, or alternatively, the odd-numbered nucleotides of the first strand are modified with a second modification. Preferably, the third modification is different from the first modification and/or the third modification is the same as the second modification. The first modification is preferably any 2' ribose modification that is of the same size or smaller in volume than a 2'-OH group, or a locked nucleic acid (LNA), or an unlocked nucleic acid (UNA), or a 2'-Fluoroarabino Nucleic Acid (FANA) modification. A 2' ribose modification that is of the same size or smaller in volume than a 2'-OH group can for example be a 2'-F, 2'-H, 2'-halo, or 2'-NH₂. The second and/or third modification is preferably any 2' ribose modification that is larger in volume than a 2'-OH group. A 2' ribose modification that is larger in volume than a 2'-OH group can for example be a 2'-OMe, 2'-O-MOE (2'-O-methoxyethyl), 2'-O-allyl or 2'-O-alkyl, with the proviso that the nucleic acid is capable of reducing the expression of the target gene to at least the same extent as the same nucleic acid without the modification(s) under comparable conditions. The first modification is preferably 2'-F and/or the second and/or third modification is/are preferably 2'-OMe. The nucleotides on the first strand are numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand.

A nucleotide of the second strand that is in a position corresponding, for example, to an even-numbered nucleotide of the first strand is a nucleotide of the second strand that is base-paired to an even-numbered nucleotide of the first strand.

In one aspect, at least one, several or preferably all the nucleotides of the second strand in a position corresponding to an odd-numbered nucleotide of the first strand are modified, preferably by a fourth modification. Preferably in the same nucleic acid nucleotides 2 and 14 or all the even numbered nucleotides of the first strand are modified with a first modification. In addition, or alternatively, the odd-numbered nucleotides of the first strand are modified with a second modification. In addition, or alternatively, all the nucleotides of the second strand in a position corresponding to an even-numbered nucleotide of the first strand are modified with a third modification. The fourth modification is preferably different from the second modification and preferably different from the third modification and the fourth modification is preferably the same as the first modification. The first and/or fourth modification is preferably any 2' ribose

modification that is of the same size or smaller in volume than a 2'-OH group, or a locked nucleic acid (LNA), or an unlocked nucleic acid (UNA), or a 2'-Fluoroarabino Nucleic Acid (FANA) modification. A 2' ribose modification that is of the same size or smaller in volume than a 2'-OH group can for example be a 2'-F, 2'-H, 2'-halo, or 2'-NH₂. The second and/or third
5 modification is preferably any 2' ribose modification that is larger in volume than a 2'-OH group. A 2' ribose modification that is larger in volume than a 2'-OH group can for example be a 2'-OMe, 2'-O-MOE (2'-O-methoxyethyl), 2'-O-allyl or 2'-O-alkyl, with the proviso that the nucleic acid is capable of reducing the expression of the target gene to at least the same extent as the same nucleic acid without the modification(s) under comparable conditions. The first and/or
10 the fourth modification is/are preferably a 2'-OMe modification and/or the second and/or third modification is/are preferably a 2'-F modification. The nucleotides on the first strand are numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand.

In one aspect of the nucleic acid, the nucleotide/nucleotides of the second strand in a position
15 corresponding to nucleotide 11 or nucleotide 13 or nucleotides 11 and 13 or nucleotides 11-13 of the first strand is/are modified by a fourth modification. Preferably, all the nucleotides of the second strand other than the nucleotide/nucleotides in a position corresponding to nucleotide 11 or nucleotide 13 or nucleotides 11 and 13 or nucleotides 11-13 of the first strand is/are modified by a third modification. Preferably in the same nucleic acid nucleotides 2 and
20 14 or all the even numbered nucleotides of the first strand are modified with a first modification. In addition, or alternatively, the odd-numbered nucleotides of the first strand are modified with a second modification. The fourth modification is preferably different from the second modification and preferably different from the third modification and the fourth modification is preferably the same as the first modification. The first and/or fourth modification is preferably
25 any 2' ribose modification that is of the same size or smaller in volume than a 2'-OH group, or a locked nucleic acid (LNA), or an unlocked nucleic acid (UNA), or a 2'-Fluoroarabino Nucleic Acid (FANA) modification. A 2' ribose modification that is of the same size or smaller in volume than a 2'-OH group can for example be a 2'-F, 2'-H, 2'-halo, or 2'-NH₂. The second and/or third modification is preferably any 2' ribose modification that is larger in volume than a 2'-OH group.
30 A 2' ribose modification that is larger in volume than a 2'-OH group can for example be a 2'-OMe, 2'-O-MOE (2'-O-methoxyethyl), 2'-O-allyl or 2'-O-alkyl, with the proviso that the nucleic acid is capable of reducing the expression of the target gene to at least the same extent as the same nucleic acid without the modification(s) under comparable conditions. The first and/or the fourth modification is/are preferably a 2'-OMe modification and/or the second and/or third
35 modification is/are preferably a 2'-F modification. The nucleotides on the first strand are numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand.

In one aspect of the nucleic acid, all the even-numbered nucleotides of the first strand are modified by a first modification, all the odd-numbered nucleotides of the first strand are modified by a second modification, all the nucleotides of the second strand in a position corresponding to an even-numbered nucleotide of the first strand are modified by a third
5 modification, all the nucleotides of the second strand in a position corresponding to an odd-numbered nucleotide of the first strand are modified by a fourth modification, wherein the first and/or fourth modification is/are 2'-F and/or the second and/or third modification is/are 2'-OMe.

In one aspect of the nucleic acid, all the even-numbered nucleotides of the first strand are
10 modified by a first modification, all the odd-numbered nucleotides of the first strand are modified by a second modification, all the nucleotides of the second strand in positions corresponding to nucleotides 11-13 of the first strand are modified by a fourth modification, all the nucleotides of the second strand other than the nucleotides corresponding to nucleotides 11-13 of the first strand are modified by a third modification, wherein the first and fourth
15 modification are 2'-F and the second and third modification are 2'-OMe. In one embodiment in this aspect, the 3' terminal nucleotide of the second strand is an inverted RNA nucleotide (i.e., the nucleotide is linked to the 3' end of the strand through its 3' carbon, rather than through its 5' carbon as would normally be the case). When the 3' terminal nucleotide of the second strand is an inverted RNA nucleotide, the inverted RNA nucleotide is preferably an unmodified
20 nucleotide in the sense that it does not comprise any modifications compared to the natural nucleotide counterpart. Specifically, the inverted RNA nucleotide is preferably a 2'-OH nucleotide. Preferably, in this aspect when the 3' terminal nucleotide of the second strand is an inverted RNA nucleotide, the nucleic acid is blunt-ended at least at the end that comprises the 5' end of the first strand.

25 One aspect of the present invention is a nucleic acid as disclosed herein for inhibiting expression of the CFB gene, preferably in a cell, wherein said first strand includes modified nucleotides or unmodified nucleotides at a plurality of positions in order to facilitate processing of the nucleic acid by RISC.

30 In one aspect, "facilitate processing by RISC" means that the nucleic acid can be processed by RISC, for example any modification present will permit the nucleic acid to be processed by RISC and preferably, will be beneficial to processing by RISC, suitably such that siRNA activity can take place.

35 A nucleic acid as disclosed herein, wherein the nucleotides at positions 2 and 14 from the 5' end of the first strand are not modified with a 2' OMe modification, and the

nucleotide/nucleotides on the second strand which corresponds to position 11 or position 13 or positions 11 and 13 or positions 11, 12 and 13 of the first strand is/are not modified with a 2'-OMe modification (in other words, they are not modified or are modified with a modification other than 2'-OMe).

5

In one aspect, the nucleotide on the second strand which corresponds to position 13 of the first strand is the nucleotide that forms a base pair with position 13 (from the 5' end) of the first strand.

10 In one aspect, the nucleotide on the second strand which corresponds to position 11 of the first strand is the nucleotide that forms a base pair with position 11 (from the 5' end) of the first strand.

In one aspect, the nucleotide on the second strand which corresponds to position 12 of the
15 first strand is the nucleotide that forms a base pair with position 12 (from the 5' end) of the first strand.

For example, in a 19-mer nucleic acid which is double-stranded and blunt ended, position 13 (from the 5' end) of the first strand would pair with position 7 (from the 5' end) of the second
20 strand. Position 11 (from the 5' end) of the first strand would pair with position 9 (from the 5' end) of the second strand. This nomenclature may be applied to other positions of the second strand.

In one aspect, in the case of a partially complementary first and second strand, the nucleotide
25 on the second strand that "corresponds to" a position on the first strand may not necessarily form a base pair if that position is the position in which there is a mismatch, but the principle of the nomenclature still applies.

One aspect is a nucleic acid as disclosed herein, wherein the nucleotides at positions 2 and
30 14 from the 5' end of the first strand are not modified with a 2'-OMe modification, and the nucleotides on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand are modified with a 2'-F modification.

One aspect is a nucleic acid as disclosed herein, wherein the nucleotides at positions 2 and
35 14 from the 5' end of the first strand are modified with a 2'-F modification, and the nucleotides on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand are not modified with a 2'-OMe modification.

One aspect is a nucleic acid as disclosed herein, wherein the nucleotides at positions 2 and 14 from the 5' end of the first strand are modified with a 2'-F modification, and the nucleotides on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand are modified with a 2'-F modification.

5

One aspect is a nucleic acid as disclosed herein wherein greater than 50% of the nucleotides of the first and/or second strand comprise a 2'-OMe modification, such as greater than 55%, 60%, 65%, 70%, 75%, 80%, or 85%, or more, of the first and/or second strand comprise a 2'-OMe modification, preferably measured as a percentage of the total nucleotides of both the first and second strands.

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One aspect is a nucleic acid as disclosed herein wherein greater than 50% of the nucleotides of the first and/or second strand comprise a naturally occurring RNA modification, such as wherein greater than 55%, 60%, 65%, 70%, 75%, 80%, or 85% or more of the first and/or second strands comprise such a modification, preferably measured as a percentage of the total nucleotides of both the first and second strands. Suitable naturally occurring modifications include, as well as 2'-OMe, other 2' sugar modifications, in particular a 2'-H modification resulting in a DNA nucleotide.

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One aspect is a nucleic acid as disclosed herein comprising no more than 20%, such as no more than 15% such as no more than 10%, of nucleotides which have 2' modifications that are not 2'-OMe modifications on the first and/or second strand, preferably as a percentage of the total nucleotides of both the first and second strands.

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One aspect is a nucleic acid as disclosed herein, wherein the number of nucleotides in the first and/or second strand with a 2'-modification that is not a 2'-OMe modification is no more than 7, more preferably no more than 5, and most preferably no more than 3.

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One aspect is a nucleic acid as disclosed herein comprising no more than 20%, (such as no more than 15% or no more than 10%) of 2'-F modifications on the first and/or second strand, preferably as a percentage of the total nucleotides of both strands.

30

One aspect is a nucleic acid as disclosed herein, wherein the number of nucleotides in the first and/or second strand with a 2'-F modification is no more than 7, more preferably no more than 5, and most preferably no more than 3.

35

One aspect is a nucleic acid as disclosed herein, wherein all nucleotides are modified with a 2'-OMe modification except positions 2 and 14 from the 5' end of the first strand and the nucleotides on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand. Preferably the nucleotides that are not modified with 2'-OMe are modified
5 with fluoro at the 2' position (2'-F modification).

In certain embodiments, a preferred aspect is a nucleic acid as disclosed herein wherein all nucleotides of the nucleic acid are modified at the 2' position of the sugar. Preferably these nucleotides are modified with a 2'-F modification where the modification is not a 2'-OMe
10 modification.

In one aspect the nucleic acid is modified on the first strand with alternating 2'-OMe modifications and 2-F modifications, and positions 2 and 14 (starting from the 5' end) are modified with 2'-F. Preferably the second strand is modified with 2'-F modifications at
15 nucleotides on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand. Preferably the second strand is modified with 2'-F modifications at positions 11-13 counting from the 3' end starting at the first position of the complementary (double-stranded) region, and the remaining modifications are naturally occurring modifications, preferably 2'-OMe. The complementary region at least in this case starts at the
20 first position of the second strand that has a corresponding nucleotide in the first strand, regardless of whether the two nucleotides are able to base pair to each other.

In one aspect of the nucleic acid, each of the nucleotides of the first strand and of the second strand is a modified nucleotide.
25

The term "odd numbered" as described herein means a number not divisible by two. Examples of odd numbers are 1, 3, 5, 7, 9, 11 and so on. The term "even numbered" as described herein means a number which is evenly divisible by two. Examples of even numbers are 2, 4, 6, 8, 10, 12, 14 and so on.
30

Unless specifically stated otherwise, herein the nucleotides of the first strand are numbered contiguously starting with nucleotide number 1 at the 5' end of the first strand. Nucleotides of the second strand are numbered contiguously starting with nucleotide number 1 at the 3' end of the second strand.
35

One or more nucleotides on the first and/or second strand may be modified, to form modified nucleotides. One or more of the odd-numbered nucleotides of the first strand may be modified.

One or more of the even-numbered nucleotides of the first strand may be modified by at least a second modification, wherein the at least second modification is different from the modification on the one or more odd nucleotides. At least one of the one or more modified even numbered-nucleotides may be adjacent to at least one of the one or more modified odd-
5 numbered nucleotides.

A plurality of odd-numbered nucleotides in the first strand may be modified in the nucleic acid of the invention. A plurality of even-numbered nucleotides in the first strand may be modified by a second modification. The first strand may comprise adjacent nucleotides that are modified
10 by a common modification. The first strand may also comprise adjacent nucleotides that are modified by a second different modification (i.e., the first strand may comprise nucleotides that are adjacent to each other and modified by a first modification as well as other nucleotides that are adjacent to each other and modified by a second modification that is different to the first modification).

15 One or more of the odd-numbered nucleotides of the second strand (wherein the nucleotides are numbered contiguously starting with nucleotide number 1 at the 3' end of the second strand) may be modified by a modification that is different to the modification of the odd-numbered nucleotides on the first strand (wherein the nucleotides are numbered contiguously
20 starting with nucleotide number 1 at the 5' end of the first strand) and/or one or more of the even-numbered nucleotides of the second strand may be modified by the same modification of the odd-numbered nucleotides of the first strand. At least one of the one or more modified even-numbered nucleotides of the second strand may be adjacent to the one or more modified odd-numbered nucleotides. A plurality of odd-numbered nucleotides of the second strand may
25 be modified by a common modification and/or a plurality of even-numbered nucleotides may be modified by the same modification that is present on the first strand odd-numbered nucleotides. A plurality of odd-numbered nucleotides on the second strand may be modified by a modification that is different from the modification of the first strand odd-numbered nucleotides.

30 The second strand may comprise adjacent nucleotides that are modified by a common modification, which may be a modification that is different from the modification of the odd-numbered nucleotides of the first strand.

35 In some aspects of the nucleic acid of the invention, each of the odd-numbered nucleotides in the first strand and each of the even-numbered nucleotides in the second strand may be modified with a common modification and, each of the even-numbered nucleotides may be

modified in the first strand with a different modification and each of the odd-numbered nucleotides may be modified in the second strand with the different modification.

5 The nucleic acid of the invention may have the modified nucleotides of the first strand shifted by at least one nucleotide relative to the unmodified or differently modified nucleotides of the second strand.

10 In certain aspects, one or more or each of the odd numbered-nucleotides may be modified in the first strand and one or more or each of the even-numbered nucleotides may be modified in the second strand. One or more or each of the alternating nucleotides on either or both strands may be modified by a second modification. One or more or each of the even-numbered nucleotides may be modified in the first strand and one or more or each of the even-numbered nucleotides may be modified in the second strand. One or more or each of the alternating nucleotides on either or both strands may be modified by a second modification. One or more or each of the odd-numbered nucleotides may be modified in the first strand and one or more of the odd-numbered nucleotides may be modified in the second strand by a common modification. One or more or each of the alternating nucleotides on either or both strands may be modified by a second modification. One or more or each of the even-numbered nucleotides may be modified in the first strand and one or more or each of the odd-numbered nucleotides may be modified in the second strand by a common modification. One or more or each of the alternating nucleotides on either or both strands may be modified by a second modification.

25 The nucleic acid of the invention may comprise single- or double-stranded constructs that comprise at least two regions of alternating modifications in one or both of the strands. These alternating regions can comprise up to about 12 nucleotides but preferably comprise from about 3 to about 10 nucleotides. The regions of alternating nucleotides may be located at the termini of one or both strands of the nucleic acid of the invention. The nucleic acid may comprise from 4 to about 10 nucleotides of alternating nucleotides at each of the termini (3' and 5') and these regions may be separated by from about 5 to about 12 contiguous unmodified or differently or commonly modified nucleotides.

35 The odd numbered nucleotides of the first strand may be modified and the even numbered nucleotides may be modified with a second modification. The second strand may comprise adjacent nucleotides that are modified with a common modification, which may be the same as the modification of the odd-numbered nucleotides of the first strand. One or more nucleotides of the second strand may also be modified with the second modification. One or more nucleotides with the second modification may be adjacent to each other and to

nucleotides having a modification that is the same as the modification of the odd-numbered nucleotides of the first strand. The first strand may also comprise phosphorothioate linkages between the two nucleotides at the 3' end and at the 5' end or a phosphorodithioate linkage between the two nucleotides at the 3' end. The second strand may comprise a
5 phosphorothioate or phosphorodithioate linkage between the two nucleotides at the 5' end. The second strand may also be conjugated to a ligand at the 5' end.

The nucleic acid of the invention may comprise a first strand comprising adjacent nucleotides that are modified with a common modification. One or more such nucleotides may be adjacent
10 to one or more nucleotides which may be modified with a second modification. One or more nucleotides with the second modification may be adjacent. The second strand may comprise adjacent nucleotides that are modified with a common modification, which may be the same as one of the modifications of one or more nucleotides of the first strand. One or more
15 nucleotides of the second strand may also be modified with the second modification. One or more nucleotides with the second modification may be adjacent. The first strand may also comprise phosphorothioate linkages between the two nucleotides at the 3' end and at the 5' end or a phosphorodithioate linkage between the two nucleotides at the 3' end. The second
strand may comprise a phosphorothioate or phosphorodithioate linkage between the two nucleotides at the 3' end. The second strand may also be conjugated to a ligand at the 5' end.

20 The nucleotides numbered from 5' to 3' on the first strand and 3' to 5' on the second strand, 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 and 25 may be modified by a modification on the first strand. The nucleotides numbered 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 may be modified by a second modification on the first strand. The nucleotides numbered 1, 3, 5, 7, 9, 11, 13,
25 15, 17, 19, 21, 23 may be modified by a modification on the second strand. The nucleotides numbered 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 may be modified by a second modification on the second strand. Nucleotides are numbered for the sake of the nucleic acid of the present invention from 5' to 3' on the first strand and 3' to 5' on the second strand.

30 The nucleotides numbered 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 may be modified by a modification on the first strand. The nucleotides numbered 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 may be modified by a second modification on the first strand. The nucleotides numbered 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 may be modified by a modification on the second strand. The nucleotides numbered 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 may be modified by a
35 second modification on the second strand.

Clearly, if the first and/or the second strand are shorter than 25 nucleotides in length, such as 19 nucleotides in length, there are no nucleotides numbered 20, 21, 22, 23, 24 and 25 to be modified. The skilled person understands the description above to apply to shorter strands, accordingly.

5

One or more modified nucleotides on the first strand may be paired with modified nucleotides on the second strand having a common modification. One or more modified nucleotides on the first strand may be paired with modified nucleotides on the second strand having a different modification. One or more modified nucleotides on the first strand may be paired with unmodified nucleotides on the second strand. One or more modified nucleotides on the second strand may be paired with unmodified nucleotides on the first strand. In other words, the alternating nucleotides can be aligned on the two strands such as, for example, all the modifications in the alternating regions of the second strand are paired with identical modifications in the first strand or alternatively the modifications can be offset by one nucleotide with the common modifications in the alternating regions of one strand pairing with dissimilar modifications (i.e., a second or further modification) in the other strand. Another option is to have dissimilar modifications in each of the strands.

The modifications on the first strand may be shifted by one nucleotide relative to the modified nucleotides on the second strand, such that common modified nucleotides are not paired with each other.

The modification and/or modifications may each and individually be selected from the group consisting of 3' terminal deoxy thymine, 2'-OMe, a 2' deoxy modification, a 2' amino modification, a 2' alkyl modification, a morpholino modification, a phosphoramidate modification, 5'-phosphorothioate group modification, a 5' phosphate or 5' phosphate mimic modification and a cholesteryl derivative or a dodecanoic acid bisdecylamide group modification and/or the modified nucleotide may be any one of a locked nucleotide, an abasic nucleotide or a non-natural base comprising nucleotide.

30

At least one modification may be 2'-OMe and/or at least one modification may be 2'-F. Further modifications as described herein may be present on the first and/or second strand.

The nucleic acid of the invention may comprise an inverted RNA nucleotide at one or several of the strand ends. Such inverted nucleotides provide stability to the nucleic acid. Preferably, the nucleic acid comprises at least an inverted nucleotide at the 3' end of the first and/or the second strand and/or at the 5' end of the second strand. More preferably, the nucleic acid

35

comprises an inverted nucleotide at the 3' end of the second strand. Most preferably, the nucleic acid comprises an inverted RNA nucleotide at the 3' end of the second strand and this nucleotide is preferably an inverted A. An inverted nucleotide is a nucleotide that is linked to the 3' end of a nucleic acid through its 3' carbon, rather than its 5' carbon as would normally be the case or is linked to the 5' end of a nucleic acid through its 5' carbon, rather than its 3' carbon as would normally be the case. The inverted nucleotide is preferably present at an end of a strand not as an overhang but opposite a corresponding nucleotide in the other strand. Accordingly, the nucleic acid is preferably blunt-ended at the end that comprises the inverted RNA nucleotide. An inverted RNA nucleotide being present at the end of a strand preferably means that the last nucleotide at this end of the strand is the inverted RNA nucleotide. A nucleic acid with such a nucleotide is stable and easy to synthesise. The inverted RNA nucleotide is preferably an unmodified nucleotide in the sense that it does not comprise any modifications compared to the natural nucleotide counterpart. Specifically, the inverted RNA nucleotide is preferably a 2'-OH nucleotide.

Nucleic acids of the invention may comprise one or more nucleotides modified at the 2' position with a 2'-H, and therefore having a DNA nucleotide within the nucleic acid. Nucleic acids of the invention may comprise DNA nucleotides at positions 2 and/or 14 of the first strand counting from the 5' end of the first strand. Nucleic acids may comprise DNA nucleotides on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand.

In one aspect there is no more than one DNA nucleotide per nucleic acid of the invention.

Nucleic acids of the invention may comprise one or more LNA nucleotides. Nucleic acids of the invention may comprise LNA nucleotides at positions 2 and/or 14 of the first strand counting from the 5' end of the first strand. Nucleic acids may comprise LNA on the second strand which correspond to position 11, or 13, or 11 and 13, or 11-13 of the first strand.

Some representative modified nucleic acid sequences of the present invention are shown in the examples. These examples are meant to be representative and not limiting.

In certain preferred embodiments, the nucleic acid may comprise a first modification and a second or further modification which are each and individually selected from the group comprising 2'-OMe modification and 2'-F modification. The nucleic acid may comprise a modification that is 2'-OMe that may be a first modification, and a second modification that is 2'-F. The nucleic acid of the invention may also include a phosphorothioate or

phosphorodithioate modification and/or a deoxy modification which may be present in or between the terminal 2 or 3 nucleotides of each or any end of each or both strands.

In one aspect of the nucleic acid, at least one nucleotide of the first and/or second strand is a modified nucleotide, wherein if the first strand comprises at least one modified nucleotide:

- (i) at least one or both of the nucleotides 2 and 14 of the first strand is/are modified by a first modification; and/or
- (ii) at least one, several, or all the even-numbered nucleotides of the first strand is/are modified by a first modification; and/or
- 10 (iii) at least one, several, or all the odd-numbered nucleotides of the first strand is/are modified by a second modification; and/or

wherein if the second strand comprises at least one modified nucleotide:

- (iv) at least one, several, or all the nucleotides of the second strand in a position corresponding to an even-numbered nucleotide of the first strand is/are modified by a third modification; and/or
- 15 (v) at least one, several, or all the nucleotides of the second strand in a position corresponding to an odd-numbered nucleotide of the first strand is/are modified by a fourth modification; and/or
- (vi) at least one, several, or all the nucleotides of the second strand in a position corresponding to nucleotide 11 or nucleotide 13 or nucleotides 11 and 13 or nucleotides 11-13 of the first strand is/are modified by a fourth modification; and/or
- 20 (vii) at least one, several, or all the nucleotides of the second strand in a position other than the position corresponding to nucleotide 11 or nucleotide 13 or nucleotides 11 and 13 or nucleotides 11-13 of the first strand is/are modified by a third modification;

- 25 wherein the nucleotides on the first strand are numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand;

wherein the modifications are preferably at least one of the following:

- (a) the first modification is preferably different from the second and from the third modification;
- 30 (b) the first modification is preferably the same as the fourth modification;
- (c) the second and the third modification are preferably the same modification;
- (d) the first modification is preferably a 2'-F modification;
- (e) the second modification is preferably a 2'-OMe modification;
- (f) the third modification is preferably a 2'-OMe modification; and/or
- 35 (g) the fourth modification is preferably a 2'-F modification; and

wherein optionally the nucleic acid is conjugated to a ligand.

One aspect is a double-stranded nucleic acid for inhibiting expression of CFB, preferably in a cell, wherein the nucleic acid comprises a first strand and a second strand, wherein the unmodified equivalent of the first strand sequence comprises a sequence of at least 15 nucleotides differing by no more than 3 nucleotides from any one of the first strand sequences shown in Table 5a, or in Table 1, wherein all the even-numbered nucleotides of the first strand are modified by a first modification, all the odd-numbered nucleotides of the first strand are modified by a second modification, all the nucleotides of the second strand in a position corresponding to an even-numbered nucleotide of the first strand are modified by a third modification, all the nucleotides of the second strand in a position corresponding to an odd-numbered nucleotide of the first strand are modified by a fourth modification, wherein the first and fourth modification are 2'-F and the second and third modification are 2'-OMe.

One aspect is a double-stranded nucleic acid for inhibiting expression of CFB, preferably in a cell, wherein the nucleic acid comprises a first strand and a second strand, wherein the unmodified equivalent of the first strand sequence comprises a sequence of at least 15 nucleotides differing by no more than 3 nucleotides from any one of the first strand sequences shown in Table 5a, or in Table 1, wherein all the even-numbered nucleotides of the first strand are modified by a first modification, all the odd-numbered nucleotides of the first strand are modified by a second modification, all the nucleotides of the second strand in positions corresponding to nucleotides 11-13 of the first strand are modified by a fourth modification, all the nucleotides of the second strand other than the nucleotides corresponding to nucleotides 11-13 of the first strand are modified by a third modification, wherein the first and fourth modification are 2'-F and the second and third modification are 2'-OMe.

The 3' and 5' ends of an oligonucleotide can be modified. Such modifications can be at the 3' end or the 5' end or both ends of the molecule. They can include modification or replacement of an entire terminal phosphate or of one or more of the atoms of the phosphate group. For example, the 3' and 5' ends of an oligonucleotide can be conjugated to other functional molecular entities such as labelling moieties, e.g., fluorophores (e.g., pyrene, TAMRA, fluorescein, Cy3 or Cy5 dyes) or protecting groups (based e.g., on sulfur, silicon, boron or ester). The functional molecular entities can be attached to the sugar through a phosphate group and/or a linker. The terminal atom of the linker can connect to or replace the linking atom of the phosphate group or the C-3' or C-5' O, N, S or C group of the sugar. Alternatively, the linker can connect to or replace the terminal atom of a nucleotide surrogate (e.g., PNAs). These spacers or linkers can include e.g., $-(CH_2)_n-$, $-(CH_2)_nN-$, $-(CH_2)_nO-$, $-(CH_2)_nS-$, $-(CH_2CH_2O)_nCH_2CH_2O-$ (e.g., $n=3$ or 6), abasic sugars, amide, carboxy, amine, oxyamine,

oximine, thioether, disulfide, thiourea, sulfonamide, or morpholino, or biotin and fluorescein reagents. The 3' end can be an —OH group.

Other examples of terminal modifications include dyes, intercalating agents (e.g., acridines),
 5 cross-linkers (e.g., psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin),
 polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial
 endonucleases, EDTA, lipophilic carriers (e.g., cholesterol, cholic acid, adamantane acetic
 acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol,
 geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl
 10 group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid,
 dimethoxytrityl, or phenoxazine) and peptide conjugates (e.g., antennapedia peptide, Tat
 peptide), alkylating agents, phosphate, amino, mercapto, PEG (e.g., PEG-40K), MPEG,
 [MPEG]2, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g.,
 biotin), transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid), synthetic
 15 ribonucleases (e.g., imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole
 conjugates, Eu3+ complexes of tetraazamacrocycles).

Terminal modifications can also be useful for monitoring distribution, and in such cases the
 groups to be added may include fluorophores, e.g., fluorescein or an Alexa dye. Terminal
 20 modifications can also be useful for enhancing uptake, useful modifications for this include
 cholesterol. Terminal modifications can also be useful for cross-linking an RNA agent to
 another moiety.

Terminal modifications can be added for a number of reasons, including to modulate activity
 25 or to modulate resistance to degradation. Terminal modifications useful for modulating activity
 include modification of the 5' end with phosphate or phosphate analogues. Nucleic acids of the
 invention, on the first or second strand, may be 5' phosphorylated or include a phosphoryl
 analogue at the 5' prime terminus. 5'-phosphate modifications include those which are
 compatible with RISC mediated gene silencing. Suitable modifications include: 5'-
 30 monophosphate ((HO)₂(O)P—O-5'); 5'-diphosphate ((HO)₂(O)P—O—P(HO)(O)—O-5'); 5'-
 triphosphate ((HO)₂(O)P—O—(HO)(O)P—O—P(HO)(O)—O-5'); 5'-guanosine cap (7-
 methylated or non-methylated) (7m-G-O-5'-(HO)(O)P—O—(HO)(O)P—O—P(HO)(O)—O-5');
 5'-adenosine cap (Appp), and any modified or unmodified nucleotide cap structure (N—O-5'-
 (HO)(O)P—O—(HO)(O)P—O—P(HO)(O)—O-5'); 5'-monothiophosphate (phosphorothioate;
 35 (HO)₂(S)P—O-5'); 5'-monodithiophosphate (phosphorodithioate; (HO)(HS)(S)P—O-5'), 5'-
 phosphorothiolate ((HO)₂(O)P—S-5'); any additional combination of oxygen/sulfur replaced
 monophosphate, diphosphate and triphosphates (e.g., 5'-alpha-thiotriphosphate, 5'-gamma-

thiotriphosphate, etc.), 5'-phosphoramidates ((HO)₂(O)P—NH-5', (HO)(NH₂)(O)P—O-5'), 5'-alkylphosphonates (alkyl=methyl, ethyl, isopropyl, propyl, etc., e.g., RP(OH)(O)—O-5' (wherein R is an alkyl), (OH)₂(O)P-5'-CH₂-), 5' vinylphosphonate, 5'-alkyletherphosphonates (alkylether=methoxymethyl (MeOCH₂-), ethoxymethyl, etc., e.g. RP(OH)(O)—O-5' (wherein R is an alkylether)).

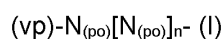
Certain moieties may be linked to the 5' terminus of the first strand or the second strand. These include abasic ribose moiety, abasic deoxyribose moiety, modifications abasic ribose and abasic deoxyribose moieties including 2'-O alkyl modifications; inverted abasic ribose and abasic deoxyribose moieties and modifications thereof, C6-imino-Pi; a mirror nucleotide including L-DNA and L-RNA; 5'OMe nucleotide; and nucleotide analogues including 4',5'-methylene nucleotide; 1-(β-D-erythrofuransyl)nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate, 3-aminopropyl phosphate; 6-aminohexyl phosphate; 12-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; alpha-nucleotide; threo-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted abasic moiety; 1,4-butanediol phosphate; 5'-amino; and bridging or non-bridging methylphosphonate and 5'-mercapto moieties.

In each sequence described herein, a C-terminal “—OH” moiety may be substituted for a C-terminal “—NH₂” moiety, and vice-versa.

The invention also provides a nucleic acid according to any aspect of the invention described herein, wherein the first strand has a terminal 5' (E)-vinylphosphonate nucleotide at its 5' end. This terminal 5' (E)-vinylphosphonate nucleotide is preferably linked to the second nucleotide in the first strand by a phosphodiester linkage. Preferably, the terminal 5' (E)-vinylphosphonate (“vp”) nucleotide is an uridine (“vp-U”).

The first strand of the nucleic acid may comprise formula (I):

30

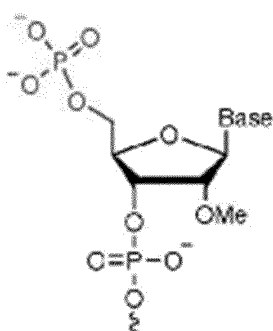


where ‘(vp)-’ is the 5' (E)-vinylphosphonate, ‘N’ is a nucleotide, ‘po’ is a phosphodiester linkage, and n is from 1 to (the total number of nucleotides in the first strand – 2), preferably wherein n is from 1 to (the total number of nucleotides in the first strand -3), more preferably wherein n is from 1 to (the total number of nucleotides in the first strand -4).

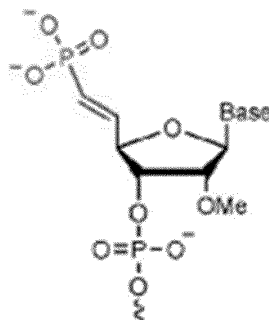
35

Preferably, the terminal 5' (E)-vinylphosphonate nucleotide is an RNA nucleotide, preferably a (vp)-U.

- 5 A terminal 5' (E)-vinylphosphonate nucleotide is a nucleotide wherein the natural phosphate group at the 5'-end has been replaced with a E-vinylphosphonate, in which the bridging 5'-oxygen atom of the terminal nucleotide of the 5' phosphorylated strand is replaced with a methynyl (-CH=) group:



Nucleotides with a natural phosphate
at the 5'-end



Nucleotide with a E-vinylphosphonate at
at the 5'-end

- 20 A 5' (E)-vinylphosphonate is a 5' phosphate mimic. A biological mimic is a molecule that is capable of carrying out the same function as and is structurally very similar to the original molecule that is being mimicked. In the context of the present invention, 5' (E)-vinylphosphonate mimics the function of a normal 5' phosphate, e.g., enabling efficient RISC loading. In addition, because of its slightly altered structure, 5' (E) vinylphosphonate is capable of stabilizing the 5'-end nucleotide by protecting it from dephosphorylation by enzymes such as phosphatases.
- 25

- In one aspect, the first strand has a terminal 5' (E)-vinylphosphonate nucleotide at its 5' end, the terminal 5' (E)-vinylphosphonate nucleotide is linked to the second nucleotide in the first strand by a phosphodiester linkage and the first strand comprises a) more than 1 phosphodiester linkage; b) phosphodiester linkages between at least the terminal three 5' nucleotides and/or c) phosphodiester linkages between at least the terminal four 5' nucleotides.
- 30

- 35 In one aspect, the first strand and/or the second strand of the nucleic acid comprises at least one phosphorothioate (ps) and/or at least one phosphorodithioate (ps2) linkage between two nucleotides.

In one aspect, the first strand and/or the second strand of the nucleic acid comprises more than one phosphorothioate and/or more than one phosphorodithioate linkage.

5 In one aspect, the first strand and/or the second strand of the nucleic acid comprises a phosphorothioate or phosphorodithioate linkage between the terminal two 3' nucleotides or phosphorothioate or phosphorodithioate linkages between the terminal three 3' nucleotides. Preferably, the linkages between the other nucleotides in the first strand and/or the second strand are phosphodiester linkages.

10 In one aspect, the first strand and/or the second strand of the nucleic acid comprises a phosphorothioate linkage between the terminal two 5' nucleotides or a phosphorothioate linkages between the terminal three 5' nucleotides.

15 In one aspect, the nucleic acid of the present invention comprises one or more phosphorothioate or phosphorodithioate modifications on one or more of the terminal ends of the first and/or the second strand. Optionally, each or either end of the first strand may comprise one or two or three phosphorothioate or phosphorodithioate modified nucleotides (internucleoside linkage). Optionally, each or either end of the second strand may comprise one or two or three phosphorothioate or phosphorodithioate modified nucleotides
20 (internucleoside linkage).

In one aspect, the nucleic acid comprises a phosphorothioate linkage between the terminal two or three 3' nucleotides and/or 5' nucleotides of the first and/or the second strand. Preferably, the nucleic acid comprises a phosphorothioate linkage between each of the
25 terminal three 3' nucleotides and the terminal three 5' nucleotides of the first strand and of the second strand. Preferably, all remaining linkages between nucleotides of the first and/or of the second strand are phosphodiester linkages.

In one aspect, the nucleic acid comprises a phosphorodithioate linkage between each of the
30 two, three or four terminal nucleotides at the 3' end of the first strand and/or comprises a phosphorodithioate linkage between each of the two, three or four terminal nucleotides at the 3' end of the second strand and/or a phosphorodithioate linkage between each of the two, three or four terminal nucleotides at the 5' end of the second strand and comprises a linkage other than a phosphorodithioate linkage between the two, three or four terminal nucleotides at
35 the 5' end of the first strand.

In one aspect, the nucleic acid comprises a phosphorothioate linkage between the terminal three 3' nucleotides and the terminal three 5' nucleotides of the first strand and of the second strand. Preferably, all remaining linkages between nucleotides of the first and/or of the second strand are phosphodiester linkages.

5

In one aspect, the nucleic acid:

- (i) has a phosphorothioate linkage between the terminal three 3' nucleotides and the terminal three 5' nucleotides of the first strand;
- (ii) is conjugated to a triantennary ligand either on the 3' end nucleotide or on the 5' end nucleotide of the second strand;
- (iii) has a phosphorothioate linkage between the terminal three nucleotides of the second strand at the end opposite to the one conjugated to the triantennary ligand; and
- (iv) optionally all remaining linkages between nucleotides of the first and/or of the second strand are phosphodiester linkages.

15

In one aspect, the nucleic acid:

- (i) has a terminal 5' (E)-vinylphosphonate nucleotide at the 5' end of the first strand;
- (ii) has a phosphorothioate linkage between the terminal three 3' nucleotides on the first and second strand and between the terminal three 5' nucleotides on the second strand or it has a phosphorodithioate linkage between the terminal two 3' nucleotides on the first and second strand and between the terminal two 5' nucleotides on the second strand; and
- (iii) optionally all remaining linkages between nucleotides of the first and/or of the second strand are phosphodiester linkages.

25

In one aspect, the nucleic acid has a terminal 5' (E)-vinylphosphonate nucleotide at the 5' end of the first strand and has a phosphorothioate linkage between the terminal three 3' nucleotides on the first and between the terminal three 3' nucleotides on the second strand; and optionally all remaining linkages between nucleotides of the first and/or of the second strand are phosphodiester linkages.

30

The use of a phosphorodithioate linkage in the nucleic acid of the invention reduces the variation in the stereochemistry of a population of nucleic acid molecules compared to molecules comprising a phosphorothioate in that same position. Phosphorothioate linkages introduce chiral centres and it is difficult to control which non-linking oxygen is substituted for sulphur. The use of a phosphorodithioate ensures that no chiral centre exists in that linkage and thus reduces or eliminates any variation in the population of nucleic acid molecules,

35

depending on the number of phosphorodithioate and phosphorothioate linkages used in the nucleic acid molecule.

In one aspect, the nucleic acid comprises a phosphorodithioate linkage between the two
5 terminal nucleotides at the 3' end of the first strand and a phosphorodithioate linkage between
the two terminal nucleotides at the 3' end of the second strand and a phosphorodithioate
linkage between the two terminal nucleotides at the 5' end of the second strand and comprises
a linkage other than a phosphorodithioate linkage between the two, three or four terminal
10 nucleotides at the 5' end of the first strand. Preferably, the first strand has a terminal 5' (E)-
vinylphosphonate nucleotide at its 5' end. This terminal 5' (E)-vinylphosphonate nucleotide is
preferably linked to the second nucleotide in the first strand by a phosphodiester linkage.
Preferably, all the linkages between the nucleotides of both strands other than the linkage
between the two terminal nucleotides at the 3' end of the first strand and the linkages between
15 the two terminal nucleotides at the 3' end and at the 5' end of the second strand are
phosphodiester linkages.

In one aspect, the nucleic acid comprises a phosphorothioate linkage between each of the
three terminal 3' nucleotides and/or between each of the three terminal 5' nucleotides on the
first strand, and/or between each of the three terminal 3' nucleotides and/or between each of
20 the three terminal 5' nucleotides of the second strand when there is no phosphorodithioate
linkage present at that end. No phosphorodithioate linkage being present at an end means that
the linkage between the two terminal nucleotides, or preferably between the three terminal
nucleotides of the nucleic acid end in question are linkages other than phosphorodithioate
linkages.

25 In one aspect, all the linkages of the nucleic acid between the nucleotides of both strands other
than the linkage between the two terminal nucleotides at the 3' end of the first strand and the
linkages between the two terminal nucleotides at the 3' end and at the 5' end of the second
strand are phosphodiester linkages.

30 Other phosphate linkage modifications are possible.

The phosphate linker can also be modified by replacement of a linking oxygen with nitrogen
(bridged phosphoroamidates), sulfur (bridged phosphorothioates) and carbon (bridged
35 methylenephosphonates). The replacement can occur at a terminal oxygen. Replacement of
the non-linking oxygens with nitrogen is possible.

The phosphate groups can also individually be replaced by non-phosphorus containing connectors.

Examples of moieties which can replace the phosphate group include siloxane, carbonate, carboxymethyl, carbamate, amide, thioether, ethylene oxide linker, sulfonate, sulfonamide, thioformacetal, formacetal, oxime, methyleneimino, methylenemethylimino, methylenehydrazo, methylenedimethylhydrazo and methyleneoxymethylimino. In certain embodiments, replacements may include the methylenecarbonylamino and methylenemethylimino groups.

10

The phosphate linker and ribose sugar may be replaced by nuclease resistant nucleotides. Examples include the morpholino, cyclobutyl, pyrrolidine and peptide nucleic acid (PNA) nucleoside surrogates. In certain embodiments, PNA surrogates may be used.

15 In one aspect, the nucleic acid, which is preferably an siRNA that inhibits expression of CFB, preferably via RNAi, and preferably in a cell, comprises one or more or all of:

- (i) a modified nucleotide;
- (ii) a modified nucleotide other than a 2'-OMe modified nucleotide at positions 2 and 14 from the 5' end of the first strand, preferably a 2'-F modified nucleotide;
- 20 (iii) each of the odd-numbered nucleotides of the first strand as numbered starting from one at the 5' end of the first strand are 2'-OMe modified nucleotides;
- (iv) each of the even-numbered nucleotides of the first strand as numbered starting from one at the 5' end of the first strand are 2'-F modified nucleotides;
- (v) the second strand nucleotide corresponding to position 11 and/or 13 or 11-13 of the first strand is modified by a modification other than a 2'-OMe modification, preferably wherein one or both or all of these positions comprise a 2'-F modification;
- 25 (vi) an inverted nucleotide, preferably a 3'-3' linkage at the 3' end of the second strand;
- (vii) one or more phosphorothioate linkages;
- (viii) one or more phosphorodithioate linkages; and/or
- 30 (ix) the first strand has a terminal 5' (E)-vinylphosphonate nucleotide at its 5' end, in which case the terminal 5' (E)-vinylphosphonate nucleotide is preferably a uridine and is preferably linked to the second nucleotide in the first strand by a phosphodiester linkage.

A nucleic acid of the present disclosure may comprise a first strand and a second strand, wherein the first strand sequence comprises a sequence of at least 15 nucleotides differing by no more than 3 nucleotides from any one of the first strand sequences shown in Table 5b.

35

A nucleic acid of the present disclosure may be a nucleic acid wherein:

- (a) the first strand sequence comprises a sequence differing by no more than 3 nucleotides from any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence differing by no more than 3 nucleotides from the corresponding second strand sequence;
- (b) the first strand sequence comprises a sequence differing by no more than 2 nucleotides from any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence differing by no more than 2 nucleotides from the corresponding second strand sequence;
- (c) the first strand sequence comprises a sequence differing by no more than 1 nucleotide from any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence differing by no more than 1 nucleotide from the corresponding second strand sequence;
- (d) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of the corresponding second strand sequence;
- (e) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of the corresponding second strand sequence;
- (f) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of the corresponding second strand sequence;
- (g) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 1 to 18 from the 5' end of the corresponding second strand sequence;
- (h) the first strand sequence comprises a sequence of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence of the corresponding second strand sequence;
- (i) the first strand sequence consists of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence consists of the sequence of the corresponding second strand sequence;
- (j) the first strand sequence consists essentially of any one of the first strand sequences with a given SEQ ID No. shown in Table 5b, and optionally wherein the second strand

- sequence consists essentially of the sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 5b; or
- (k) the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 5b,
- 5 wherein said first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 5b, and
- 10 optionally wherein the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 5b;
- (l) the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 5b,
- 15 wherein said first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 5b, and
- 20 wherein said first strand sequence consists of a contiguous region of from 17-25 nucleotides in length, preferably of from 18-24 nucleotides in length, complementary to the CFB transcript of SEQ ID NO. 758, and
- 25 optionally wherein the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 5b;
- (m) the first strand and the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are present on a single strand wherein the first strand and the second strand are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length; or
- 30 (n) the first strand and the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are on two separate strands that are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length.
- 35

A nucleic acid of the present disclosure may comprise a first strand and a second strand, wherein the first strand sequence comprises a sequence of at least 15 nucleotides differing by no more than 3 nucleotides from any one of the first strand sequences shown in Table 2.

5 For example, a nucleic acid of the present disclosure may be a nucleic acid wherein:

- (a) the first strand sequence comprises a sequence differing by no more than 3 nucleotides from any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence differing by no more than 3 nucleotides from the corresponding second strand sequence;
- 10 (b) the first strand sequence comprises a sequence differing by no more than 2 nucleotides from any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence differing by no more than 2 nucleotides from the corresponding second strand sequence;
- (c) the first strand sequence comprises a sequence differing by no more than 1 nucleotide from any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence differing by no more than 1 nucleotide from the corresponding second strand sequence;
- 15 (d) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of the corresponding second strand sequence;
- 20 (e) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of the corresponding second strand sequence;
- 25 (f) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of the corresponding second strand sequence;
- 30 (g) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 1 to 18 from the 5' end of the corresponding second strand sequence;
- 35 (h) the first strand sequence comprises a sequence of any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence of the corresponding second strand sequence;

- (i) the first strand sequence consists of any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence consists of the sequence of the corresponding second strand sequence;
- (j) the first strand sequence consists essentially of any one of the first strand sequences with a given SEQ ID No. shown in Table 2, and optionally wherein the second strand sequence consists essentially of the sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 2; or
- (k) the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 2, wherein said first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 2, and optionally wherein the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 2;
- (l) the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 2, wherein said first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 2, and wherein said first strand sequence consists of a contiguous region of from 17-25 nucleotides in length, preferably of from 18-24 nucleotides in length, complementary to the CFB transcript of SEQ ID NO. 758, and optionally wherein the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 2;
- (m) the first strand and the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are present on a single strand wherein the first strand and the second strand are able to hybridise to each other and to thereby form a double stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length; or

- (n) the first strand and the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are on two separate strands that are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length.

5

Table 2:

First strand sequence (SEQ ID No.)	Second strand sequence (SEQ ID No.)
417	725
431	726
655	728
561	729
407	730
679	733
609	739
740	730
741	728
742	729
746	726
750	725
740	759
742	760

All the features of the nucleic acids can be combined with all other aspects of the invention disclosed herein.

10

Heterologous moieties

The nucleic acids of the invention may be conjugated to a heterologous moiety. A heterologous moiety is any moiety which is not a nucleic acid molecule capable of inhibiting expression of CFB. A heterologous moiety may be, or may comprise, a peptide (or polypeptide), a saccharide (or polysaccharide), a lipid, a different nucleic acid, or any other suitable molecule.

15

Any given nucleic acid may be conjugated to a plurality of heterologous moieties, which may be the same or different.

20

An individual heterologous moiety may itself comprise one or more functional moieties (such as targeting agents as described in more detail below), each optionally covalently associated to the nucleic acid via a linker.

A heterologous moiety, or the functional component thereof, may serve for example to modulate bioavailability or pharmacokinetics. For example, it may increase half life *in vivo*.

Alternatively, a heterologous moiety (or the functional component thereof) may comprise a targeting agent. Efficient delivery of oligonucleotides, in particular double-stranded nucleic acids of the invention, to cells *in vivo* is important and requires specific targeting and substantial protection from the extracellular environment, particularly serum proteins. One method of achieving specific targeting is to conjugate a targeting agent to the nucleic acid, wherein the targeting agent helps in targeting the nucleic acid to a target cell which has a cell surface receptor that binds to the targeting agent.

In this context, the term "receptor" is used to include any molecule on the surface of a target cell capable of binding to the targeting agent, and should not be taken to imply any particular function for the cell surface receptor. The targeting agent may be regarded as a "ligand" for the cell surface receptor. The terms "targeting agent" and "ligand" may be used interchangeably. Again, this terminology should not be taken to imply any particular function for the targeting agent or the cell surface receptor, or any particular relationship between the two molecules other than the ability of one to bind to the other.

Thus, the targeting agent may be any moiety having affinity for the chosen receptor. It may, for example, be an affinity protein (such as an antibody or a fragment thereof having affinity for the chosen receptor), an aptamer, or any other suitable moiety. In some embodiments, the targeting agent may be a physiological ligand for the receptor.

Binding between the targeting agent and the receptor may promote uptake of the conjugated nucleic acid by the target cell, e.g., via internalisation of the receptor, or any other suitable mechanism. Thus appropriate ligands for the desired receptor molecules may be used as targeting agents in order for the conjugated nucleic acids to be taken up by the target cells by mechanisms such as different receptor-mediated endocytosis pathways or functionally analogous processes. In other embodiments, a ligand which can mediate internalization of the nucleic acid into a target cell by mechanisms other than receptor mediated endocytosis may alternatively be conjugated to a nucleic acid of the invention for cell or tissue specific targeting.

One example of a ligand that mediates receptor mediated endocytosis is the GalNAc moiety described herein, which has high affinity to the asialoglycoprotein receptor complex (ASGP-R). The ASGP-R complex is composed of varying ratios of multimers of membrane ASGR1 and ASGR2 receptors, which are highly abundant on hepatocytes. One of the first disclosures

of the use of triantennary cluster glycosides as conjugated ligands was in US patent number US 5,885,968. Conjugates having three GalNAc ligands and comprising phosphate groups are known and are described in Dubber et al. (Bioconjug. Chem. 2003 Jan-Feb;14(1):239-46.). The ASGP-R complex shows a 50-fold higher affinity for N-Acetyl-D-Galactosamine (GalNAc) than D-Gal.

The ASGP-R complex recognizes specifically terminal β -galactosyl subunits of glycosylated proteins or other oligosaccharides (Weigel, P.H. et. al., Biochim. Biophys. Acta. 2002 Sep 19;1572(2-3):341-63) and can be used for delivering a drug to the liver's hepatocytes expressing the receptor complex by covalent coupling of galactose or galactosamine to the drug substance (Ishibashi, S.; et. al., J Biol. Chem. 1994 Nov 11;269(45):27803-6). Furthermore, the binding affinity can be significantly increased by the multi-valency effect, which is achieved by the repetition of the targeting moiety (Biessen EA, et al., J Med Chem. 1995 Apr 28;38(9):1538-46).

The ASGP-R complex is a mediator for an active uptake of terminal β -galactosyl containing glycoproteins to the cell's endosomes. Thus, the ASGPR is highly suitable for targeted delivery of drug candidates conjugated to such ligands like, e.g., nucleic acids into receptor-expressing cells (Akinc et al., Mol Ther. 2010 Jul;18(7):1357-64).

More generally the ligand can comprise a saccharide that is selected to have an affinity for at least one type of receptor on a target cell. In particular, the receptor is on the surface of a mammalian liver cell, for example, the hepatic asialoglycoprotein receptor complex described before (ASGP-R).

The saccharide may be selected from N-acetyl galactosamine, mannose, galactose, glucose, glucosamine and fucose. The saccharide may be N-acetyl galactosamine (GalNAc). The heterologous moiety may comprise a plurality of such saccharides, e.g., two or especially three such saccharides, e.g., three GalNAc groups.

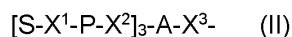
A heterologous moiety may therefore comprise (i) one or more functional components, and (ii) a linker, wherein the linker conjugates the functional components to a nucleic acid as defined in any preceding aspects. The linker may be a monovalent structure or bivalent or trivalent or tetravalent branched structure. The nucleotides may be modified as defined herein.

The functional components may therefore be ligands (or targeting agents). Where multiple functional components are present, they may be the same or different. Where the functional

components are ligands, they may be saccharides, and may therefore be (or comprise) GalNAc.

In one aspect, the nucleic acid is conjugated to a heterologous moiety comprising a

5 compound of formula (II):



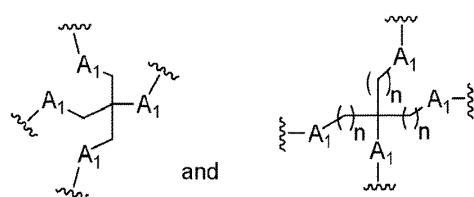
wherein:

- S represents a functional component, e.g., a ligand, such as a saccharide, preferably wherein the saccharide is N-acetyl galactosamine;
- 10 X^1 represents C_3 - C_6 alkylene or $(-CH_2-CH_2-O)_m(-CH_2)_2-$ wherein m is 1, 2, or 3;
- P is a phosphate or modified phosphate, preferably a thiophosphate;
- X^2 is alkylene or an alkylene ether of the formula $(-CH_2)_n-O-CH_2-$ where n = 1- 6;
- A is a branching unit;
- X^3 represents a bridging unit;
- 15 wherein a nucleic acid according to the present invention is conjugated to X^3 via a phosphate or modified phosphate, preferably a thiophosphate.

In formula (II), the branching unit "A" preferably branches into three in order to accommodate three saccharide ligands. The branching unit is preferably covalently attached to the remaining

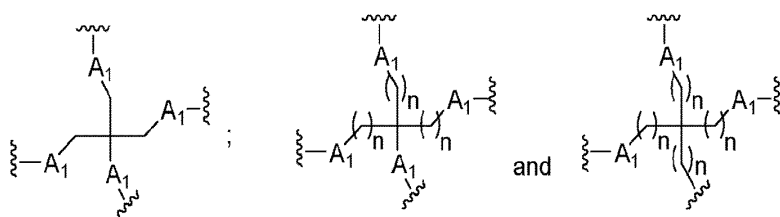
20 tethered portions of the ligand and the nucleic acid. The branching unit may comprise a branched aliphatic group comprising groups selected from alkyl, amide, disulphide, polyethylene glycol, ether, thioether and hydroxyamino groups. The branching unit may comprise groups selected from alkyl and ether groups.

25 The branching unit A may have a structure selected from:



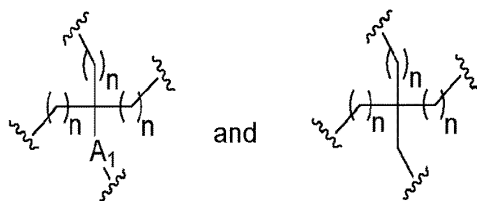
wherein each A₁ independently represents O, S, C=O or NH; and each n independently represents an integer from 1 to 20.

30 The branching unit may have a structure selected from:



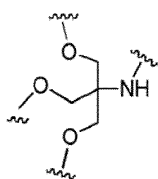
wherein each A_1 independently represents O, S, C=O or NH; and each n independently represents an integer from 1 to 20.

- 5 The branching unit may have a structure selected from:



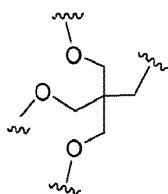
wherein A_1 is O, S, C=O or NH; and each n independently represents an integer from 1 to 20.

The branching unit may have the structure:

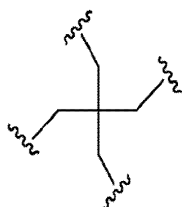


10

The branching unit may have the structure:

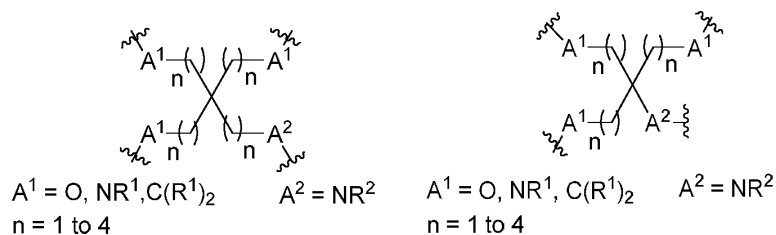


The branching unit may have the structure:



15

Alternatively, the branching unit A may have a structure selected from:



wherein:

- 5 R1 is hydrogen or C1-C10 alkylene;
 and R2 is C1-C10 alkylene.

Optionally, the branching unit consists of only a carbon atom.

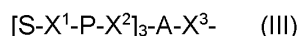
- 10 The "X³" portion is a bridging unit. The bridging unit is linear and is covalently bound to the branching unit and the nucleic acid.

X³ may be selected from -C₁-C₂₀ alkylene-, -C₂-C₂₀ alkenylene-, an alkylene ether of formula -
 (C₁-C₂₀ alkylene)-O-(C₁-C₂₀ alkylene)-, -C(O)-C₁-C₂₀ alkylene-, -C₀-C₄ alkylene(Cy)C₀-C₄
 15 alkylene- wherein Cy represents a substituted or unsubstituted 5 or 6 membered cycloalkylene,
 arylene, heterocyclylene or heteroarylene ring, -C₁-C₄ alkylene-NHC(O)-C₁-C₄ alkylene-, -C₁-
 C₄ alkylene-C(O)NH-C₁-C₄ alkylene-, -C₁-C₄ alkylene-SC(O)-C₁-C₄ alkylene-, -C₁-C₄ alkylene-
 C(O)S-C₁-C₄ alkylene-, -C₁-C₄ alkylene-OC(O)-C₁-C₄ alkylene-, -C₁-C₄ alkylene-C(O)O-C₁-C₄
 alkylene-, and -C₁-C₆ alkylene-S-S-C₁-C₆ alkylene-.

20

X³ may be an alkylene ether of formula -(C₁-C₂₀ alkylene)-O-(C₁-C₂₀ alkylene)-. X³ may be an
 alkylene ether of formula -(C₁-C₂₀ alkylene)-O-(C₄-C₂₀ alkylene)-, wherein said (C₄-C₂₀
 alkylene) is linked to Z. X³ may be selected from the group consisting of -CH₂-O-C₃H₆-, -CH₂-
 O-C₄H₈-, -CH₂-O-C₆H₁₂-, and -CH₂-O-C₈H₁₆-, especially -CH₂-O-C₄H₈-, -CH₂-O-C₆H₁₂- and -
 25 CH₂-O-C₈H₁₆-, wherein in each case the -CH₂- group is linked to A.

In one aspect, the nucleic acid is conjugated to a heterologous moiety of formula (III):

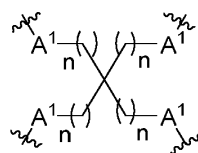


wherein:

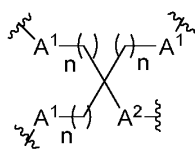
- 30 S represents a functional component, e.g., a ligand, such as a saccharide, preferably
 GalNAc;
 X¹ represents C₃-C₆ alkylene or -(CH₂-CH₂-O)_m-(CH₂)₂- wherein m is 1, 2, or 3;
 P is a phosphate or modified phosphate, preferably a thiophosphate;

X^2 is C_1 - C_8 alkylene;

A is a branching unit selected from:



$A^1 = O, NH$
 $n = 1$ to 4

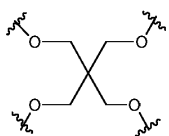


$A^1 = O, NH$ $A^2 = NH, CH_2, O$
 $n = 1$ to 4

X^3 is a bridging unit;

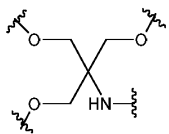
- 5 wherein a nucleic acid according to the present invention is conjugated to X^3 via a phosphate or a modified phosphate, preferably a thiophosphate.

The branching unit A may have the structure:



10

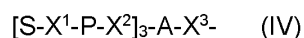
The branching unit A may have the structure:



, wherein X^3 is attached to the nitrogen atom.

- 15 X^3 may be C_1 - C_{20} alkylene. Preferably, X^3 is selected from the group consisting of $-C_3H_6-$, $-C_4H_8-$, $-C_6H_{12}-$ and $-C_8H_{16}-$, especially $-C_4H_8-$, $-C_6H_{12}-$ and $-C_8H_{16}-$.

In one aspect, the nucleic acid is conjugated to a ligand comprising a compound of formula (IV):



- 20 wherein:

S represents a functional component, e.g., a ligand, such as a saccharide, preferably GalNAc;

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

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

- 25 X^2 is an alkylene ether of formula $-C_3H_6-O-CH_2-$;

A is a branching unit;

X³ is an alkylene ether of formula selected from the group consisting of -CH₂-O-CH₂-, -CH₂-O-C₂H₄-, -CH₂-O-C₃H₆-, -CH₂-O-C₄H₈-, -CH₂-O-C₅H₁₀-, -CH₂-O-C₆H₁₂-, -CH₂-O-C₇H₁₄-, and -CH₂-O-C₈H₁₆-, wherein in each case the -CH₂- group is linked to A, and wherein X³ is conjugated to a nucleic acid according to the present invention by a phosphate or modified phosphate, preferably a thiophosphate.

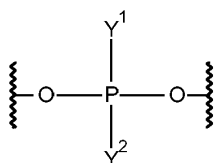
The branching unit may comprise carbon. Preferably, the branching unit is a carbon.

X³ may be selected from the group consisting of -CH₂-O-C₄H₈-, -CH₂-O-C₅H₁₀-, -CH₂-O-C₆H₁₂-, -CH₂-O-C₇H₁₄-, and -CH₂-O-C₈H₁₆-. Preferably, X³ is selected from the group consisting of -CH₂-O-C₄H₈-, -CH₂-O-C₆H₁₂- and -CH₂-O-C₈H₁₆.

X¹ may be (-CH₂-CH₂-O)(-CH₂)₂-. X¹ may be (-CH₂-CH₂-O)₂(-CH₂)₂-. X¹ may be (-CH₂-CH₂-O)₃(-CH₂)₂-. Preferably, X¹ is (-CH₂-CH₂-O)₂(-CH₂)₂-. Alternatively, X¹ represents C₃-C₆ alkylene. X¹ may be propylene. X¹ may be butylene. X¹ may be pentylene. X¹ may be hexylene. Preferably the alkyl is a linear alkylene. In particular, X¹ may be butylene.

X² represents an alkylene ether of formula -C₃H₆-O-CH₂- i.e., C₃ alkoxy methylene, or -CH₂CH₂CH₂OCH₂-.

For any of the above aspects, when P represents a modified phosphate group, P can be represented by:



wherein Y¹ and Y² each independently represent =O, =S, -O⁻, -OH, -SH, -BH₃, -OCH₂CO₂-, -OCH₂CO₂R^x, -OCH₂C(S)OR^x, and -OR^x, wherein R^x represents C₁-C₆ alkyl and wherein  indicates attachment to the remainder of the compound.

By modified phosphate it is meant a phosphate group wherein one or more of the non-linking oxygens is replaced. Examples of modified phosphate groups include phosphorothioate, phosphorodithioates, phosphoroselenates, borano phosphates, borano phosphate esters, hydrogen phosphonates, phosphoroamidates, alkyl or aryl phosphonates and phosphotriesters. Phosphorodithioates have both non-linking oxygens replaced by sulphur. One, each or both non-linking oxygens in the phosphate group can be independently any one of S, Se, B, C, H, N, or OR (R is alkyl or aryl).

The phosphate can also be modified by replacement of a linking oxygen with nitrogen (bridged phosphoramidates), sulfur (bridged phosphorothioates) and carbon (bridged methylenephosphonates). The replacement can occur at a terminal oxygen. Replacement of
5 the non-linking oxygens with nitrogen is possible.

For example, Y¹ may represent -OH and Y² may represent =O or =S; or
Y¹ may represent -O⁻ and Y² may represent =O or =S;
Y¹ may represent =O and Y² may represent -CH₃, -SH, -OR^x, or -BH₃
10 Y¹ may represent =S and Y² may represent -CH₃, OR^x or -SH.

It will be understood by the skilled person that in certain instances there will be delocalisation between Y¹ and Y².

15 Preferably, the modified phosphate group is a thiophosphate group. Thiophosphate groups include bithiophosphate (i.e., where Y¹ represents =S and Y² represents -S⁻) and monothiophosphate (i.e., where Y¹ represents -O⁻ and Y² represents =S, or where Y¹ represents =O and Y² represents -S⁻). Preferably, P is a monothiophosphate. The inventors have found that conjugates having thiophosphate groups in replacement of phosphate groups
20 have improved potency and duration of action *in vivo*.

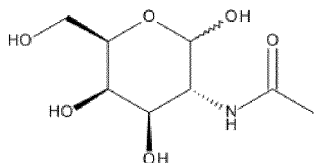
P may also be an ethylphosphate (i.e., where Y¹ represents =O and Y² represents OCH₂CH₃).

The ligand, e.g., saccharide, may be selected to have an affinity for at least one type of receptor
25 on a target cell. In particular, the receptor is on the surface of a mammalian liver cell, for example, the hepatic asialoglycoprotein receptor complex (ASGP-R).

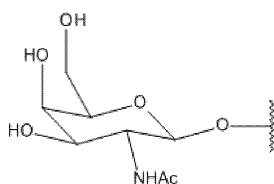
For any of the above or below aspects, the saccharide may be selected from N-acetyl with one or more of galactosamine, mannose, galactose, glucose, glucosamine and fructose. Typically
30 a ligand to be used in the present invention may include N-acetyl galactosamine (GalNAc). Preferably the compounds of the invention may have 3 ligands, which will each preferably include N-acetyl galactosamine.

"GalNAc" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose, commonly referred to in the
35 literature as N-acetyl galactosamine. Reference to "GalNAc" or "N-acetyl galactosamine" includes both the β- form: 2-(Acetylamino)-2-deoxy-β-D-galactopyranose and the α-form: 2-(Acetylamino)-2-deoxy-α-D- galactopyranose. In certain embodiments, both the β-form: 2-

(Acetylamino)-2-deoxy- β -D-galactopyranose and α -form: 2-(Acetylamino)-2-deoxy- α -D-galactopyranose may be used interchangeably. Preferably, the compounds of the invention comprise the β -form, 2-(Acetylamino)-2-deoxy- β -D-galactopyranose.

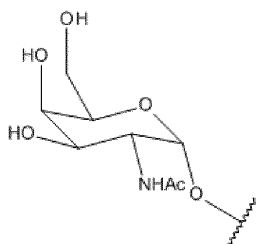


2-(Acetylamino)-2-deoxy-D-galactopyranose



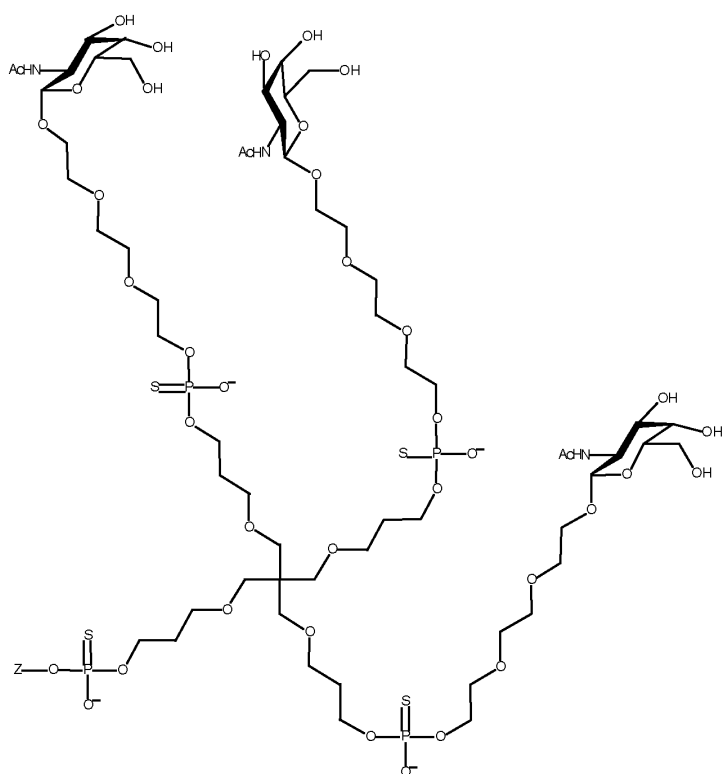
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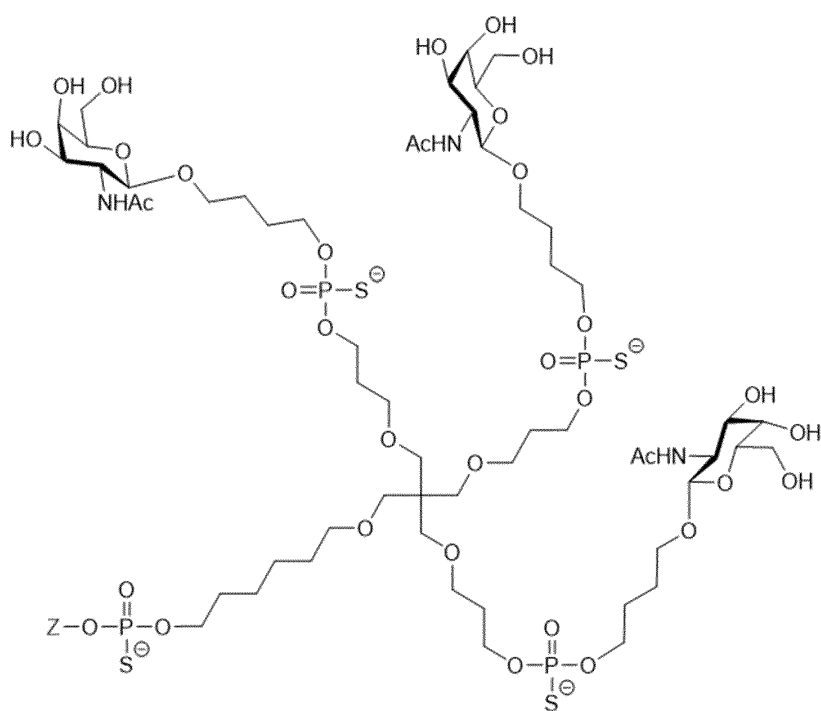
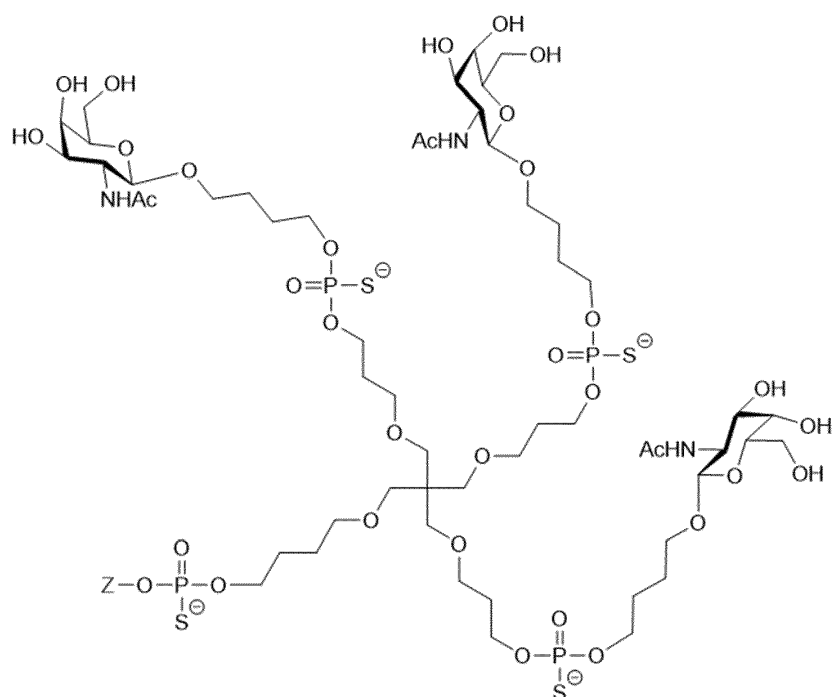
2-(Acetylamino)-2-deoxy- β -D-galactopyranose

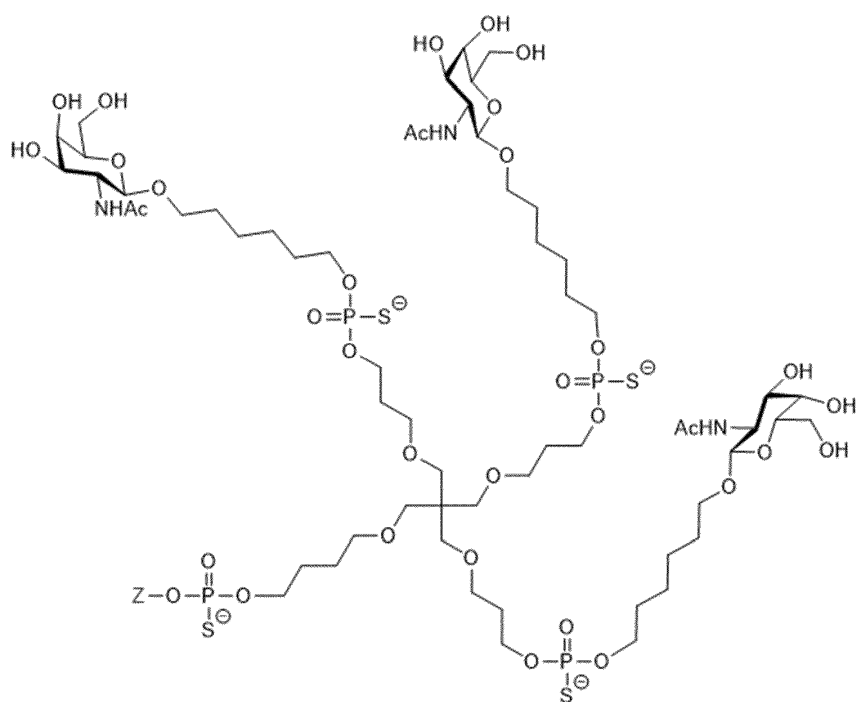
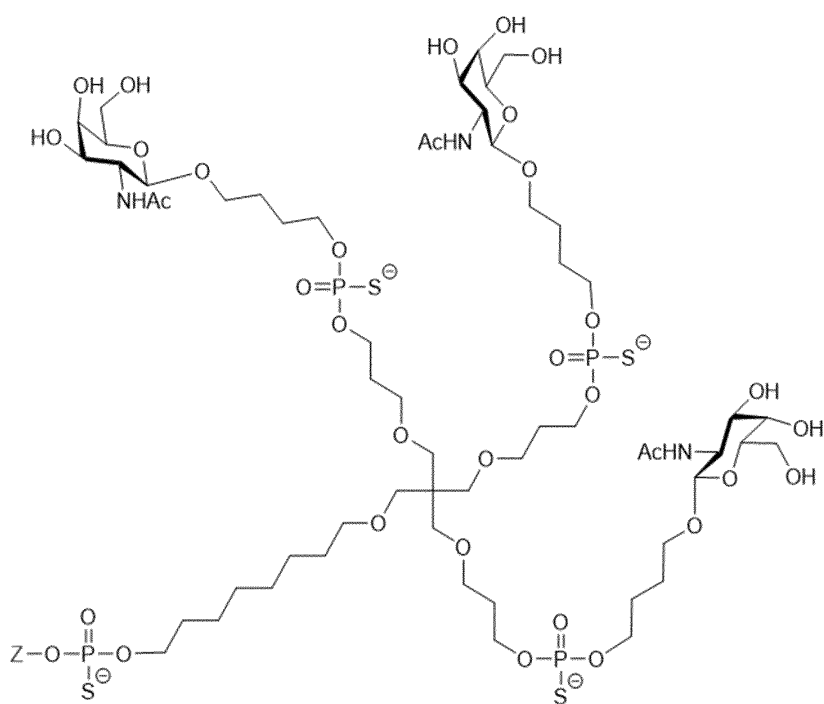


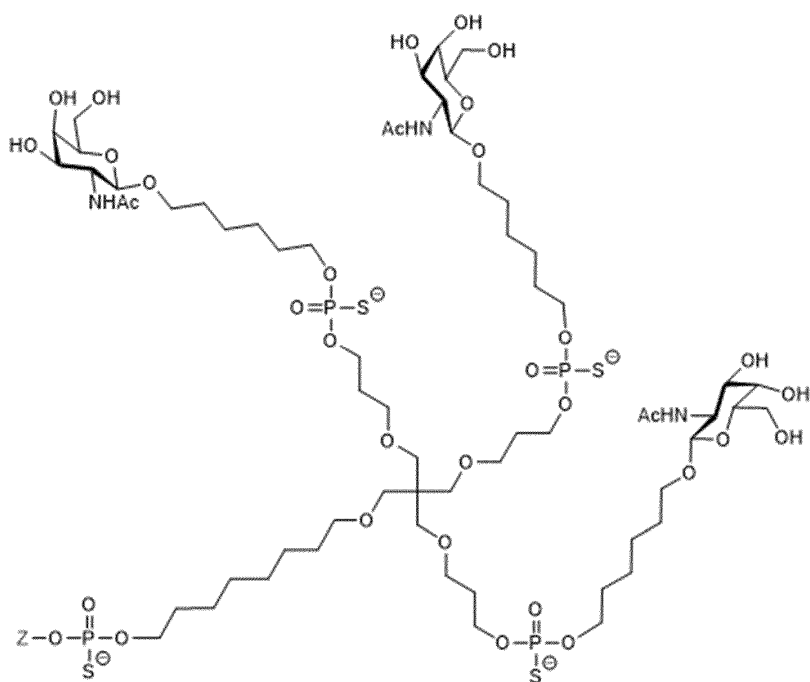
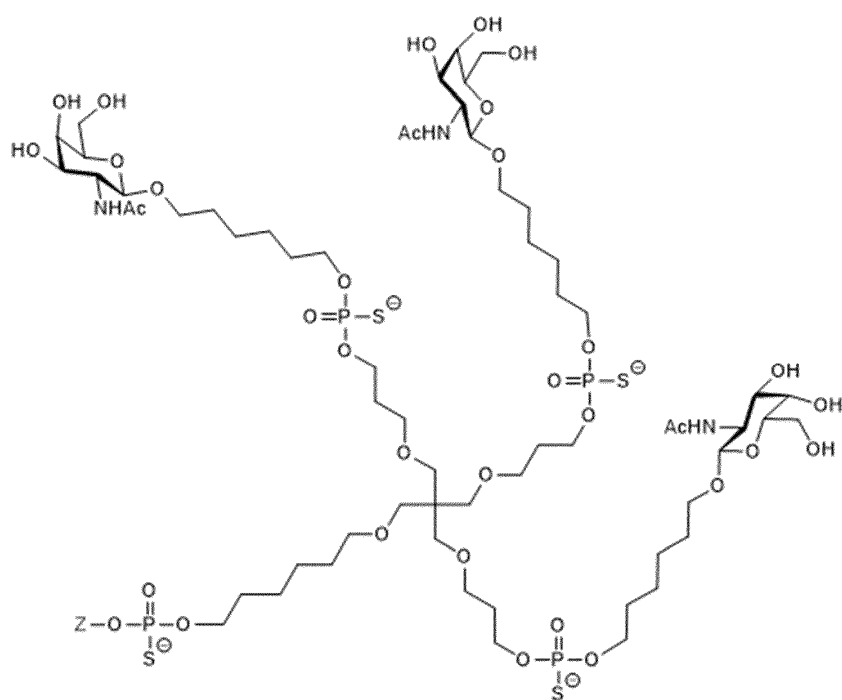
2-(Acetylamino)-2-deoxy- α -D-galactopyranose

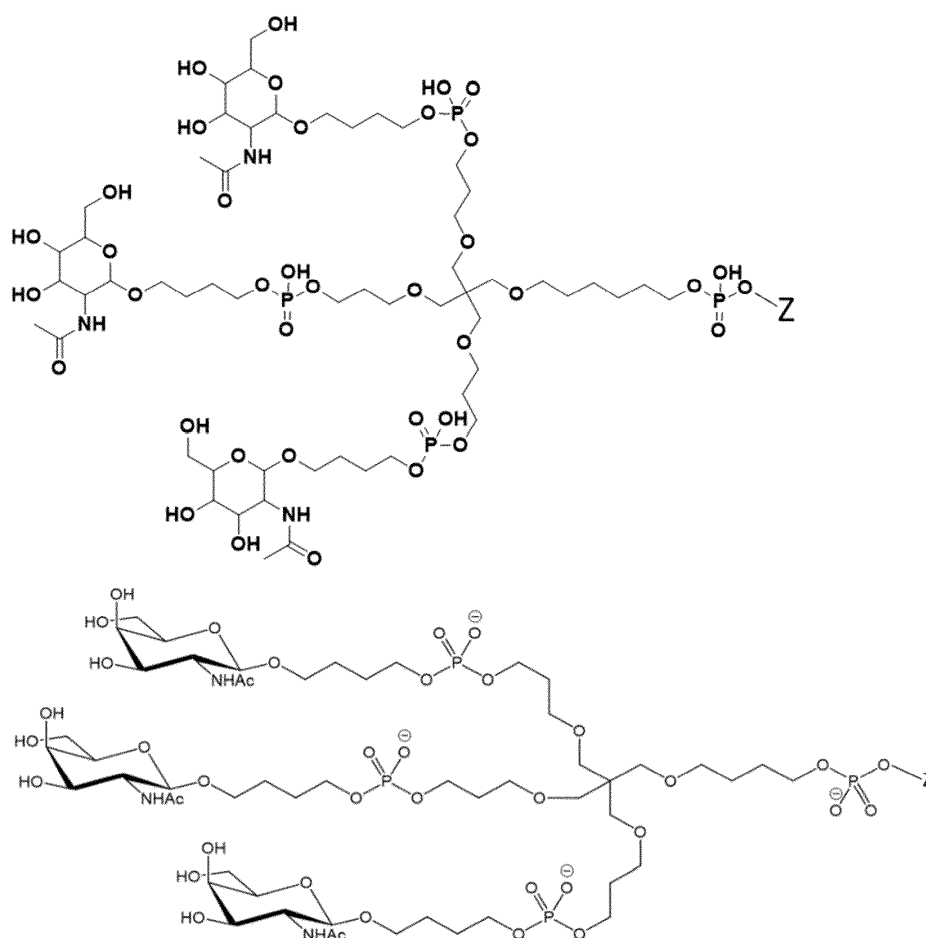
- 15 In one aspect, the nucleic acid is a conjugated nucleic acid, wherein the nucleic acid is conjugated to a heterologous moiety with one of the following structures, which may be referred to as “triantennary ligands” for ease of reference:











wherein Z is any nucleic acid as defined herein. In certain embodiments, the heterologous moiety ("triantennary ligand") is conjugated to the 5' end of the second (sense) strand of Z (which is also referred to as strand "B" in Tables 5a, 5b, 5c).

In certain embodiments, the nucleic acid Z is conjugated to the triantennary ligand via the phosphate or thiophosphate group which links the triantennary ligand to the 3' or 5' position of the sugar, particularly to the 3' or 5' position of the ribose, of the terminal nucleotide of said nucleic acid Z.

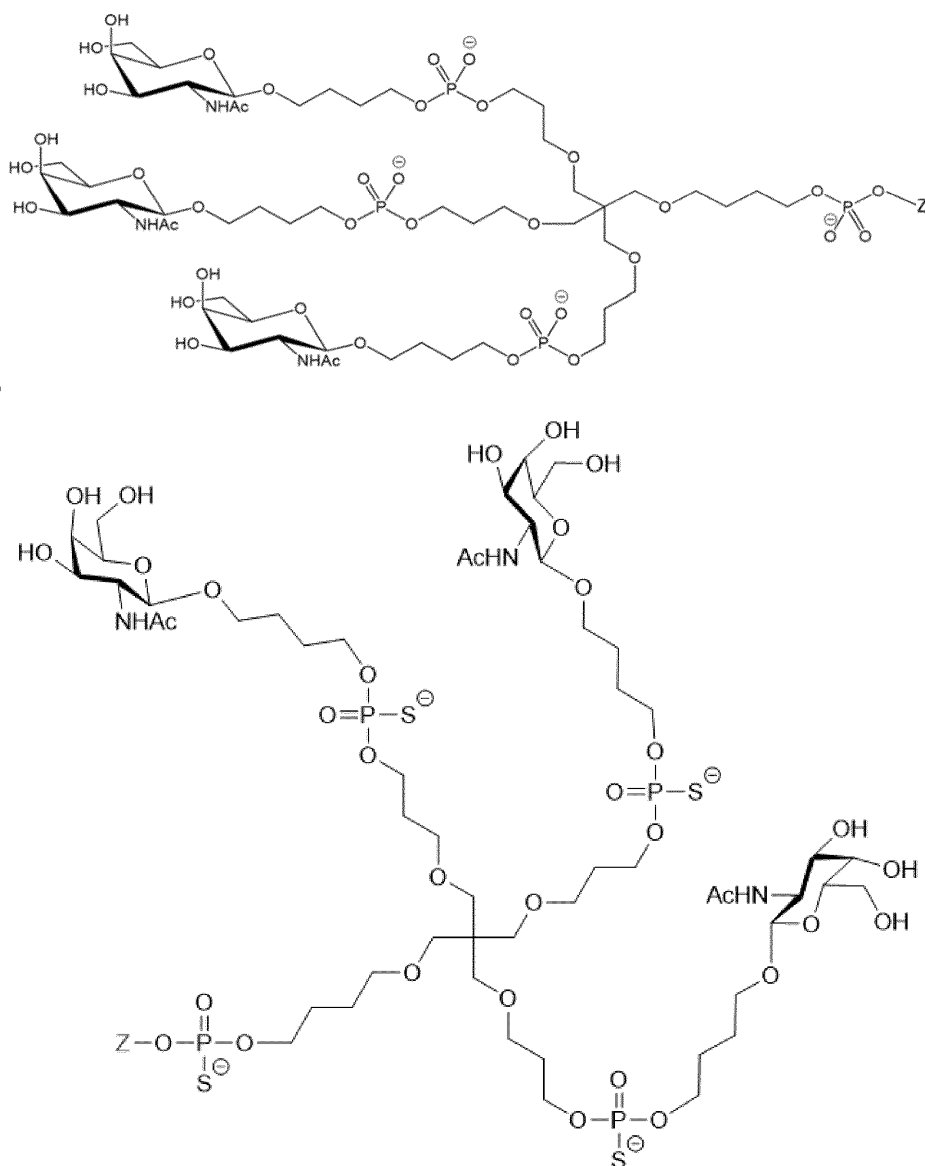
In certain embodiments, the heterologous moiety ("triantennary ligand") is conjugated to the 3' position of the ribose of the terminal nucleotide of the second (sense) strand of Z (which is also referred to as strand "B" in Tables 5a, 5b, 5c).

In other embodiments, the heterologous moiety ("triantennary ligand") is conjugated to the 5' position of the ribose of the terminal nucleotide of the second (sense) strand of Z (which is also referred to as strand "B" in Tables 5a, 5b, 5c).

- 5 In other embodiments, the heterologous moiety ("triantennary ligand") is conjugated to the 3' position of the ribose of the terminal nucleotide of the first (antisense) strand of Z (which is also referred to as strand "A" in Tables 5a, 5b, 5c).

Preferably, the nucleic acid is a conjugated nucleic acid, wherein the nucleic acid is conjugated to a triantennary ligand with one of the following structures:

10



wherein Z is any nucleic acid as defined herein. Preferably, the heterologous moiety ("triantennary ligand") is conjugated to the 5' end of the second (sense) strand of Z (which is also referred to as strand "B" in Tables 5a, 5b, 5c).

- 5 In a preferred embodiment, the nucleic acid Z is conjugated to the triantennary ligand via the phosphate or thiophosphate group which links the triantennary ligand to the 3' or 5' position of the ribose of the terminal nucleotide of said nucleic acid Z.

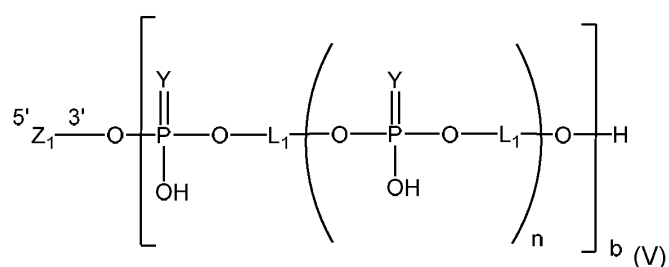
- 10 Preferably, the triantennary ligand" is conjugated to the 5' position of the ribose of the terminal nucleotide of the second (sense) strand of Z (which is also referred to as strand "B" in Tables 5a, 5b, 5c).

- 15 A heterologous moiety of formula (II), (III) or (IV) or any one of the triantennary ligands disclosed herein can be attached at the 3'-end of the first (antisense) strand and/or at any of the 3' and/or 5' end of the second (sense) strand. The nucleic acid can comprise more than one heterologous moiety of formula (II), (III) or (IV) or any one of the triantennary ligands disclosed herein. However, a single heterologous moiety of formula (II), (III) or (IV) or any one of the triantennary ligands disclosed herein is preferred because a single such moiety is sufficient for efficient targeting of the nucleic acid to the target cells. Preferably in that case, at least the last two, preferably at least the last three and more preferably at least the last four nucleotides at the end of the nucleic acid to which the ligand is attached are linked by a phosphodiester linkage.

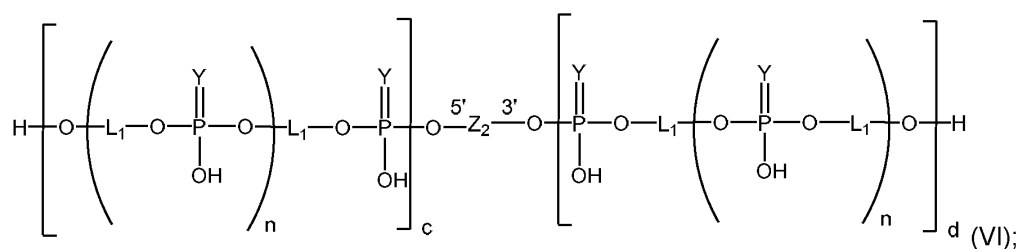
- 25 Preferably, the 5'-end of the first (antisense) strand is not attached to a heterologous moiety, since attachment at this position can potentially interfere with the biological activity of the nucleic acid.

- 30 A nucleic acid with a single heterologous moiety (e.g., of formula (II), (III) or (IV) or any one of the triantennary ligands disclosed herein) at the 5' end of a strand is easier and therefore cheaper to synthesise than the same nucleic acid with the same group at the 3' end. Preferably therefore, a single heterologous moiety (e.g., of any of formulae (II), (III) or (IV) or any one of the triantennary ligands disclosed herein) is covalently attached to (conjugated with) the 5' end of the second strand of the nucleic acid.

- 35 In one aspect, the first strand of the nucleic acid is a compound of formula (V):



wherein b is preferably 0 or 1; and
the second strand is a compound of formula (VI):



5 wherein:

c and d are independently preferably 0 or 1;

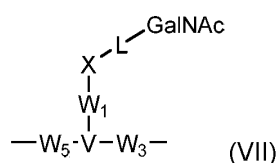
Z₁ and Z₂ are respectively the first and second strand of the nucleic acid;

Y is independently O or S;

n is independently 0, 1, 2 or 3; and

10 L₁ is a linker to which a ligand is attached, wherein L₁ is the same or different in formulae (V) and (VI), and is the same or different within formulae (V) and (VI) when L₁ is present more than once within the same formula, wherein L₁ is preferably of formula (VII);
and wherein b + c + d is preferably 2 or 3.

15 Preferably, L₁ in formulae (V) and (VI) is of formula (VII):



wherein:

L is selected from the group comprising, or preferably consisting of:

20 $-(CH_2)_r-C(O)-$, wherein r = 2-12;
 $-(CH_2-CH_2-O)_s-CH_2-C(O)-$, wherein s = 1-5;
 $-(CH_2)_t-CO-NH-(CH_2)_t-NH-C(O)-$, wherein t is independently 1-5;
 $-(CH_2)_u-CO-NH-(CH_2)_u-C(O)-$, wherein u is independently 1-5; and
 $-(CH_2)_v-NH-C(O)-$, wherein v is 2-12; and

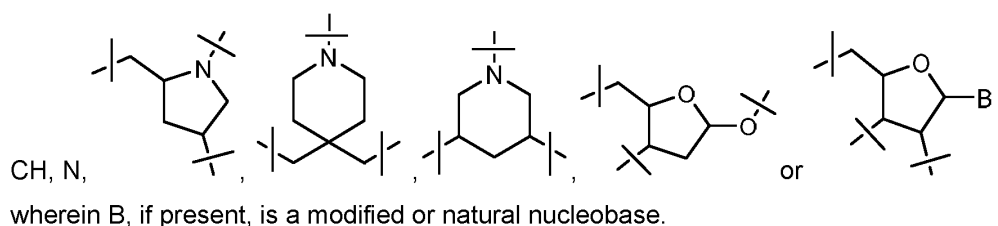
wherein the terminal C(O), if present, is attached to X of formula (VII), or if X is absent, to W₁ of formula (VII), or if W₁ is absent, to V of formula (VII);

W₁, W₃ and W₅ are individually absent or selected from the group comprising, or preferably consisting of:

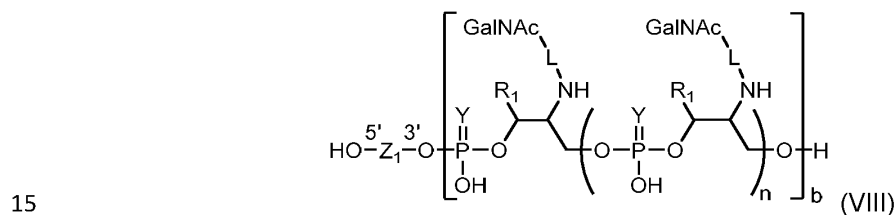
- 5 -(CH₂)_r-, wherein r = 1-7;
 -(CH₂)_s-O-(CH₂)_s-, wherein s is independently 0-5;
 -(CH₂)_t-S-(CH₂)_t-, wherein t is independently 0-5;

X is absent or is selected from the group comprising, or preferably consisting of: NH, NCH₃ or NC₂H₅;

- 10 V is selected from the group comprising, or preferably consisting of:

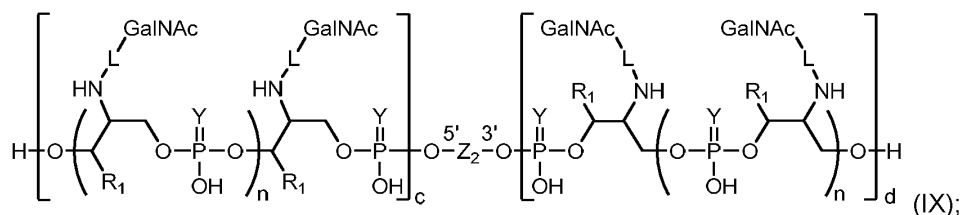


In one aspect, the first strand is a compound of formula (VIII)



wherein b is preferably 0 or 1; and

the second strand is a compound of formula (IX):



wherein c and d are independently preferably 0 or 1;

- 20 wherein:

Z₁ and Z₂ are respectively the first and second strand of the nucleic acid;

Y is independently O or S;

R₁ is H or methyl;

n is independently preferably 0, 1, 2 or 3; and

L is the same or different in formulae (VIII) and (IX), and is the same or different within formulae (VIII) and (IX) when L is present more than once within the same formula, and is selected from the group comprising, or preferably consisting of:

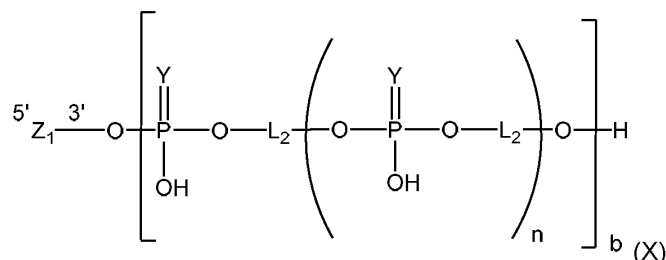
- $(\text{CH}_2)_r\text{C}(\text{O})-$, wherein $r = 2-12$;
- 5 $-(\text{CH}_2\text{-CH}_2\text{-O})_s\text{-CH}_2\text{-C}(\text{O})-$, wherein $s = 1-5$;
- $(\text{CH}_2)_t\text{-CO-NH-}(\text{CH}_2)_t\text{-NH-C}(\text{O})-$, wherein t is independently 1-5;
- $(\text{CH}_2)_u\text{-CO-NH-}(\text{CH}_2)_u\text{-C}(\text{O})-$, wherein u is independently 1-5; and
- $(\text{CH}_2)_v\text{-NH-C}(\text{O})-$, wherein v is 2-12; and

wherein the terminal C(O), if present, is attached to the NH group (of the linker, not of the targeting ligand);

10

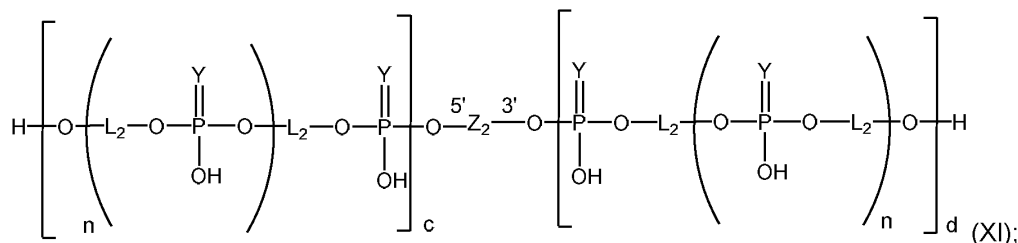
and wherein $b + c + d$ is preferably 2 or 3.

In one aspect, the first strand of the nucleic acid is a compound of formula (X):



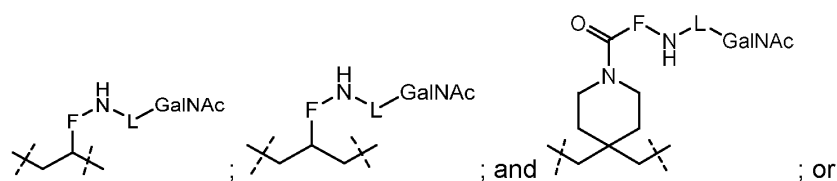
15 wherein b is preferably 0 or 1; and

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

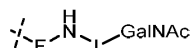


wherein:

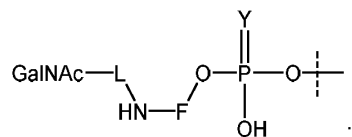
- c and d are independently preferably 0 or 1;
- 20 Z_1 and Z_2 are respectively the first and second RNA strand of the nucleic;
- Y is independently O or S;
- n is independently preferably 0, 1, 2 or 3; and
- L_2 is the same or different in formulae (X) and (XI) and is the same or different in moieties bracketed by b , c and d , and is selected from the group comprising, or preferably
- 25 consisting of:



n is 0 and L₂ is:



and the terminal OH group is absent such that the following moiety is formed:



5

wherein:

F is a saturated branched or unbranched (such as unbranched) C₁₋₈alkyl (e.g., C₁₋₆alkyl) chain wherein one of the carbon atoms is optionally replaced with an oxygen atom provided that said oxygen atom is separated from another heteroatom (e.g., an O or N atom) by at least 2 carbon atoms;

10

L is the same or different in formulae (X) and (XI) and is selected from the group comprising, or preferably consisting of:

-(CH₂)_r-C(O)-, wherein r = 2-12;

-(CH₂-CH₂-O)_s-CH₂-C(O)-, wherein s = 1-5;

15

-(CH₂)_t-CO-NH-(CH₂)_t-NH-C(O)-, wherein t is independently 1-5;

-(CH₂)_u-CO-NH-(CH₂)_u-C(O)-, wherein u is independently 1-5; and

-(CH₂)_v-NH-C(O)-, wherein v is 2-12; and

wherein the terminal C(O), if present, is attached to the NH group (of the linker, not of the targeting ligand);

20

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

In one aspect, b is 0, c is 1 and d is 1; b is 1, c is 0 and d is 1; b is 1, c is 1 and d is 0; or b is 1, c is 1 and d is 1 in any of the nucleic acids of formulae (V) and (VI) or (VIII) and (IX) or (X) and (XI). Preferably, b is 0, c is 1 and d is 1; b is 1, c is 0 and d is 1; or b is 1, c is 1 and d is 1.

25

Most preferably, b is 0, c is 1 and d is 1.

In one aspect, Y is O in any of the nucleic acids of formulae (V) and (VI) or (VIII) and (IX) or (X) and (XI). In another aspect, Y is S. In a preferred aspect, Y is independently selected from O or S in the different positions in the formulae.

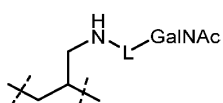
30

In one aspect, R_1 is H or methyl in any of the nucleic acids of formulae (VIII) and (IX). In one aspect, R_1 is H. In another aspect, R_1 is methyl.

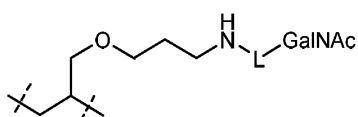
In one aspect, n is 0, 1, 2 or 3 in any of the nucleic acids of formulae (V) and (VI) or (VIII) and (IX) or (X) and (XI). Preferably, n is 0.

Examples of F moieties in any of the nucleic acids of formulae (X) and (XI) include $(CH_2)_{1-6}$ e.g., $(CH_2)_{1-4}$ e.g. CH_2 , $(CH_2)_4$, $(CH_2)_5$ or $(CH_2)_6$, or $CH_2O(CH_2)_{2-3}$, e.g., $CH_2O(CH_2)CH_3$.

10 In one aspect, L_2 in formulae (X) and (XI) is:

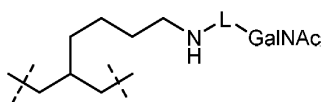


In one aspect, L_2 is:

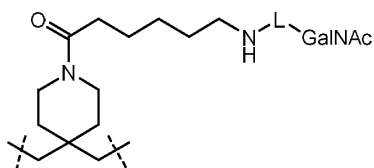


15

In one aspect, L_2 is:

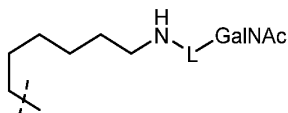


In one aspect, L_2 is:

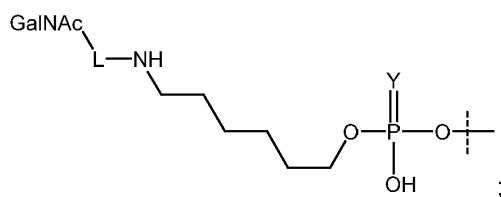


20

In one aspect, n is 0 and L_2 is:



and the terminal OH group is absent such that the following moiety is formed:



wherein Y is O or S.

In one aspect, L in the nucleic acids of formulae (V) and (VI) or (VIII) and (IX) or (X) and (XI),

5 is selected from the group comprising, or preferably consisting of:

-(CH₂)_r-C(O)-, wherein r = 2-12;

-(CH₂-CH₂-O)_s-CH₂-C(O)-, wherein s = 1-5;

-(CH₂)_t-CO-NH-(CH₂)_t-NH-C(O)-, wherein t is independently 1-5;

-(CH₂)_u-CO-NH-(CH₂)_u-C(O)-, wherein u is independently 1-5; and

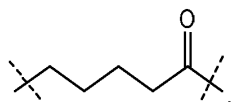
10 -(CH₂)_v-NH-C(O)-, wherein v is 2-12;

wherein the terminal C(O) is attached to the NH group.

Preferably, L is -(CH₂)_r-C(O)-, wherein r = 2-12, more preferably r = 2-6 even more preferably, r = 4 or 6 e.g., 4.

15

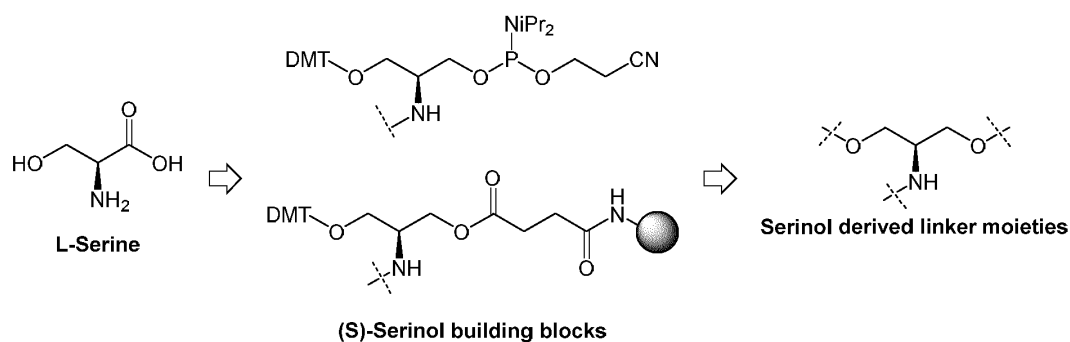
Preferably, L is:



Within the moiety bracketed by b, c and d, L₂ in the nucleic acids of formulae (X) and (XI) is typically the same. Between moieties bracketed by b, c and d, L₂ may be the same or different. In an embodiment, L₂ in the moiety bracketed by c is the same as the L₂ in the moiety bracketed by d. In an embodiment, L₂ in the moiety bracketed by c is not the same as L₂ in the moiety bracketed by d. In an embodiment, the L₂ in the moieties bracketed by b, c and d is the same, for example when the linker moiety is a serinol-derived linker moiety.

25

Serinol derived linker moieties may be based on serinol in any stereochemistry i.e., derived from L-serine isomer, D-serine isomer, a racemic serine or other combination of isomers. In a preferred aspect of the invention, the serinol-GalNAc moiety (SerGN) has the following stereochemistry:



i.e., is based on an (S)-serinol-amidite or (S)-serinol succinate solid supported building block derived from L-serine isomer.

- 5 In a preferred aspect, the first strand of the nucleic acid is a compound of formula (VIII) and the second strand of the nucleic acid is a compound of formula (IX), wherein:

b is 0;

c and d are 1,

n is 0,

- 10 Z_1 and Z_2 are respectively the first and second strand of the nucleic acid,

Y is S,

R_1 is H, and

L is $-(CH_2)_4-C(O)-$, wherein the terminal C(O) of L is attached to the N atom of the linker (ie not a possible N atom of a targeting ligand).

15

In another preferred aspect, the first strand of the nucleic acid is a compound of formula (V) and the second strand of the nucleic acid is a compound of formula (VI), wherein:

b is 0,

c and d are 1,

- 20 n is 0,

Z_1 and Z_2 are respectively the first and second strand of the nucleic acid,

Y is S,

L_1 is of formula (VII), wherein:

W_1 is $-CH_2-O-(CH_2)_3-$,

- 25 W_3 is $-CH_2-$,

W_5 is absent,

V is CH,

X is NH, and

- 30 L is $-(CH_2)_4-C(O)-$ wherein the terminal C(O) of L is attached to the N atom of X in formula (VII).

In another preferred aspect, the first strand of the nucleic acid is a compound of formula (V) and the second strand of the nucleic acid is a compound of formula (VI), wherein:

b is 0,

c and d are 1,

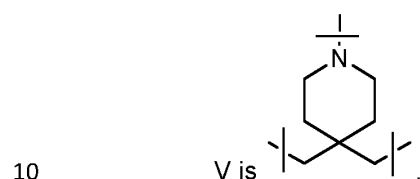
5 n is 0,

Z₁ and Z₂ are respectively the first and second strand of the nucleic acid,

Y is S,

L₁ is of formula (VII), wherein:

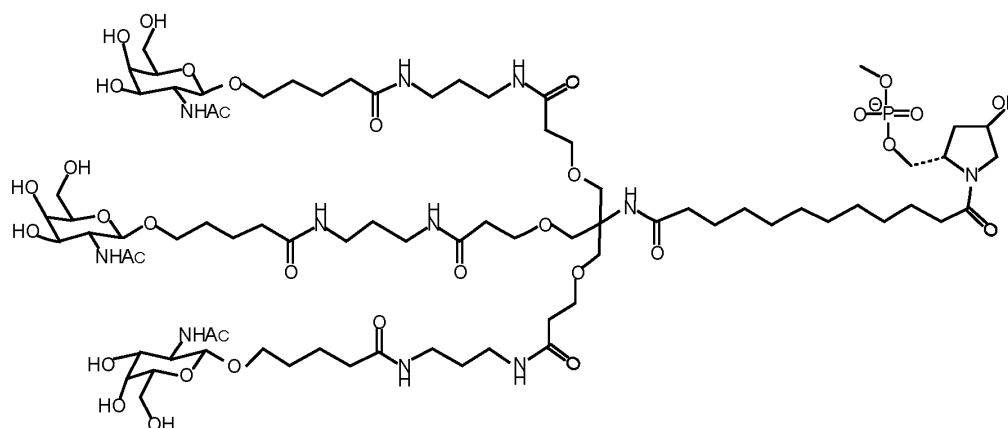
W₁, W₃ and W₅ are absent,



X is absent, and

L is $-(CH_2)_4-C(O)-NH-(CH_2)_5-C(O)-$, wherein the terminal C(O) of L is attached to the N atom of V in formula (VII).

15 In one aspect, the nucleic acid is conjugated to a triantennary ligand with the following structure:



20 wherein the nucleic acid is conjugated to the triantennary ligand via the phosphate group of the ligand a) to the last nucleotide at the 5' end of the second strand; b) to the last nucleotide at the 3' end of the second strand; or c) to the last nucleotide at the 3' end of the first strand.

In one aspect of the nucleic acid, the cells that are targeted by the nucleic acid with a ligand are hepatocytes.

In any one of the above ligands where GalNAc is present, the GalNAc may be substituted for any other targeting ligand, such as those mentioned herein, in particular mannose, galactose, glucose, glucosamine and fucose.

- 5 In one aspect, the nucleic acid is conjugated to a heterologous moiety that comprises a lipid, and more preferably, a cholesterol.

In one aspect, the double-stranded nucleic acid for inhibiting expression of complement factor B (CFB) is one of the duplexes shown in Table 5c, which may be referred to by their Duplex
10 ID number.

In one preferred aspect, the double-stranded nucleic acid for inhibiting expression of complement factor B (CFB) is the duplex having the structure defined by one of the following Duplex IDs shown in Table 5c: EV2181, EV2182, EV2184, EV2185, EV2186, EV2189,
15 EV2195, EV2196, EV2197, EV2198, EV2201, EV2204.

In one preferred aspect the double-stranded nucleic acid for inhibiting expression of complement factor B (CFB) is a nucleic acid, wherein the first strand sequence comprises (vp)-mU fC mA fC mA fA mA fC mA fG mA fG mC fU mU fU mG (ps) fA (ps) mU (SEQ ID No.
20 740) and optionally wherein the second strand sequence comprises [ST23(ps)]3 ST41 (ps) mA mU mC mA mA mA fG fC fU mC mU mG mU mU mU mG mU (ps) mG (ps) mU (SEQ ID No: 730).

In one preferred aspect the double-stranded nucleic acid for inhibiting expression of complement factor B (CFB) is a nucleic acid, wherein the first strand sequence consists of
25 (vp)-mU fC mA fC mA fA mA fC mA fG mA fG mC fU mU fU mG (ps) fA (ps) mU (SEQ ID No. 740) and optionally wherein the second strand sequence consists of [ST23(ps)]3 ST41 (ps) mA mU mC mA mA mA fG fC fU mC mU mG mU mU mU mG mU (ps) mG (ps) mU (SEQ ID No: 730).

30

In one preferred aspect the double-stranded nucleic acid for inhibiting expression of complement factor B (CFB) is a nucleic acid, wherein the first strand sequence comprises (vp)-mU fU mA fU mC fC mU fU mG fA mC fU mU fU mG fA mA (ps) fC (ps) mA (SEQ ID No. 742) and optionally wherein the second strand sequence comprises
35 [ST23(ps)]3 ST41 (ps) mU mG mU mU mC mA fA fA fG mU mC mA mA mG mG mA mU (ps) mA (ps) mU (SEQ ID No: 729).

In one preferred aspect the double-stranded nucleic acid for inhibiting expression of complement factor B (CFB) is a nucleic acid, wherein the first strand sequence consists of (vp)-mU fU mA fU mC fC mU fU mG fA mC fU mU fU mG fA mA (ps) fC (ps) mA (SEQ ID No. 742) and optionally wherein the second strand sequence consists of

- 5 [ST23(ps)]3 ST41 (ps) mU mG mU mU mC mA fA fA fG mU mC mA mA mG mG mA mU (ps) mA (ps) mU (SEQ ID No: 729).

Compositions, uses and methods

- 10 The present invention also provides compositions comprising a nucleic acid of the invention. The nucleic acids and compositions may be used as therapeutic or diagnostic agents, alone or in combination with other agents. For example, one or more nucleic acid(s) of the invention can be combined with a delivery vehicle (e.g., liposomes) and/or excipients, such as carriers, diluents. Other agents such as preservatives and stabilizers can also be added.
- 15 Pharmaceutically acceptable salts or solvates of any of the nucleic acids of the invention are likewise within the scope of the present invention. Methods for the delivery of nucleic acids are known in the art and within the knowledge of the person skilled in the art.

- Compositions disclosed herein are particularly pharmaceutical compositions. Such
- 20 compositions are suitable for administration to a subject.

- In one aspect, the composition comprises a nucleic acid disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and a solvent (preferably water) and/or a delivery vehicle and/or a physiologically acceptable excipient and/or a carrier and/or a salt
- 25 and/or a diluent and/or a buffer and/or a preservative.

- Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and transdermal) administration. The formulations may conveniently be presented
- 30 in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Subcutaneous or transdermal modes of administration may be particularly suitable for the compounds described herein.

- The prophylactically or therapeutically effective amount of a nucleic acid of the present
- 35 invention will depend on the route of administration, the type of mammal being treated, and the physical characteristics of the specific mammal under consideration. These factors and their relationship to determining this amount are well known to skilled practitioners in the

medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy, and may depend on such factors as weight, diet, concurrent medication and other factors, well known to those skilled in the medical arts. The dosage sizes and dosing regimen most appropriate for human use may be guided by the results obtained by the present invention, and may be confirmed in properly designed clinical trials.

An effective dosage and treatment protocol may be determined by conventional means, starting with a low dose in laboratory animals and then increasing the dosage while monitoring the effects, and systematically varying the dosage regimen as well. Numerous factors may be taken into consideration by a clinician when determining an optimal dosage for a given subject. Such considerations are known to the skilled person.

Nucleic acids of the present invention, or salts thereof, may be formulated as pharmaceutical compositions prepared for storage or administration, which typically comprise a prophylactically or therapeutically effective amount of a nucleic acid of the invention, or a salt thereof, in a pharmaceutically acceptable carrier.

The nucleic acid or conjugated nucleic acid of the present invention can also be administered in combination with other therapeutic compounds, either administered separately or simultaneously, e.g., as a combined unit dose. The invention also includes a composition comprising one or more nucleic acids according to the present invention in a physiologically/pharmaceutically acceptable excipient, such as a stabilizer, preservative, diluent, buffer, and the like.

In one aspect, the composition comprises a nucleic acid disclosed herein and a further therapeutic agent selected from the group comprising an oligonucleotide, a small molecule, a monoclonal antibody, a polyclonal antibody and a peptide. Preferably, the further therapeutic agent is an agent that targets, preferably inhibits the expression or the activity, of CFB or of another element, such as a protein, of the immune system or more specifically of the complement pathway. Preferably, the further therapeutic agent is one of the following: a) a peptide that inhibits the expression or activity of one of the components of the complement pathway, preferably CFB, C3, C5 or one of their subunits or proteolytic cleavage products; b) an antibody that specifically binds under physiological conditions to one of the components of the complement pathway, preferably CFB, C3, C5 or one of their subunits or proteolytic cleavage products; c) Eculizumab or an antigen-binding derivative thereof.

Eculizumab is a humanised monoclonal antibody that specifically binds to the complement component C5 and is commercialised under the trade name SOLIRIS®. It specifically binds the complement component C5 with high affinity and inhibits cleavage of C5 to C5a and C5b. The antibody is for example described in the patent EP 0 758 904 B1 and its family members.

5

In certain embodiments, two or more nucleic acids of the invention with different sequences may be administered simultaneously or sequentially.

10 In another aspect, the present invention provides a composition, e.g., a pharmaceutical composition, comprising one or a combination of different nucleic acids of the invention and at least one pharmaceutically acceptable carrier.

Dosage levels for the therapeutic agents and compositions of the invention can be determined by those skilled in the art by experimentation. In one aspect, a unit dose may contain between
15 about 0.01 mg/kg and about 100 mg/kg body weight of nucleic acid or conjugated nucleic acid. Alternatively, the dose can be from 10 mg/kg to 25 mg/kg body weight, or 1 mg/kg to 10 mg/kg body weight, or 0.05 mg/kg to 5 mg/kg body weight, or 0.1 mg/kg to 5 mg/kg body weight, or 0.1 mg/kg to 1 mg/kg body weight, or 0.1 mg/kg to 0.5 mg/kg body weight, or 0.5 mg/kg to 1 mg/kg body weight. Alternatively, the dose can be from about 0.5 mg/kg to about 10 mg/kg
20 body weight, or about 0.6 mg/kg to about 8 mg/kg body weight, or about 0.7 mg/kg to about 7 mg/kg body weight, or about 0.8 mg/kg to about 6 mg/kg body weight, or about 0.9 mg/kg to about 5.5 mg/kg body weight, or about 1 mg/kg to about 5 mg/kg body weight, or about 1 mg/kg body weight, or about 3 mg/kg body weight, or about 5 mg/kg body weight, wherein "about" is a deviation of up to 30%, preferably up to 20%, more preferably up to 10%, yet more preferably
25 up to 5% and most preferably 0% from the indicated value. Dosage levels may also be calculated via other parameters such as, e.g., body surface area.

A dose unit of these nucleic acids preferably comprises about 1 mg/kg to about 5 mg/kg body weight, or about 1 mg/kg to about 3 mg/kg body weight, or about 1 mg/kg body weight, or
30 about 3 mg/kg body weight, or about 5 mg/kg body weight. The CFB mRNA level in the liver and/or the CFB protein level in the plasma or blood of a subject treated by a dose unit of the nucleic acid is preferably decreased at the time point of maximum effect by at least 30%, at least 40%, at least 50%, at least 60% or at least 70% as compared to a control that was not treatment with the nucleic acid or treated with a control nucleic acid under comparable
35 conditions.

The dosage and frequency of administration may vary depending on whether the treatment is therapeutic or prophylactic (e.g., preventative), and may be adjusted during the course of treatment. In certain prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a relatively long period of time. Some subjects may continue
5 to receive treatment over their lifetime. In certain therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient may be switched to a suitable prophylactic dosing regimen.

10 Actual dosage levels of a nucleic acid of the invention alone or in combination with one or more other active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without causing deleterious side effects to the subject or patient. A selected dosage level will
15 depend upon a variety of factors, such as pharmacokinetic factors, including the activity of the particular nucleic acid or composition employed, the route of administration, the time of administration, the rate of excretion of the particular nucleic acid being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior
20 medical history of the subject or patient being treated, and similar factors well known in the medical arts.

The pharmaceutical composition may be a sterile injectable aqueous suspension or solution, or in a lyophilized form.

25 The pharmaceutical compositions can be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The
30 unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms. It may be provided in single dose injectable form, for example in the form of a pen. Compositions may be formulated for any suitable route and means of administration.

35 The therapeutic agents and pharmaceutical compositions of the present invention may be administered to a mammalian subject in a pharmaceutically effective dose. The mammal may be selected from a human, a non-human primate, a simian or prosimian, a dog, a cat, a horse,

cattle, a pig, a goat, a sheep, a mouse, a rat, a hamster, a hedgehog and a guinea pig, or other species of relevance. On this basis, "CFB" as used herein denotes nucleic acid or protein in any of the above-mentioned species, if expressed therein naturally or artificially, but preferably this wording denotes human nucleic acids or proteins.

5

Pharmaceutical compositions of the invention may be administered alone or in combination with one or more other therapeutic or diagnostic agents. A combination therapy may include a nucleic acid of the present invention combined with at least one other therapeutic agent selected based on the particular patient, disease or condition to be treated. Examples of other
10 such agents include, *inter alia*, a therapeutically active small molecule or polypeptide, a single chain antibody, a classical antibody or fragment thereof, or a nucleic acid molecule which modulates gene expression of one or more additional genes, and similar modulating therapeutics which may complement or otherwise be beneficial in a therapeutic or prophylactic treatment regimen.

15

Pharmaceutical compositions are typically sterile and stable under the conditions of manufacture and storage. The composition may be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier may be a solvent or dispersion medium containing, for example, water, alcohol such as ethanol, polyol
20 (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), or any suitable mixtures. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by use of surfactants according to formulation chemistry well known in the art. In certain embodiments, isotonic agents, e.g., sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride may be
25 desirable in the composition. Prolonged absorption of injectable compositions may be brought about by including in the composition an agent that delays absorption for example, monostearate salts and gelatine.

30

One aspect of the invention is a nucleic acid or a composition disclosed herein for use as a therapeutic agent. The nucleic acid or composition is preferably for use in the prophylaxis or treatment of a disease, disorder or syndrome.

35

The present invention provides a nucleic acid for use, alone or in combination with one or more additional therapeutic agents in a pharmaceutical composition, for treatment or prophylaxis of conditions, diseases and disorders responsive to inhibition of CFB expression.

One aspect of the invention is the use of a nucleic acid or a composition as disclosed herein in the prophylaxis or treatment of a disease, disorder or syndrome.

5 Nucleic acids and pharmaceutical compositions of the invention may be used in the treatment of a variety of conditions, disorders or diseases. Treatment with a nucleic acid of the invention preferably leads to *in vivo* CFB depletion, preferably in the liver and/or in blood. As such, nucleic acids of the invention, and compositions comprising them, will be useful in methods for treating a variety of pathological disorders in which inhibiting the expression of CFB may be beneficial. The present invention provides methods for treating a disease, disorder or syndrome comprising the step of administering to a subject in need thereof a prophylactically or therapeutically effective amount of a nucleic acid of the invention.

10 The invention thus provides methods of prophylaxis or treatment of a disease, disorder or syndrome, the method comprising the step of administering to a subject (e.g., a patient) in need thereof a therapeutically effective amount of a nucleic acid or pharmaceutical composition comprising a nucleic acid of the invention.

20 The most desirable therapeutically effective amount is an amount that will produce a desired efficacy of a particular treatment selected by one of skill in the art for a given subject in need thereof. This amount will vary depending upon a variety of factors understood by the skilled worker, including but not limited to the characteristics of the therapeutic compound (including activity, pharmacokinetics, pharmacodynamics, and bioavailability), the physiological condition of the subject (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication), the nature of the pharmaceutically acceptable carrier or carriers in the formulation, and the route of administration. One skilled in the clinical and pharmacological arts will be able to determine a therapeutically effective amount through experimentation, namely by monitoring a subject's response to administration of a compound and adjusting the dosage accordingly. See, e.g., Remington: The Science and Practice of Pharmacy 21st Ed., Univ. of Sciences in Philadelphia (USIP), Lippincott Williams & Wilkins, Philadelphia, PA, 2005.

In certain embodiments, nucleic acids and pharmaceutical compositions of the invention may be used to treat or prevent a disease, disorder or syndrome.

35 In certain embodiments, the present invention provides methods for prophylaxis or treatment of a disease, disorder or syndrome in a mammalian subject, such as a human, the method

comprising the step of administering to a subject in need thereof a prophylactically or therapeutically effective amount of a nucleic acid as disclosed herein.

Administration of a "therapeutically effective dosage" of a nucleic acid of the invention may
5 result in a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction.

10 Nucleic acids of the invention may be beneficial in treating or diagnosing a disease, disorder or syndrome that may be diagnosed or treated using the methods described herein. Treatment and diagnosis of other diseases, disorders or syndromes are also considered to fall within the scope of the present invention.

One aspect of the invention is a method of prophylaxis or treatment of a disease, disorder or
15 syndrome comprising administering a pharmaceutically effective dose or amount a nucleic acid or a composition disclosed herein to an individual in need of treatment, preferably wherein the nucleic acid or composition is administered to the subject subcutaneously, intravenously or by oral, rectal, pulmonary, intramuscular or intraperitoneal administration. Preferably, it is administered subcutaneously.

20 The relevant disease, disorder or syndrome is preferably a complement-mediated disease, disorder or syndrome or a disease disorder or syndrome associated with the complement pathway, and particularly the alternative complement pathway.

25 The disease, disorder or syndrome is typically associated with aberrant activation and/or over-activation (hyper-activation) of the complement pathway (particularly the alternative pathway) and/or with over-expression or ectopic expression or localisation or accumulation of CFB, or the complement component C3. One example of a disease that involves accumulation of C3 is C3 glomerulopathy (C3G). In this disease, CFB accumulates in the kidney glomeruli. The
30 aberrant or over activation of the complement pathway may have genetic causes or may be acquired.

The disease, disorder or syndrome may be a) selected from the group comprising, and preferably consisting of C3 glomerulopathy (C3G), paroxysmal nocturnal hemoglobinuria
35 (PNH), atypical hemolytic uremic syndrome (aHUS), lupus nephritis, IgA nephropathy (IgA N), myasthenia gravis (MG), primary membranous nephropathy, immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), systemic

lupus erythematosus (SLE), ischemia/reperfusion injury, age-related macular degeneration (AMD), rheumatoid arthritis (RA), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), dysbiotic periodontal disease, malarial anaemia, neuromyelitis optica, post-HCT / solid organ transplant (TMAs), Guillain-Barré syndrome, membranous glomerulonephritis, thrombotic thrombocytopenic purpura and sepsis; or b) selected from the group comprising, or preferably consisting of C3 glomerulopathy (C3G), paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), lupus nephritis, IgA nephropathy (IgA N) and primary membranous nephropathy; or c) selected from the group comprising, or preferably consisting of C3 glomerulopathy (C3G), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), atypical hemolytic uremic syndrome (aHUS), myasthenia gravis (MG), IgA nephropathy (IgA N), paroxysmal nocturnal hemoglobinuria (PNH); d) selected from the group comprising, or preferably consisting of C3 glomerulopathy (C3G), myasthenia gravis (MG), neuromyelitis optica, atypical hemolytic uremic syndrome (aHUS), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), IgA nephropathy (IgA N), post-HCT / solid organ transplant (TMAs), Guillain-Barré syndrome, paroxysmal nocturnal hemoglobinuria (PNH), membranous glomerulonephritis, lupus nephritis and thrombotic thrombocytopenic purpura; e) C3 glomerulopathy (C3G) and IgA nephropathy (IgA N); or f) it is C3 glomerulopathy (C3G). The subjects to be treated with a nucleic acid or composition according to the invention are preferably subjects that are affected by or are at risk of being affected by one of these diseases, disorders or syndromes.

A nucleic acid or compositions disclosed herein may be for use in a regimen comprising treatments once or twice weekly, every week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, every eight weeks, every nine weeks, every ten weeks, every eleven weeks, every twelve weeks, every three months, every four months, every five months, every six months or in regimens with varying dosing frequency such as combinations of the before-mentioned intervals. The nucleic acid or composition may be for use subcutaneously, intravenously or using any other application routes such as oral, rectal, pulmonary, or intraperitoneal. Preferably, it is for use subcutaneously.

In cells and/or subjects treated with or receiving a nucleic acid or composition as disclosed herein, the CFB expression may be inhibited compared to untreated cells and/or subjects by a range from 15% up to 100% but at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% or intermediate values. The level of inhibition may allow treatment of a disease associated with CFB expression or overexpression or complement over-activation, or may serve to further investigate the functions and physiological roles of the CFB gene products. The level of inhibition is preferably measured in the liver or in

the blood or in the kidneys, preferably in the blood, of the subject treated with the nucleic acid or composition.

One aspect is the use of a nucleic acid or composition as disclosed herein in the manufacture of a medicament for treating a disease, disorder or syndromes, such as those as listed above or additional pathologies associated with elevated levels of CFB, preferably in the blood or in the kidneys, or over activation of the complement pathway, or additional therapeutic approaches where inhibition of CFB expression is desired. A medicament is a pharmaceutical composition.

Each of the nucleic acids of the invention and pharmaceutically acceptable salts and solvates thereof constitutes an individual embodiment of the invention.

Also included in the invention is a method of prophylaxis or treatment of a disease, disorder or syndrome, such as those listed above, comprising administration of a composition comprising a nucleic acid or composition as described herein, to an individual in need thereof. The nucleic acid or composition may, for example, be administered in a regimen comprising treatments twice every week, once every week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, or every eight to twelve or more weeks or in regimens with varying dosing frequency such as combinations of the before-mentioned intervals. The nucleic acid or conjugated nucleic acid may be for use subcutaneously or intravenously or other application routes such as oral, rectal or intraperitoneal.

A nucleic acid of the invention may be administered by any appropriate administration pathway known in the art, including but not limited to aerosol, enteral, nasal, ophthalmic, oral, parenteral, rectal, vaginal, or transdermal (e.g., topical administration of a cream, gel or ointment, or by means of a transdermal patch). "Parenteral administration" is typically associated with injection at or in communication with the intended site of action, including infraorbital, infusion, intraarterial, intracapsular, intracardiac, intradermal, intramuscular, intraperitoneal, intrapulmonary, intraspinal, intrasternal, intrathecal, intrauterine, intravenous, subarachnoid, subcapsular, subcutaneous, transmucosal, or transtracheal administration.

The use of a chemical modification pattern of the nucleic acids confers nuclease stability in serum and makes for example subcutaneous application route feasible.

Solutions or suspensions used for intradermal or subcutaneous application typically include one or more of: a sterile diluent such as water for injection, saline solution, fixed oils,

polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates; and/or tonicity adjusting agents such as, e.g., sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide, or buffers with citrate, phosphate, acetate and the like. Such preparations may be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Sterile injectable solutions may be prepared by incorporating a nucleic acid in the required amount in an appropriate solvent with one or a combination of ingredients described above, as required, followed by sterilization microfiltration. Dispersions may be prepared by incorporating the active compound into a sterile vehicle that contains a dispersion medium and optionally other ingredients, such as those described above. In the case of sterile powders for the preparation of sterile injectable solutions, the methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient in addition to any additional desired ingredient from a sterile-filtered solution thereof.

When a prophylactically or therapeutically effective amount of a nucleic acid of the invention is administered by, e.g., intravenous, cutaneous or subcutaneous injection, the nucleic acid will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. Methods for preparing parenterally acceptable solutions, taking into consideration appropriate pH, isotonicity, stability, and the like, are within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection will contain, in addition to a nucleic acid, an isotonic vehicle such as sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection, or other vehicle as known in the art. A pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives well known to those of skill in the art.

The amount of nucleic acid which can be combined with a carrier material to produce a single dosage form will vary depending on a variety of factors, including the subject being treated, and the particular mode of administration. In general, it will be an amount of the composition that produces an appropriate therapeutic effect under the particular circumstances. Generally, out of one hundred percent, this amount will range from about 0.01% to about 99% of nucleic acid, from about 0.1% to about 70%, or from about 1% to about 30% of nucleic acid in combination with a pharmaceutically acceptable carrier.

The nucleic acid may be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

Dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a dose may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the particular circumstances of the therapeutic situation, on a case-by-case basis. It is especially advantageous to formulate parenteral compositions in dosage unit forms for ease of administration and uniformity of dosage when administered to the subject or patient. As used herein, a dosage unit form refers to physically discrete units suitable as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce a desired therapeutic effect. The specification for the dosage unit forms of the invention depends on the specific characteristics of the active compound and the particular therapeutic or prophylactic effect(s) to be achieved and the treatment and sensitivity of any individual patient.

The nucleic acid or composition of the present invention can be produced using routine methods in the art including chemical synthesis, such as solid phase chemical synthesis.

Nucleic acids or compositions of the invention may be administered with one or more of a variety of medical devices known in the art. For example, in one embodiment, a nucleic acid of the invention may be administered with a needleless hypodermic injection device. Examples of well-known implants and modules useful in the present invention are in the art, including e.g., implantable micro-infusion pumps for controlled rate delivery; devices for administering through the skin; infusion pumps for delivery at a precise infusion rate; variable flow implantable infusion devices for continuous drug delivery; and osmotic drug delivery systems. These and other such implants, delivery systems, and modules are known to those skilled in the art.

In certain embodiments, the nucleic acid or composition of the invention may be formulated to ensure a desired distribution *in vivo*. To target a therapeutic compound or composition of the invention to a particular *in vivo* location, they can be formulated, for example, in liposomes

which may comprise one or more moieties that are selectively transported into specific cells or organs, thus enhancing targeted drug delivery.

The invention is characterized by high specificity at the molecular and tissue-directed delivery
5 level. The sequences of the nucleic acids of the invention are highly specific for their target, meaning that they do not inhibit the expression of genes that they are not designed to target or only minimally inhibit the expression of genes that they are not designed to target and/or only inhibit the expression of a low number of genes that they are not designed to target. A further level of specificity is achieved when nucleic acids are linked to a ligand that is
10 specifically recognised and internalised by a particular cell type. This is for example the case when a nucleic acid is linked to a ligand comprising GalNAc moieties, which are specifically recognised and internalised by hepatocytes. This leads to the nucleic acid inhibiting the expression of their target only in the cells that are targeted by the ligand to which they are linked. These two levels of specificity potentially confer a better safety profile than the currently
15 available treatments. In certain embodiments, the present invention thus provides nucleic acids of the invention linked to a ligand comprising one or more GalNAc moieties, or comprising one or more other moieties that confer cell-type or tissue-specific internalisation of the nucleic acid thereby conferring additional specificity of target gene knockdown by RNA interference.

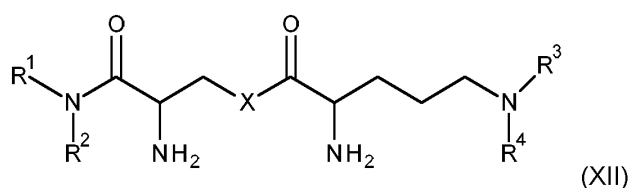
20 The nucleic acid as described herein may be formulated with a lipid in the form of a liposome. Such a formulation may be described in the art as a lipoplex. The composition with a lipid/liposome may be used to assist with delivery of the nucleic acid of the invention to the target cells. The lipid delivery system herein described may be used as an alternative to a conjugated ligand. The modifications herein described may be present when using the nucleic
25 acid of the invention with a lipid delivery system or with a ligand conjugate delivery system.

Such a lipoplex may comprise a lipid composition comprising:

- i) a cationic lipid, or a pharmaceutically acceptable salt thereof;
- ii) a steroid;
- 30 iii) a phosphatidylethanolamine phospholipid; and/or
- iv) a PEGylated lipid.

The cationic lipid may be an amino cationic lipid.

35 The cationic lipid may have the formula (XII):



or a pharmaceutically acceptable salt thereof, wherein:

X represents O, S or NH;

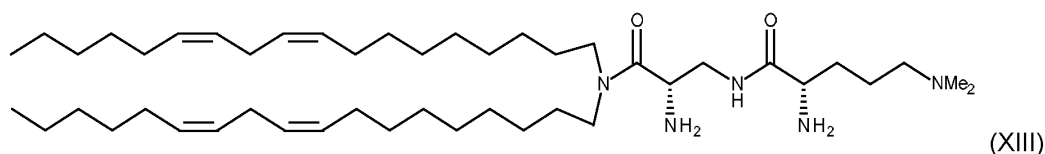
R¹ and R² each independently represents a C₄-C₂₂ linear or branched alkyl chain or a C₄-C₂₂

5 linear or branched alkenyl chain with one or more double bonds, wherein the alkyl or alkenyl chain optionally contains an intervening ester, amide or disulfide;

when X represents S or NH, R³ and R⁴ each independently represent hydrogen, methyl, ethyl, a mono- or polyamine moiety, or R³ and R⁴ together form a heterocyclyl ring;

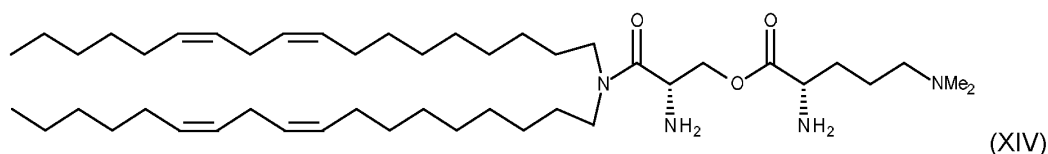
when X represents O, R³ and R⁴ each independently represent hydrogen, methyl, ethyl, a
10 mono- or polyamine moiety, or R³ and R⁴ together form a heterocyclyl ring, or R³ represents hydrogen and R⁴ represents C(NH)(NH₂).

The cationic lipid may have the formula (XIII):



15 or a pharmaceutically acceptable salt thereof.

The cationic lipid may have the formula (XIV):



or a pharmaceutically acceptable salt thereof.

20

The content of the cationic lipid component may be from about 55 mol% to about 65 mol% of the overall lipid content of the composition. In particular, the cationic lipid component is about 59 mol% of the overall lipid content of the composition.

25 The compositions can further comprise a steroid. The steroid may be cholesterol. The content of the steroid may be from about 26 mol% to about 35 mol% of the overall lipid content of the lipid composition. More particularly, the content of steroid may be about 30 mol% of the overall lipid content of the lipid composition.

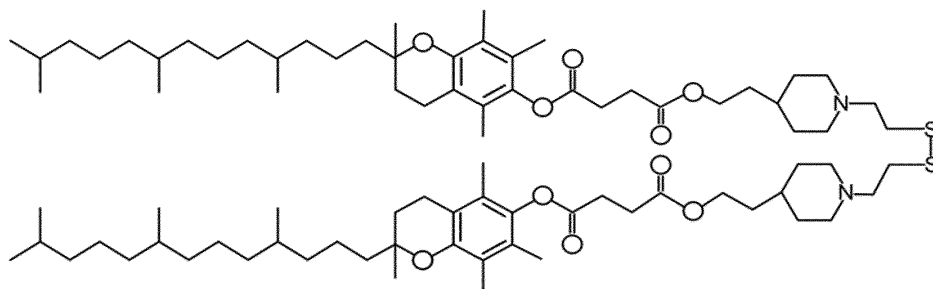
The phosphatidylethanolamine phospholipid may be selected from the group consisting of 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (DPhyPE), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), 1,2-Dilauroyl-sn-glycero-3-phosphoethanolamine (DLPE), 1,2-Dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE), 1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE), 1,2-Dilinoleoyl-sn-glycero-3-phosphoethanolamine (DLoPE), 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine (POPE), 1,2-Dierucoyl-sn-glycero-3-phosphoethanolamine (DEPE), 1,2-Disqualeoyl-sn-glycero-3-phosphoethanolamine (DSQPE) and 1-Stearoyl-2-linoleoyl-sn-glycero-3-phosphoethanolamine (SLPE). The content of the phospholipid may be about 10 mol% of the overall lipid content of the composition.

The PEGylated lipid may be selected from the group consisting of 1,2-dimyristoyl-sn-glycerol, methoxypolyethylene glycol (DMG-PEG) and C16-Ceramide-PEG. The content of the PEGylated lipid may be about 1 to 5 mol% of the overall lipid content of the composition.

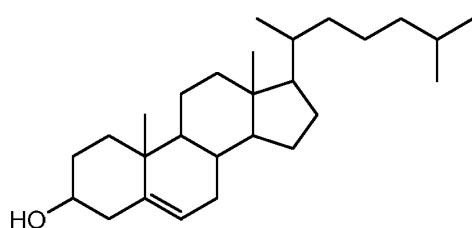
The content of the cationic lipid component in the composition may be from about 55 mol% to about 65 mol% of the overall lipid content of the lipid composition, preferably about 59 mol% of the overall lipid content of the lipid composition.

The composition may have a molar ratio of the components of i):ii):iii):iv) selected from 55:34:10:1; 56:33:10:1; 57:32:10:1; 58:31:10:1; 59:30:10:1; 60:29:10:1; 61:28:10:1; 62:27:10:1; 63:26:10:1; 64:25:10:1; and 65:24:10:1.

The composition may comprise a cationic lipid having the structure

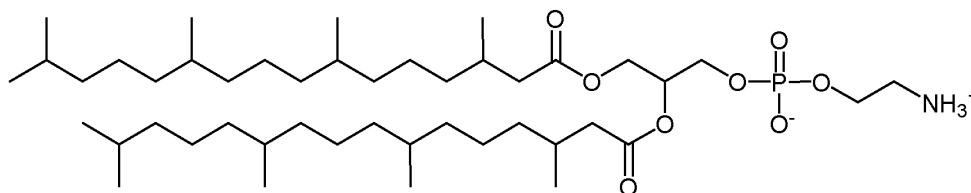


a steroid having the structure



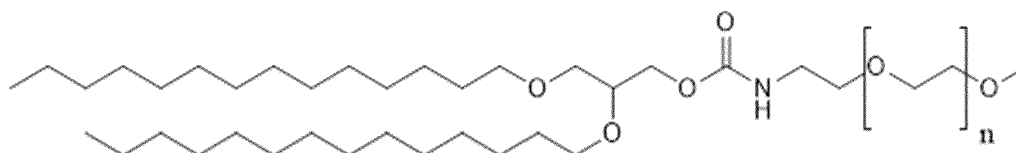
Cholesterol

a phosphatidylethanolamine phospholipid having the structure



DPhyPE

and a PEGylated lipid having the structure



mPEG-2000-DMG

5

Neutral liposome compositions may be formed from, for example, dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions may be formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes may be formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition may be formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

15 A positively charged synthetic cationic lipid, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of fusing with the negatively charged lipids of the cell membranes of tissue culture cells. DOTMA analogues can also be used to form liposomes.

20

Derivatives and analogues of lipids described herein may also be used to form liposomes.

A liposome containing a nucleic acid can be prepared by a variety of methods. In one example, the lipid component of a liposome is dissolved in a detergent so that micelles are formed with the lipid component. For example, the lipid component can be an amphipathic cationic lipid or lipid conjugate. The detergent can have a high critical micelle concentration and may be nonionic. Exemplary detergents include cholate, CHAPS, octylglucoside, deoxycholate, and lauroyl sarcosine. The nucleic acid preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the nucleic acid and condense around the nucleic acid to form a liposome. After condensation, the detergent is removed, e.g., by dialysis, to yield a liposomal preparation of nucleic acid.

If necessary, a carrier compound that assists in condensation can be added during the condensation reaction, e.g., by controlled addition. For example, the carrier compound can be a polymer other than a nucleic acid (e.g., spermine or spermidine). pH can also be adjusted to favour condensation.

Nucleic acid formulations of the present invention may include a surfactant. In one embodiment, the nucleic acid is formulated as an emulsion that includes a surfactant.

A surfactant that is not ionized is a non-ionic surfactant. Examples include non-ionic esters, such as ethylene glycol esters, propylene glycol esters, glyceryl esters etc., nonionic alkanolamides, and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers.

A surfactant that carries a negative charge when dissolved or dispersed in water is an anionic surfactant. Examples include carboxylates, such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates.

A surfactant that carries a positive charge when dissolved or dispersed in water is a cationic surfactant. Examples include quaternary ammonium salts and ethoxylated amines.

A surfactant that has the ability to carry either a positive or negative charge is an amphoteric surfactant. Examples include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

"Micelles" are defined herein as a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions of the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic. A micelle
5 may be formed by mixing an aqueous solution of the nucleic acid, an alkali metal alkyl sulphate, and at least one micelle forming compound.

Exemplary micelle forming compounds include lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber
10 extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerol, polyglycerol, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof.

15 Phenol and/or m-cresol may be added to the mixed micellar composition to act as a stabiliser and preservative. An isotonic agent such as glycerine may as be added.

A nucleic acid preparation may be incorporated into a particle such as a microparticle.
20 Microparticles can be produced by spray-drying, lyophilisation, evaporation, fluid bed drying, vacuum drying, or a combination of these methods.

Definitions

25 As used herein, the terms "inhibit", "down-regulate", or "reduce" with respect to gene expression mean that the expression of the gene, or the level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits (e.g., mRNA), or the activity of one or more proteins or protein subunits, is reduced below that observed either in the absence of the nucleic acid or conjugated nucleic acid of the invention or as compared to that
30 obtained with an siRNA molecule with no known homology to the human transcript (herein termed non-silencing control). Such control may be conjugated and modified in an analogous manner to the molecule of the invention and delivered into the target cell by the same route. The expression after treatment with the nucleic acid of the invention may be reduced to 95%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 15%, 10%, 5% or 0% or to intermediate values,
35 or less than that observed in the absence of the nucleic acid or conjugated nucleic acid. The expression may be measured in the cells to which the nucleic acid is applied. Alternatively, especially if the nucleic acid is administered to a subject, the level can be measured in a

different group of cells or in a tissue or an organ or in a body fluid such as blood or plasma. The level of inhibition is preferably measured in conditions that have been selected because they show the greatest effect of the nucleic acid on the target mRNA level in cells treated with the nucleic acid *in vitro*. The level of inhibition may for example be measured after 24 hours or
5 48 hours of treatment with a nucleic acid at a concentration of between 0.038 nM – 10 µM, preferably 0.5 nM, 1 nM, 10 nM or 100 nM. These conditions may be different for different nucleic acid sequences or for different types of nucleic acids, such as for nucleic acids that are unmodified or modified or conjugated to a ligand or not. Examples of suitable conditions for determining levels of inhibition are described in the examples.

10

By nucleic acid it is meant a nucleic acid comprising two strands comprising nucleotides, that is able to interfere with gene expression. Inhibition may be complete or partial and results in down regulation of gene expression in a targeted manner. The nucleic acid comprises two separate polynucleotide strands; the first strand, which may also be a guide strand; and a
15 second strand, which may also be a passenger strand. The first strand and the second strand may be part of the same polynucleotide molecule that is self-complementary which 'folds' back to form a double-stranded molecule. The nucleic acid may be an siRNA molecule.

20

The nucleic acid may comprise ribonucleotides, modified ribonucleotides, deoxynucleotides, deoxyribonucleotides, or nucleotide analogues non-nucleotides that are able to mimic nucleotides such that they may 'pair' with the corresponding base on the target sequence or complementary strand. The nucleic acid may further comprise a double-stranded nucleic acid portion or duplex region formed by all or a portion of the first strand (also known in the art as a guide strand) and all or a portion of the second strand (also known in the art as a passenger
25 strand). The duplex region is defined as beginning with the first base pair formed between the first strand and the second strand and ending with the last base pair formed between the first strand and the second strand, inclusive.

30

By duplex region it is meant the region in two complementary or substantially complementary oligonucleotides that form base pairs with one another, either by Watson-Crick base pairing or any other manner that allows for a duplex between oligonucleotide strands that are complementary or substantially complementary. For example, an oligonucleotide strand having 21 nucleotide units can base pair with another oligonucleotide of 21 nucleotide units, yet only 19 nucleotides on each strand are complementary or substantially complementary,
35 such that the "duplex region" consists of 19 base pairs. The remaining base pairs may exist as 5' and 3' overhangs, or as single-stranded regions. Further, within the duplex region, 100% complementarity is not required; substantial complementarity is allowable within a duplex

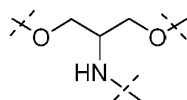
region. Substantial complementarity refers to complementarity between the strands such that they are capable of annealing under biological conditions. Techniques to empirically determine if two strands are capable of annealing under biological conditions are well known in the art. Alternatively, two strands can be synthesised and added together under biological conditions to determine if they anneal to one another. The portion of the first strand and second strand that forms at least one duplex region may be fully complementary and is at least partially complementary to each other. Depending on the length of a nucleic acid, a perfect match in terms of base complementarity between the first strand and the second strand is not necessarily required. However, the first and second strands must be able to hybridise under physiological conditions.

As used herein, the terms “non-pairing nucleotide analogue” means a nucleotide analogue which includes a non-base pairing moiety including but not limited to: 6 des amino adenosine (Nebularine), 4-Me-indole, 3-nitropyrrole, 5-nitroindole, Ds, Pa, N3-Me ribo U, N3-Me riboT, N3-Me dC, N3-Me-dT, N1-Me-dG, N1-Me-dA, N3-ethyl-dC, and N3-Me dC. In some embodiments the non-base pairing nucleotide analogue is a ribonucleotide. In other embodiments it is a deoxyribonucleotide.

As used herein, the term, “terminal functional group” includes without limitation a halogen, alcohol, amine, carboxylic, ester, amide, aldehyde, ketone, and ether groups.

An “overhang” as used herein has its normal and customary meaning in the art, i.e., a single-stranded portion of a nucleic acid that extends beyond the terminal nucleotide of a complementary strand in a double-strand nucleic acid. The term “blunt end” includes double-stranded nucleic acid whereby both strands terminate at the same position, regardless of whether the terminal nucleotide(s) are base-paired. The terminal nucleotide of a first strand and a second strand at a blunt end may be base paired. The terminal nucleotide of a first strand and a second strand at a blunt end may not be paired. The terminal two nucleotides of a first strand and a second strand at a blunt end may be base-paired. The terminal two nucleotides of a first strand and a second strand at a blunt end may not be paired.

The term “serinol-derived linker moiety” means the linker moiety comprises the following structure:



An O atom of said structure typically links to an RNA strand and the N atom typically links to the targeting ligand.

The terms "patient," "subject," and "individual" may be used interchangeably and refer to either a human or a non-human animal. These terms include mammals such as humans, primates, livestock animals (e.g., bovines, porcines), companion animals (e.g., canines, felines) and rodents (e.g., mice and rats).

5

As used herein, "treating" or "treatment" and grammatical variants thereof refer to an approach for obtaining beneficial or desired clinical results. The term may refer to slowing the onset or rate of development of a condition, disorder or disease, reducing or alleviating symptoms associated with it, generating a complete or partial regression of the condition, or some combination of any of the above. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, reduction or alleviation of symptoms, diminishment of extent of disease, stabilization (i.e., not worsening) of state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival relative to expected survival time if not receiving treatment. A subject (e.g., a human) in need of treatment may thus be a subject already afflicted with the disease or disorder in question. The term "treatment" includes inhibition or reduction of an increase in severity of a pathological state or symptoms relative to the absence of treatment, and is not necessarily meant to imply complete cessation of the relevant disease, disorder or condition.

20

As used herein, the terms "prophylaxis" and grammatical variants thereof refer to an approach for inhibiting or preventing the development, progression, or time or rate of onset of a condition, disease or disorder, and may relate to pathology and/or symptoms. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, prevention, inhibition or slowing of symptoms, progression or development of a disease, whether detectable or undetectable. A subject (e.g., a human) in need of prophylaxis may thus be a subject not yet afflicted with the disease or disorder in question. The term "prophylaxis" includes slowing the onset of disease relative to the absence of treatment, and is not necessarily meant to imply permanent prevention of the relevant disease, disorder or condition. Thus "prophylaxis" of a condition may in certain contexts refer to reducing the risk of developing the condition, or preventing, inhibiting or delaying the development of symptoms associated with the condition. It will be understood that prophylaxis may be considered as treatment or therapy.

35 As used herein, an "effective amount," "prophylactically effective amount", "therapeutically effective amount" or "effective dose" is an amount of a composition (e.g., a therapeutic composition or agent) that produces at least one desired therapeutic effect in a subject, such

as preventing or treating a target condition or beneficially alleviating a symptom associated with the condition.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt that is not harmful
5 to a patient or subject to which the salt in question is administered. It may be a salt chosen,
e.g., among acid addition salts and basic salts. Examples of acid addition salts include chloride
salts, citrate salts and acetate salts. Examples of basic salts include salts wherein the cation
is selected from alkali metal cations, such as sodium or potassium ions, alkaline earth metal
cations, such as calcium or magnesium ions, as well as substituted ammonium ions, such as
10 ions of the type $N(R^1)(R^2)(R^3)(R^4)^+$, wherein R^1 , R^2 , R^3 and R^4 independently will typically
designate hydrogen, optionally substituted C1-6-alkyl groups or optionally substituted C2-6-
alkenyl groups. Examples of relevant C1-6-alkyl groups include methyl, ethyl, 1-propyl and 2-
propyl groups. Examples of C2-6-alkenyl groups of possible relevance include ethenyl, 1-
propenyl and 2-propenyl. Other examples of pharmaceutically acceptable salts are described
15 in "Remington's Pharmaceutical Sciences", 17th edition, Alfonso R. Gennaro (Ed.), Mark
Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the
"Encyclopaedia of Pharmaceutical Technology", 3rd edition, James Swarbrick (Ed.), Informa
Healthcare USA (Inc.), NY, USA, 2007, and in J. Pharm. Sci. 66: 2 (1977). A "pharmaceutically
acceptable salt" retains qualitatively a desired biological activity of the parent compound
20 without imparting any undesired effects relative to the compound. Examples of
pharmaceutically acceptable salts include acid addition salts and base addition salts. Acid
addition salts include salts derived from nontoxic inorganic acids, such as hydrochloric, nitric,
phosphorous, phosphoric, sulfuric, hydrobromic, hydroiodic and the like, or from nontoxic
organic acids such as aliphatic mono- and di-carboxylic acids, phenyl-substituted alkanolic
25 acids, hydroxy alkanolic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the
like. Base addition salts include salts derived from alkaline earth metals, such as sodium,
potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such
as N, N'-dibenzylethylenediamine, N-methylglucamine, chlorprocaine, choline,
diethanolamine, ethylenediamine, procaine and the like.

30

The term "pharmaceutically acceptable carrier" includes any of the standard pharmaceutical
carriers. Pharmaceutically acceptable carriers for therapeutic use are well known in the
pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences,
Mack Publishing Co. (A. R. Gennaro edit. 1985). For example, sterile saline and phosphate-
35 buffered saline at slightly acidic or physiological pH may be used. Exemplary pH buffering
agents include phosphate, citrate, acetate, tris(hydroxymethyl)aminomethane (TRIS), N-
Tris(hydroxymethyl)methyl-3-aminopropanesulphonic acid (TAPS), ammonium bicarbonate,

diethanolamine, histidine, which is a preferred buffer, arginine, lysine, or acetate or mixtures thereof. The term further encompasses any agents listed in the US Pharmacopeia for use in animals, including humans. A "pharmaceutically acceptable carrier" includes any and all physiologically acceptable, i.e., compatible, solvents, dispersion media, coatings, antimicrobial agents, isotonic and absorption delaying agents, and the like. In certain embodiments, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion). Depending on selected route of administration, the nucleic acid may be coated in a material or materials intended to protect the compound from the action of acids and other natural inactivating conditions to which the nucleic acid may be exposed when administered to a subject by a particular route of administration.

The term "solvate" in the context of the present invention refers to a complex of defined stoichiometry formed between a solute (*in casu*, a nucleic acid compound or pharmaceutically acceptable salt thereof according to the invention) and a solvent. The solvent in this connection may, for example, be water or another pharmaceutically acceptable, typically small-molecular organic species, such as, but not limited to, acetic acid or lactic acid. When the solvent in question is water, such a solvate is normally referred to as a hydrate.

The invention will now be described with reference to the following non-limiting Figures and Examples.

Brief description of the Figures

Figure 1 shows relative CFB mRNA expression in primary Cynomolgus monkey hepatocytes after incubation with GalNAc conjugated siRNAs normalized to PPIB mRNA. Ut represents target expression in untreated cells, and Ctr represents target expression after incubation with a non-targeting control siRNA.

Figure 2 shows relative CFB mRNA expression in primary human hepatocytes after incubation with GalNAc conjugated siRNAs normalized to PPIB mRNA. Ut represents target expression in untreated cells, and Ctr represents target expression after incubation with a non-targeting control siRNA.

Figure 3 shows relative CFB mRNA expression in primary murine hepatocytes after incubation with siRNA GalNAc-conjugates normalized to APOB mRNA. Ut represents target expression

in untreated cells, and Ctr represents target expression after incubation with a non-targeting control siRNA.

Figure 4 shows relative CFB mRNA expression in primary mouse (A), human (B) and
5 Cynomolgus monkey (C) hepatocytes after incubation with GalNAc-conjugated siRNAs to ApoB (A) or PPIB (B, C) mRNA.

Figure 5A shows relative CFB mRNA expression in % in murine liver 14 days after a single dosing of 1 or 5 mg/kg of GalNAc conjugated siRNA EV2184, EV2185, EV2187, EV2188 and
10 EV2195. One group dosed with PBS served as control. Data is shown in bar charts as mean $\pm$ SD (n=5 per group). **Figure 5B** shows relative CFB mRNA expression in % in murine liver 21 and 42 days after a single dosing of 1 or 5 mg/kg of GalNAc conjugated siRNA EV2184, EV2197, EV2185 and EV2200. One group dosed with PBS served as control. Data is shown in bar charts as mean $\pm$ SD (n=4 per group).

15

Figure 6 shows CFB mRNA reduction at 4 and 8 weeks post single subcutaneous dose of GalNAc conjugated siRNAs EV2196, EV2204 and EV2198.

20

Examples

Example 1

- 5 In vitro study in HepG2 cells showing CFB knockdown efficacy of tested siRNAs after transfection of 0.5nM and 10 nM siRNA.

CFB knockdown efficacy of siRNAs EV2001-EV2180 (Table 5b) was determined after transfection of 0.5 or 10 nM siRNA in HepG2 cells. The results are depicted in Table 3 below. At 10 nM remaining CFB levels after knockdown were in the range of 6% to 84%, at 0.5 nM
10 between 14% and 95 %. At 10 nM the most potent siRNAs were EV2160, EV2159, EV2167, EV2050, EV2036, EV2101 and EV2042.

For transfection of HepG2 cells with siRNAs, cells were seeded at a density of 15,000 cells / well in 96-well tissue culture plates (TPP, Cat. 92096, Switzerland). Transfection of siRNA was carried out with Lipofectamine RNAiMax (Invitrogen/Life Technologies, Cat. 13778-500,
15 Germany) according to manufacturer's instructions directly before seeding. The dual dose screen was performed with CFB siRNAs in triplicates at 10nM and 0.5 nM, respectively, with scrambled siRNA and luciferase-targeting siRNA as unspecific controls. After 24h of incubation with siRNAs, medium was removed, and cells were lysed in 250µl Lysis Buffer (InviTrap RNA Cell HTS96 Kit/C (Stratec, Cat. 7061300400, Germany)) and then frozen at -80°C . RNA was
20 isolated using the InviTrap RNA Cell HTS96 Kit/C (Stratec, Cat. 7061300400, Germany). RT-qPCR was performed using CFB and PPIB specific primer probe sets and Takyon™ One-Step Low Rox Probe 5X MasterMix dTTP on the QuantStudio6 device from Applied Biosystems in single-plex 384 well format. Expression differences were calculated using the delta delta Ct method and relative expression of CFB normalized to the house keeping gene PPIB was
25 determined. Results are expressed as % remaining CFB mRNA after siRNA transfection in Table 3.

Duplex	% remaining mRNA at 10 nM		% remaining mRNA at 0,5 nM	
	Mean	SD	Mean	SD
EV2001	40,6	3,3	84,7	10,1
EV2002	16,4	5,0	62,2	7,1
EV2003	32,6	5,2	87,9	2,9
EV2004	34,3	7,5	79,5	3,5
EV2005	8,9	2,0	32,9	4,3
EV2006	12,4	4,8	53,3	14,2
EV2007	38,7	6,6	75,3	6,1
EV2008	12,1	3,4	36,4	3,7
EV2009	13,3	2,3	39,8	0,3
EV2010	9,4	2,5	31,0	9,5
EV2011	12,1	0,6	28,2	7,1
EV2012	10,4	1,8	34,2	12,9
EV2013	12,0	3,4	46,3	12,2
EV2014	76,2	5,6	91,5	7,2
EV2015	20,6	3,6	72,8	6,8
EV2016	14,0	4,6	48,1	2,8
EV2017	8,1	0,7	32,5	8,2
EV2018	12,6	1,2	28,7	4,8
EV2019	13,2	1,8	44,9	4,0
EV2020	11,3	1,3	35,4	2,6
EV2021	36,6	3,7	82,6	6,4
EV2022	8,8	1,9	29,7	1,6
EV2023	12,4	0,8	31,7	1,8
EV2024	9,1	0,6	24,3	1,9
EV2025	18,2	0,4	70,9	9,6
EV2026	9,3	1,8	31,4	7,2
EV2027	13,6	2,9	45,4	5,6
EV2028	13,8	2,2	55,7	3,4
EV2029	9,9	1,8	23,2	3,8
EV2030	12,6	2,1	53,7	3,6
EV2031	10,8	1,3	32,3	4,1
EV2032	10,8	3,4	43,5	4,1
EV2033	21,7	2,6	61,7	2,8
EV2034	15,3	2,9	54,3	3,4
EV2035	16,8	3,0	46,3	5,9
EV2036	7,2	2,3	15,5	1,6
EV2037	29,6	1,9	75,2	4,8
EV2038	11,2	3,5	34,3	5,2
EV2039	32,9	2,3	76,2	5,4
EV2040	8,5	2,2	24,6	3,8
EV2041	9,8	1,0	23,7	3,2

Duplex	% remaining mRNA at 10 nM		% remaining mRNA at 0,5 nM	
EV2042	7,8	2,2	41,1	11,9
EV2043	60,6	8,8	86,7	5,6
EV2044	9,8	1,2	26,8	2,3
EV2045	15,9	4,5	58,4	6,4
EV2046	9,5	4,4	33,0	6,8
EV2047	11,6	1,5	18,5	2,3
EV2048	9,3	1,6	17,9	1,7
EV2049	9,8	2,0	26,7	1,3
EV2050	7,2	0,5	13,6	1,4
EV2051	12,9	1,4	34,2	9,3
EV2052	23,2	2,9	46,0	7,6
EV2053	17,3	2,0	48,0	6,2
EV2054	23,9	1,3	77,8	7,3
EV2055	37,2	0,9	83,3	9,4
EV2056	52,6	4,9	77,6	4,4
EV2057	49,0	2,9	89,4	6,5
EV2058	54,1	3,8	81,9	8,3
EV2059	38,0	3,2	86,9	2,8
EV2060	50,9	8,5	93,5	2,0
EV2061	53,6	7,6	94,7	2,6
EV2062	29,1	6,8	82,7	2,1
EV2063	19,3	2,6	52,8	7,7
EV2064	45,5	2,2	82,0	3,4
EV2065	15,4	1,8	62,0	5,7
EV2066	15,6	4,1	42,0	4,8
EV2067	49,9	1,8	89,6	4,4
EV2068	70,2	5,4	93,9	8,7
EV2069	26,7	3,0	64,2	2,6
EV2070	15,4	3,4	54,1	3,7
EV2071	23,9	0,3	60,5	6,8
EV2072	22,1	5,0	76,3	7,7
EV2073	15,2	3,7	51,4	8,9
EV2074	18,3	1,6	44,2	5,0
EV2075	27,0	4,6	66,8	7,6
EV2076	19,7	2,3	43,7	7,5
EV2077	28,0	5,6	68,9	6,0
EV2078	41,5	4,3	78,3	4,4
EV2079	40,5	0,9	82,4	1,7
EV2080	31,5	1,5	75,3	6,1
EV2081	15,3	3,0	27,8	2,1
EV2082	16,8	1,4	45,0	6,9
EV2083	26,3	6,1	64,8	3,3
EV2084	17,9	2,8	38,9	7,7

Duplex	% remaining mRNA at 10 nM		% remaining mRNA at 0,5 nM	
EV2085	31,8	1,0	65,6	7,9
EV2086	19,3	2,6	37,7	4,1
EV2087	15,2	1,0	39,3	6,8
EV2088	20,9	2,8	43,8	5,2
EV2089	20,1	1,2	39,0	9,0
EV2090	20,8	3,7	57,5	10,1
EV2091	28,4	5,5	72,8	10,2
EV2092	51,7	6,9	76,7	3,4
EV2093	28,2	1,4	75,5	2,3
EV2094	24,3	5,5	66,1	4,3
EV2095	10,9	3,1	35,3	11,4
EV2096	21,6	4,8	63,1	7,8
EV2097	20,1	2,6	45,7	10,6
EV2098	18,9	2,0	55,8	10,2
EV2099	13,1	2,2	38,6	8,2
EV2100	12,2	0,5	23,0	3,5
EV2101	7,5	0,2	17,4	1,5
EV2102	9,3	0,5	51,3	8,4
EV2103	16,7	1,3	42,6	5,8
EV2104	11,4	0,1	48,0	6,8
EV2105	9,1	1,0	23,4	1,5
EV2106	9,0	0,9	28,0	6,1
EV2107	7,8	1,2	20,7	1,1
EV2108	10,6	1,1	29,1	3,1
EV2109	38,3	8,7	93,7	6,7
EV2110	9,7	0,8	35,7	6,3
EV2111	29,7	3,4	73,6	6,6
EV2112	17,1	1,0	47,5	7,7
EV2113	18,4	1,8	61,8	9,7
EV2114	12,4	0,5	32,2	0,5
EV2115	14,4	1,4	37,4	0,8
EV2116	24,4	2,8	46,6	6,9
EV2117	8,1	2,9	48,9	4,9
EV2118	19,4	1,1	55,1	2,5
EV2119	42,8	5,6	94,3	7,5
EV2120	40,5	2,8	92,1	6,0
EV2121	18,5	0,8	70,9	1,2
EV2122	26,4	1,2	75,8	5,2
EV2123	31,2	2,1	62,8	4,8
EV2124	22,0	3,4	71,3	3,3
EV2125	9,9	0,7	29,1	5,4
EV2126	15,5	3,4	49,8	5,5
EV2127	21,7	2,8	75,5	8,0

Duplex	% remaining mRNA at 10 nM		% remaining mRNA at 0,5 nM	
EV2128	17,6	0,4	49,1	1,0
EV2129	23,5	3,2	57,7	4,2
EV2130	21,6	1,4	66,7	4,1
EV2131	20,4	2,0	46,0	2,0
EV2132	60,1	3,3	91,2	4,4
EV2133	15,4	6,7	35,2	3,5
EV2134	12,8	2,3	53,1	5,9
EV2135	15,4	6,7	39,7	3,9
EV2136	52,7	7,1	81,8	3,2
EV2137	15,0	2,7	40,8	6,7
EV2138	14,8	3,1	52,1	7,2
EV2139	17,2	2,8	46,0	3,4
EV2140	48,1	1,2	83,5	2,1
EV2141	12,3	0,8	35,6	7,4
EV2142	10,8	1,8	29,9	6,8
EV2143	13,4	3,0	22,0	5,3
EV2144	13,6	3,7	22,0	6,3
EV2145	21,4	4,1	19,3	4,5
EV2146	16,7	4,3	32,7	5,4
EV2147	13,3	3,2	22,8	2,7
EV2148	14,1	4,4	14,6	2,1
EV2149	11,7	5,1	22,5	2,8
EV2150	22,0	1,0	66,3	3,9
EV2151	75,6	6,3	87,6	4,5
EV2152	27,9	12,0	55,6	1,3
EV2153	59,5	9,8	93,3	2,3
EV2154	30,4	7,8	72,3	6,7
EV2155	33,7	6,7	80,0	4,9
EV2156	11,2	5,1	38,0	3,8
EV2157	21,7	5,6	40,4	5,9
EV2158	13,3	4,8	40,1	6,3
EV2159	6,8	1,8	18,7	6,9
EV2160	6,1	1,4	21,0	5,1
EV2161	20,7	2,8	65,5	11,6
EV2162	83,9	2,7	93,8	1,5
EV2163	12,7	0,7	52,2	8,7
EV2164	11,2	1,4	46,1	12,3
EV2165	16,2	4,2	54,8	12,1
EV2166	26,8	4,0	79,2	2,9
EV2167	7,1	2,1	32,3	2,9
EV2168	14,6	6,9	63,4	6,8
EV2169	20,4	1,0	88,4	2,5
EV2170	11,1	1,1	30,5	6,8

Duplex	% remaining mRNA at 10 nM		% remaining mRNA at 0,5 nM	
EV2171	13,4	2,4	38,6	6,0
EV2172	14,3	2,0	54,0	5,8
EV2173	16,2	2,6	26,6	2,0
EV2174	52,9	3,7	74,6	8,0
EV2175	12,0	3,4	23,6	2,7
EV2176	14,1	5,3	51,7	6,5
EV2177	20,6	6,3	46,0	2,9
EV2178	16,6	1,9	51,7	9,1
EV2179	30,5	3,5	76,7	9,8
EV2180	84,3	3,9	86,4	6,4

Table 3: Results of dual dose screening (10 nM and 0.5 nM) of siRNAs targeting CFB.

The identity of the single strands forming each of the siRNA duplexes as well as their sequences and modifications are to be found in the tables at the end of the description.

Example 2

- 10 *In vitro* study in primary Cynomolgus monkey hepatocytes showing CFB knockdown efficacy of tested siRNA-GalNAc-conjugates.

Expression of CFB mRNA was assessed after incubation with the GalNAc siRNA conjugates at 100 nM, 10 nM, 1 nM, 0.1 nM and 0.01 nM. siRNA conjugates are listed in Table 5c. mRNA level of the house keeping gene PPIB served as control.

- 15 To test the knockdown efficacy of the GalNAc conjugated siRNAs for CFB in primary Cynomolgus monkey hepatocytes, 45,000 cells per well (Supplier: Life Technologies and Primacyt) were seeded on collagen-coated 96-well plates (Life Technologies). siRNAs in concentrations between 100nM and 0.01 nM were added immediately after seeding. 24 hours post treatment, cells were lysed using InviTrap RNA Cell HTS96 Kit/C (Strattec). RT-qPCR was
- 20 performed using mRNA-specific primers and probes against CFB and PPIB. Expression differences were calculated using the delta delta Ct method and relative expression of CFB normalized to the house keeping gene PPIB were determined. Results are expressed as ratio of CFB to PPIB mRNA relative to untreated levels and can be found in Figure 1.

Dose dependent knockdown of CFB mRNA was observed for all tested GalNAc conjugates, with the strongest dose dependent target knockdown observed with EV2181, EV2182, EV2185, EV2186, EV2190 and EV2195.

5 Example 3

In vitro study in primary human hepatocytes showing CFB knockdown efficacy of tested siRNA-GalNAc-conjugates.

10 Expression of CFB mRNA was assessed after incubation with the GalNAc siRNA conjugates at 100 nM, 20 nM, 4 nM, 0.8 nM and 0.16 nM. Tested siRNA conjugates are listed in Table 5c. mRNA levels of the house keeping gene PPIB served as control.

To test the knockdown efficacy of the GalNAc conjugated siRNAs for CFB in primary human hepatocytes 35 000 cells per well (Supplier: Life technologies) were seeded on collagen-coated 96-well plates (Life technologies). siRNAs in concentrations between 100nM and 0.16
15 nM were added immediately after seeding. 24 hours post treatment, cells were lysed using Invitrap RNA Cell HTS96 Kit/C (Strattec). RT-qPCR was performed using mRNA-specific primers and probes against CFB and PPIB. Expression differences were calculated using the delta delta Ct method and relative expression of CFB was normalized to expression of the house keeping gene PPIB. Results are expressed as ratio of CFB to PPIB mRNA relative to
20 untreated levels and can be found in Figure 2.

Dose dependent knockdown of CFB mRNA was observed for all tested GalNAc conjugates, strongest dose dependent target knockdown was observed with EV2181, EV2182, EV2184, EV2185, EV2186, EV2190 and EV2193.

25

Example 4

In vitro study in primary mouse hepatocytes showing CFB knockdown efficacy of tested siRNA-GalNAc-conjugates.

30 Expression of CFB mRNA was assessed after incubation with the GalNAc siRNA conjugates at 100 nM, 10 nM, 1 nM, 0.1 nM and 0.01 nM. siRNA conjugates are listed in Table 5c. mRNA level of the house keeping gene ApoB served as control.

To test the knockdown efficacy of the GalNAc conjugated siRNAs for CFB in primary mouse hepatocytes, 25,000 cells per well (Supplier: Life Technologies and Primacyt) were seeded on
35 collagen-coated 96-well plates (Life Technologies). siRNAs in concentrations between 100nM

and 0.01 nM were added immediately after seeding. 24 hours post treatment, cells were lysed using InviTrap RNA Cell HTS96 Kit/C (Strattec). qPCR was performed using mRNA-specific primers and probes against CFB and ApoB. Expression differences were calculated using the delta delta Ct method and relative expression of CFB was normalized to expression of the house keeping gene ApoB. Results are expressed as ratio of CFB to ApoB mRNA relative to untreated levels and can be found in Figure 3.

Dose dependent knockdown of CFB mRNA was observed for all tested GalNAc conjugates, strongest dose dependent target knockdown was observed with EV2184, EV2185 and EV2188.

Example 5

In vitro study in primary mouse, human and Cynomolgus monkey hepatocytes showing CFB knockdown efficacy of tested siRNA-GalNAc conjugates.

Expression of CFB mRNA after incubation with the GalNAc siRNA conjugates EV2196, EV2197, EV2198, EV2199, EV2200, EV2201, EV2202, EV2203, EV2204, EV2205 and EV2206

siRNA conjugates are listed in Table 5c. mRNA level of the house keeping gene PPIB (for Cynomolgus monkey and human cells) or APOB (for mouse cells) served as control.

Mouse, human or cynomolgus monkey primary hepatocytes were seeded into collagen I-coated 96-well plates at a density of 25,000, 30,000 or 40,000 cells per well, respectively. GalNAc-conjugated siRNAs were added immediately after plating in the previously defined media to final siRNA concentrations from 100nM to 0.01 nM. Plates were then incubated at 37 °C in a 5% CO₂ atmosphere for 24 hours. Subsequently, cells were lysed and RNA was isolated using InviTrap RNA Cell HTS96 Kit/C (Strattec). Ten µl of RNA-solution was used for gene expression analysis by reverse transcription quantitative polymerase chain reaction (RT-qPCR) performed with amplicon sets/sequences for CFB and PPIB or ApoB. Data was calculated by using the comparative CT method also known as the 2^{-delta delta Ct} method.

All tested GalNAc-conjugated siRNAs decreased CFB mRNA expression concentration-dependently.

Results are shown in Figure 4, where panels (A), (B) and (C) respectively show relative CFB mRNA expression in primary mouse (A), human (B) and Cynomolgus monkey (C) hepatocytes.

Example 6

In vivo study showing knockdown of CFB mRNA in murine liver tissue after single
5 subcutaneous dosing of 1 or 5 mg/kg GalNAc conjugated siRNA at different time points.

siRNA conjugates are listed in Table 5c. mRNA level of the house keeping gene ACTB served
as housekeeping control.

Male C57BL/6 mice with an age of 8 weeks were obtained from Janvier, France. Animal
10 experiments were performed according to ethical guidelines of the German Protection of
Animals Act in its version of July 2013. Mice were randomized according to weight into groups
of 4 or 5 mice. On day 0 of the studies animals received a single subcutaneous dose of 1 or 5
mg/kg siRNA dissolved in phosphate buffered saline (PBS) or PBS only as control. The
viability, body weight and behaviour of the mice was monitored during the study without
15 pathological findings.

At day 14 (Figure 5A), or at day 21 and day 42 (Figure 5B) the studies were terminated, animals
were euthanized, and liver samples were snap frozen and stored at – 80°C until further
analysis. For analysis, in summary, total RNA was prepared with RNeasy Fibrous Tissue Mini
Kit (QIAGEN, Venlo, Netherlands) according to the manufacturer's instruction. To assess the
20 integrity of isolated RNA, automated electrophoresis was performed using a 2100 Bioanalyzer
(Agilent Technologies, Inc., Santa Clara, USA). One hundred nanograms per reaction of total
RNA was used for RT-qPCR with the amplicon sets specific for mouse CFB and ACTB.

Expression differences were calculated using the delta delta Ct method and relative expression
of CFB versus the house keeping gene ACTB normalized to the PBS was used for comparison
25 of the different siRNAs. EV2184, EV2185, EV2187, EV2188 and EV2195 induced a dose
dependent knockdown of liver CFB mRNA. The maximum achieved knockdown was observed
after 14 days using EV2184, EV2187 and EV2188 at 5 mg/kg siRNA, with 90%, 89% and 87%
respectively (Figure 5A).

30 siRNA conjugates EV2184, EV2197, EV2185 and EV2200 in the second experiment also
induced a dose dependent knockdown of liver CFB mRNA. The maximum achieved
knockdown was observed after 21 days using the siRNAs EV2197 and EV2200 at 5 mg/kg
siRNA (with 94 % and 88%, respectively). The maximum achieved knockdown after 42 days
was 88 % and 77 %, respectively using EV2197 and EV2200 at 5 mg/kg siRNA (Figure 5B).

Example 7

Synthesis of (vp)-mU-phos was performed as described in Prakash, Nucleic Acids Res. 2015, 43(6), 2993-3011 and Haraszti, Nucleic Acids Res. 2017, 45(13), 7581-7592. Synthesis of the phosphoramidite derivatives of ST41 (ST41-phos) as well as ST23 (ST23-phos) can be performed as described in WO2017/174657. Synthesis of Phosphorothioamidites was performed as described in Caruthers, J. Org. Chem. 1996, 61, 4272-4281.

Example 8

Example compounds were synthesized according to methods described below and known to persons of skill in the art. Assembly of the oligonucleotide chain and linker building blocks was performed by solid phase synthesis applying phosphoramidite methodology.

Downstream cleavage, deprotection and purification were performed following standard procedures that are well known in the art.

Oligonucleotide syntheses was performed on an AKTA oligopilot 10 using commercially available 2'-O-Methyl RNA and 2'-Fluoro-2'-Deoxy RNA base loaded CPG solid support and phosphoramidites (all standard protection, ChemGenes, LinkTech) were used.

Ancillary reagents were purchased from EMP Biotech and Biosolve. Synthesis was performed using a 0.1 M solution of the phosphoramidite in dry acetonitrile (<20 ppm H₂O) and benzylthiotetrazole (BTT) was used as activator (0.3M in acetonitrile). Coupling time was 10 min. If phosphorothioamidites were used to introduce a phosphordithioate linkage (PS2) a repeated coupling wash cycle over 60 min was performed. A Cap/OX/Cap or Cap/Thio/Cap cycle was applied (Cap: Ac₂O/NMI/Lutidine/Acetonitrile, Oxidizer: 0.05M I₂ in pyridine/H₂O). Phosphorothioates and phosphordithioates were introduced using commercially available thiolation reagent 50mM EDITH in acetonitrile (Link technologies). DMT cleavage was achieved by treatment with 3% dichloroacetic acid in toluene. Upon completion of the programmed synthesis cycles a diethylamine (DEA) wash was performed. All oligonucleotides were synthesized in DMT-off mode.

Tri-antennary GalNAc clusters (ST23/ST41) were introduced by successive coupling of the branching trebler amidite derivative (C4XLT-phos) followed by the GalNAc amidite (ST23-phos). Attachment of (vp)-mU moiety was achieved by use of (vp)-mU-phos in the last

synthesis cycle. The (vp)-mU-phos does not provide a hydroxy group suitable for further synthesis elongation and therefore, does not possess an DMT-group. Hence coupling of (vp)-mU-phos results in synthesis termination.

- 5 For the removal of the methyl esters masking the vinylphosphonate, the CPG carrying the fully assembled oligonucleotide was dried under reduced pressure and transferred into a 20 ml PP syringe reactor for solid phase peptide synthesis equipped with a disc frit (Carl Roth GmbH). The CPG was then brought into contact with a solution of 250 μ L TMSBr and 177 μ L pyridine in CH_2Cl_2 (0.5 ml/ μ mol solid support bound oligonucleotide) at room temperature and the
10 reactor was sealed with a Luer cap. The reaction vessels were slightly agitated over a period of 2x15 min, the excess reagent discarded, and the residual CPG washed 2x with 10 ml acetonitrile. Further downstream processing did not alter from any other example compound.

- The single strands were cleaved off the CPG by 40% aq. methylamine treatment (in presence
15 of 20 mM DTT if phosphorodithioate linkages were present) in 90 min at RT. The resulting crude oligonucleotide was purified by ion exchange chromatography (Resource Q, 6 ml, GE Healthcare) on an AKTA Pure HPLC System using a sodium chloride gradient. Product containing fractions were pooled, desalted on a size exclusion column (Zetadex, EMP Biotech) and lyophilized until further use.

- 20 All final single-stranded products were analysed by AEX-HPLC to prove their purity. Identity of the respective single-stranded products was proved by LC-MS analysis.

Example 9

- 25 Individual single strands were dissolved in a concentration of 60 OD/ml in H_2O . Both individual oligonucleotide solutions were added together in a reaction vessel. For easier reaction monitoring a titration was performed. The first strand was added in 25% excess over the second strand as determined by UV-absorption at 260 nm. The reaction mixture was heated
30 to 80°C for 5 min and then slowly cooled to RT. Double-strand formation was monitored by ion pairing reverse phase HPLC. From the UV-area of the residual single strand the needed amount of the second strand was calculated and added to the reaction mixture. The reaction was heated to 80°C again and slowly cooled to RT. This procedure was repeated until less than 10% of residual single strand was detected.

- 35

Example 10

In vitro study in HepG2 cells showing *CFB* knockdown efficacy of tested siRNAs after transfection of 20, 4, 0.8, 0.16, or 0.032 nM siRNA.

- 5 *CFB* knockdown efficacy of selected siRNAs (Table 5b) was determined after transfection of 20, 4, 0.8, or 0.16 nM siRNA in HepG2 cells. The results are depicted in Table 6 below. At 20 nM, remaining *CFB* levels after knockdown reached a minimum of 32 % and at 4 nM reached a minimum of 43 %.

- For transfection of HepG2 cells with siRNAs, cells were seeded at a density of 40,000 cells /
 10 well in 96-well tissue culture plates (TPP, Cat. 92096, Switzerland). Transfection of siRNA was carried out with Lipofectamine RNAiMax (Invitrogen/Life Technologies, Cat. 13778-500, Germany) according to manufacturer's instructions directly before seeding. The dose-response screen was performed with *CFB* siRNAs in triplicates at 20, 4, 0.8, 0.16, or 0.032 nM, respectively, with scrambled siRNA and luciferase-targeting siRNA as unspecific controls.
 15 After 24 h of incubation with siRNAs, medium was removed, and cells were lysed in 250 μ L Lysis Buffer (InviTrap RNA Cell HTS96 Kit/C (Stratec, Cat. 7061300400, Germany)) and then frozen at -80°C. RNA was isolated using the InviTrap RNA Cell HTS96 Kit/C (Stratec, Cat. 7061300400, Germany). RT-qPCR was performed using *CFB* and *PPIB* specific primer probe sets and Takyon™ One-Step Low Rox Probe 5X MasterMix dTTP on the QuantStudio6 device
 20 from Applied Biosystems in single-plex 384 well format. Expression differences were calculated using the delta delta Ct method and relative expression of *CFB* normalized to the house keeping gene *PPIB* was determined. Results are expressed as % remaining *CFB* mRNA after siRNA transfection in Table 6.

- Table 6:** Results of dose-response screening (20, 4, 0.8, 0.16, 0.032 nM) of siRNAs targeting
 25 *CFB*.

The identity of the single strands forming each of the siRNA duplexes as well as their sequences and modifications are to be found in Table 5b.

Duplex	Concentration (nM)	% remaining mRNA	
		Mean	SD
EV2211	20	32	1
	4	43	3
	0.8	52	9
	0.16	63	9

	0.032	70	4
EV2212	20	34	3
	4	49	8
	0.8	59	10
	0.16	66	6
	0.032	85	6

Example 11

In vivo study showing knockdown of CFB mRNA in non-human primates (NHP).

5

The objective of this experiment was to determine mRNA knockdown efficacy of siRNA GalNAc conjugates targeting CFB in vivo in non-human primates (NHPs).

Purpose bred cynomolgus monkeys (24 to 48 months old, males and females) were allocated to different treatment groups (4 animals per group). On day 1, each group was treated with a single dose of 3 mg GalNAc siRNA per kg body weight by subcutaneous injection, while control animals received the vehicle, 0.9% saline, by subcutaneous injection. Pre-dose, after 4 weeks and after 8 weeks liver samples were collected from each animal by survival biopsy and snap frozen. RNA was extracted from liver samples and CFB and ApoB mRNA levels were determined by Taqman qRT-PCR. Values obtained for CFB mRNA were normalized to values generated for the house keeping gene, Apo B. CFB mRNA expression relative to ApoB expression at the predose timepoint for each individual was set at 1-fold target gene expression.

Results of CFB mRNA reduction 4 and 8 weeks post single subcutaneous dose of GalNAc conjugated siRNAs EV2196, EV2204 and EV2198 are shown in Figure 6. CFB levels in liver tissue of cynomolgus monkeys collected 4 weeks after single treatment with EV2196 were reduced on average by 61% and after 8 weeks by 55%. CFB levels in liver tissue of cynomolgus monkeys collected 4 weeks after single treatment with EV2204 were reduced on average by 22% and after 8 weeks no reduction could be observed. CFB levels in liver tissue of cynomolgus monkeys collected 4 weeks after single treatment with EV2198 were reduced on average by 57% and after 8 weeks by 32%.

Statements

The following statements represent aspects of the invention.

- 5 1. A double-stranded nucleic acid for inhibiting expression of complement factor B (CFB),
 wherein the nucleic acid comprises a first strand and a second strand, wherein the
 unmodified equivalent of the first strand sequence comprises a sequence of at least 15
 nucleotides differing by no more than 3 nucleotides from any one of the first strand
 sequences shown in Table 5a, or of Table 1.
- 10 2. The nucleic acid of statement 1, wherein the first strand and the second strand are
 separate strands and are each 18-25 nucleotides in length.
3. The nucleic acid of statement 1 or statement 2, wherein the first strand and the second
15 strand form a duplex region of from 17-25 nucleotides in length.
4. The nucleic acid of any one of the preceding statements, wherein the duplex region
 consists of 17-25 consecutive nucleotide base pairs.
- 20 5. The nucleic acid of any one of the preceding statements, wherein said nucleic acid:
 a) is blunt ended at both ends;
 b) has an overhang at one end and a blunt end at the other end; or
 c) has an overhang at both ends.
- 25 6. The nucleic acid of any one of the preceding statements, wherein the nucleic acid is a
 siRNA.
7. The nucleic acid of any one of the preceding statements, wherein the nucleic acid
 mediates RNA interference.
- 30 8. The nucleic acid of any one of the preceding statements wherein:
 (a) the unmodified equivalent of the first strand sequence comprises a sequence differing
 by no more than 3 nucleotides from any one of the first strand sequences of Table 5a,
 and optionally wherein the unmodified equivalent of the second strand sequence
35 comprises a sequence differing by no more than 3 nucleotides from the corresponding
 second strand sequence;

- (b) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 2 nucleotides from any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence differing by no more than 2 nucleotides from the corresponding second strand sequence;
- 5
- (c) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 1 nucleotide from any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence differing by no more than 1 nucleotide from the corresponding
- 10
- second strand sequence;
- (d) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the
- 15
- 5' end of the corresponding second strand sequence;
- (e) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the
- 20
- 5' end of the corresponding second strand sequence;
- (f) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the
- 25
- 5' end of the corresponding second strand sequence;
- (g) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 1 to 18 from the
- 30
- 5' end of the corresponding second strand sequence;
- (h) the unmodified equivalent of the first strand sequence comprises a sequence of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence of the corresponding second strand sequence; or
- 35
- (i) the unmodified equivalent of the first strand sequence consists of any one of the first strand sequences of Table 5a, and optionally wherein the unmodified equivalent of the

second strand sequence consists of the sequence of the corresponding second strand sequence.

9. The nucleic acid of statement 8 wherein:
- 5 (a) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 3 nucleotides from any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence differing by no more than 3 nucleotides from the corresponding second strand sequence;
- 10 (b) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 2 nucleotides from any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence differing by no more than 2 nucleotides from the corresponding second strand sequence;
- 15 (c) the unmodified equivalent of the first strand sequence comprises a sequence differing by no more than 1 nucleotide from any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence differing by no more than 1 nucleotide from the corresponding second strand sequence;
- 20 (d) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of the corresponding second strand sequence;
- 25 (e) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of the corresponding second strand sequence;
- 30 (f) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of the corresponding second strand sequence;
- 35 (g) the unmodified equivalent of the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second

- strand sequence comprises a sequence corresponding to nucleotides 1 to 18 from the 5' end of the corresponding second strand sequence;
- (h) the unmodified equivalent of the first strand sequence comprises a sequence of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises a sequence of the corresponding second strand sequence;
- (i) the unmodified equivalent of the first strand sequence consists of any one of the first strand sequences of Table 1, and optionally wherein the unmodified equivalent of the second strand sequence consists of the sequence of the corresponding second strand sequence;
- (j) the unmodified equivalent of the first strand sequence consists essentially of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, and optionally wherein the unmodified equivalent of the second strand sequence consists essentially of the sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 1;
- (k) the unmodified equivalent of the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, wherein said unmodified equivalent of the first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, and optionally wherein the unmodified equivalent of the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown Table 1;
- (l) the unmodified equivalent of the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, wherein said unmodified equivalent of the first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 1, and wherein said unmodified equivalent of the first strand sequence consists of a contiguous region of from 17-25 nucleotides in length, preferably of from 18-24 nucleotides in length, complementary to the CFB transcript of SEQ ID NO. 758; and

optionally wherein the unmodified equivalent of the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 1;

- 5 (m) unmodified equivalent of the first strand and the unmodified equivalent of the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are present on a single strand wherein the unmodified equivalent of the first strand and the unmodified equivalent of the second strand are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length; or
- 10 (n) the unmodified equivalent of the first strand and the unmodified equivalent of the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are on two separate strands that are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length.
- 15
10. The nucleic acid of any one of the preceding statements, wherein at least one nucleotide of the first and/or second strand is a modified nucleotide.
- 20 11. The nucleic acid of statement 10, wherein at least nucleotides 2 and 14 of the first strand are modified by a first modification, the nucleotides being numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand.
- 25 12. The nucleic acid of statement 10 or statement 11, wherein each of the even-numbered nucleotides of the first strand are modified by a first modification, the nucleotides being numbered consecutively starting with nucleotide number 1 at the 5' end of the first strand.
- 30 13. The nucleic acid of statement 11 or statement 12, wherein the odd-numbered nucleotides of the first strand are modified by a second modification, wherein the second modification is different from the first modification.
- 35 14. The nucleic acid of any one of statements 11 to 13, wherein the nucleotides of the second strand in a position corresponding to an even-numbered nucleotide of the first strand are modified by a third modification, wherein the third modification is different from the first modification.
15. The nucleic acid of any one of statements 11 to 14, wherein the nucleotides of the second strand in a position corresponding to an odd-numbered nucleotide of the first strand are

modified by a fourth modification, wherein the fourth modification is different from the second modification and different from the third modification when a second and/or a third modification are present.

- 5 16. The nucleic acid of any one of statements 11 to 13, wherein the nucleotide/nucleotides of the second strand in a position corresponding to nucleotide 11 or nucleotide 13 or nucleotides 11 and 13 or nucleotides 11-13 of the first strand is/are modified by a fourth modification and preferably wherein the nucleotides of the second strand that are not modified by a fourth modification are modified by a third modification.
- 10 17. The nucleic acid of any one of statements 11 to 16, wherein the first modification is the same as the fourth modification if both modifications are present in the nucleic acid and preferably wherein the second modification is the same as the third modification if both modifications are present in the nucleic acid.
- 15 18. The nucleic acid of any one of statements 11 to 17, wherein the first modification is a 2'-F modification; the second modification, if present in the nucleic acid, is preferably a 2'-OMe modification; the third modification, if present in the nucleic acid, is preferably a 2'-OMe modification; and the fourth modification, if present in the nucleic acid, is preferably
- 20 a 2'-F modification.
19. The nucleic acid of any one statements 10 to 18, wherein each of the nucleotides of the first strand and of the second strand is a modified nucleotide.
- 25 20. The nucleic acid of any one statements 10 to 18, wherein the first strand has a terminal 5' (E)-vinylphosphonate nucleotide at its 5' end and wherein the terminal 5' (E)-vinylphosphonate nucleotide is preferably linked to the second nucleotide in the first strand by a phosphodiester linkage.
- 30 21. The nucleic acid of any one of the preceding statements, wherein the nucleic acid comprises a phosphorothioate linkage between the terminal two or three 3' nucleotides and/or 5' nucleotides of the first and/or the second strand and preferably wherein the linkages between the remaining nucleotides are phosphodiester linkages.
- 35 22. The nucleic acid of any one of statements 1 to 20, comprising a phosphorodithioate linkage between each of the two, three or four terminal nucleotides at the 3' end of the first strand and/or comprising a phosphorodithioate linkage between each of the two,

three or four terminal nucleotides at the 3' end of the second strand and/or a phosphorodithioate linkage between each of the two, three or four terminal nucleotides at the 5' end of the second strand and comprising a linkage other than a phosphorodithioate linkage between the two, three or four terminal nucleotides at the 5' end of the first strand.

23. The nucleic acid of statement 22, wherein the nucleic acid comprises a phosphorothioate linkage between each of the three terminal 3' nucleotides and/or between each of the three terminal 5' nucleotides on the first strand, and/or between each of the three terminal 3' nucleotides and/or between each of the three terminal 5' nucleotides of the second strand when there is no phosphorodithioate linkage present at that end.

24. The nucleic acid of statement 22, wherein all the linkages between the nucleotides of both strands other than the linkage between the two terminal nucleotides at the 3' end of the first strand and the linkages between the two terminal nucleotides at the 3' end and at the 5' end of the second strand are phosphodiester linkages.

25. The nucleic acid of any one of statements 10 to 24 wherein:

(a) the first strand sequence comprises a sequence differing by no more than 3 nucleotides from any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence differing by no more than 3 nucleotides from the corresponding second strand sequence;

(b) the first strand sequence comprises a sequence differing by no more than 2 nucleotides from any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence differing by no more than 2 nucleotides from the corresponding second strand sequence;

(c) the first strand sequence comprises a sequence differing by no more than 1 nucleotide from any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence differing by no more than 1 nucleotide from the corresponding second strand sequence;

(d) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of the corresponding second strand sequence;

(e) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of any one of the first strand sequences of Table 5b, and optionally

- wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of the corresponding second strand sequence;
- (f) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of the corresponding second strand sequence;
- (g) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 1 to 18 from the 5' end of the corresponding second strand sequence;
- (h) the first strand sequence comprises a sequence of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence comprises a sequence of the corresponding second strand sequence; or
- (i) the first strand sequence consists of any one of the first strand sequences of Table 5b, and optionally wherein the second strand sequence consists of the sequence of the corresponding second strand sequence.
26. The nucleic acid of statement 25 wherein:
- (a) the first strand sequence comprises a sequence differing by no more than 3 nucleotides from any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence differing by no more than 3 nucleotides from the corresponding second strand sequence;
- (b) the first strand sequence comprises a sequence differing by no more than 2 nucleotides from any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence differing by no more than 2 nucleotides from the corresponding second strand sequence;
- (c) the first strand sequence comprises a sequence differing by no more than 1 nucleotide from any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence differing by no more than 1 nucleotide from the corresponding second strand sequence;
- (d) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence corresponding to nucleotides 2 to 17 from the 5' end of the corresponding second strand sequence;
- (e) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of any one of the first strand sequences of Table 2, and optionally wherein

- the second strand sequence comprises a sequence corresponding to nucleotides 2 to 18 from the 5' end of the corresponding second strand sequence;
- (f) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 2, and optionally wherein
- 5 the second strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of the corresponding second strand sequence;
- (g) the first strand sequence comprises a sequence corresponding to nucleotides 2 to 19 from the 5' end of any one of the first strand sequences of Table 2, and optionally wherein
- 10 the second strand sequence comprises a sequence corresponding to nucleotides 1 to 18 from the 5' end of the corresponding second strand sequence;
- (h) the first strand sequence comprises a sequence of any one of the first strand sequences of Table 2, and optionally wherein the second strand sequence comprises a sequence of the corresponding second strand sequence;
- (i) the first strand sequence consists of any one of the first strand sequences of Table 2,
- 15 and optionally wherein the second strand sequence consists of the sequence of the corresponding second strand sequence;
- (j) the first strand sequence consists essentially of any one of the first strand sequences with a given SEQ ID No. shown in Table 2, and optionally wherein the second strand sequence consists essentially of the sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 2; or
- 20 (k) the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 2,
- wherein said first strand sequence further consists of 1 (nucleotide 20 counted from the
- 25 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24 and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 2, and
- optionally wherein the second strand sequence comprises or consists essentially of or
- 30 consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 2;
- (l) the first strand sequence consists of a sequence corresponding to nucleotides 1 to 19 from the 5' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 2,
- 35 wherein said first strand sequence further consists of 1 (nucleotide 20 counted from the 5' end), 2 (nucleotides 20 and 21), 3 (nucleotides 20, 21 and 22), 4 (nucleotides 20, 21, 22 and 23), 5 (nucleotides 20, 21, 22, 23 and 24) or 6 (nucleotides 20, 21, 22, 23, 24

- and 25) additional nucleotide(s) at the 3' end of any one of the first strand sequences with a given SEQ ID No. shown in Table 2, and wherein said first strand sequence consists of a contiguous region of from 17-25 nucleotides in length, preferably of from 18-24 nucleotides in length, complementary to the CFB transcript of SEQ ID NO. 758, and optionally wherein the second strand sequence comprises or consists essentially of or consists of a sequence of the corresponding second strand sequence with a given SEQ ID No. shown in Table 2;
- (m) the first strand and the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are present on a single strand wherein the first strand and the second strand are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length; or
- (n) the first strand and the second strand of any one of the nucleic acid molecules of subsections (a) to (l) above are on two separate strands that are able to hybridise to each other and to thereby form a double-stranded nucleic acid with a duplex region of 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length.
27. The nucleic acid of any one of the preceding statements, wherein the nucleic acid is conjugated to a heterologous moiety.
28. The nucleic acid of statement 27, wherein the heterologous moiety comprises (i) one or more N-acetyl galactosamine (GalNAc) moieties or derivatives thereof, and (ii) a linker, wherein the linker conjugates the at least one GalNAc moiety or derivative thereof to the nucleic acid.
29. The nucleic acid of statement 27 or statement 28, wherein the nucleic acid is conjugated to a heterologous moiety comprising a compound of formula (II):



wherein:

S represents a functional component, e.g., a ligand, such as a saccharide, preferably wherein the saccharide is N-acetyl galactosamine;

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

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

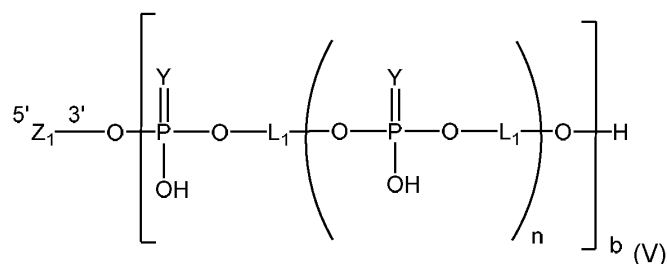
X^2 is alkylene or an alkylene ether of the formula $(-CH_2)_n-O-CH_2-$ where n = 1- 6;

A is a branching unit;

X_3 represents a bridging unit;

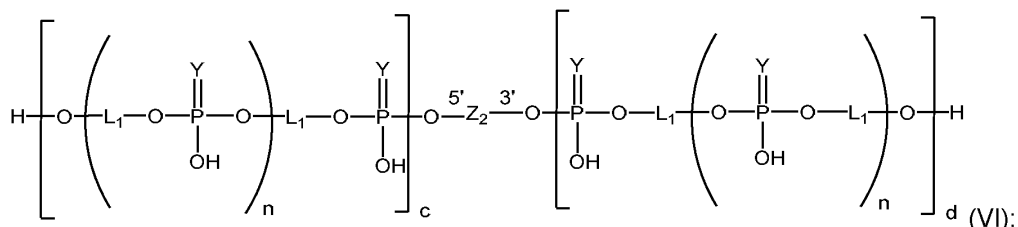
wherein a nucleic acid as defined in any of statements 1 to 27 is conjugated to X^3 via a phosphate or modified phosphate, preferably a thiophosphate.

- 5 30. The nucleic acid of any one of statements 27 to 29, wherein the first strand of the nucleic acid is a compound of formula (V):



wherein b is 0 or 1; and

wherein the second strand is a compound of formula (VI):



10

wherein:

c and d are independently 0 or 1;

Z_1 and Z_2 are respectively the first and second strand of the nucleic acid;

Y is independently O or S;

15

n is independently 0, 1, 2 or 3; and

L_1 is a linker to which a ligand is attached, wherein L_1 is the same or different in formulae (V) and (VI), and is the same or different within formulae (V) and (VI) when L_1 is present more than once within the same formula;

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

20

31. The nucleic acid of any one of statements 27 to 30 which is one of the duplexes shown in Table 5c.

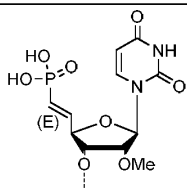
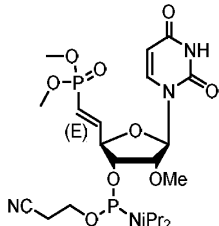
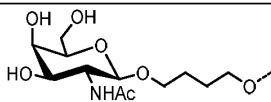
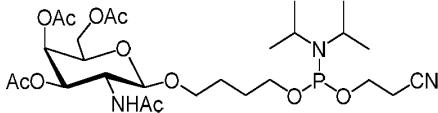
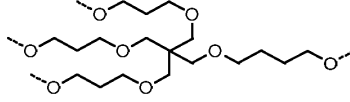
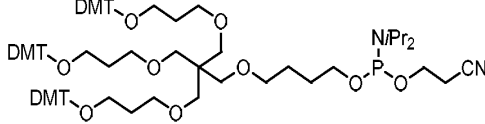
25

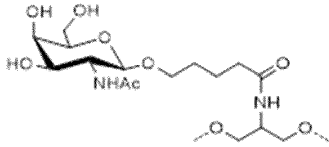
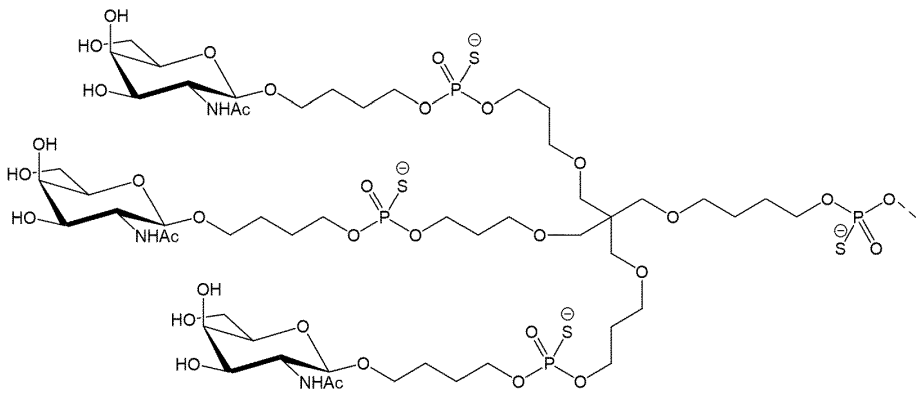
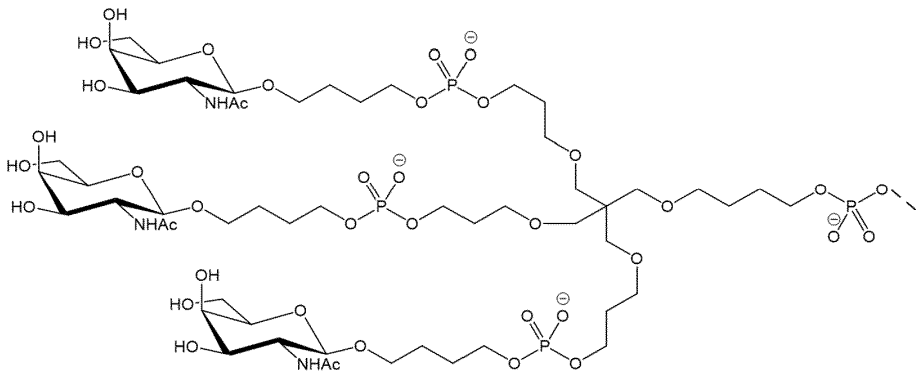
32. A composition comprising a nucleic acid of any of the previous statements and a solvent and/or a delivery vehicle and/or a physiologically acceptable excipient and/or a carrier and/or a salt and/or a diluent and/or a buffer and/or a preservative.

33. A composition comprising a nucleic acid of any one of statements 1 to 31 and a further therapeutic agent selected from the group comprising an oligonucleotide, a small molecule, a monoclonal antibody, a polyclonal antibody and a peptide.
- 5 34. A nucleic acid of any one of statements 1 to 31 or a composition of statement 32 or 33 for use as a therapeutic agent.
35. A nucleic acid of any one of statements 1 to 31 or a composition of statement 32 or 33 for use in the prophylaxis or treatment of a disease, disorder or syndrome.
- 10 36. The nucleic acid or composition for use according to statement 35, wherein the disease, disorder or syndrome is a complement-mediated disease, disorder or syndrome.
- 15 37. The nucleic acid or composition for use according to statement 35 or 36, wherein the disease, disorder or syndrome is associated with aberrant activation or over-activation of the complement pathway and/or with over-expression or ectopic expression or localisation or accumulation of CFB.
- 20 38. The nucleic acid or composition for use according to any one of statements 35 to 37, wherein the disease, disorder or syndrome is:
- 25 a) selected from the group comprising C3 glomerulopathy (C3G), paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), lupus nephritis, IgA nephropathy (IgA N), myasthenia gravis (MG), primary membranous nephropathy, immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), systemic lupus erythematosus (SLE), ischemia/reperfusion injury, age-related macular degeneration (AMD), rheumatoid arthritis (RA), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), dysbiotic periodontal disease, malarial anaemia, neuromyelitis optica, post-HCT / solid organ transplant (TMAs),
- 30 Guillain-Barré syndrome, membranous glomerulonephritis, thrombotic thrombocytopenic purpura and sepsis;
- b) selected from the group comprising C3 glomerulopathy (C3G), paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), lupus nephritis, IgA nephropathy (IgA N) and primary membranous nephropathy;
- 35 c) selected from the group comprising C3 glomerulopathy (C3G), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), atypical hemolytic

- uremic syndrome (aHUS), myasthenia gravis (MG), IgA nephropathy (IgA N), paroxysmal nocturnal hemoglobinuria (PNH);
- 5 d) selected from the group comprising C3 glomerulopathy (C3G), myasthenia gravis (MG), neuromyelitis optica, atypical hemolytic uremic syndrome (aHUS), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), IgA nephropathy (IgA N), post-HCT / Solid Organ Transplant (TMAs), Guillain-Barré syndrome, paroxysmal nocturnal hemoglobinuria (PNH), membranous glomerulonephritis, lupus nephritis and thrombotic thrombocytopenic purpura
- 10 e) selected from the group comprising C3 glomerulopathy (C3G) and IgA nephropathy (IgA N); or
- f) C3 glomerulopathy (C3G).
39. Use of a nucleic acid of any one of statements 1 to 31 or a composition of statement 32 or 33 in the preparation of a medicament for prophylaxis or treatment of a disease, disorder or syndrome.
- 15
40. A method of prophylaxis or treatment of a disease, disorder or syndrome comprising administering a pharmaceutically effective dose of a nucleic acid of any one of statements 1 to 31 or a composition of statement 23 or 33 to an individual in need of treatment, preferably wherein the nucleic acid or composition is administered to the subject subcutaneously, intravenously or by oral, rectal or intraperitoneal administration.
- 20

Summary abbreviations table – Table 4

Abbreviation	Meaning
mA, mU, mC, mG	2'-O-Methyl RNA nucleotides
2'-OMe	2'-O-Methyl modification
fA, fU, fC, fG	2' deoxy-2'-F RNA nucleotides
2'-F	2'-fluoro modification
(ps)	phosphorothioate
(ps2)	phosphorodithioate
(vp)	Vinyl-(E)-phosphonate
(vp)-mU	
(vp)-mU-phos	
ivA, ivC, ivU, ivG	inverted RNA (3'-3') nucleotides
ST23	
ST23-phos	
ST41 (or C4XLT)	
ST41-phos (or C4XLT-phos)	

Ser(GN) (when at the end of a chain, one of the O--- is OH)	
[ST23 (ps)]3 ST41 (ps)	
[ST23]3 ST41	

The abbreviations as shown in the above abbreviation table may be used herein. The list of abbreviations may not be exhaustive and further abbreviations and their meaning may be found throughout this document.

Summary sequence tables

Table 5a – Unmodified duplexes

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.
SX001	SX001-A	CUAGACCUGGUCACAUUCC	1
SX001	SX001-B	GGAAUGUGACCAGGUCUAG	2
SX002	SX002-A	UCCAAGCUGAAACUCCAGA	3
SX002	SX002-B	UCUGGAGUUUCAGCUUGGA	4
SX003	SX003-A	UGUCCAAGCUGAAACUCCA	5
SX003	SX003-B	UGGAGUUUCAGCUUGGACA	6
SX004	SX004-A	GUGUCCAAGCUGAAACUCC	7
SX004	SX004-B	GGAGUUUCAGCUUGGACAC	8
SX005	SX005-A	CAAGAUAAAGGGCAUCAGG	9
SX005	SX005-B	CCUGAUGCCCUUUAUCUUG	10
SX006	SX006-A	GUAUUCCCCGUUCUGAAG	11
SX006	SX006-B	CUUCGAGAACGGGGAAUAC	12
SX007	SX007-A	ACCUUCCUUGUGCCAAUGG	13
SX007	SX007-B	CCAUUGGCACAAGGAAGGU	14
SX008	SX008-A	GAAAGCUUCGGCCACCUCU	15
SX008	SX008-B	AGAGGUGGCCGAAGCUUUC	16
SX009	SX009-A	AUGUUCAUGGAGCCUGAAG	17
SX009	SX009-B	CUUCAGGCUCCAUGAACAU	18
SX010	SX010-A	UAGAUGUUAUGGAGCCUG	19
SX010	SX010-B	CAGGCUCCAUGAACAUUA	20
SX011	SX011-A	AUUAAGUUGACUAGACACU	21
SX011	SX011-B	AGUGUCUAGUCAACUAAU	22
SX012	SX012-A	CAAUUAAGUUGACUAGACA	23
SX012	SX012-B	UGUCUAGUCAACUAAUUG	24
SX013	SX013-A	CUCAAUUAAGUUGACUAGA	25
SX013	SX013-B	UCUAGUCAACUAAUUGAG	26
SX014	SX014-A	UUCUCAAUUAAGUUGACUA	27
SX014	SX014-B	UAGUCAACUAAUUGAGAA	28
SX015	SX015-A	UUCGUGACCCAGUCUGCAU	29
SX015	SX015-B	AUGCAGACUGGGUCACGAA	30
SX016	SX016-A	UCAUGCUGUACACUGCCUG	31
SX016	SX016-B	CAGGCAGUGUACAGCAUGA	32
SX017	SX017-A	UCAUCAUAGACAGUAAUUG	33
SX017	SX017-B	CAAUUAACUGUCAUUGAUGA	34
SX018	SX018-A	AAACACAUAGACAUCCAGA	35
SX018	SX018-B	UCUGGAUGUCUAUGUGUUU	36
SX019	SX019-A	AAAGCAUUGAUGUUCACUU	37
SX019	SX019-B	AAGUGAACAUCAAUGCUUU	38
SX020	SX020-A	CUUGACUUUGAACACAUGU	39
SX020	SX020-B	ACAUGUGUUCAAAGUCAAG	40

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.
SX021	SX021-A	GUCAUAAAAUUCAGGAUUU	41
SX021	SX021-B	AAUUCCUGAAUUUUUUGAC	42
SX022	SX022-A	AUAGUCAUAAAAUUCAGGA	43
SX022	SX022-B	UCCUGAAUUUUUUGACUAAU	44
SX023	SX023-A	AGACAAAUGGGCCUGAUAG	45
SX023	SX023-B	CUAUCAGGCCCAUUUGUCU	46
SX024	SX024-A	ACACAAACAGAGCUUUGAU	47
SX024	SX024-B	AUCAAAAGCUCUGUUUGUGU	48
SX025	SX025-A	GGCAUAUUGAGCAUCUCUC	49
SX025	SX025-B	GAGAGAUAGCUCAAUAGCC	50
SX026	SX026-A	AUGUCCUUGACUUUGUCAU	51
SX026	SX026-B	AUGACAAAGUCAAGGACAU	52
SX027	SX027-A	AAGUAUUUGGGGUCAGCAUA	53
SX027	SX027-B	UAUGCUGACCCCAUACUU	54
SX028	SX028-A	UGAACUAUCAAGGGGCCGC	55
SX028	SX028-B	GCGGCCCUUGAUAGUUA	56
SX029	SX029-A	AAUGAAACGACUUCUCUUG	57
SX029	SX029-B	CAAGAGAAGUCGUUUAUU	58
SX030	SX030-A	UGAAUGAAACGACUUCUCU	59
SX030	SX030-B	AGAGAAGUCGUUUAUUA	60
SX031	SX031-A	ACUUGAAUGAAACGACUUC	61
SX031	SX031-B	GAAGUCGUUUAUUAAGU	62
SX032	SX032-A	ACCAACUUGAAUGAAACGA	63
SX032	SX032-B	UCGUUUAUUAAGUUGGU	64
SX033	SX033-A	UGUGAAAGUCUCGGGCGUG	65
SX033	SX033-B	CACGCCGAGACUUUCACA	66
SX034	SX034-A	UGUUUUAAUCAAUCCAC	67
SX034	SX034-B	GUGGGAUUGAAUUAACA	68
SX035	SX035-A	CAGCUGUUUAAUUAUUAUC	69
SX035	SX035-B	GAUUGAAUUAACAGCUG	70
SX036	SX036-A	GUUGUCGAGCUGUUUUA	71
SX036	SX036-B	UUAAAACAGCUGCGACAAC	72
SX037	SX037-A	CACUAGACCAUAUCUUGGC	73
SX037	SX037-B	GCCAAGAUUGGUCUAGUG	74
SX038	SX038-A	UGUCACUAGACCAUAUCUU	75
SX038	SX038-B	AAGAUUUGGUCUAGUGACA	76
SX039	SX039-A	UUCUUGGUGUUAGUCCUG	77
SX039	SX039-B	CAGGGACUAACACCAAGAA	78
SX040	SX040-A	UCAGUCAUGAGGAUGAUGA	79
SX040	SX040-B	UCAUCAUCCUAGACUGA	80
SX041	SX041-A	GAUUACACCAACUUGAAUG	81
SX041	SX041-B	CAUUAAGUUGGUGUAUC	82
SX042	SX042-A	UUGUAGUAGGGAGACCGGG	83
SX042	SX042-B	CCCGGUCUCCUACUACAA	84

Duplex ID	Strand Name (*)	Sequence (5' → 3')	SEQ ID No.
SX043	SX043-A	UCCAAGAGCCACCUUCCUG	85
SX043	SX043-B	CAGGAAGGUGGCUCUUGGA	86
SX044	SX044-A	UCGUACAUGAAGGAGUCUU	87
SX044	SX044-B	AAGACUCCUUAUGUACGA	88
SX045	SX045-A	CUCUUGAGGGGUGUCGUAC	89
SX045	SX045-B	GUACGACACCCCUCAAGAG	90
SX046	SX046-A	UUGGCUCCUGUGAAGUUGC	91
SX046	SX046-B	GCAACUUCACAGGAGCCAA	92
SX047	SX047-A	AUAACUUGCCACCUUCUCA	93
SX047	SX047-B	UGAGAAGGUGGCAAGUUAU	94
SX048	SX048-A	AGCCAAAGCAUUGAUGUUC	95
SX048	SX048-B	GAACAUCAAUGCUUUGGCU	96
SX049	SX049-A	GAAGCCAAAGCAUUGAUGU	97
SX049	SX049-B	ACAUCA AUGCUUUGGCUUC	98
SX050	SX050-A	GAACACAUGUUGCUCUUG	99
SX050	SX050-B	CAAUGAGCAACAUGUGUUC	100
SX051	SX051-A	GCCGCCUUUGAUCUCUACC	101
SX051	SX051-B	GGUAGAGAUCAAAGGCGGC	102
SX052	SX052-A	GAGCCGCCUUUGAUCUCUA	103
SX052	SX052-B	UAGAGAUCAAAGGCGGCUC	104
SX053	SX053-A	AAGGAGCCGCCUUUGAUCU	105
SX053	SX053-B	AGAUCAAAGGCGGCUCCUU	106
SX054	SX054-A	GGAAGGAGCCGCCUUUGAU	107
SX054	SX054-B	AUCAAAGGCGGCUCCUCC	108
SX055	SX055-A	GGGUAGAAGCCAGAAGGAC	109
SX055	SX055-B	GUCCUUCUGGCUUCUACCC	110
SX056	SX056-A	CAGAGCCCCGAGAGUGUA	111
SX056	SX056-B	UACACUCUCCGGGGCUCUG	112
SX057	SX057-A	UUGGCAGGUGCGAUUGGCA	113
SX057	SX057-B	UGCCAAUCGCACCUGCCAA	114
SX058	SX058-A	AUUCACUUGGCAGGUGCGA	115
SX058	SX058-B	UCGCACCUGCCAAGUGAAU	116
SX059	SX059-A	CCAUUCACUUGGCAGGUGC	117
SX059	SX059-B	GCACCUGCCAAGUGAAUGG	118
SX060	SX060-A	CCCACCUUCCUUGUGCCAA	119
SX060	SX060-B	UUGGCACAAGGAAGGUGGG	120
SX061	SX061-A	UCUUCAAGGCGGUACUGGC	121
SX061	SX061-B	GCCAGUACCGCCUUGAAGA	122
SX062	SX062-A	GUCUUCAAGGCGGUACUGG	123
SX062	SX062-B	CCAGUACCGCCUUGAAGAC	124
SX063	SX063-A	ACAUGAAGGAGUCUUGGCA	125
SX063	SX063-B	UGCCAAGACUCCUUAUGU	126
SX064	SX064-A	UUCGGCCACCUUUGAGGG	127
SX064	SX064-B	CCCUCAAGAGGUGGCCGAA	128

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.
SX065	SX065-A	CUUCUAUGGUCUCUGUCAG	129
SX065	SX065-B	CUGACAGAGACCAUAGAAG	130
SX066	SX066-A	AUCCUCAGCAUCGACUCCU	131
SX066	SX066-B	AGGAGUCGAUGCUGAGGAU	132
SX067	SX067-A	CCCAUCCUCAGCAUCGACU	133
SX067	SX067-B	AGUCGAUGCUGAGGAUGGG	134
SX068	SX068-A	GUGCCCAUCCUCAGCAUCG	135
SX068	SX068-B	CGAUGCUGAGGAUGGGCAC	136
SX069	SX069-A	UAGCACCAGGUAGAUGUUC	137
SX069	SX069-B	GAACAUCUACCUUGGUGCUA	138
SX070	SX070-A	UCUAGCACCAGGUAGAUGU	139
SX070	SX070-B	ACAUCUACCUUGGUGCUAGA	140
SX071	SX071-A	UCCAUCUAGCACCAGGUAG	141
SX071	SX071-B	CUACCUUGGUGCUAGAUGGA	142
SX072	SX072-A	GAUCCAUCUAGCACCAGGU	143
SX072	SX072-B	ACCUUGGUGCUAGAUGGAUC	144
SX073	SX073-A	UGAUCCAUCUAGCACCAGG	145
SX073	SX073-B	CCUGGUGCUAGAUGGAUCA	146
SX074	SX074-A	GUCUGAUCCAUCUAGCACC	147
SX074	SX074-B	GGUGCUAGAUGGAUCAGAC	148
SX075	SX075-A	UGUCUGAUCCAUCUAGCAC	149
SX075	SX075-B	GUGCUAGAUGGAUCAGACA	150
SX076	SX076-A	GCUGUCUGAUCCAUCUAGC	151
SX076	SX076-B	GCUAGAUGGAUCAGACAGC	152
SX077	SX077-A	AUGCUGUCUGAUCCAUCUA	153
SX077	SX077-B	UAGAUGGAUCAGACAGCAU	154
SX078	SX078-A	CAAUGCUGUCUGAUCCAUC	155
SX078	SX078-B	GAUGGAUCAGACAGCAUUG	156
SX079	SX079-A	CCAAUGCUGUCUGAUCCAUC	157
SX079	SX079-B	AUGGAUCAGACAGCAUUGG	158
SX080	SX080-A	CCUGUGAAGUUGCUGGCCC	159
SX080	SX080-B	GGGCCAGCAACUUCACAGG	160
SX081	SX081-A	UAACUUGCCACCUUCUCAA	161
SX081	SX081-B	UUGAGAAGGUGGCAAGUUA	162
SX082	SX082-A	UGGCAUAUGUCACUAGACC	163
SX082	SX082-B	GGUCUAGUGACAU AUGCCA	164
SX083	SX083-A	UGGUCUUAUAAUUGAUUU	165
SX083	SX083-B	AAAUCAAUUAUGAAGACCA	166
SX084	SX084-A	GUGGUCUUAUAAUUGAUU	167
SX084	SX084-B	AAUCAAUUAUGAAGACCAC	168
SX085	SX085-A	UUGUGGUCUUAUAAUUGA	169
SX085	SX085-B	UCAAUUAUGAAGACCACAA	170
SX086	SX086-A	UCAACUUGUGGUCUUAUA	171
SX086	SX086-B	UAUGAAGACCACAAGUUGA	172

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.
SX087	SX087-A	CUUCAACUUGUGGUCUUA	173
SX087	SX087-B	UGAAGACCACAAGUUGAAG	174
SX088	SX088-A	ACUUCAACUUGUGGUCUUC	175
SX088	SX088-B	GAAGACCACAAGUUGAAGU	176
SX089	SX089-A	UGGUGUUAGUCCUGACUU	177
SX089	SX089-B	AAGUCAGGGACUAACACCA	178
SX090	SX090-A	UCUUGGUGUUAGUCCUGA	179
SX090	SX090-B	UCAGGGACUAACACCAAGA	180
SX091	SX091-A	AUGAUGACAUGGCGGGUGC	181
SX091	SX091-B	GCACCCGCCAUGUCAUCAU	182
SX092	SX092-A	GGAUGAUGACAUGGCGGGU	183
SX092	SX092-B	ACCCGCCAUGUCAUCAUCC	184
SX093	SX093-A	AGGAUGAUGACAUGGCGGG	185
SX093	SX093-B	CCCGCCAUGUCAUCAUCCU	186
SX094	SX094-A	UGUGCAAUCCAUCAGUCAU	187
SX094	SX094-B	AUGACUGAUGGAUUGCACA	188
SX095	SX095-A	UGUUGUGCAAUCCAUCAGU	189
SX095	SX095-B	ACUGAUGGAUUGCACAACA	190
SX096	SX096-A	CCAUGUUGUGCAAUCCAUC	191
SX096	SX096-B	GAUGGAUUGCACAACAUGG	192
SX097	SX097-A	ACAUCCAGAUAAUCCUCCC	193
SX097	SX097-B	GGGAGGAUUAUCUGGAUGU	194
SX098	SX098-A	ACCCCAAACACAUAGACAU	195
SX098	SX098-B	AUGUCUAUGUGUUUGGGGU	196
SX099	SX099-A	ACACAUGUUGCUCAUUGUC	197
SX099	SX099-B	GACAAUGAGCAACAUGUGU	198
SX100	SX100-A	AUCCUUGACUUUGAACACA	199
SX100	SX100-B	UGUGUUCAAAGUCAAGGAU	200
SX101	SX101-A	AUAUCCUUGACUUUGAACA	201
SX101	SX101-B	UGUUCAAAGUCAAGGAUUAU	202
SX102	SX102-A	UUCCAUAUCCUUGACUUUG	203
SX102	SX102-B	CAAAGUCAAGGAUAUGGAA	204
SX103	SX103-A	GUUUUCCAUAUCCUUGACU	205
SX103	SX103-B	AGUCAAGGAUAUGGAAAAC	206
SX104	SX104-A	AGGUUUUCCAUAUCCUUGA	207
SX104	SX104-B	UCAAGGAUAUGGAAAACCU	208
SX105	SX105-A	AUCAUUUGGUAGAAAACAU	209
SX105	SX105-B	AUGUUUUUCUACCAAAUGAU	210
SX106	SX106-A	GAUCAUUUGGUAGAAAACA	211
SX106	SX106-B	UGUUUUUCUACCAAAUGAUC	212
SX107	SX107-A	UCAUCGAUCAUUUGGUAGA	213
SX107	SX107-B	UCUACCAAAUGAUCGAUGA	214
SX108	SX108-A	AUGCCACAGAGACUCAGAG	215
SX108	SX108-B	CUCUGAGUCUCUGUGGCAU	216

Duplex ID	Strand Name (*)	Sequence (5' → 3')	SEQ ID No.
SX109	SX109-A	ACCAUGCCACAGAGACUCA	217
SX109	SX109-B	UGAGUCUCUGUGGCAUGGU	218
SX110	SX110-A	AACCAUGCCACAGAGACUC	219
SX110	SX110-B	GAGUCUCUGUGGCAUGGUU	220
SX111	SX111-A	CAAACCAUGCCACAGAGAC	221
SX111	SX111-B	GUCUCUGUGGCAUGGUUUG	222
SX112	SX112-A	UCCCAAACCAUGCCACAGA	223
SX112	SX112-B	UCUGUGGCAUGGUUUGGGA	224
SX113	SX113-A	UCUUGGCCUGCCAUGGUUG	225
SX113	SX113-B	CAACCAUGGCAGGCCAAGA	226
SX114	SX114-A	AGAUCUUGGCCUGCCAUGG	227
SX114	SX114-B	CCAUGGCAGGCCAAGAUCU	228
SX115	SX115-A	UGAGAUCUUGGCCUGCCAU	229
SX115	SX115-B	AUGGCAGGCCAAGAUCUCA	230
SX116	SX116-A	ACUGAGAUCUUGGCCUGCC	231
SX116	SX116-B	GGCAGGCCAAGAUCUCAGU	232
SX117	SX117-A	CGAAUGACUGAGAUCUUGG	233
SX117	SX117-B	CCAAGAUCUCAGUCAUUCG	234
SX118	SX118-A	GGGCGAAUGACUGAGAUCU	235
SX118	SX118-B	AGAUCUCAGUCAUUCGCCC	236
SX119	SX119-A	CAAAGUACUCAGACACCAC	237
SX119	SX119-B	GUGGUGUCUGAGUACUUUG	238
SX120	SX120-A	ACAAAGUACUCAGACACCA	239
SX120	SX120-B	UGGUGUCUGAGUACUUUGU	240
SX121	SX121-A	GCACAAAGUACUCAGACAC	241
SX121	SX121-B	GUGUCUGAGUACUUUGUGC	242
SX122	SX122-A	CAGCACAAGUACUCAGAC	243
SX122	SX122-B	GUCUGAGUACUUUGUGCUG	244
SX123	SX123-A	AUGGGCCUGAUAGUCUGGC	245
SX123	SX123-B	GCCAGACUAUCAGGCCCAU	246
SX124	SX124-A	GUGCAGGGGAGACAAAUGG	247
SX124	SX124-B	CCAUUUGUCUCCCUGCAC	248
SX125	SX125-A	AAACAGAGCUUUGAUUCC	249
SX125	SX125-B	GGAUAUCAAAGCUCUGUUU	250
SX126	SX126-A	ACAAACAGAGCUUUGAUU	251
SX126	SX126-B	AUAUCAAGCUCUGUUUGU	252
SX127	SX127-A	GACACAAACAGAGCUUUGA	253
SX127	SX127-B	UCAAGCUCUGUUUGUGUC	254
SX128	SX128-A	AUGUAGACCUCCUCCGAG	255
SX128	SX128-B	CUCGGAAGGAGGUCUACAU	256
SX129	SX129-A	GAUGUAGACCUCCUCCGA	257
SX129	SX129-B	UCGGAAGGAGGUCUACAUC	258
SX130	SX130-A	UCUUGAUGUAGACCUCCU	259
SX130	SX130-B	AAGGAGGUCUACAUCAAGA	260

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.
SX131	SX131-A	AUUCUUGAUGUAGACCUCC	261
SX131	SX131-B	GGAGGUCUACAUCAGAAU	262
SX132	SX132-A	CCCAUUCUUGAUGUAGACC	263
SX132	SX132-B	GGUCUACAUCAGAAUGGG	264
SX133	SX133-A	UCCCCAUUCUUGAUGUAGA	265
SX133	SX133-B	UCUACAUCAGAAUGGGGA	266
SX134	SX134-A	CUUAUCCCCAUUCUUGAUG	267
SX134	SX134-B	CAUCAAGAAUGGGGAUAAG	268
SX135	SX135-A	AUUGGGGUCAGCAUAGGGA	269
SX135	SX135-B	UCCCUAUGCUGACCCCAAU	270
SX136	SX136-A	GUUUUGGGGUCAGCAUAGG	271
SX136	SX136-B	CCUAUGCUGACCCCAAUAC	272
SX137	SX137-A	UACACCAACUUGAAUGAAA	273
SX137	SX137-B	UUUCAUUAAGUUGGUGUA	274
SX138	SX138-A	UCCACUACUCCCCAGCUGA	275
SX138	SX138-B	UCAGCUGGGGAGUAGUGGA	276
SX139	SX139-A	ACAUCCACUACUCCCCAGC	277
SX139	SX139-B	GCUGGGGAGUAGUGGAUGU	278
SX140	SX140-A	GCAGACAUCCACUACUCCC	279
SX140	SX140-B	GGGAGUAGUGGAUGUCUGC	280
SX141	SX141-A	UUUGCAGACAUCCACUACU	281
SX141	SX141-B	AGUAGUGGAUGUCUGCAAA	282
SX142	SX142-A	ACCCAAAUCCUCAUCUUGG	283
SX142	SX142-B	CCAAGAUAGAGGAUUUGGGU	284
SX143	SX143-A	AACCCAAAUCCUCAUCUUG	285
SX143	SX143-B	CAAGAUAGGGAUUUGGGUU	286
SX144	SX144-A	AAACCCAAAUCCUCAUCUU	287
SX144	SX144-B	AAGAUAGAGGAUUUGGGUUU	288
SX145	SX145-A	AAAACCCAAAUCCUCAUCU	289
SX145	SX145-B	AGAUGAGGAUUUGGGUUUU	290
SX146	SX146-A	GAAAACCCAAAUCCUCAUC	291
SX146	SX146-B	GAUGAGGAUUUGGGUUUUC	292
SX147	SX147-A	UAGAAAACCCAAAUCCUCA	293
SX147	SX147-B	UGAGGAUUUGGGUUUUUCUA	294
SX148	SX148-A	UUUAUAGAAAACCCAAAUCC	295
SX148	SX148-B	GGAUUUUGGGUUUUCUAUAA	296
SX149	SX149-A	UUGGAGAAGUCGGAAGGAG	297
SX149	SX149-B	CUCCUUCGACUUCUCCAA	298
SX150	SX150-A	GUCUGCACAGGGUACGGGU	299
SX150	SX150-B	ACCCGUACCCUGUGCAGAC	300
SX151	SX151-A	UACAUGAAGGAGUCUUGGC	301
SX151	SX151-B	GCCAAGACUCCUUAUGUA	302
SX152	SX152-A	GUGUUAGUCCUGACUUCA	303
SX152	SX152-B	UGAAGUCAGGGACUAACAC	304

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.
SX153	SX153-A	CCCAUGUUGUGCAAUCCA	305
SX153	SX153-B	AUGGAUUGCACAACAUGGG	306
SX154	SX154-A	AUCUUGGCCUGCCAUGGUU	307
SX154	SX154-B	AACCAUGGCAGGCCAAGAU	308
SX155	SX155-A	GAGAUUCUUGGCCUGCCAUG	309
SX155	SX155-B	CAUGGCAGGCCAAGAUCUC	310
SX156	SX156-A	AGACACAAACAGAGCUUUG	311
SX156	SX156-B	CAAAGCUCUGUUUGUGUCU	312
SX157	SX157-A	UAUUGGGGUCAGCAUAGGG	313
SX157	SX157-B	CCCUAUGCUGACCCCAAUA	314
SX158	SX158-A	UACGUGUCUGCACAGGGUA	315
SX158	SX158-B	UACCCUGUGCAGACACGUA	316
SX159	SX159-A	GUGGAAAGAGAUUCUCAUCA	317
SX159	SX159-B	UGAUGAGAUUCUCUUUCCAC	318
SX160	SX160-A	ACCGUCAUAGCAGUGGAAA	319
SX160	SX160-B	UUUCCACUGCUAUGACGGU	320
SX161	SX161-A	UGGUAGGUGACGCUGUCUU	321
SX161	SX161-B	AAGACAGCGUCACCUACCA	322
SX162	SX162-A	ACCUUCCUGACACGUUCGC	323
SX162	SX162-B	GCGAACGUGUCAGGAAGGU	324
SX163	SX163-A	AGCAUCGACUCCUUCUAUG	325
SX163	SX163-B	CAUAGAAGGAGUCGAUGCU	326
SX164	SX164-A	ACCAUAACUUGCCACCUUC	327
SX164	SX164-B	GAAGGUGGCAAGUUAUGGU	328
SX165	SX165-A	AUGACAUUGCGGGUGCGGU	329
SX165	SX165-B	ACCGCACCCGCCAUGUCAU	330
SX166	SX166-A	GACAGUAAUUGGGUCCCCG	331
SX166	SX166-B	CGGGGACCCAAUUCUGUC	332
SX167	SX167-A	AACACAUAGACAUCCAGAU	333
SX167	SX167-B	AUCUGGAUGUCUAUGUGUU	334
SX168	SX168-A	GCAUUGAUGUUCACUUGGU	335
SX168	SX168-B	ACCAAGUGAACAUCAAUGC	336
SX169	SX169-A	CACAUGUUGCUCUUGUCU	337
SX169	SX169-B	AGACAAUGAGCAACAUGUG	338
SX170	SX170-A	AGACUCAGAGACUGGCUUU	339
SX170	SX170-B	AAAGCCAGUCUCUGAGUCU	340
SX171	SX171-A	GUGUUCCCAAACCAUGCCA	341
SX171	SX171-B	UGGCAUGGUUUUGGGAACAC	342
SX172	SX172-A	GUUGCUUGUGGUAAUCGGU	343
SX172	SX172-B	ACCGAUUACCACAAGCAAC	344
SX173	SX173-A	AACGUCAUAGUCAUAAAAU	345
SX173	SX173-B	AUUUUUAUGACUAUGACGUU	346
SX174	SX174-A	ACAAAUGGGCCUGAUAGUC	347
SX174	SX174-B	GACUAUCAGGCCCAUUUGU	348

Duplex ID	Strand Name (*)	Sequence (5' → 3')	SEQ ID No.
SX175	SX175-A	UCAAAGCUCGAGUUGUUCC	349
SX175	SX175-B	GGAACAACUCGAGCUUUGA	350
SX176	SX176-A	UGUUGCUGGCAAGUGGUAG	351
SX176	SX176-B	CUACCACUUGCCAGCAACA	352
SX177	SX177-A	AUAGCCUGGGGCAUAUUGA	353
SX177	SX177-B	UCAAUAUGCCCCAGGCUAU	354
SX178	SX178-A	UACAAAGGAACCGAGGGGU	355
SX178	SX178-B	ACCCUCUGGUUCCUUUGUA	356
SX179	SX179-A	CUUUUGCCGCUUCUGGUUU	357
SX179	SX179-B	AAACCAGAAGCGGCAAAAG	358
SX180	SX180-A	GUCUUGGCAGGAAGGCUCC	359
SX180	SX180-B	GGAGCCUUCUGCCAAGAC	360
SX181	SX181-A	UCACAAACAGAGCUUUGAU	721
SX181	SX024-B	AUCAAAGCUCUGUUUGUGU	48
SX182	SX182-A	UUAUCCUUGACUUUGAACA	722
SX182	SX101-B	UGUUCAAGUCAAGGAUUAU	202
SX183	SX183-A	UUUGUCGAGCUGUUUUAA	723
SX183	SX036-B	UUAAAACAGCUGCGACAAC	72
SX184	SX184-A	UAUGAAACGACUUCUCUUG	724
SX184	SX029-B	CAAGAGAAGUCGUUUCAUU	58

The duplexes listed in Table 5b have various modifications as shown, with reference to Table 4 for an explanation of the abbreviations used. Where appropriate, the sequence of the equivalent unmodified strand from Table 5a is also indicated.

Table 5b – Modified duplexes

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2001	EV2001-A	mC (ps) fU (ps) mA fG mA fC mC fU mG fG mU fC mA fC mA fU mU (ps) fC (ps) mC	361	1
EV2001	EV2001-B	mG (ps) mG (ps) mA mA mU mG fU fG fA mC mC mA mG mU mC mU (ps) mA (ps) mG	362	2
EV2002	EV2002-A	mU (ps) fC (ps) mC fA mA fG mC fU mG fA mA fA mC fU mC fC mA (ps) fG (ps) mA	363	3
EV2002	EV2002-B	mU (ps) mC (ps) mU mG mG mA fG fU fU mU mC mA mG mC mU mU mG (ps) mG (ps) mA	364	4
EV2003	EV2003-A	mU (ps) fG (ps) mU fC mC fA mA fG mC fU mG fA mA fA mC fU mC (ps) fC (ps) mA	365	5
EV2003	EV2003-B	mU (ps) mG (ps) mG mA mG mU fU fC mA mG mC mU mU mG mG mA (ps) mC (ps) mA	366	6
EV2004	EV2004-A	mG (ps) fU (ps) mG fU mC fC mA fA mG fC mU fG mA fA mA fC mU (ps) fC (ps) mC	367	7
EV2004	EV2004-B	mG (ps) mG (ps) mA mG mU mU fU fC fA mG mC mU mU mG mG mA mC (ps) mA (ps) mC	368	8
EV2005	EV2005-A	mC (ps) fA (ps) mA fG mA fU mA fA mA fG mG fG mC fA mU fC mA (ps) fG (ps) mG	369	9
EV2005	EV2005-B	mC (ps) mC (ps) mU mG mA mU fG fC fC mC mU mU mU mA mU mC mU (ps) mU (ps) mG	370	10
EV2006	EV2006-A	mG (ps) fU (ps) mA fU mU fC mC fC mC fG mU fU mC fU mC fG mA (ps) fA (ps) mG	371	11
EV2006	EV2006-B	mC (ps) mU (ps) mU mC mG mA fG fA mC mG mG mG mA mU mU (ps) mA (ps) mC	372	12
EV2007	EV2007-A	mA (ps) fC (ps) mC fU mU fC mC fU mU fG mU fG mC fC mA fA mU (ps) fG (ps) mG	373	13
EV2007	EV2007-B	mC (ps) mC (ps) mA mU mU mG fG fC fA mC mA mA mG mG mA mA mG (ps) mU	374	14
EV2008	EV2008-A	mG (ps) fA (ps) mA fA mG fC mU fU mC fG mG fC mC fA mC fC mU (ps) fC (ps) mU	375	15
EV2008	EV2008-B	mA (ps) mG (ps) mA mG mG mU fG fG fC mC mG mA mA mG mC mU mU (ps) mC	376	16
EV2009	EV2009-A	mA (ps) fU (ps) mG fU mU fC mA fU mG fG mA fG mC fC mU fG mA (ps) fA (ps) mG	377	17
EV2009	EV2009-B	mC (ps) mU (ps) mU mC mA mG fG fC fU mC mC mA mU mG mA mA mC (ps) mA (ps) mU	378	18
EV2010	EV2010-A	mU (ps) fA (ps) mG fA mU fG mU fU mC fA mU fG mG fA mG fC mC (ps) fU (ps) mG	379	19
EV2010	EV2010-B	mC (ps) mA (ps) mG mG mC mU fC fC fA mU mG mA mA mC mA mU mC (ps) mU (ps) mA	380	20

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2011	EV2011-A	mA (ps) fU (ps) mU fA mA fG mU fU mG fA mC fU mA fG mA fC mA (ps) fC (ps) mU	381	21
EV2011	EV2011-B	mA (ps) mG (ps) mU mG mU mC fU fA fG mU mC mA mA mC mU mU mA (ps) mA (ps) mU	382	22
EV2012	EV2012-A	mC (ps) fA (ps) mA fU mU fA mA fG mU fU mG fA mC fU mA fG mA (ps) fC (ps) mA	383	23
EV2012	EV2012-B	mU (ps) mG (ps) mU mC mU mA fG fU fC mA mA mC mU mU mA mA mU (ps) mU (ps) mG	384	24
EV2013	EV2013-A	mC (ps) fU (ps) mC fA mA fU mU fA mA fG mU fU mG fA mC fU mA (ps) fG (ps) mA	385	25
EV2013	EV2013-B	mU (ps) mC (ps) mU mA mG mU fC fA mA mC mU mU mA mA mU mU mG (ps) mA (ps) mG	386	26
EV2014	EV2014-A	mU (ps) fU (ps) mC fU mC fA mA fU mU fA mA fG mU fU mG fA mC (ps) fU (ps) mA	387	27
EV2014	EV2014-B	mU (ps) mA (ps) mG mU mC mA fA fC fU mU mA mA mU mU mG mA mG (ps) mA (ps) mA	388	28
EV2015	EV2015-A	mU (ps) fU (ps) mC fG mU fG mA fC mC fC mA fG mU fC mU fG mC (ps) fA (ps) mU	389	29
EV2015	EV2015-B	mA (ps) mU (ps) mG mC mA mG fA fC fU mG mG mU mC mA mC mG (ps) mA (ps) mA	390	30
EV2016	EV2016-A	mU (ps) fC (ps) mA fU mG fC mU fG mU fA mC fA mC fU mG fC mC (ps) fU (ps) mG	391	31
EV2016	EV2016-B	mC (ps) mA (ps) mG mG mC mA fG fU fG mU mA mC mA mG mC mA mU (ps) mG (ps) mA	392	32
EV2017	EV2017-A	mU (ps) fC (ps) mA fU mC fA mA fU mG fA mC fA mG fU mA fA mU (ps) fU (ps) mG	393	33
EV2017	EV2017-B	mC (ps) mA (ps) mA mU mU mA fC fU fG mU mC mA mU mU mG mA mU (ps) mG (ps) mA	394	34
EV2018	EV2018-A	mA (ps) fA (ps) mA fC mA fC mA fU mA fG mA fC mA fU mC fC mA (ps) fG (ps) mA	395	35
EV2018	EV2018-B	mU (ps) mC (ps) mU mG mG mA fU fG fU mC mU mA mU mG mU mG mU (ps) mU (ps) mU	396	36
EV2019	EV2019-A	mA (ps) fA (ps) mA fG mC fA mU fU mG fA mU fG mU fU mC fA mC (ps) fU (ps) mU	397	37
EV2019	EV2019-B	mA (ps) mA (ps) mG mU mG mA fA fC fA mU mC mA mA mU mG mC mU (ps) mU (ps) mU	398	38
EV2020	EV2020-A	mC (ps) fU (ps) mU fG mA fC mU fU mU fG mA fA mC fA mC fA mU (ps) fG (ps) mU	399	39
EV2020	EV2020-B	mA (ps) mC (ps) mA mU mG mU fG fU fU mC mA mA mA mG mU mC mA (ps) mG	400	40
EV2021	EV2021-A	mG (ps) fU (ps) mC fA mU fA mA fA mA fU mU fC mA fG mG fA mA (ps) fU (ps) mU	401	41
EV2021	EV2021-B	mA (ps) mA (ps) mU mU mC mC fU fG fA mA mU mU mU mU mU mG (ps) mA (ps) mC	402	42
EV2022	EV2022-A	mA (ps) fU (ps) mA fG mU fC mA fU mA fA mA fA mU fU mC fA mG (ps) fG (ps) mA	403	43
EV2022	EV2022-B	mU (ps) mC (ps) mC mU mG mA fA fU fU mU mU mA mU mG mA mC mU (ps) mU	404	44
EV2023	EV2023-A	mA (ps) fG (ps) mA fA mA fU mG fG mG fC mC fU mG fA mU (ps) fA (ps) mG	405	45
EV2023	EV2023-B	mC (ps) mU (ps) mA mU mC mA fG fG fC mC mA mU mU mU mU mU mG mU (ps) mC (ps) mU	406	46

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EV2024	EV2024-A	mA (ps) fC (ps) mA fC mA fA mA fC mA fG mA fG mC fU mU fU mG (ps) fA (ps) mU	407	47
EV2024	EV2024-B	mA (ps) mU (ps) mC mA mA mA fG fC fU mC mU mU mU mG (ps) mU mG (ps) mU	408	48
EV2025	EV2025-A	mG (ps) fG (ps) mC fA mU fA mU fU mG fA mG fC mA fU mC fU mC (ps) fU (ps) mC	409	49
EV2025	EV2025-B	mG (ps) mA (ps) mG mA mG mA fU fG fC mU mC mA mA mA mU mU mG (ps) mC (ps) mC	410	50
EV2026	EV2026-A	mA (ps) fU (ps) mG fU mC fC mU fU mG fA mC fU mU fU mG fU mC (ps) fA (ps) mU	411	51
EV2026	EV2026-B	mA (ps) mU (ps) mG mA mC mA fA fA fG mU mC mA mA mG mG mA mC (ps) mA (ps) mU	412	52
EV2027	EV2027-A	mA (ps) fA (ps) mG fU mA fU mU fG mG fG mG fU mC fA mG fC mA (ps) fU (ps) mA	413	53
EV2027	EV2027-B	mU (ps) mA (ps) mU mG mC mU fG fA fC mC mC mC mA mA mU mA mC (ps) mU (ps) mU	414	54
EV2028	EV2028-A	mU (ps) fG (ps) mA fA mC fU mA fU mC fA mA fG mG fG mC (ps) fG (ps) mC	415	55
EV2028	EV2028-B	mG (ps) mC (ps) mG mG mC mC fC fC fU mU mG mA mU mA mG mU mU mC (ps) mA	416	56
EV2029	EV2029-A	mA (ps) fA (ps) mU fG mA fA mA fC mG fA mC fU mU fC mU (ps) fU (ps) mG	417	57
EV2029	EV2029-B	mC (ps) mA (ps) mA mG mA mG fA fA fG mU mC mG mU mU mC mA (ps) mU (ps) mU	418	58
EV2030	EV2030-A	mU (ps) fG (ps) mA fA mU fG mA fA mA fC mG fA mC fU mU fC mU (ps) fC (ps) mU	419	59
EV2030	EV2030-B	mA (ps) mG (ps) mA mG mA mA fG fU fC mG mU mU mU mC mA mU mU mC (ps) mA	420	60
EV2031	EV2031-A	mA (ps) fC (ps) mU fU mG fA mA fU mG fA mA fA mC fG mA fC mU (ps) fU (ps) mC	421	61
EV2031	EV2031-B	mG (ps) mA (ps) mA mG mU mC fG fU fU mU mC mA mU mU mC mA mA (ps) mU	422	62
EV2032	EV2032-A	mA (ps) fC (ps) mC fA mA fC mU fU mG fA mA fU mG fA mA fA mC (ps) fG (ps) mA	423	63
EV2032	EV2032-B	mU (ps) mC (ps) mG mU mU mU fC fA fU mU mC mA mA mG mU mU mG (ps) mU	424	64
EV2033	EV2033-A	mU (ps) fG (ps) mU fG mA fA mA fG mU fC mU fC mG fG mG fC mG (ps) fU (ps) mG	425	65
EV2033	EV2033-B	mC (ps) mA (ps) mC mG mC mC fC fG fA mG mA mC mU mU mU mC mA (ps) mC (ps) mA	426	66
EV2034	EV2034-A	mU (ps) fG (ps) mU fU mU fU mA fA mU fU mC fA mA fU mC fC mC (ps) fA (ps) mC	427	67
EV2034	EV2034-B	mG (ps) mU (ps) mG mG mG mA fU fU fG mA mA mU mU mA mA mA mA (ps) mC (ps) mA	428	68
EV2035	EV2035-A	mC (ps) fA (ps) mG fC mU fG mU fU mU fU mA fA mU fU mC fA mA (ps) fU (ps) mC	429	69
EV2035	EV2035-B	mG (ps) mA (ps) mU mU mG mA fA fU fU mA mA mA mA mC mA mG mC (ps) mU (ps) mG	430	70
EV2036	EV2036-A	mG (ps) fU (ps) mU fG mU fC mG fC mA fG mC fU mG fU mU fU mU (ps) fA (ps) mA	431	71
EV2036	EV2036-B	mU (ps) mU (ps) mA mA mA mA fC fA fG mC mU mG mC mA mC mA (ps) mA (ps) mC	432	72

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EV2037	EV2037-A	mC (ps) fA (ps) mC fU mA fG mA fC mC fA mU fA mU fC mU fU mG (ps) fG (ps) mC	433	73
EV2037	EV2037-B	mG (ps) mC (ps) mC mA mA mG fA fU fA mU mG mG mU mC mU mA mG (ps) mU (ps) mG	434	74
EV2038	EV2038-A	mU (ps) fG (ps) mU fC mA fC mU fA mG fA mC fC mA fU mA fU mC (ps) fU (ps) mU	435	75
EV2038	EV2038-B	mA (ps) mA (ps) mG mA mU mA fU fG fG mU mC mU mA mG mU mG mA (ps) mC (ps) mA	436	76
EV2039	EV2039-A	mU (ps) fU (ps) mC fU mU fG mG fU mG fU mU fA mG fU mC fC mC (ps) fU (ps) mG	437	77
EV2039	EV2039-B	mC (ps) mA (ps) mG mG mA fC fU fA mA mC mA mC mA mG (ps) mA (ps) mA	438	78
EV2040	EV2040-A	mU (ps) fC (ps) mA fG mU fC mA fU mG fA mG fG mA fU mG fA mU (ps) fG (ps) mA	439	79
EV2040	EV2040-B	mU (ps) mC (ps) mA mA mU mC mA fU fC fC mU mC mA mU mG mA mC mU (ps) mG (ps) mA	440	80
EV2041	EV2041-A	mG (ps) fA (ps) mU fU mA fC mA fC mC fA mA fC mU fU mG fA mA (ps) fU (ps) mG	441	81
EV2041	EV2041-B	mC (ps) mA (ps) mU mU mC mA fA fG fU mU mG mG mU mG mU mA mA (ps) mU (ps) mC	442	82
EV2042	EV2042-A	mU (ps) fU (ps) mG fU mA fG mU fA mG fG mG fA mG fA mC fC mG (ps) fG (ps) mG	443	83
EV2042	EV2042-B	mC (ps) mC (ps) mC mG mG mU fC fU fC mC mC mU mA mC mU mA mC (ps) mA (ps) mA	444	84
EV2043	EV2043-A	mU (ps) fC (ps) mC fA mA fG mA fG mC fC mA fC mC fU mU fC mC (ps) fU (ps) mG	445	85
EV2043	EV2043-B	mC (ps) mA (ps) mG mG mA mA fG fG fU mG mG mC mU mC mU mU mG (ps) mG (ps) mA	446	86
EV2044	EV2044-A	mU (ps) fC (ps) mG fU mA fC mA fU mG fA mA fG mG fA mG fU mC (ps) fU (ps) mU	447	87
EV2044	EV2044-B	mA (ps) mA (ps) mG mA mC mU fC fC fU mU mC mA mU mG mU mA mC (ps) mG (ps) mA	448	88
EV2045	EV2045-A	mC (ps) fU (ps) mC fU mU fG mA fG mG fG mG fU mG fU mC fG mU (ps) fA (ps) mC	449	89
EV2045	EV2045-B	mG (ps) mU (ps) mA mC mG mA fC fA fC mC mC mC mU mC mA mA mG (ps) mA (ps) mG	450	90
EV2046	EV2046-A	mU (ps) fU (ps) mG fG mC fU mC fC mU fG mU fG mA fA mG fU mU (ps) fG (ps) mC	451	91
EV2046	EV2046-B	mG (ps) mC (ps) mA mA mC mU fU fC fA mC mA mG mG mA mG mC mC (ps) mA (ps) mA	452	92
EV2047	EV2047-A	mA (ps) fU (ps) mA fA mC fU mU fG mC fC mA fC mC fU mU fC mU (ps) fC (ps) mA	453	93
EV2047	EV2047-B	mU (ps) mG (ps) mA mA mG mA fG fG fU mG mG mC mA mA mG mU mU (ps) mA (ps) mU	454	94
EV2048	EV2048-A	mA (ps) fG (ps) mC fC mA fA mA fG mC fA mU fU mG fA mU fG mU (ps) fU (ps) mC	455	95
EV2048	EV2048-B	mG (ps) mA (ps) mA mC mA mU fC fA fA mU mG mC mU mU mU mG mG (ps) mC (ps) mU	456	96
EV2049	EV2049-A	mG (ps) fA (ps) mA fG mC fC mA fA mA fG mC fA mU fU mG fA mU (ps) fG (ps) mU	457	97
EV2049	EV2049-B	mA (ps) mC (ps) mA mU mC mA fA fU fG mC mU mU mU mG mG mC mU (ps) mU (ps) mC	458	98

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EV2050	EV2050-A	mG (ps) fA (ps) mA fC mA fC mA fU mG fU mU fG mC fU mC fA mU (ps) fU (ps) mG	459	99
EV2050	EV2050-B	mC (ps) mA (ps) mA mU mG mA fG fC fA mA mC mA mU mG mU (ps) mU (ps) mC	460	100
EV2051	EV2051-A	mG (ps) fC (ps) mC fG mC fC mU fU mU fG mA fU mC fU mC fU mA (ps) fC (ps) mC	461	101
EV2051	EV2051-B	mG (ps) mG (ps) mU mA mG mA fG fA fU mC mA mA mA mG mG mC mG (ps) mG (ps) mC	462	102
EV2052	EV2052-A	mG (ps) fA (ps) mG fC mC fG mC fC mU fU mU fG mA fU mC fU mC (ps) fU (ps) mA	463	103
EV2052	EV2052-B	mU (ps) mA (ps) mG mA mG mA fU fC fA mA mA mG mG mC mG (ps) mU (ps) mC	464	104
EV2053	EV2053-A	mA (ps) fA (ps) mG fG mA fG mC fC mG fC mC fU mU fU mG fA mU (ps) fC (ps) mU	465	105
EV2053	EV2053-B	mA (ps) mG (ps) mA mU mC mA fA fA fG mG mC mG mC mU mC mC (ps) mU (ps) mU	466	106
EV2054	EV2054-A	mG (ps) fG (ps) mA fA mG fG mA fG mC fC mG fC mC fU mU fU mG (ps) fA (ps) mU	467	107
EV2054	EV2054-B	mA (ps) mU (ps) mC mA mA mA fG fG fC mG mG mC mU mC mC mU mU (ps) mC (ps) mC	468	108
EV2055	EV2055-A	mG (ps) fG (ps) mG fU mA fG mA fA mG fC mC fA mG fA mA fG mG (ps) fA (ps) mC	469	109
EV2055	EV2055-B	mG (ps) mU (ps) mC mC mU mU fC fU fG mG mC mU mU mC mU mA mC (ps) mC (ps) mC	470	110
EV2056	EV2056-A	mC (ps) fA (ps) mG mA mG fC mC fC mC fG mG fA mG fA mG fU mG (ps) fU (ps) mA	471	111
EV2056	EV2056-B	mU (ps) mA (ps) mC mA mC mU fC fU fC mC mG mG mG mC mU mC (ps) mU (ps) mG	472	112
EV2057	EV2057-A	mU (ps) fU (ps) mG fG mC fA mG fG mU fG mC fG mA fU mU fG mG (ps) fC (ps) mA	473	113
EV2057	EV2057-B	mU (ps) mG (ps) mC mC mA mA fU fC fG mC mA mC mC mU mG mC mC (ps) mA (ps) mA	474	114
EV2058	EV2058-A	mA (ps) fU (ps) mU fC mA fC mU fU mG fG mC fA mG fG mU fG mC (ps) fG (ps) mA	475	115
EV2058	EV2058-B	mU (ps) mC (ps) mG mC mA mC fC fU fG mC mC mA mA mG mU mG mA (ps) mA (ps) mU	476	116
EV2059	EV2059-A	mC (ps) fC (ps) mA fU mU fC mA fC mU fU mG fG mC fA mG fG mU (ps) fG (ps) mC	477	117
EV2059	EV2059-B	mG (ps) mC (ps) mA mC mC mU fG fC fC mA mA mG mU mG mA mU (ps) mG (ps) mG	478	118
EV2060	EV2060-A	mC (ps) fC (ps) mC fA mC fC mU fU mC fC mU fU mG fU mG fC mC (ps) fA (ps) mA	479	119
EV2060	EV2060-B	mU (ps) mU (ps) mG mG mC mA fC fA mA mG mG mA mA mG mG mU mG (ps) mG (ps) mG	480	120
EV2061	EV2061-A	mU (ps) fC (ps) mU fU mC fA mA fG mG fC mG fG mU fA mC fU mG (ps) fG (ps) mC	481	121
EV2061	EV2061-B	mG (ps) mC (ps) mC mA mG mU fA fC fC mG mC mC mU mU mG mA mA (ps) mG (ps) mA	482	122
EV2062	EV2062-A	mG (ps) fU (ps) mC fU mU fC mA fA mG fG mC fG mG fU mA fC mU (ps) fG (ps) mG	483	123
EV2062	EV2062-B	mC (ps) mC (ps) mA mG mU mA fC fC fG mC mC mU mU mG mA mA mG (ps) mA (ps) mC	484	124

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2063	EV2063-A	mA (ps) fC (ps) mA fU mG fA mA fG mG fA mC fU mU fG mG (ps) fC (ps) mA	485	125
EV2063	EV2063-B	mU (ps) mG (ps) mC mC mA mA fG fA fC mU mC mC mU mU mC mA mU (ps) mG (ps) mU	486	126
EV2064	EV2064-A	mU (ps) fU (ps) mC fG mG fC mC fA mC fC mU fU mG fA mG (ps) fG (ps) mG	487	127
EV2064	EV2064-B	mC (ps) mC (ps) mC mU mC mA fA fG fA mG mG mU mG mG mC mC mG (ps) mA (ps) mA	488	128
EV2065	EV2065-A	mC (ps) fU (ps) mU fC mU fA mU fG mG fU mC fU mC fU mC fU mC (ps) fA (ps) mG	489	129
EV2065	EV2065-B	mC (ps) mU (ps) mG mA mC mA fG fA fG mA mC mC mA mU mA mG mA (ps) mA (ps) mG	490	130
EV2066	EV2066-A	mA (ps) fU (ps) mC fC mU fC mA fG mC fA mU fC mG fA mC fU mC (ps) fC (ps) mU	491	131
EV2066	EV2066-B	mA (ps) mG (ps) mG mA mG mU fC fG fA mU mG mC mU mG mA mG mG (ps) mA (ps) mU	492	132
EV2067	EV2067-A	mC (ps) fC (ps) mC fA mU fC mC fU mC fA mG fC mA fU mC fG mA (ps) fC (ps) mU	493	133
EV2067	EV2067-B	mA (ps) mG (ps) mU mC mG mA fU fG fC mU mG mA mG mC mU mG mG (ps) mG (ps) mG	494	134
EV2068	EV2068-A	mG (ps) fU (ps) mG fC mC fC mA fU mC fC mU fC mA fG mC fA mU (ps) fC (ps) mG	495	135
EV2068	EV2068-B	mC (ps) mG (ps) mA mU mG mC fU fG fA mG mG mA mU mG mG mC (ps) mA (ps) mC	496	136
EV2069	EV2069-A	mU (ps) fA (ps) mG fC mA fC mC fA mG fG mU fA mG fA mU fG mU (ps) fU (ps) mC	497	137
EV2069	EV2069-B	mG (ps) mA (ps) mA mC mA mU fC fU fA mC mC mU mG mG mU mG mC (ps) mU (ps) mA	498	138
EV2070	EV2070-A	mU (ps) fC (ps) mU fA mG fC mA fC mC fA mG fG mU fA mG fA mU (ps) fG (ps) mU	499	139
EV2070	EV2070-B	mA (ps) mC (ps) mA mU mC mU fA fC fC mU mG mG mU mG mC mU mA (ps) mG (ps) mA	500	140
EV2071	EV2071-A	mU (ps) fC (ps) mC fA mU fC mU fA mG fC mA fC mC fA mG fG mU (ps) fA (ps) mG	501	141
EV2071	EV2071-B	mC (ps) mU (ps) mA mC mC mU fG fG fU mG mC mU mA mG mA mU mG (ps) mG (ps) mA	502	142
EV2072	EV2072-A	mG (ps) fA (ps) mU fC mC fA mU fC mU fA mG fC mA fC mC fA mG (ps) fG (ps) mU	503	143
EV2072	EV2072-B	mA (ps) mC (ps) mC mU mG mG fU fG fC mU mA mG mA mU mG mA (ps) mU (ps) mC	504	144
EV2073	EV2073-A	mU (ps) fG (ps) mA fU mC fC mA fU mC fU mA fG mC fA mC fC mA (ps) fG (ps) mG	505	145
EV2073	EV2073-B	mC (ps) mC (ps) mU mG mG mU fG fC fU mA mG mA mU mG mG mA mU (ps) mC (ps) mA	506	146
EV2074	EV2074-A	mG (ps) fU (ps) mC fU mG fA mU fC mC fA mU fC mU fA mG fC mA (ps) fC (ps) mC	507	147
EV2074	EV2074-B	mG (ps) mG (ps) mU mG mC mU fA fG fA mU mG mG mA mU mC mA mG (ps) mA (ps) mC	508	148
EV2075	EV2075-A	mU (ps) fG (ps) mU fC mU fG mA fU mC fC mA fU mC fU mA fG mC (ps) fA (ps) mC	509	149
EV2075	EV2075-B	mG (ps) mU (ps) mG mC mU mA fG fA fU mG mG mA mU mC mA mG mA (ps) mC (ps) mA	510	150

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EV2076	EV2076-A	mG (ps) fc (ps) mU fg mU fc mU fg mA fU mC fc mA fU mC fU mA (ps) fg (ps) mC	511	151
EV2076	EV2076-B	mG (ps) mC (ps) mU mA mG mA fU fg fG mA mU mC mA mG mA mC mA (ps) mG (ps) mC	512	152
EV2077	EV2077-A	mA (ps) fU (ps) mG fc mU fg mU fc mU fg mA fU mC fc mA fU mC (ps) fU (ps) mA	513	153
EV2077	EV2077-B	mU (ps) mA (ps) mG mA mU mG fg fA fU mC mA mG mA mC mA mG mC (ps) mA (ps) mU	514	154
EV2078	EV2078-A	mC (ps) fA (ps) mA fU mG fc mU fg mU fc mU fg mA fU mC fc mA (ps) fU (ps) mC	515	155
EV2078	EV2078-B	mG (ps) mA (ps) mU mG mG mA fU fc fA mG mA mC mA mG mC mA mU (ps) mU (ps) mG	516	156
EV2079	EV2079-A	mC (ps) fc (ps) mA fA mU fg mC fU mG fU mC fU mG fA mU fc mC (ps) fA (ps) mU	517	157
EV2079	EV2079-B	mA (ps) mU (ps) mG mG mA mU fc fA fg mA mC mA mG mC mA mU mU (ps) mG (ps) mG	518	158
EV2080	EV2080-A	mC (ps) fc (ps) mU fg mU fg mA fA mG fU mU fg mC fU mG fc mC (ps) fc (ps) mC	519	159
EV2080	EV2080-B	mG (ps) mG (ps) mG mC mC mA fg fc fA mA mC mU mU mC mA mC mA (ps) mG (ps) mG	520	160
EV2081	EV2081-A	mU (ps) fA (ps) mA fc mU fU mG fc mC fA mC fc mU fU mC fU mC (ps) fA (ps) mA	521	161
EV2081	EV2081-B	mU (ps) mU (ps) mG mA mG mA fA fg fG mU mG mG mC mA mA mG mU (ps) mU (ps) mA	522	162
EV2082	EV2082-A	mU (ps) fg (ps) mG fc mA fU mA fU mG fU mC fA mC fU mA fg mA (ps) fc (ps) mC	523	163
EV2082	EV2082-B	mG (ps) mG (ps) mU mC mU mA fg fU fg mA mC mA mU mA mU mG mC (ps) mC (ps) mA	524	164
EV2083	EV2083-A	mU (ps) fg (ps) mG fU mC fU mU fc mA fU mA fA mU fU mG fA mU (ps) fU (ps) mU	525	165
EV2083	EV2083-B	mA (ps) mA (ps) mA mU mC mA fA fU fU mA mU mG mA mA mG mA mC (ps) mC (ps) mA	526	166
EV2084	EV2084-A	mG (ps) fU (ps) mG fg mU fc mU fU mC fA mU fA mA fU mU fg mA (ps) fU (ps) mU	527	167
EV2084	EV2084-B	mA (ps) mA (ps) mU mC mA mA fU fU fA mU mG mA mA mG mA mC mC (ps) mA (ps) mC	528	168
EV2085	EV2085-A	mU (ps) fU (ps) mG fU mG fg mU fc mU fU mC fA mU fA mA fU mU (ps) fg (ps) mA	529	169
EV2085	EV2085-B	mU (ps) mC (ps) mA mA mU mU fA fU fg mA mA mG mA mC mC mA mC (ps) mA (ps) mA	530	170
EV2086	EV2086-A	mU (ps) fc (ps) mA fA mC fU mU fg mU fg mG fU mC fU mU fc mA (ps) fU (ps) mA	531	171
EV2086	EV2086-B	mU (ps) mA (ps) mU mG mA mA fG fA fc mC mA mC mA mG mU mU (ps) mG (ps) mA	532	172
EV2087	EV2087-A	mC (ps) fU (ps) mU fc mA fA mC fU mU fg mU fg mG fU mC fU mU (ps) fc (ps) mA	533	173
EV2087	EV2087-B	mU (ps) mG (ps) mA mA mG mA fc fc fA mC mA mA mG mU mU mG mA (ps) mA (ps) mG	534	174
EV2088	EV2088-A	mA (ps) fc (ps) mU fU mC fA mA fc mU fU mG fU mG fg mU fc mU (ps) fU (ps) mC	535	175
EV2088	EV2088-B	mG (ps) mA (ps) mA mG mA mC fc fA fc mA mA mG mU mU mG mA mA (ps) mG (ps) mU	536	176

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EV2089	EV2089-A	mU (ps) fG (ps) mG fU mG fU mU fA mG fU mC fC mC fU mG fA mC (ps) fU (ps) mU	537	177
EV2089	EV2089-B	mA (ps) mA (ps) mG mU mC mA fG fG mA mC mU mA mC mA mC (ps) mC (ps) mA	538	178
EV2090	EV2090-A	mU (ps) fC (ps) mU fU mG fG mU fU mU fU mU fU mU fC mU fC mU fG (ps) mA	539	179
EV2090	EV2090-B	mU (ps) mC (ps) mA mG mG mG fA fC fU mA mA mC mA mC mC mA mA (ps) mG (ps) mA	540	180
EV2091	EV2091-A	mA (ps) fU (ps) mG fA mU fG mA fC mA fU mG fC mC fG mU (ps) fG (ps) mC	541	181
EV2091	EV2091-B	mG (ps) mC (ps) mA mC mC mC fG fC mA mU mG mU mC mA mU mC (ps) mA (ps) mU	542	182
EV2092	EV2092-A	mG (ps) fG (ps) mA fU mG fA mU fG mA fC mA fU mG fG mC fG mG (ps) fG (ps) mU	543	183
EV2092	EV2092-B	mA (ps) mC (ps) mC mC mG mC fC fA fU mG mU mC mA mU mC mA mU (ps) mC (ps) mC	544	184
EV2093	EV2093-A	mA (ps) fG (ps) mG fA mU fG mA fU mG fA mC fA mU fG mG fC mG (ps) fG (ps) mG	545	185
EV2093	EV2093-B	mC (ps) mC (ps) mC mG mC mC fA fU fG mU mC mA mU mC mA mU mC (ps) mC (ps) mU	546	186
EV2094	EV2094-A	mU (ps) fG (ps) mU fG mC fA mA fU mC fC mA fU mC fA mG fU mC (ps) fA (ps) mU	547	187
EV2094	EV2094-B	mA (ps) mU (ps) mG mA mC mU fG fA fU mG mG mA mU mU mG mC mA (ps) mC (ps) mA	548	188
EV2095	EV2095-A	mU (ps) fG (ps) mU fU mG fU mG fC mA fA mU fC mC fA mU fC mA (ps) fG (ps) mU	549	189
EV2095	EV2095-B	mA (ps) mC (ps) mU mG mA mU fG fG fA mU mU mG mC mA mC mA mA (ps) mC (ps) mA	550	190
EV2096	EV2096-A	mC (ps) fC (ps) mA fU mG fU mU fG mU fG mC fA mA fU mC fC mA (ps) fU (ps) mC	551	191
EV2096	EV2096-B	mG (ps) mA (ps) mU mG mG mA fU fU fG mC mA mC mA mA mC mA mU (ps) mG (ps) mG	552	192
EV2097	EV2097-A	mA (ps) fC (ps) mA fU mC fC mA fG mA fU mA fA mU fC mC fU mC (ps) fC (ps) mC	553	193
EV2097	EV2097-B	mG (ps) mG (ps) mG mA mG mG fA fU fU mA mU mC mU mG mG mA mU (ps) mG (ps) mU	554	194
EV2098	EV2098-A	mA (ps) fC (ps) mC fC mA fA mA fA mC fA mC fA mU fA mG fA mC (ps) fA (ps) mU	555	195
EV2098	EV2098-B	mA (ps) mU (ps) mG mU mC mU fA fU fG mU mG mU mU mU mG mG mG (ps) mG (ps) mU	556	196
EV2099	EV2099-A	mA (ps) fC (ps) mA fC mA fU mG fU mU fG mC fU mC fA mU fU mG (ps) fU (ps) mC	557	197
EV2099	EV2099-B	mG (ps) mA (ps) mC mA mA mU fG fA fG mC mA mA mC mA mU mG mU (ps) mG (ps) mU	558	198
EV2100	EV2100-A	mA (ps) fU (ps) mC fC mU fU mG fA mC fU mU fU mG fA mA fC mA (ps) fC (ps) mA	559	199
EV2100	EV2100-B	mU (ps) mG (ps) mU mG mU mU fC fA fA mA mG mU mC mA mA mG mG (ps) mA (ps) mU	560	200
EV2101	EV2101-A	mA (ps) fU (ps) mA fU mC fC mU fU mG fA mC fU mU fU mG fA mA (ps) fC (ps) mA	561	201
EV2101	EV2101-B	mU (ps) mG (ps) mU mU mC mA fA fA fG mU mC mA mA mG mG mA mU (ps) mA (ps) mU	562	202

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2102	EV2102-A	mU (ps) fU (ps) mC fC mA fU mA fU mC fC mU fU mG fA mC fU mU (ps) fU (ps) mG	563	203
EV2102	EV2102-B	mC (ps) mA (ps) mA mG mU fC fA fA mG mA mU mG mG (ps) mA (ps) mA	564	204
EV2103	EV2103-A	mG (ps) fU (ps) mU fU mU fC mC fA mU fA mU fC mC fU mU fG mA (ps) fC (ps) mU	565	205
EV2103	EV2103-B	mA (ps) mG (ps) mU mC mA mA fG fG fA mU mA mU mG mG mA mA mA (ps) mA (ps) mC	566	206
EV2104	EV2104-A	mA (ps) fG (ps) mG fU mU fU mU fC mC fA mU fA mU fC mC fU mU (ps) fG (ps) mA	567	207
EV2104	EV2104-B	mU (ps) mC (ps) mA mA mG mG fA fU fA mU mG mG mA mA mA mC (ps) mC (ps) mU	568	208
EV2105	EV2105-A	mA (ps) fU (ps) mC fA mU fU mU fG mG fU mA fG mA fA mA fA mC (ps) fA (ps) mU	569	209
EV2105	EV2105-B	mA (ps) mU (ps) mG mU mU mU fU fC fU mA mC mC mA mA mA mU mG (ps) mA (ps) mU	570	210
EV2106	EV2106-A	mG (ps) fA (ps) mU fC mA fU mU fU mG fG mU fA mG fA mA fA mA (ps) fC (ps) mA	571	211
EV2106	EV2106-B	mU (ps) mG (ps) mU mU mU fC fU fA mC mC mA mA mA mU mG mA (ps) mU (ps) mC	572	212
EV2107	EV2107-A	mU (ps) fC (ps) mA fU mC fG mA fU mC fA mU fU mU fG mG fU mA (ps) fG (ps) mA	573	213
EV2107	EV2107-B	mU (ps) mC (ps) mU mA mC mC fA fA fA mU mG mA mU mC mG mA mU (ps) mG (ps) mA	574	214
EV2108	EV2108-A	mA (ps) fU (ps) mG fC mC fA mC fA mG fA mG fA mC fU mC fA mG (ps) fA (ps) mG	575	215
EV2108	EV2108-B	mC (ps) mU (ps) mC mU mG mA fG fU fC mU mC mU mG mU mG mG mC (ps) mA (ps) mU	576	216
EV2109	EV2109-A	mA (ps) fC (ps) mC fA mU fG mC fC mA fC mA fG mA fG mA fC mU (ps) fC (ps) mA	577	217
EV2109	EV2109-B	mU (ps) mG (ps) mA mG mU mC fU fC fU mG mU mG mG mC mA mU mG (ps) mG (ps) mU	578	218
EV2110	EV2110-A	mA (ps) fA (ps) mC fC mA fU mG fC mC fA mC fA mG fA mC (ps) fU (ps) mC	579	219
EV2110	EV2110-B	mG (ps) mA (ps) mG mU mC mU fC fU fG mU mG mG mC mA mU mG mG (ps) mU (ps) mU	580	220
EV2111	EV2111-A	mC (ps) fA (ps) mA fA mC fC mA fU mG fC mC fA mC fA mG fA mG (ps) fA (ps) mC	581	221
EV2111	EV2111-B	mG (ps) mU (ps) mC mU mC mU fG fU fG mG mC mA mU mG mG mU mU (ps) mU (ps) mG	582	222
EV2112	EV2112-A	mU (ps) fC (ps) mC fC mA fA mA fC mC fA mU fG mC fC mA fC mA fC (ps) fG (ps) mA	583	223
EV2112	EV2112-B	mU (ps) mC (ps) mU mG mU mG fG fC fA mU mG mG mU mU mU mG mG (ps) mA	584	224
EV2113	EV2113-A	mU (ps) fC (ps) mU fU mG fG mC fC mU fG mC fC mA fU mG fG mU (ps) fU (ps) mG	585	225
EV2113	EV2113-B	mC (ps) mA (ps) mA mC mC mA fU fG fG mC mA mG mG mC mC mA mA (ps) mG (ps) mA	586	226
EV2114	EV2114-A	mA (ps) fG (ps) mA fU mC fU mU fG mG fC mC fU mG fC mC fA mU (ps) fG (ps) mG	587	227
EV2114	EV2114-B	mC (ps) mC (ps) mA mU mG mG fC fA fG mG mC mC mA mA mG mA mU (ps) mC (ps) mU	588	228

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2115	EV2115-A	mU (ps) fG (ps) mA fG mA fU mC fU mU fG mG fC mC fU mG fC mC (ps) fA (ps) mU	589	229
EV2115	EV2115-B	mA (ps) mU (ps) mG mC mA fG fC mC mA mA mG mA mU mC mU (ps) mC (ps) mA	590	230
EV2116	EV2116-A	mA (ps) fC (ps) mU fG mA fG mA fU mC fU mU fG mG fC mC fU mG (ps) fC (ps) mC	591	231
EV2116	EV2116-B	mG (ps) mG (ps) mC mA mG mG fC fC fA mA mG mA mU mC mU mC mA (ps) mG (ps) mU	592	232
EV2117	EV2117-A	mC (ps) fG (ps) mA fA mU fG mA fC mU fG mA fG mA fU mC fU mU (ps) fG (ps) mG	593	233
EV2117	EV2117-B	mC (ps) mC (ps) mA mA mG mA fU fC fU mC mA mG mU mC mA mU mU (ps) mC (ps) mG	594	234
EV2118	EV2118-A	mG (ps) fG (ps) mG fC mG fA mA fU mG fA mC fU mG fA mC fA mU (ps) fC (ps) mU	595	235
EV2118	EV2118-B	mA (ps) mG (ps) mA mU mC mU fC fA fG mU mC mA mU mC mG mC (ps) mC (ps) mC	596	236
EV2119	EV2119-A	mC (ps) fA (ps) mA fA mG fU mA fC mU fC mA fG mA fC mA fC mC (ps) fA (ps) mC	597	237
EV2119	EV2119-B	mG (ps) mU (ps) mG mG mU mG fU fC fU mG mA mG mU mA mC mU mU (ps) mU (ps) mG	598	238
EV2120	EV2120-A	mA (ps) fC (ps) mA fA mA fG mU fA mC fU mC fA mG fA mC fA mC (ps) fC (ps) mA	599	239
EV2120	EV2120-B	mU (ps) mG (ps) mG mU mG mU fC fU fG mA mG mU mA mC mU mU mU (ps) mG (ps) mU	600	240
EV2121	EV2121-A	mG (ps) fC (ps) mA fC mA fA mA fG mU fA mC fU mC fA mG fA mC (ps) fA (ps) mC	601	241
EV2121	EV2121-B	mG (ps) mU (ps) mG mU mC mU fG fA fG mU mA mC mU mU mU mG mU (ps) mG (ps) mC	602	242
EV2122	EV2122-A	mC (ps) fA (ps) mG fC mA fC mA fA mA fA mA fG mU fA mC fU mC fA mG (ps) fA (ps) mC	603	243
EV2122	EV2122-B	mG (ps) mU (ps) mC mU mG mA fG fU fA mC mU mU mU mG mU mG mC (ps) mU (ps) mG	604	244
EV2123	EV2123-A	mA (ps) fU (ps) mG fG mG fC mC fU mG fA mU fA mG fU mC fU mG (ps) fG (ps) mC	605	245
EV2123	EV2123-B	mG (ps) mC (ps) mC mA mG mA fC fU fA mU mC mA mG mG mC mC mC (ps) mA (ps) mU	606	246
EV2124	EV2124-A	mG (ps) fU (ps) mG fC mA fG mG fG mG fA mG fA mC fA mA fA mU (ps) fG (ps) mG	607	247
EV2124	EV2124-B	mC (ps) mC (ps) mA mU mU mU fG fU fC mU mC mC mC mU mG mC mU mG mC (ps) mC	608	248
EV2125	EV2125-A	mA (ps) fA (ps) mA fC mA fG mA fG mC fU mU fU mG fA mU fA mU (ps) fC (ps) mC	609	249
EV2125	EV2125-B	mG (ps) mG (ps) mA mU mA mU fC fA fA mA mG mC mU mC mU mG mU (ps) mU (ps) mU	610	250
EV2126	EV2126-A	mA (ps) fC (ps) mA fA mA fC mA fG mA fG mC fU mU fU mG fA mU (ps) fA (ps) mU	611	251
EV2126	EV2126-B	mA (ps) mU (ps) mA mU mC mA fA fA fG mC mU mC mU mG mU mU mU (ps) mG (ps) mU	612	252
EV2127	EV2127-A	mG (ps) fA (ps) mC fA mA fA mA fA mC fA mG fA mG fC mU fU mU (ps) fG (ps) mA	613	253
EV2127	EV2127-B	mU (ps) mC (ps) mA mA mA mG fC fU fC mU mG mU mU mU mG mU mU mU (ps) mC	614	254

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2128	EV2128-A	mA (ps) fU (ps) mG fU mA fG mA fC mC fU mC fC mU fU mC fC mG (ps) fA (ps) mG	615	255
EV2128	EV2128-B	mC (ps) mU (ps) mC mG mG mA fA fG fG mA mG mG mU mC mU mA mC (ps) mA (ps) mU	616	256
EV2129	EV2129-A	mG (ps) fA (ps) mU fG mU fA mG fA mC fC mU fC mC fU mU fC mC (ps) fG (ps) mA	617	257
EV2129	EV2129-B	mU (ps) mC (ps) mG mG mA mA fG fA mG mG mU mC mU mA mC mA (ps) mU (ps) mC	618	258
EV2130	EV2130-A	mU (ps) fC (ps) mU fU mG fA mU fG mU fA mG fA mC fC mU fC mC (ps) fU (ps) mU	619	259
EV2130	EV2130-B	mA (ps) mA (ps) mG mG mA mG fG fU fC mU mA mC mA mU mC mA (ps) mG (ps) mA	620	260
EV2131	EV2131-A	mA (ps) fU (ps) mU fC mU fU mG fA mU fG mU fA mG fA mC fC mU (ps) fC (ps) mC	621	261
EV2131	EV2131-B	mG (ps) mG (ps) mA mG mG mU fC fU fA mC mA mU mC mA mA mG mA (ps) mA (ps) mU	622	262
EV2132	EV2132-A	mC (ps) fC (ps) mC fA mU fU mC fU mU fG mA fU mG fU mA fG mA (ps) fC (ps) mC	623	263
EV2132	EV2132-B	mG (ps) mG (ps) mU mC mU mA fC fA fU mC mA mA mG mA mA mU mG (ps) mG (ps) mG	624	264
EV2133	EV2133-A	mU (ps) fC (ps) mC fC mC fA mU fU mC fU mU fG mA fU mG fU mA (ps) fG (ps) mA	625	265
EV2133	EV2133-B	mU (ps) mC (ps) mU mA mC mA fU fC fA mA mG mA mA mU mG mG mG (ps) mG (ps) mA	626	266
EV2134	EV2134-A	mC (ps) fU (ps) mU fA mU fC mC fC mC fA mU fU mC fU mU fG mA (ps) fU (ps) mG	627	267
EV2134	EV2134-B	mC (ps) mA (ps) mU mC mA mA fG fA fA mU mG mG mG mG mA mU mA (ps) mA (ps) mG	628	268
EV2135	EV2135-A	mA (ps) fU (ps) mU fG mG fG mG fU mC fA mG fC mA fU mA fG mG (ps) fG (ps) mA	629	269
EV2135	EV2135-B	mU (ps) mC (ps) mC mC mU mA fU fG fC mU mG mA mC mC mA (ps) mA (ps) mU	630	270
EV2136	EV2136-A	mG (ps) fU (ps) mA fU mU fG mG fG mG fU mC fA mG fC mA fU mA (ps) fG (ps) mG	631	271
EV2136	EV2136-B	mC (ps) mC (ps) mU mA mU mG fC fU fG mA mC mC mC mA mU (ps) mA (ps) mC	632	272
EV2137	EV2137-A	mU (ps) fA (ps) mC fA mC fC mA fA mC fU mU fG mA fA mU fG mA (ps) fA (ps) mA	633	273
EV2137	EV2137-B	mU (ps) mU (ps) mU mC mA mU fU fC fA mA mG mU mU mG mG mU mG (ps) mA	634	274
EV2138	EV2138-A	mU (ps) fC (ps) mC fA mC fU mA fC mU fC mC fC mC fA mG fC mU (ps) fG (ps) mA	635	275
EV2138	EV2138-B	mU (ps) mC (ps) mA mG mC mU fG fG mG mA mG mU mA mG mU mG (ps) mG (ps) mA	636	276
EV2139	EV2139-A	mA (ps) fC (ps) mA fU mC fC mA fC mU fA mC fU mC fC mC fC mA (ps) fG (ps) mC	637	277
EV2139	EV2139-B	mG (ps) mC (ps) mU mG mG mG fG fA fG mU mA mG mU mG mG mA mU (ps) mG (ps) mU	638	278
EV2140	EV2140-A	mG (ps) fC (ps) mA fG mA fC mA fU mC fC mA fC mU fA mC fU mC (ps) fC (ps) mC	639	279
EV2140	EV2140-B	mG (ps) mG (ps) mG mA mG mU fA fG fU mG mG mA mU mG mU mC mU (ps) mG (ps) mC	640	280

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EV2141	EV2141-A	mU (ps) fU (ps) mU fG mC fA mG fA mC fA mU fC mC fA mC fU mA (ps) fC (ps) mU	641	281
EV2141	EV2141-B	mA (ps) mG (ps) mU mA mG mU fG fG fA mU mG mU mC mU mG mC mA (ps) mA (ps) mA	642	282
EV2142	EV2142-A	mA (ps) fC (ps) mC fC mA fA mA fU mC fC mU fC mA fU mC fU mU (ps) fG (ps) mG	643	283
EV2142	EV2142-B	mC (ps) mC (ps) mA mA mG mA fU fG fA mG mG mA mU mU mG mG (ps) mG (ps) mU	644	284
EV2143	EV2143-A	mA (ps) fA (ps) mC fC mC fA mA fA mU fC mC fU mC fA mU fC mU (ps) fU (ps) mG	645	285
EV2143	EV2143-B	mC (ps) mA (ps) mA mG mA mU fG fA fG mG mA mU mU mG mG (ps) mU (ps) mU	646	286
EV2144	EV2144-A	mA (ps) fA (ps) mA fC mC fC mA fA mA fU mC fC mU fC mA fU mC (ps) fU (ps) mU	647	287
EV2144	EV2144-B	mA (ps) mA (ps) mG mA mU mG fA fG fG mA mU mU mU mG mG mU (ps) mU (ps) mU	648	288
EV2145	EV2145-A	mA (ps) fA (ps) mA fA mC fC mC fA mA fA mU fC mC fU mC fA mU (ps) fC (ps) mU	649	289
EV2145	EV2145-B	mA (ps) mG (ps) mA mU mG mA fG fG fA mU mU mU mG mG mU mU (ps) mU (ps) mU	650	290
EV2146	EV2146-A	mG (ps) fA (ps) mA fA mA fC mC fC mA fA mA fU mC fC mU fC mA (ps) fU (ps) mC	651	291
EV2146	EV2146-B	mG (ps) mA (ps) mU mG mA mG fG fA fU mU mU mG mG mU mU mU (ps) mU (ps) mC	652	292
EV2147	EV2147-A	mU (ps) fA (ps) mG fA mA fA mA fC mC fC mA fA mA fU mC fC mU (ps) fC (ps) mA	653	293
EV2147	EV2147-B	mU (ps) mG (ps) mA mG mG mA fU fU mG mG mG mU mU mU mC (ps) mU (ps) mA	654	294
EV2148	EV2148-A	mU (ps) fU (ps) mA fU mA fG mA fA mA fA mC fC mC fA mA fA mU (ps) fC (ps) mC	655	295
EV2148	EV2148-B	mG (ps) mG (ps) mA mU mU mU fG fG mU mU mU mU mU mC mU mA mU (ps) mA (ps) mA	656	296
EV2149	EV2149-A	mU (ps) fU (ps) mG fG mA fG mA fA mG fU mC fG mG fA mA fG mG (ps) fA (ps) mG	657	297
EV2149	EV2149-B	mC (ps) mU (ps) mC mC mU mU fC fC fG mA mC mU mU mC mU mC mC (ps) mA (ps) mA	658	298
EV2150	EV2150-A	mG (ps) fU (ps) mC fU mG fC mA fC mA fG mG fG mU fA mC fG mG (ps) fG (ps) mU	659	299
EV2150	EV2150-B	mA (ps) mC (ps) mC mC mG mU fA fC fC mC mU mG mU mG mC mA mG (ps) mA (ps) mC	660	300
EV2151	EV2151-A	mU (ps) fA (ps) mC fA mU fG mA fA mG fG mA fG mU fC mU fU mG (ps) fG (ps) mC	661	301
EV2151	EV2151-B	mG (ps) mC (ps) mC mA mA mG fA fC fU mC mC mU mU mC mA mU mG (ps) mU (ps) mA	662	302
EV2152	EV2152-A	mG (ps) fU (ps) mG fU mU fA mG fU mC fC mC fU mG fA mC fU mU (ps) fC (ps) mA	663	303
EV2152	EV2152-B	mU (ps) mG (ps) mA mA mG mU fC fA fG mG mG mA mC mU mA mC (ps) mA (ps) mC	664	304
EV2153	EV2153-A	mC (ps) fC (ps) mC fA mU fG mU fU mG fU mG fC mA fA mU fC mC (ps) fA (ps) mU	665	305
EV2153	EV2153-B	mA (ps) mU (ps) mG mG mA mU fU fG fC mA mC mA mC mA mU mG (ps) mG (ps) mG	666	306

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2154	EV2154-A	mA (ps) fU (ps) mC fU mU fG mG fC mC fU mG fC mC fA mU fG mG (ps) fU (ps) mU	667	307
EV2154	EV2154-B	mA (ps) mA (ps) mC mC mA mU fG fG fC mA mG mG mC mA mA mG (ps) mA (ps) mU	668	308
EV2155	EV2155-A	mG (ps) fA (ps) mG fA mU fC mU fU mG fG mC fC mU fG mC fC mA (ps) fU (ps) mG	669	309
EV2155	EV2155-B	mC (ps) mA (ps) mU mG mG mC fA fG fG mC mC mA mA mG mA mU mC (ps) mU (ps) mC	670	310
EV2156	EV2156-A	mA (ps) fG (ps) mA fC mA fC mA fA mA fC mA fG mA fG mC fU mU (ps) fU (ps) mG	671	311
EV2156	EV2156-B	mC (ps) mA (ps) mA mA mG mC fU fC fU mG mU mU mU mG mU mU mC (ps) mU	672	312
EV2157	EV2157-A	mU (ps) fA (ps) mU fU mG fG mG fG mU fC mA fG mC fA mU fA mG (ps) fG (ps) mG	673	313
EV2157	EV2157-B	mC (ps) mC (ps) mC mU mA mU fG fC fU mG mA mC mC mC mA mA (ps) mU (ps) mA	674	314
EV2158	EV2158-A	mU (ps) fA (ps) mC fG mU fG mU fC mU fG mC fA mC fA mG fG mG (ps) fU (ps) mA	675	315
EV2158	EV2158-B	mU (ps) mA (ps) mC mC mC mU fG fU fG mC mA mG mA mC mA mC mG (ps) mU (ps) mA	676	316
EV2159	EV2159-A	mG (ps) fU (ps) mG fG mA fA mA fG mA fG mA fU mC fU mC fA mU (ps) fC (ps) mA	677	317
EV2159	EV2159-B	mU (ps) mG (ps) mA mU mG mA fG fA fU mC mU mC mU mU mC mC (ps) mA (ps) mC	678	318
EV2160	EV2160-A	mA (ps) fC (ps) mC fG mU fC mA fU mA fG mC fA mG fU mG fG mA (ps) fA (ps) mA	679	319
EV2160	EV2160-B	mU (ps) mU (ps) mU mC mC mA fC fU fG mC mU mA mU mG mA mC mG (ps) mU	680	320
EV2161	EV2161-A	mU (ps) fG (ps) mG fU mA fG mG fU mG fA mC fG mC fU mG fU mC (ps) fU (ps) mU	681	321
EV2161	EV2161-B	mA (ps) mA (ps) mG mA mC mA fG fC fG mU mC mA mC mC mU mA mC (ps) mA	682	322
EV2162	EV2162-A	mA (ps) fC (ps) mC fU mU fC mC fU mG fA mC fA mC fG mU fU mC (ps) fG (ps) mC	683	323
EV2162	EV2162-B	mG (ps) mC (ps) mG mA mA mC fG fU fG mU mC mA mG mG mA mA mG (ps) mU	684	324
EV2163	EV2163-A	mA (ps) fG (ps) mC fA mU fC mG fA mC fU mC fC mU fU mC fU mA (ps) fU (ps) mG	685	325
EV2163	EV2163-B	mC (ps) mA (ps) mU mA mG mA fA fG fG mA mG mU mC mG mA mU mG (ps) mU	686	326
EV2164	EV2164-A	mA (ps) fC (ps) mC fA mU fA mA fC mU fU mG fC mC fA mC fC mU (ps) fU (ps) mC	687	327
EV2164	EV2164-B	mG (ps) mA (ps) mA mG mG mU fG fC mA mA mG mU mU mA mU mG (ps) mU	688	328
EV2165	EV2165-A	mA (ps) fU (ps) mG fA mC fA mU fG mG fC mG fG mG fU mG fC mG (ps) fU (ps) mU	689	329
EV2165	EV2165-B	mA (ps) mC (ps) mC mG mC mA fC fC fC mG mC mC mA mU mG mU mC (ps) mU	690	330
EV2166	EV2166-A	mG (ps) fA (ps) mC fA mG fU mA fA mU fU mG fG mG fU mC fC mC (ps) fC (ps) mG	691	331
EV2166	EV2166-B	mC (ps) mG (ps) mG mG mA fC fC fC mA mA mU mA mC mU mG (ps) mU (ps) mC	692	332

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2167	EV2167-A	mA (ps) fA (ps) mC fA mU fA mG fA mC fA mU fC mC fA mG (ps) fA (ps) mU	693	333
EV2167	EV2167-B	mA (ps) mU (ps) mC mU mG mG fA fU fG mU mC mU mA mU mG mU (ps) mU	694	334
EV2168	EV2168-A	mG (ps) fC (ps) mA fU mU fG mA fU mG fU mU fC mA fC mU fU mG (ps) fG (ps) mU	695	335
EV2168	EV2168-B	mA (ps) mC (ps) mC mA mA mG fU fG fA mA mC mA mU mC mA mA mU (ps) mG (ps) mC	696	336
EV2169	EV2169-A	mC (ps) fA (ps) mC fA mU fG mU fU mG fC mU fC mA fU mU fG mU (ps) fC (ps) mU	697	337
EV2169	EV2169-B	mA (ps) mG (ps) mA mC mA mA fU fG fA mG mC mA mA mC mA mU mG (ps) mU (ps) mG	698	338
EV2170	EV2170-A	mA (ps) fG (ps) mA fC mU fC mA fG mA fG mA fC mU fG fC mU (ps) fU (ps) mU	699	339
EV2170	EV2170-B	mA (ps) mA (ps) mA mG mC mC fA fG fU mC mU mC mU mG mA mG mU (ps) mC (ps) mU	700	340
EV2171	EV2171-A	mG (ps) fU (ps) mG fU mU fC mC fC mA fA mA fC mC fA mU fG mC (ps) fC (ps) mA	701	341
EV2171	EV2171-B	mU (ps) mG (ps) mG mC mA mU fG fG fU mU mU mG mG mG mA mA mC (ps) mA (ps) mC	702	342
EV2172	EV2172-A	mG (ps) fU (ps) mU fG mC fU mU fG mU fG mG fU mA fA mU fC mG (ps) fG (ps) mU	703	343
EV2172	EV2172-B	mA (ps) mC (ps) mC mG mA mU fU fA fC mC mA mC mA mA mG mC mA (ps) mA (ps) mC	704	344
EV2173	EV2173-A	mA (ps) fA (ps) mC fG mU fC mA fU mA fG mU fC mA fU mA fA mA (ps) fA (ps) mU	705	345
EV2173	EV2173-B	mA (ps) mU (ps) mU mU mU mA fU fG fA mC mU mA mU mG mA mC mG (ps) mU (ps) mU	706	346
EV2174	EV2174-A	mA (ps) fC (ps) mA fA mA fU mG fG mG fC mC fU mG fA mU fA mG (ps) fU (ps) mC	707	347
EV2174	EV2174-B	mG (ps) mA (ps) mC mU mA mU fC fA fG mG mC mC mA mU mU (ps) mG (ps) mU	708	348
EV2175	EV2175-A	mU (ps) fC (ps) mA fA mA fG mC fU mC fG mA fG mU fU mG fU mU (ps) fC (ps) mC	709	349
EV2175	EV2175-B	mG (ps) mG (ps) mA mA mC mA fA fC fU mC mG mA mG mC mU mU mU (ps) mG (ps) mA	710	350
EV2176	EV2176-A	mU (ps) fG (ps) mU fU mG fC mU fG mG fC mA fA mA fG fU mG fG mU (ps) fA (ps) mG	711	351
EV2176	EV2176-B	mC (ps) mU (ps) mA mC mC mA fC fU fU mG mC mC mA mG mC mA mA (ps) mC (ps) mA	712	352
EV2177	EV2177-A	mA (ps) fU (ps) mA fG mC fC mU fG mG fG mG fC mA fU mA fU mU (ps) fG (ps) mA	713	353
EV2177	EV2177-B	mU (ps) mC (ps) mA mA mU mA fU fG fC mC mC mC mA mG mG mC mU (ps) mA (ps) mU	714	354
EV2178	EV2178-A	mU (ps) fA (ps) mC fA mA fA mG fG mA fA mC fC mG fA mG fG mG (ps) fG (ps) mU	715	355
EV2178	EV2178-B	mA (ps) mC (ps) mC mC mC mU fC fG fG mU mU mC mC mU mU mU mG (ps) mU (ps) mA	716	356
EV2179	EV2179-A	mC (ps) fU (ps) mU fU mU fG mC fC mG fC mU fU mC fU mG fG mU (ps) fU (ps) mU	717	357
EV2179	EV2179-B	mA (ps) mA (ps) mA mC mC mA fG fA fA mG mC mG mC mA mA mA mA (ps) mA (ps) mG	718	358

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2180	EV2180-A	mG (ps) fU (ps) mC fU mU fG mG fC mA fG mG fA mA fG mG fC mU fC (ps) mC	719	359
EV2180	EV2180-B	mG (ps) mG (ps) mA mG mC mC fU fU fC mC mU mG mC mA mA mG (ps) mA (ps) mC	720	360
EV2207	EV2207-A	mU (ps) fC (ps) mA fC mA fA mA fC mA fG mA fG mC fU mU fU mG (ps) fA (ps) mU	754	721
EV2207	EV2207-B	mA (ps) mU (ps) mC mA mA mA fG fC fU mC mU mG mU mU mU mG mU (ps) mG (ps) mU	408	48
EV2208	EV2208-A	mU (ps) fU (ps) mA fU mC fC mU fU mG fA mC fU mU fU mG fA mA (ps) fC (ps) mA	755	722
EV2208	EV2208-B	mU (ps) mG (ps) mU mU mC mA fA fG mU mC mA mA mG mG mA mU (ps) mA (ps) mU	562	202
EV2209	EV2209-A	mU (ps) fU (ps) mU fG mU fC mG fC mA fG mC fU mG fU mU fU mU (ps) fA (ps) mA	756	723
EV2209	EV2209-B	mU (ps) mU (ps) mA mA mA mA fC fA fG mC mU mG mC mG mA mC mA (ps) mA (ps) mC	432	72
EV2210	EV2210-A	mU (ps) fA (ps) mU fG mA fA mA fC mG fA mC fU mU fC mU fC mU (ps) fU (ps) mG	757	724
EV2210	EV2209-B	mC (ps) mA (ps) mA mG mA mG fA fA fG mU mC mG mU mU mU mC mA (ps) mU (ps) mU	418	58
EV2211	EV2196-A	(vp)-mU fC mA fC mA fA mA fC mA fG mA fG mC fU mU fU mG (ps) fA (ps) mU	740	721
EV2211	EV2211-B	mA mU mC mA mA mA fG fC fU mC mU mG mU mU mU mU mG mU (ps) mG (ps) mU	759	48
EV2212	EV2198-A	(vp)-mU fU mA fU mC fC mU fU mG fA mC fU mU fU mG fA mA (ps) fC (ps) mA	742	722
EV2212	EV2212-B	mU mG mU mU mC mA fA fG mU mC mA mA mG mG mA mU (ps) mA (ps) mU	760	202

*: A = 1st strand; B = 2nd strand

The conjugated duplexes listed in Table 5c have various modifications as shown, with reference to Table 4 for an explanation of the abbreviations used. Where appropriate, the sequence of the equivalent unmodified strand from Table 5a is also indicated.

Table 5c – Conjugated duplexes

Duplex ID	Strand Name (*)	Sequence (5' → 3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2181	EV2029-A	mA (ps) fA (ps) mU fG mA fA mA fC mG fA mC fU mU fC mU fC mU (ps) fU (ps) mG	417	57
EV2181	EV2181-B	[ST23(ps)]3 ST41 (ps) mC mA mA mG mA mG fA fA fG mU mC mG mU mU mC mA (ps) mU (ps) mU	725	58
EV2182	EV2036-A	mG (ps) fU (ps) mU fG mU fC mG fC mA fG mC fU mG fU mU fU mU (ps) fA (ps) mA	431	71
EV2182	EV2182-B	[ST23(ps)]3 ST41 (ps) mU mU mA mA mA mA fC fA fG mC mU mG mC mA (ps) mA (ps) mC	726	72
EV2183	EV2050-A	mG (ps) fA (ps) mA fC mA fC mA fU mG fU mU fG mC fU mC fA mU (ps) fU (ps) mG	459	99
EV2183	EV2183-B	[ST23(ps)]3 ST41 (ps) mC mA mA mU mG mA fG fC fA mA mC mA mU mG mU (ps) mU (ps) mC	727	100
EV2184	EV2148-A	mU (ps) fU (ps) mA fU mA fG mA fA mA fA mC fC mC fA mA fA mU (ps) fC (ps) mC	655	295
EV2184	EV2184-B	[ST23(ps)]3 ST41 (ps) mG mG mA mU mU mU fG fG mU mU mU mU mC mU mA mU (ps) mA (ps) mA	728	296
EV2185	EV2101-A	mA (ps) fU (ps) mA fU mC fC mU fU mG fA mC fU mU fU mG fA mA (ps) fC (ps) mA	561	201
EV2185	EV2185-B	[ST23(ps)]3 ST41 (ps) mU mG mU mU mC mA fA fA fG mU mC mA mA mG mG mA mU (ps) mA (ps) mU	729	202
EV2186	EV2024-A	mA (ps) fC (ps) mA fC mA fA mA fC mA fG mA fG mC fU mU fU mG (ps) fA (ps) mU	407	47
EV2186	EV2186-B	[ST23(ps)]3 ST41 (ps) mA mU mC mA mA mA fG fC fU mC mU mG mU mU mG mU (ps) mG (ps) mU	730	48
EV2187	EV2108-A	mA (ps) fU (ps) mG fC mC fA mC fA mG fA mG fA mC fU mC fA mG (ps) fA (ps) mG	575	215
EV2187	EV2187-B	[ST23(ps)]3 ST41 (ps) mC mU mC mU mG mA fG fU fC mU mC mU mG mU mG mC (ps) mA (ps) mU	731	216
EV2188	EV2144-A	mA (ps) fA (ps) mA fC mC fC mA fA mA fU mC fC mU fC mA fU mC (ps) fU (ps) mU	647	287
EV2188	EV2188-B	[ST23(ps)]3 ST41 (ps) mA mA mG mA mU mG fA fG fG mA mU mU mU mG mG mU (ps) mU (ps) mU	732	288
EV2189	EV2160-A	mA (ps) fC (ps) mC fG mU fC mA fU mA fG mC fA mG fU mG fG mA (ps) fA (ps) mA	679	319
EV2189	EV2189-B	[ST23(ps)]3 ST41 (ps) mU mU mU mC mC mA fC fU fG mC mU mA mU mG mA mC mG (ps) mU	733	320
EV2190	EV2047-A	mA (ps) fU (ps) mA fA mC fU mU fG mC fC mA fC mC fU mU fC mU (ps) fC (ps) mA	453	93
EV2190	EV2190-B	[ST23(ps)]3 ST41 (ps) mU mG mA mG mA mA fG fG fU mG mG mC mA mA mG mU mU (ps) mA (ps) mU	734	94
EV2191	EV2048-A	mA (ps) fG (ps) mC fC mA fA mA fG mC fA mU fU mG fA mU fG mU (ps) fU (ps) mC	455	95

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2191	EV2191-B	[ST23(ps)]3 ST41 (ps) mG mA mA mC mA mU fc fA fA mU mG mC mU mU mG mG (ps) mC (ps) mU	735	96
EV2192	EV2159-A	mG (ps) fU (ps) mG fG mA fA mA fG mA fG mA fU mC fU mC fA mU (ps) fc (ps) mA	677	317
EV2192	EV2192-B	[ST23(ps)]3 ST41 (ps) mU mG mA mU mG mA fG fA fU mC mU mC mU mU mC mC (ps) mA (ps) mC	736	318
EV2193	EV2141-A	mU (ps) fU (ps) mU fG mC fA mG fA mC fA mU fc mC fA mC fU mA (ps) fc (ps) mU	641	281
EV2193	EV2193-B	[ST23(ps)]3 ST41 (ps) mA mG mU mA mG mU fG fG fA mU mG mU mC mU mG mC mA (ps) mA	737	282
EV2194	EV2167-A	mA (ps) fA (ps) mC fA mC fA mU fA mG fA mC fA mU fc mC fA mG (ps) fA (ps) mU	693	333
EV2194	EV2194-B	[ST23(ps)]3 ST41 (ps) mA mU mC mU mG mG fA fU fG mU mC mU mA mU mG mU mU (ps) mU	738	334
EV2195	EV2125-A	mA (ps) fA (ps) mA fc mA fG mA fG mC fU mU fU mG fA mU fA mU (ps) fc (ps) mC	609	249
EV2195	EV2195-B	[ST23(ps)]3 ST41 (ps) mG mG mA mU mA mU fc fA fA mA mG mC mU mC mU mG mU (ps) mU	739	250
EV2196	EV2196-A	(vp)-mU fc mA fc mA fA mC fA mG fA mC fU mU fU mG (ps) fA (ps) mU	740	721
EV2196	EV2186-B	[ST23(ps)]3 ST41 (ps) mA mU mC mA mA mA fG fc fU mC mU mG mU mU mG mU (ps) mG (ps) mU	730	48
EV2197	EV2197-A	(vp)-mU fU mA fU mA fG mA fA mA fA mC fc mC fA mA fA mU (ps) fc (ps) mC	741	295
EV2197	EV2184-B	[ST23(ps)]3 ST41 (ps) mG mG mA mU mU mU fG fG mU mU mU mC mU mA mU (ps) mA	728	296
EV2198	EV2198-A	(vp)-mU fU mA fU mC fc mU fU mG fA mC fU mU fU mG fA mA (ps) fc (ps) mA	742	722
EV2198	EV2185-B	[ST23(ps)]3 ST41 (ps) mU mG mU mU mC mA fA fA fG mU mC mA mA mG mG mA mU (ps) mU	729	202
EV2199	EV2199-A	mA (ps) fU (ps) mA fU mC fc mU fU mG fA mC fU mU fU mG fA mA fc (ps2) mA	743	201
EV2199	EV2199-B	[ST23]3 ST41 mU (ps2) mG mU mU mC mA fA fA fG mU mC mA mG mA mU mA (ps2) mU	744	202
EV2200	EV2200-A	(vp)-mU fU mA fU mC fc mU fU mG fA mC fU mU fU mG fA mA fc (ps2) mA	745	722
EV2200	EV2199-B	[ST23]3 ST41 mU (ps2) mG mU mU mC mA fA fA fG mU mC mA mA mG mA mU mA (ps2) mU	744	202
EV2201	EV2201-A	(vp)-mU fU mU fG mU fc mG fc mA fG mC fU mG fU mU fU mU (ps) fA (ps) mA	746	723
EV2201	EV2182-B	[ST23(ps)]3 ST41 (ps) mU mU mA mA mA mA fc fA fG mC mU mG mC mA mC mA (ps) mC	726	72
EV2202	EV2202-A	mG (ps) fU (ps) mU fG mU fc mG fc mA fG mC fU mG fU mU fU mU fA (ps2) mA	747	71
EV2202	EV2202-B	[ST23]3 ST41 mU (ps2) mU mA mA mA mA fc fA fG mC mU mG mC mA mA (ps2) mC	748	72
EV2203	EV2203-A	(vp)-mU fU mU fG mU fc mG fc mA fG mC fU mG fU mU fU mU fA (ps2) mA	749	723
EV2203	EV2202-B	[ST23]3 ST41 mU (ps2) mU mA mA mA mA fc fA fG mC mU mG mC mA mC mA (ps2) mC	748	72
EV2204	EV2204-A	(vp)-mU fA mU fG mA fA mA fc mG fA mC fU mU fc mU (ps) fU (ps) mG	750	724

Duplex ID	Strand Name (*)	Sequence (5'→3')	SEQ ID No.	Unmodified equivalent SEQ ID No.
EV2204	EV2181-B	[ST23(ps)]3 ST41 (ps) mC mA mG mA mG fA fG mU mC mG mU mU mU mC mA (ps) mU (ps) mU	725	58
EV2205	EV2205-A	mA (ps) fA (ps) mU fG mA fA mA fC mG fA mC fU mU fC mU fU (ps2) mG	751	57
EV2205	EV2205-B	[ST23]3 ST41 mC (ps2) mA mA mG mA mG fA fG mU mC mG mU mU mU mC mA mU (ps2) mU	752	58
EV2206	EV2206-A	(vp)-mU fA mU fG mA fA mA fC mG fA mC fU mU fC mU fU (ps2) mG	753	724
EV2206	EV2205-B	[ST23]3 ST41 mC (ps2) mA mA mG mA mG fA fG mU mC mG mU mU mU mC mA mU (ps2) mU	752	58

*: A = 1st strand; B = 2nd strand

SEQ ID No. 758

>NM_001710.6 Homo sapiens complement factor B (CFB), mRNA

5 GGGAAAGGGAATGTGACCAGGTCTAGGTCTGGAGTTTCAGCTTGGACACTGAGCCAAGCAGACAAGCAAAG
CAAGCCAGGACACACCATCCTGCCCCAGGCCAGCTTCTCTCCTGCCCTTCCAACGCCATGGGGAGCAATC
TCAGCCCCCAACTCTGCCTGATGCCCTTTATCTTGGGCCTCTTGTCTGGAGGTGTGACCACCACTCCATG
GTCTTTGGCCCCGGCCCCAGGGATCCTGCTCTCTGGAGGGGGTAGAGATCAAAGGCGGCTCCTTCCGACTT
10 CTCCAAGAGGGCCAGGCACTGGAGTACGTGTGTCTTCTGGCTTCTACCCGTACCCTGTGCAGACACGTA
CCTGCAGATCTACGGGGTCTGGAGCACCTGAAGACTCAAGACCAAAAGACTGTGAGGAAGGCAGAGTG
CAGAGCAATCCACTGTCCAAGACCACAGACTTCGAGAACGGGGAATACTGGCCCCGGTCTCCCTACTAC
AATGTGAGTGATGAGATCTCTTTCCACTGCTATGACGGTTACACTCTCCGGGGCTCTGCCAATCGCACCT
GCCAAGTGAATGGCCGATGGAGTGGGCAGACAGCGATCTGTGACAACGGAGCGGGGTACTGCTCCAACCC
GGGCATCCCCATTGGCACAAGGAAGGTGGGCAGCCAGTACCGCCTTGAAGACAGCGTCACCTACCACTGC
15 AGCCGGGGGCTTACCCTGCGTGGCTCCAGCGGCGAACGTGTCAGGAAGGTGGCTCTTGGAGCGGGACGG
AGCCTTCTGCCAAGACTCCTTCATGTACGACACCCCTCAAGAGGTGGCCGAAGCTTTCCTGTCTTCCCT
GACAGAGACCATAGAAGGAGTCGATGCTGAGGATGGGCACGGCCAGGGGAACAACAGAAGCGGAAGATC
GTCCTGGACCCTTCAGGCTCCATGAACATCTACCTGGTGCTAGATGGATCAGACAGCATTGGGGCCAGCA
ACTTCACAGGAGCCAAAAAGTGTCTAGTCAACTTAATTGAGAAGGTGGCAAGTTATGGTGTGAAGCCAAG
20 ATATGGTCTAGTGACATATGCCACATACCCCAAAATTTGGGTCAAAGTGTCTGAAGCAGACAGCAGTAAT
GCAGACTGGGTACGAAAGCAGCTCAATGAAATCAATTATGAAGACCACAAGTTGAAGTCAGGGACTAACA
CCAAGAAGGCCCTCCAGGCAGTGTACAGCATGATGAGCTGGCCAGATGACGTCCCTCCTGAAGGCTGGAA
CCGCACCCGCCATGTCATCATCCTCATGACTGATGGATTGCACAACATGGGCGGGGACCCAATTACTGTC
ATTGATGAGATCCGGGACTTGCTATACATTGGCAAGGATCGCAAAAACCCAAGGAGGATTATCTGGATG
25 TCTATGTGTTTGGGGTCGGGCCTTTGGTGAACCAAGTGAACATCAATGCTTTGGCTTCCAAGAAAGACAA
TGAGCAACATGTGTTCAAAGTCAAGGATATGGAAAACCTGGAAGATGTTTTCTACCAAATGATCGATGAA
AGCCAGTCTCTGAGTCTCTGTGGCATGGTTTGGGAACACAGGAAGGGTACCGATTACCACAAGCAACCAT
GGCAGGCCAAGATCTCAGTCATTGCGCCTTCAAAGGGACACGAGAGCTGTATGGGGGTGTGGTGTCTGA
GTACTTTGTGCTGACAGCAGCACATTGTTTCACTGTGGATGACAAGGAACACTCAATCAAGGTGAGCGTA
30 GGAGGGGAGAAGCGGGACCTGGAGATAGAAGTAGTCCTATTTCACCCCAACTACAACATTAATGGGAAAA
AAGAAGCAGGAATTCCTGAATTTTATGACTATGACGTTGCCCTGATCAAGCTCAAGAATAAGCTGAAATA
TGGCCAGACTATCAGGCCCATTTGTCTCCCCTGCACCGAGGGAACAACCTCGAGCTTTGAGGCTTCCTCCA
ACTACCACTTGCCAGCAACAAAAGGAAGAGCTGCTCCCTGCACAGGATATCAAAGCTCTGTTTGTGTCTG
AGGAGGAGAAAAAGCTGACTCGGAAGGAGGTCTACATCAAGAATGGGGATAAGAAAGGCAGCTGTGAGAG
35 AGATGCTCAATATGCCCCAGGCTATGACAAAGTCAAGGACATCTCAGAGGTGGTCACCCCTCGGTTCCCTT
TGTAAGGAGGAGTGAGTCCCTATGCTGACCCCAACTTGCAGAGGTGATTCTGGCGGCCCTTGATAG
TTCACAAGAGAAGTCGTTTCATTCAAGTTGGTGTAAATCAGCTGGGGAGTAGTGGATGTCTGCAAAAACCA
GAAGCGGCAAAAGCAGGTACCTGCTCACGCCCCGAGACTTTCACATCAACCTCTTCAAGTGCTGCCCTGG
CTGAAGGAGAACTCCAAGATGAGGATTTGGGTTTTCTATAAGGGGTTTTCTGCTGGACAGGGGCGTGGG
40 ATTGAATTAAACAGCTGCGACAACA

Claims

1. A double-stranded nucleic acid for inhibiting expression of complement factor B (CFB), wherein the nucleic acid comprises a first strand and a second strand, wherein the
5 unmodified equivalent of the first strand sequence comprises a sequence from any one of the first strand sequences of SEQ ID No. 721, 57, 71, 295, 201, 47, 319, 249, 295, 722, 723, 724.
2. The nucleic acid of claim 1, wherein the unmodified equivalent of the second strand
10 sequence comprises a sequence from any one of the corresponding second strand sequences of 48, 58, 72, 296, 202, 48, 320, 250, 296, 202, 72, 58.
3. The nucleic acid of any of the preceding claims, wherein the first strand and the second
strand form a duplex region of from 17-25 nucleotides in length.
- 15 4. The nucleic acid of any of the preceding claims, wherein the nucleic acid mediates RNA interference.
5. The nucleic acid of any of the preceding claims, wherein the first strand sequence
20 comprises SEQ ID No. 721 and wherein the second strand comprises SEQ ID No: 48.
6. The nucleic acid of any of the preceding claims, wherein the first strand sequence
consists of SEQ ID No. 721 and optionally wherein the second strand consists of SEQ
ID NO: 48.
- 25 7. The nucleic acid of any one of the preceding claims, wherein at least one nucleotide of the first and/or second strand is a modified nucleotide.
8. The nucleic acid of any one of the preceding claims, wherein the first strand has a
30 terminal 5' (E)-vinylphosphonate nucleotide at its 5' end.
9. The nucleic acid of any one of the preceding claims, wherein the nucleic acid comprises
a phosphorothioate linkage between the terminal two or three 3' nucleotides and/or 5'
nucleotides of the first and/or the second strand and preferably wherein the linkages
35 between the remaining nucleotides are phosphodiester linkages.

10. The nucleic acid of any of claims 1 to 5 or of any of claims 7 to 9, wherein the first strand sequence comprises
(vp)-mU fC mA fC mA fA mA fC mA fG mA fG mC fU mU fU mG (ps) fA (ps) mU (SEQ ID No. 740) and optionally wherein the second strand sequence comprises
5 mA mU mC mA mA mA fG fC fU mC mU mG mU mU mU mG mU (ps) mG (ps) mU (SEQ ID No: 759).
11. The nucleic acid of any one of the preceding claims, wherein the nucleic acid is conjugated to a heterologous moiety.
10
12. The nucleic acid of claim 11, wherein the heterologous moiety comprises (i) one or more N-acetyl galactosamine (GalNAc) moieties or derivatives thereof, and (ii) a linker, wherein the linker conjugates the at least one GalNAc moiety or derivative thereof to the nucleic acid.
15
13. The nucleic acid of claims 11 or 12, wherein the first strand sequence comprises (vp)-mU fC mA fC mA fA mA fC mA fG mA fG mC fU mU fU mG (ps) fA (ps) mU (SEQ ID No. 740) and optionally wherein the second strand sequence comprises
[ST23(ps)]3 ST41 (ps) mA mU mC mA mA mA fG fC fU mC mU mG mU mU mU mG
20 mU (ps) mG (ps) mU (SEQ ID No: 730).
14. A composition comprising a nucleic acid of any one of the preceding claims and a solvent and/or a delivery vehicle and/or a physiologically acceptable excipient and/or a carrier and/or a salt and/or a diluent and/or a buffer and/or a preservative. and/or a further
25 therapeutic agent selected from the group comprising an oligonucleotide, a small molecule, a monoclonal antibody, a polyclonal antibody and a peptide.
15. A nucleic acid of any one of claims 1 to 13 or a composition of claim 14 for use as a
30 therapeutic agent.