DOUBLE STRANDED RNA COMPOUNDS TO RHOA AND USE THEREOF

RELATED PATENT APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 61/358012, filed June 24, 2010, entitled "siRNA COMPOUNDS TO RHOA AND USE THEREOF" and incorporated herein by reference in its entirety and for all purposes.

SEQUENCE LISTING

The instant application contains a Sequence Listing which is entitled 221-PCT1_ST25_21-June-2011.txt, said ASCII copy, created on June 21, 2011 and 38 kb in size, is hereby incorporated by reference in its entirety.

Throughout this application various patents and publications are cited. The disclosures of these documents in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains

FIELD OF THE INVENTION

The present application relates to double stranded nucleotide compounds, pharmaceutical compositions comprising same and methods of use thereof for the down-regulation of Ras homolog gene family, member A (RhoA) expression.

BACKGROUND OF THE INVENTION

PCT Patent Publication Nos. WO 2008/050329 and a WO 2009/044392 assigned to the assignee of the present invention disclose certain RhoA oligonucleotides and structural motifs useful in the preparation of chemically modified siRNA compounds.

SUMMARY

In one apsect, there is provided a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand are selected from the oligonucleotides described as RHOA_48 (SEQ ID NOS: 79 and 113) or the oligonucleotides described as RHOA_48u (SEQ ID NOS: 80 and 114); or a pharmaceutically acceptable salt of such nucleic acid molecule;

wherein the double stranded nucleic acid molecule is a siRNA; and

wherein the double-stranded nucleic acid molecule has the structure:

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5′     UGUAGCAAGAUGACUUCUG -Z  3′ (antisense SEQ ID NO:113)
       ||||||||||||||||||||
3′ Z′-ACAUCGUUCUACUGAAGAC -z″ 5′ (sense SEQ ID NO:79)
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or

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5′     AGUAGCAAGAUGACUUCUG -Z  3′ (antisense SEQ ID NO:114)
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3′ Z′-UCAUCGUUCUACUGAAGAC -z″ 5′ (sense SEQ ID NO:80)
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wherein each " | " represents base pairing;

wherein each of A, C, G and U is independently an unmodified ribonucleotide, a modified ribonucleotide, or an unconventional moiety;

wherein said unconventional moiety is selected from a mirror nucleotide and a nucleotide joined to an adjacent nucleotide by a 2'-5' internucleotide phosphate bond;

wherein each of Z and Z' is independently 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; wherein z" is a capping moiety covalently attached at the 5' terminus of the sense strand.

In another aspect, there is provided a pharmaceutical composition comprising the nucleic acid molecule or a pharmaceutically acceptable salt of such nucleic acid molecule of the present disclosure; and a pharmaceutically acceptable carrier.

In another aspect, there is provided a pharmaceutical composition comprising the nucleic acid molecule or a pharmaceutically acceptable salt of such nucleic acid molecule of the present disclosure, in an amount effective to down-regulate expression of a RHOA gene; and a pharmaceutically acceptable carrier.

In another aspect, there is provided use of the nucleic acid molecule or a pharmaceutically acceptable salt of such nucleic acid molecule of the present disclosure, in the manufacture of a medicament for treating an individual at risk of or suffering from an injury, a disease or a disorder associated with RHOA expression.

In yet another aspect, there is provided use of the nucleic acid molecule or a pharmaceutically acceptable salt of such nucleic acid molecule of the present disclosure, in the manufacture of a medicament for effecting neuroprotection or neural regeneration to a

neuron damaged, or at risk of damage, by an injury, a disease, or a disorder in a central nervous system (CNS).

In a further aspect, there is provided a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand are selected from an oligonucleotide described as RHOA_48 (SEQ ID NOS: 79 and 113) or RHOA_48u (SEQ ID NOS: 80 and 114), wherein said molecule is a siRNA; or a pharmaceutically acceptable salt of such nucleic acid molecule.

Nucleic acid molecules for down-regulating expression of RhoA, compositions and kits comprising same and methods of use thereof are provided herein. The compositions, methods and kits may involve use of nucleic acid molecules (for example, short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA) or short hairpin RNA (shRNA)) that bind a nucleotide sequence (such as an mRNA sequence) encoding RhoA, for example, the mRNA coding sequence

(SEQ ID NO:1) for human RhoA protein exemplified by SEQ ID NO:2. In certain examples, the compositions, methods and kits disclosed herein inhibit expression of RhoA. In various examples the nucleic acid molecule is selected from the group consisting of unmodified or chemically modified dsRNA compound or siRNA or shRNA that down-regulates RhoA expression. In some examples the inhibitor is a synthetic, chemically modified double stranded RNA (dsRNA) compound that down-regulates RhoA expression. The chemically modified nucleic acid molecules and compositions exhibit beneficial properties including at least one of increased serum stability, improved cellular uptake, reduced off target activity, reduced immunogenicity, improved endosomal release, improved specific delivery to target tissue or cell and increased knock down activity when compared to unmodified molecules.

Further disclosed herein are methods for treating or preventing the incidence or severity of a disease or condition in a subject in need thereof wherein the disease or condition and/or a symptom associated therewith is associated with expression of the RhoA gene, such as a disease, injury, condition or pathology of the central nervous system (CNS). In some examples the subject is a mammal. In some examples the subject is a human subject.

In some examples, chemically modified dsRNA compounds that target RhoA, compositions and kits comprising same and methods of use thereof in the treatment of a CNS condition or pathology, particularly neuropatic pain (e.g., allodynia), spinal cord injury (SCI) and glaucoma are provided herein. Other conditions to be treated include any condition in which RhoA expression is detrimental to neuron survival, neuronal growth, neural regeneration or other cellular functions. Accordingly, conditions which require regeneration of neurons or protection of neurons or the nervous system, including but not limited to multiple sclerosis, stroke, traumatic brain injury, peripheral neuropathies and acute and chronic neurodegenerative diseases, are treated with the compounds of the present disclosure.

Stable and active dsRNA compounds and compositions comprising the same useful in treating the above mentioned diseases, conditions, injury and disorders would be of great therapeutic value.

In one example, provided are nucleic acid molecules (e.g., dsRNA molecules) in which (a) the nucleic acid molecule is a duplex which includes a sense strand and a complementary

antisense strand; (b) each strand of the nucleic acid molecule is independently 18 to 49 nucleotides in length; (c) an 18 to 49 nucleotide sequence of the antisense strand is complementary to a consecutive sequence of a mRNA encoding mammalian RhoA (e.g., SEQ ID NO: 1); and (d) the sense strand and antisense strand comprise sequence pairs set forth in any of Tables I, II, III or IV.

In certain examples, the sequence of the antisense strand that is complementary to a consecutive sequence of a mRNA encoding human RhoA (set forth in SEQ ID NO:1) includes a sequence complimentary to a nucleotide sequence in the ranges 290-350; or 350-414; or 414-507; or 531-551; or 557-627; or 634-651; or 627-698; or 698-757; or 919-973; or 973-990, or 1134-1346; or 1346-1369; or 1804-1926; of SEQ ID NO: 1.

In certain examples, the antisense strand of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein includes a sequence corresponding to any one of the antisense sequences shown on Table III (SEQ ID NOS:149-162). In some examples the sense strand and the antisense strand are selected from the sequence pairs shown in Table III. In some examples the sense strands and the antisense strands are selected from the sequence pairs set forth in RHOA_31 (SEQ ID NOS:135 and 149), RHOA_33 (SEQ ID NOS:136 and 150), RHOA_37 (SEQ ID NOS:137 and 151), RHOA_38 (SEQ ID NOS:138 and 152), RHOA_43 (SEQ ID NOS:139 and 153), RHOA_52 (SEQ ID NOS:140 and 154), RHOA_56 (SEQ ID NOS:141 and 155), RHOA_57 (SEQ ID NOS:142 and 156), RHOA_58 (SEQ ID NOS:143 and 157), RHOA_68 (SEQ ID NOS:144 and 158), RHOA_69 (SEQ ID NOS:145 and 159), RHOA_70 (SEQ ID NOS:146 and 160), RHOA_73 (SEQ ID NOS:147 and 161) and RHOA_76 (SEQ ID NOS:148 and 162).

In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein includes the sequence pair set forth in RHOA_31 (SEQ ID NOS:135 and 149). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_33 (SEQ ID NOS:136 and 150). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_37 (SEQ ID NOS:137 and 151). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_38 (SEQ ID NOS:138 and 152). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the

sequence pair set forth in RHOA_43 (SEQ ID NOS:139 and 153). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_52 (SEQ ID NOS:140 and 154). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_56 (SEQ ID NOS:141 and 155). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_57 (SEQ ID NOS:142 and 156). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pairs set forth in RHOA_58 (SEQ ID NOS:143 and 157). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_68 (SEQ ID NOS:144 and 158). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_69 (SEQ ID NOS:145 and 159). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_70 (SEQ ID NOS:146 and 160). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_73 (SEQ ID NOS:147 and 161). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_76 (SEQ ID NOS:148 and 162).

In some examples the sense strand and the antisense strand comprise the sequence pair set forth in RHOA_58 (SEQ ID NOS:143 and 157). In some examples the sense strand and the antisense strand comprise the sequence pair set forth in RHOA_70 (SEQ ID NOS:146 and 160).

In certain examples, the antisense strand of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein includes a sequence corresponding to any one of the antisense sequences shown on Table IV (SEQ ID NOS:167-170). In some examples the sense strand and the antisense strand are selected from the sequence pairs shown in Table IV and are selected from the sequence pairs set forth in RHOA_23 (SEQ ID NOS:163 and 167), RHOA_24 (SEQ ID NOS:164 and 168), RHOA_26 (SEQ ID NOS:165 and 169) or RHOA_29 (SEQ ID NOS:166 and 170).

In certain examples, the antisense strand of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein includes a sequence corresponding to any one of the antisense sequences shown in Table II. In certain examples the antisense strand and the strand are selected from the sequence pairs shown in Table II.

In some examples a nucleic acid molecule disclosed herein includes the antisense and sense strands selected from the sequence pairs set forth in RHOA_32 (SEQ ID NOS:67 and 101), RHOA_34 (SEQ ID NOS:68 and 102), RHOA_35 (SEQ ID NOS:69 and 103), RHOA_36 (SEQ ID NOS:70 and 104), RHOA_39 (SEQ ID NOS:71 and 105), RHOA_40 (SEQ ID NOS:72 and 106), RHOA_41 (SEQ ID NOS:73 and 107), RHOA_42 (SEQ ID NOS:74 and 108), RHOA_44 (SEQ ID NOS:75 and 109), RHOA_45 (SEQ ID NOS:76 and 110), RHOA_46 (SEQ ID NOS:77 and 111), RHOA_47 (SEQ ID NOS:78 and 112), RHOA_48 (SEQ ID NOS:79 and 113), RHOA_48u (SEQ ID NOS:80 and 114), RHOA_49 (SEQ ID NOS:81 and 115), RHOA_50 (SEQ ID NOS:82 and 116) RHOA_51 (SEQ ID NOS:83 and 117), RHOA_53 (SEQ ID NOS:84 and 118), RHOA_54 (SEQ ID NOS:85 and 119), RHOA_55 (SEQ ID NOS:86 and 120), RHOA_59 (SEQ ID NOS:87 and 121), RHOA_60 (SEQ ID NOS:88 and 122), RHOA_61 (SEQ ID NOS:89 and 123), RHOA_61u (SEQ ID NOS:90 and 124), RHOA_62 (SEQ ID NOS:91 and 125), RHOA_63 (SEQ ID NOS:92 and 126) RHOA_64 (SEQ ID NOS:93 and 127), RHOA_65 (SEQ ID NO:94 and 128), RHOA_66 (SEQ ID NOS:95 and 129) RHOA_67 (SEQ ID NOS:96 and 130), RHOA_71 (SEQ ID NOS:97 and 131), RHOA_72 (SEQ ID NOS:98 and 132), RHOA_74 (SEQ ID NOS:99 and 133) and RHOA_75 (SEQ ID NOS:100 and 134).

In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_32 (SEQ ID NOS:67 and 101). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_34 (SEQ ID NOS:68 and 102). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_35 (SEQ ID NOS:69 and 103). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_36 (SEQ ID NOS:70 and 104). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth

in RHOA_39 (SEQ ID NOS:71 and 105). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed hereininclude the sequence pair set forth in RHOA_40 (SEQ ID NOS:72 and 106). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_41 (SEQ ID NOS:73 and 107). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_42 (SEQ ID NOS:74 and 108). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed hereininclude the sequence pair set forth in RHOA_44 (SEQ ID NOS:75 and 109). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_45 (SEQ ID NOS:76 and 110). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_46 (SEQ ID NOS:77 and 111) In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_47 (SEQ ID NOS:78 and 112). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_48 (SEQ ID NOS:79 and 113), RHOA_48u (SEQ ID NOS:80 and 114), RHOA_49 (SEQ ID NOS:81 and 115). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_50 (SEQ ID NOS:82 and 116). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_51 (SEQ ID NOS:83 and 117). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_53 (SEQ ID NOS:84 and 118). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_54 (SEQ ID NOS:85 and 119). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_55 (SEQ ID NOS:86 and 120). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_59 (SEQ ID NOS:87 and 121). In some examples the

antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_60 (SEQ ID NOS:88 and 122). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_61 (SEQ ID NOS:89 and 123). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_61u (SEQ ID NOS:90 and 124). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_62 (SEQ ID NOS:91 and 125). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_63 (SEQ ID NOS:92 and 126). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_64 (SEQ ID NOS:93 and 127). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_65 (SEQ ID NO:94 and 128). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_66 (SEQ ID NOS:95 and 129). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_67 (SEQ ID NOS:96 and 130). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_71 (SEQ ID NOS:97 and 131), RHOA_72 (SEQ ID NOS:98 and 132), RHOA_74 (SEQ ID NOS:99 and 133). In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_75 (SEQ ID NOS:100 and 134).

In some examples the antisense and sense strands of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein include the sequence pair set forth in RHOA_48 (SEQ ID NOS: 79 and 113), RHOA_48u (SEQ ID NOS: 80 and 114), RHOA_50 (SEQ ID NOS: 82 and 116), RHOA_ 61 (SEQ ID NOS: 89 and 123), RHOA_ 61u (SEQ ID NOS: 90 and 124) or RHOA_75 (SEQ ID NOS: 100 and 134).

In some examples the antisense and sense strands comprise the sequence pair set forth in RHOA_48 (SEQ ID NOS: 79 and 113). In some examples the antisense and sense strands comprise the sequence pair set forth in RHOA_48u (SEQ ID NOS: 80 and 114). In some examples the antisense and sense strands comprise the sequence pair set forth in RHOA_50 (SEQ ID NOS: 82 and 116).

In various examples of nucleic acid molecules (e.g., dsRNA molecules) as disclosed herein, the antisense strand may be 18 to 49 nucleotides in length (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49 nucleotides in length); or 18-35 nucleotides in length; or 18-30 nucleotides in length; or 18-25 nucleotides in length; or 18-23 nucleotides in length; or 19-21 nucleotides in length; or 25-30 nucleotides in length; or 26-28 nucleotides in length. In some examples of nucleic acid molecules (e.g., dsRNA molecules) as disclosed herein, the antisense strand is 19 nucleotides in length. Similarly the sense strand of nucleic acid molecules (e.g., dsRNA molecules) as disclosed herein may be 18 to 49 nucleotides in length (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49 nucleotides in length); or 18-35 nucleotides in length; or 18-30 nucleotides in length; or 18-25 nucleotides in length; or 18-23 nucleotides in length; or 19-21 nucleotides in length; or 25-30 nucleotides in length; or 26-28 nucleotides in length. In some examples of nucleic acid molecules (e.g., dsRNA molecules) as disclosed herein, the sense strand is 19 nucleotides in length. In some examples of nucleic acid molecules (e.g., dsRNA molecules) as disclosed herein, each of the antisense strand and the sense strand are 19 nucleotides in length. The duplex region of the nucleic acid molecules (e.g., dsRNA molecules) as disclosed herein may be 18-49 nucleotides in length (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48 or 49 nucleotides in length), 18-35 nucleotides in length; or 18-30 nucleotides in length; or about 18-25 nucleotides in length; or 18-25 nucleotides in length; or 18-23 nucleotides in length; or 18-21 nucleotides in length; or 25-30 nucleotides in length; or 25-28 nucleotides in length. In various examples of nucleic acid molecules (e.g., dsRNA molecules) as disclosed herein, the duplex region is 19 nucleotides in length.

In certain examples, the sense strand and the antisense strand of a nucleic acid (e.g., an dsRNA nucleic acid molecule) as provided herein are separate polynucleotide strands. In some examples, the separate sense and antisense strands form a double stranded

structure, also known as a duplex, via hydrogen bonding, for example, Watson-Crick base pairing. In some examples one or more nucleotide pairs form non-Watson-Crick base pairing. In some examples the sense and antisense strands are two separate strands that are covalently linked to each other. In other examples, the sense and antisense strands are part of a single polynucleotide strand having both a sense and antisense region; in some examples the polynucleotide strand has a hairpin structure.

In certain examples, the nucleic acid molecule is a double stranded nucleic acid (dsRNA) molecule that is symmetrical with regard to overhangs, and has a blunt end on both ends. In other examples the nucleic acid molecule is a dsRNA molecule that is symmetrical with regard to overhangs, and has a nucleotide or a non-nucleotide or a combination of a nucleotide and non-nucleotide overhang on both ends of the dsRNA molecule. In certain examples, the nucleic acid molecule is a dsRNA molecule that is asymmetrical with regard to overhangs, and has a blunt end on one end of the molecule and an overhang on the other end of the molecule. In some examples an asymmetrical dsRNA molecule has a 3'-overhang on one side of a duplex occurring on the sense strand; and a blunt end on the other side of the molecule. In some examples an asymmetrical dsRNA molecule has a 5'-overhang on one side of a duplex occurring on the sense strand; and a blunt end on the other side of the molecule. In other examples an asymmetrical dsNA molecule has a 3'-overhang on one side of a duplex occurring on the antisense strand; and a blunt end on the other side of the molecule. In some examples an asymmetrical dsRNA molecule has a 5'-overhang on one side of a duplex occurring on the antisense strand; and a blunt end on the other side of the molecule. In some examples the overhangs are nucleotide overhangs, in other examples the overhangs are non-nucleotide overhangs. In some examples the overhangs are 5' overhangs; in alternative examples the overhangs are 3' overhangs.

In some examples, the nucleic acid molecule has a hairpin structure (having the sense strand and antisense strand on one polynucleotide), with a loop structure on one end and a blunt end on the other end. In some examples, the nucleic acid molecule has a hairpin structure, with a loop structure on one end and an overhang end on the other end; in certain examples, the overhang is a 3'-overhang; in certain examples the overhang is a 5'-overhang; in certain examples the overhang is on the sense strand; in certain examples the overhang is on the antisense strand.

The nucleic acid molecules (e.g., dsRNA molecule) disclosed herein may include one or more modifications or modified nucleotides such as described herein. For example, a nucleic acid molecule (e.g., dsRNA molecule) as provided herein may include a modified nucleotide having a modified sugar; a modified nucleotide having a modified nucleobase; or a modified nucleotide having a modified phosphate group. Similarly, a nucleic acid molecule (e.g., dsRNA molecule) as provided herein may include a modified phosphodiester backbone and/or may include a modified terminal phosphate group.

Nucleic acid molecules (e.g., dsRNA molecules) as provided may have one or more nucleotides that include a modified sugar moiety, for example a 2'alkoxy modified sugar moiety. In some examples the modified sugar comprises a 2'-O-methyl .

Nucleic acid molecules (e.g., dsRNA molecules) as provided may have one or more modified nucleobase(s) for example as described herein, which may be selected from the group consisting of xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, amino, thiol, thioalkyl, hydroxyl and other 8-substituted adenines and guanines, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine, and acyclonucleotides.

Nucleic acid molecules (e.g., dsRNA molecules) as provided may have one or more modifications to the phosphodiester backbone, for example as described herein. In some examples the phosphodiester bond is modified by substituting the phosphodiester bond with a phosphorothioate, 3'-(or -5')deoxy-3'-(or -5')thio-phosphorothioate, phosphorodithioate, phosphoroselenate, 3'-(or -5')deoxy phosphinate, borano phosphate, 3'-(or -5')deoxy-3'-(or 5'-)amino phosphoramidate, hydrogen phosphonate, borano phosphate ester, phosphoramidate, alkyl or aryl phosphonate and a phosphotriester.

In various examples, the provided nucleic acid molecules (e.g., dsRNA molecules) may include an unmodified antisense strand and a sense strand having one or more modifications. . In some examples the provided nucleic acid molecules (e.g., dsRNA molecules) include an unmodified sense strand and one an antisense strand having or more modifications. . In some examples the provided nucleic acid molecules (e.g.,

dsRNA molecules) include one or more modified nucleotides in the both the sense strand and the antisense strand.

The nucleic acid molecules (e.g., dsRNA molecules) as provided herein may include a phosphate group at the 5' end of the sense and/or the antisense strand. In some examples the dsRNA molecules disclosed herein include a phosphate group at the 5' terminus of the antisense strand.

In some examples provided are double stranded nucleic acid compounds useful for down-regulating expression of RhoA. In some examples provided herein is a double stranded RNA compound having the structure (A1):

(A1) 5' (N)x – Z 3' (antisense strand)

3' Z'-(N')y –z" 5' (sense strand)

wherein each N and N' is a ribonucleotide which may be unmodified or modified, or an unconventional moiety;

wherein each of (N)x and (N')y is an oligonucleotide in which each consecutive N or N' is joined to the next N or N' by a covalent bond;

wherein each of Z and Z' is independently present or absent, but if present independently comprises 1-5 consecutive nucleotides, 1-5 consecutive non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present;

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of (N')y;

each of x and y is independently an integer from 18 to 40;

wherein the sequence of (N')y is complementary to the sequence of (N)x; and wherein (N)x comprises an antisense sequence set forth in Table III or Table IV.

The sense and antisense sequences useful in generating dsRNA compounds provided in Table III are RHOA_31 (SEQ ID NOS:135 and 149), RHOA_33 (SEQ ID NOS:136 and 150), RHOA_37 (SEQ ID NOS:137 and 151), RHOA_38 (SEQ ID NOS:138 and 152), RHOA_43 (SEQ ID NOS:139 and 153), RHOA_52 (SEQ ID NOS:140 and 154), RHOA_56 (SEQ ID NOS:141 and 155), RHOA_57 (SEQ ID NOS:142 and 156), RHOA_58 (SEQ ID NOS:143 and 157), RHOA_68 (SEQ ID NOS:144 and 158),

RHOA_69 (SEQ ID NOS:145 and 159), RHOA_70 (SEQ ID NOS:146 and 160), RHOA_73 (SEQ ID NOS:147 and 161) and RHOA_76 (SEQ ID NOS:148 and 162). The sense and antisense sequences useful in generating dsRNA compounds provided in Table IV are set forth in RHOA_23 (SEQ ID NOS:163 and 167), RHOA_24 (SEQ ID NOS:164 and 168), RHOA_26 (SEQ ID NOS:165 and 169) or RHOA_29 (SEQ ID NOS:166 and 170).

In some examples the covalent bond joining each consecutive N and/or N' is a phosphodiester bond.

In some examples x = y and each of x and y is 19, 20, 21, 22 or 23. In some examples x = y =19.

In some examples of nucleic acid molecules (e.g., dsRNA molecules) as disclosed herein, the double stranded nucleic acid molecule is a siRNA, siNA or a miRNA.

In some examples the sense and antisense strands comprise the sequence pairs set forth in RHOA_58 (SEQ ID NOS: 143 and 157). In some examples the sense and antisense strands comprise the sequence pairs set forth in RHOA_70 (SEQ ID NOS: 146 and 160).

In some examples the double stranded nucleic acid molecules comprise a DNA moiety or a mismatch to the target at position 1 of the antisense strand (5' terminus). Such a duplex structure is described herein. According to one example provided are double stranded siRNA compounds having a structure (A2) set forth below:

(A2) 5' N1-(N)x - Z 3' (antisense strand)

3' Z'-N2-(N')y–z" 5' (sense strand)

wherein each N1, N2, N and N' is independently an unmodified or modified nucleotide, or an unconventional moiety;

wherein each of (N)x and (N')y is an oligonucleotide in which each consecutive N or N' is joined to the adjacent N or N' by a covalent bond;

wherein each of x and y is independently an integer between 17 and 39;

wherein N2 is covalently bound to (N')y;

wherein N1 is covalently bound to (N)x and is mismatched to the target mRNA (SEQ ID NO:1) or is a complementary DNA moiety to the target mRNA;

wherein N1 is a moiety selected from the group consisting of natural or modified: uridine, deoxyribouridine, ribothymidine, deoxyribothymidine, adenosine or deoxyadenosine, an abasic ribose moiety and an abasic deoxyribose moiety;

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N2- (N')y;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides, 1-5 consecutive non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein the sequence of (N')y is complementary to the sequence of (N)x; and wherein the sequence of (N)x comprises an antisense sequence set forth in Table I.

In various examples the sequence of N1-(N)x comprises an antisense sequence set forth in Table II. In some examples the N2-(N')y and N1-(N)x useful in generating dsRNA compounds are presented in Table II and set forth in RHOA_32 (SEQ ID NOS:67 and 101), RHOA_34 (SEQ ID NOS:68 and 102), RHOA_35 (SEQ ID NOS:69 and 103), RHOA_36 (SEQ ID NOS:70 and 104), RHOA_39 (SEQ ID NOS:71 and 105), RHOA_40 (SEQ ID NOS:72 and 106), RHOA_41 (SEQ ID NOS:73 and 107), RHOA_42 (SEQ ID NOS:74 and 108), RHOA_44 (SEQ ID NOS:75 and 109), RHOA_45 (SEQ ID NOS:76 and 110), RHOA_46 (SEQ ID NOS:77 and 111), RHOA_47 (SEQ ID NOS:78 and 112), RHOA_48 (SEQ ID NOS:79 and 113), RHOA_48u (SEQ ID NOS:80 and 114), RHOA_49 (SEQ ID NOS:81 and 115), RHOA_50 (SEQ ID NOS:82 and 116) RHOA_51 (SEQ ID NOS:83 and 117), RHOA_53 (SEQ ID NOS:84 and 118), RHOA_54 (SEQ ID NOS:85 and 119), RHOA_55 (SEQ ID NOS:86 and 120), RHOA_59 (SEQ ID NOS:87 and 121), RHOA_60 (SEQ ID NOS:88 and 122), RHOA_61 (SEQ ID NOS:89 and 123), RHOA_61u (SEQ ID NOS:90 and 124), RHOA_62 (SEQ ID NOS:91 and 125), RHOA_63 (SEQ ID NOS:92 and 126) RHOA_64 (SEQ ID NOS:93 and 127), RHOA_65 (SEQ ID NO:94 and 128), RHOA_66 (SEQ ID NOS:95 and 129) RHOA_67 (SEQ ID NOS:96 and 130), RHOA_71 (SEQ ID NOS:97 and 131), RHOA_72 (SEQ ID NOS:98 and 132), RHOA_74 (SEQ ID NOS:99 and 133) and RHOA_75 (SEQ ID NOS:100 and 134).

In certain examples, (N)x of a nucleic acid molecule (e.g., a dsRNA molecule) as disclosed herein includes a sequence corresponding to any one of the antisense sequences

shown in Table I. In certain examples (N)x and (N')y are selected from the sequence pairs shown in Table I.

In some examples a nucleic acid molecule disclosed herein include an (N)x and an (N')y selected from the sequence pairs set forth in RHOA_32-1 (SEQ ID NOS:3 and 35), RHOA_34-1 (SEQ ID NOS:4 and 36), RHOA_35-1 (SEQ ID NOS:5 and 37), RHOA_36-1 (SEQ ID NOS:6 and 38), RHOA_39-1 (SEQ ID NOS:7 and 39), RHOA_40-1 (SEQ ID NOS:8 and 40), RHOA_41-1 (SEQ ID NOS:9 and 41), RHOA_42-1 (SEQ ID NOS:10 and 42), RHOA_44-1 (SEQ ID NOS:11 and 43), RHOA_45-1 (SEQ ID NOS:12 and 44), RHOA_46-1 (SEQ ID NOS:13 and 45), RHOA_47-1 (SEQ ID NOS:14 and 46), RHOA_48-1 (SEQ ID NOS:15 and 47), RHOA_49-1 (SEQ ID NOS:16 and 48), RHOA_50-1 (SEQ ID NOS:17 and 49), RHOA_51-1 (SEQ ID NOS:18 and 50), RHOA_53-1 (SEQ ID NOS:19 and 51), RHOA_54-1 (SEQ ID NOS:20 and 52), RHOA_55-1 (SEQ ID NOS:21 and 53), RHOA_59-1 (SEQ ID NOS:22 and 54), RHOA_60-1 (SEQ ID NOS:23 and 55), RHOA_61-1 (SEQ ID NOS:24 and 56), RHOA_62-1 (SEQ ID NOS:25 and 57), RHOA_63-1 (SEQ ID NOS:26 and 58) RHOA_64-1 (SEQ ID NOS:27 and 59), RHOA_65-1 (SEQ ID NO:28 and 60), RHOA_66-1 (SEQ ID NOS:29 and 61), RHOA_67-1 (SEQ ID NOS:30 and 62), RHOA_71-1 (SEQ ID NOS:31 and 63), RHOA_72-1 (SEQ ID NOS:32 and 64), RHOA_74-1 (SEQ ID NOS:33 and 65) and RHOA_75-1 (SEQ ID NOS:34 and 66).

In some examples the sequence of (N')y is fully complementary to the sequence of (N)x. In various examples sequence of N2-(N')y is complementary to the sequence of N1-(N)x. In some examples (N)x comprises an antisense that is fully complementary to about 17 to about 39 consecutive nucleotides in a target mRNA. In other examples (N)x comprises an antisense that is substantially complementary to about 17 to about 39 consecutive nucleotides in a target mRNA set forth in SEQ ID NO:1.

In some examples N1 and N2 form a Watson-Crick base pair. In other examples N1 and N2 form a non-Watson-Crick base pair. In some examples a base pair is formed between a ribonucleotide and a deoxyribonucleotide.

In some examples x=y=18, x=y=19 or x=y=20. In some examples x=y=18. When x=18 in N1-(N)x , N1 refers to position 1and positions 2-19 are included in (N)18. When y=18 in N2-(N')y, N2 refers to position 19 and positions 1-18 are included in (N')18 .

In some examples N1 is covalently bound to (N)x and is mismatched to the target mRNA. In various examples N1 is covalently bound to (N)x and is a DNA moiety complementary to the target mRNA.

In some examples a uridine in position 1 of the antisense strand is substituted with an N1 selected from natural or modified: adenosine, deoxyadenosine, uridine, deoxyuridine (dU), ribothymidine or deoxythymidine. In various examples N1 is selected from natural or modified: adenosine, deoxyadenosine or deoxyuridine. For example, in some examples a cytidine in position 1 is replaced with an adenine or a uridine; a guanosine in position 1 is replaced with an adenine or a uridine; or an adenine is replaced with a uridine.

In some examples guanosine in position 1 (N1) of the antisense strand is substituted with a natural or modified: adenosine, deoxyadenosine, uridine, deoxyuridine, ribothymidine or deoxythymidine. In various examples N1 is selected from natural or modified: adenosine, deoxyadenosine, uridine or deoxyuridine.

In some examples cytidine in position 1 (N1) of the antisense strand is substituted with a natural or modified: adenosine, deoxyadenosine, uridine, deoxyuridine, ribothymidine or deoxythymidine. In various examples N1 is selected from natural or modified: adenosine, deoxyadenosine, uridine or deoxyuridine.

In some examples adenosine in position 1 (N1)of the antisense strand is substituted with a natural or modified: deoxyadenosine, deoxyuridine, ribothymidine or deoxythymidine.

In some examples N1 and N2 form a base pair between natural or modified: uridine or deoxyuridine, and adenosine or deoxyadenosine. In other examples N1 and N2 form a base pair between natural or modified: deoxyuridine and adenosine.

In some examples the double stranded nucleic acid molecule is a siRNA, siNA or a miRNA. The double stranded nucleic acid molecules as provided herein are also refered to as "duplexes".

In some examples of Structure A2 x =y=18.In some examples x=y=18 and (N)x consists of an antisense oligonucleotide present in Table I. In some examples N1 is selected from a natural uridine and a modified uridine. In some examples N1 is a natural uridine. In some examples N1-(N)x consists of an antisense oligonucleotide

present in Table II. In some examples x=y=19 or x=y=20. In some examples x=y=19 or x=y=20 and (N)x comprises an antisense oligonucleotide present in Table I.

In some examples the preferred sense and antisense sequences useful in generating dsRNA compounds are selected from the sequence pairs set forth in Table II: RHOA_48 (SEQ ID NOS: 79 and 113), RHOA_48u (SEQ ID NOS: 80 and 114), RHOA_50 (SEQ ID NOS: 82 and 116), RHOA_61 (SEQ ID NOS: 89 and 123), RHOA_61u (SEQ ID NOS: 90 and 124), and RHOA _75 (SEQ ID NOS: 100 and 134).

In some examples of Structure (A2), N1 is a 2'OMe sugar-modified uridine or a 2'OMe sugar-modified adenosine. In certain examples of structure (A2), N^2 is a 2'OMe sugar modified ribonucleotide or deoxyribonucleotide.

In some examples of Structure (A1) and/or Structure (A2) each N consists of an unmodified ribonucleotide. In some examples of Structure (A1) and/or Structure (A2) each N' consists of an unmodified nucleotide. In some examples at least one of N and/or N' comprises a chemically modified nucleotide or an unconventional moiety. In some examples the unconventional moiety is selected from a mirror nucleotide, an abasic ribose moiety and an abasic deoxyribose moiety. In some examples the unconventional moiety is a mirror nucleotide, preferably an L-DNA moiety. In some examples at least one of N or N' comprises a 2'OMe sugar-modified ribonucleotide.

In some examples of Structure (A1) and/or Structure (A2) the sequence of (N')y is fully complementary to the sequence of (N)x. In other examples of Structure (A1) and/or Structure (A2) the sequence of (N')y is substantially complementary to the sequence of (N)x.

In some examples of Structure (A1) and/or Structure (A2) (N)x includes an antisense sequence that is fully complementary to about 17 to about 39 consecutive nucleotides in a target mRNA. In other examples of Structure A1 and/or Structure A2 (N)x includes an antisense that is substantially complementary to about 17 to about 39 consecutive nucleotides in a target mRNA. In some examples of Structure (A1) and/or Structure (A2) the dsRNA compound is blunt ended, for example, wherein each of z", Z and Z' is absent. In an alternative embodiment, at least one of z", Z or Z' is present.

In various examples Z and Z' independently include one or more covalently linked modified and or unmodified nucleotides, including deoxyribonucleotides and ribonucleotides, or one or more unconventional moieties for example inverted abasic

deoxyribose moiety or abasic ribose moiety or a mirror nucleotide; one or more non-nucleotide C3, C4 or C5 moiety, an amino-C6 moiety, and the like. In some examples Z' is absent and Z is present and includes one or more non-nucleotide C3 moieties. In some examples Z is absent and Z' is present and includes one or more non-nucleotide C3 moieties. In some examples each of Z and Z' independently comprises one or more non-nucleotide C3 moieties or one or more amino-C6 moieties. In some examples z" is present and is selected from a mirror nucleotide, an abasic moiety and an inverted abasic moiety. In some examples of Structures A1 and A2 each of Z and Z' includes an abasic moiety, for example a deoxyriboabasic moiety (referred to herein as "dAb") or riboabasic moiety (referred to herein as "rAb"). In some examples each of Z and/or Z' comprises two covalently linked abasic moieties and is for example dAb-dAb or rAb-rAb or dAb-rAb or rAb-dAb, wherein each moiety is covalently attached to an adjacent moiety, preferably via a phospho-based bond. In some examples the phospho-based bond includes a phosphorothioate, a phosphonoacetate or a phosphodiester bond. In some examples the phospho-based bond includes a phosphodiester bond.

In some examples each of Z and/or Z' independently includes an alkyl moiety, optionally propane [$(CH2)_3$] moiety (C3) or a derivative thereof including propanol (C3OH) and phospho derivative of propanediol ("C3Pi"). In some examples each of Z and/or Z' includes two alkyl moieties and in some examples is C3Pi-C3OH. The 3' terminus of the antisense strand and/or the 3' terminus of the sense strand is covalently attached to a C3 moiety via a phospho-based bond and the C3 moiety is covalently conjugated a C3OH moiety via a phospho-based bond. In some examples the phospho-based bonds include a phosphorothioate, a phosphonoacetate or a phosphodiester bond. In some examples the phospho-based bond includes a phosphodiester bond.

In some examples of Structures A1 and A2, Z comprises C3Pi-C3OH. In some examples of Structures A1 and A2, Z' comprises C3Pi or C3OH. In some examples of Structures A1 and A2, a double stranded nucleic acid molecule includes a C3Pi-C3OH moiety covalently attached to the 3' terminus of the antisense strand and a C3Pi or C3OH moiety covalently attached to the 3' terminus of the sense strand.

In some examples of Structure (A1) and/or Structure (A2) each N consists of an unmodified nucleotide. In some examples of Structure (A1) and/or Structure (A2) each N' consists of an unmodified nucleotide. In some examples, at least one of N and/or N' is a modified ribonucleotide or an unconventional moiety.

In other examples a compound of Structure A1 and/or Structure A2 includes at least one ribonucleotide modified in its sugar residue. In some examples the compound comprises a modification at the 2' position of the sugar residue. In some examples the modification in the 2' position comprises the presence of an amino, a fluoro, an alkoxy or an alkyl moiety. In certain examples the 2' modification includes an alkoxy moiety. In some examples the alkoxy moiety is a methoxy moiety (also known as 2'-O-methyl; 2'OMe; 2'-OCH_3). In some examples anucleic acid compound includes 2'OMe sugar modified alternating ribonucleotides in one or both of the antisense strand and the sense strand. In other examples a compound includes 2'OMe sugar modified ribonucleotides in the antisense strand, (N)x or N^1-(N)x, only. In certain examples the middle ribonucleotide of the antisense strand; e.g. ribonucleotide in position 10 in a 19-mer strand, is unmodified. In various examples the nucleic acid compound includes at least 5 alternating 2'OMe sugar modified ribonucleotides and unmodified ribonucleotides. In additional examples a compound of Structure A1 and/or Structure A2 includes modified ribonucleotides in alternating positions wherein each ribonucleotide at the 5' and 3' termini of (N)x or N^1-(N)x are modified in their sugar residues, and each ribonucleotide at the 5' and 3' termini of (N')y or N^2-(N)y are unmodified in their sugar residues. In various examples the ribonucleotides in alternating positions are modified at the 2' position of the sugar residue.

In some examples the nucleic acid compound includes at least 5 alternating 2'OMe sugar modified ribonucleotides and unmodified ribonucleotides, for example at positions 1, 3, 5, 7 and 9 or positions 11, 13, 15, 17, 19 (5'>3'). In some examples, (N)x of Structure (A1) or N1-(N)x of Structure (A2) includes 2'OMe modified ribonucleotides in positions 2, 4, 6, 8, 11, 13, 15, 17 and 19. In some examples, (N)x of Structure (A1) or N1-(N)x of Structure (A2) includes 2'OMe modified ribonucleotides in positions 1, 3, 5, 7, 9, 11, 13, 15, 17 and 19. In some examples, (N)x of Structure (A1) or N1-(N)x of Structure (A2) includes 2'OMe modified ribonucleotides in one or pyrimidines.

In some examples of Structure A1 and/or Structure A2, neither of the sense strand nor the antisense strand is phosphorylated at the 3' and 5' termini. In other examples one or both of the sense strand or the antisense strand are phosphorylated at the 3' termini. In other examples one or both of the sense strand or the antisense strand are phosphorylated at the 5' termini.

In some examples the double stranded molecules disclosed herein include one or more of the following modifications:

N in at least one of positions 5, 6, 7, 8, or 9 from the 5' terminus of the antisense strand is selected from a DNA, TNA, a 2'5' nucleotide or a mirror nucleotide;

N' in at least one of positions 9 or 10 from the 5' terminus of the sense strand is selected from a TNA, 2'5' nucleotide and a pseudoUridine; and

N' in 4, 5, or 6 consecutive positions at the 3' terminus positions of (N')y comprises a 2'5' nucleotide.

In some examples the double stranded molecules include a combination of the following modifications

the antisense strand includes a DNA, TNA, a 2'5' nucleotide or a mirror nucleotide in at least one of positions 5, 6, 7, 8, or 9 from the 5' terminus; and

the sense strand includes at least one of a TNA, a 2'5' nucleotide and a pseudoUridine in positions 9 or 10 from the 5' terminus.

In some examples the double stranded molecules include a combination of the following modifications

the antisense strand includes a DNA, 2'5' nucleotide or a mirror nucleotide in at least one of positions 5, 6, 7, 8, or 9 from the 5' terminus; and

the sense strand includes 4, 5, or 6 consecutive 2'5' nucleotides at the 3' penultimate or 3' terminal positions.

In some examples of Structure A1 and/or Structure A2 (N)y includes at least one unconventional moiety selected from a mirror nucleotide, a 2'5' nucleotide and a TNA. In some examples the unconventional moiety is a mirror nucleotide. In various examples the mirror nucleotide is selected from an L-ribonucleotide (L-RNA) and an L-deoxyribonucleotide (L-DNA). In some examples the mirror nucleotide is L-DNA. In certain examples the sense strand comprises an unconventional moiety in position 9 or 10 (from the 5' terminus). In some examples the sense strand includes an unconventional moiety in position 9 (from the 5' terminus). In some examples the sense strand is 19 nucleotides in length and comprises 4, 5, or 6 consecutive unconventional moieties in positions 15, (from the 5' terminus). In some examples the sense strand includes 4 consecutive 2'5' ribonucleotides in positions 15,

16, 17, and 18. In some examples the sense strand includes 5 consecutive 2'5' ribonucleotides in positions 15, 16, 17, 18 and 19. In various examples the sense strand further comprises Z'. In some examples Z' includes a C3OH moiety or a C3Pi moiety.

In some examples of Structure A1 and/or Structure A2 (N)y comprises at least one unconventional moiety selected from a mirror nucleotide and a nucleotide joined to an adjacent nucleotide by a 2'-5' internucleotide phosphate bond. In some examples the unconventional moiety is a mirror nucleotide. In various examples the mirror nucleotide is selected from an L-ribonucleotide (L-RNA) and an L-deoxyribonucleotide (L-DNA). In some examples the mirror nucleotide is L-DNA.

In some examples of Structure A1 (N')y comprises at least one L-DNA moiety. In some examples x=y=19 and (N')y, consists of unmodified ribonucleotides at positions 1-17 and 19 and one L-DNA at the 3' penultimate position (position 18). In other examples x=y=19 and (N')y consists of unmodified ribonucleotides at position 1-16 and 19 and two consecutive L-DNA at the 3' penultimate position (positions 17 and 18). In various examples the unconventional moiety is a nucleotide joined to an adjacent nucleotide by a 2'-5' internucleotide phosphate linkage. According to various examples (N')y comprises 2, 3, 4, 5, or 6 consecutive ribonucleotides at the 3' terminus linked by 2'-5' internucleotide linkages. In one example, four consecutive nucleotides at the 3' terminus of (N')y are joined by three 2'-5' phosphodiester bonds. In one example, five consecutive nucleotides at the 3' terminus of (N')y are joined by four 2'-5' phosphodiester bonds. In some examples, wherein one or more of the 2'-5' nucleotides form a 2'-5' phosphodiester bonds the nucleotide further comprises a 3'-O-methyl (3'OMe) sugar modification. In some examples the 3' terminal nucleotide of (N')y comprises a 3'OMe sugar modification. In certain examples x=y=19 and (N')y comprises two or more consecutive nucleotides at positions 15, 16, 17, 18 and 19 comprise a nucleotide joined to an adjacent nucleotide by a 2'-5' internucleotide bond. In various examples the nucleotide forming the 2'-5' internucleotide bond comprises a 3' deoxyribose nucleotide or a 3' methoxy nucleotide. In some examples x=y=19 and (N')y comprises nucleotides joined to the adjacent nucleotide by a 2'-5' internucleotide bond between positions 15-16, 16-17 and 17-18 or between positions 16-17, 17-18 and 18-19. In some examples x=y=19 and (N')y comprises nucleotides joined to the adjacent nucleotide by a 2'-5' internucleotide bond between positions 16-17 and 17-18 or between

positions 17-18 and 18-19 or between positions 15-16 and 17-18. In other examples the pyrimidine ribonucleotides (rU, rC) in (N')y are substituted with nucleotides joined to the adjacent nucleotide by a 2'-5' internucleotide bond.

In some examples of Structure A2 (N)y comprises at least one L-DNA moiety. In some examples x=y=18 and N^2-(N')y, consists of unmodified ribonucleotides at positions 1-17 and 19 and one L-DNA at the 3' penultimate position (position 18). In other examples x=y=18 and N^2-(N')y consists of unmodified ribonucleotides at position 1-16 and 19 and two consecutive L-DNA at the 3' penultimate position (positions 17 and 18). In various examples the unconventional moiety is a nucleotide joined to an adjacent nucleotide by a 2'-5' internucleotide phosphate linkage. According to various examples N^2-(N')y comprises 2, 3, 4, 5, or 6 consecutive ribonucleotides at the 3' terminus linked by 2'-5' internucleotide linkages. In one example, four consecutive nucleotides at the 3' terminus of N^2- (N')y are joined by three 2'-5' phosphodiester bonds, wherein one or more of the 2'-5' nucleotides which form the 2'-5' phosphodiester bonds further comprises a 3'-O-methyl (3'OMe) sugar modification. In some examples the 3' terminal nucleotide of N^2-(N')y comprises a 2'OMe sugar modification. In certain examples x=y=18 and N^2- (N')y comprises two or more consecutive nucleotides at positions 15, 16, 17, 18 and 19 comprise a nucleotide joined to an adjacent nucleotide by a 2'-5' internucleotide bond. In various examples the nucleotide forming the 2'-5' internucleotide bond comprises a 3' deoxyribose nucleotide or a 3' methoxy nucleotide. In some examples x=y=18 and N^2-(N')y comprises nucleotides joined to the adjacent nucleotide by a 2'-5' internucleotide bond between positions 16-17 and 17-18 or between positions 17-18 and 18-19 or between positions 15-16 and 17-18. In other examples the pyrimidine ribonucleotides (rU, rC) in (N')y comprise nucleotides joined to the adjacent nucleotide by a 2'-5' internucleotide bond.

In further examples of Structures A1 and A2 (N')y comprises 1-8 modified ribonucleotides wherein the modified ribonucleotide is a deoxyribose (DNA) nucleotide. In certain examples (N')y comprises 1, 2, 3, 4, 5, 6, 7, or up to 8 DNA moieties.

In some examples provided herein is a double stranded RNA molecule which includes a sense strand and an antisense strand selected from the oligonucleotide pairs set forth in Table II and identified herein as RHOA_48 (SEQ ID NOS: 79 and 113), RHOA_48u (SEQ ID NOS: 80 and 114), RHOA_50 (SEQ ID NOS: 82 and 116), RHOA_61 (SEQ ID NOS: 89 and 123) and RHOA_61u (SEQ ID NOS: 90 and 124).

In some examples provided herein is a double stranded RNA molecule which includes a sense strand and an antisense strand selected from the oligonucleotide pairs set forth in Table II and identified herein as RHOA_48 (SEQ ID NOS: 79 and 113), RHOA_48u (SEQ ID NOS: 80 and 114), RHOA_50 (SEQ ID NOS: 82 and 116), RHOA_61 (SEQ ID NOS: 89 and 123) and RHOA_61u (SEQ ID NOS: 90 and 124). Unless otherwise stated all positions along a sense strand or antisense strand are counted from the 5' to the 3' (5'>3').

In some examples a double stranded nucleic acid molecule includes the antisense strand set forth in SEQ ID NO:113 and sense strand set forth in SEQ ID NO:79; identified herein as RHOA_48. In some examples the double stranded nucleic acid molecule has the structure

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5′    UGUAGCAAGAUGACUUCUG -Z  3′       (antisense SEQ ID NO:113)
      ||||||||||||||||||||
3′ Z′-ACAUCGUUCUACUGAAGAC -z″ 5′ (sense SEQ ID NO:79)
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wherein each " | " represents base parining between the ribonucleotides;

wherein each of A, C, G, U is independently an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of the sense strand.

In some examples the double stranded nucleic acid molecule comprises modified ribonucleotides and unconventional moieties.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes a mirror nucleotide or a 2'-5' linked nucleotide in one or more of positions 5, 6, 7 or 8 (5'>3'), and a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus. In some examples the antisense strand further includes one or more 2'OMe sugar modified ribonucleotides. In some examples the sense strand (SEQ ID NO:79) includes 4 or 5 consecutive 2'-5' linked nucleotides at the 3' terminal or penultimate positions, a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus, one or more 2'OMe sugar

modified nucleotides, and a cap moiety covalently attached at the 5' terminus. The molecule may include a 5' phosphate on the antisense strand.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a 3' terminal nucleotide or non-nucleotide overhang; and a cap moiety covalently attached at the 5' terminus. In some examples the antisense strand further includes a 2'-5' linked ribonucleotide at position 6, at position 7 or at positions 6 and 7.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 6, 11, 14, 15, 17 and 18, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi or C3OH moiety covalently attached to the 3' terminus; and a cap moiety covalently attached at the 5' terminus.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 6, 11, 14, 15, 17 and 18, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi covalently attached to the 3 terminus and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, as set forth in compound RHOA_48_S1833.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, a 2'-5' linked nucleotide or a mirror nucleotide in one or more of positions 6, 7 and 8, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a 3' terminal nucleotide or non-nucleotide overhang; and a cap moiety covalently attached at the 5' terminus.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 6, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi or C3OH moiety covalently attached to the 3' terminus; and a cap moiety selected from an abasic moiety, an inverted abasic moiety, a C6 amino and a mirror nucleotide covalently attached at the 5' terminus.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 6, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi covalently attached to the 3 terminus and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in compound RHOA_48_S1857.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 6, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi covalently attached to the 3 terminus and a mirror nucleotide (L-deoxyriboguanosine-3'-phosphate) covalently attached at the 5' terminus, set forth in compound RHOA_48_S1873.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 6, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 7, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') an optional 2'OMe sugar modified ribonucleotide at position 1, 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi or C3OH moiety covalently attached to the 3' terminus; and a cap moiety selected from an abasic moiety, an inverted abasic moiety, a C6 amino and a mirror nucleotide covalently attached at the 5' terminus.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 6, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 7, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') a 2'OMe sugar modified ribonucleotide at position 1, a C3Pi moiety covalently attached to the 3 terminus and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus; as set forth in compound RHOA_48_S1856.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 6, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 7, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') includes a 2'OMe sugar modified ribonucleotide at position 1, and 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi covalently attached to the 3 terminus and a mirror nucleotide (L-deoxyriboguanosine-3'-phosphate) covalently attached at the 5' terminus, as set forth in compound RHOA_48_S1872.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, and 2'-5' linked ribonucleotide at positions 6 and 7 and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') an optional 2'OMe sugar modified ribonucleotide at position 1, and 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi or C3OH moiety covalently attached to the 3' terminus and a cap moiety selected from an abasic moiety, an inverted abasic moiety and a mirror nucleotide covalently attached at the 5' terminus.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at positions 6 and 7 and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') includes a 2'OMe sugar modified ribonucleotide at position 1, and 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi moiety covalently attached to the 3 terminus and an inverted abasic

deoxyribonucleotide cap moiety covalently attached at the 5' terminus, as set forth in compound RHOA_48_S1858.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, a mirror nucleotide at position 6 and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') a 2'OMe sugar modified ribonucleotide at position 1, and 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi moiety covalently attached to the 3 terminus and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus as set forth in compound RHOA_48_S1859.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:113) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, a mirror nucleotide at position 8 and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:79) includes (5'>3') a 2'OMe sugar modified ribonucleotide at position 1, and 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi moiety covalently attached to the 3 terminus and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, as set forth in compound RHOA_48_S1860.

In some examples provided is a double stranded nucleic acid molecule wherein the sense strand (SEQ ID NO:79) includes (5'>3') a 2'OMe sugar modified ribonucleotide at position 1, and 2'-5' linked ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi moiety covalently attached to the 3 terminus and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, and the antisense strand (SEQ ID NO:113) is selected from

an antisense oligonucleotide which includes (5'>3') a U to dT substitution in position 1, a 5' phosphate covalently attached to the deoxyribothymidine in position 1, 2'OMe sugar modified ribonucleotides at positions 3, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 7 and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and as set forth in compound RHOA_48_S1884; or

an antisense oligonucleotide which includes (5'>3') a a 5' phosphate covalently attached to the uridine in position 1, 2'OMe sugar modified ribonucleotides at positions 3, 11, 14, 15,

17 and 18, a 2'-5' linked ribonucleotide at position 7 and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and as set forth in compound RHOA_48_S1885; or

an antisense oligonucleotide which includes (5'>3') a U to C3 substitution in position 1, a 5' phosphate covalently attached to the C3 in position 1, 2'OMe sugar modified ribonucleotides at positions 3, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 7 and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and as set forth in compound RHOA_48_S1886; or

an antisense oligonucleotide which includes (5'>3') a 5' phosphate covalently attached to the uridine in position 1, 2'OMe sugar modified ribonucleotides at positions 1, 3, 11, 14, 15, 17 and 18, a 2'-5' linked ribonucleotide at position 7 and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and as set forth in compound RHOA_48_S1887.

In some examples the double stranded nucleic acid molecule includes the antisense strand set forth in SEQ ID NO:114 and sense strand set forth in SEQ ID NO:80; identified herein as RHOA_48u. In some examples the double stranded nucleic acid molecule has the structure

```
5'    AGUAGCAAGAUGACUUCUG -Z 3'   (antisense SEQ ID NO:114)
      ||||||||||||||||||||
3' Z'-UCAUCGUUCUACUGAAGAC -z" 5'  (sense SEQ ID NO:80)
```

wherein each " | " represents base parining between the ribonucleotides;

wherein each of A, C, G, U is independently an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of the sense strand.

In some examples the double stranded nucleic acid molecule comprises modified ribonucleotides and unconventional moieties.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:114) includes (5'>3') one or more 2'OMe sugar modified ribonucleotides, a mirror nucleotide or a 2'-5' linked ribonucleotide in one or more of

positions 5, 6, 7 or 8 (5'>3'), and a 3' terminal nucleotide or non-nucleotide overhang. The antisense strand may further include a 5' terminal phosphate. In some examples the sense strand (SEQ ID NO:80) includes (5'>3') 4 or 5 consecutive 2'-5' linked nucleotides at the 3' terminal or penultimate positions, a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus and a cap moiety covalently attached at the 5' terminus. In other examples the sense strand (SEQ ID NO:80) further includes one or more 2'OMe sugar modified ribonucleotides.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:114) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions (5'>3') 3, 6, 11, 14, 15, 17 and 18, a 2'-5' ribonucleotide at position 7, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:80) includes (5'>3') 2'-5' ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi moiety covalently attached at the 3' terminus; and an inverted abasic deoxyribonucleotide moiety covalently attached at the 5' terminus, set forth in compound RHOA_48u _S1812.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:114) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions (5'>3') 3, 6, 11, 14, 15, 17 and 18, a 2'-5' ribonucleotide at position 7, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:80) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 13 and 16, a 2'-5' linked ribonucleotide at position 9, a C3Pi moiety covalently attached at the 3' terminus; and an inverted abasic deoxyribonucleotide moiety covalently attached at the 5' terminus, set forth in compound RHOA_48u_ S1813.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:114) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions (5'>3') 3, 6, 11, 14, 15, 17 and 18, a 2'-5' ribonucleotide at position 7, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:80) includes (5'>3') a 2'OMe sugar modified ribonucleotide at position 1, and 2'-5' ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi moiety covalently attached at the 3' terminus; and a mirror nucleotide (L-deoxyriboguanosine-3'-phosphate) covalently attached at the 5' terminus, set forth in compound RHOA_48u _S1870.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:114) includes (5'>3') 2'OMe sugar modified ribonucleotides

at positions (5'>3') 3, 6, 11, 14, 15, 17 and 18, a 2'-5' ribonucleotide at position 7, and a C3Pi-C3OH moiety covalently attached to the 3' terminus; and the sense strand (SEQ ID NO:80) includes (5'>3') a 2'OMe sugar modified ribonucleotide at position 1, and 2'-5' ribonucleotides at positions 15, 16, 17, 18 and 19, a C3Pi moiety covalently attached at the 3' terminus; and an inverted abasic deoxyribonucleotide covalently attached at the 5' terminus, set forth in compound RHOA_48u _S1871.

In some examples a double stranded nucleic acid molecule includes the antisense strand set forth in SEQ ID NO:116 and sense strand set forth in SEQ ID NO:82; identified herein as RHOA_50. In some examples the double stranded nucleic acid molecule has the structure

```
5′    UGAACUGUAACUCUGCCAC -Z  3′    (antisense SEQ ID NO:116)
      ||||||||||||||||||||
3′ Z′-ACUUGACAUUGAGACGGUG -z″ 5′    (sense SEQ ID NO:82)
```

wherein each " | " represents base parining between the ribonucleotides;

wherein each of A, C, G, U is independently an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of the sense strand.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:116) includes (5'>3') a DNA, a mirror nucleotide or a 2'-5' linked nucleotide in one or more of positions 5, 6, 7 or 8, a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus and one or more 2'OMe sugar modified nucleotides. In some examples the antisense strand (SEQ ID NO:116) includes (5'>3') alternating 2'OMe sugar modified ribonucleotides, a mirror nucleotide or a 2'-5' linked ribonucleotide in one or more of positions 5, 6, 7 or 8, and a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus. In some examples the antisense strand further includes a U (uridine) to dU (deoxyuridine) substitution in position 1. The antisense strand may further include a 5' terminal phosphate.

In some examples the sense strand (SEQ ID NO:82) includes (5'>3') a mirror nucleotide or a 2'-5' linked nucleotide in one or more of positions 9 or 10, a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus, one or more 2'OMe sugar modified nucleotides, and a cap moiety covalently attached at the 5' terminus.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:116) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 3, 5, 9, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide in position 7, C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and a U (uridine) to dU (deoxyuridine) substitution in position 1; and the sense strand (SEQ ID NO:82) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, 2'OMe sugar modified nucleotides at positions 11, 13 and 18, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_50_S1796.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:116) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 4, 6, 8, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide in position 7, a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and a U (uridine) to dU (deoxyuridine) substitution in position 1; and the sense strand (SEQ ID NO:82) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, a 2'OMe sugar modified nucleotides at position 18, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_50_S1798.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:116) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 3, 5, 9, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide in position 7, a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and a U (uridine) to dU (deoxyuridine) substitution in position 1; and the sense strand (SEQ ID NO:82) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, a 2'OMe sugar modified nucleotides at position 18, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_50_S1799.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:116) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 4, 6, 8, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide in position 7, a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and a U (uridine) to dU (deoxyuridine) substitution in position 1; and the sense strand (SEQ ID NO:82) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, a 2'OMe sugar modified nucleotides at positions 17 and 18, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_50_S1865.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:116) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 3, 5, 9, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide in position 7, a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and a U (uridine) to dU (deoxyuridine) substitution in position 1; and the sense strand (SEQ ID NO:82) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, a 2'OMe sugar modified nucleotides at positions 17 and 18, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_50_S1866.

In some examples a double stranded nucleic acid molecule includes the antisense strand set forth in SEQ ID NO:123 and sense strand set forth in SEQ ID NO:89; identified herein as RHOA_61. In some examples the double stranded nucleic acid molecule has the structure

```
5'     UCUCAUCAUUCCGAAGAUC -Z   3'    (antisense SEQ ID NO:123)
       ||||||||||||||||||||
3' Z'-AGAGUAGUAAGGCUUCUAG -z" 5'    (sense SEQ ID NO:89)
```

wherein each " | " represents base parining between the ribonucleotides;

wherein each of A, C, G, U is independently an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of the sense strand.

In some examples the double stranded nucleic acid molecule comprises modified ribonucleotides and unconventional moieties.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:123) includes a DNA, a mirror nucleotide or a 2'-5' linked nucleotide in one or more of positions 5, 6, 7 or 8 (5'>3'), a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus and one or more 2'OMe sugar modified nucleotides. In some examples the sense strand (SEQ ID NO:89) includes 4 or 5 consecutive 2'-5' linked nucleotides at the 3' terminal or penultimate positions or one or more 2'OMe sugar modified nucleotides, a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus, and a cap moiety covalently attached at the 5' terminus. In some examples the sense strands further includes a DNA, a mirror nucleotide or a 2'5' linked nucleotide in one or both positions 9 and 10.

In some examples a double stranded nucleic acid molecule includes the antisense strand set forth in SEQ ID NO:124 and sense strand set forth in SEQ ID NO:90; identified herein as RHOA_61U. In some examples the double stranded nucleic acid molecule has the structure

```
5'     ACUCAUCAUUCCGAAGAUC -Z  3'    (antisense SEQ ID NO:124)
       ||||||||||||||||||||
3' Z'-UGAGUAGUAAGGCUUCUAG -z" 5'    (sense SEQ ID NO:90)
```

wherein each " | " represents base parining between the ribonucleotides;

wherein each of A, C, G, U is independently an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of the sense strand.

In some examples the double stranded nucleic acid molecule comprises modified ribonucleotides and unconventional moieties.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:124) includes a DNA, a mirror nucleotide or a 2'-5' linked nucleotide in one or more of positions 5, 6, 7 or 8 (5'>3'), a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus and one or more 2'OMe sugar modified nucleotides. In some examples the sense strand (SEQ ID NO:90) includes 4 or 5 consecutive 2'-5' linked nucleotides at the 3' terminal or penultimate positions or one or more 2'OMe sugar modified nucleotides, a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus, and a cap moiety covalently attached at the 5' terminus. In some examples the sense strands further includes a DNA, a mirror nucleotide or a 2'5' linked nucleotide in one or both positions 9 and 10.

In some examples provided herein is a double stranded RNA molecule which includes a sense strand and an antisense strand selected from the oligonucleotide pairs set forth in Table III and identified herein as RHOA_58 (SEQ ID NOS: 143 and 157) and RHOA_70 (SEQ ID NOS: 146 and 160).

In some examples a double stranded nucleic acid molecule includes the antisense strand set forth in SEQ ID NO:157 and sense strand set forth in SEQ ID NO:143; identified herein as RHOA_58. In some examples the double stranded nucleic acid molecule has the structure

```
5'     AGAACUGUAACUCUGCCAC -Z  3'    (antisense SEQ ID NO:157)
       ||||||||||||||||||||
3' Z'-UCUUGACAUUGAGACGGUG -z" 5'    (sense SEQ ID NO:143)
```

wherein each " | " represents base parining between the ribonucleotides;

wherein each of A, C, G, U is independently an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of the sense strand.

In some examples the double stranded nucleic acid molecule comprises modified ribonucleotides and unconventional moieties.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:157) includes a mirror nucleotide or a 2'-5' linked ribonucleotide in one or more of positions 5, 6, 7 or 8 (5'>3'), a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus and one or more 2'OMe sugar modified nucleotides. In some examples the antisense strand further includes a 5' terminal phosphate. In some examples the sense strand (SEQ ID NO:143) includes 4 or 5 consecutive 2'-5' linked nucleotides at the 3' terminal or penultimate positions or one or more 2'OMe sugar modified nucleotides, a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus, and a cap moiety covalently attached at the 5' terminus. In some examples the sense strands further includes (5'>3') a DNA, a mirror nucleotide or a 2'-5' linked nucleotide in one or both positions 9 and 10.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:157) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 4, 6, 8, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide at position 7, and a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and the sense strand (SEQ ID NO:143) includes (5'>3') 5 consecutive 2'-5' linked nucleotides at positions 15, 16, 17, 18 and 19, a C3Pi non-nucleotide moiety covalently attached at the 3' terminus and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_58_S1801.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:157) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 4, 6, 8, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide at position 7, and a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and the sense strand (SEQ ID NO:143) includes (5'>3') 5 consecutive 2'-5' linked nucleotides at positions 15, 16, 17, 18 and 19, a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_58_S1804.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:1157) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 3, 5, 9, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide in positions 7, and a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and the sense strand (SEQ ID NO:143) includes (5'>3') a C3Pi non-nucleotide

moiety covalently attached at the 3' terminus, 2'OMe sugar modified nucleotides at positions 11, 13 and 17, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_58_S1806.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:157) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 4, 8, 11, 13, 15, 17 and 19, a 2'-5' linked nucleotide in position 6, and a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus; and the sense strand (SEQ ID NO:143) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, 2'OMe sugar modified nucleotides at positions 11, 13 and 17, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_58_S1861.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:157) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 4, 8, 11, 13, 15, 17 and 19, a U to dT substitution in position 6, and a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus; and the sense strand (SEQ ID NO:143) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, 2'OMe sugar modified nucleotides at positions 11, 13 and 17, a 2'-5' linked nucleotide at position 9 and an inverted abasic deoxyribonucleotide cap moiety covalently attached at the 5' terminus, set forth in RHOA_58_S1862.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:157) includes (5'>3') 2'OMe sugar modified ribonucleotides at positions 3, 5, 9, 11, 13, 15, 17 and 19, a 2'-5' linked ribonucleotide in positions 7, and a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus and the sense strand (SEQ ID NO:143) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, 2'OMe sugar modified nucleotides at positions 11, 13 and 17, a 2'-5' linked nucleotide at position 9 and a mirror nucleotide (L-deoxyriboguanosine-3'-phosphate) cap moiety covalently attached at the 5' terminus, set forth in RHOA_58_S1877.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:157) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 4, 8, 11, 13, 15, 17 and 19, a 2'-5' linked nucleotide in position 6, and a C3Pi-

C3OH non-nucleotide moiety covalently attached at the 3' terminus; and the sense strand (SEQ ID NO:143) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, 2'OMe sugar modified nucleotides at positions 11, 13 and 17, a 2'-5' linked nucleotide at position 9 and a mirror nucleotide (L-deoxyriboguanosine-3'-phosphate) cap moiety covalently attached at the 5' terminus, set forth in RHOA_58_S1878.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:157) includes (5'>3') 2'OMe sugar modified ribonucleotides in positions 4, 8, 11, 13, 15, 17 and 19, a dT in position 6, and a C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus; and the sense strand (SEQ ID NO:143) includes (5'>3') a C3Pi non-nucleotide moiety covalently attached at the 3' terminus, 2'OMe sugar modified nucleotides at positions 11, 13 and 17, a 2'-5' linked nucleotide at position 9 and a mirror nucleotide (L-deoxyriboguanosine-3'-phosphate) cap moiety covalently attached at the 5' terminus, set forth in RHOA_58_S1879.

In some examples a double stranded nucleic acid molecule includes the antisense strand set forth in SEQ ID NO:160 and sense strand set forth in SEQ ID NO:146; identified herein as RHOA_70. In some examples the double stranded nucleic acid molecule has the structure

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5'     ACUAUCAGGGCUGUCGAUG -Z   3'     (antisense SEQ ID NO:160)
       ||||||||||||||||||||
3' Z'-UGAUAGUCCCGACAGCUAC -z"  5'     (sense SEQ ID NO:146)
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wherein each " | " represents base parining between the ribonucleotides;

wherein each of A, C, G, U is independently an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of the sense strand.

In some examples the double stranded nucleic acid molecule comprises modified ribonucleotides and unconventional moieties.

In some examples provided is a double stranded nucleic acid molecule wherein the antisense strand (SEQ ID NO:160) includes a DNA, a mirror nucleotide or a 2'-5' linked nucleotide in one or more of positions 5, 6, 7 or 8 (5'>3'), a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus and one or more 2'OMe sugar modified nucleotides. In some examples the antisense strand further includes a 5' terminal phosphate. In some examples the sense strand (SEQ ID NO:146) includes 4 or 5 consecutive 2'-5' linked nucleotides at the 3' terminal or penultimate positions or one or more 2'OMe sugar modified nucleotides, a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus, and a cap moiety covalently attached at the 5' terminus. In some examples the sense strands further includes (5'>3') a DNA, a mirror nucleotide or a 2'5' linked nucleotide in one or both positions 9 and 10.

The present disclosure also provides pharmaceutical compositions comprising one or more such nucleic acid compounds according to the present disclosure; and a pharmaceutically acceptable excipient. In some examples the dsRNA is administered as naked dsRNA. In other examples the compound is encapsulated in a drug carrier.

The present disclosure also provides compound according to the present application for use in treating a subject suffering from disease or disorder in the CNS, PNS, vestibular sensory sytem, visual system and/or circulatory (vascular, arterial) system or for use in treating a subject suffering from a malignant disease or disorder, e.g. cancer. Provided herein is a method for prevention, inhibition or treatment of neuronal degeneration caused by injury, disease, disorder or condition in the central nervous system (CNS) and/or the peripheral nervous system (PNS), comprising administering to an individual in need thereof an amount effective to treat said injury, disease, disorder or condition, of a nucleic acid compound according to Structure A1 and/or Structure A2. Also provided is a method for conferring neuroprotection to an individual afflicted with a neurological injury, which comprises administering to said individual a compound according to Structure A1 and/or Structure A2 or pharmaceutically acceptable salt thereof in an amount effective to ameliorate the neurodegeneration associated with said neurological injury.

In another example provided is use of a nucleic acid compound disclosed herein for the preparation of a medicament for the treatment of a disease or disorder in the CNS, PNS, vestibular sensory sytem, visual system and/or circulatory (vascular, arterial) system. In another example provided is use of a nucleic acid compound disclosed herein for the

preparation of a medicament for the treatment of a malignant disease or disorder, e.g. cancer. In some examples, the disclosure provides chemically modified dsRNA oligonucleotides, compositions comprising same and methods of use thereof in the treatment of diseases, disorders, injuries and conditions of the central nervous system (CNS) including, without being limited to, conditions related to neuroregeneration and neuroprotection, injury of the central nervous system (CNS), spinal cord injury (SCI), brain injury, peripheral nerve injury (PNI), neurological disorders, ocular diseases and disorders and diseases and disorders of the vestibular system. In some examples the compounds disclosed herein attenuate neuronal degeneration. Neuronal degeneration includes for example degeneration of the optic nerve and retina including retinal ganglion cells. It also includes degeneration of the auditory nerve, (also known as the vestibulocochlear nerve or acoustic nerve) responsible for transmitting sound and equilibrium information from the inner ear to the brain. The hair cells of the inner ear transmit information to the brain via the auditory nerve, which consists of the cochlear nerve, and the vestibular nerve, and emerges from the medulla oblongata and enters the inner skull via the internal acoustic meatus (or internal auditory meatus) in the temporal bone, along with the facial nerve.

In some examples the present disclosure provides a method of attenuating neuronal degeneration in the optic nerve and or retinal ganglion cells of a subject comprising administering to the subject a therapeutically effective amount of a nucleic acid molecule disclosed herein. In some examples the subject is afflicted with glaucoma or NAION.

In some examples the present disclosure provides a method of attenuating neuronal degeneration in the auditory nerve of a subject comprising administering to the subject a therapeutically effective amount of a nucleic acid molecule disclosed herein. In some examples the subject is afflicted with Meniere's disease.

In some examples the present disclosure provides a method of conferring neuroprotection to the optic nerve and or retinal ganglion cells in a subject comprising administering to the subject a therapeutically effective amount of a nucleic acid molecule disclosed herein. In some examples the subject is afflicted with glaucoma or NAION.

In some examples the present disclosure provides a method of conferring neuroprotection to the auditory nerve and or spiral ganglion cells in a subject comprising

administering to the subject a therapeutically effective amount of a nucleic acid molecule disclosed herein. In some examples the subject is afflicted with Meniere's disease.

In some examples the present disclosure provides a method of treating a neuropathy in a subject comprising administering to the subject a therapeutically effective amount of a nucleic acid molecule disclosed herein. In some examples the subject is afflicted with autonomic neuropathy, cancer-related neuropathy, compressive neuropathy, diabetic neuropathy, drug-induced neuropathy, toxic neuropathy, chemotherapy-induced neuropathy, gastrointestinal neuropathy, nutrition-related neuropathy, hereditary neuropathy, immune-mediated neuropathy and chronic immune-mediated poly neuropathy, infectious neuropathy or neuropatic pain. In some examples the subject is afflicted with diabetic neuropathy. In some examples the subject is afflicted with allodynia. In some examples the present disclosure provides a method of treating a subject suffering from a disease or disorder associated with aberrant and/or disrupted cell motility, cytoskeleton regulation and/or microtubule organization comprising administering to the subject a therapeutically effective amount of a nucleic acid molecule disclosed herein. In some examples the subject is afflicted with angiogenic disorder, vascular diseases and/or arterial diseases. In some examples the subject is suffering from ocular angiogenic disease or disorder, slected from corneal angiogenic disease or disorder, retinal angiogenic disease or disorder, choroidal angiogenic disease or disorder or a combination thereof. In some examples the subject is suffering from retinopathy, e.g., diabetic retinopathy. In some examples the subject is a corneal transplant patient at risk of or suffering from corneal graft rejection. In some examples the subject is at risk of or suffering from restenosis.

Such methods involve administering to a mammal in need of such treatment a prophylactically or therapeutically effective amount of one or more nucleic acid molecules disclosed herein which inhibit or reduce expression or activity of RhoA.

In another example, the present disclosure relates to a method for the treatment of a subject in need of treatment for a disease or disorder or symptoms associated with the disease or disorder, associated with the expression of RhoA, comprising administering to the subject an amount of nucleic acid molecule which reduces or inhibits expression of RhoA set forth in SEQ ID NO:1.

2. The double–stranded nucleic acid molecule of claim 1, wherein in the antisense strand a mirror nucleotide or a 2'-5' linked ribonucleotide is present in at least one of positions 5, 6, 7 or 8 (5'>3'), one or more 2′-O-Methyl sugar-modified ribonucleotide is present and Z is a nucleotide moiety or a non-nucleotide moiety covalently attached at the 3' terminus; and
wherein in the sense strand Z is a nucleotide or non-nucleotide moiety covalently attached at the 3' terminus, one or more 2′-O-Methyl sugar-modified ribonucleotide is present, and z″ is present.

3. The double–stranded nucleic acid molecule of claim 2, wherein in the sense strand 4 or 5 consecutive 2'-5' linked ribonucleotides are present at the 3' terminal or penultimate positions.

4. The double-stranded nucleic acid molecule of claim 2, wherein in the antisense strand (5'>3') 2′-O-Methyl sugar-modified ribonucleotides are present at positions 1, 3, 11, 14, 15, 17 and 18 (5'>3'); and
wherein in the sense strand (5'>3') a 2′-O-Methyl sugar modified ribonucleotide is present at position 1; or
a pharmaceutically acceptable salt of such nucleic acid molecule.

5. The double-stranded nucleic acid molecule of claim 4, wherein in the sense strand 2'-5' linked ribonucleotides are present at positions 15, 16, 17, 18 and 19.

6. The double-stranded nucleic acid molecule of claim 2, wherein in the sense strand Z′ is a non-nucleotide C3Pi moiety covalently attached to the 3 terminus; or

a pharmaceutically acceptable salt of such nucleic acid molecule.