

SNCA iRNA COMPOSITIONS AND METHODS OF USE THEREOF FOR TREATING OR PREVENTING SNCA-ASSOCIATED NEURODEGENERATIVE DISEASES

CROSS-REFERENCE TO RELATED APPLICATION

The present application is related to and claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application No. 63/086,495, entitled “SNCA iRNA Compositions and Methods of Use Thereof for Treating or Preventing SNCA-Associated Neurodegenerative Diseases,” filed October 1, 2020. The entire content of the aforementioned patent application is incorporated herein by this reference.

FIELD OF THE INVENTION

The instant disclosure relates generally to SNCA-targeting RNAi agents and methods.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been filed electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on September 28, 2021, is named BN00007_0161_ALN_364WO_SL.txt and is 687 KB in size.

BACKGROUND OF THE INVENTION

The SNCA gene encodes a presynaptic neuronal protein, α -synuclein (also referred to as alpha-synuclein or synuclein-alpha herein), and has been linked genetically and neuropathologically to Parkinson's disease (PD) (Stefanis, L. *Cold Spring Harb Perspect Med.* 2: a009399). α -Synuclein is viewed to contribute to PD pathogenesis in a number of ways, but it is generally believed that aberrant soluble oligomeric conformations of α -synuclein, termed protofibrils, are the toxic species that mediate disruption of cellular homeostasis and neuronal death, through effects on various intracellular targets, including synaptic function. Furthermore, secreted α -synuclein is believed to exert deleterious effects on neighboring cells, including seeding of aggregation, thus possibly contributing to disease propagation. Although the extent to which α -synuclein is involved in all cases of PD is not clear, targeting the toxic functions conferred by this protein when it is dysregulated presents a potentially valuable therapeutic

strategy, not only for PD, but also for other neurodegenerative conditions, termed synucleinopathies, which all exhibit common neuropathological hallmarks as a result of alpha-synuclein accumulation, referred to as Lewy bodies (LBs) and Lewy neurites (LNs). In addition to PD, such documented or suspected SNCA-related synucleinopathies include, without limitation, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

PD and LBD are the two most prevalent examples of neurodegenerative disorders with SNCA brain pathology. PD is the most common movement disorder and is characterized by rigidity, hypokinesia, tremor and postural instability. PD is believed to affect approximately four to six million people worldwide. LBD represents 5-15 % of all dementia. In addition to forgetfulness and other dementing symptoms that often fluctuate, LBD patients typically suffer from recurrent falls and visual hallucinations.

Apart from the neuropathological changes observed in α -synucleinopathies, levels of α -synuclein protein are generally increased in affected brain regions (Klucken *et al.*, 2006).

α -Synuclein monomers, tetramers and fibrillar aggregates are a major component of Lewy body (LB)-like intraneuronal inclusions, glial inclusions and axonal spheroids in neurodegeneration with brain iron accumulation. Lewy-related pathology (LRP), primarily comprised of α -synuclein, is present in a majority of Alzheimer's autopsies, and higher levels of α -synuclein in patients have been linked to cognitive decline (Twohig *et al.* (2019) *Molecular Neurodegeneration*). Autosomal dominant mutations in the SNCA gene including, among others, A53T, A30P, E46K, and H50Q (Zarranz *et al.* (2004) *Ann. Neurol.* 55,164-173, Choi *et al.* (2004) *FEBS Lett.* 576, 363-368, and Tsigelny *et al.* (2015) *ACS Chem. Neurosci.* 6, 403-416), A53T (Polymeropoulos *et al.* (1997) *Science*), as well as triplications and duplications, have been identified to run in families afflicted with associated neurodegenerative diseases. The preceding indicates that not only pathogenic mutations in SNCA, but also increases in alpha-synuclein protein, impact disease outcome.

The role of SNCA mutations in disease onset is not well understood, however evidence points to a toxic gain-of-function inherent in the normal α -synuclein protein when it exceeds a certain level (Stefanis et al. (2012) *Cold Spring Harb Perspect Med.*) and/or interacts aberrantly with cellular lipids and vesicles (reviewed in Kiechler et al. (2020) *Front. Cell Dev. Biol.*). In apparent agreement with this, SNCA null mice, in contrast to transgenic over-expressors, displayed no overt neuropathological or behavioral phenotype (Abeliovich et al. (2000) *Neuron*). Posttranscriptional regulation of SNCA was also shown to occur through endogenous micro RNAs, binding to the 3' end of the gene (Junn et al. (2009) *PNAS* 106: 13052–13057; Doxakis (2010), *JBC*). Further, studies on the familial point mutations in SNCA demonstrated suppressed expression, especially in cases with prolonged disease onset (Markopoulou et al. (1999) *Ann Neurol.* 46(3):374-81 and Kobayashi et al. (2003) *Brain* 126(Pt 1):32-42). Similarly, Voutsinas et al. (2010) *Hum Mutat.* 31(6):685-91) found that over-expression of even wild-type SNCA messenger RNA (mRNA) was responsible for disease onset. These data indicate that suppression of total SNCA levels would lower α -synuclein-induced toxicity.

There are no disease modifying treatments for synucleinopathies, including PD, multiple system atrophy, and Lewy body dementia, and treatment options are limited, e.g., merely palliative. For example, at present, only symptomatic treatments are available for PD patients (by substituting the loss of active dopamine in the brain) and AD patients (*i.e.*, cholinesterase inhibitors). None of the existing treatment strategies for α -synucleinopathies are directed against the underlying disease processes.

Thus, noting the described involvement of SNCA in several neurodegenerative disorders (synucleinopathies), there remains a need for an agent that can selectively and efficiently silence the SNCA gene (e.g., eliminating or reducing the effect of toxic α -synuclein species) using the cell's own RNAi machinery that has both high biological activity and *in vivo* stability, and that can effectively inhibit expression of a target SNCA gene.

BRIEF SUMMARY OF THE INVENTION

The present disclosure provides RNAi agent compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a Synuclein alpha (SNCA) gene. The SNCA gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The present disclosure also provides methods of using the RNAi agent compositions of the disclosure

for inhibiting the expression of a SNCA gene or for treating a subject who would benefit from inhibiting or reducing the expression of a SNCA gene, *e.g.*, a subject suffering or prone to suffering from a SNCA-associated neurodegenerative disease or disorder, *e.g.*, PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease and Huntington's disease.

Accordingly, in one aspect, the instant disclosure provides a double stranded ribonucleic acid (RNAi) agent for inhibiting expression of SNCA, where the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, where the sense strand harbors a nucleotide sequence including at least 15 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO: 1, or a nucleotide sequence having at least 90% nucleotide sequence identity to a portion of the nucleotide sequence of SEQ ID NO: 1, and the antisense strand harbors a nucleotide sequence including at least 15 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 2, or a nucleotide sequence having at least 90% nucleotide sequence identity to a portion of the nucleotide sequence of SEQ ID NO: 2.

In another aspect, the instant disclosure provides a double stranded ribonucleic acid (RNAi) agent for inhibiting expression of a SNCA gene, where the RNAi agent includes a sense strand and an antisense strand, and where the antisense strand includes a region of complementarity which includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the antisense sequences listed in **Tables 2, 3, 12 or 13**.

Optionally, the sense strand or the antisense strand is conjugated to one or more lipophilic moieties.

In certain embodiments, the sense strand harbors a nucleotide sequence including at least 17 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO: 1, and the antisense strand harbors a nucleotide sequence including at least 17 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of

SEQ ID NO: 2, such that the sense strand is complementary to the at least 17 contiguous nucleotides in the antisense strand.

In some embodiments, the sense strand harbors a nucleotide sequence including at least 19 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO: 1, and the antisense strand harbors a nucleotide sequence including at least 19 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 2, such that the sense strand is complementary to the at least 19 contiguous nucleotides in the antisense strand.

In embodiments, the sense strand harbors a nucleotide sequence including at least 21 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO: 1, and the antisense strand harbors a nucleotide sequence including at least 21 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 2, such that the sense strand is complementary to the at least 21 contiguous nucleotides in the antisense strand.

In certain embodiments, the antisense strand includes a region of complementarity which includes at least 15 contiguous nucleotides of any one of the antisense sequences listed in **Tables 2, 3, 12 or 13**. In certain embodiments, the antisense strand includes a region of complementarity which includes at least 19 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the antisense sequences listed in **Tables 2, 3, 12 or 13**. In certain embodiments, the antisense strand includes a region of complementarity which includes at least 19 contiguous nucleotides of any one of the antisense sequences listed in **Tables 2, 3, 12 or 13**. In certain embodiments, thymine-to-uracil or uracil-to-thymine differences between aligned (compared) sequences are not counted as nucleotides that differ between the aligned (compared) sequences.

In some embodiments, the agents include one or more lipophilic moieties conjugated to one or more nucleotide positions (optionally internal nucleotide positions), optionally via a linker or carrier. In certain embodiments, the lipophilic moiety is conjugated to one or more positions in the double stranded region of the dsRNA agent. Optionally, the one or more lipophilic moieties are conjugated to at least the sense strand. In certain embodiments, the one or more lipophilic moieties are conjugated to at least the antisense strand. In embodiments, the one or more lipophilic moieties are conjugated to both strands.

In embodiments, lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

In some embodiments, the hydrophobicity of the double-stranded RNAi agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNAi agent, exceeds 0.2. Optionally, the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

Another aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene, where the dsRNA agent includes a sense strand and an antisense strand, where the sense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the sense strand sequences presented in **Tables 2, 3, 12 or 13**; and where the antisense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of antisense strand nucleotide sequences presented in **Tables 2, 3, 12 or 13**. In certain embodiments, the sense strand includes at least 15 contiguous nucleotides of any one of the sense strand sequences presented in **Tables 2, 3, 12 or 13**; and where the antisense strand includes at least 15 contiguous nucleotides of any one of antisense strand nucleotide sequences presented in **Tables 2, 3, 12 or 13**. In certain embodiments, the sense strand includes at least 19 contiguous nucleotides of any one of the sense strand sequences presented in **Tables 2, 3, 12 or 13**; and where the antisense strand includes at least 19 contiguous nucleotides of any one of antisense strand nucleotide sequences presented in **Tables 2, 3, 12 or 13** (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of antisense strand nucleotide sequences presented in **Tables 2, 3, 12 or 13**.

An additional aspect of the disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene, where the dsRNA agent includes a sense strand and an antisense strand, where the sense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 1, 3, 5, or 7, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of any one of SEQ ID NOs: 1, 3, 5, or 7, where a substitution of a uracil for any thymine of SEQ ID NOs: 1, 3, 5, or 7 (when comparing aligned sequences) does not count as a difference that contributes to the differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 1, 3, 5, or 7, or the nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95,

96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of any one of SEQ ID NOs: 1, 3, 5, or 7; and where the antisense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NOs: 2, 4, 6, or 8, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of any one of SEQ ID NOs: 2, 4, 6, or 8, where a substitution of a uracil for any thymine of SEQ ID NOs: 2, 4, 6, or 8 (when comparing aligned sequences) does not count as a difference that contributes to the differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NOs: 2, 4, 6, or 8, or the nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of any one of SEQ ID NOs: 2, 4, 6, or 8, where at least one of the sense strand and the antisense strand includes one or more lipophilic moieties conjugated to one or more internal nucleotide positions, optionally via a linker or carrier.

In one embodiment, the double stranded RNAi agent targeted to SNCA comprises a sense strand which includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from the nucleotide sequence of the sense strand nucleotide sequence of a duplex in **Tables 2, 3, 12 or 13**.

In one embodiment, the double stranded RNAi agent targeted to SNCA comprises an antisense strand which includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from the antisense nucleotide sequence of a duplex in one of **Tables 2, 3, 12 or 13**.

Optionally, the double stranded RNAi agent includes at least one modified nucleotide. In embodiments, no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides.

In certain embodiments, substantially all of the nucleotides of the sense strand are modified nucleotides. Optionally, all of the nucleotides of the sense strand are modified nucleotides.

In some embodiments, substantially all of the nucleotides of the antisense strand are modified nucleotides. Optionally, all of the nucleotides of the antisense strand are modified nucleotides.

Optionally, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, at least one of the modified nucleotides is a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, or a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group.

In a related embodiment, the modified nucleotide is a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxy-thymine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

In one embodiment, the modified nucleotide includes a short sequence of 3'-terminal deoxy-thymine nucleotides (dT).

In another embodiment, the modifications on the nucleotides are 2'-O-methyl, 2' fluoro and GNA modifications.

In an additional embodiment, the double stranded RNAi agent includes at least one phosphorothioate internucleotide linkage. Optionally, the double stranded RNAi agent includes 6-8 (*e.g.*, 6, 7, or 8) phosphorothioate internucleotide linkages.

In certain embodiments, the region of complementarity is at least 17 nucleotides in length. Optionally, the region of complementarity is 19-23 nucleotides in length. Optionally, the region of complementarity is 19 nucleotides in length.

In one embodiment, each strand is no more than 30 nucleotides in length.

In another embodiment, at least one strand includes a 3' overhang of at least 1 nucleotide. Optionally, at least one strand includes a 3' overhang of at least 2 nucleotides.

In embodiments, the double stranded region is 15-30 nucleotide pairs in length.

Optionally, the double stranded region is 17-23 nucleotide pairs in length.

In some embodiments, the double stranded region is 17-25 nucleotide pairs in length.

In certain embodiments, the double stranded region is 23-27 nucleotide pairs in length.

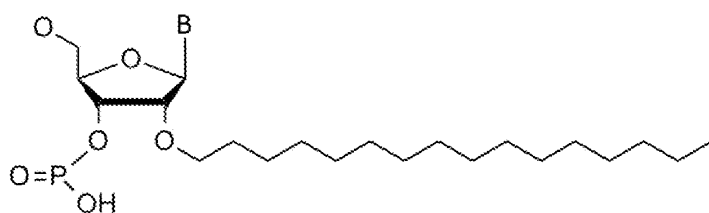
In embodiments, the double stranded region is 19-21 nucleotide pairs in length.

In another embodiment, the double stranded region is 21-23 nucleotide pairs in length.

In embodiments, each strand has 19-30 nucleotides. Optionally, each strand has 19-23 nucleotides. In certain embodiments, each strand has 21-23 nucleotides.

In some embodiments, the double stranded RNAi agent further includes a lipophilic ligand, *e.g.*, a C16 ligand, conjugated to the 3' end of the sense strand through a monovalent or branched bivalent or trivalent linker.

In one embodiment, the ligand is



where B is a nucleotide base or a nucleotide base analog, optionally where B is adenine, guanine, cytosine, thymine or uracil.

In other embodiments, the agent further comprises a targeting ligand that targets a liver tissue, *e.g.*, one or more GalNAc derivatives, optionally conjugated to the double stranded RNAi agent via a linker or carrier.

In yet other embodiments, the agents further comprise a lipophilic ligand, *e.g.*, a C16 ligand, conjugated to the 3' end of the sense strand through a monovalent or branched bivalent or trivalent linker and a targeting ligand that targets a liver tissue, *e.g.*, one or more GalNAc derivatives conjugated to the 3' end of the sense strand through a monovalent or branched bivalent or trivalent linker.

In another embodiment, the region of complementarity to SNCA includes any one of the antisense sequences in **Tables 2, 3, 12 or 13**.

In an additional embodiment, the region of complementarity to SNCA is that of any one of the antisense sequences in **Tables 2, 3, 12 or 13**. In some embodiments, the internal nucleotide positions include all positions except the terminal two positions from each end of the strand.

In a related embodiment, the internal positions include all positions except terminal three positions from each end of the strand. Optionally, the internal positions exclude the cleavage site region of the sense strand.

In some embodiments, the internal positions exclude positions 9-12, counting from the 5'-end of the sense strand. In certain embodiments, the sense strand is 21 nucleotides in length.

In other embodiments, the internal positions exclude positions 11-13, counting from the 3'-end of the sense strand. Optionally, the internal positions exclude the cleavage site region of the antisense strand. In certain embodiments, the sense strand is 21 nucleotides in length.

In some embodiments, the internal positions exclude positions 12-14, counting from the 5'-end of the antisense strand. In certain embodiments, the antisense strand is 23 nucleotides in length.

In another embodiment, the internal positions excluding positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end. In certain embodiments, the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

In an additional embodiment, one or more lipophilic moieties are conjugated to one or more of the following internal positions: positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5' end of each strand. Optionally, one or more lipophilic moieties are conjugated to one or more of the following internal positions: positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand. In certain embodiments, the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

Optionally, the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.

In certain embodiments, the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.

In embodiments, the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.

In some embodiments, the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.

In embodiments, the lipophilic moiety is conjugated to position 16 of the antisense strand.

In certain embodiments, the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound. Optionally, the lipophilic moiety is lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

In some embodiments, the lipophilic moiety contains a saturated or unsaturated C₄-C₃₀ hydrocarbon chain, and an optional functional group selected that is hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, or alkyne.

In certain embodiments, the lipophilic moiety contains a saturated or unsaturated C₆-C₁₈ hydrocarbon chain. Optionally, the lipophilic moiety contains a saturated or unsaturated C₁₆ hydrocarbon chain. In a related embodiment, the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s). In certain embodiments, the carrier is a cyclic group that is pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, or decalanyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

In embodiments, the saturated or unsaturated C₁₆ hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

In some embodiments, the lipophilic moiety is conjugated to the double-stranded RNAi agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

In one embodiment, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

In another embodiment, the double-stranded RNAi agent further includes a phosphate or phosphate mimic at the 5'-end of the antisense strand. In one embodiment, the phosphate mimic is a 5'-vinyl phosphonate (VP). In another embodiment, the phosphate mimic is a 5'-cyclopropyl phosphonate.

In certain embodiments, the double-stranded RNAi agent further includes a targeting ligand that targets a receptor which mediates delivery to a CNS tissue, *e.g.*, a hydrophilic ligand. In certain embodiments, the targeting ligand is a C16 ligand.

In some embodiments, the double-stranded RNAi agent further includes a targeting ligand that targets a brain tissue, *e.g.*, striatum.

In some embodiments, the double-stranded RNAi agent further includes a targeting ligand that targets a liver tissue, *e.g.*, hepatocytes.

In one embodiment, the lipophilic moiety or targeting ligand is conjugated via a bio-cleavable linker that is DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, or a combination thereof.

In a related embodiment, the 3' end of the sense strand is protected via an end cap which is a cyclic group having an amine, the cyclic group being pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, or decalinyl.

In one embodiment, the RNAi agent includes at least one modified nucleotide that is a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a nucleotide that includes a glycol nucleic acid (GNA) or a nucleotide that includes a vinyl phosphonate. Optionally, the RNAi agent includes at least one of each of the following modifications: 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a nucleotide comprising a glycol nucleic acid (GNA) and a nucleotide comprising vinyl phosphonate.

In another embodiment, the RNAi agent includes a pattern of modified nucleotides as provided below in **Tables 2 or 12**, optionally where locations of 2'-C16, 2'-O-methyl, GNA, phosphorothioate and 2'-fluoro modifications are irrespective of the individual nucleotide base sequences of the displayed RNAi agents.

In embodiments, the dsRNA agent further includes: a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; or a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.

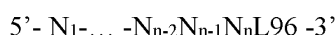
In some embodiments, the dsRNA agent further includes: a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; or a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In certain embodiments, the dsRNA agent further includes: a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; or a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

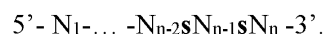
In embodiments, the dsRNA agent further includes: a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; or a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further includes: a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration; a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration; or a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In other embodiments, each of the duplexes of **Tables 2, 9, and 12** may be particularly modified to provide another double-stranded iRNA agent of the present disclosure. In one example, the 3'-terminus of each sense strand may be modified by removing the 3'-terminal L96 ligand and exchanging the two phosphodiester internucleotide linkages between the three 3'-terminal nucleotides with phosphorothioate internucleotide linkages. That is, the three 3'-terminal nucleotides (N) of a sense sequence of the formula:



may be replaced with



That is, for example, for AD-1549052, the sense sequence:



may be replaced with



while the antisense sequence remains unchanged to provide another double-stranded iRNA agent of the present disclosure. In other examples, the sense strand of each of the following duplexes are modified according to the preceding description to provide a duplex of the disclosure: AD-596172, AD-596323, AD-596177, AD-596137, AD-596130, AD-596231, AD-595926, AD-596124, AD-596133, AD-595854, AD-596175, AD-596170, AD-596436, AD-596319, AD-596168, AD-596215, AD-596425, AD-595769, AD-596171, AD-596392, AD-596402, AD-596144, AD-596396, AD-596517, AD-596426, AD-596169, AD-596391, AD-596320, AD-596283, AD-596362, AD-596431, AD-596515, AD-596128, AD-596235, AD-596322, AD-596427, AD-596127, AD-595855, AD-596129, and AD-595866. In other examples, the sense strand of each of the following duplexes are modified according to the preceding description to provide a duplex of

the disclosure: AD-596137.1, AD-596319.1, AD-596177.1, AD-596172.1, AD-596323.1, AD-596215.1, AD-596231.1, AD-596170.1, AD-596168.1, AD-596130.1, AD-595854.1, AD-595926.1, AD-596133.1, AD-596175.1, AD-596171.1, AD-595769.1, AD-596392.1, AD-596425.1, AD-596515.1, AD-596144.1, AD-596436.1, AD-596124.1, AD-596402.1, AD-596517.1, AD-596391.1, AD-596169.1, AD-596396.1, AD-596427.1, AD-596426.1, AD-595866.1, AD-596431.1, AD-596362.1, AD-596320.1, AD-595855.1, AD-596235.1, AD-596283.1, AD-596129.1, AD-596390.1, AD-596131.1, AD-58643.17, AD-596322.1, AD-596128.1, and AD-596127.1. In other examples, the sense strand of each of the following duplexes are modified according to the preceding description to provide a duplex of the disclosure: AD-595769.2, AD-595770.1, AD-595773.1, AD-595774.1, AD-595926.2, AD-595933.1, AD-595935.1, AD-595937.1, AD-595938.1, AD-596099.1, AD-596215.2, AD-596217.1, AD-596276.1, AD-596328.1, AD-596390.2, AD-596391.2, AD-596392.2, AD-596393.1, AD-596394.1, AD-596395.1, AD-596396.2, AD-596397.1, AD-596398.1, AD-596401.1, AD-596402.2, AD-596403.1, AD-596521.1, AD-596564.1, AD-689314.1, AD-689315.1, AD-689316.1, AD-689318.1, AD-689319.1, AD-689320.1, AD-689452.1, AD-689459.1, AD-689461.1, AD-689462.1, AD-689463.1, AD-689464.1, AD-689615.1, AD-689616.1, AD-689747.1, AD-689748.1, AD-689753.1, AD-689755.1, AD-689786.1, AD-689787.1, AD-689788.1, AD-689835.1, AD-689907.1, AD-689925.1, AD-689926.1, AD-689927.1, AD-689928.1, AD-689929.1, AD-689930.1, AD-689931.1, AD-689932.1, AD-689933.1, AD-689934.1, AD-689935.1, AD-689936.1, AD-689937.1, AD-689938.1, AD-689939.1, AD-690068.1, AD-690079.1, AD-690080.1, AD-690092.1, AD-691823.1, AD-691824.1, AD-691843.1, AD-691844.1, AD-691845.1, AD-691875.1, AD-691953.1, AD-691954.1. In other examples, the sense strand of each of the following duplexes are modified according to the preceding description to provide a duplex of the disclosure: AD-1549052.1, AD-1549359.1, AD-1549054.1, AD-1571262.1, AD-1549333.1, AD-1549407.1, AD-1548854.1, AD-1549403.1, AD-1549283.1, AD-1549641.1, AD-1549267.1, AD-1548851.1, AD-1548869.1, AD-1549272.1, AD-1571164.1, AD-1549354.1, AD-1571188.1, AD-1549401.1, AD-1548886.1, AD-1571191.1, AD-1571193.1, AD-1548884.1, AD-1571187.1, AD-1549357.1, AD-1571194.1, AD-1549285.1, AD-1549266.1, AD-1549351.1, AD-1548870.1, AD-1549245.1, AD-1549334.1, AD-1549397.1, AD-1549290.1, AD-1549525.1, AD-1549406.1, AD-1549284.1, AD-1549439.1, AD-1549269.1, AD-1549518.1, AD-1549628.1, AD-1571199.1, AD-1549442.1, AD-1549596.1, AD-1549400.1, AD-

1549280.1, AD-1549441.1, AD-1549556.1, AD-1571202.1, AD-1549271.1, AD-1549517.1, AD-1549293.1, AD-1549639.1, AD-1549443.1, AD-1571195.1, AD-1549595.1, AD-1549546.1, AD-1549246.1, AD-1571192.1, AD-1571165.1, AD-1549270.1, AD-1549521.1, AD-1549541.1, AD-1549552.1, AD-1549522.1, AD-1549545.1, AD-1549519.1, AD-1549630.1, AD-1549353.1, AD-1549544.1, AD-1549642.1, AD-1549438.1, AD-1549412.1, AD-1571198.1, AD-1571258.1, AD-1571201.1, AD-1549640.1, AD-1571266.1, AD-1571172.1, AD-1549527.1, AD-1549547.1, AD-1549037.1, AD-1571205.1, AD-1549053.1, AD-1571264.1, AD-1571186.1, AD-1571204.1, AD-1549555.1, AD-1548887.1, AD-1549426.1, AD-1548844.1, AD-1549520.1, AD-1549543.1, AD-1549548.1, AD-1571206.1, AD-1549210.1, AD-1571200.1, AD-1571207.1, AD-1549542.1, AD-1549211.1, AD-1571263.1, AD-1549391.1, AD-1549212.1, AD-1549268.1, AD-1549352.1, AD-1571261.1, AD-1549044.1, AD-1549554.1, AD-1548975.1, AD-1549432.1, AD-1549524.1, AD-1549643.1, AD-1571196.1, AD-1571203.1, AD-1549425.1, AD-1549264.1, AD-1549249.1, AD-1571257.1, AD-1549265.1, AD-1548843.1, AD-1548845.1, AD-1571256.1, AD-1571255.1, AD-1571174.1, AD-1571173.1, AD-1548876.1, AD-1549615.1, AD-1571166.1, AD-1571269.1, AD-1548976.1, AD-1549038.1, AD-1571167.1, AD-1571170.1, AD-1548888.1, AD-1571189.1, AD-1571259.1, AD-1549224.1, AD-1571208.1, AD-1549222.1, AD-1571268.1, AD-1571270.1, AD-1549217.1, AD-1571184.1, AD-1571271.1, AD-1571272.1, AD-1571190.1, AD-1549055.1, AD-1571169.1, and AD-1571265.1.

An additional aspect of the instant disclosure provides a cell harboring a dsRNA agent of the instant disclosure.

One aspect of the instant disclosure provides a pharmaceutical composition for inhibiting expression of a gene encoding SNCA that includes a dsRNA agent of the instant disclosure.

An additional aspect of the disclosure provides a method of inhibiting expression of a SNCA gene in a cell, the method involving: (a) contacting the cell with a double stranded RNAi agent of the instant disclosure or a pharmaceutical composition of the instant disclosure; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a SNCA gene, thereby inhibiting expression of the SNCA gene in the cell.

In one embodiment, the cell is within a subject. Optionally, the subject is a human.

In certain embodiments, the subject is a rhesus monkey, a cynomolgous monkey, a mouse, or a rat.

In embodiments, the expression of SNCA is inhibited by at least 50%.

In certain embodiments, the subject meets at least one diagnostic criterion for a SNCA-associated disease.

In certain embodiments, the human subject has been diagnosed with or suffers from a SNCA-associated neurodegenerative disease, *e.g.*, a synucleinopathy, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

In certain embodiments, the method further involves administering an additional therapeutic agent or therapy to the subject. Exemplary additional therapeutics and treatments include, for example, sedatives, antidepressants, clonazepam, sodium valproate, opiates, antiepileptic drugs, cholinesterase inhibitors, memantine, benzodiazepines, levodopa, COMT inhibitors (*e.g.*, tolcapone and entacapone), dopamine agonists (*e.g.*, bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine and lisuride), MAO-B inhibitors (*e.g.*, safinamide, selegiline and rasagiline), amantadine, an anticholinergic, modafinil, pimavanserin, doxepin, rasagiline, an antipsychotic, an atypical antipsychotic (*e.g.*, amisulpride, olanzapine, risperidone, and clozapine), riluzole, edaravone, deep brain stimulation, non-invasive ventilation (NIV), invasive ventilation physical therapy, occupational therapy, speech therapy, dietary changes and swallowing technique a feeding tube, a PEG tube, probiotics, and psychological therapy.

In certain embodiments, the double stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 50 mg/kg.

In some embodiments, the double stranded RNAi agent is administered to the subject intrathecally.

In one embodiment, the method reduces the expression of a SNCA gene in a brain (*e.g.*, striatum) or spine tissue. Optionally, the brain or spine tissue is striatum, cortex, cerebellum, cervical spine, lumbar spine, or thoracic spine.

In some embodiments, the double stranded RNAi agent is administered to the subject subcutaneously.

In one embodiment, the method reduces the expression of a SNCA gene in the liver.

In other embodiments, the method reduces the expression of a SNCA gene in the liver and the brain.

Another aspect of the instant disclosure provides a method of treating a subject diagnosed with a SNCA-associated neurodegenerative disease, the method involving administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition of the instant disclosure, thereby treating the subject.

In one embodiment, treating involves amelioration of at least one sign or symptom of the disease.

In certain embodiments, treating includes prevention of progression of the disease.

In embodiments, the SNCA-associated disease is characterized by symptoms of Parkinson's Disease (PD), such as tremors, slowed movement (bradykinesia), rigid muscles, impaired posture and balance, loss of automatic movements, speech changes, writing changes; symptoms of Lewy body dementia such as visual, auditory, olfactory, or tactile hallucinations, signs of Parkinson's disease (parkinsonian signs), poor regulation of body functions (autonomic nervous systems) such as dizziness, falls and bowel issues, cognitive problems such as confusion, poor attention, visual-spatial problems and memory loss, sleep difficulties such as rapid eye movement (REM) sleep behavior disorder (in which dreams are physically acted out while asleep), fluctuating attention including episodes of drowsiness, long periods of staring into space, long naps during the day or disorganized speech, depression, and apathy, symptoms of pure autonomic failure such as orthostatic hypotension (a sudden drop in blood pressure that occurs when a person stands up, causing a person to feel dizzy and lightheaded, and the need to sit, squat, or lie down in order to prevent fainting), symptoms of multiple system atrophy such as slowness of movement, tremor, rigidity (stiffness), clumsiness or incoordination, impaired speech, a croaky, quivering voice, fainting or lightheadedness due to orthostatic hypotension, bladder control problems, such as a sudden urge to urinate or difficulty emptying the bladder, contractures (chronic shortening of muscles or tendons around joints, which prevents the joints from moving freely) in the hands or limbs, Pisa syndrome (an abnormal posture in which the body appears to be leaning to one side), antecollis (in which the neck bends forward and the head drops down), involuntary and

uncontrollable sighing or gasping, and sleep difficulties such as rapid eye movement (REM) sleep behavior disorder.

In certain embodiments, the SNCA-associated disease is a synucleinopathy, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomatosis, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

An additional aspect of the disclosure provides a method of preventing development of a SNCA-associated neurodegenerative disease in a subject meeting at least one diagnostic criterion for a SNCA-associated neurodegenerative disease, the method involving administering to the subject a therapeutically effective amount of a dsRNA agent or pharmaceutical composition of the disclosure, thereby preventing the development of a SNCA-associated neurodegenerative disease in the subject meeting at least one diagnostic criterion for a SNCA-associated neurodegenerative disease.

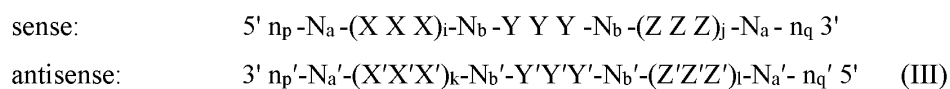
In certain embodiments, the method further involves administering to the subject an additional agent or a therapy suitable for treatment or prevention of a SNCA-associated disease or disorder.

Another aspect of the instant disclosure provides a method of inhibiting the expression of SNCA in a subject, the method involving: administering to the subject a therapeutically effective amount of a double stranded RNAi agent of the disclosure or a pharmaceutical composition of the disclosure, thereby inhibiting the expression of SNCA in the subject.

An additional aspect of the disclosure provides a method for treating or preventing a disorder or SNCA-associated neurodegenerative disease or disorder in a subject, the method involving administering to the subject a therapeutically effective amount of a double stranded RNAi agent of the disclosure or a pharmaceutical composition of the disclosure, thereby treating or preventing a SNCA-associated neurodegenerative disease or disorder in the subject.

Another aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene, where the double stranded RNAi agent includes a sense

strand complementary to an antisense strand, where the antisense strand includes a region complementary to part of an mRNA encoding SNCA, where each strand is about 14 to about 30 nucleotides in length, where the double stranded RNAi agent is represented by formula (III):



where:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and $N_{a'}$ independently represents an oligonucleotide sequence including 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence including at least two differently modified nucleotides;

each N_b and $N_{b'}$ independently represents an oligonucleotide sequence including 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p , $n_{p'}$, n_q , and $n_{q'}$, each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides; modifications on N_b differ from the modification on Y and modifications on $N_{b'}$ differ from the modification on Y'; and

where the sense strand is conjugated to at least one ligand.

In one embodiment, i is 0; j is 0; i is 1; j is 1; both i and j are 0; or both i and j are 1.

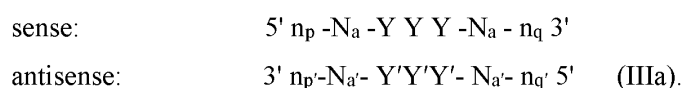
In another embodiment, k is 0; l is 0; k is 1; l is 1; both k and l are 0; or both k and l are 1.

In certain embodiments, XXX is complementary to X'X'X', YYY is complementary to Y'Y'Y', and ZZZ is complementary to Z'Z'Z'.

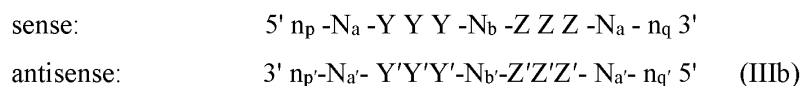
In another embodiment, the YYY motif occurs at or near the cleavage site of the sense strand.

In an additional embodiment, the Y'Y'Y' motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end. Optionally, the Y' is 2'-O-methyl.

In some embodiments, formula (III) is represented by formula (IIIa):

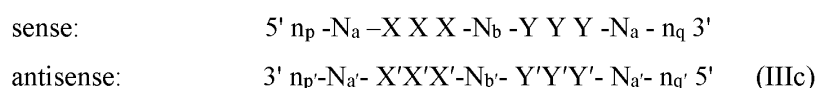


In another embodiment, formula (III) is represented by formula (IIIb):



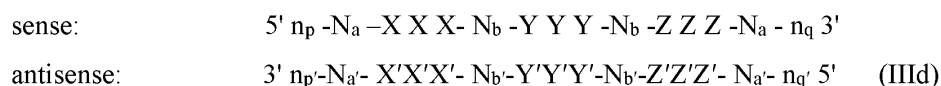
where each N_b and N_b' independently represents an oligonucleotide sequence including 1-5 modified nucleotides.

In an additional embodiment, formula (III) is represented by formula (IIIc):



where each N_b and N_b' independently represents an oligonucleotide sequence including 1-5 modified nucleotides.

In certain embodiments, formula (III) is represented by formula (IIId):



where each N_b and N_b' independently represents an oligonucleotide sequence including 1-5 modified nucleotides and each N_a and N_a' independently represents an oligonucleotide sequence including 2-10 modified nucleotides.

In another embodiment, the double stranded region is 15-30 nucleotide pairs in length. Optionally, the double stranded region is 17-23 nucleotide pairs in length.

In certain embodiments, the double stranded region is 17-25 nucleotide pairs in length. Optionally, the double stranded region is 23-27 nucleotide pairs in length.

In some embodiments, the double stranded region is 19-21 nucleotide pairs in length. Optionally, the double stranded region is 21-23 nucleotide pairs in length.

In certain embodiments, each strand has 15-30 nucleotides. Optionally, each strand has 19-30 nucleotides. Optionally, each strand has 19-23 nucleotides.

In certain embodiments, the double stranded region is 19-21 nucleotide pairs in length and each strand has 19-23 nucleotides.

In another embodiment, the modifications on the nucleotides of the RNAi agent are LNA, glycol nucleic acid (GNA), HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy or 2'-hydroxyl, and combinations thereof. Optionally, the modifications on nucleotides include 2'-O-methyl, 2'-fluoro or GNA, and combinations thereof. In a related embodiment, the modifications on the nucleotides are 2'-O-methyl or 2'-fluoro modifications.

In one embodiment the RNAi agent includes a ligand that is or includes one or more lipophilic, *e.g.*, C16, moieties attached through a bivalent or trivalent branched linker.

In other embodiments, the agent further comprises a targeting ligand that targets a liver tissue, *e.g.*, one or more GalNAc derivatives.

In yet other embodiments, the agents further comprise a lipophilic ligand, *e.g.*, a C16 ligand, conjugated to the 3' end of the sense strand through a monovalent or branched bivalent or trivalent linker and a targeting ligand that targets a liver tissue, *e.g.*, one or more GalNAc derivatives conjugated to the 3' end of the sense strand through a monovalent or branched bivalent or trivalent linker.

In certain embodiments, the ligand is attached to the 3' end of the sense strand.

In some embodiments, the RNAi agent further includes at least one phosphorothioate or methylphosphonate internucleotide linkage. In a related embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. Optionally, the strand is the antisense strand. In another embodiment, the strand is the sense strand. In a related embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. Optionally, the strand is the antisense strand. In another embodiment, the strand is the sense strand.

In another embodiment, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. Optionally, the strand is the antisense strand. In another embodiment, the strand is the sense strand.

In an additional embodiment, the base pair at the 1 position of the 5'-end of the antisense strand of the RNAi agent duplex is an A:U base pair.

In certain embodiments, the Y nucleotides contain a 2'-fluoro modification.

In some embodiments, the Y' nucleotides contain a 2'-O-methyl modification.

In certain embodiments, $p' > 0$. Optionally, $p' = 2$.

In some embodiments, $q' = 0$, $p = 0$, $q = 0$, and p' overhang nucleotides are complementary to the target mRNA.

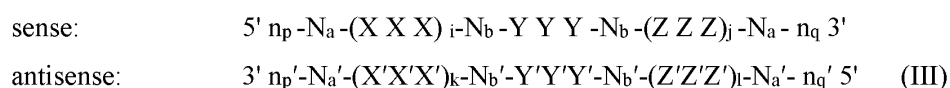
In certain embodiments, $q' = 0$, $p = 0$, $q = 0$, and p' overhang nucleotides are non-complementary to the target mRNA.

In one embodiment, the sense strand of the RNAi agent has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

In another embodiment, at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage. Optionally, all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

In certain embodiments, the SNCA RNAi agent of the instant disclosure is one of those listed in **Tables 2, 3, 12 or 13**. In some embodiments, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand include a modification.

Another aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene in a cell, where the double stranded RNAi agent includes a sense strand complementary to an antisense strand, where the antisense strand includes a region complementary to part of an mRNA encoding a SNCA gene, where each strand is about 14 to about 30 nucleotides in length, where the double stranded RNAi agent is represented by formula (III):



where:

$i, j, k,$ and l are each independently 0 or 1;

$p, p', q,$ and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence including 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence including at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence including 0-10 nucleotides which are either modified or unmodified or combinations thereof;

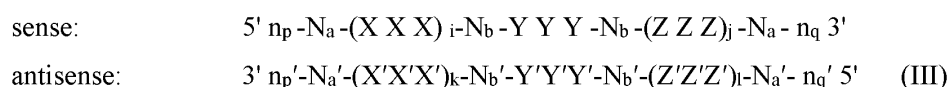
each $n_p, n_p', n_q,$ and n_q' , each of which may or may not be present independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and where the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

where the sense strand is conjugated to at least one ligand, optionally where the ligand is one or more lipophilic, *e.g.*, C16, ligands, or one or more GalNAc derivatives.

An additional aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene in a cell, where the double stranded RNAi agent includes a sense strand complementary to an antisense strand, where the antisense strand includes a region complementary to part of an mRNA encoding SNCA, where each strand is about 14 to about 30 nucleotides in length, where the double stranded RNAi agent is represented by formula (III):



where:

i, j, k, and l are each independently 0 or 1;

each n_p , n_q , and n_q' , each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q' are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence including 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence including at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence including 0-10 nucleotides which are either modified or unmodified or combinations thereof;

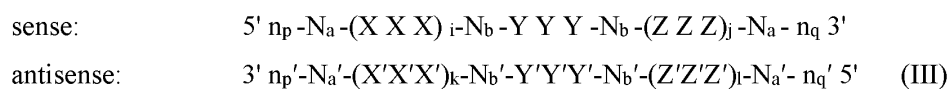
XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides, and where the modifications are 2'-O-methyl, glycol nucleic acid (GNA) or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y'; and

where the sense strand is conjugated to at least one ligand, optionally where the ligand is one or more lipophilic, *e.g.*, C16, ligands, or one or more GalNAc derivatives.

Another aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene in a cell, where the double stranded RNAi agent includes a sense strand complementary to an antisense strand, where the antisense strand includes a region complementary to part of an mRNA encoding SNCA (SEQ ID NO: 1, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100%

identity, to the entire nucleotide sequence of SEQ ID NO: 1), where each strand is about 14 to about 30 nucleotides in length, where the double stranded RNAi agent is represented by formula (III):



where:

$i, j, k,$ and l are each independently 0 or 1;

each $n_p, n_q,$ and $n_{q'}$, each of which may or may not be present, independently represents an overhang nucleotide;

$p, q,$ and q' are each independently 0-6;

$n_{p'} > 0$ and at least one $n_{p'}$ is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and $N_{a'}$ independently represents an oligonucleotide sequence including 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence including at least two differently modified nucleotides;

each N_b and $N_{b'}$ independently represents an oligonucleotide sequence including 0-10 nucleotides which are either modified or unmodified or combinations thereof;

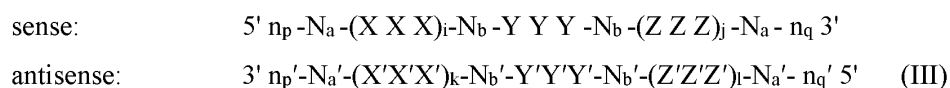
$XXX, YYY, ZZZ, X'X'X', Y'Y'Y',$ and $Z'Z'Z'$ each independently represent one motif of three identical modifications on three consecutive nucleotides, and where the modifications are 2'-O-methyl or 2'-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on $N_{b'}$ differ from the modification on Y' ; and

where the sense strand is conjugated to at least one ligand, optionally where the ligand is one or more lipophilic, *e.g.*, C16, ligands, or one or more GalNAc derivatives.

An additional aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene in a cell, where the double stranded RNAi agent includes a sense strand complementary to an antisense strand, where the antisense strand includes a region complementary to part of an mRNA encoding SNCA (SEQ ID NO: 1, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of SEQ ID NO: 1), where each strand is about 14 to

about 30 nucleotides in length, where the double stranded RNAi agent is represented by formula (III):



where:

$i, j, k,$ and l are each independently 0 or 1;

each $n_p, n_q,$ and $n_{q'}$, each of which may or may not be present, independently represents an overhang nucleotide;

$p, q,$ and q' are each independently 0-6;

$n_{p'} > 0$ and at least one $n_{p'}$ is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and $N_{a'}$ independently represents an oligonucleotide sequence including 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence including at least two differently modified nucleotides;

each N_b and $N_{b'}$ independently represents an oligonucleotide sequence including 0-10 nucleotides which are either modified or unmodified or combinations thereof;

$XXX, YYY, ZZZ, X'X'X', Y'Y'Y',$ and $Z'Z'Z'$ each independently represent one motif of three identical modifications on three consecutive nucleotides, and where the modifications are 2'-O-methyl or 2'-fluoro modifications;

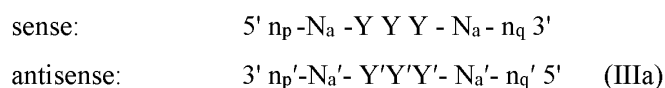
modifications on N_b differ from the modification on Y and modifications on $N_{b'}$ differ from the modification on Y' ;

where the sense strand includes at least one phosphorothioate linkage; and

where the sense strand is conjugated to at least one ligand, optionally where the ligand is one or more lipophilic, *e.g.*, C16, ligands or one or more GalNAc derivatives.

Another aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene in a cell, where the double stranded RNAi agent includes a sense strand complementary to an antisense strand, where the antisense strand includes a region complementary to part of an mRNA encoding SNCA (SEQ ID NO: 1, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of SEQ ID NO: 1), where each strand is about 14 to

about 30 nucleotides in length, where the double stranded RNAi agent is represented by formula (III):



where:

each n_p , n_q , and n_q' , each of which may or may not be present, independently represents an overhang nucleotide;

p , q , and q' are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence including 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence including at least two differently modified nucleotides;

YYY and Y'Y'Y' each independently represent one motif of three identical modifications on three consecutive nucleotides, and where the modifications are 2'-O-methyl or 2'-fluoro modifications;

where the sense strand includes at least one phosphorothioate linkage; and

where the sense strand is conjugated to at least one ligand, optionally where the ligand is one or more lipophilic, *e.g.*, C16 ligands, or one or more GalNAc derivatives.

An additional aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene, where the double stranded RNAi agent targeted to SNCA includes a sense strand and an antisense strand forming a double stranded region, where the sense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 1, 3, 5, and 7, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of any one of SEQ ID NOs: 1, 3, 5, or 7, and the antisense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 2, 4, 6, and 8, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of any one of SEQ ID NOs: 2, 4, 6, and 8; where a substitution

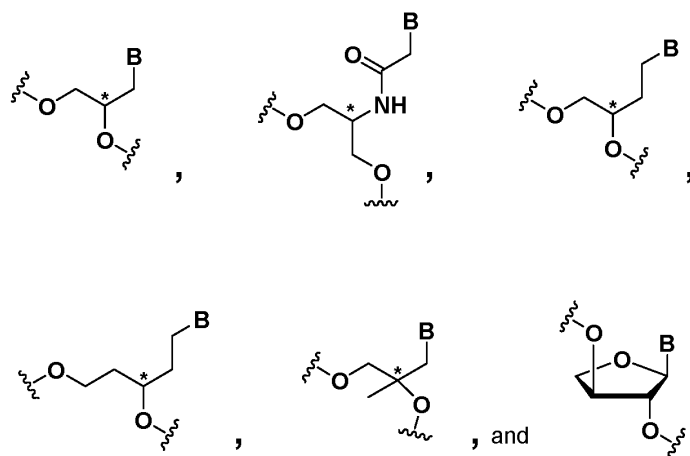
of a uracil for any thymine in the sequences provided in the SEQ ID NOs: 1-8 (when comparing aligned sequences) does not count as a difference that contributes to the differing by no more than 3 nucleotides from any one of the nucleotide sequences provided in SEQ ID NOs: 1-8, where substantially all of the nucleotides of the sense strand include a modification that is a 2'-O-methyl modification, a GNA or a 2'-fluoro modification, where the sense strand includes two phosphorothioate internucleotide linkages at the 5'-terminus, where substantially all of the nucleotides of the antisense strand include a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, where the antisense strand includes two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and where the sense strand is conjugated to one or more lipophilic, *e.g.*, C16, ligands, optionally, further comprising a liver targeting ligand, *e.g.*, a ligand comprising one or more GalNAc derivatives.

Another aspect of the instant disclosure provides a double stranded RNAi agent for inhibiting expression of a SNCA gene, where the double stranded RNAi agent targeted to SNCA includes a sense strand and an antisense strand forming a double stranded region, where the sense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 1, 3, 5, and 7, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of any one of SEQ ID NOs: 1, 3, 5, or 7, and the antisense strand includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides) from any one of the nucleotide sequences of SEQ ID NOs: 2, 4, 6, and 8, or a nucleotide sequence having at least 90% nucleotide sequence identity, *e.g.* 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identity, to the entire nucleotide sequence of any one of SEQ ID NOs: 2, 4, 6, and 8, where a substitution of a uracil for any thymine in the sequences provided in the SEQ ID NOs: 1-8 (when comparing aligned sequences) does not count as a difference that contributes to the differing by no more than 3 nucleotides from any one of the nucleotide sequences provided in SEQ ID NOs: 1-8; where the sense strand includes at least one 3'-terminal deoxy-thymine nucleotide (dT), and where the antisense strand includes at least one 3'-terminal deoxy-thymine nucleotide (dT).

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In another embodiment, each strand has 19-30 nucleotides.

In certain embodiments, the antisense strand of the RNAi agent includes at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5' region or a precursor thereof. Optionally, the thermally destabilizing modification of the duplex is one or more of



where B is nucleobase.

Another aspect of the instant disclosure provides a cell containing a double stranded RNAi agent of the instant disclosure.

An additional aspect of the instant disclosure provides a pharmaceutical composition for inhibiting expression of a SNCA gene that includes a double stranded RNAi agent of the instant disclosure.

In one embodiment, the double stranded RNAi agent is administered in an unbuffered solution. Optionally, the unbuffered solution is saline or water.

In another embodiment, the double stranded RNAi agent is administered with a buffer solution. Optionally, the buffer solution includes acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof. In another embodiment, the buffer solution is phosphate buffered saline (PBS).

Another aspect of the disclosure provides a pharmaceutical composition that includes a double stranded RNAi agent of the instant disclosure and a lipid formulation.

In one embodiment, the lipid formulation includes a lipid nanoparticle (LNP).

Another aspect of the instant disclosure provides a kit for performing a method of the instant disclosure, the kit including: a) a double stranded RNAi agent of the instant disclosure, and b) instructions for use, and c) optionally, a device for administering the double stranded RNAi agent to the subject.

An additional aspect of the instant disclosure provides a double stranded ribonucleic acid (RNAi) agent for inhibiting expression of a SNCA gene, where the RNAi agent possesses a sense strand and an antisense strand, and where the antisense strand includes a region of complementarity which includes at least 15 contiguous nucleotides differing by no more than 3 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides), *e.g.*, at least 15 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides), at least 19 nucleotides (*i.e.*, differing by 3, 2, 1, or 0 nucleotides), from any one of the antisense strand nucleobase sequences of **Tables 2, 3, 12 or 13**. In one embodiment, the RNAi agent includes one or more of the following modifications: a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-C-alkyl-modified nucleotide, a nucleotide comprising a glycol nucleic acid (GNA), a phosphorothioate (PS) and a vinyl phosphonate (VP). Optionally, the RNAi agent includes at least one of each of the following modifications: a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-C-alkyl-modified nucleotide, a nucleotide comprising a glycol nucleic acid (GNA), a phosphorothioate and a vinyl phosphonate (VP).

In another embodiment, the RNAi agent includes four or more PS modifications, optionally six to ten PS modifications, optionally eight PS modifications.

In an additional embodiment, each of the sense strand and the antisense strand of the RNAi agent possesses a 5'-terminus and a 3'-terminus, and the RNAi agent includes eight PS modifications positioned at each of the penultimate and ultimate internucleotide linkages from the respective 3'- and 5'-termini of each of the sense and antisense strands of the RNAi agent.

In another embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes only one nucleotide including a GNA. Optionally, the nucleotide including a GNA is positioned on the antisense strand at the seventh nucleobase residue from the 5'-terminus of the antisense strand.

In an additional embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes one to four 2'-C-alkyl-modified nucleotides. Optionally, the 2'-C-alkyl-modified nucleotide is a 2'-C16-modified nucleotide. Optionally, the RNAi agent includes a single 2'-C-alkyl, *e.g.*, C16-modified

nucleotide. Optionally, the single 2'-C-alkyl, *e.g.*, C16-modified nucleotide is located on the sense strand at the sixth nucleobase position from the 5'-terminus of the sense strand.

In another embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes two or more 2'-fluoro modified nucleotides. Optionally, each of the sense strand and the antisense strand of the RNAi agent includes two or more 2'-fluoro modified nucleotides. Optionally, the 2'-fluoro modified nucleotides are located on the sense strand at nucleobase positions 7, 9, 10 and 11 from the 5'-terminus of the sense strand and on the antisense strand at nucleobase positions 2, 14 and 16 from the 5'-terminus of the antisense strand.

In an additional embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes one or more VP modifications. Optionally, the RNAi agent includes a single VP modification at the 5'-terminus of the antisense strand.

In another embodiment, each of the sense strand and the antisense strand of the RNAi agent includes a 5'-terminus and a 3'-terminus, and the RNAi agent includes two or more 2'-O-methyl modified nucleotides. Optionally, the RNAi agent includes 2'-O-methyl modified nucleotides at all nucleobase locations not modified by a 2'-fluoro, a 2'-C-alkyl or a glycol nucleic acid (GNA). Optionally, the two or more 2'-O-methyl modified nucleotides are located on the sense strand at positions 1, 2, 3, 4, 5, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21 from the 5'-terminus of the sense strand and on the antisense strand at positions 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22 and 23 from the 5'-terminus of the antisense strand.

Definitions

That the present disclosure may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this disclosure.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element, *e.g.*, a plurality of elements.

The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise.

The term "about" is used herein to mean within the typical ranges of tolerances in the art. For example, "about" can be understood as about 2 standard deviations from the mean. In certain embodiments, about means $\pm 10\%$. In certain embodiments, about means $\pm 5\%$. When about is present before a series of numbers or a range, it is understood that "about" can modify each of the numbers in the series or range.

The term "at least" prior to a number or series of numbers is understood to include the number adjacent to the term "at least", and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, "at least 18 nucleotides of a 21 nucleotide nucleic acid molecule" means that 18, 19, 20, or 21 nucleotides have the indicated property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

As used herein, "no more than" or "less than" is understood as the value adjacent to the phrase and logical lower values or integers, as logical from context, to zero. For example, a duplex with an overhang of "no more than 2 nucleotides" has a 2, 1, or 0 nucleotide overhang. When "no more than" is present before a series of numbers or a range, it is understood that "no more than" can modify each of the numbers in the series or range. As used herein, ranges include both the upper and lower limit.

As used herein, methods of detection can include determination that the amount of analyte present is below the level of detection of the method.

In the event of a conflict between an indicated target site and the nucleotide sequence for a sense or antisense strand, the indicated sequence takes precedence.

In the event of a conflict between a chemical structure and a chemical name, the chemical structure takes precedence.

The term "SNCA," " α -synuclein," "synuclein alpha," or "alpha-synuclein," refers to a gene associated with neurodegenerative diseases, termed "synucleinopathies," as well as the proteins encoded by that gene. The human SNCA gene region covers approximately 114 kb. The

SNCA transcript contains 13 exons, and 15 mRNA isoforms have been identified or otherwise predicted as produced. Nucleotide and amino acid sequences of SNCA may be found, for example, at GenBank Accession No. NM_007308.3 (*Homo sapiens* SNCA, SEQ ID NO: 1, reverse complement, SEQ ID NO: 2); GenBank Accession No. XM_005555421 (*Macaca fascicularis* SNCA, SEQ ID NO: 3, reverse complement, SEQ ID NO: 4); GenBank Accession No.: NM_009221 (*Mus musculus* SNCA, SEQ ID NO: 5, reverse complement, SEQ ID NO: 6); GenBank Accession No. NM_019169.2 (*Rattus norvegicus* SNCA, SEQ ID NO: 7, reverse complement, SEQ ID NO: 8); and GenBank Accession No. XM_535656.7 (*Canis lupus familiaris* SNCA, SEQ ID NO: 1806, reverse complement, SEQ ID NO: 3600).

The term “SNCA” as used herein also refers to variations of the SNCA gene including naturally occurring sequence variants provided, for example, isoform 1 transcript NM_000345.4 (SEQ ID NO: 1809), which encodes polypeptide NP_000336.1; isoform 2 transcript NM_001146054.2 (SEQ ID NO: 1807), which encodes polypeptide NP_001139526.1; isoform 3 transcript NM_001146055.2 (SEQ ID NO: 1808), which encodes polypeptide NP_001139527.1; isoform 4 transcript NM_007308.3 (SEQ ID NO: 1) as mentioned above, which encodes polypeptide NP_009292.1; isoform 5 transcript NM_001375285.1 (SEQ ID NO: 1810), which encodes polypeptide NP_001362214.1; isoform 6 transcript NM_001375286.1 (SEQ ID NO: 1811), which encodes polypeptide NP_001362215.1; isoform 7 transcript NM_001375287.1 (SEQ ID NO: 1812), which encodes polypeptide NP_001362216.1; isoform 8 transcript NM_001375288.1 (SEQ ID NO: 1813), which encodes polypeptide NP_001362217.1; isoform 9 transcript NM_001375290.1 (SEQ ID NO: 1814), which encodes polypeptide NP_001362219.1; as well as predicted isoform X1 transcript XM_011532203.1 (SEQ ID NO: 1815), which encodes polypeptide XP_011530505.1; predicted isoform X2 transcript XM_011532204.3 (SEQ ID NO: 1816), which encodes polypeptide XP_011530506.1; predicted isoform X3 transcript XM_011532205.2 (SEQ ID NO: 1817), which encodes polypeptide XP_011530507.1; predicted isoform X4 transcript XM_011532206.1 (SEQ ID NO: 1818), which encodes polypeptide XP_011530508.1; predicted isoform X5 transcript XM_011532207.1 (SEQ ID NO: 1819), which encodes polypeptide XP_011530509.1; and predicted isoform X8 transcript XM_017008563.1 (SEQ ID NO: 1820), which encodes polypeptide XP_016864052.1 (the unique sequence associated with each of the preceding Accession Numbers is incorporated herein by reference in the form available on the filing date of the instant application). Additional examples of SNCA

sequences can be found in publicly available databases, for example, GenBank, OMIM, UniProt, NCBI dbSNP (see, *e.g.*, www.ncbi.nlm.nih.gov/gene/6622), and the Macaca genome project web site (macaque.genomics.org.cn/page/species/index.jsp). Additional information on SNCA can be found, for example, at www.ncbi.nlm.nih.gov/gene/6622. The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

Three protein isoforms of α -synuclein have been described in UniProt. The longest α -synuclein isoform is an approximately 14 kDa protein (Isoform 1 UniProt, P37840 of 140 amino acids). Other α -synuclein isoforms in UniProt include: Isoform 2-4, P37840-2 of 112 amino acids; and Isoform 2-5, P37840-3 of 126 amino acids. The 140 amino acid α -Synuclein protein is encoded by 5 exon pairs mapping to chromosome loci 4q21.3-q22. The α -synuclein protein has an N-terminal region composed of incomplete KXKEGV motifs, an extremely hydrophobic NAC domain and a highly acidic C-terminal domain. At physiological conditions, SNCA is believed to be an intrinsically disordered monomer or helically folded tetramer. α -Synuclein composes 1% of all proteins in the cytosol of brain cells, and is predominantly expressed in the neocortex, hippocampus, substantia nigra, thalamus, and cerebellum. α -Synuclein is also expressed in lower amounts in the in heart, skeletal muscle and pancreas. Although the function of SNCA is not well understood, evidence suggests it plays an important role in maintaining an adequate supply of synaptic vesicles in presynaptic terminals. α -Synuclein is implicated in the regulation of dopamine release and transport, fibrillization of microtubule associated protein tau, and the regulation of a neuroprotective phenotype in non-dopaminergic neurons by regulating the inhibition of both p53 expression and transactivation of proapoptotic genes, leading to decreased caspase-3 activation. The primary mechanism by which α -synuclein induces neurodegenerative diseases such as Parkinson's, Lewy body dementia, and multiple system atrophy, appears to be elevated levels of the α -synuclein protein resulting in α -synuclein fibrillary aggregates.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a SNCA gene, including mRNA that is a product of RNA processing of a primary transcription product. In one embodiment, the target portion of the sequence will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during

the transcription of a SNCA gene. In one embodiment, the target sequence is within the protein coding region of the SNCA gene. In another embodiment, the target sequence is within the 3' UTR of the SNCA gene.

The target sequence may be from about 9-36 nucleotides in length, *e.g.*, about 15-30 nucleotides in length. For example, the target sequence can be from about 15-30 nucleotides, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. In some embodiments, the target sequence is about 19 to about 30 nucleotides in length. In other embodiments, the target sequence is about 19 to about 25 nucleotides in length. In still other embodiments, the target sequence is about 19 to about 23 nucleotides in length. In some embodiments, the target sequence is about 21 to about 23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

As used herein, the term “strand comprising a sequence” refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

“G,” “C,” “A,” “T,” and “U” each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine, and uracil as a base, respectively in the context of a modified or unmodified nucleotide. However, it will be understood that the term “ribonucleotide” or “nucleotide” can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety (see, *e.g.*, **Table 1**). The skilled person is well aware that guanine, cytosine, adenine, thymidine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can be replaced in the nucleotide sequences of dsRNA featured in the disclosure by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to

form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured in the disclosure.

The terms “iRNA”, “RNAi agent,” “iRNA agent,” “RNA interference agent” as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing complex (RISC) pathway. RNA interference (RNAi) is a process that directs the sequence-specific degradation of mRNA. RNAi modulates, *e.g.*, inhibits, the expression of SNCA in a cell, *e.g.*, a cell within a subject, such as a mammalian subject.

In one embodiment, an RNAi agent of the disclosure includes a single stranded RNAi that interacts with a target RNA sequence, *e.g.*, a SNCA target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory it is believed that long double stranded RNA introduced into cells is broken down into double-stranded short interfering RNAs (siRNAs) comprising a sense strand and an antisense strand by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15: 485). Dicer, a ribonuclease-III-like enzyme, processes these dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409: 363). These siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107: 309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15: 188). Thus, in one aspect the disclosure relates to a single stranded RNA (ssRNA) (the antisense strand of a siRNA duplex) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.*, a SNCA gene. Accordingly, the term “siRNA” is also used herein to refer to an RNAi as described above.

In another embodiment, the RNAi agent may be a single-stranded RNA that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents bind to the RISC endonuclease, Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are chemically modified. The design and testing of single-stranded RNAs are described in U.S. Patent No. 8,101,348 and in Lima *et al.*, (2012) *Cell* 150: 883-894, the entire contents of each of which are hereby incorporated herein by reference. Any of the antisense nucleotide sequences described herein may be used as a single-stranded siRNA as

described herein or as chemically modified by the methods described in Lima *et al.*, (2012) *Cell* 150: 883-894.

In another embodiment, a “RNAi agent” for use in the compositions and methods of the disclosure is a double stranded RNA and is referred to herein as a “double stranded RNAi agent,” “double stranded RNA (dsRNA) molecule,” “dsRNA agent,” or “dsRNA”. The term “dsRNA” refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having “sense” and “antisense” orientations with respect to a target RNA, *i.e.*, a SNCA gene. In some embodiments of the disclosure, a double stranded RNA (dsRNA) triggers the degradation of a target RNA, *e.g.*, an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

In general, a dsRNA molecule can include ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide, a modified nucleotide. In addition, as used in this specification, an “RNAi agent” may include ribonucleotides with chemical modifications; an RNAi agent may include substantial modifications at multiple nucleotides.

As used herein, the term “modified nucleotide” refers to a nucleotide having, independently, a modified sugar moiety, a modified internucleotide linkage, or a modified nucleobase. Thus, the term modified nucleotide encompasses substitutions, additions or removal of, *e.g.*, a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. The modifications suitable for use in the agents of the disclosure include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by “RNAi agent” for the purposes of this specification and claims.

In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide – which is acknowledged as a naturally occurring form of nucleotide – if present within an RNAi agent can be considered to constitute a modified nucleotide.

The duplex region may be of any length that permits specific degradation of a desired target RNA through a RISC pathway, and may range from about 9 to 36 base pairs in length, *e.g.*, about 15-30 base pairs in length, for example, about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 base pairs in length, such as about 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30,

18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a "hairpin loop." A hairpin loop can comprise at least one unpaired nucleotide. In some embodiments, the hairpin loop can comprise at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 23 or more unpaired nucleotides or nucleotides not directed to the target site of the dsRNA. In some embodiments, the hairpin loop can be 10 or fewer nucleotides. In some embodiments, the hairpin loop can be 8 or fewer unpaired nucleotides. In some embodiments, the hairpin loop can be 4-10 unpaired nucleotides. In some embodiments, the hairpin loop can be 4-8 nucleotides.

In certain embodiments, the two strands of double-stranded oligomeric compound can be linked together. The two strands can be linked to each other at both ends, or at one end only. By linking at one end is meant that 5'-end of first strand is linked to the 3'-end of the second strand or 3'-end of first strand is linked to 5'-end of the second strand. When the two strands are linked to each other at both ends, 5'-end of first strand is linked to 3'-end of second strand and 3'-end of first strand is linked to 5'-end of second strand. The two strands can be linked together by an oligonucleotide linker including, but not limited to, (N)_n; wherein N is independently a modified or unmodified nucleotide and n is 3-23. In some embodiments, n is 3-10, *e.g.*, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, the oligonucleotide linker is selected from the group consisting of GNRA, (G)₄, (U)₄, and (dT)₄, wherein N is a modified or unmodified nucleotide and R is a modified or unmodified purine nucleotide. Some of the nucleotides in the linker can be involved in base-pair interactions with other nucleotides in the linker. The two strands can also be linked together by a non-nucleosidic linker, *e.g.* a linker described herein. It will be appreciated by one of skill in the art that any oligonucleotide chemical modifications or variations describe herein can be used in the oligonucleotide linker.

Hairpin and dumbbell type oligomeric compounds will have a duplex region equal to or at least 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotide pairs. The duplex region can be equal to or less than 200, 100, or 50, in length. In some embodiments, ranges for the duplex region are 15-30, 17 to 23, 19 to 23, and 19 to 21 nucleotides pairs in length.

The hairpin oligomeric compounds can have a single strand overhang or terminal unpaired region, in some embodiments at the 3', and in some embodiments on the antisense side of the hairpin. In some embodiments, the overhangs are 1-4, more generally 2-3 nucleotides in length. The hairpin oligomeric compounds that can induce RNA interference are also referred to as "shRNA" herein.

Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a "linker." The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs.

In one embodiment, an RNAi agent of the disclosure is a dsRNA, each strand of which is 24-30 nucleotides in length, that interacts with a target RNA sequence, *e.g.*, a SNCA target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory, long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15: 485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409: 363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107: 309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15: 188).

In one embodiment, an RNAi agent of the disclosure is a dsRNA agent, each strand of which comprises 19-23 nucleotides that interacts with a SNCA RNA sequence to direct the cleavage of the target RNA. Without wishing to be bound by theory, long double stranded RNA introduced

into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15: 485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409: 363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107: 309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15: 188). In one embodiment, an RNAi agent of the disclosure is a dsRNA of 24-30 nucleotides that interacts with a SNCA RNA sequence to direct the cleavage of the target RNA.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an RNAi agent, *e.g.*, a dsRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively, the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, at least five nucleotides or more. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA.

In one embodiment of the dsRNA, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In other embodiments, at least one strand of the RNAi agent comprises a 5' overhang of at least 1 nucleotide. In certain embodiments, at least one strand comprises a 5' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In still other embodiments, both the 3' and the 5' end of one strand of the RNAi agent comprise an overhang of at least 1 nucleotide.

In one embodiment, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, 0-3, 1-3, 2-4, 2-5, 4-10, 5-10, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end, the 5'-end, at both ends, or at neither end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end, the 5'-end, at

both ends, or at neither end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

In certain embodiments, the overhang on the sense strand or the antisense strand, or both, can include extended lengths longer than 10 nucleotides, *e.g.*, 1-30 nucleotides, 2-30 nucleotides, 10-30 nucleotides, or 10-15 nucleotides in length. In certain embodiments, an extended overhang is on the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 3' end of the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 5' end of the antisense strand of the duplex. In certain embodiments, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate. In certain embodiments, the overhang includes a self-complementary portion such that the overhang is capable of forming a hairpin structure that is stable under physiological conditions.

The terms "blunt" or "blunt ended" as used herein in reference to a dsRNA mean that there are no unpaired nucleotides or nucleotide analogs at a given terminal end of a dsRNA, *i.e.*, no nucleotide overhang. One or both ends of a dsRNA can be blunt. Where both ends of a dsRNA are blunt, the dsRNA is said to be blunt ended. To be clear, a "blunt ended" dsRNA is a dsRNA that is blunt at both ends, *i.e.*, no nucleotide overhang at either end of the molecule. Most often such a molecule will be double stranded over its entire length.

The term "antisense strand" or "guide strand" refers to the strand of an RNAi agent, *e.g.*, a dsRNA, which includes a region that is substantially complementary to a target sequence, *e.g.*, a SNCA mRNA.

As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence, *e.g.*, a SNCA nucleotide sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the molecule. Generally, the most tolerated mismatches are in the terminal regions, *e.g.*, within 5, 4, 3, or 2 nucleotides of the 5'- or 3'-terminus of the RNAi agent.

In some embodiments, a double stranded RNA agent of the disclosure includes a nucleotide mismatch in the antisense strand.

In some embodiments, the antisense strand of the double stranded RNA agent of the disclosure includes no more than 4 mismatches with the target mRNA, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the target mRNA. In some embodiments, the antisense strand double stranded RNA agent of the disclosure includes no more than 4 mismatches with the sense strand, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the sense strand. In some embodiments, a double stranded RNA agent of the disclosure includes a nucleotide mismatch in the sense strand. In some embodiments, the sense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the antisense strand, *e.g.*, the sense strand includes 4, 3, 2, 1, or 0 mismatches with the antisense strand. In some embodiments, the nucleotide mismatch is, for example, within 5, 4, 3 nucleotides from the 3'-end of the iRNA. In another embodiment, the nucleotide mismatch is, for example, in the 3'-terminal nucleotide of the iRNA agent. In some embodiments, the mismatch(s) is not in the seed region.

Thus, an RNAi agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an RNAi agent as described herein contains no more than 3 mismatches (*i.e.*, 3, 2, 1, or 0 mismatches). In one embodiment, an RNAi agent as described herein contains no more than 2 mismatches. In one embodiment, an RNAi agent as described herein contains no more than 1 mismatch. In one embodiment, an RNAi agent as described herein contains 0 mismatches. In certain embodiments, if the antisense strand of the RNAi agent contains mismatches to the target sequence, the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of a SNCA gene, generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of a SNCA gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of a SNCA gene is important, especially if the particular region of complementarity in a SNCA gene is known to have polymorphic sequence variation within the population.

The term "sense strand" or "passenger strand" as used herein, refers to the strand of an RNAi agent that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

As used herein, “substantially all of the nucleotides are modified” are largely but not wholly modified and can include not more than 5, 4, 3, 2, or 1 unmodified nucleotides.

As used herein, the term “cleavage region” refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some embodiments, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage site specifically occurs at the site bound by nucleotides 10 and 11 of the antisense strand, and the cleavage region comprises nucleotides 11, 12 and 13.

As used herein, and unless otherwise indicated, the term “complementary,” when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions can include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing (see, *e.g.*, “Molecular Cloning: A Laboratory Manual, Sambrook, *et al.* (1989) Cold Spring Harbor Laboratory Press). Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Complementary sequences within an RNAi agent, *e.g.*, within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as “fully complementary” with respect to each other herein. However, where a first sequence is referred to as “substantially complementary” with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more, but generally not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, *e.g.*, inhibition of gene expression via a RISC pathway. However, where two oligonucleotides are designed to

form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as “fully complementary” for the purposes described herein.

“Complementary” sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs or base pairs formed from non-natural and modified nucleotides, in so far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs include, but are not limited to, G:U Wobble or Hoogsteen base pairing.

The terms “complementary,” “fully complementary” and “substantially complementary” herein can be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between the antisense strand of an RNAi agent and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is “substantially complementary to at least part of” a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding SNCA). For example, a polynucleotide is complementary to at least a part of a SNCA mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding SNCA.

Accordingly, in some embodiments, the antisense strand polynucleotides disclosed herein are fully complementary to the target SNCA sequence.

In certain embodiments, the antisense strand polynucleotides disclosed herein are substantially complementary to the target SNCA sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 1, 3, 5, or 7 for SNCA, or a fragment of SEQ ID NOs: 1, 3, 5, or 7, such as about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target SNCA sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand

nucleotide sequences in **Tables 2, 3, 12 or 13**, or a fragment of any one of the sense strand nucleotide sequences in **Tables 2, 3, 12 or 13**, such as about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target SNCA sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 2, 4, 6, or 8, or a fragment of any one of SEQ ID NOs: 2, 4, 6, or 8, such as about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In some embodiments, an iRNA of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target SNCA sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in **Tables 2, 3, 12 or 13**, or a fragment of any one of the antisense strand nucleotide sequences in **Tables 2, 3, 12 or 13**, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In some embodiments, the double-stranded region of a double-stranded iRNA agent is equal to or at least, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more nucleotide pairs in length.

In some embodiments, the antisense strand of a double-stranded iRNA agent is equal to or at least 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In some embodiments, the sense strand of a double-stranded iRNA agent is equal to or at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each 15 to 30 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each 19 to 25 nucleotides in length.

In one embodiment, the sense and antisense strands of the double-stranded iRNA agent are each 21 to 23 nucleotides in length.

In one embodiment, the sense strand of the iRNA agent is 21- nucleotides in length, and the antisense strand is 23-nucleotides in length, wherein the strands form a double-stranded region of 21 consecutive base pairs having a 2-nucleotide long single stranded overhangs at the 3'-end.

In some embodiments, the majority of nucleotides of each strand are ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide or a modified nucleotide. In addition, an “iRNA” may include ribonucleotides with chemical modifications. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in an iRNA molecule, are encompassed by “iRNA” for the purposes of this specification and claims.

In one aspect of the disclosure, an agent for use in the methods and compositions of the disclosure is a single-stranded antisense nucleic acid molecule that inhibits a target mRNA *via* an antisense inhibition mechanism. The single-stranded antisense RNA molecule is complementary to a sequence within the target mRNA. The single-stranded antisense oligonucleotides can inhibit translation in a stoichiometric manner by base pairing to the mRNA and physically obstructing the translation machinery, see Dias, N. *et al.*, (2002) *Mol Cancer Ther* 1: 347-355. The single-stranded antisense RNA molecule may be about 15 to about 30 nucleotides in length and have a sequence that is complementary to a target sequence. For example, the single-stranded antisense RNA molecule may comprise a sequence that is at least about 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from any one of the antisense sequences described herein.

In one embodiment, at least partial suppression of the expression of a SNCA gene, is assessed by a reduction of the amount of SNCA mRNA which can be isolated from or detected in a first cell or group of cells in which a SNCA gene is transcribed and which has or have been treated such that the expression of a SNCA gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells). The degree of inhibition may be expressed in terms of:

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} * 100\%$$

The phrase “contacting a cell with an RNAi agent,” such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an RNAi agent includes contacting a cell *in vitro* with the RNAi agent or contacting a cell *in vivo* with the RNAi agent. The contacting may be done directly or indirectly. Thus, for example, the RNAi agent may be put into physical contact with the cell by the individual performing the method, or alternatively, the RNAi agent may be put into a situation that will permit or cause it to subsequently come into contact with the cell.

Contacting a cell *in vitro* may be done, for example, by incubating the cell with the RNAi agent. Contacting a cell *in vivo* may be done, for example, by injecting the RNAi agent into or near the tissue where the cell is located, or by injecting the RNAi agent into another area, *e.g.*, the central nervous system (CNS), optionally *via* intrathecal, intravitreal or other injection, or to the bloodstream or the subcutaneous space, such that the agent will subsequently reach the tissue where the cell to be contacted is located. For example, the RNAi agent may contain or be coupled to a ligand, *e.g.*, a lipophilic moiety or moieties as described below and further detailed, *e.g.*, in PCT/US2019/031170, which is incorporated herein by reference, that directs or otherwise stabilizes the RNAi agent at a site of interest, *e.g.*, the CNS. In some embodiments, the RNAi agent may contain or be coupled to a ligand, *e.g.*, one or more GalNAc derivatives as described below, that directs or otherwise stabilizes the RNAi agent at a site of interest, *e.g.*, the liver. In other embodiments, the RNAi agent may contain or be coupled to a lipophilic moiety or moieties and one or more GalNAc derivatives. Combinations of *in vitro* and *in vivo* methods of contacting are also possible. For example, a cell may also be contacted *in vitro* with an RNAi agent and subsequently transplanted into a subject.

In one embodiment, contacting a cell with an RNAi agent includes “introducing” or “delivering the RNAi agent into the cell” by facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an RNAi agent can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. Introducing an RNAi agent into a cell may be *in vitro* or *in vivo*. For example, for *in vivo* introduction, an RNAi agent can be injected into a tissue site or administered systemically. *In vitro* introduction into a cell includes methods known in the art

such as electroporation and lipofection. Further approaches are described herein below or are known in the art.

The term “lipophile” or “lipophilic moiety” broadly refers to any compound or chemical moiety having an affinity for lipids. One way to characterize the lipophilicity of the lipophilic moiety is by the octanol-water partition coefficient, $\log K_{ow}$, where K_{ow} is the ratio of a chemical's concentration in the octanol-phase to its concentration in the aqueous phase of a two-phase system at equilibrium. The octanol-water partition coefficient is a laboratory-measured property of a substance. However, it may also be predicted by using coefficients attributed to the structural components of a chemical which are calculated using first-principle or empirical methods (see, for example, Tetko *et al.*, *J. Chem. Inf. Comput. Sci.* 41: 1407-21 (2001), which is incorporated herein by reference in its entirety). It provides a thermodynamic measure of the tendency of the substance to prefer a non-aqueous or oily milieu rather than water (*i.e.* its hydrophilic/lipophilic balance). In principle, a chemical substance is lipophilic in character when its $\log K_{ow}$ exceeds 0. Typically, the lipophilic moiety possesses a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10. For instance, the $\log K_{ow}$ of 6-amino hexanol, for instance, is predicted to be approximately 0.7. Using the same method, the $\log K_{ow}$ of cholesteryl N-(hexan-6-ol) carbamate is predicted to be 10.7.

The lipophilicity of a molecule can change with respect to the functional group it carries. For instance, adding a hydroxyl group or amine group to the end of a lipophilic moiety can increase or decrease the partition coefficient (*e.g.*, $\log K_{ow}$) value of the lipophilic moiety.

Alternatively, the hydrophobicity of the double-stranded RNAi agent, conjugated to one or more lipophilic moieties, can be measured by its protein binding characteristics. For instance, in certain embodiments, the unbound fraction in the plasma protein binding assay of the double-stranded RNAi agent could be determined to positively correlate to the relative hydrophobicity of the double-stranded RNAi agent, which could then positively correlate to the silencing activity of the double-stranded RNAi agent.

In one embodiment, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. An exemplary protocol of this binding assay is illustrated in detail in, *e.g.*, PCT/US2019/031170. The hydrophobicity of the double-stranded RNAi agent, measured by fraction of unbound siRNA in the binding assay,

exceeds 0.15, exceeds 0.2, exceeds 0.25, exceeds 0.3, exceeds 0.35, exceeds 0.4, exceeds 0.45, or exceeds 0.5 for an enhanced *in vivo* delivery of siRNA.

Accordingly, conjugating the lipophilic moieties to the internal position(s) of the double-stranded RNAi agent provides optimal hydrophobicity for the enhanced *in vivo* delivery of siRNA.

The term “lipid nanoparticle” or “LNP” refers to a vesicle comprising a lipid layer encapsulating a pharmaceutically active molecule, such as a nucleic acid molecule, *e.g.*, an RNAi agent or a plasmid from which an RNAi agent is transcribed. LNPs are described in, for example, U.S. Patent Nos. 6,858,225, 6,815,432, 8,158,601, and 8,058,069, the entire contents of which are hereby incorporated herein by reference.

As used herein, a “subject” is an animal, such as a mammal, including a primate (such as a human, a non-human primate, *e.g.*, a monkey, and a chimpanzee), or a non-primate (such as a rat, or a mouse). In a preferred embodiment, the subject is a human, such as a human being treated or assessed for a disease, disorder, or condition that would benefit from reduction in SNCA expression; a human at risk for a disease, disorder, or condition that would benefit from reduction in SNCA expression; a human having a disease, disorder, or condition that would benefit from reduction in SNCA expression; or human being treated for a disease, disorder, or condition that would benefit from reduction in SNCA expression as described herein.

As used herein, the terms “treating” or “treatment” refer to a beneficial or desired result including, but not limited to, alleviation or amelioration of one or more signs or symptoms associated with SNCA gene expression or SNCA protein production, *e.g.*, SNCA-associated neurodegenerative disease, *e.g.*, synucleinopathies, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, LYTIC-BODIG disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease, decreased expression or activity of SNCA in regions of increased neuronal dysfunction or death, in subjects having such neurodegenerative diseases. “Treatment” can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term “lower” in the context of the level of SNCA in a subject or a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, 15%, 20%, 25%, 30%, %, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In certain embodiments, a decrease is at least 20%. In certain embodiments, the decrease is at least 50% in a disease marker, e.g., protein or gene expression level. “Lower” in the context of the level of SNCA in a subject is optionally down to a level accepted as within the range of normal for an individual without such disorder. In certain embodiments, “lower” is the decrease in the difference between the level of a marker or symptom for a subject suffering from a disease and a level accepted within the range of normal for an individual, e.g., the level of decrease in speed of movement (bradykinesia) and ability to regulate posture and balance in an individual having Parkinson’s and an individual not having Parkinson’s or having symptoms that are within the range of normal.

As used herein, “prevention” or “preventing,” when used in reference to a disease or disorder, that would benefit from a reduction in expression of a SNCA gene or production of SNCA protein, e.g., in a subject susceptible to a SNCA-associated disorder due to, e.g., genetic factors or age, wherein the subject does not yet meet the diagnostic criteria for the SNCA-associated disorder. As used herein, prevention can be understood as administration of an agent to a subject who does not yet meet the diagnostic criteria for the SNCA-associated disorder to delay or reduce the likelihood that the subject will develop the SNCA-associated disorder. As the agent is a pharmaceutical agent, it is understood that administration typically would be under the direction of a health care professional capable of identifying a subject who does not yet meet the diagnostic criteria for a SNCA-associated disorder as being susceptible to developing a SNCA-associated disorder.

The term “synucleinopathies” refers to a group of neurodegenerative disorders characterized by fibrillary aggregates of α -synuclein protein that tend to accumulate in the cytoplasm of selective populations of neurons and glia. Synucleinopathies are therefore a class of SNCA-associated neurodegenerative diseases and disorders, which include Parkinson’s disease (PD), Lewy body dementia (LBD), pure autonomic failure (PAF), and multiple system atrophy (MSA), among other neurodegenerative diseases. Clinically, synucleinopathies are characterized by a chronic and progressive decline in motor, cognitive, behavioral, and autonomic functions, depending on the distribution of the lesions in the brain. Because of clinical overlap, differential

diagnosis is sometimes very difficult. Parkinsonism is the predominant symptom of PD, but it can be indistinguishable from the parkinsonism of LBD and MSA. Autonomic dysfunction, which is an isolated finding in PAF, may be present in PD and LBD, but is usually more prominent and appears earlier in MSA. LBD could be the same disease as PD but with widespread cortical pathological states, leading to dementia, fluctuating cognition, and the characteristic visual hallucinations.

The likelihood of developing a synucleinopathy, e.g., PD, LBD, etc., is reduced, for example, when an individual having one or more risk factors for PD or for LBD (or other synucleinopathy) either fails to develop PD or LBD (or other synucleinopathy) or develops PD or LBD (or other synucleinopathy) with less severity relative to a population having the same risk factors and not receiving treatment as described herein. The failure to develop a SNCA-associated disorder, e.g., PD or LBD (or other synucleinopathy), or a delay in the time to develop PD or LBD (or other synucleinopathy) by months or years is considered effective prevention. Prevention may require administration of more than one dose of the iRNA agent. Provided with appropriate methods to identify subjects at risk to develop any of the SNCA-associated diseases above, the iRNA agents provided herein can be used as pharmaceutical agents for or in methods of prevention of SNCA-associated diseases. Risk factors for various SNCA-associated diseases are discussed herein.

As used herein, the term “Parkinson’s disease” or “PD” refers to a progressive nervous system disorder that affects movement. The main pathological characteristics of PD are cell death in the brain's basal ganglia (affecting up to 70% of the dopamine secreting neurons in the substantia nigra pars compacta by the end of life) and the presence of Lewy bodies (accumulations of the SNCA-encoded α -synuclein protein) in many of the remaining neurons. Symptoms start gradually, sometimes with a barely noticeable tremor in just one hand, or stiffness or slowing of movement. Other early symptoms include lack of facial expression, lack of arm movement while walking, and slurring during speech. Parkinson's disease symptoms worsen over time. The average onset of PD is age 60, and later onset is associated with greater symptom severity. Clinical features include, but are not limited to, more severe tremors, slowed movement (bradykinesia), rigid muscles, impaired posture and balance, loss of automatic movements, speech changes, and eventually, dementia, hallucinations, and wheelchair confinement.

As used herein, the term “Lewy body dementia (LBD)” refers to a type of progressive dementia that leads to a decline in thinking, reasoning and independent function caused by the aggregation of α -synuclein protein within diseased brain neurons, known as Lewy bodies and Lewy neurites. Aggregates of α -synuclein protein lead to sub-optimal functioning and eventual death of the affected neurons. Symptoms include visual, auditory, olfactory, or tactile hallucinations, signs of Parkinson's disease (parkinsonian signs), poor regulation of body functions (autonomic nervous system) such as dizziness, falls and bowel issues, cognitive problems such as confusion, poor attention, visual-spatial problems and memory loss, sleep difficulties such as rapid eye movement (REM) sleep behavior disorder (in which dreams are physically acted out while asleep), fluctuating attention including episodes of drowsiness, long periods of staring into space, long naps during the day or disorganized speech, depression, and apathy.

In one embodiment, a SNCA-associated disease or disorder (synucleinopathy) is one of Parkinson's disease, Lewy body dementia, multiple system atrophy (MSA), and pure autonomic failure (PAF).

"Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a SNCA-associated disease, is sufficient to effect treatment of the disease (*e.g.*, by diminishing, ameliorating, or maintaining the existing disease or one or more symptoms of disease). The "therapeutically effective amount" may vary depending on the RNAi agent, how the agent is administered, the disease and its severity and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the subject to be treated.

“Prophylactically effective amount,” as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a SNCA-associated disorder, is sufficient to prevent or ameliorate the disease or one or more symptoms of the disease. Ameliorating the disease includes slowing the course of the disease or reducing the severity of later-developing disease. The "prophylactically effective amount" may vary depending on the RNAi agent, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

A "therapeutically-effective amount" or "prophylactically effective amount" also includes an amount of an RNAi agent that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. An RNAi agent employed in the methods of the present disclosure may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

The term “sample,” as used herein, includes a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Examples of biological fluids include blood, serum and serosal fluids, plasma, cerebrospinal fluid, ocular fluids, lymph, urine, saliva, and the like. Tissue samples may include samples from tissues, organs or localized regions. For example, samples may be derived from particular organs, parts of organs, or fluids or cells within those organs. In certain embodiments, samples may be derived from the brain (*e.g.*, whole brain or certain segments of brain, *e.g.*, striatum, or certain types of cells in the brain, such as, *e.g.*, neurons and glial cells (astrocytes, oligodendrocytes, microglial cells)). In other embodiments, a “sample derived from a subject” refers to liver tissue (or subcomponents thereof) derived from the subject. In some embodiments, a “sample derived from a subject” refers to blood drawn from the subject or plasma or serum derived therefrom. In further embodiments, a “sample derived from a subject” refers to brain tissue (or subcomponents thereof) or retinal tissue (or subcomponents thereof) derived from the subject.

It will be understood that, although the sequences in **Tables 2 or 12** are described as modified or conjugated sequences, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA of the disclosure, may comprise any one of the sequences set forth in **Tables 2, 3, 12 or 13** that is unmodified, un-conjugated, or modified or conjugated differently than described therein. That is, the modified sequences provided in **Tables 2 or 12** do not require the L96 ligand, or any ligand. A lipophilic ligand can be included in any of the positions provided in the instant application.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the effects of selected SNCA-targeting RNAi agents on SNCA levels in human SNCA-AAV over-expressing mice. To identify RNA *in vivo* efficacy of the RNAi compounds in mice, a full-length human SNCA was first transduced by AAV. At 7 days post AAV-administration, the following selected duplexes were delivered: duplexes targeting the 3'UTR of human SNCA AD-464778, AD-464782, AD-464694, AD-464634, AD-464779; and duplexes targeting the coding sequence of SNCA AD-464590, AD-464313, AD-464314, AD-464585, AD-464586, AD-464592, and AD-464229. Data were normalized to PBS-treated samples.

FIG. 2 shows a schematic representation of the respective sequences and modification patterns of two selected SNCA-targeting RNAi duplexes: AD-464634 sense (SEQ ID NO: 924)

and antisense (SEQ ID NO: 1016) strands, and AD-464314 sense (SEQ ID NO: 915) and antisense (SEQ ID NO: 1007) strands. Both duplexes were modified on antisense strands with a vinyl phosphate group and on sense strands with a triantennary GalNAc moiety (thereby promoting liver delivery). Indicated residues were also 2' fluoro- or 2'-O-methyl-modified, and phosphorothioate internucleoside linkages were included at ultimate and penultimate linkages (both 3' and 5' ends for antisense strands, only 5' end for sense strands), where shown.

FIG. 3 shows human SNCA knockdown results obtained in optimizing for *in vivo* activity of RNAi agents in huSNCA AAV-transformed mice (AAV incubation at 2e10 viral particles/mouse generated reliable data). Robust knockdown of human SNCA was observed in mice treated with both the huSNCA 3'-UTR-targeting AD-464634 duplex and the huSNCA coding sequence-targeting AD-464314 duplex, at both day 7 and day 14 time points. Dose-response was observed for both tested duplexes, particularly at the 14 day time point. With strong huSNCA knockdown observed even at the 14 day time point, both duplexes were identified as suitable for further *in vivo* lead development studies.

FIG. 4 shows human SNCA expression levels observed in liver tissue of huSNCA AAV-transduced mice (respectively huSNCA AAV-transduced with 2e10 or 2e11 viral particles), with huSNCA levels measured at days 7, 14 and 21.

FIG. 5 shows that mouse/rat cross-reactive duplexes inhibited rat SNCA *in vivo* when administered to rat SNCA-AAV-transduced mice. The selected RNAi agents included AD-476344, AD-475666, AD-476306, AD-476061, AD-464814, AD-475728, and AD-4644229. Data were normalized to PBS-treated samples.

FIG. 6 shows the strong correlation observed between measured SNCA knockdown levels in the hotspot walk of **Table 14** and the calculated 1 nM fit values that were used to rank-order duplexes in **Table 14**.

The present invention is further illustrated by the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides RNAi compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a SNCA gene. The SNCA gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The present disclosure also provides methods of using the RNAi compositions of the disclosure for inhibiting the

expression of a SNCA gene or for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of a SNCA gene, *e.g.*, a SNCA-associated disease, *e.g.*, a synucleinopathy, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomatosis, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

The RNAi agents of the disclosure include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a SNCA gene. In certain embodiments, the RNAi agents of the disclosure include an RNA strand (the antisense strand) having a region which is about 21-23 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a SNCA gene.

In certain embodiments, the RNAi agents of the disclosure include an RNA strand (the antisense strand) which can include longer lengths, for example up to 66 nucleotides, *e.g.*, 36-66, 26-36, 25-36, 31-60, 22-43, 27-53 nucleotides in length with a region of at least 19 contiguous nucleotides that is substantially complementary to at least a part of an mRNA transcript of a SNCA gene. These RNAi agents with the longer length antisense strands optionally include a second RNA strand (the sense strand) of 20-60 nucleotides in length wherein the sense and antisense strands form a duplex of 18-30 contiguous nucleotides.

The use of these RNAi agents enables the targeted degradation of mRNAs of a SNCA gene in mammals. Thus, methods and compositions including these RNAi agents are useful for treating a subject who would benefit by a reduction in the levels or activity of a SNCA protein, such as a subject having a SNCA-associated neurodegenerative disease, *e.g.* a synucleinopathy, such as PD,

multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

Intraneuronal accumulation of α -synuclein has been described as either resulting in the formation of Lewy bodies, round eosinophilic hyaline 10-20 μ m large inclusions, or Lewy neurites, elongated thread-like dystrophic axons and dendrites. In the PD brain, deposition of Lewy bodies and Lewy neurites are mostly limited to neurons connecting striatum with substantia nigra. These cells are crucial for the execution of movement and postural functions, explaining the nature of PD symptoms. In the LBD brain, widespread depositions of Lewy bodies and Lewy neurites are found both in midbrain and cortical areas.

α -Synuclein is a protein which is mainly found intraneuronally. Within the neuron, α -synuclein is predominantly located presynaptically and it has therefore been speculated that it plays a role in the regulation of synaptic activity. Three main isoforms of α -synuclein have been identified, of which the longest and most common form comprises 140 amino acids.

Oxidative stress has been implicated in a number of neurodegenerative disorders characterized by the pathological accumulation of misfolded α -synuclein. Various reactive oxygen species can induce peroxidation of lipids such as cellular membranes or lipoproteins and also result in the generation of highly reactive aldehydes from poly-unsaturated fatty acids (Yoritaka *et al.*, 1996)

Brain pathology indicative of Alzheimer's disease (AD), i.e. amyloid plaques and neurofibrillary tangles, are seen in approximately 50% of cases with LBD. It is unclear whether the existence of parallel pathologies implies two different diseases or just represents a variant of each respective disorder. Sometimes the cases with co-pathology are described as having a Lewy body variant of AD (Hansen *et al.*, 1990).

Research has also implicated a role of SNCA in AD and Down's syndrome, as the α -synuclein protein has been demonstrated to accumulate in the limbic region in these disorders (Crews *et al.*, 2009).

Rare dominantly inherited forms of PD and LBD can be caused by point mutations or duplications of the SNCA gene. The pathogenic mutations A30P and A53T (Kruger *et al.*, 1998) (Polymeropoulos *et al.*, 1998) and duplication of the gene (Chartier-Harlin *et al.*, 2004) have been described to cause familial PD, whereas one other α -synuclein mutation, E46K (Zarranz *et al.*, 2004) as well as triplication of the α -synuclein gene (Singleton *et al.*, 2003) have been reported to cause either PD or LBD.

The pathogenic consequences of the α -synuclein mutations are only partly understood. However, *in vitro* data have shown that the A30P and A53T mutations increase the rate of aggregation (Conway *et al.*, 2000). A broad range of differently composed α -synuclein species (monomers, dimers, oligomers, including protofibrils) are involved in the aggregation process, all of which may have different toxic properties. It is not clear which molecular species exert toxic effects in the brain. However, research has indicated that oligomeric forms of α -synuclein are particularly neurotoxic. Additional evidence for the role of oligomers is given by the observation that certain α -synuclein mutations (A30P and A53T) causing hereditary Parkinson's disease, lead to an increased rate of oligomerization.

It is not completely known how the α -synuclein aggregation cascade begins. Possibly, an altered conformation of monomeric α -synuclein initiates formation of dimers and trimers, which continue to form higher soluble oligomers, including protofibrils, before these intermediately sized species are deposited as insoluble fibrils in Lewy bodies. It is also conceivable that the α -synuclein oligomers, once they are formed, can bind new monomers and/or smaller multimers of α -synuclein and hence accelerate the fibril formation process. Such seeding effects can possibly also occur in the extracellular space as some evidence suggests that α -synuclein pathology may propagate from neuron to neuron in the diseased brain.

The following detailed description discloses how to make and use compositions containing RNAi agents to inhibit the expression of a SNCA gene, as well as compositions and methods for treating subjects having diseases and disorders that would benefit from inhibition or reduction of the expression of the genes.

I. RNAi Agents of the Disclosure

Described herein are RNAi agents which inhibit the expression of a SNCA gene. In one embodiment, the RNAi agent includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of a SNCA gene in a cell, such as a cell within a subject, *e.g.*, a mammal, such as a human having a SNCA-associated neurodegenerative disease, *e.g.*, a synucleinopathy, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease. The dsRNA includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of a SNCA gene. In embodiments, the region of complementarity is about 15-30 nucleotides or less in length. Upon contact with a cell expressing the SNCA gene, the RNAi agent inhibits the expression of the SNCA gene (*e.g.*, a human gene, a primate gene, a non-primate gene) by at least 50% as assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by immunofluorescence analysis, using, for example, western blotting or flow cytometric techniques.

A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of a SNCA gene. The other strand (the sense strand) includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be

contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

Generally, the duplex structure is 15 to 30 base pairs in length, *e.g.*, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain preferred embodiments, the duplex structure is 18 to 25 base pairs in length, *e.g.*, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24, 20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 base pairs in length, for example, 19-21 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

Similarly, the region of complementarity to the target sequence is 15 to 30 nucleotides in length, *e.g.*, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, for example 19-23 nucleotides in length or 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

In some embodiments, the dsRNA is 15 to 23 nucleotides in length, or 24 to 30 nucleotides in length (optionally, 25 to 30 nucleotides in length). In general, the dsRNA can be long enough to serve as a substrate for the Dicer enzyme. For example, it is well known in the art that dsRNAs longer than about 21-23 nucleotides can serve as substrates for Dicer. As the ordinarily skilled person will also recognize, the region of an RNA targeted for cleavage will most often be part of a larger RNA molecule, often an mRNA molecule. Where relevant, a “part” of an mRNA target is a contiguous sequence of an mRNA target of sufficient length to allow it to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway).

One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, *e.g.*, a duplex region of about 15 to 36 base pairs, *e.g.*, 15-36, 15-35, 15-34, 15-33, 15-32, 15-31, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20,

15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs, for example, 19-21 base pairs. Thus, in one embodiment, to the extent that it becomes processed to a functional duplex, of *e.g.*, 15-30 base pairs, that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a dsRNA. Thus, an ordinarily skilled artisan will recognize that in one embodiment, a miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an RNAi agent useful to target SNCA expression is not generated in the target cell by cleavage of a larger dsRNA.

A dsRNA as described herein can further include one or more single-stranded nucleotide overhangs *e.g.*, 1, 2, 3, or 4 nucleotides. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA. In certain embodiments, longer, extended overhangs are possible.

A dsRNA can be synthesized by standard methods known in the art as further discussed below, *e.g.*, by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc.

siRNA compounds of the disclosure may be prepared using a two-step procedure. First, the individual strands of the double stranded RNA molecule are prepared separately. Then, the component strands are annealed. The individual strands of the siRNA compound can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide strands comprising unnatural or modified nucleotides can be easily prepared. Single-stranded oligonucleotides of the disclosure can be prepared using solution-phase or solid-phase organic synthesis or both.

An siRNA can be produced, *e.g.*, in bulk, by a variety of methods. Exemplary methods include: organic synthesis and RNA cleavage, *e.g.*, *in vitro* cleavage.

An siRNA can be made by separately synthesizing a single stranded RNA molecule, or each respective strand of a double-stranded RNA molecule, after which the component strands can then be annealed.

A large bioreactor, *e.g.*, the OligoPilot II from Pharmacia Biotec AB (Uppsala Sweden), can be used to produce a large amount of a particular RNA strand for a given siRNA. The OligoPilotII reactor can efficiently couple a nucleotide using only a 1.5 molar excess of a phosphoramidite nucleotide. To make an RNA strand, ribonucleotides amidites are used. Standard cycles of monomer addition can be used to synthesize the 21 to 23 nucleotide strand for the siRNA. Typically, the two complementary strands are produced separately and then annealed, *e.g.*, after release from the solid support and deprotection.

Organic synthesis can be used to produce a discrete siRNA species. The complementary of the species to a SNCA gene can be precisely specified. For example, the species may be complementary to a region that includes a polymorphism, *e.g.*, a single nucleotide polymorphism. Further the location of the polymorphism can be precisely defined. In some embodiments, the polymorphism is located in an internal region, *e.g.*, at least 4, 5, 7, or 9 nucleotides from one or both of the termini.

In one embodiment, RNA generated is carefully purified to remove ends. iRNA is cleaved *in vitro* into siRNAs, for example, using a Dicer or comparable RNase III-based activity. For example, the dsRNA can be incubated in an *in vitro* extract from *Drosophila* or using purified components, *e.g.*, a purified RNase or RISC (RNA-induced silencing complex). See, *e.g.*, Ketting *et al. Genes Dev* 2001 Oct 15;15(20): 2654-9 and Hammond *Science* 2001 Aug 10;293(5532): 1146-50.

dsRNA cleavage generally produces a plurality of siRNA species, each being a particular 21 to 23 nt fragment of a source dsRNA molecule. For example, siRNAs that include sequences complementary to overlapping regions and adjacent regions of a source dsRNA molecule may be present.

Regardless of the method of synthesis, the siRNA preparation can be prepared in a solution (*e.g.*, an aqueous or organic solution) that is appropriate for formulation. For example, the siRNA preparation can be precipitated and re-dissolved in pure double-distilled water, and lyophilized. The dried siRNA can then be resuspended in a solution appropriate for the intended formulation process.

In one aspect, a dsRNA of the disclosure includes at least two nucleotide sequences, a sense sequence and an antisense sequence. The sense strand sequence for SNCA may be selected from the group of sequences provided in **Tables 2, 3, 12 or 13**, and the corresponding nucleotide

sequence of the antisense strand of the sense strand may be selected from the group of sequences in **Tables 2, 3, 12 or 13**. In this aspect, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an mRNA generated in the expression of a SNCA gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand (passenger strand) in **Tables 2, 3, 12 or 13**, and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in **Tables 2, 3, 12 or 13** for SNCA.

In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

It will be understood that, although the sequences provided herein are described as modified or conjugated sequences, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA of the disclosure, may comprise any one of the sequences set forth in **Tables 2, 3, 12 or 13** that is un-modified, un-conjugated, or modified or conjugated differently than described therein. One or more lipophilic ligands or one or more GalNAc ligands can be included in any of the positions of the RNAi agents provided in the instant application.

The skilled person is well aware that dsRNAs having a duplex structure of about 20 to 23 base pairs, *e.g.*, 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, (2001) *EMBO J.*, 20: 6877-6888). However, others have found that shorter or longer RNA duplex structures can also be effective (Chu and Rana (2007) *RNA* 14: 1714-1719; Kim *et al.* (2005) *Nat Biotech* 23: 222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided herein, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides derived from one of the sequences provided herein, and differing in their ability to inhibit the expression of a SNCA gene by not more than 10, 15, 20, 25, or 30 % inhibition from a dsRNA comprising the full sequence using the *in vitro* assay with Be(2)-C cells and a 10 nM concentration of the RNA agent and the PCR assay as provided in the examples herein, are contemplated to be within the scope of the present disclosure.

One benchmark assay for inhibition of SNCA involves contacting human Be(2)-C cells with a dsRNA agent as disclosed herein, where sufficient or effective SNCA inhibition is identified if at least 5% reduction, at least 10% reduction, at least 15% reduction, at least 20% reduction, at least 25% reduction, at least 30% reduction, at least 35% reduction, at least 40% reduction, at least 45% reduction, at least 50% reduction, at least 55% reduction, at least 60% reduction, at least 65% reduction, at least 70% reduction, at least 75% reduction, at least 80% reduction, at least 85% reduction, at least 90% reduction, at least 95% reduction, at least 97% reduction, at least 98% reduction, at least 99% reduction, or more of SNCA transcript or protein is observed in contacted cells, as compared to an appropriate control (e.g., cells not contacted with SNCA-targeting dsRNA). Optionally, a dsRNA agent of the disclosure is administered at 10 nM concentration, and the PCR assay is performed as provided in the examples herein (e.g., Example 2 below).

In addition, the RNAs described herein identify a site(s) in a SNCA transcript that is susceptible to RISC-mediated cleavage. As such, the present disclosure further features RNAi agents that target within this site(s). As used herein, an RNAi agent is said to target within a particular site of an RNA transcript if the RNAi agent promotes cleavage of the transcript anywhere within that particular site. Such an RNAi agent will generally include at least about 15 contiguous nucleotides, optionally at least 19 nucleotides, from one of the sequences provided herein coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in a SNCA gene.

An RNAi agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an RNAi agent as described herein contains no more than 3 mismatches (*i.e.*, 3, 2, 1, or 0 mismatches). In one embodiment, an RNAi agent as described herein contains no more than 2 mismatches. In one embodiment, an RNAi agent as described herein contains no more than 1 mismatch. In one embodiment, an RNAi agent as described herein contains 0 mismatches. In certain embodiments, if the antisense strand of the RNAi agent contains mismatches to the target sequence, the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of a SNCA gene generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of a

SNCA gene. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of a SNCA gene is important, especially if the particular region of complementarity in a SNCA gene is known to have polymorphic sequence variation within the population.

II. Modified RNAi Agents of the Disclosure

In one embodiment, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA, is unmodified, and does not comprise, *e.g.*, chemical modifications or conjugations known in the art and described herein. In preferred embodiments, the RNA of an RNAi agent of the disclosure, *e.g.*, a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the disclosure, substantially all of the nucleotides of an RNAi agent of the disclosure are modified. In other embodiments of the disclosure, all of the nucleotides of an RNAi agent of the disclosure are modified. RNAi agents of the disclosure in which “substantially all of the nucleotides are modified” are largely but not wholly modified and can include not more than 5, 4, 3, 2, or 1 unmodified nucleotides. In still other embodiments of the disclosure, RNAi agents of the disclosure can include not more than 5, 4, 3, 2 or 1 modified nucleotides.

The nucleic acids featured in the disclosure can be synthesized or modified by methods well established in the art, such as those described in “Current protocols in nucleic acid chemistry,” Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, *etc.*); base modifications, *e.g.*, replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNAi agents useful in the embodiments described herein include, but are not limited to, RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides.

In some embodiments, a modified RNAi agent will have a phosphorus atom in its internucleoside backbone.

Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, *e.g.*, sodium salts, mixed salts and free acid forms are also included.

Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6,239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and US Pat RE39464, the entire contents of each of which are hereby incorporated herein by reference.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts.

Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134;

5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and, 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

In other embodiments, suitable RNA mimetics are contemplated for use in RNAi agents, in which both the sugar and the internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, the entire contents of each of which are hereby incorporated herein by reference. Additional PNA compounds suitable for use in the RNAi agents of the disclosure are described in, for example, in Nielsen *et al.*, *Science*, 1991, 254, 1497-1500.

Some embodiments featured in the disclosure include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH₂--NH--CH₂--, --CH₂--N(CH₃)--O--CH₂--[known as a methylene (methylimino) or MMI backbone], --CH₂--O--N(CH₃)--CH₂--, --CH₂--N(CH₃)--N(CH₃)--CH₂-- and --N(CH₃)--CH₂--CH₂--[wherein the native phosphodiester backbone is represented as --O--P--O--CH₂--] of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced US5,034,506.

Modified RNAs can also contain one or more substituted sugar moieties. The RNAi agents, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Exemplary suitable modifications include O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C₁ to C₁₀ lower

alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an RNAi agent, or a group for improving the pharmacodynamic properties of an RNAi agent, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78: 486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, *i.e.*, a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH₂--O--CH₂--N(CH₂)₂. Further exemplary modifications include: 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂), 2'-O-hexadecyl, and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an RNAi agent, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. RNAi agents can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application. The entire contents of each of the foregoing are hereby incorporated herein by reference.

An RNAi agent of the disclosure can also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-

propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, those disclosed by Englisch *et al.*, (1991) *Angewandte Chemie, International Edition*, 30: 613, and those disclosed by Sanghvi, Y S., Chapter 15, dsRNA Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the disclosure. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2 °C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Patent Nos. 3,687,808, 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the entire contents of each of which are hereby incorporated herein by reference.

An RNAi agent of the disclosure can also be modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic

acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1): 439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3): 833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12): 3185-3193).

An RNAi agent of the disclosure can also be modified to include one or more bicyclic sugar moieties. A “bicyclic sugar” is a furanosyl ring modified by the bridging of two atoms. A “bicyclic nucleoside” (“BNA”) is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring. Thus, in some embodiments an agent of the disclosure may include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH₂-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1): 439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3): 833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12): 3185-3193). Examples of bicyclic nucleosides for use in the polynucleotides of the disclosure include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the disclosure include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to 4'-(CH₂)—O-2' (LNA); 4'-(CH₂)—S-2'; 4'-(CH₂)₂—O-2' (ENA); 4'-CH(CH₃)—O-2' (also referred to as “constrained ethyl” or “cEt”) and 4'-CH(CH₂OCH₃)—O-2' (and analogs thereof; see, *e.g.*, U.S. Pat. No. 7,399,845); 4'-C(CH₃)(CH₃)—O-2' (and analogs thereof; see *e.g.*, US Patent No. 8,278,283); 4'-CH₂—N(OCH₃)-2' (and analogs thereof; see *e.g.*, US Patent No. 8,278,425); 4'-CH₂—O—N(CH₃)-2' (see, *e.g.*, U.S. Patent Publication No. 2004/0171570); 4'-CH₂—N(R)—O-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group (see, *e.g.*, U.S. Pat. No. 7,427,672); 4'-CH₂—C(H)(CH₃)-2' (see, *e.g.*, Chattopadhyaya *et al.*, *J. Org. Chem.*, 2009, 74, 118-134); and 4'-CH₂—C(=CH₂)-2' (and analogs thereof; see, *e.g.*, US Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

Additional representative US Patents and US Patent Publications that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: US Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133; 7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US 2009/0012281, the entire contents of each of which are hereby incorporated herein by reference.

Any of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α -L-ribofuranose and β -D-ribofuranose (see WO 99/14226).

An RNAi agent of the disclosure can also be modified to include one or more constrained ethyl nucleotides. As used herein, a "constrained ethyl nucleotide" or "cEt" is a locked nucleic acid comprising a bicyclic sugar moiety comprising a 4'-CH(CH₃)-O-2' bridge. In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as "S-cEt."

An RNAi agent of the disclosure may also include one or more "conformationally restricted nucleotides" ("CRN"). CRN are nucleotide analogs with a linker connecting the C2' and C4' carbons of ribose or the C3' and C5' carbons of ribose. CRN lock the ribose ring into a stable conformation and increase the hybridization affinity to mRNA. The linker is of sufficient length to place the oxygen in an optimal position for stability and affinity resulting in less ribose ring puckering.

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, US 2013/0190383; and WO 2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

In some embodiments, an RNAi agent of the disclosure comprises one or more monomers that are UNA (unlocked nucleic acid) nucleotides. UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomer with bonds between C1'-C4' have been removed (*i.e.* the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (*i.e.* the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed (see *Nuc. Acids Symp. Series*, 52, 133-134 (2008) and Fluiter et al., *Mol. Biosyst.*, 2009, 10, 1039 hereby incorporated by reference).

Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

Potentially stabilizing modifications to the ends of RNA molecules can include N-(acetylaminoacetyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(acetyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3'-phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in WO 2011/005861.

Other modifications of an RNAi agent of the disclosure include a 5' phosphate or 5' phosphate mimic, *e.g.*, a 5'-terminal phosphate or phosphate mimic on the antisense strand of an RNAi agent. Suitable phosphate mimics are disclosed in, for example US 2012/0157511, the entire contents of which are incorporated herein by reference.

A. Modified RNAi agents Comprising Motifs of the Disclosure

In certain aspects of the disclosure, the double-stranded RNAi agents of the disclosure include agents with chemical modifications as disclosed, for example, in WO 2013/075035, the entire contents of which are incorporated herein by reference. As shown herein and in WO 2013/075035, a superior result may be obtained by introducing one or more motifs of three identical modifications on three consecutive nucleotides into a sense strand or antisense strand of an RNAi agent, particularly at or near the cleavage site. In some embodiments, the sense strand and antisense strand of the RNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense or antisense strand. The RNAi agent may be optionally conjugated with a lipophilic ligand, *e.g.*, a C16 ligand, for instance on the sense strand. The RNAi agent may be optionally modified with a (S)-glycol nucleic acid (GNA) modification, for instance on one or more residues of the antisense strand. The resulting RNAi agents present superior gene silencing activity.

Accordingly, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of a target gene (*i.e.*, a SNCA gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may be 15-30 nucleotides in length. For example, each strand may be 16-30 nucleotides in length, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30 nucleotides in length, 17-23 nucleotides in length, 17-21 nucleotides

in length, 17-19 nucleotides in length, 19-25 nucleotides in length, 19-23 nucleotides in length, 19-21 nucleotides in length, 21-25 nucleotides in length, or 21-23 nucleotides in length. In certain embodiments, each strand is 19-23 nucleotides in length.

The sense strand and antisense strand typically form a duplex double stranded RNA ("dsRNA"), also referred to herein as an "RNAi agent." The duplex region of an RNAi agent may be 15-30 nucleotide pairs in length. For example, the duplex region can be 16-30 nucleotide pairs in length, 17-30 nucleotide pairs in length, 27-30 nucleotide pairs in length, 17 - 23 nucleotide pairs in length, 17-21 nucleotide pairs in length, 17-19 nucleotide pairs in length, 19-25 nucleotide pairs in length, 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-25 nucleotide pairs in length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length. In preferred embodiments, the duplex region is 19-21 nucleotide pairs in length.

In one embodiment, the RNAi agent may contain one or more overhang regions or capping groups at the 3'-end, 5'-end, or both ends of one or both strands. The overhang can be 1-6 nucleotides in length, for instance 2-6 nucleotides in length, 1-5 nucleotides in length, 2-5 nucleotides in length, 1-4 nucleotides in length, 2-4 nucleotides in length, 1-3 nucleotides in length, 2-3 nucleotides in length, or 1-2 nucleotides in length. In preferred embodiments, the nucleotide overhang region is 2 nucleotides in length. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence. The first and second strands can also be joined, *e.g.*, by additional bases to form a hairpin, or by other non-base linkers.

In one embodiment, the nucleotides in the overhang region of the RNAi agent can each independently be a modified or unmodified nucleotide including, but not limited to 2'-sugar modified, such as, 2'-F, 2'-O-methyl, thymidine (T), and any combinations thereof.

For example, TT can be an overhang sequence for either end on either strand. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence.

The 5'- or 3'- overhangs at the sense strand, antisense strand or both strands of the RNAi agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides

can be the same or different. In one embodiment, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In one embodiment, this 3'-overhang is present in the antisense strand. In one embodiment, this 3'-overhang is present in the sense strand.

The RNAi agent may contain only a single overhang, which can strengthen the interference activity of the RNAi, without affecting its overall stability. For example, the single-stranded overhang may be located at the 3'-terminal end of the sense strand or, alternatively, at the 3'-terminal end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (or the 3'-end of the sense strand) or *vice versa*. Generally, the antisense strand of the RNAi has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. While not wishing to be bound by theory, the asymmetric blunt end at the 5'-end of the antisense strand and 3'-end overhang of the antisense strand favor the guide strand loading into RISC process.

In one embodiment, the RNAi agent is a double ended bluntmer of 19 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7, 8, 9 from the 5' end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5' end.

In another embodiment, the RNAi agent is a double ended bluntmer of 20 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 8, 9, 10 from the 5' end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5' end.

In yet another embodiment, the RNAi agent is a double ended bluntmer of 21 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, 11 from the 5' end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5' end.

In one embodiment, the RNAi agent comprises a 21 nucleotide sense strand and a 23 nucleotide antisense strand, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, 11 from the 5' end; the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5' end, wherein one end of the RNAi agent is blunt,

while the other end comprises a 2 nucleotide overhang. Optionally, the 2 nucleotide overhang is at the 3'-end of the antisense strand. When the 2 nucleotide overhang is at the 3'-end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. In one embodiment, the RNAi agent additionally has two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand. In one embodiment, every nucleotide in the sense strand and the antisense strand of the RNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In one embodiment each residue is independently modified with a 2'-O-methyl or 3'-fluoro, *e.g.*, in an alternating motif. Optionally, the RNAi agent further comprises a ligand (*e.g.*, a lipophilic ligand, optionally a C16 ligand).

In one embodiment, the RNAi agent comprises a sense and an antisense strand, wherein the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1) positions 1 to 23 of the first strand comprise at least 8 ribonucleotides; the antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, comprises at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when the double stranded nucleic acid is introduced into a mammalian cell; and wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

In one embodiment, the RNAi agent comprises sense and antisense strands, wherein the RNAi agent comprises a first strand having a length which is at least 25 and at most 29 nucleotides and a second strand having a length which is at most 30 nucleotides with at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at position 11, 12, 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region which is at least 25 nucleotides in length, and the second strand is sufficiently complementary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein dicer cleavage of the RNAi agent preferentially results in an siRNA comprising the 3' end of the second strand, thereby reducing expression of the target gene in the mammal. Optionally, the RNAi agent further comprises a ligand.

In one embodiment, the sense strand of the RNAi agent contains at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at the cleavage site in the sense strand.

In one embodiment, the antisense strand of the RNAi agent can also contain at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at or near the cleavage site in the antisense strand.

For an RNAi agent having a duplex region of 17-23 nucleotide in length, the cleavage site of the antisense strand is typically around the 10, 11 and 12 positions from the 5'-end. Thus the motifs of three identical modifications may occur at the 9, 10, 11 positions; 10, 11, 12 positions; 11, 12, 13 positions; 12, 13, 14 positions; or 13, 14, 15 positions of the antisense strand, the count starting from the 1st nucleotide from the 5'-end of the antisense strand, or, the count starting from the 1st paired nucleotide within the duplex region from the 5'- end of the antisense strand. The cleavage site in the antisense strand may also change according to the length of the duplex region of the RNAi from the 5'-end.

The sense strand of the RNAi agent may contain at least one motif of three identical modifications on three consecutive nucleotides at the cleavage site of the strand; and the antisense strand may have at least one motif of three identical modifications on three consecutive nucleotides at or near the cleavage site of the strand. When the sense strand and the antisense strand form a dsRNA duplex, the sense strand and the antisense strand can be so aligned that one motif of the

three nucleotides on the sense strand and one motif of the three nucleotides on the antisense strand have at least one nucleotide overlap, *i.e.*, at least one of the three nucleotides of the motif in the sense strand forms a base pair with at least one of the three nucleotides of the motif in the antisense strand. Alternatively, at least two nucleotides may overlap, or all three nucleotides may overlap.

In one embodiment, the sense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides. The first motif may occur at or near the cleavage site of the strand and the other motifs may be a wing modification. The term “wing modification” herein refers to a motif occurring at another portion of the strand that is separated from the motif at or near the cleavage site of the same strand. The wing modification is either adjacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other, the chemistry of the motifs are distinct from each other; and when the motifs are separated by one or more nucleotide, the chemistries can be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

Like the sense strand, the antisense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

In one embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two terminal nucleotides at the 3'-end, 5'-end or both ends of the strand.

In another embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two paired nucleotides within the duplex region at the 3'-end, 5'-end or both ends of the strand.

When the sense strand and the antisense strand of the RNAi agent each contain at least one wing modification, the wing modifications may fall on the same end of the duplex region, and have an overlap of one, two or three nucleotides.

When the sense strand and the antisense strand of the RNAi agent each contain at least two wing modifications, the sense strand and the antisense strand can be so aligned that two

modifications each from one strand fall on one end of the duplex region, having an overlap of one, two or three nucleotides; two modifications each from one strand fall on the other end of the duplex region, having an overlap of one, two or three nucleotides; two modifications one strand fall on each side of the lead motif, having an overlap of one, two, or three nucleotides in the duplex region.

In one embodiment, the RNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch may occur in the overhang region or the duplex region. The base pair may be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C (I=inosine) is preferred over G:C. Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

In one embodiment, the RNAi agent comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'-end of the antisense strand independently selected from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

In one embodiment, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'-end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'-end of the antisense strand is an AU base pair.

In another embodiment, the nucleotide at the 3'-end of the sense strand is deoxy-thymine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxy-thymine (dT). In one embodiment, there is a short sequence of deoxy-thymine nucleotides, for example, two dT nucleotides on the 3'-end of the sense or antisense strand.

In one embodiment, the sense strand sequence may be represented by formula (I):



wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

each N_a independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p and n_q independently represent an overhang nucleotide;

wherein N_b and Y do not have the same modification; and

XXX, YYY and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. Optionally YYY is all 2'-F modified nucleotides.

In one embodiment, the N_a or N_b comprise modifications of alternating pattern.

In one embodiment, the YYY motif occurs at or near the cleavage site of the sense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotides in length, the YYY motif can occur at or the vicinity of the cleavage site (*e.g.*: can occur at positions 6, 7, 8, 7, 8, 9, 8, 9, 10, 9, 10, 11, 10, 11, 12 or 11, 12, 13) of - the sense strand, the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end.

In one embodiment, i is 1 and j is 0, or i is 0 and j is 1, or both i and j are 1. The sense strand can therefore be represented by the following formulas:

5' n_p-N_a-YYY-N_b-ZZZ-N_a-n_q 3' (Ib);

5' n_p-N_a-XXX-N_b-YYY-N_a-n_q 3' (Ic); or

5' n_p-N_a-XXX-N_b-YYY-N_b-ZZZ-N_a-n_q 3' (Id).

When the sense strand is represented by formula (Ib), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides.

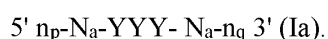
Each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Ic), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Optionally, N_b is 0, 1, 2, 3, 4, 5 or 6. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

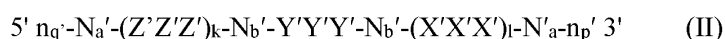
Each of X, Y and Z may be the same or different from each other.

In other embodiments, i is 0 and j is 0, and the sense strand may be represented by the formula:



When the sense strand is represented by formula (Ia), each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

In one embodiment, the antisense strand sequence of the RNAi may be represented by formula (II):



wherein:

k and l are each independently 0 or 1;

p' and q' are each independently 0-6;

each N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p' and n_q' independently represent an overhang nucleotide;

wherein N_b' and Y' do not have the same modification;

and

$X'X'X'$, $Y'Y'Y'$ and $Z'Z'Z'$ each independently represent one motif of three identical modifications on three consecutive nucleotides.

In one embodiment, the N_a' or N_b' comprise modifications of alternating pattern.

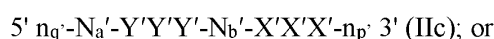
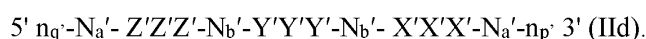
The $Y'Y'Y'$ motif occurs at or near the cleavage site of the antisense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotide in length, the $Y'Y'Y'$ motif can occur at positions 9, 10, 11; 10, 11, 12; 11, 12, 13; 12, 13, 14; or 13, 14, 15 of the antisense strand, with the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the

1st paired nucleotide within the duplex region, from the 5'- end. Optionally, the Y'Y'Y' motif occurs at positions 11, 12, 13.

In one embodiment, Y'Y'Y' motif is all 2'-OMe modified nucleotides.

In one embodiment, k is 1 and l is 0, or k is 0 and l is 1, or both k and l are 1.

The antisense strand can therefore be represented by the following formulas:

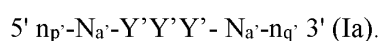


When the antisense strand is represented by formula (IIb), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the antisense strand is represented as formula (IIc), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the antisense strand is represented as formula (IId), each N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Optionally, N_b is 0, 1, 2, 3, 4, 5 or 6.

In other embodiments, k is 0 and l is 0 and the antisense strand may be represented by the formula:



When the antisense strand is represented as formula (IIa), each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X', Y' and Z' may be the same or different from each other.

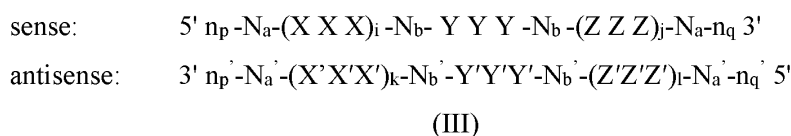
Each nucleotide of the sense strand and antisense strand may be independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-hydroxyl, or 2'-fluoro. For example, each nucleotide of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. Each X, Y, Z, X', Y' and Z', in particular, may represent a 2'-O-methyl modification or a 2'-fluoro modification.

In one embodiment, the sense strand of the RNAi agent may contain YYY motif occurring at 9, 10 and 11 positions of the strand when the duplex region is 21 nt, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end; and Y represents 2'-F modification. The sense strand may additionally contain XXX motif or ZZZ motifs as wing modifications at the opposite end of the duplex region; and XXX and ZZZ each independently represents a 2'-OMe modification or 2'-F modification.

In one embodiment the antisense strand may contain Y'Y'Y' motif occurring at positions 11, 12, 13 of the strand, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end; and Y' represents 2'-O-methyl modification. The antisense strand may additionally contain X'X'X' motif or Z'Z'Z' motifs as wing modifications at the opposite end of the duplex region; and X'X'X' and Z'Z'Z' each independently represents a 2'-OMe modification or 2'-F modification.

The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with an antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

Accordingly, the RNAi agents for use in the methods of the disclosure may comprise a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, the RNAi duplex represented by formula (III):



wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

wherein

each n_p' , n_p , n_q' , and n_q , each of which may or may not be present, independently represents an overhang nucleotide; and

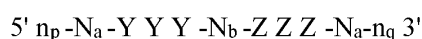
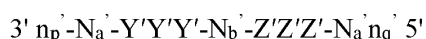
XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides.

In one embodiment, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In another embodiment, k is 0 and l is 0; or k is 1 and l is 0; k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

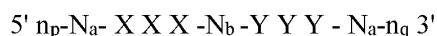
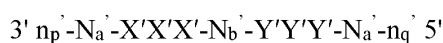
Exemplary combinations of the sense strand and antisense strand forming an RNAi duplex include the formulas below:



(IIIa)



(IIIb)



(IIIc)



(IIId)

When the RNAi agent is represented by formula (IIIa), each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented by formula (IIIb), each N_b independently represents an oligonucleotide sequence comprising 1-10, 1-7, 1-5 or 1-4 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (IIIc), each N_b , N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (IIId), each N_b , N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a , N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of N_a , N_a' , N_b and N_b' independently comprises modifications of alternating pattern.

In one embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications. In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications and $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide a via phosphorothioate linkage. In yet another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, and the sense strand is conjugated to one or more C16 (or related) moieties attached through a bivalent or trivalent branched linker (described below). In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more lipophilic, *e.g.*, C16 (or related) moieties, optionally attached through a bivalent or trivalent branched linker.

In one embodiment, when the RNAi agent is represented by formula (IIIa), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more lipophilic, *e.g.*, C16 (or related) moieties attached through a bivalent or trivalent branched linker.

In one embodiment, the RNAi agent is a multimer containing at least two duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

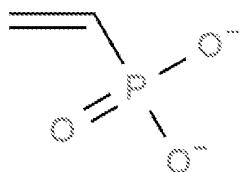
In one embodiment, the RNAi agent is a multimer containing three, four, five, six or more duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are

connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In one embodiment, two RNAi agents represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally conjugated to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

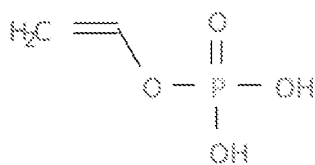
Various publications describe multimeric RNAi agents that can be used in the methods of the disclosure. Such publications include WO2007/091269, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520; and US 7858769, the entire contents of each of which are hereby incorporated herein by reference.

In certain embodiments, the compositions and methods of the disclosure include a vinyl phosphonate (VP) modification of an RNAi agent as described herein. In exemplary embodiments, a vinyl phosphonate of the disclosure has the following structure:



A vinyl phosphonate of the instant disclosure may be attached to either the antisense or the sense strand of a dsRNA of the disclosure. In certain preferred embodiments, a vinyl phosphonate of the instant disclosure is attached to the antisense strand of a dsRNA, optionally at the 5' end of the antisense strand of the dsRNA.

Vinyl phosphate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphate structure is:

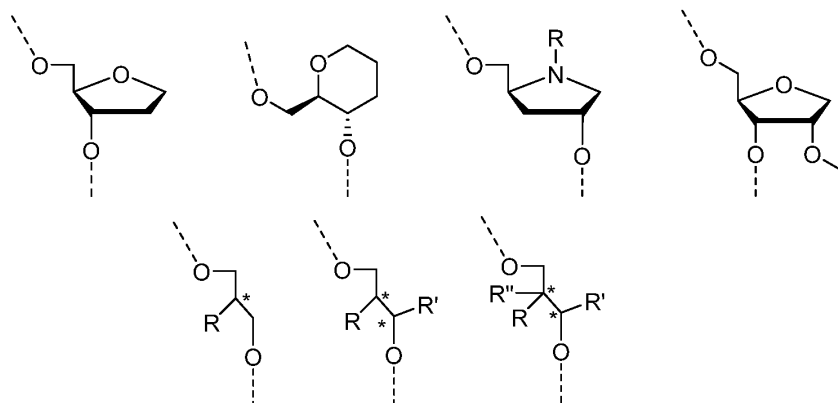


B. Thermally Destabilizing Modifications

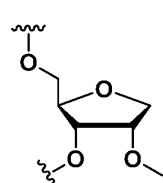
In certain embodiments, a dsRNA molecule can be optimized for RNA interference by incorporating thermally destabilizing modifications in the seed region of the antisense strand (*i.e.*, at positions 2-9 of the 5'-end of the antisense strand) to reduce or inhibit off-target gene silencing. It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, the antisense strand comprises at least one (*e.g.*, one, two, three, four, five or more) thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5' region of the antisense strand. In some embodiments, one or more thermally destabilizing modification(s) of the duplex is/are located in positions 2-9, or optionally positions 4-8, from the 5'-end of the antisense strand. In some further embodiments, the thermally destabilizing modification(s) of the duplex is/are located at position 6, 7 or 8 from the 5'-end of the antisense strand. In still some further embodiments, the thermally destabilizing modification of the duplex is located at position 7 from the 5'-end of the antisense strand. The term "thermally destabilizing modification(s)" includes modification(s) that would result with a dsRNA with a lower overall melting temperature (T_m) (optionally a T_m with one, two, three or four degrees lower than the T_m of the dsRNA without having such modification(s)). In some embodiments, the thermally destabilizing modification of the duplex is located at position 2, 3, 4, 5 or 9 from the 5'-end of the antisense strand.

The thermally destabilizing modifications can include, but are not limited to, abasic modification; mismatch with the opposing nucleotide in the opposing strand; and sugar modification such as 2'-deoxy modification or acyclic nucleotide, *e.g.*, unlocked nucleic acids (UNA) or glycol nucleic acid (GNA).

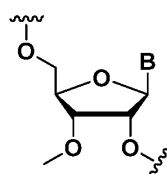
Exemplified abasic modifications include, but are not limited to the following:



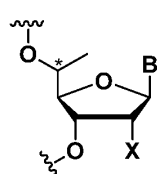
Wherein R = H, Me, Et or OMe; R' = H, Me, Et or OMe; R'' = H, Me, Et or OMe



Mod2
(2'-OMe Abasic
Spacer)

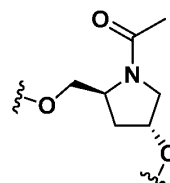


Mod3
(3'-OMe)



Mod4
(5'-Me)

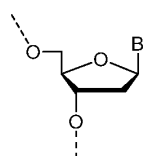
X = OMe, F



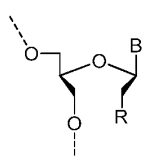
Mod5
(Hyp-spacer)

wherein B is a modified or unmodified nucleobase.

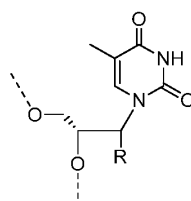
Exemplified sugar modifications include, but are not limited to the following:



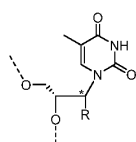
2'-deoxy



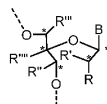
unlocked nucleic acid
R = H, OH, O-alkyl



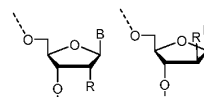
glycol nucleic acid
R = H, OH, O-alkyl



glycol nucleic acid
R = H, OH, O-alkyl



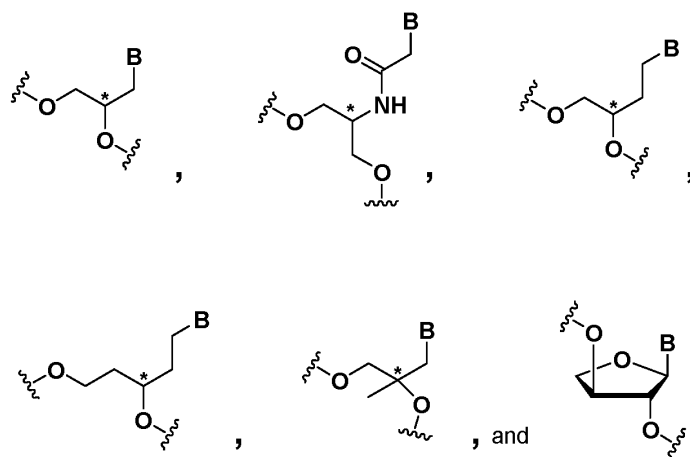
unlocked nucleic acid
R = H, OH, CH₃, CH₂CH₃, O-alkyl, NH₂, NHMe, NMe₂
R' = H, OH, CH₃, CH₂CH₃, O-alkyl, NH₂, NHMe, NMe₂
R'' = H, OH, CH₃, CH₂CH₃, O-alkyl, NH₂, NHMe, NMe₂
R''' = H, OH, CH₃, CH₂CH₃, O-alkyl, NH₂, NHMe, NMe₂
R'''' = H, OH, CH₃, CH₂CH₃, O-alkyl, NH₂, NHMe, NMe₂



R = H, methyl, ethyl

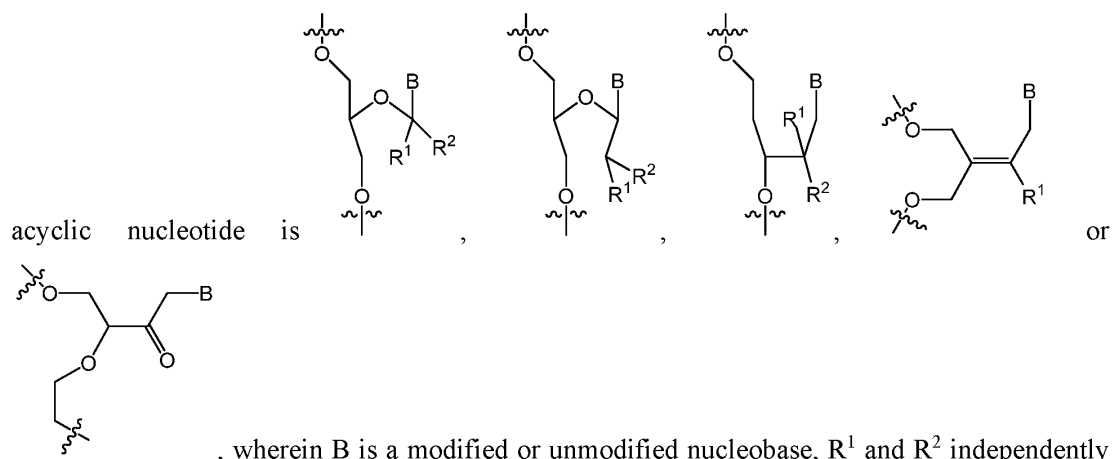
wherein B is a modified or unmodified nucleobase.

In some embodiments the thermally destabilizing modification of the duplex is selected from the group consisting of:



wherein B is a modified or unmodified nucleobase and the asterisk on each structure represents either *R*, *S* or *racemic*.

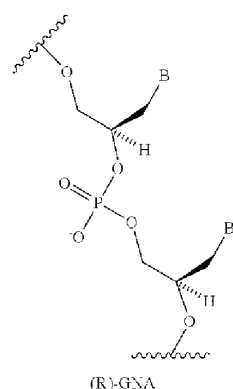
The term "acyclic nucleotide" refers to any nucleotide having an acyclic ribose sugar, for example, where any of bonds between the ribose carbons (*e.g.*, C1'-C2', C2'-C3', C3'-C4', C4'-O4', or C1'-O4') is absent or at least one of ribose carbons or oxygen (*e.g.*, C1', C2', C3', C4' or O4') are independently or in combination absent from the nucleotide. In some embodiments,



, wherein B is a modified or unmodified nucleobase, R¹ and R² independently are H, halogen, OR₃, or alkyl; and R₃ is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar). The term "UNA" refers to unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses

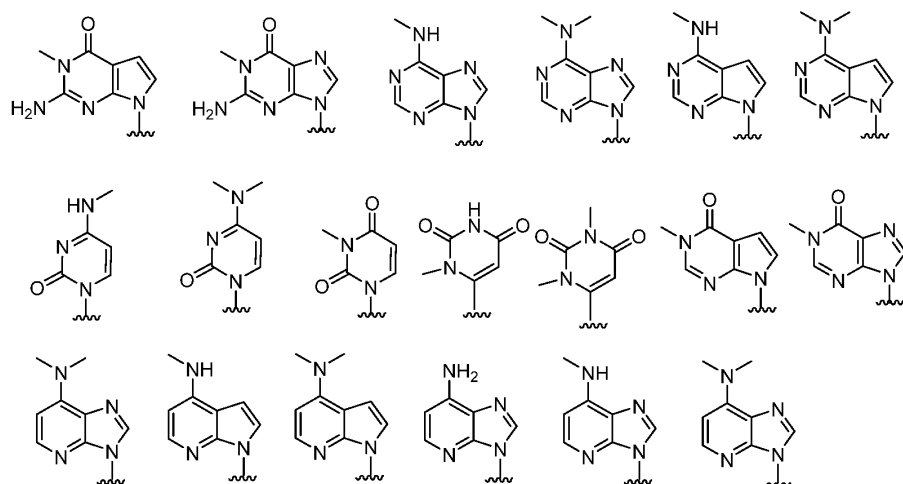
monomers with bonds between C1'-C4' being removed (*i.e.* the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (*i.e.* the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar is removed (see Mikhailov et al., Tetrahedron Letters, 26 (17): 2059 (1985); and Fluiter et al., Mol. Biosyst., 10: 1039 (2009), which are hereby incorporated by reference in their entirety). The acyclic derivative provides greater backbone flexibility without affecting the Watson-Crick pairings. The acyclic nucleotide can be linked via 2'-5' or 3'-5' linkage.

The term 'GNA' refers to glycol nucleic acid which is a polymer similar to DNA or RNA but differing in the composition of its "backbone" in that is composed of repeating glycerol units linked by phosphodiester bonds:



The thermally destabilizing modification of the duplex can be mismatches (*i.e.*, noncomplementary base pairs) between the thermally destabilizing nucleotide and the opposing nucleotide in the opposite strand within the dsRNA duplex. Exemplary mismatch base pairs include G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, U:T, or a combination thereof. Other mismatch base pairings known in the art are also amenable to the present disclosure. A mismatch can occur between nucleotides that are either naturally occurring nucleotides or modified nucleotides, *i.e.*, the mismatch base pairing can occur between the nucleobases from respective nucleotides independent of the modifications on the ribose sugars of the nucleotides. In certain embodiments, the dsRNA molecule contains at least one nucleobase in the mismatch pairing that is a 2'-deoxy nucleobase; *e.g.*, the 2'-deoxy nucleobase is in the sense strand.

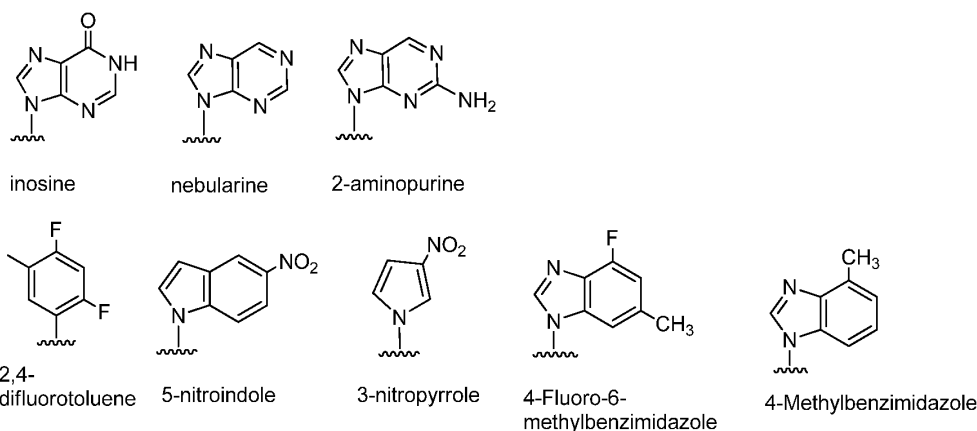
In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes nucleotides with impaired W-C H-bonding to complementary base on the target mRNA, such as:



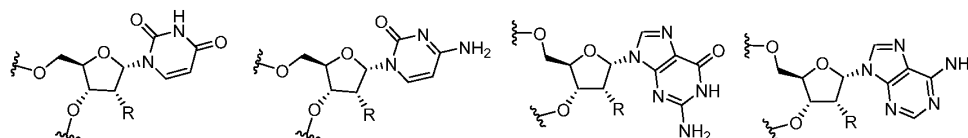
More examples of abasic nucleotide, acyclic nucleotide modifications (including UNA and GNA), and mismatch modifications have been described in detail in WO 2011/133876, which is herein incorporated by reference in its entirety.

The thermally destabilizing modifications may also include universal base with reduced or abolished capability to form hydrogen bonds with the opposing bases, and phosphate modifications.

In some embodiments, the thermally destabilizing modification of the duplex includes nucleotides with non-canonical bases such as, but not limited to, nucleobase modifications with impaired or completely abolished capability to form hydrogen bonds with bases in the opposite strand. These nucleobase modifications have been evaluated for destabilization of the central region of the dsRNA duplex as described in WO 2010/0011895, which is herein incorporated by reference in its entirety. Exemplary nucleobase modifications are:

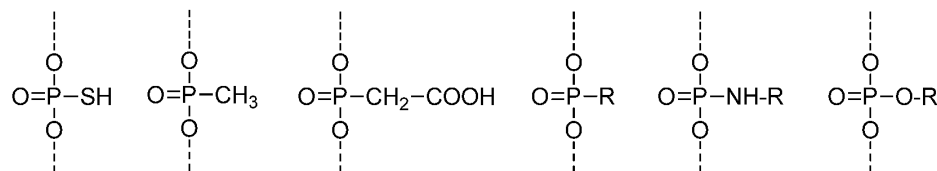


In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes one or more α -nucleotide complementary to the base on the target mRNA, such as:



wherein R is H, OH, OCH₃, F, NH₂, NHMe, NMe₂ or O-alkyl.

Exemplary phosphate modifications known to decrease the thermal stability of dsRNA duplexes compared to natural phosphodiester linkages are:



R = alkyl

The alkyl for the R group can be a C₁-C₆alkyl. Specific alkyls for the R group include, but are not limited to methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl.

As the skilled artisan will recognize, in view of the functional role of nucleobases is defining specificity of an RNAi agent of the disclosure, while nucleobase modifications can be performed in the various manners as described herein, *e.g.*, to introduce destabilizing modifications into an RNAi agent of the disclosure, *e.g.*, for purpose of enhancing on-target effect relative to off-target effect, the range of modifications available and, in general, present upon RNAi agents of the disclosure tends to be much greater for non-nucleobase modifications, *e.g.*, modifications to sugar

groups or phosphate backbones of polyribonucleotides. Such modifications are described in greater detail in other sections of the instant disclosure and are expressly contemplated for RNAi agents of the disclosure, either possessing native nucleobases or modified nucleobases as described above or elsewhere herein.

In addition to the antisense strand comprising a thermally destabilizing modification, the dsRNA can also comprise one or more stabilizing modifications. For example, the dsRNA can comprise at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, the stabilizing modifications all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two stabilizing modifications. The stabilizing modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the stabilizing modification can occur on every nucleotide on the sense strand or antisense strand; each stabilizing modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both stabilizing modification in an alternating pattern. The alternating pattern of the stabilizing modifications on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the stabilizing modifications on the sense strand can have a shift relative to the alternating pattern of the stabilizing modifications on the antisense strand.

In some embodiments, the antisense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, a stabilizing modification in the antisense strand can be present at any positions. In some embodiments, the antisense comprises stabilizing modifications at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense comprises stabilizing modifications at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense comprises stabilizing modifications at positions 2, 14, and 16 from the 5'-end.

In some embodiments, the antisense strand comprises at least one stabilizing modification adjacent to the destabilizing modification. For example, the stabilizing modification can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand comprises a stabilizing modification at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

In some embodiments, the antisense strand comprises at least two stabilizing modifications at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

In some embodiments, the sense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, a stabilizing modification in the sense strand can be present at any positions. In some embodiments, the sense strand comprises stabilizing modifications at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises stabilizing modifications at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises stabilizing modifications at positions opposite or complimentary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises stabilizing modifications at positions opposite or complimentary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three, or four stabilizing modifications.

In some embodiments, the sense strand does not comprise a stabilizing modification in position opposite or complimentary to the thermally destabilizing modification of the duplex in the antisense strand.

Exemplary thermally stabilizing modifications include, but are not limited to, 2'-fluoro modifications. Other thermally stabilizing modifications include, but are not limited to, LNA.

In some embodiments, the dsRNA of the disclosure comprises at least four (*e.g.*, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, the 2'-fluoro nucleotides all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two 2'-fluoro nucleotides. The 2'-fluoro modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the 2'-fluoro modification can occur on every nucleotide on the sense strand or antisense strand; each 2'-fluoro modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both 2'-fluoro modifications in an alternating pattern. The alternating pattern of the 2'-fluoro modifications on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the 2'-fluoro modifications on the sense strand can have a shift relative to the alternating pattern of the 2'-fluoro modifications on the antisense strand.

In some embodiments, the antisense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the antisense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 14, and 16 from the 5'-end.

In some embodiments, the antisense strand comprises at least one 2'-fluoro nucleotide adjacent to the destabilizing modification. For example, the 2'-fluoro nucleotide can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand comprises a 2'-fluoro nucleotide at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

In some embodiments, the antisense strand comprises at least two 2'-fluoro nucleotides at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

In some embodiments, the sense strand comprises at least two (*e.g.*, two, three, four, five, six, seven, eight, nine, ten or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the sense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complimentary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complimentary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three or four 2'-fluoro nucleotides.

In some embodiments, the sense strand does not comprise a 2'-fluoro nucleotide in position opposite or complimentary to the thermally destabilizing modification of the duplex in the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises a 21 nucleotides (nt) sense strand and a 23 nucleotides (nt) antisense, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide occurs in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), wherein one end of the dsRNA is blunt, while the other end is comprises a 2 nt overhang, and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a blunt end at 5'-end of the antisense strand. Optionally, the 2 nt overhang is at the 3'-end of the antisense.

In some embodiments, the dsRNA molecule of the disclosure comprising a sense and antisense strands, wherein: the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1), positions 1 to 23 of said sense strand comprise at least 8 ribonucleotides; antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when said double stranded nucleic acid is introduced into a mammalian cell; and wherein the antisense strand contains at least one thermally destabilizing nucleotide, where at least one thermally destabilizing nucleotide is in the seed region of the antisense strand (*i.e.* at position 2-9 of the 5'-end of the antisense strand). For example, the

thermally destabilizing nucleotide occurs between positions opposite or complimentary to positions 14-17 of the 5'-end of the sense strand, and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5, or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4, or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; and (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a duplex region of 12-30 nucleotide pairs in length.

In some embodiments, the dsRNA molecule of the disclosure comprises a sense and antisense strands, wherein said dsRNA molecule comprises a sense strand having a length which is at least 25 and at most 29 nucleotides and an antisense strand having a length which is at most 30 nucleotides with the sense strand comprises a modified nucleotide that is susceptible to enzymatic degradation at position 11 from the 5' end, wherein the 3' end of said sense strand and the 5' end of said antisense strand form a blunt end and said antisense strand is 1-4 nucleotides longer at its 3' end than the sense strand, wherein the duplex region which is at least 25 nucleotides in length, and said antisense strand is sufficiently complementary to a target mRNA along at least 19 nt of said antisense strand length to reduce target gene expression when said dsRNA molecule is introduced into a mammalian cell, and wherein dicer cleavage of said dsRNA preferentially results in an siRNA comprising said 3' end of said antisense strand, thereby reducing expression of the target gene in the mammal, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide is in the seed region of the antisense strand (*i.e.* at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5, or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4, or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; and (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA has a duplex region of 12-29 nucleotide pairs in length.

In some embodiments, every nucleotide in the sense strand and antisense strand of the dsRNA molecule may be modified. Each nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2' hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with “dephospho” linkers; modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

As nucleic acids are polymers of subunits, many of the modifications occur at a position which is repeated within a nucleic acid, *e.g.*, a modification of a base, or a phosphate moiety, or a non-linking O of a phosphate moiety. In some cases, the modification will occur at all of the subject positions in the nucleic acid but in many cases it will not. By way of example, a modification may only occur at a 3' or 5' terminal position, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double strand region, a single strand region, or in both. A modification may occur only in the double strand region of an RNA or may only occur in a single strand region of an RNA. *E.g.*, a phosphorothioate modification at a non-linking O position may only occur at one or both termini, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand, or may occur in double strand and single strand regions, particularly at termini. The 5' end or ends can be phosphorylated.

It may be possible, *e.g.*, to enhance stability, to include particular bases in overhangs, or to include modified nucleotides or nucleotide surrogates, in single strand overhangs, *e.g.*, in a 5' or 3' overhang, or in both. *E.g.*, it can be desirable to include purine nucleotides in overhangs. In some embodiments all or some of the bases in a 3' or 5' overhang may be modified, *e.g.*, with a modification described herein. Modifications can include, *e.g.*, the use of modifications at the 2' position of the ribose sugar with modifications that are known in the art, *e.g.*, the use of deoxyribonucleotides, 2'-deoxy-2'-fluoro (2'-F) or 2'-O-methyl modified instead of the ribosugar of the nucleobase, and modifications in the phosphate group, *e.g.*, phosphorothioate modifications. Overhangs need not be homologous with the target sequence.

In some embodiments, each residue of the sense strand and antisense strand is independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C-allyl, 2'-deoxy, or 2'-fluoro. The strands can contain more than one modification. In some

embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. It is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

At least two different modifications are typically present on the sense strand and antisense strand. Those two modifications may be the 2'-deoxy, 2'-O-methyl or 2'-fluoro modifications, acyclic nucleotides or others. In some embodiments, the sense strand and antisense strand each comprises two differently modified nucleotides selected from 2'-O-methyl or 2'-deoxy. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl nucleotide, 2'-deoxy nucleotide, 2'-deoxy-2'-fluoro nucleotide, 2'-O-N-methylacetamido (2'-O-NMA) nucleotide, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleotide, 2'-O-aminopropyl (2'-O-AP) nucleotide, or 2'-ara-F nucleotide. Again, it is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises modifications of an alternating pattern, particular in the B1, B2, B3, B1', B2', B3', B4' regions. The term "alternating motif" or "alternative pattern" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB...", "AABBAABBAABB...", "AABAABAABAAB...", "AAABAAABAAAB...", "AAABBBAAABBB...", or "ABCABCABCABC..." etc.

The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, *i.e.*, modifications on every other nucleotide, may be the same, but each of the sense strand or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB...", "ACACAC..." "BDBDBD..." or "CDCDCD..." etc.

In some embodiments, the dsRNA molecule of the disclosure comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the

antisense strand and vice versa. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with “ABABAB” from 5’-3’ of the strand and the alternating motif in the antisense strand may start with “BABABA” from 3’-5’ of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with “AABBAABB” from 5’-3’ of the strand and the alternating motif in the antisense strand may start with “BBAABBAA” from 3’-5’ of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

The dsRNA molecule of the disclosure may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand or antisense strand or both in any position of the strand. For instance, the internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand.

In some embodiments, the dsRNA molecule comprises the phosphorothioate or methylphosphonate internucleotide linkage modification in the overhang region. For example, the overhang region comprises two nucleotides having a phosphorothioate or methylphosphonate internucleotide linkage between the two nucleotides. Internucleotide linkage modifications also may be made to link the overhang nucleotides with the terminal paired nucleotides within duplex region. For example, at least 2, 3, 4, or all the overhang nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage, and optionally, there may be additional phosphorothioate or methylphosphonate internucleotide linkages linking the overhang nucleotide with a paired nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleotide linkages between the terminal three nucleotides, in which two of the three nucleotides are overhang nucleotides, and the third is a paired nucleotide

next to the overhang nucleotide. Optionally, these terminal three nucleotides may be at the 3'-end of the antisense strand.

In some embodiments, the sense strand of the dsRNA molecule comprises 1-10 blocks of two to ten phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said sense strand is paired with an antisense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of three phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of four phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising

any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of five phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of six phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of seven phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, or 8 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of eight phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, or 6 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of nine phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, or 4 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the termini position(s) of the sense or antisense strand. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage at one end or both ends of the sense or antisense strand.

In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the internal region of the duplex of each of the sense or antisense strand. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate methylphosphonate internucleotide linkage at position 8-16 of the duplex region counting from the 5'-end of the sense strand; the dsRNA molecule can optionally further comprise one or more phosphorothioate or methylphosphonate internucleotide linkage modification within 1-10 of the termini position(s).

In some embodiments, the dsRNA molecule of the disclosure further comprises one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 1-5 and one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 18-23 of the sense strand (counting from the 5'-end), and one to five phosphorothioate or methylphosphonate internucleotide linkage modification at positions 1 and 2 and one to five within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate or methylphosphonate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate or methylphosphonate

internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modification at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 (counting from the 5'-end) of the sense strand, and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 (counting from the 5'-end) of the sense strand, and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 20 and 21 of the sense strand

(counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 20 and 21 the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 21 and 22 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 21 and 22 the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 22 and 23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two

phosphorothioate internucleotide linkage modifications at positions 23 and 23 the antisense strand (counting from the 5'-end).

In some embodiments, compound of the disclosure comprises a pattern of backbone chiral centers. In some embodiments, a common pattern of backbone chiral centers comprises at least 5 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 6 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 7 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 8 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 9 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 16 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 17 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 18 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 19 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no

more than 5 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages which are not chiral (as a non-limiting example, a phosphodiester). In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration, and no more than 8 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration, and no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration, and no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 15

internucleotidic linkages in the Sp configuration, and no more than 4 internucleotidic linkages which are not chiral. In some embodiments, the internucleotidic linkages in the Sp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages in the Rp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages which are not chiral are optionally contiguous or not contiguous.

In some embodiments, compound of the disclosure comprises a block is a stereochemistry block. In some embodiments, a block is an Rp block in that each internucleotidic linkage of the block is Rp. In some embodiments, a 5'-block is an Rp block. In some embodiments, a 3'-block is an Rp block. In some embodiments, a block is an Sp block in that each internucleotidic linkage of the block is Sp. In some embodiments, a 5'-block is an Sp block. In some embodiments, a 3'-block is an Sp block. In some embodiments, provided oligonucleotides comprise both Rp and Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Rp but no Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Sp but no Rp blocks. In some embodiments, provided oligonucleotides comprise one or more PO blocks wherein each internucleotidic linkage in a natural phosphate linkage.

In some embodiments, compound of the disclosure comprises a 5'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block comprises 4 or more nucleoside units. In some embodiments, a 5'-block comprises 5 or more nucleoside units. In some embodiments, a 5'-block comprises 6 or more nucleoside units. In some embodiments, a 5'-block comprises 7 or more nucleoside units. In some embodiments, a 3'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block comprises 4 or more nucleoside units. In some embodiments, a 3'-block comprises 5 or more nucleoside units. In some embodiments, a 3'-

block comprises 6 or more nucleoside units. In some embodiments, a 3'-block comprises 7 or more nucleoside units.

In some embodiments, compound of the disclosure comprises a type of nucleoside in a region or an oligonucleotide is followed by a specific type of internucleotidic linkage, *e.g.*, natural phosphate linkage, modified internucleotidic linkage, Rp chiral internucleotidic linkage, Sp chiral internucleotidic linkage, etc. In some embodiments, A is followed by Sp. In some embodiments, A is followed by Rp. In some embodiments, A is followed by natural phosphate linkage (PO). In some embodiments, U is followed by Sp. In some embodiments, U is followed by Rp. In some embodiments, U is followed by natural phosphate linkage (PO). In some embodiments, C is followed by Sp. In some embodiments, C is followed by Rp. In some embodiments, C is followed by natural phosphate linkage (PO). In some embodiments, G is followed by Sp. In some embodiments, G is followed by Rp. In some embodiments, G is followed by natural phosphate linkage (PO). In some embodiments, C and U are followed by Sp. In some embodiments, C and U are followed by Rp. In some embodiments, C and U are followed by natural phosphate linkage (PO). In some embodiments, A and G are followed by Sp. In some embodiments, A and G are followed by Rp.

In some embodiments, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense

strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the sense strand is conjugated with a ligand; (iii) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (iv) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (v) the dsRNA comprises at least four 2'-fluoro modifications; (vi) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the sense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (v) the sense strand comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the sense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the sense

strand is conjugated with a ligand; (iii) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (iv) the sense strand comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (v) the dsRNA comprises at least four 2'-fluoro modifications; (vi) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (vii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch can occur in the overhang region or the duplex region. The base pair can be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

In some embodiments, the dsRNA molecule of the disclosure comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'- end of the antisense strand can be chosen independently from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

In some embodiments, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair.

It was found that introducing 4'-modified or 5'-modified nucleotide to the 3'-end of a phosphodiester (PO), phosphorothioate (PS), or phosphorodithioate (PS2) linkage of a dinucleotide at any position of single stranded or double stranded oligonucleotide can exert steric effect to the internucleotide linkage and, hence, protecting or stabilizing it against nucleases.

In some embodiments, 5'-modified nucleoside is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 5'-alkylated

nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 5' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleoside is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-modified nucleoside is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 4'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 4' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleoside is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer. Alternatively, a 4'-*O*-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The 4'-*O*-alkyl of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleoside is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 5'-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleoside is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 4'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleoside is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-*O*-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleoside is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, the dsRNA molecule of the disclosure can comprise 2'-5' linkages (with 2'-H, 2'-OH and 2'-OMe and with P=O or P=S). For example, the 2'-5' linkages

modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

In another embodiment, the dsRNA molecule of the disclosure can comprise L sugars (*e.g.*, L ribose, L-arabinose with 2'-H, 2'-OH and 2'-OMe). For example, these L sugars modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

Various publications describe multimeric siRNA which can all be used with the dsRNA of the disclosure. Such publications include WO2007/091269, US 7858769, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520 which are hereby incorporated by their entirety.

As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to an RNAi agent can optimize one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose sugar of one or more ribonucleotide subunits of a dsRNA agent can be replaced with another moiety, *e.g.*, a non-carbohydrate (optionally cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, *i.e.*, all ring atoms are carbon atoms, or a heterocyclic ring system, *i.e.*, one or more ring atoms may be a heteroatom, *e.g.*, nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, *e.g.* fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

The ligand may be attached to the polynucleotide via a carrier. The carriers include (i) at least one "backbone attachment point," optionally two "backbone attachment points" and (ii) at least one "tethering attachment point." A "backbone attachment point" as used herein refers to a functional group, *e.g.* a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier into the backbone, *e.g.*, the phosphate, or modified phosphate, *e.g.*, sulfur containing, backbone, of a ribonucleic acid. A "tethering attachment point" (TAP) in some embodiments refers to a constituent ring atom of the cyclic carrier, *e.g.*, a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a

selected moiety. The moiety can be, *e.g.*, a carbohydrate, *e.g.* monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and polysaccharide. Optionally, the selected moiety is connected by an intervening tether to the cyclic carrier. Thus, the cyclic carrier will often include a functional group, *e.g.*, an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, *e.g.*, a ligand to the constituent ring.

The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be a cyclic group or an acyclic group. Optionally, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and decalin. Optionally, the acyclic group is selected from serinol backbone and diethanolamine backbone.

In certain specific embodiments, the RNAi agent for use in the methods of the disclosure is an agent selected from the group of agents listed in **Tables 2, 3, 12 or 13**. These agents may further comprise a ligand, such as one or more lipophilic moieties, one or more GalNAc derivatives, or both of one or more lipophilic moieties and one or more GalNAc derivatives.

III. iRNAs Conjugated to Ligands

Another modification of the RNA of an iRNA of the disclosure involves chemically linking to the iRNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the iRNA, *e.g.*, into a cell. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 1989, 86: 6553-6556), cholic acid (Manoharan *et al.*, *Biorg. Med. Chem. Lett.*, 1994, 4: 1053-1060), a thioether, *e.g.*, beryl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660: 306-309; Manoharan *et al.*, *Biorg. Med. Chem. Lett.*, 1993, 3: 2765-2770), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20: 533-538), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J*, 1991, 10: 1111-1118; Kabanov *et al.*, *FEBS Lett.*, 1990, 259: 327-330; Svinarchuk *et al.*, *Biochimie*, 1993, 75: 49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36: 3651-3654; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18: 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995,

14: 969-973), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36: 3651-3654), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264: 229-237), or an octadecylamine or hexylamino-carboxyloxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277: 923-937).

In certain embodiments, a ligand alters the distribution, targeting or lifetime of an iRNA agent into which it is incorporated. In some embodiments, a ligand provides an enhanced affinity for a selected target, *e.g.*, molecule, cell or cell type, compartment, *e.g.*, a cellular or organ compartment, tissue, organ or region of the body, as, *e.g.*, compared to a species absent such a ligand. Typical ligands will not take part in duplex pairing in a duplexed nucleic acid.

Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolid) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazene. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an α -helical peptide.

Ligands can also include targeting groups, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, or an RGD peptide or RGD peptide mimetic. In certain embodiments, the ligand is a multivalent galactose, *e.g.*, an N-acetyl-galactosamine.

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

Ligands can be proteins, *e.g.* glycoproteins, or peptides, *e.g.* molecules having a specific affinity for a co-ligand, or antibodies *e.g.* an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell. Ligands may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF- κ B.

The ligand can be a substance, *e.g.* a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.* by disrupting the cell's microtubules, microfilaments, or intermediate filaments. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

In some embodiments, a ligand attached to an iRNA as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins *etc.* Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E, biotin *etc.* Oligonucleotides that comprise a number of phosphorothioate linkages are also known

to bind to serum protein, thus short oligonucleotides, *e.g.*, oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone are also amenable to the present disclosure as ligands (*e.g.* as PK modulating ligands). In addition, aptamers that bind serum components (*e.g.* serum proteins) are also suitable for use as PK modulating ligands in the embodiments described herein.

Ligand-conjugated iRNAs of the disclosure may be synthesized by the use of an oligonucleotide that bears a pendant reactive functionality, such as that derived from the attachment of a linking molecule onto the oligonucleotide (described below). This reactive oligonucleotide may be reacted directly with commercially-available ligands, ligands that are synthesized bearing any of a variety of protecting groups, or ligands that have a linking moiety attached thereto.

The oligonucleotides used in the conjugates of the present disclosure may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems® (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is also known to use similar techniques to prepare other oligonucleotides, such as the phosphorothioates and alkylated derivatives.

In the ligand-conjugated oligonucleotides and ligand-molecule bearing sequence-specific linked nucleosides of the present disclosure, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. In some embodiments, the oligonucleotides or linked nucleosides of the present disclosure are synthesized by an automated synthesizer using phosphoramidites derived from ligand-nucleoside conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

A. Lipid Conjugates

In certain embodiments, the ligand or conjugate is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule can typically bind a serum protein, such as human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, *e.g.*, a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, naproxen or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, or (c) can be used to adjust binding to a serum protein, *e.g.*, HSA.

A lipid-based ligand can be used to modulate, *e.g.*, control (*e.g.*, inhibit) the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney.

In certain embodiments, the lipid-based ligand binds HSA. For example, the ligand can bind HSA with a sufficient affinity such that distribution of the conjugate to a non-kidney tissue is enhanced. However, the affinity is typically not so strong that the HSA-ligand binding cannot be reversed.

In certain embodiments, the lipid-based ligand binds HSA weakly or not at all, such that distribution of the conjugate to the kidney is enhanced. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid-based ligand.

In another aspect, the ligand is a moiety, *e.g.*, a vitamin, which is taken up by a target cell, *e.g.*, a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, *e.g.*, of the malignant or non-malignant type, *e.g.*, cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include are B vitamin, *e.g.*, folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by cancer cells. Also included are HSA and low density lipoprotein (LDL).

B. Cell Permeation Agents

In another aspect, the ligand is a cell-permeation agent, such as a helical cell-permeation agent. In certain embodiments, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopodia. If the agent is a peptide, it can be modified, including a peptidylmimetic,

invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is typically an α -helical agent and can have a lipophilic and a lipophobic phase.

The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp, or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 9). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 10)) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a “delivery” peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRPPQ (SEQ ID NO: 11)) and the *Drosophila Antennapedia* protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 12)) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, *Nature*, 354: 82-84, 1991). Typically, the peptide or peptidomimetic tethered to a dsRNA agent via an incorporated monomer unit is a cell targeting peptide such as an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

An RGD peptide for use in the compositions and methods of the disclosure may be linear or cyclic, and may be modified, *e.g.*, glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidomimetics may include D-amino acids, as well

as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand. Preferred conjugates of this ligand target PECAM-1 or VEGF.

An RGD peptide moiety can be used to target a particular cell type, *e.g.*, a tumor cell, such as an endothelial tumor cell or a breast cancer tumor cell (Zitzmann *et al.*, *Cancer Res.*, 62: 5139-43, 2002). An RGD peptide can facilitate targeting of an dsRNA agent to tumors of a variety of other tissues, including the lung, kidney, spleen, or liver (Aoki *et al.*, *Cancer Gene Therapy* 8: 783-787, 2001). Typically, the RGD peptide will facilitate targeting of an iRNA agent to the kidney. The RGD peptide can be linear or cyclic, and can be modified, *e.g.*, glycosylated or methylated to facilitate targeting to specific tissues. For example, a glycosylated RGD peptide can deliver an iRNA agent to a tumor cell expressing $\alpha v \beta_3$ (Haubner *et al.*, *Jour. Nucl. Med.*, 42: 326-336, 2001).

A “cell permeation peptide” is capable of permeating a cell, *e.g.*, a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α -helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β -defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, *Nucl. Acids Res.* 31: 2717-2724, 2003).

C. Carbohydrate Conjugates

In some embodiments of the compositions and methods of the disclosure, an iRNA further comprises a carbohydrate. The carbohydrate conjugated iRNA are advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, “carbohydrate” refers to a compound which is either a carbohydrate *per se* made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri- and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9

monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.*, C5, C6, C7, or C8) sugars; di- and tri-saccharides include sugars having two or three monosaccharide units (*e.g.*, C5, C6, C7, or C8).

In certain embodiments, a carbohydrate conjugate comprises a monosaccharide.

In certain embodiments, the monosaccharide is an N-acetylgalactosamine (GalNAc). GalNAc conjugates, which comprise one or more N-acetylgalactosamine (GalNAc) derivatives, are described, for example, in US 8,106,022, the entire content of which is hereby incorporated herein by reference. In some embodiments, the GalNAc conjugate serves as a ligand that targets the iRNA to particular cells. In some embodiments, the GalNAc conjugate targets the iRNA to liver cells, *e.g.*, by serving as a ligand for the asialoglycoprotein receptor of liver cells (*e.g.*, hepatocytes).

In some embodiments, the carbohydrate conjugate comprises one or more GalNAc derivatives. The GalNAc derivatives may be attached via a linker, *e.g.*, a bivalent or trivalent branched linker. In some embodiments the GalNAc conjugate is conjugated to the 3' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 3' end of the sense strand) via a linker, *e.g.*, a linker as described herein. In some embodiments the GalNAc conjugate is conjugated to the 5' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 5' end of the sense strand) via a linker, *e.g.*, a linker as described herein.

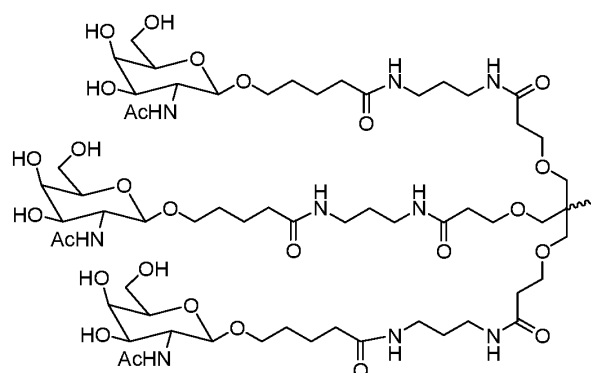
In certain embodiments of the disclosure, the GalNAc or GalNAc derivative is attached to an iRNA agent of the disclosure via a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the disclosure via a bivalent linker. In yet other embodiments of the disclosure, the GalNAc or GalNAc derivative is attached to an iRNA agent of the disclosure via a trivalent linker. In other embodiments of the disclosure, the GalNAc or GalNAc derivative is attached to an iRNA agent of the disclosure via a tetravalent linker.

In certain embodiments, the double stranded RNAi agents of the disclosure comprise one GalNAc or GalNAc derivative attached to the iRNA agent. In certain embodiments, the double stranded RNAi agents of the disclosure comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of monovalent linkers.

In some embodiments, for example, when the two strands of an iRNA agent of the disclosure are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached via a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

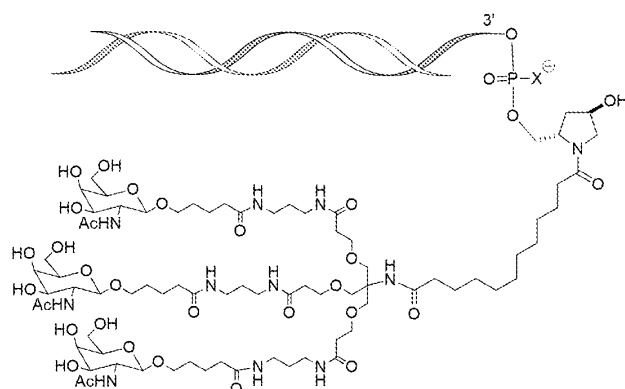
In some embodiments, for example, when the two strands of an iRNA agent of the disclosure are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached via a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

In some embodiments, the GalNAc conjugate is

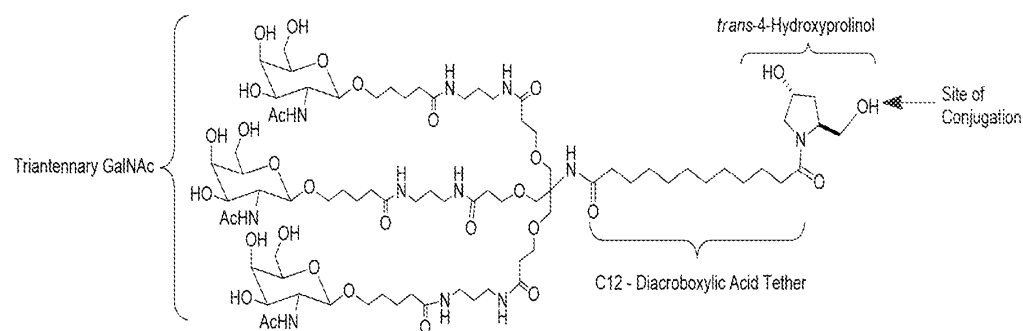


Formula II.

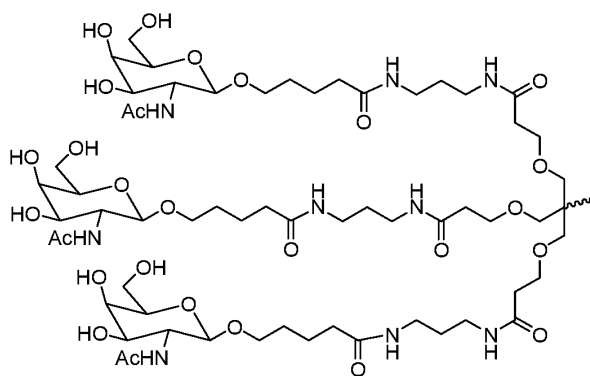
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate via a linker as shown in the following schematic, wherein X is O or S



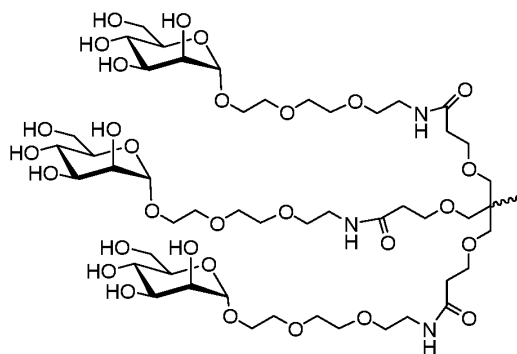
In some embodiments, the RNAi agent is conjugated to L96 as defined in **Table 1** and shown below:



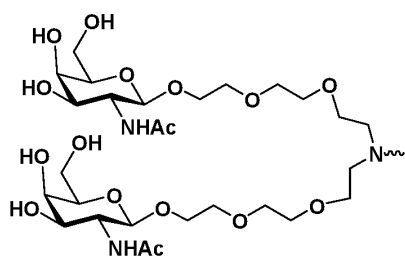
In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the disclosure is selected from the group consisting of:



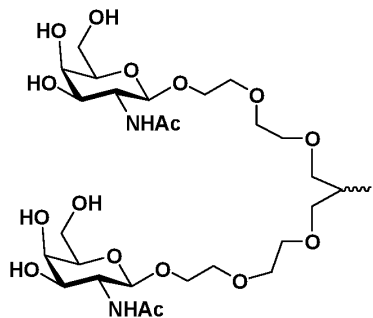
Formula II,



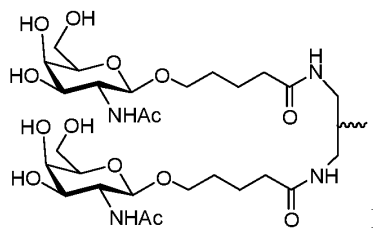
Formula III,



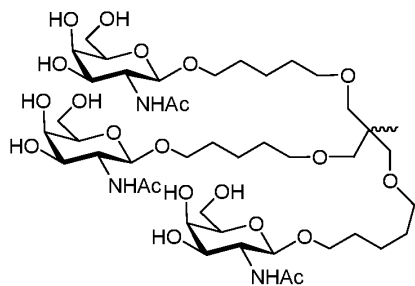
Formula IV,



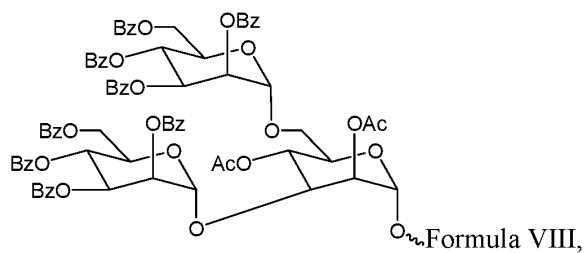
Formula V,



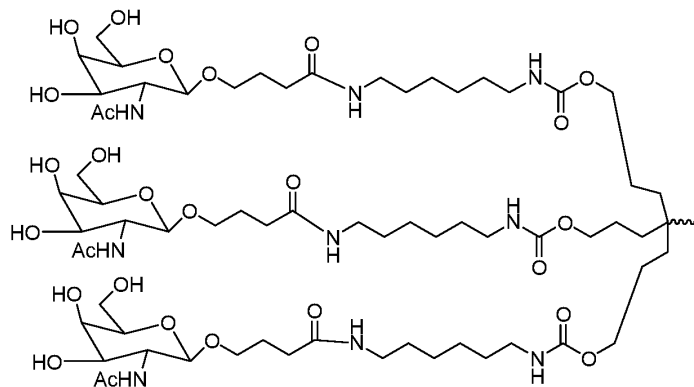
Formula VI,



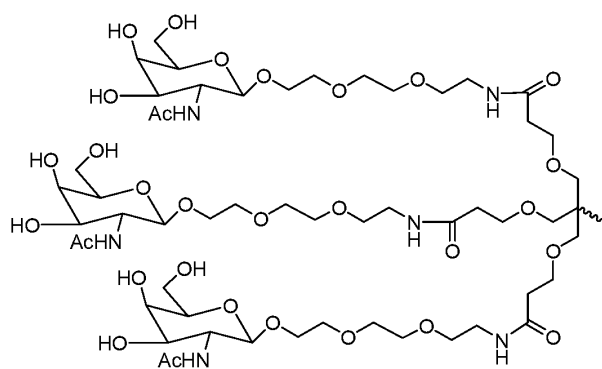
Formula VII,



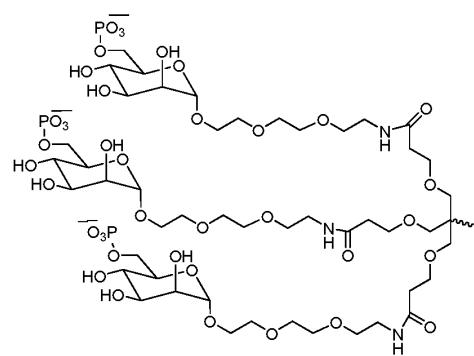
Formula VIII,



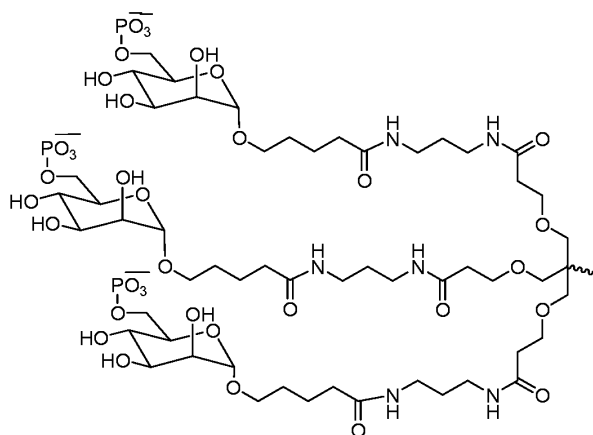
Formula IX,



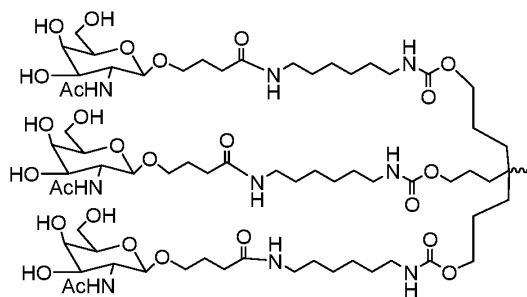
Formula X,



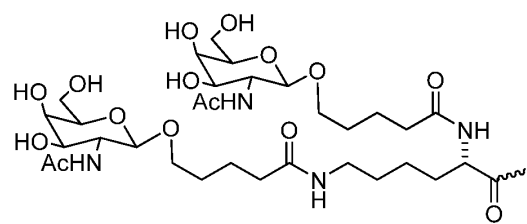
Formula XI,



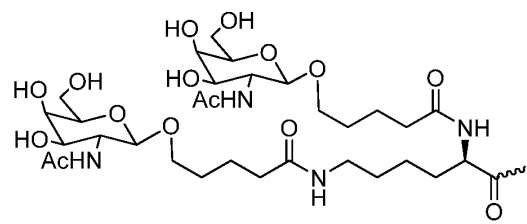
Formula XII,



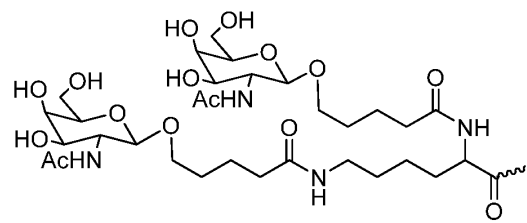
Formula XIII,



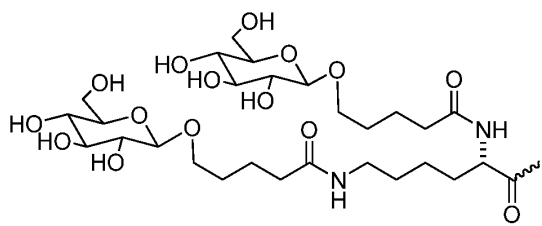
Formula XIV,



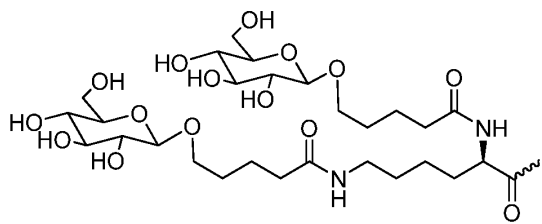
Formula XV,



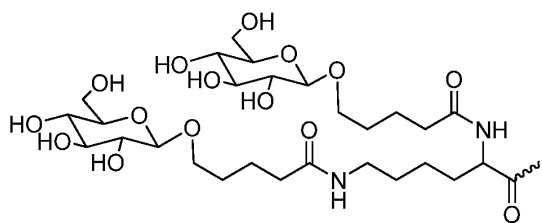
Formula XVI,



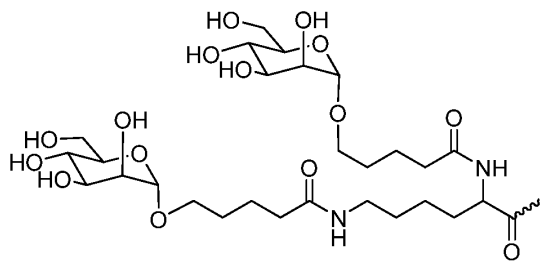
Formula XVII,



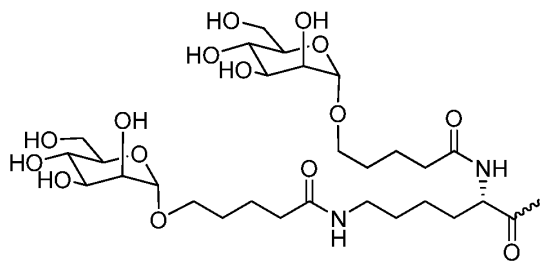
Formula XVIII,



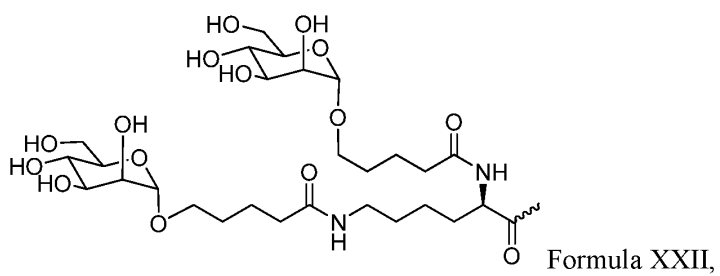
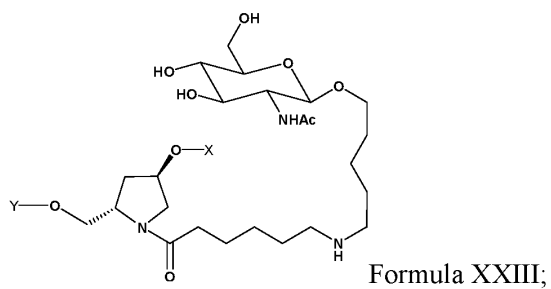
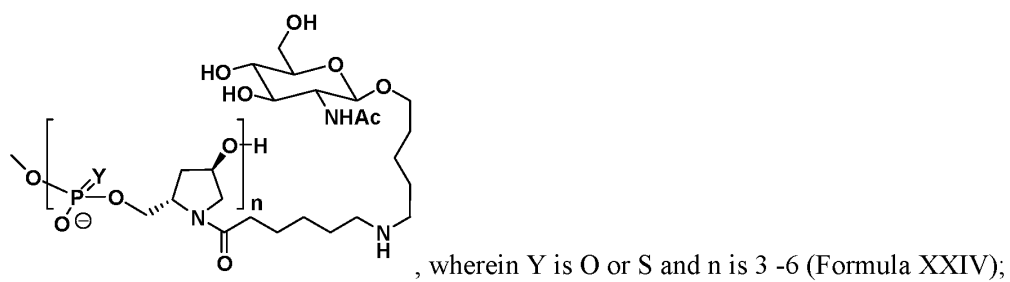
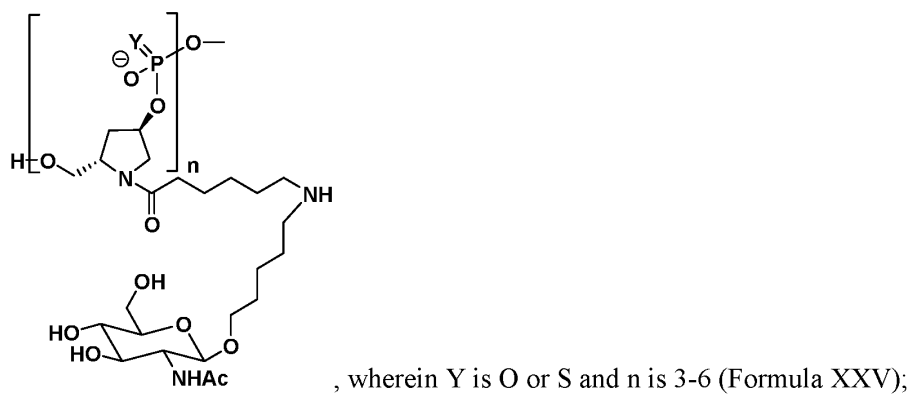
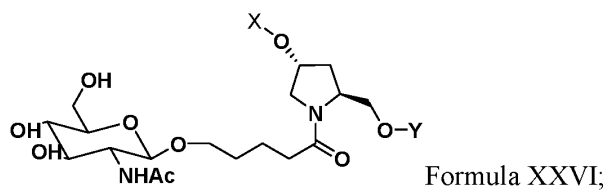
Formula XIX,

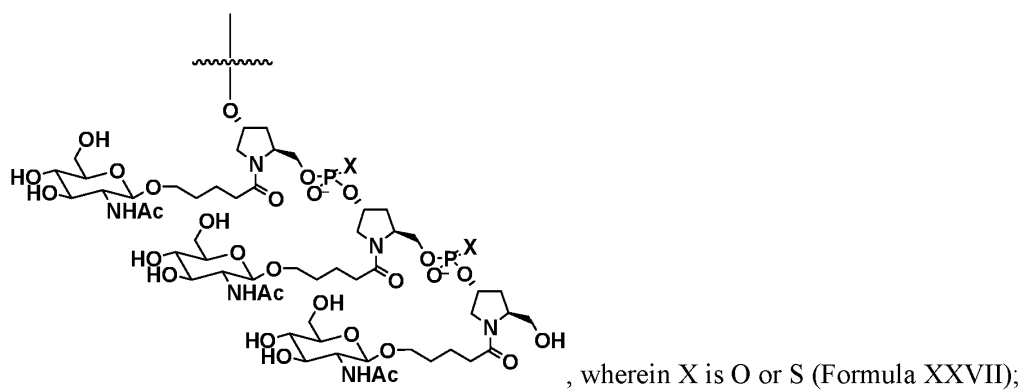
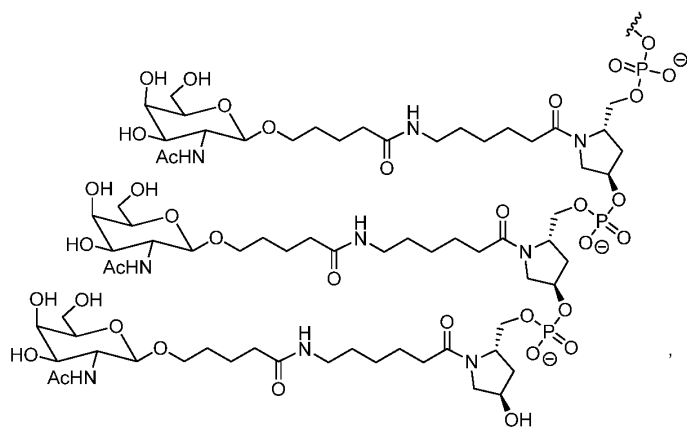
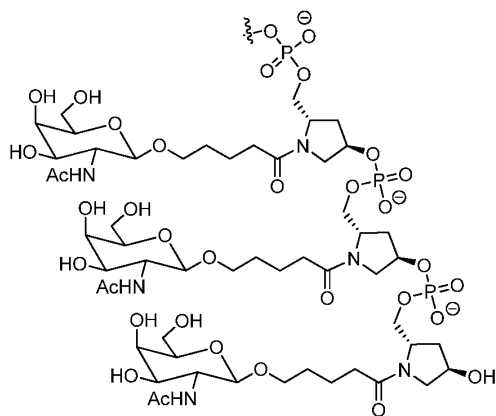


Formula XX,



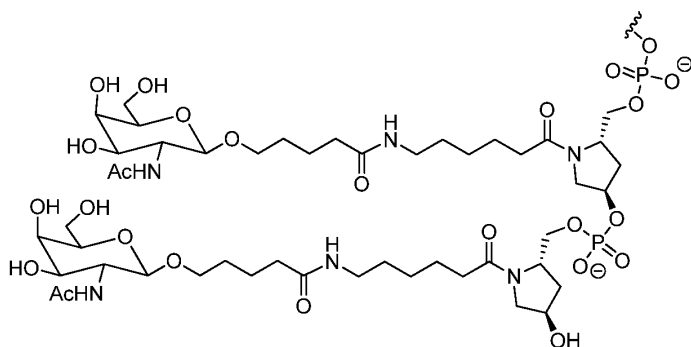
Formula XXI,



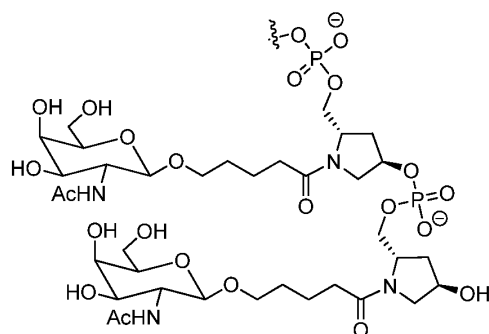


Formula XXVII; Formula

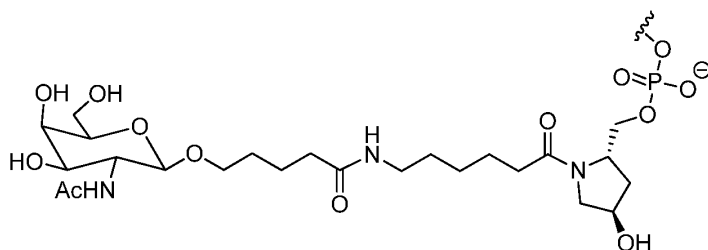
XXIX;



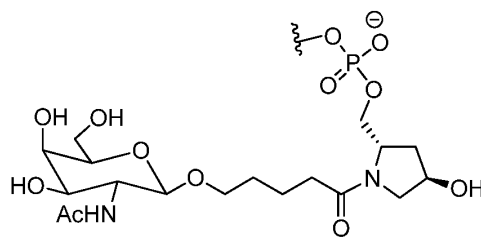
Formula XXXI;



Formula XXX;

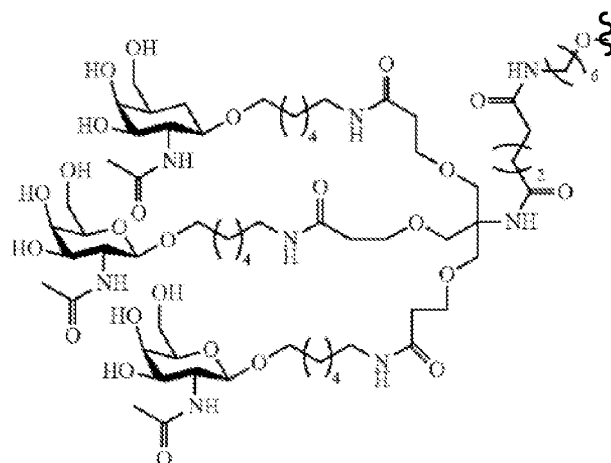


, and



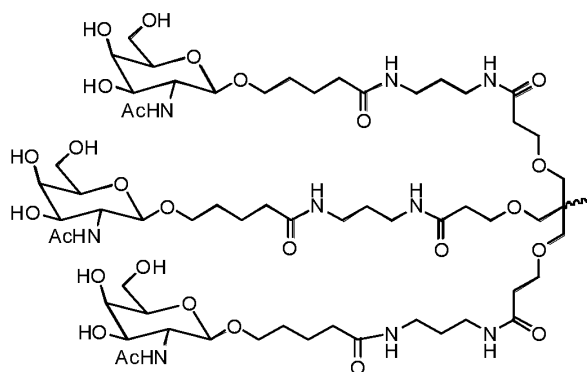
Formula XXXII;

Formula XXXIII.



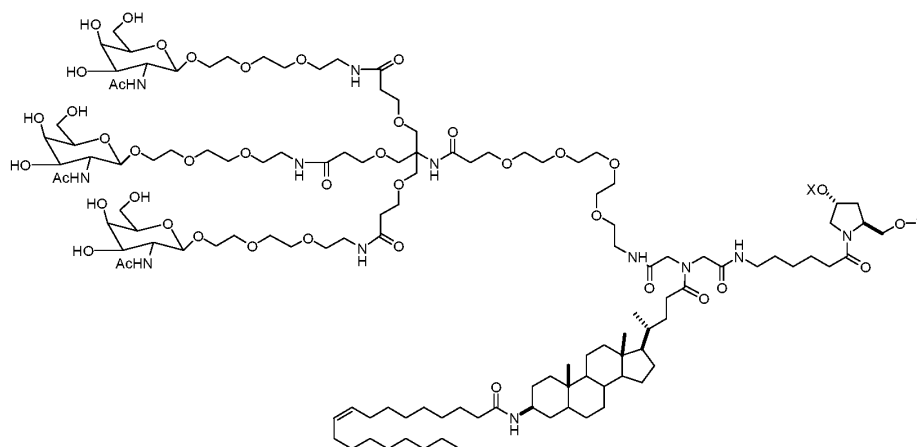
Formula XXXIV.

In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the disclosure is a monosaccharide. In certain embodiments, the monosaccharide is an N-acetylgalactosamine, such as



Formula II.

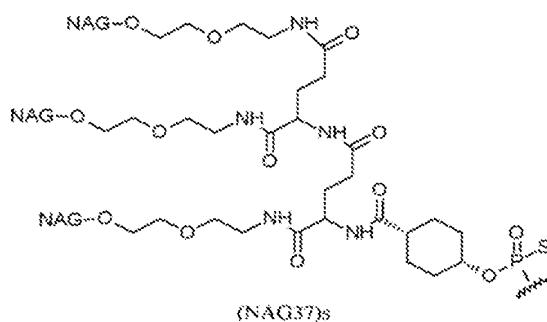
Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(Formula XXXVI),

when one of X or Y is an oligonucleotide, the other is a hydrogen.

In some embodiments, a suitable ligand is a ligand disclosed in WO 2019/055633, the entire contents of which are incorporated herein by reference. In one embodiment the ligand comprises the structure below:



In certain embodiments, the RNAi agents of the disclosure may include GalNAc ligands, even if such GalNAc ligands are currently projected to be of limited value for the preferred intrathecal/CNS delivery route(s) of the instant disclosure.

In certain embodiments of the disclosure, the GalNAc or GalNAc derivative is attached to an iRNA agent of the disclosure *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the disclosure *via* a bivalent linker. In yet other embodiments of the disclosure, the GalNAc or GalNAc derivative is attached to an iRNA agent of the disclosure *via* a trivalent linker. In other embodiments of the disclosure, the GalNAc or GalNAc derivative is attached to an iRNA agent of the disclosure *via* a tetravalent linker.

In certain embodiments, the double stranded RNAi agents of the disclosure comprise one GalNAc or GalNAc derivative attached to the iRNA agent, *e.g.*, the 5' end of the sense strand of a dsRNA agent, or the 5' end of one or both sense strands of a dual targeting RNAi agent as described herein. In certain embodiments, the double stranded RNAi agents of the disclosure comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of monovalent linkers.

In some embodiments, for example, when the two strands of an iRNA agent of the disclosure are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker.

In some embodiments, the carbohydrate conjugate further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator or a cell permeation peptide.

Additional carbohydrate conjugates and linkers suitable for use in the present disclosure include those described in WO 2014/179620 and WO 2014/179627, the entire contents of each of which are incorporated herein by reference.

D. Linkers

In some embodiments, the conjugate or ligand described herein can be attached to an iRNA oligonucleotide with various linkers that can be cleavable or non-cleavable.

The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.*, covalently attaches two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR₈, C(O), C(O)NH, SO, SO₂, SO₂NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl,

alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylheteroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, N(R₈), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R₈ is hydrogen, acyl, aliphatic or substituted aliphatic. In certain embodiments, the linker is of a length of about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18 atoms, 7-17, 8-17, 6-16, 7-16, or 8-16 atoms.

A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In a preferred embodiment, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times or more, or at least about 100 times faster in a target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

Cleavable linking groups are susceptible to cleavage agents, *e.g.*, pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.*, oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.*, those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more

acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a preferred pH, thereby releasing a cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted. For example, a liver-targeting ligand can be linked to a cationic lipid through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.*, blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It can be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In preferred embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

i. Redox cleavable linking groups

In certain embodiments, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable “reductively cleavable linking group,” or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using

reagents known in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

ii. Phosphate-based cleavable linking groups

In certain embodiments, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. Preferred embodiments are -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-P(S)(OH)-S-, -S-P(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O-, -S-P(S)(H)-O-, -S-P(O)(H)-S-, -O-P(S)(H)-S-. A preferred embodiment is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

iii. Acid cleavable linking groups

In certain embodiments, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In preferred embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.75, 5.5, 5.25, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). A preferred embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is

an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

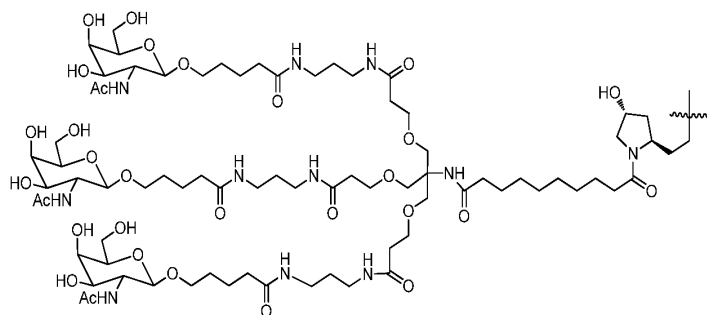
iv. Ester-based cleavable linking groups

In certain embodiments, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula $-C(O)O-$, or $-OC(O)-$. These candidates can be evaluated using methods analogous to those described above.

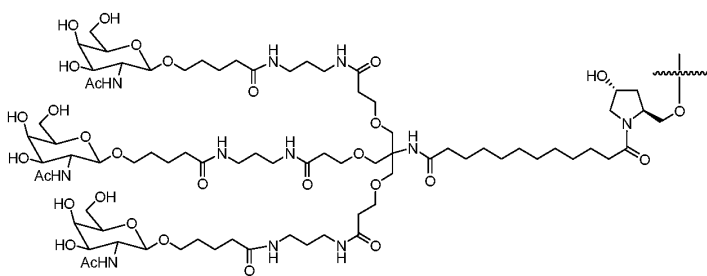
v. Peptide-based cleavable linking groups

In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group $(-C(O)NH-)$. The amide group can be formed between any alkylene, alkenylene or alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide-based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula $-NHCH(R_A)C(O)NHCH(R_B)C(O)-$, where R_A and R_B are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

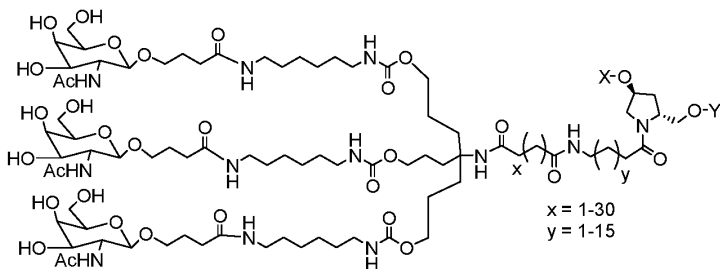
In some embodiments, an iRNA of the disclosure is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the disclosure include, but are not limited to,



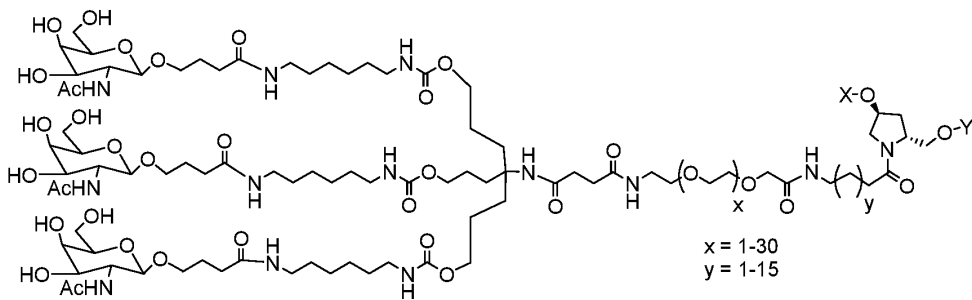
(Formula XXXVII),



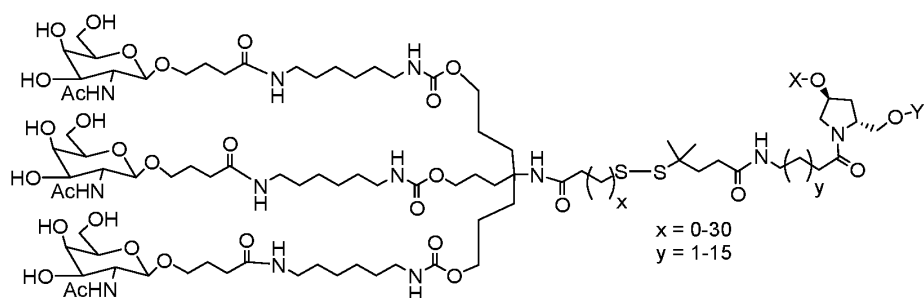
(Formula XXXVIII),



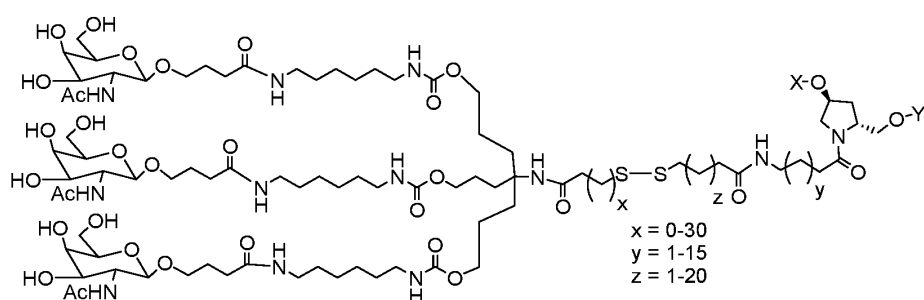
(Formula XXXIX),



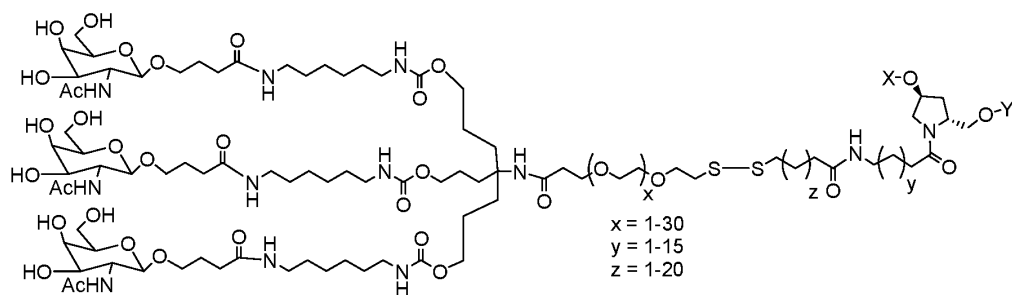
(Formula XL),



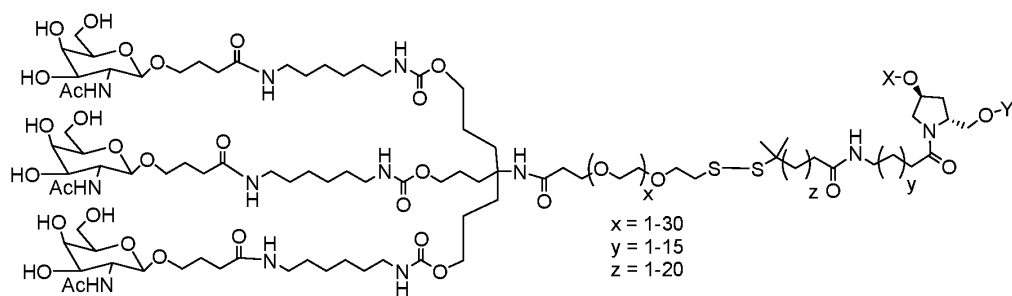
(Formula XLI),



(Formula XLII),



(Formula XLIII), and

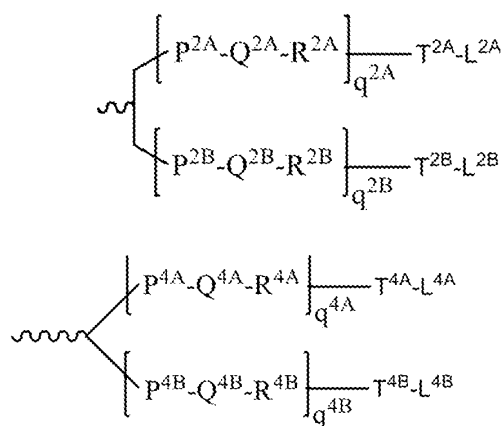


(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

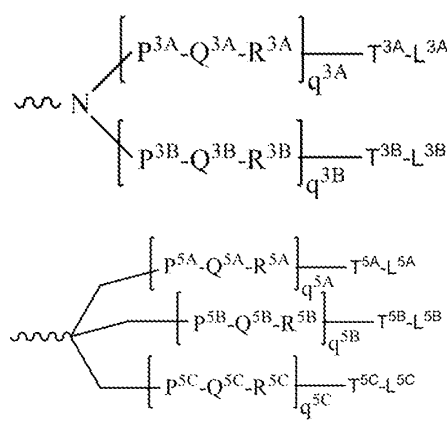
In certain embodiments of the compositions and methods of the disclosure, a ligand is one or more “GalNAc” (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

In certain embodiments, a dsRNA of the disclosure is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVI):

Formula XXXXV



Formula XLVI



Formula XLVII

wherein:

q^{2A}, q^{2B}, q^{3A}, q^{3B}, q^{4A}, q^{4B}, q^{5A}, q^{5B} and q^{5C} represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{5A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH₂, CH₂NH or CH₂O;

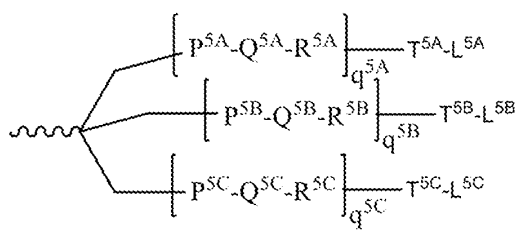
Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C} are independently for each occurrence absent, alkylene, substituted alkylene wherein one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO₂, N(R^N), C(R')=C(R''), C≡C or C(O);

R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O, S, CH₂, C(O)O, C(O)NH, NHCH(R^a)C(O), -C(O)-CH(R^a)-NH-, CO, CH=N-O,

heterocyclyl;

L^{2A} , L^{2B} , L^{3A} , L^{3B} , L^{4A} , L^{4B} , L^{5A} , L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; and R^a is H or amino acid side chain. Trivalent conjugating GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XLIX):

Formula XLIX



wherein L^{5A} , L^{5B} and L^{5C} represent a monosaccharide, such as GalNAc derivative.

Examples of suitable bivalent and trivalent branched linker groups conjugating GalNAc derivatives include, but are not limited to, the structures recited above as formulas II, VII, XI, X, and XIII.

Representative U.S. Patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Patent Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928; 5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; and 8,106,022, the entire contents of each of which are hereby incorporated herein by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications can be incorporated in a single compound or even at a single nucleoside within an iRNA. The present disclosure also includes iRNA compounds that are chimeric compounds.

“Chimeric” iRNA compounds or “chimeras,” in the context of this disclosure, are iRNA compounds, optionally dsRNA agents, that contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, or increased binding affinity for the target nucleic acid. An additional region of the iRNA can serve as a substrate for enzymes capable of cleaving RNA: DNA or RNA: RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA: DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

In certain instances, the RNA of an iRNA can be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to iRNAs in order to enhance the activity, cellular distribution or cellular uptake of the iRNA, and procedures for performing such conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Kubo, T. *et al.*, *Biochem. Biophys. Res. Comm.*, 2007, 365(1): 54-61; Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 1989, 86: 6553), cholic acid (Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1994, 4: 1053), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660: 306; Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1993, 3: 2765), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20: 533), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J.*, 1991, 10: 111; Kabanov *et al.*, *FEBS Lett.*, 1990, 259: 327; Svinarchuk *et al.*, *Biochimie*, 1993, 75: 49), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36: 3651; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18: 3777), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14: 969), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36: 3651), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264: 229), or an octadecylamine or hexylamino-carbonyl-oxysterol moiety (Crooke *et al.*, *J. Pharmacol. Exp.*

Ther., 1996, 277: 923). Representative United States patents that teach the preparation of such RNA conjugates have been listed above. Typical conjugation protocols involve the synthesis of RNAs bearing an aminolinker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction can be performed either with the RNA still bound to the solid support or following cleavage of the RNA, in solution phase. Purification of the RNA conjugate by HPLC typically affords the pure conjugate.

IV. *In Vivo* Testing of SNCA Knockdown

A wide variety of α -synuclein PD animal models are available (Gómez-Benito *et al. Front Pharmacol.* 11: 356). A number of rodent models of PD rely upon intracerebral or systemic administration of either α -synuclein pre-formed fibrils (PFFs) or brain extracts containing Lewy bodies and α -synuclein derived from PD patients or transgenic mice exhibiting α -synuclein pathology. More relevant to assessment of SNCA RNAi agents, genetic models of PD have also been made. Recombinant adeno-associated virus vectors (rAAV) overexpressing the SNCA gene have been used to model PD: overexpression of wild type α -synuclein or PD-associated mutants (A53T or A30P α -synuclein) utilizing rAAV has been described as leading to a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), a loss of dopamine terminals in the striatum (Koprich *et al. Mol Neurodegener.* 5: 43; Koprich *et al. PLoS One.* 6: e17698; Oliveras-Salvá *et al. Mol Neurodegener.* 8: 44; Bourdenx *et al. Acta Neuropathol Commun.* 3: 46; Caudal *et al. Exp Neurol.* 273: 243-52; Lu *et al. Biochem Biophys Res Commun.* 464: 988-993; Ip *et al. Biochem Biophys Res Commun.* 464: 988-993), and a reduction of striatal dopamine content (Koprich *et al. PLoS One.* 6: e17698; Ip *et al.*). However, the extent of neurodegeneration achieved with the rAAV model has been variable among the different studies. Several serotypes, promoters, α -synuclein species, doses, and time-course after injection have been tested, and all these factors influence the parkinsonian phenotype achieved.

Several transgenic mice lines expressing E46K α -synuclein have also been generated (Emmer *et al. J Biol Chem.* 286: 35104-18; Nuber *et al. Neuron.* 100: 75-90.e5), while E46K human α -synuclein has been overexpressed using viral vectors in mice. In the rAAV- α -synuclein model, the presence of p α -synuclein inclusions in the nigrostriatal system is concomitant with a significant loss of nigral dopaminergic neurons and the reduction in tyrosine hydroxylase

immunoreactivity in the striatum. Overexpression of wild type or A53T human α -synuclein induces a progressive loss of dopaminergic neurons in the SN over time (Oliveras-Salvá *et al. Mol Neurodegener.* 8: 44).

Some studies have shown that rAAV- α -synuclein expression causes the development of motor alterations, such as an increased apomorphine or amphetamine-induced rotation, defects in the stepping test or increased forepaw asymmetry in the cylinder test (Kirik *et al. J Neurosci.* 22: 2780-91; Decressac *et al. Brain.* 134(Pt 8): 2302-11; Koprach *et al. PLoS One.* 6: e17698; Decressac *et al. Neurobiol Dis.* 45: 939-53; Gaugler *et al. Acta Neuropathol.* 123: 653-69; Gombash *et al. PLoS One.* 8: e81426; Oliveras-Salvá *et al. Mol Neurodegener.* 8: 44; Bourdenx *et al. Acta Neuropathol Commun.* 3: 46; Caudal *et al. Exp Neurol.* 273: 243-52; Ip *et al. Biochem Biophys Res Commun.* 464: 988-993). These motor deficits appear several weeks after injection in animals with a significant loss of dopaminergic neurons.

Such models have been used to develop and evaluate potential therapies aimed at reducing the aggregation of α -synuclein and preventing against neurodegeneration induced by α -synuclein (Decressac *et al. Proc Natl Acad Sci U S A.* 110: E1817-26; Xilouri *et al. Autophagy.* 9: 2166-8; Rocha *et al. Neurobiol Dis.* 82: 495-503), and can further be used to demonstrate the *in vivo* efficacy of the RNAi agents provided herein. Such models may contain constitutive or inducible expression, *e.g.*, overexpression, of, for example, human or rat SNCA, in some instances comprising a pathogenic mutation. Examples of overexpression models used herein include AAV induced expression of the full-length *Homo sapiens* SNCA transcript Hs00240906_m1 and 3' UTR, and AAV induced expression of the full-length *Rattus norvegicus* SNCA transcript NM_019169.2 and 3' UTR.

V. Delivery of an RNAi Agent of the Disclosure

The delivery of an RNAi agent of the disclosure to a cell *e.g.*, a cell within a subject, such as a human subject (*e.g.*, a subject in need thereof, such as a subject having a SNCA-associated disorder, *e.g.*, PD, multiple system atrophy, Lewy body dementia (LBD), etc., can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an RNAi agent of the disclosure either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an RNAi agent, *e.g.*, a dsRNA, to a subject. Alternatively, *in vivo* delivery may be performed indirectly by administering one or more vectors

that encode and direct the expression of the RNAi agent. These alternatives are discussed further below.

In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with an RNAi agent of the disclosure (see *e.g.*, Akhtar S. and Julian RL., (1992) *Trends Cell. Biol.* 2(5): 139-144 and WO94/02595, which are incorporated herein by reference in their entireties). For *in vivo* delivery, factors to consider for delivering an RNAi agent include, for example, biological stability of the delivered agent, prevention of non-specific effects, and accumulation of the delivered agent in the target tissue. The non-specific effects of an RNAi agent can be minimized by local administration, for example, by direct injection or implantation into a tissue or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that can otherwise be harmed by the agent or that can degrade the agent, and permits a lower total dose of the RNAi agent to be administered. Several studies have shown successful knockdown of gene products when an RNAi agent is administered locally. For example, intraocular delivery of a VEGF dsRNA by intravitreal injection in cynomolgus monkeys (Tolentino, MJ. *et al.*, (2004) *Retina* 24: 132-138) and subretinal injections in mice (Reich, SJ. *et al.* (2003) *Mol. Vis.* 9: 210-216) were both shown to prevent neovascularization in an experimental model of age-related macular degeneration. In addition, direct intratumoral injection of a dsRNA in mice reduces tumor volume (Pille, J. *et al.* (2005) *Mol. Ther.* 11: 267-274) and can prolong survival of tumor-bearing mice (Kim, WJ. *et al.*, (2006) *Mol. Ther.* 14: 343-350; Li, S. *et al.*, (2007) *Mol. Ther.* 15: 515-523). RNA interference has also shown success with local delivery to the CNS by direct injection (Dorn, G. *et al.*, (2004) *Nucleic Acids* 32: e49; Tan, PH. *et al.* (2005) *Gene Ther.* 12: 59-66; Makimura, H. *et al.* (2002) *BMC Neurosci.* 3: 18; Shishkina, GT., *et al.* (2004) *Neuroscience* 129: 521-528; Thakker, ER., *et al.* (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101: 17270-17275; Akaneya, Y., *et al.* (2005) *J. Neurophysiol.* 93: 594-602) and to the lungs by intranasal administration (Howard, KA. *et al.*, (2006) *Mol. Ther.* 14: 476-484; Zhang, X. *et al.*, (2004) *J. Biol. Chem.* 279: 10677-10684; Bitko, V. *et al.*, (2005) *Nat. Med.* 11: 50-55). For administering an RNAi agent systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases *in vivo*. Modification of the RNA or the pharmaceutical carrier can also permit targeting of the RNAi agent to the target tissue and avoid undesirable off-target effects

(e.g., without wishing to be bound by theory, use of GNAs as described herein has been identified to destabilize the seed region of a dsRNA, resulting in enhanced preference of such dsRNAs for on-target effectiveness, relative to off-target effects, as such off-target effects are significantly weakened by such seed region destabilization). RNAi agents can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an RNAi agent directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J. *et al.*, (2004) *Nature* 432: 173-178). Conjugation of an RNAi agent to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model of prostate cancer (McNamara, JO. *et al.*, (2006) *Nat. Biotechnol.* 24: 1005-1015). In an alternative embodiment, the RNAi agent can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of molecule RNAi agent (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an RNAi agent by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an RNAi agent, or induced to form a vesicle or micelle (see *e.g.*, Kim SH. *et al.*, (2008) *Journal of Controlled Release* 129(2): 107-116) that encases an RNAi agent. The formation of vesicles or micelles further prevents degradation of the RNAi agent when administered systemically. Methods for making and administering cationic- RNAi agent complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR., *et al.* (2003) *J. Mol. Biol* 327: 761-766; Verma, UN. *et al.*, (2003) *Clin. Cancer Res.* 9: 1291-1300; Arnold, AS *et al.* (2007) *J. Hypertens.* 25: 197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of RNAi agents include DOTAP (Sorensen, DR., *et al.* (2003), *supra*; Verma, UN. *et al.*, (2003), *supra*), Oligofectamine, "solid nucleic acid lipid particles" (Zimmermann, TS. *et al.*, (2006) *Nature* 441: 111-114), cardiolipin (Chien, PY. *et al.*, (2005) *Cancer Gene Ther.* 12: 321-328; Pal, A. *et al.*, (2005) *Int J. Oncol.* 26: 1087-1091), polyethyleneimine (Bonnet ME. *et al.*, (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3: 472-487), and polyamidoamines (Tomalia, DA. *et al.*, (2007) *Biochem. Soc. Trans.* 35: 61-67; Yoo, H. *et al.*, (1999) *Pharm. Res.* 16: 1799-1804). In some embodiments, an RNAi agent forms a complex with cyclodextrin for systemic administration. Methods for administration and

pharmaceutical compositions of RNAi agents and cyclodextrins can be found in U.S. Patent No. 7,427,605, which is herein incorporated by reference in its entirety.

Certain aspects of the instant disclosure relate to a method of reducing the expression of a SNCA target gene in a cell, comprising contacting said cell with the double-stranded RNAi agent of the disclosure. In one embodiment, the cell is a hepatic cell, optionally a hepatocyte. In one embodiment, the cell is an extrahepatic cell, optionally a CNS cell.

Another aspect of the disclosure relates to a method of reducing the expression of a SNCA target gene in a subject, comprising administering to the subject the double-stranded RNAi agent of the disclosure.

Another aspect of the disclosure relates to a method of treating a subject having a SNCA-associated disorder, comprising administering to the subject a therapeutically effective amount of the double-stranded RNAi agent of the disclosure, thereby treating the subject. Exemplary CNS disorders that can be treated by the method of the disclosure include synucleinopathies, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomatosis, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

In one embodiment, the double-stranded RNAi agent is administered subcutaneously.

In one embodiment, the double-stranded RNAi agent is administered intrathecally. By intrathecal administration of the double-stranded RNAi agent, the method can reduce the expression of a SNCA target gene in a brain (*e.g.*, striatum) or spine tissue, for instance, cortex, cerebellum, cervical spine, lumbar spine, and thoracic spine.

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to modified siRNA compounds. It may be understood, however, that these formulations, compositions and methods can be practiced with other siRNA compounds, *e.g.*, unmodified siRNA compounds, and such practice is within the disclosure. A composition that includes an RNAi agent can be delivered to a subject by a variety of routes. Exemplary routes include: intrathecal, intravenous, topical, rectal, anal, vaginal, nasal, pulmonary, and ocular.

The RNAi agents of the disclosure can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically include one or more species of RNAi agent and a pharmaceutically acceptable carrier. As used herein the language “pharmaceutically acceptable carrier” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The pharmaceutical compositions of the present disclosure may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic, vaginal, rectal, intranasal, transdermal), oral, or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, or intrathecal or intraventricular administration.

The route and site of administration may be chosen to enhance targeting. For example, to target muscle cells, intramuscular injection into the muscles of interest would be a logical choice. Lung cells might be targeted by administering the RNAi agent in aerosol form. The vascular endothelial cells could be targeted by coating a balloon catheter with the RNAi agent and mechanically introducing the RNA.

Formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids, and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

Compositions for oral administration include powders or granules, suspensions or solutions in water, syrups, elixirs or non-aqueous media, tablets, capsules, lozenges, or troches. In the case of tablets, carriers that can be used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the nucleic acid compositions can be combined with

emulsifying and suspending agents. If desired, certain sweetening or flavoring agents can be added.

Compositions for intrathecal or intraventricular administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives.

Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir. For intravenous use, the total concentration of solutes may be controlled to render the preparation isotonic.

In one embodiment, the administration of the siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, composition is parenteral, *e.g.*, intravenous (*e.g.*, as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular, intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral, or ocular. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The medication can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are discussed in more detail below.

Intrathecal Administration

In one embodiment, the double-stranded RNAi agent is delivered by intrathecal injection (*i.e.*, injection into the spinal fluid which bathes the brain and spinal cord tissue). Intrathecal injection of RNAi agents into the spinal fluid can be performed as a bolus injection or via minipumps which can be implanted beneath the skin, providing a regular and constant delivery of siRNA into the spinal fluid. The circulation of the spinal fluid from the choroid plexus, where it is produced, down around the spinal cord and dorsal root ganglia and subsequently up past the cerebellum and over the cortex to the arachnoid granulations, where the fluid can exit the CNS, that, depending upon size, stability, and solubility of the compounds injected, molecules delivered intrathecally could hit targets throughout the entire CNS.

In some embodiments, the intrathecal administration is via a pump. The pump may be a surgically implanted osmotic pump. In one embodiment, the osmotic pump is implanted into the subarachnoid space of the spinal canal to facilitate intrathecal administration.

In some embodiments, the intrathecal administration is via an intrathecal delivery system for a pharmaceutical including a reservoir containing a volume of the pharmaceutical agent, and a

pump configured to deliver a portion of the pharmaceutical agent contained in the reservoir. More details about this intrathecal delivery system may be found in WO 2015/116658, which is incorporated by reference in its entirety.

The amount of intrathecally injected RNAi agents may vary from one target gene to another target gene and the appropriate amount that has to be applied may have to be determined individually for each target gene. Typically, this amount ranges from 10 µg to 2 mg, optionally 50 µg to 1500 µg, more optionally 100 µg to 1000 µg.

Vector-encoded RNAi agents of the Disclosure

RNAi agents targeting the SNCA gene can be expressed from transcription units inserted into DNA or RNA vectors (see, *e.g.*, Couture, A, *et al.*, *TIG.* (1996), 12: 5-10; WO 00/22113, WO 00/22114, and US 6,054,299). Expression is optionally sustained (months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, *et al.*, (1995) *Proc. Natl. Acad. Sci. USA* 92: 1292).

The individual strand or strands of an RNAi agent can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (*e.g.*, by transfection or infection) into a target cell. Alternatively, each individual strand of a dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In one embodiment, a dsRNA is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

RNAi agent expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, optionally those compatible with vertebrate cells, can be used to produce recombinant constructs for the expression of an RNAi agent as described herein. Delivery of RNAi agent expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but

not limited to lentiviral vectors, moloney murine leukemia virus, *etc.*; (c) adeno-associated virus (AAV) vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, *e.g.*, vaccinia virus vectors or avipox, *e.g.* canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct can be incorporated into vectors capable of episomal replication, *e.g.* EPV and EBV vectors. Constructs for the recombinant expression of an RNAi agent will generally require regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the RNAi agent in target cells. Other aspects to consider for vectors and constructs are known in the art.

VI. Pharmaceutical Compositions of the Invention

The present disclosure also includes pharmaceutical compositions and formulations which include the RNAi agents of the disclosure. In one embodiment, provided herein are pharmaceutical compositions containing an RNAi agent, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the RNAi agent are useful for treating a disease or disorder associated with the expression or activity of SNCA, *e.g.*, a SNCA-associated neurodegenerative disease, such as a synucleinopathy, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, LYTIC-BODIG disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration via parenteral delivery, *e.g.*, by intravenous (IV), intramuscular (IM), or for subcutaneous (subQ) delivery. Another example is compositions that are formulated for direct delivery into the CNS, *e.g.*, by intrathecal

or intravitreal routes of injection, optionally by infusion into the brain (*e.g.*, striatum), such as by continuous pump infusion.

In some embodiments, the pharmaceutical compositions of the disclosure are pyrogen free or non-pyrogenic.

The pharmaceutical compositions of the disclosure may be administered in dosages sufficient to inhibit expression of a SNCA gene. In general, a suitable dose of an RNAi agent of the disclosure will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day.

A repeat-dose regimen may include administration of a therapeutic amount of an RNAi agent on a regular basis, such as monthly to once every six months. In certain embodiments, the RNAi agent is administered about once per quarter (*i.e.*, about once every three months) to about twice per year.

After an initial treatment regimen (*e.g.*, loading dose), the treatments can be administered on a less frequent basis.

In other embodiments, a single dose of the pharmaceutical compositions can be long lasting, such that subsequent doses are administered at not more than 1, 2, 3, or 4 or more month intervals. In some embodiments of the disclosure, a single dose of the pharmaceutical compositions of the disclosure is administered once per month. In other embodiments of the disclosure, a single dose of the pharmaceutical compositions of the disclosure is administered once per quarter to twice per year.

The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments.

Advances in mouse genetics have generated mouse models for the study of SNCA-associated diseases that would benefit from reduction in the expression of SNCA. Such models can be used for *in vivo* testing of RNAi agents, as well as for determining a therapeutically effective dose. Suitable mouse models are known in the art and include, for example, the mouse models described elsewhere herein.

The pharmaceutical compositions of the present disclosure can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (*e.g.*, by a transdermal patch), pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, *e.g.*, via an implanted device; or intracranial, *e.g.*, by intraparenchymal, intrathecal or intraventricular, administration.

The RNAi agents can be delivered in a manner to target a particular tissue, such as the liver, the CNS (*e.g.*, neuronal, glial or vascular tissue of the brain), or both the liver and CNS.

Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like can be necessary or desirable. Coated condoms, gloves and the like can also be useful. Suitable topical formulations include those in which the RNAi agents featured in the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (*e.g.*, dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearoylphosphatidyl choline) negative (*e.g.*, dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.*, dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). RNAi agents featured in the disclosure can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, RNAi agents can be complexed to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C₁₋₂₀ alkyl ester (*e.g.*, isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in US 6,747,014, which is incorporated herein by reference.

A. RNAi Agent Formulations Comprising Membranous Molecular Assemblies

An RNAi agent for use in the compositions and methods of the disclosure can be formulated for delivery in a membranous molecular assembly, *e.g.*, a liposome or a micelle. As used herein, the term “liposome” refers to a vesicle composed of amphiphilic lipids arranged in at least one bilayer, *e.g.*, one bilayer or a plurality of bilayers. Liposomes include unilamellar and multilamellar vesicles that have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the RNAi agent composition. The lipophilic material isolates the aqueous interior from an aqueous exterior, which typically does not include the RNAi agent composition, although in some examples, it may. Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomal bilayer fuses with bilayer of the cellular membranes. As the merging of the liposome and cell progresses, the internal aqueous contents that include the RNAi agent are delivered into the cell where the RNAi agent can specifically bind to a target RNA and can mediate RNAi. In some cases, the liposomes are also specifically targeted, *e.g.*, to direct the RNAi agent to particular cell types.

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

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

Methods for producing stable polynucleotide delivery vehicles, which incorporate a polynucleotide/cationic lipid complex as structural components of the delivery vehicle, are further described in, *e.g.*, WO 96/37194, the entire contents of which are incorporated herein by reference.

Liposome formation can also include one or more aspects of exemplary methods described in Felgner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8: 7413-7417; United States Patent No. 4,897,355; United States Patent No. 5,171,678; Bangham *et al.*, (1965) *M. Mol. Biol.* 23: 238; Olson *et al.*, (1979) *Biochim. Biophys. Acta* 557: 9; Szoka *et al.*, (1978) *Proc. Natl. Acad. Sci.* 75: 4194; Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775: 169; Kim *et al.*, (1983) *Biochim. Biophys. Acta* 728: 339; and Fukunaga *et al.*, (1984) *Endocrinol.* 115: 757. Commonly used techniques for preparing lipid aggregates of appropriate size for use as delivery vehicles include sonication and freeze-thaw plus extrusion (see, *e.g.*, Mayer *et al.*, (1986) *Biochim. Biophys. Acta* 858: 161. Microfluidization can be used when consistently small (50 to 200 nm) and relatively uniform aggregates are desired (Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775: 169. These methods are readily adapted to packaging RNAi agent preparations into liposomes.

Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged nucleic acid molecules to form a stable complex. The positively charged nucleic acid/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang *et al.* (1987) *Biochem. Biophys. Res. Commun.*, 147: 980-985).

Liposomes, which are pH-sensitive or negatively charged, entrap nucleic acids rather than complex with them. Since both the nucleic acid and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some nucleic acid is entrapped within the aqueous interior of these liposomes. pH sensitive liposomes have been used to deliver nucleic acids encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.* (1992) *Journal of Controlled Release*, 19: 269-274).

One major type of liposomal composition includes phospholipids other than naturally-derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for

example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid or phosphatidylcholine or cholesterol.

Examples of other methods to introduce liposomes into cells *in vitro* and *in vivo* include United States Patent No. 5,283,185; United States Patent No. 5,171,678; WO 94/00569; WO 93/24640; WO 91/16024; Felgner, (1994) *J. Biol. Chem.* 269: 2550; Nabel, (1993) *Proc. Natl. Acad. Sci.* 90: 11307; Nabel, (1992) *Human Gene Ther.* 3: 649; Gershon, (1993) *Biochem.* 32: 7143; and Strauss, (1992) *EMBO J.* 11: 417.

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporine A into different layers of the skin (Hu *et al.*, (1994) *S.T.P.Pharma. Sci.*, 4(6): 466).

Liposomes also include “sterically stabilized” liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside GM₁, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen *et al.*, (1987) *FEBS Letters*, 223: 42; Wu *et al.*, (1993) *Cancer Research*, 53: 3765).

Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos *et al.* (*Ann. N.Y. Acad. Sci.*, (1987), 507: 64) reported the ability of monosialoganglioside GM₁, galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon *et al.* (*Proc. Natl. Acad. Sci. U.S.A.*, (1988), 85: 6949). United States Patent No. 4,837,028 and WO 88/04924, both to Allen

et al., disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside GM₁ or a galactocerebroside sulfate ester. United States Patent No. 5,543,152 (Webb *et al.*) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim *et al.*).

In one embodiment, cationic liposomes are used. Cationic liposomes possess the advantage of being able to fuse to the cell membrane. Non-cationic liposomes, although not able to fuse as efficiently with the plasma membrane, are taken up by macrophages *in vivo* and can be used to deliver RNAi agents to macrophages.

Further advantages of liposomes include: liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated RNAi agents in their internal compartments from metabolism and degradation (Rosoff, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

A positively charged synthetic cationic lipid, N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of fusing with the negatively charged lipids of the cell membranes of tissue culture cells, resulting in delivery of RNAi agent (see, *e.g.*, Felgner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8: 7413-7417, and United States Patent No. 4,897,355 for a description of DOTMA and its use with DNA).

A DOTMA analogue, 1,2-bis(oleoyloxy)-3-(trimethylammonia)propane (DOTAP) can be used in combination with a phospholipid to form DNA-complexing vesicles. Lipofectin™ (Bethesda Research Laboratories, Gaithersburg, Md.) is an effective agent for the delivery of highly anionic nucleic acids into living tissue culture cells that comprise positively charged DOTMA liposomes which interact spontaneously with negatively charged polynucleotides to form complexes. When enough positively charged liposomes are used, the net charge on the resulting complexes is also positive. Positively charged complexes prepared in this way spontaneously attach to negatively charged cell surfaces, fuse with the plasma membrane, and efficiently deliver functional nucleic acids into, for example, tissue culture cells. Another commercially available cationic lipid, 1,2-bis(oleoyloxy)-3,3-(trimethylammonia)propane ("DOTAP") (Boehringer

Mannheim, Indianapolis, Indiana) differs from DOTMA in that the oleoyl moieties are linked by ester, rather than ether linkages.

Other reported cationic lipid compounds include those that have been conjugated to a variety of moieties including, for example, carboxyspermine which has been conjugated to one of two types of lipids and includes compounds such as 5-carboxyspermylglycine dioctaoyleamide (“DOGS”) (Transfectam™, Promega, Madison, Wisconsin) and dipalmitoylphosphatidylethanolamine 5-carboxyspermyl-amide (“DPPES”) (see, *e.g.*, United States Patent No. 5,171,678).

Another cationic lipid conjugate includes derivatization of the lipid with cholesterol (“DC-Chol”) which has been formulated into liposomes in combination with DOPE (See, Gao, X. and Huang, L., (1991) *Biochim. Biophys. Res. Commun.* 179: 280). Lipopolylysine, made by conjugating polylysine to DOPE, has been reported to be effective for transfection in the presence of serum (Zhou, X. *et al.*, (1991) *Biochim. Biophys. Acta* 1065: 8). For certain cell lines, these liposomes containing conjugated cationic lipids, are said to exhibit lower toxicity and provide more efficient transfection than the DOTMA-containing compositions. Other commercially available cationic lipid products include DMRIE and DMRIE-HP (Vical, La Jolla, California) and Lipofectamine (DOSPA) (Life Technology, Inc., Gaithersburg, Maryland). Other cationic lipids suitable for the delivery of oligonucleotides are described in WO 98/39359 and WO 96/37194.

Liposomal formulations are particularly suited for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer RNAi agent into the skin. In some implementations, liposomes are used for delivering RNAi agent to epidermal cells and also to enhance the penetration of RNAi agent into dermal tissues, *e.g.*, into skin. For example, the liposomes can be applied topically. Topical delivery of drugs formulated as liposomes to the skin has been documented (see, *e.g.*, Weiner *et al.*, (1992) *Journal of Drug Targeting*, vol. 2, 405-410 and du Plessis *et al.*, (1992) *Antiviral Research*, 18: 259-265; Mannino, R. J. and Fould-Fogerite, S., (1998) *Biotechniques* 6: 682-690; Itani, T. *et al.*, (1987) *Gene* 56: 267-276; Nicolau, C. *et al.* (1987) *Meth. Enzymol.* 149: 157-176; Straubinger, R. M. and Papahadjopoulos, D. (1983) *Meth. Enzymol.* 101: 512-527; Wang, C. Y. and Huang, L., (1987) *Proc. Natl. Acad. Sci. USA* 84: 7851-7855).

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver a drug into the dermis of mouse skin. Such formulations with RNAi agent are useful for treating a dermatological disorder.

Liposomes that include RNAi agents can be made highly deformable. Such deformability can enable the liposomes to penetrate through pore that are smaller than the average radius of the liposome. For example, transfersomes (highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles) are a type of deformable liposomes. Transfersomes can be described as lipid droplets which are so highly deformable that they are easily able to penetrate through pores which are smaller than the droplet. Transfersomes are adaptable to the environment in which they are used, *e.g.*, they are self-optimizing (adaptive to the shape of pores in the skin), self-repairing, frequently reach their targets without fragmenting, and often self-loading. Transfersomes can be made by adding surface edge activators, usually surfactants, to a standard liposomal composition. Transfersomes have been used to deliver serum albumin to the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin. Transfersomes that include RNAi agent can be delivered, for example, subcutaneously by infection in order to deliver RNAi agent to keratinocytes in the skin. In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. In addition, due to the lipid properties, these transfersomes can be self-optimizing (adaptive to the shape of pores, *e.g.*, in the skin), self-repairing, and can frequently reach their targets without fragmenting, and often self-loading.

Other formulations amenable to the present disclosure are described in United States provisional application serial Nos. 61/018,616, filed January 2, 2008; 61/018,611, filed January 2, 2008; 61/039,748, filed March 26, 2008; 61/047,087, filed April 22, 2008 and 61/051,528, filed May 8, 2008. PCT application number PCT/US2007/080331, filed October 3, 2007, also describes formulations that are amenable to the present disclosure.

Surfactants find wide application in formulations such as those described herein, particularly in emulsions (including microemulsions) and liposomes. The most common way of

classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general, their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

The RNAi agent for use in the methods of the disclosure can also be provided as micellar formulations. "Micelles" are defined herein as a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions

of the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic.

A mixed micellar formulation suitable for delivery through transdermal membranes may be prepared by mixing an aqueous solution of the siRNA composition, an alkali metal C₈ to C₂₂ alkyl sulphate, and a micelle forming compounds. Exemplary micelle forming compounds include lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof. The micelle forming compounds may be added at the same time or after addition of the alkali metal alkyl sulphate. Mixed micelles will form with substantially any kind of mixing of the ingredients but vigorous mixing in order to provide smaller size micelles.

In one method a first micellar composition is prepared which contains the siRNA composition and at least the alkali metal alkyl sulphate. The first micellar composition is then mixed with at least three micelle forming compounds to form a mixed micellar composition. In another method, the micellar composition is prepared by mixing the siRNA composition, the alkali metal alkyl sulphate and at least one of the micelle forming compounds, followed by addition of the remaining micelle forming compounds, with vigorous mixing.

Phenol or m-cresol may be added to the mixed micellar composition to stabilize the formulation and protect against bacterial growth. Alternatively, phenol or m-cresol may be added with the micelle forming ingredients. An isotonic agent such as glycerin may also be added after formation of the mixed micellar composition.

For delivery of the micellar formulation as a spray, the formulation can be put into an aerosol dispenser and the dispenser is charged with a propellant. The propellant, which is under pressure, is in liquid form in the dispenser. The ratios of the ingredients are adjusted so that the aqueous and propellant phases become one, *i.e.*, there is one phase. If there are two phases, it is necessary to shake the dispenser prior to dispensing a portion of the contents, *e.g.*, through a metered valve. The dispensed dose of pharmaceutical agent is propelled from the metered valve in a fine spray.

Propellants may include hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. In certain embodiments, HFA 134a (1,1,1,2-tetrafluoroethane) may be used.

The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. For absorption through the oral cavities, it is often desirable to increase, *e.g.*, at least double or triple, the dosage for through injection or administration through the gastrointestinal tract.

Lipid particles

RNAi agents, *e.g.*, dsRNAs of in the disclosure may be fully encapsulated in a lipid formulation, *e.g.*, a LNP, or other nucleic acid-lipid particle.

As used herein, the term "LNP" refers to a stable nucleic acid-lipid particle. LNPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.*, a PEG-lipid conjugate). LNPs are extremely useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (*i.v.*) injection and accumulate at distal sites (*e.g.*, sites physically separated from the administration site). LNPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in WO 00/03683. The particles of the present disclosure typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid-lipid particles of the present disclosure are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, *e.g.*, U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; United States Patent publication No. 2010/0324120 and WO 96/40964.

In one embodiment, the lipid to drug ratio (mass/mass ratio) (*e.g.*, lipid to dsRNA ratio) will be in the range of from about 1:1 to about 50:1, from about 1:1 to about 25:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

Certain specific LNP formulations for delivery of RNAi agents have been described in the art, including, *e.g.*, "LNP01" formulations as described in, *e.g.*, WO 2008/042973, which is hereby incorporated by reference.

Additional exemplary lipid-dsRNA formulations are identified in the chart below.

	Ionizable/Cationic Lipid	cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid: siRNA ratio
SNALP-1	1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid: siRNA ~ 7: 1
2-XTC	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid: siRNA ~ 7: 1
LNP05	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid: siRNA ~ 6: 1
LNP06	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid: siRNA ~ 11: 1
LNP07	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid: siRNA ~ 6: 1
LNP08	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid: siRNA ~ 11: 1
LNP09	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid: siRNA 10: 1
LNP10	(3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid: siRNA 10: 1
LNP11	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid: siRNA 10: 1
LNP12	1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-	Tech G1/DSPC/Cholesterol/PEG-DMG

	hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyldidodecan-2-ol (Tech G1)	50/10/38.5/1.5 Lipid: siRNA 10: 1
LNP13	XTC	XTC/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid: siRNA: 33: 1
LNP14	MC3	MC3/DSPC/Chol/PEG-DMG 40/15/40/5 Lipid: siRNA: 11: 1
LNP15	MC3	MC3/DSPC/Chol/PEG-DSG/GalNAc-PEG-DSG 50/10/35/4.5/0.5 Lipid: siRNA: 11: 1
LNP16	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid: siRNA: 7: 1
LNP17	MC3	MC3/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid: siRNA: 10: 1
LNP18	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid: siRNA: 12: 1
LNP19	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/35/5 Lipid: siRNA: 8: 1
LNP20	MC3	MC3/DSPC/Chol/PEG-DPG 50/10/38.5/1.5 Lipid: siRNA: 10: 1
LNP21	C12-200	C12-200/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid: siRNA: 7: 1
LNP22	XTC	XTC/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid: siRNA: 10: 1

DSPC: distearoylphosphatidylcholine

DPPC: dipalmitoylphosphatidylcholine

PEG-DMG: PEG-didimyristoyl glycerol (C14-PEG, or PEG-C14) (PEG with avg mol wt of 2000)

PEG-DSG: PEG-distyryl glycerol (C18-PEG, or PEG-C18) (PEG with avg mol wt of 2000)

PEG-cDMA: PEG-carbamoyl-1,2-dimyristyloxypropylamine (PEG with avg mol wt of 2000)

SNALP (1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in WO 2009/127060, which is hereby incorporated by reference.

XTC comprising formulations are described in WO 2010/088537, the entire contents of which are hereby incorporated herein by reference.

MC3 comprising formulations are described, *e.g.*, in United States Patent Publication No. 2010/0324120, the entire contents of which are hereby incorporated by reference.

ALNY-100 comprising formulations are described in WO 2010/054406, the entire contents of which are hereby incorporated herein by reference.

C12-200 comprising formulations are described in WO 2010/129709, the entire contents of which are hereby incorporated herein by reference.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitabets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders can be desirable. In some embodiments, oral formulations are those in which dsRNAs featured in the disclosure are administered in conjunction with one or more penetration enhancer surfactants and chelators. Suitable surfactants include fatty acids or esters or salts thereof, bile acids or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprinate, tricaprinate, monoolein, dilaurin, glyceryl 1-monocaprinate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (*e.g.*, sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is

the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the disclosure can be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. DsRNA complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (*e.g.*, p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcyanoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Patent 6,887,906, U.S. 2003/0027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intraventricular or intrahepatic administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Pharmaceutical compositions of the present disclosure include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions can be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Particularly preferred are formulations that target the brain when treating APP-associated diseases or disorders.

The pharmaceutical formulations of the present disclosure, which can conveniently be presented in unit dosage form, can be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations

are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions of the present disclosure can be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present disclosure can also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol or dextran. The suspension can also contain stabilizers.

Additional Formulations

i. Emulsions

The compositions of the present disclosure can be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 μ m in diameter (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L.V., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions can be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions can contain additional components in addition to the dispersed phases, and the active drug which can be present as a solution in either aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed. Pharmaceutical emulsions can also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o)

and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise, a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion can be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that can be incorporated into either phase of the emulsion. Emulsifiers can broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants can be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic and amphoteric (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives and antioxidants (Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that can readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used can be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

The application of emulsion formulations via dermatological, oral and parenteral routes and methods for their manufacture have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

ii. Microemulsions

In one embodiment of the present disclosure, the compositions of RNAi agents and nucleic acids are formulated as microemulsions. A microemulsion can be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically, microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotropically clear dispersions of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: Controlled Release of Drugs: Polymers and Aggregate Systems, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215). Microemulsions commonly are prepared via a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used, and on the structure

and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 271).

The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions can, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase can typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase can include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (see *e.g.*, U.S. Patent Nos.

6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, Pharmaceutical Research, 1994, 11, 1385-1390; Ritschel, Meth. Find. Exp. Clin. Pharmacol., 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, Pharmaceutical Research, 1994, 11, 1385; Ho *et al.*, J. Pharm. Sci., 1996, 85, 138-143). Often microemulsions can form spontaneously when their components are brought together at ambient temperature. This can be particularly advantageous when formulating thermolabile drugs, peptides or RNAi agents. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present disclosure will facilitate the increased systemic absorption of RNAi agents and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of RNAi agents and nucleic acids.

Microemulsions of the present disclosure can also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the RNAi agents and nucleic acids of the present disclosure. Penetration enhancers used in the microemulsions of the present disclosure can be classified as belonging to one of five broad categories--surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p. 92). Each of these classes has been discussed above.

iii. Microparticles

An RNAi agent of the disclosure may be incorporated into a particle, *e.g.*, a microparticle. Microparticles can be produced by spray-drying, but may also be produced by other methods including lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination of these techniques.

iv. Penetration Enhancers

In one embodiment, the present disclosure employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly RNAi agents, to the skin of animals. Most drugs

are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs can cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers can be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92). Each of the above-mentioned classes of penetration enhancers are described below in greater detail.

Surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of RNAi agents through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92); and perfluorochemical emulsions, such as FC-43. Takahashi *et al.*, J. Pharm. Pharmacol., 1988, 40, 252).

Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprinate, tricaprinate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprinate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C₁₋₂₀ alkyl esters thereof (*e.g.*, methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (*i.e.*, oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, *etc.*) (see *e.g.*, Touitou, E., *et al.* Enhancement in Drug Delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; El Hariri *et al.*, J. Pharm. Pharmacol., 1992, 44, 651-654).

The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery,

Informa Health Care, New York, NY, 2002; Brunton, Chapter 38 in: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman *et al.* Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucolic acid (sodium glucolate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Swinyard, Chapter 39 In: Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Yamamoto *et al.*, J. Pharm. Exp. Ther., 1992, 263, 25; Yamashita *et al.*, J. Pharm. Sci., 1990, 79, 579-583).

Chelating agents, as used in connection with the present disclosure, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of RNAi agents through the mucosa is enhanced. With regards to their use as penetration enhancers in the present disclosure, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, J. Chromatogr., 1993, 618, 315-339). Suitable chelating agents include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (*e.g.*, sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laureth-9 and N-amino acyl derivatives of beta-diketones (enamines)(see *e.g.*, Katdare, A. *et al.*, Excipient development for pharmaceutical, biotechnology, and drug delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Buur *et al.*, J. Control Rel., 1990, 14, 43-51).

As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of RNAi agents through the alimentary mucosa (see *e.g.*, Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33). This class of penetration enhancers includes, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin and phenylbutazone (Yamashita *et al.*, *J. Pharm. Pharmacol.*, 1987, 39, 621-626).

Agents that enhance uptake of RNAi agents at the cellular level can also be added to the pharmaceutical and other compositions of the present disclosure. For example, cationic lipids, such as lipofectin (Junichi *et al.*, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (WO 97/30731), are also known to enhance the cellular uptake of dsRNAs.

Other agents can be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

vi. Excipients

In contrast to a carrier compound, a “pharmaceutical carrier” or “excipient” is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient can be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, *etc.*, when combined with a nucleic acid and the other components of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, *etc.*); fillers (*e.g.*, lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, *etc.*); lubricants (*e.g.*, magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, *etc.*); disintegrants (*e.g.*, starch, sodium starch glycolate, *etc.*); and wetting agents (*e.g.*, sodium lauryl sulphate, *etc.*).

Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present disclosure. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Formulations for topical administration of nucleic acids can include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions can also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used.

Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

vii. Other Components

The compositions of the present disclosure can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can contain additional materials useful in physically formulating various dosage forms of the compositions of the present disclosure, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present disclosure. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

Aqueous suspensions can contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol or dextran. The suspension can also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the disclosure include (a) one or more RNAi agents and (b) one or more agents which function by a non-RNAi mechanism and which are useful in treating a SNCA-associated neurodegenerative disorder. Examples of such agents include, but are not limited to dopamine agonists and promoters, among others, including carbidopa-levodopa, levodopa, entacapone, tolcapone, opicapone, pramipexole, ropinirole, apomorphine, rotigotine, selegiline, rasagiline, safinamide, amantadine, istradefylline, trihexyphenidyl, benztropine, rivastigmine, donepezil, galantamine and memantine.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds that exhibit high therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured herein in the disclosure lies generally within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods featured in the disclosure, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (*e.g.*, achieving a decreased concentration of the polypeptide) that includes the IC₅₀ (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the RNAi agents featured in the disclosure can be administered in combination with other known agents effective in treatment of pathological processes mediated by nucleotide repeat expression. In any event, the administering physician can adjust the amount and timing of RNAi agent administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

VII. Kits

In certain aspects, the instant disclosure provides kits that include a suitable container containing a pharmaceutical formulation of a siRNA compound, *e.g.*, a double-stranded siRNA compound, or siRNA compound, (*e.g.*, a precursor, *e.g.*, a larger siRNA compound which can be processed into a siRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or siRNA compound, or precursor thereof). In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container. Alternatively, it may be desirable to provide the components of the pharmaceutical formulation separately in two or more containers, *e.g.*, one container for a siRNA compound preparation, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

VIII. Methods for Inhibiting SNCA Expression

The present disclosure also provides methods of inhibiting expression of a SNCA gene in a cell. The methods include contacting a cell with an RNAi agent, *e.g.*, double stranded RNAi agent, in an amount effective to inhibit expression of SNCA in the cell, thereby inhibiting expression of SNCA in the cell. In certain embodiments of the disclosure, SNCA is inhibited preferentially in CNS (*e.g.*, brain) cells. In other embodiments of the disclosure, SNCA is inhibited preferentially in the liver (*e.g.*, hepatocytes). In certain embodiments of the disclosure, SNCA is inhibited in CNS (*e.g.*, brain) cells and in liver (*e.g.*, hepatocytes) cells.

Contacting of a cell with an RNAi agent, *e.g.*, a double stranded RNAi agent, may be done *in vitro* or *in vivo*. Contacting a cell *in vivo* with the RNAi agent includes contacting a cell or group of cells within a subject, *e.g.*, a human subject, with the RNAi agent. Combinations of *in vitro* and *in vivo* methods of contacting a cell are also possible.

Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished via a targeting ligand, including any ligand described herein or known in the art. In some embodiments, the targeting ligand is a carbohydrate moiety, *e.g.*, a GalNAc ligand, or any other ligand that directs the RNAi agent to a site of interest.

The term “inhibiting,” as used herein, is used interchangeably with “reducing,” “silencing,” “downregulating,” “suppressing” and other similar terms, and includes any level of inhibition. In certain embodiments, a level of inhibition, *e.g.*, for an RNAi agent of the instant disclosure, can be assessed in cell culture conditions, *e.g.*, wherein cells in cell culture are transfected *via* LipofectamineTM-mediated transfection at a concentration in the vicinity of a cell of 10 nM or less, 1 nM or less, *etc.* Knockdown of a given RNAi agent can be determined *via* comparison of pre-treated levels in cell culture versus post-treated levels in cell culture, optionally also comparing against cells treated in parallel with a scrambled or other form of control RNAi agent. Knockdown in cell culture of, *e.g.*, optionally 50% or more, can thereby be identified as indicative of “inhibiting” or “reducing,” “downregulating” or “suppressing,” *etc.* having occurred. It is expressly contemplated that assessment of targeted mRNA or encoded protein levels (and therefore an extent of “inhibiting,” *etc.* caused by an RNAi agent of the disclosure) can also be assessed in *in vivo* systems for the RNAi agents of the instant disclosure, under properly controlled conditions as described in the art.

The phrase “inhibiting expression of a SNCA gene” or “inhibiting expression of SNCA,” as used herein, includes inhibition of expression of any SNCA gene (such as, *e.g.*, a mouse SNCA gene, a rat SNCA gene, a monkey SNCA gene, or a human SNCA gene) as well as variants or mutants of a SNCA gene that encode a SNCA protein. Thus, the SNCA gene may be a wild-type SNCA gene, a mutant SNCA gene, or a transgenic SNCA gene in the context of a genetically manipulated cell, group of cells, or organism.

“Inhibiting expression of a SNCA gene” includes any level of inhibition of a SNCA gene, *e.g.*, at least partial suppression of the expression of a SNCA gene, such as an inhibition by at least 20%. In certain embodiments, inhibition is by at least 30%, at least 40%, optionally at least 50%, at least about 60%, at least 70%, at least about 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%; or to below the level of detection of the assay method.

The expression of a SNCA gene may be assessed based on the level of any variable associated with SNCA gene expression, *e.g.*, SNCA mRNA level or SNCA protein level, or, for example, the level of neuroinflammation, *e.g.*, microglial and astrocyte activation, and SNCA deposition in areas of the brain associated with neuronal cell death and/or levels of SNCA mRNA/protein within exosomes (neuronal or otherwise).

Inhibition may be assessed by a decrease in an absolute or relative level of one or more of these variables compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.*, a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.*, buffer only control or inactive agent control).

In some embodiments of the methods of the disclosure, expression of a SNCA gene is inhibited by at least 20%, 30%, 40%, optionally at least 50%, 60%, 70%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay. In certain embodiments, the methods include a clinically relevant inhibition of expression of SNCA, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of SNCA.

Inhibition of the expression of a SNCA gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which a SNCA gene is transcribed and which has or have been treated (*e.g.*, by contacting the cell or cells with an RNAi agent of the disclosure, or by administering an RNAi agent of the disclosure to a subject in which the cells are or were present) such that the expression of a SNCA gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s) not treated with an RNAi agent or not treated with an RNAi agent targeted to the gene of interest). The degree of inhibition may be expressed in terms of:

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} \bullet 100\%$$

In other embodiments, inhibition of the expression of a SNCA gene may be assessed in terms of a reduction of a parameter that is functionally linked to a SNCA gene expression, *e.g.*, SNCA protein expression. SNCA gene silencing may be determined in any cell expressing SNCA, either endogenous or heterologous from an expression construct, and by any assay known in the art.

Inhibition of the expression of a SNCA protein may be manifested by a reduction in the level of the SNCA protein that is expressed by a cell or group of cells (*e.g.*, the level of protein expressed in a sample derived from a subject). As explained above, for the assessment of mRNA suppression, the inhibition of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells.

A control cell or group of cells that may be used to assess the inhibition of the expression of a SNCA gene includes a cell or group of cells that has not yet been contacted with an RNAi agent of the disclosure. For example, the control cell or group of cells may be derived from an individual subject (*e.g.*, a human or animal subject) prior to treatment of the subject with an RNAi agent.

The level of SNCA mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing mRNA expression. In one embodiment, the level of expression of SNCA in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.*, mRNA of the SNCA gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasyTM RNA preparation kits (Qiagen®) or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays, northern blotting, *in situ* hybridization, and microarray analysis. Circulating SNCA mRNA may be detected using methods the described in WO2012/177906, the entire contents of which are hereby incorporated herein by reference.

In some embodiments, the level of expression of SNCA is determined using a nucleic acid probe. The term “probe”, as used herein, refers to any molecule that is capable of selectively binding to a specific SNCA nucleic acid or protein, or fragment thereof. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses and probe arrays. One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to SNCA mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix[®] gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of SNCA mRNA.

An alternative method for determining the level of expression of SNCA in a sample involves the process of nucleic acid amplification or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, *e.g.*, by RT-PCR (the experimental embodiment set forth in Mullis, 1987, US Patent No. 4,683,202), ligase chain reaction (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88: 189-193), self-sustained sequence replication (Guatelli *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87: 1874-1878), transcriptional amplification system (Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86: 1173-1177), Q-Beta Replicase (Lizardi *et al.* (1988) *Bio/Technology* 6: 1197), rolling circle replication (Lizardi *et al.*, US Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the disclosure, the level of expression of SNCA is determined by quantitative fluorogenic RT-PCR (*i.e.*, the TaqMan™ System), by a Dual-Glo® Luciferase assay, or by other art-recognized method for measurement of SNCA expression or mRNA level.

The expression level of SNCA mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See US Patent Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The determination of SNCA expression level may also comprise using nucleic acid probes in solution.

In some embodiments, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR). The use of this PCR method is described and exemplified in the Examples presented herein. Such methods can also be used for the detection of SNCA nucleic acids.

The level of SNCA protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays,

electrochemiluminescence assays, and the like. Such assays can also be used for the detection of proteins indicative of the presence or replication of SNCA proteins.

In some embodiments, the efficacy of the methods of the disclosure in the treatment of a SNCA-related disease is assessed by a decrease in SNCA mRNA level (*e.g.*, by assessment of a CSF sample for SNCA level, by brain biopsy, or otherwise).

In some embodiments, the efficacy of the methods of the disclosure in the treatment of a SNCA-related disease is assessed by a decrease in SNCA mRNA level (*e.g.*, by assessment of a liver sample for SNCA level, by biopsy, or otherwise).

In some embodiments of the methods of the disclosure, the RNAi agent is administered to a subject such that the RNAi agent is delivered to a specific site within the subject. The inhibition of expression of SNCA may be assessed using measurements of the level or change in the level of SNCA mRNA or SNCA protein in a sample derived from a specific site within the subject, *e.g.*, CNS cells. In certain embodiments, the methods include a clinically relevant inhibition of expression of SNCA, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of SNCA.

As used herein, the terms detecting or determining a level of an analyte are understood to mean performing the steps to determine if a material, *e.g.*, protein, RNA, is present. As used herein, methods of detecting or determining include detection or determination of an analyte level that is below the level of detection for the method used.

IX. Methods of Treating or Preventing SNCA-Associated Neurodegenerative Diseases

The present disclosure also provides methods of using an RNAi agent of the disclosure or a composition containing an RNAi agent of the disclosure to reduce or inhibit SNCA expression in a cell. The methods include contacting the cell with a dsRNA of the disclosure and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcript of a SNCA gene, thereby inhibiting expression of the SNCA gene in the cell. Reduction in gene expression can be assessed by any methods known in the art. For example, a reduction in the expression of SNCA may be determined by determining the mRNA expression level of SNCA using methods routine to one of ordinary skill in the art, *e.g.*, northern blotting, qRT-PCR; by determining the protein level of

SNCA using methods routine to one of ordinary skill in the art, such as western blotting, immunological techniques, and mass-spectrometry.

In the methods of the disclosure the cell may be contacted *in vitro* or *in vivo*, *i.e.*, the cell may be within a subject.

A cell suitable for treatment using the methods of the disclosure may be any cell that expresses a SNCA gene. A cell suitable for use in the methods of the disclosure may be a mammalian cell, *e.g.*, a primate cell (such as a human cell or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), a non-primate cell (such as a rat cell, or a mouse cell. In one embodiment, the cell is a human cell, *e.g.*, a human CNS cell. In one embodiment, the cell is a human cell, *e.g.*, a human liver cell. In one embodiment, the cell is a human cell, *e.g.*, a human CNS cell and a human liver cell.

SNCA expression is inhibited in the cell by at least about 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or about 100%, *i.e.*, to below the level of detection. In preferred embodiments, SNCA expression is inhibited by at least 50 %.

The *in vivo* methods of the disclosure may include administering to a subject a composition containing an RNAi agent, where the RNAi agent includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the SNCA gene of the mammal to be treated. When the organism to be treated is a mammal such as a human, the composition can be administered by any means known in the art including, but not limited to oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular, intraparenchymal, and intrathecal), intravenous, intramuscular, intravitreal, subcutaneous, transdermal, airway (aerosol), nasal, rectal, and topical (including buccal and sublingual) administration. In certain embodiments, the compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection. In certain embodiments, the compositions are administered by intrathecal injection.

In some embodiments, the administration is *via* a depot injection. A depot injection may release the RNAi agent in a consistent way over a prolonged time period. Thus, a depot injection may reduce the frequency of dosing needed to obtain a desired effect, *e.g.*, a desired inhibition of SNCA, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In preferred embodiments, the depot injection is a subcutaneous injection.

In some embodiments, the administration is *via* a pump. The pump may be an external pump or a surgically implanted pump. In certain embodiments, the pump is a subcutaneously implanted osmotic pump. In other embodiments, the pump is an infusion pump. An infusion pump may be used for intracranial, intravenous, subcutaneous, arterial, or epidural infusions. In preferred embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the RNAi agent to the CNS.

The mode of administration may be chosen based upon whether local or systemic treatment is desired and based upon the area to be treated. The route and site of administration may be chosen to enhance targeting.

In one aspect, the present disclosure also provides methods for inhibiting the expression of a SNCA gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets a SNCA gene in a cell of the mammal and maintaining the mammal for a time sufficient to obtain degradation of the mRNA transcript of the SNCA gene, thereby inhibiting expression of the SNCA gene in the cell. Reduction in gene expression can be assessed by any methods known in the art and by methods, *e.g.* qRT-PCR, described herein. Reduction in protein production can be assessed by any methods known in the art and by methods, *e.g.* ELISA, described herein. In one embodiment, a CNS biopsy sample or a cerebrospinal fluid (CSF) sample serves as the tissue material for monitoring the reduction in SNCA gene or protein expression (or of a proxy therefore).

The present disclosure further provides methods of treatment of a subject in need thereof. The treatment methods of the disclosure include administering an RNAi agent of the disclosure to a subject, *e.g.*, a subject that would benefit from inhibition of SNCA expression, in a therapeutically effective amount of an RNAi agent targeting a SNCA gene or a pharmaceutical composition comprising an RNAi agent targeting a SNCA gene.

In addition, the present disclosure provides methods of preventing, treating or inhibiting the progression of a SNCA-associated neurodegenerative disease or disorder, such as a synucleinopathy, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, LYTICODIG disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease,

lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

The methods include administering to the subject a therapeutically effective amount of any of the RNAi agent, *e.g.*, dsRNA agents, or the pharmaceutical composition provided herein, thereby preventing, treating or inhibiting the progression of the SNCA-associated neurodegenerative disease or disorder in the subject.

An RNAi agent of the disclosure may be administered as a "free RNAi agent." A free RNAi agent is administered in the absence of a pharmaceutical composition. The naked RNAi agent may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the RNAi agent can be adjusted such that it is suitable for administering to a subject.

Alternatively, an RNAi agent of the disclosure may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

Subjects that would benefit from a reduction or inhibition of SNCA gene expression are those having a SNCA-associated neurodegenerative disease.

The disclosure further provides methods for the use of an RNAi agent or a pharmaceutical composition thereof, *e.g.*, for treating a subject that would benefit from reduction or inhibition of SNCA expression, *e.g.*, a subject having a SNCA-associated neurodegenerative disorder, in combination with other pharmaceuticals or other therapeutic methods, *e.g.*, with known pharmaceuticals or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. For example, in certain embodiments, an RNAi agent targeting SNCA is administered in combination with, *e.g.*, an agent useful in treating a SNCA-associated neurodegenerative disorder as described elsewhere herein or as otherwise known in the art. For example, additional agents and treatments suitable for treating a subject that would benefit from reduction in SNCA expression, *e.g.*, a subject having a SNCA-associated neurodegenerative disorder, may include agents currently used to treat symptoms of SNCA. The RNAi agent and additional therapeutic agents may be administered at the same time or in the same combination, *e.g.*, intrathecally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times or by another method known in the art or described herein.

Exemplary additional therapeutics and treatments include dopamine-modulating agents, among others, for example, carbidopa-levodopa, levodopa, entacapone, tolcapone, opicapone, pramipexole, ropinirole, apomorphine, rotigotine, selegiline, rasagiline, safinamide, amantadine, istradefylline, trihexyphenidyl, benztropine, rivastigmine, donepezil, galantamine and memantine, as well as physical, occupational and speech therapy, an exercise program including cardiorespiratory, resistance, flexibility, and gait and balance exercises, and deep brain stimulation (DBS) involving the implantation of an electrode into a targeted area of the brain.

In one embodiment, the method includes administering a composition featured herein such that expression of the target SNCA gene is decreased, for at least one month. In certain embodiments, expression is decreased for at least 2 months, 3 months, or 6 months.

Optionally, the RNAi agents useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target SNCA gene. Compositions and methods for inhibiting the expression of these genes using RNAi agents can be prepared and performed as described herein.

Administration of the dsRNA according to the methods of the disclosure may result in a reduction of the severity, signs, symptoms, or markers of such diseases or disorders in a patient with a SNCA-associated neurodegenerative disorder. By “reduction” in this context is meant a statistically significant or clinically significant decrease in such level. The reduction can be, for example, at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or about 100%.

Efficacy of treatment or prevention of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. For example, efficacy of treatment of a SNCA-associated neurodegenerative disorder may be assessed, for example, by periodic monitoring of a subject's cognition, learning, or memory. Comparisons of the later readings with the initial readings provide a physician an indication of whether the treatment is effective. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In

connection with the administration of an RNAi agent targeting SNCA or pharmaceutical composition thereof, "effective against" a SNCA-associated neurodegenerative disorder indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating SNCA-associated neurodegenerative disorders and the related causes.

A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and optionally at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given RNAi agent drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant reduction in a marker or symptom is observed.

Alternatively, the efficacy can be measured by a reduction in the severity of disease as determined by one skilled in the art of diagnosis based on a clinically accepted disease severity grading scale. Any positive change resulting in *e.g.*, lessening of severity of disease measured using the appropriate scale, represents adequate treatment using an RNAi agent or RNAi agent formulation as described herein.

Subjects can be administered a therapeutic amount of dsRNA, such as about 0.01 mg/kg to about 200 mg/kg.

The RNAi agent can be administered intrathecally, via intravitreal injection, or by intravenous infusion over a period of time, on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. Administration of the RNAi agent can reduce SNCA levels, *e.g.*, in a cell, tissue, blood, CSF sample or other compartment of the patient by at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or at least about 99% or more. In a preferred embodiment, administration of the RNAi agent can reduce SNCA levels, *e.g.*, in a cell, tissue, blood, CSF sample or other compartment of the patient by at least 50%.

Before administration of a full dose of the RNAi agent, patients can be administered a smaller dose, such as a 5% infusion reaction, and monitored for adverse effects, such as an allergic reaction. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (*e.g.*, TNF-alpha or INF-alpha) levels.

Alternatively, the RNAi agent can be administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired, *e.g.*, monthly dose of RNAi agent to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimen may include administration of a therapeutic amount of RNAi agent on a regular basis, such as monthly or extending to once a quarter, twice per year, once per year. In certain embodiments, the RNAi agent is administered about once per month to about once per quarter (*i.e.*, about once every three months).

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the RNAi agents and methods featured in the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

An informal Sequence Listing is also filed herewith and forms part of the specification as filed.

EXAMPLES

Example 1: Materials and Methods

Bioinformatics

A set of siRNAs targeting the human Synuclein alpha gene (SNCA; human NCBI refseq ID NM_007308.3; NCBI GeneID: 6622; SEQ ID NO: 1) as well the toxicology-species SNCA (XM_005555422.2; SEQ ID NO: 3) ortholog from cynomolgus monkey were designed using

custom R and Python scripts. All the siRNAs were designed to have a perfect match to the human SNCA transcripts and a subset either perfect or near-perfect matches to the cynomolgus monkey ortholog. The human SNCA NM_007308 REFSEQ mRNA, version 3 (SEQ ID NO: 1), has a length of 3312 bases. The rationale and method for the set of siRNA designs follows. The predicted efficacy for every potential 23mer siRNA from position 10 through the end was determined with a random forest model derived from the direct measure of mRNA knockdown from several thousand distinct siRNA designs targeting a diverse set of vertebrate genes. For each strand of the siRNA, a custom Python script was used in a brute force search to measure the number and positions of mismatches between the siRNA and all potential alignments in the human transcriptome. Extra weight was given to mismatches in the seed region, defined here as positions 2-9 of the antisense oligonucleotide, as well the cleavage site of the siRNA, defined here as positions 10-11 of the antisense oligonucleotide. The relative weight of the mismatches was 2.8, 1.2, 1 for seed mismatches, cleavage site, and other positions up through antisense position 19. Mismatches in the first position were ignored. A specificity score was calculated for each strand by summing the value of each weighted mismatch. Preference was given to siRNAs whose antisense score in human and cynomolgus monkey was ≥ 2 and predicted efficacy was $\geq 50\%$ knockdown.

In Vitro Screening - Dual-Glo® Luciferase Assay

Cos-7 cells (ATCC, Manassas, VA) were grown to near confluence at 37°C in an atmosphere of 5% CO₂ in DMEM (ATCC) supplemented with 10% FBS, before being released from the plate by trypsinization. Multi-dose experiments were performed at 10nM and 0.1nM. siRNA and psiCHECK2-SNCAs (human NM_007308 and mouse NM_009221) plasmid transfections were carried out with plasmids containing the 3' untranslated region (UTR). Transfection was carried out by adding 5 µL of siRNA duplexes and 5 µL (5 ng) of psiCHECK2 plasmid per well along with 4.9 µL of Opti-MEM plus 0.1 µL of Lipofectamine 2000 per well (Invitrogen, Carlsbad CA. cat # 13778-150) and then incubated at room temperature for 15 minutes. The mixture was then added to the cells which were re-suspended in 35 µL of fresh complete media. The transfected cells were incubated at 37°C in an atmosphere of 5% CO₂.

Forty-eight hours after the siRNAs and psiCHECK2 plasmid were transfected, Firefly (transfection control) and *Renilla* (fused to SNCA target sequence) luciferase were measured.

First, media was removed from cells. Then Firefly luciferase activity was measured by adding a mixture of 20 μ L Dual-Glo® Luciferase Reagent and 20 μ L DMEM to each well. The mixture was incubated at room temperature for 30 minutes before luminescence (500nm) was measured on a Spectramax (Molecular Devices) to detect the Firefly luciferase signal. *Renilla* luciferase activity was measured by adding a mixture of 20 μ L of room temperature of Dual-Glo® Stop & Glo® Buffer and 0.1 μ L Dual-Glo® Stop & Glo® Substrate to each well and the plates were incubated for 10-15 minutes before luminescence was again measured to determine the *Renilla* luciferase signal. The Dual-Glo® Stop & Glo® mixture quenches the firefly luciferase signal and sustained luminescence for the *Renilla* luciferase reaction. siRNA activity was determined by normalizing the *Renilla* (SNCA) signal to the Firefly (control) signal within each well. The magnitude of siRNA activity was then assessed relative to cells that were transfected with the same vector but were not treated with siRNA or were treated with a non-targeting siRNA. All transfections were done with n=4.

In Vitro Screening - Cell Culture and Transfections

Cells were transfected by adding 4.9 μ L of Opti-MEM plus 0.1 μ L of RNAiMAX per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5 μ L of siRNA duplexes per well, with 4 replicates of each siRNA duplex, into a 384-well plate, and incubated at room temperature for 15 minutes. 40 μ L of MEDIA containing $\sim 5 \times 10^3$ cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Experiments were performed at 10nM and 0.1nM. Transfection experiments were performed in human hepatoma Hep3B cells (ATCC HB-8064) with EMEM (ATCC catalog no. 30-2003), mouse neuroblastoma Neuro-2A cells (ATCC CCL-131) with EMEM media, and human neuroblastoma BE(2)-C, HeLa, and B16F10 cells. BE(2)-C cells (ATCC CRL-2268) were grown in EMEM:F12 media (Gibco catalog no. 11765054). HeLa cells and B16F10 cells were grown according to standard protocols.

In Vitro Screening - cDNA Synthesis Using ABI High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, Cat #4368813)

12 μ L of a master mix containing 1.2 μ L 10X Buffer, 0.48 μ L 25X dNTPs, 1.2 μ L 10x Random primers, 0.6 μ L Reverse Transcriptase, 0.6 μ L RNase inhibitor and 7.92 μ L of H₂O per reaction was added to the bead bound RNA isolated above. Plates were sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2h

incubation at 37°C. Branched DNA assays were also performed using the aforementioned protocol.

In Vitro Screening - Real Time PCR

2 µL of cDNA were added to a master mix containing 0.5 µL of human or mouse GAPDH TaqMan Probe (ThermoFisher cat 4352934E or 4351309) and 0.5 µL of appropriate SNCA probe (Thermo Fisher Taqman human: Hs00268077, mouse: Mm00485946) and 5 µL Lightcycler 480 probe master mix (Roche Cat # 04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done in a LightCycler480 Real Time PCR system (Roche). Each duplex was tested with N=4 and data were normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data were analyzed using the $\Delta\Delta C_t$ method and normalized to assays performed with cells transfected with a non-targeting control siRNA.

Example 2: Knock-Down of Endogenous SNCA and SNCA Expressed *Via* Dual-Luciferase psiCHECK2 Vector

A series of SNCA iRNA agents were generated, for which modified (based on key in **Table 1**) and unmodified sequences are listed in **Tables 2 and 3**. BE2-(C), HeLa, and B16F10 cells were used to screen for knock-down of endogenous SNCA transcript using the duplexes shown in **Tables 2 and 3**. Cos7 cells expressing the dual-luciferase psiCHECK2 vector were used to screen for inhibition of exogenous SNCA transcript using the duplexes of **Tables 2 and 3**. Duplex siRNA was added to cells at concentrations of 10 nM and 0.1 nM. The observed levels of SNCA transcript in BE(2)-Cells are shown in **Tables 4, 5, and 9**. The observed levels of SNCA transcript in HeLa and B16F10 cells are shown in **Table 6**. The observed levels of SNCA observed via the dual-luciferase system are shown in **Table 7**. Many duplexes were identified that showed robust SNCA inhibition.

Example 3: *In Vivo* Evaluation of SNCA RNAi Agents

Selected SNCA-targeting RNAi agents were evaluated for *in vivo* efficacy and lead compound identification, by screening for human SNCA knockdown in mice expressing human SNCA *via* AAV transgene. The selected RNAi agents for such studies included: duplexes targeting the 3'UTR of SNCA: AD-464778, AD-464782, AD-464694, AD-464634, AD-464779; and

duplexes targeting the coding sequence of SNCA: AD-464590, AD-464313, AD-464314, AD-464585, AD-464586, AD-464592, and AD-464229. All aforementioned duplexes were chemically modified sequences having L96 GalNAc ligands (**Table 2**) as indicated in **Table 1**. Corresponding unmodified sequences are shown in **Table 3**.

To identify RNAi *in vivo* efficacy in mice, human SNCA was first transduced in the mice. A construct encoding the full *Homo sapiens* SNCA transcript and 3' UTR (refer to Hs00240906_m1) was packaged in AAV8 capsids and transduced at a level of 2.0E+10 genome copies/dose in 8-week-old C57BL/6 female mice. At 7 days post-AAV administration, the duplexes recited above or 1x PBS were subcutaneously injected at 3 mg/kg. 1 week post duplex dosing, mouse livers were harvested and SNCA expression was assessed using Taq Man assay Hs00240906_m1. Data were normalized to PBS-treated samples. cDNA synthesis and qRT-PCR were performed using routine techniques. Results are shown in **FIG. 1** and **Table 8**. A majority of tested RNAi agents exhibited SNCA inhibition *in vivo*.

The *in vivo* efficacies of a specific huSNCA 3'-UTR-targeting duplex, AD-464634, and a specific huSNCA coding sequence-targeting duplex, AD-464314, were assessed further (refer to **FIG. 2** for AD-464634 and AD-464314 sequences and modification patterns), at 3 mg/kg and 10 mg/kg doses, and at 7 day and 14 day time points. Robust knockdown of human SNCA was observed in mice treated with both the huSNCA 3'-UTR-targeting AD-464634 duplex and the huSNCA coding sequence-targeting AD-464314 duplex, at both day 7 and day 14 time points (**FIG. 3**). Dose-response was observed for both tested duplexes, particularly at the 14 day time point. With strong huSNCA knockdown observed even at the 14 day time point, both duplexes were identified as suitable for further *in vivo* lead development studies.

The efficacy of AAV transduction in producing mice that expressed human SNCA in the liver was also confirmed by real-time PCR. Human SNCA expression levels were specifically assessed in liver tissue of huSNCA AAV-transduced mice (respectively huSNCA AAV-transduced with 2e10 or 2e11 viral particles), with huSNCA levels measured at days 7, 14 and 21 post-transduction. Detectable levels of human SNCA in mouse liver were observed at all time points, in a dose-responsive manner with respect to levels of viral particles administered (higher levels of AAV transduction yielded lower threshold cycle counts (cT); **FIG. 4**).

The mouse/rat cross-reactivities of selected duplexes were also assessed *in vivo*, in rat SNCA AAV-transduced mice. In mice were also examined in mice transduced with rat SNCA. A

construct encoding the full *Rattus norvegicus* SNCA transcript and 3' UTR (refer to NM_019169.2) was packaged in AAV8 capsids and transduced at a level of 2.0E+10 genome copies/dose in 8-week-old C57BL/6 female mice. At 14 days week post-AAV administration, duplexes (AD-476344, AD-475666, AD-476306, AD-476061, AD-464814, AD-475728, and AD-4644229) or 1xPBS were subcutaneously injected at 3 mg/kg in the mice. 14 days post duplex dosing, livers were harvested and SNCA expression was assessed using Taq Man assay Rn00569821_m1. Data were normalized to PBS-treated samples. cDNA synthesis and qRT-PCR were performed using routine techniques. AD-476061, AD-464814 and AD-475728, as well as possibly AD-464229, exhibited significant rat SNCA knockdown (**FIG. 5**).

Example 4: A Hotspot Walk Across the SNCA Transcript Identified Many Further RNAi Agents with Robust SNCA Knockdown Properties

Additional modified SNCA-targeting RNAi duplexes possessing sequences and modification patterns as shown in **Table 12** were synthesized and assessed for human SNCA knockdown when administered at 0.1 nM, 1.0 nM and 10 nM in the environment of Be(2)C cells. Human SNCA knockdown results were obtained, and siRNAs and associated knockdown results were rank-ordered by 1 nM fit value (**Table 14**). A variety of further SNCA-targeting duplexes capable of inhibiting human SNCA were thereby identified, with strong correlation between measured SNCA knockdown levels in the hotspot walk and calculated 1 nM fit values used to rank-order duplexes observed (**FIG. 6**).

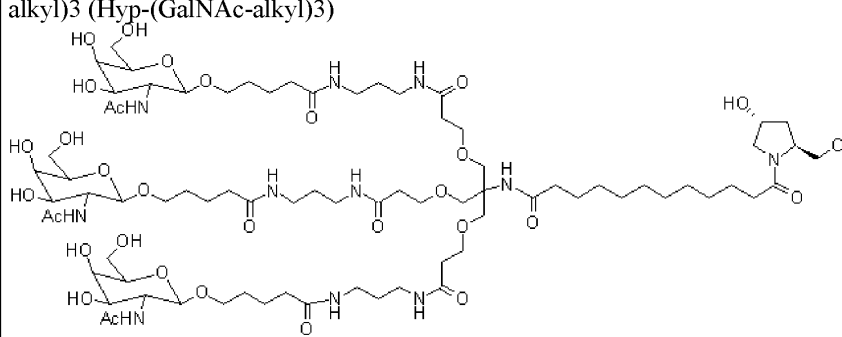
The "mRNA" sequences of the Informal Sequence Listing and certain of the "mRNA target" sequences listed herein may be noted as reciting thymine (T) residues rather than uracil (U) residues. As is apparent to one of ordinary skill in the art, such sequences reciting "T" residues rather than "U" residues can be derived from NCBI accession records that list, as "mRNA" sequences, the DNA sequences (not RNA sequences) that directly correspond to mRNA sequences. Such DNA sequences that directly correspond to mRNA sequences technically constitute the DNA sequence that is the complement of the cDNA (complementary DNA) sequence for an indicated mRNA. Thus, while the mRNA target sequence does, in fact, actually

include uracil (U) rather than thymine (T), the NCBI record-derived "mRNA" sequence includes thymine (T) residues rather than uracil (U) residues.

Table 1. Abbreviations of nucleotide monomers used in nucleic acid sequence representation.

It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds.

Abbreviation	Nucleotide(s)
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3'-phosphate
Abs	beta-L-adenosine-3'-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3'-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3'-phosphate
Gbs	beta-L-guanosine-3'-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
Us	uridine -3'-phosphorothioate
N	any nucleotide, modified or unmodified
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'-phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'-phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'-phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
s	phosphorothioate linkage

Abbreviation	Nucleotide(s)
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl]-4-hydroxyprolinol Hyp-(GalNAc-alkyl) ₃ (Hyp-(GalNAc-alkyl) ₃) 
Y34	2-hydroxymethyl-tetrahydrofuran-4-methoxy-3-phosphate (abasic 2'-OMe furanose)
Y44	inverted abasic DNA (2-hydroxymethyl-tetrahydrofuran-5-phosphate)
(Agn)	Adenosine-glycol nucleic acid (GNA) S-Isomer
(Cgn)	Cytidine-glycol nucleic acid (GNA) S-Isomer
(Ggn)	Guanosine-glycol nucleic acid (GNA) S-Isomer
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	vinyl phosphonate (i.e., 5'-(E)-vinylphosphonate)
(Aam)	2'-O-(N-methylacetamide)adenosine-3'-phosphate
(Aams)	2'-O-(N-methylacetamide)adenosine-3'-phosphorothioate
(Gam)	2'-O-(N-methylacetamide)guanosine-3'-phosphate
(Gams)	2'-O-(N-methylacetamide)guanosine-3'-phosphorothioate
(Tam)	2'-O-(N-methylacetamide)thymidine-3'-phosphate
(Tams)	2'-O-(N-methylacetamide)thymidine-3'-phosphorothioate
dA	2'-deoxyadenosine-3'-phosphate
dAs	2'-deoxyadenosine-3'-phosphorothioate
dC	2'-deoxycytidine-3'-phosphate
dCs	2'-deoxycytidine-3'-phosphorothioate
dG	2'-deoxyguanosine-3'-phosphate
dGs	2'-deoxyguanosine-3'-phosphorothioate
dT	2'-deoxythymidine-3'-phosphate
dTs	2'-deoxythymidine-3'-phosphorothioate
dU	2'-deoxyuridine
dUs	2'-deoxyuridine-3'-phosphorothioate
(Aeo)	2'-O-methoxyethyladenosine-3'-phosphate
(Aeos)	2'-O-methoxyethyladenosine-3'-phosphorothioate
(Geo)	2'-O-methoxyethylguanosine-3'-phosphate
(Geos)	2'-O-methoxyethylguanosine-3'-phosphorothioate
(Teo)	2'-O-methoxyethyl-5-methyluridine-3'-phosphate
(Teos)	2'-O-methoxyethyl-5-methyluridine-3'-phosphorothioate
(m5Ceo)	2'-O-methoxyethyl-5-methylcytidine-3'-phosphate
(m5Ceos)	2'-O-methoxyethyl-5-methylcytidine-3'-phosphorothioate
(A3m)	3'-O-methyladenosine-2'-phosphate
(A3mx)	3'-O-methyl-xylofuranosyladenosine-2'-phosphate

Abbreviation	Nucleotide(s)
(G3m)	3'-O-methylguanosine-2'-phosphate
(G3mx)	3'-O-methyl-xylofuranosylguanosine-2'-phosphate
(C3m)	3'-O-methylcytidine-2'-phosphate
(C3mx)	3'-O-methyl-xylofuranosylcytidine-2'-phosphate
(U3m)	3'-O-methyluridine-2'-phosphate
U3mx)	3'-O-methyl-xylofuranosyluridine-2'-phosphate
(m5Cam)	2'-O-(N-methylacetamide)-5-methylcytidine-3'-phosphate
(m5Cams)	2'-O-(N-methylacetamide)-5-methylcytidine-3'-phosphorothioate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahds)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Ghds)	2'-O-hexadecyl-guanosine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate
(pshe)	Hydroxyethylphosphorothioate
(A2p)	adenosine-2'-phosphate
(C2p)	cytidine-2'-phosphate
(G2p)	guanosine-2'-phosphate
(U2p)	uridine-2'-phosphate
(A2ps)	adenosine-2'-phosphorothioate
(C2ps)	cytidine-2'-phosphorothioate
(G2ps)	guanosine-2'-phosphorothioate
(U2ps)	uridine-2'-phosphorothioate

Table 2. Modified Sense and Antisense Strand Sequences of Human and Primate SNCA siRNAs.

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-595724	A-1142132.1	gsasctat(Chd)AfgUfGfUfgguguaaagaL96	13	A-1142133.1	VPusCfsnuua(Cgm)accacaCfuGfucnuesgsa	103	UGGACGACAGUGUGGUGUAAGG	193
AD-595769	A-1142222.1	asusgaat(Ahd)GfgAfCfUfucuaagagcaL96	14	A-1142223.1	VPusGfscuu(Tgn)gaagaCfcUfucnuesgsa	104	UCAUGAAAGGACUUUCAAAGGCC	194
AD-595854	A-1142392.1	asasaga(Chd)GfgUfGfUfucnuaunguaL96	15	A-1142393.1	VPusAfscaua(Cgm)agaacaCfcCfucnuesug	105	CAAAAGAGGGUGUUCUCUAUGUA	195
AD-595855	A-1142394.1	asasaga(Chd)GfgUfGfUfucnuaunguaL96	16	A-1142395.1	VPusUfsacua(Cgm)gagaacAfcCfucnuesusu	106	AAAAAGAGGGUGUUCUCUAUGUAG	196
AD-595866	A-1142416.1	csuscuat(Uhd)GfuAfGfGfucuaaacaL96	17	A-1142417.1	VPusGfsuuui(Cgm)gagccuAfcAfuagagsasa	107	UUCUCUAUGUAGGCUCCAAAACC	197
AD-595926	A-1142536.1	asasgaat(Chd)AfuAfGfAfgcuaugacalL96	18	A-1142537.1	VPusGfsuac(Tgn)ugcucuUfuGfucnuescu	108	AGAAAGACCAAGAGCAAGUGACA	198
AD-596096	A-1142876.1	ascsaui(Chd)AfgCfCfUfuaagaagaL96	19	A-1142877.1	VPusCfsuui(Cgm)auaagcCfuCfuaugscsa	109	UGACAAUGAGGCUUAUGAAUUGC	199
AD-596100	A-1142884.1	usgsagga(Chd)UfuAfUfGfaaagccuaL96	20	A-1142885.1	VPusAfsagac(Agm)uuucaAfaGfucnuescu	110	AAUGAGGCUUAUGAAAUGCCUUC	200
AD-596124	A-1142932.1	gsgsaag(Chd)GfuAfUfCfaagacuacgaL96	21	A-1142933.1	VPusCfsuag(Tgn)cuuagauAfcCfucnuescsc	111	GAGGAAGGUAUCAAGACUACGA	201
AD-596126	A-1142936.1	asasgga(Chd)AfuCfAfaGfuaacgaalL96	22	A-1142937.1	VPusUfsuicu(Agm)gucungAfuAfcenuescsc	112	GGAAAGGUUAUCAAGACUACGAAC	202
AD-596127	A-1142938.1	asgsagui(Chd)UfcAfAfGfuaacgaacalL96	23	A-1142939.1	VPusGfsuac(Tgn)agucuuGfaUfaccnuesc	113	GAAGGGUAUCAAGACUACGAACC	203
AD-596128	A-1142940.1	gsgsgua(Uhd)CfaAfGfAfcuaagacalL96	24	A-1142941.1	VPusGfsguic(Cgm)uagucuUfgAfuaccsusu	114	AAGGGUAUCAAGACUACGAACCU	204
AD-596129	A-1142942.1	gsgsuui(Chd)AfaGfAfcuaagacualL96	25	A-1142943.1	VPusAfsagui(Cgm)uagucuUfuGfuaaccsusu	115	AGGGUAUCAAGACUACGAACCU	205
AD-596130	A-1142944.1	gsusauc(Ahd)AfgAfCfUfuaagacualL96	26	A-1142945.1	VPusCfsaggu(Tgn)cuuagauCfuUfguaaccsc	116	GGUAUCAAGACUACGAACCU	206
AD-596131	A-1142946.1	usasauc(Ahd)GfaCfUfAfgaaccuagaaL96	27	A-1142947.1	VPusUfscag(Tgn)ucunguUfcUfuaaccsc	117	GGUAUCAAGACUACGAACCU	207
AD-596133	A-1142950.1	uscsaag(Ahd)CfuAfCfGfuaaccuagaaL96	28	A-1142951.1	VPusCfsuica(Cgm)gucucuAfgUfucnuesasa	118	UAUCAAGACUACGAACCU	208
AD-596137	A-1142958.1	gsasua(Chd)GfaAfCfCfuaagacuaL96	29	A-1142959.1	VPusUfsgagc(Tgn)ucagucuUfcGfuaaccsusu	119	AAGACUACGAACCUUAGGCCUA	209
AD-596144	A-1142972.1	asascuu(Chd)AfaGfCfCfuaagaauaalL96	30	A-1142973.1	VPusUfsuuui(Cgm)uagucuUfuCfagunuescg	120	CGAAACCUAGAGCCUAAGAAUAU	210
AD-596147	A-1142978.1	csusgaat(Chd)CfcUfAfAfgaauaauaalL96	31	A-1142979.1	VPusAfsaui(Cgm)uucuuGfgCfuaaccgsu	121	ACCUAGAGCCUAAGAAUAU	211
AD-596168	A-1143020.1	usgsuic(Chd)CfaCfUfUfuaagaaalL96	32	A-1143021.1	VPusAfsuic(Agm)agaauUfgGfagacasa	122	UUUGCUCCAGUUUUCUUGAGAU	212
AD-596169	A-1143022.1	gscsuic(Chd)AfgUfUfUfuaagaaalL96	33	A-1143023.1	VPusGfsuic(Cgm)agaauCfuGfagacasa	123	UUGCUCCAGUUUUCUUGAGAU	213

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-596170	A-1143024.1	csusccc(Ahd)GfuUfUfCfuugagaucaL96	34	A-1143025.1	VpusAfsgauc(Tgn)caagaaAfcUfaggagsgca	124	UGCUCCCAAGUUUUCUUGAGAUUCUG	214
AD-596171	A-1143026.1	uscsccat(Ghd)UfuUfCfuUfugagaucaL96	35	A-1143027.1	VpusCfsagau(Cgn)ucnaaaAfaCfuggagsgsc	125	GCUCCCAAGUUUUCUUGAGAUUCUGC	215
AD-596172	A-1143028.1	csccscag(Uhd)UfuUfCfuUfugagaucaL96	36	A-1143029.1	VpusGfscag(Tgn)caucaagAfaAfcuagsgsg	126	CUCCCAAGUUUUCUUGAGAUUCUGCU	216
AD-596175	A-1143034.1	asgsuui(Chd)UfuUfCfuAfcuagcucaL96	37	A-1143035.1	VpusUfscag(Cgn)gaucacAfaGfaacugsg	127	CCAGUUUUCUUGAGAUUCUGGAC	217
AD-596177	A-1143038.1	ususuui(Uhd)GfuGfuAfcuagcucaL96	38	A-1143039.1	VpusUfsguca(Cgn)caagacUfcAfagaascsu	128	AGUUUUCUUGAGAUUCUGGACAG	218
AD-596215	A-1143114.1	asgsuui(Uhd)CfuGfuUfUfcauagcucaL96	39	A-1143115.1	VpusGfscac(Tgn)uggaacUfgAfcuacugsg	129	CAAGUGGCUAGUUUCCAAUGUGCC	219
AD-596231	A-1143146.1	gsusgcc(Chd)AfcUfCfuAfcuagcucaL96	40	A-1143147.1	VpusGfscac(Tgn)ucnaagCfuGfaggacscsu	130	AUGUGCCAGUCAUGACAUUUCU	220
AD-596235	A-1143154.1	csccsag(Uhd)AfuGfuAfcuagcucaL96	41	A-1143155.1	VpusUfsgag(Cgn)gaugacAfuGfaucugsgsc	131	GCCCAGUCAGACAUUUCUCAA	221
AD-596283	A-1143250.1	csasica(Ghd)CfuGfuUfGfaugcucaL96	42	A-1143251.1	VpusUfscac(Cgn)gaucacUfgCfugaugsgsa	132	UCCAUCAGCAGUGAUUGAAGUAU	222
AD-596319	A-1143322.1	ususuca(Chd)UfgAfcuagcucaL96	43	A-1143323.1	VpusAfsgua(Tgn)ucacuuCfaGfugaasgsg	133	CCUUUCACUGAAGUGAAUACAUG	223
AD-596320	A-1143324.1	ususcac(Uhd)GfuAfcuagcucaL96	44	A-1143325.1	VpusCfsaui(Cgn)ucacuuUfcAfugaasag	134	CUUUCACUGAAGUGAAUACAUGG	224
AD-596322	A-1143328.1	csasucg(Ahd)AfcUfGfuAfcuagcucaL96	45	A-1143329.1	VpusAfscac(Cgn)uacuuCfuUfcuaggsa	135	UUCACUGAAGUGAAUACAUGGUA	225
AD-596323	A-1143330.1	ascsuag(Ahd)GfuGfuAfcuagcucaL96	46	A-1143331.1	VpusUfscac(Tgn)gaucacAfcUfucagsgsa	136	UCACUGAAGUGAAUACAUGGUAG	226
AD-596325	A-1143334.1	usgsaag(Uhd)GfuAfcuagcucaL96	47	A-1143335.1	VpusGfscac(Cgn)gaugacUfcAfcuacsgsu	137	ACUGAAGUGAAUACAUGGUAGCA	227
AD-596326	A-1143336.1	gsasagu(Ghd)AfaUfAfcuagcucaL96	48	A-1143337.1	VpusUfsguca(Cgn)caugacUfuCfucucsgsg	138	CUGAAGUGAAUACAUGGUAGCAG	228
AD-596362	A-1143408.1	usgsuag(Uhd)UfuGfuUfGfucuaucal96	49	A-1143409.1	VpusGfscag(Cgn)agccacAfaAfaucacsa	139	UGUGGAUUUUGUGGCUUCAUUCU	229
AD-596390	A-1143464.1	asasaat(Chd)AfcUfCfuAfcuagcucaL96	50	A-1143465.1	VpusGfscag(Cgn)acuuagGfuGfuucuuasa	140	UUAAAAACACCUAAAGUGACUACC	230
AD-596391	A-1143466.1	asasaac(Ahd)CfcUfAfcuagcucaL96	51	A-1143467.1	VpusGfscag(Tgn)caucuaGfuUfuuuuusa	141	UAAAAACACCUAAAGUGACUACCA	231
AD-596392	A-1143468.1	asasaca(Chd)CfuAfcuagcucaL96	52	A-1143469.1	VpusUfsgua(Cgn)ucacuuAfcGfugaucuuusu	142	AAAAACACCUAAAGUGACUACCAC	232
AD-596396	A-1143476.1	ascsuac(Ahd)GfuGfuAfcuagcucaL96	53	A-1143477.1	VpusUfscag(Cgn)gaucacAfcUfuaugsgsu	143	ACACCUAAAGUGACUACCACUUAU	233
AD-596402	A-1143488.1	gsusgac(Uhd)AfcCfuAfcuagcucaL96	54	A-1143489.1	VpusUfscag(Cgn)gaugacGfuAfcuacscsu	144	AAGUGACUACCACUUAUUUCUAA	234
AD-596425	A-1143534.1	csusguu(Ghd)UfuCfuAfcuagcucaL96	55	A-1143535.1	VpusUfscac(Agn)cuuagAfaCfucagsgsa	145	UGCUGUUUUCAGAGAUUGUUUAG	235

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-596426	A-1143536.1	usgsuug(Uhd)UfcAfGfAfaguuuuuagL96	56	A-1143537.1	VpusCfsuac(Agm)acuuuGfaAfcacagsc	146	GCUGUUGUUCAGAAUGUUGUAGU	236
AD-596427	A-1143538.1	gsusug(Uhd)CfaGfAfAfguuuuuagL96	57	A-1143539.1	VpusAfsuac(Cgm)aacuuUfgAfacaacstg	147	CUGUUGUUCAGAAUGUUGUAGU	237
AD-596431	A-1143546.1	usiscag(Ahd)AfgUfUfGfuuuuuuuagL96	58	A-1143547.1	VpusAfsuac(Cgm)uacuuCfuUfugucasesa	148	UGUUCAGAAUGUUGUUGUAGU	238
AD-596436	A-1143556.1	asasgum(Ghd)UfuAfGfUfguuuuuuuagL96	59	A-1143557.1	VpusUfsagca(Agm)uacuuAfaCfacauescu	149	AGAAUGUUGUUGUUGUUGUAGU	239
AD-596469	A-1143622.1	usuuuu(Ahd)UfgAfUfAfGfuuuuuuuagL96	60	A-1143623.1	VpusCfsuac(Agm)uacuuCfaUfuuaaagssa	150	UCUUUAAUGAUACUGUCUAAAGA	240
AD-596477	A-1143638.1	asusacu(Ghd)UfcUfAfAfguuuuuuuagL96	61	A-1143639.1	VpusUfscuu(Agm)uucuuGfaCfaguuuacsa	151	UGAUACUGUCUAAAGAAUAAUGAC	241
AD-596515	A-1143714.1	asgsacu(Ghd)AfaAfCfUfaguuuuuuuagL96	62	A-1143715.1	VpusUfsaggu(Ggm)uacuuUfuCfaguuuacsa	152	UGAGCAUGAAACUUAUGCACCUAU	242
AD-596517	A-1143718.1	csasug(Ahd)AfcUfAfUfaguuuuuuuagL96	63	A-1143719.1	VpusUfsuag(Ggm)uacuuGfuUfucuuuacsa	153	AGCAUGAAACUUAUGCACCUAU	243
AD-596605	A-1143894.1	usuuuu(Ghd)CfcAfUfCfuuuuuuuagL96	64	A-1143895.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	154	UUUUUACCCAUUCACUUUAAUA	244
AD-596606	A-1143896.1	usuuuu(Ghd)CfcAfUfCfuuuuuuuagL96	65	A-1143897.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	155	UUUUUACCCAUUCACUUUAAUA	245
AD-596609	A-1143902.1	usccacu(Uhd)CfuCfAfCfuuuuuuuagL96	66	A-1143903.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	156	UUUUUACCCAUUCACUUUAAUA	246
AD-596709	A-1144102.1	asasacu(Ghd)GfaAfCfAfuuuuuuuagL96	67	A-1144103.1	VpusUfsaggu(Ggm)uacuuUfuCfaguuuacsa	157	AGAAUUGGAAACUUAACCCUAC	247
AD-597019	A-1144722.1	asuuuu(Ghd)AfcUfAfUfaguuuuuuuagL96	68	A-1144723.1	VpusUfsuag(Cgm)uacuuGfuUfucuuuacsa	158	ACAUUAGCACAUAUAGCACAUAU	248
AD-597232	A-1145148.1	usuuuu(Ghd)UfcUfAfGfuuuuuuuagL96	69	A-1145149.1	VpusUfsaggu(Ggm)uacuuGfuUfucuuuacsa	159	UUUUUACCCAUUCACUUUAAUA	249
AD-597297	A-1145278.1	asasguc(Ahd)CfuAfGfUfaguuuuuuuagL96	70	A-1145279.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	160	UUUUUACCCAUUCACUUUAAUA	250
AD-597298	A-1145280.1	asgsacu(Ghd)UfgUfAfAfguuuuuuuagL96	71	A-1145281.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	161	UUUUUACCCAUUCACUUUAAUA	251
AD-597325	A-1145334.1	csasgaa(Uhd)AfuUfCfUfaguuuuuuuagL96	72	A-1145335.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	162	UUUUUACCCAUUCACUUUAAUA	252
AD-597326	A-1145336.1	asgsacu(Ahd)UfuUfCfUfaguuuuuuuagL96	73	A-1145337.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	163	UUUUUACCCAUUCACUUUAAUA	253
AD-597327	A-1145338.1	gsasuu(Uhd)UfcUfAfGfuuuuuuuagL96	74	A-1145339.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	164	UUUUUACCCAUUCACUUUAAUA	254
AD-597335	A-1145354.1	usasgac(Ahd)UfgCfUfAfGfuuuuuuuagL96	75	A-1145355.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	165	UUUUUACCCAUUCACUUUAAUA	255
AD-597397	A-1145478.1	gsasgaa(Ahd)UfgAfGfUfaguuuuuuuagL96	76	A-1145479.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	166	UUUUUACCCAUUCACUUUAAUA	256
AD-597398	A-1145480.1	asgsaa(Uhd)GfaGfUfGfuuuuuuuagL96	77	A-1145481.1	VpusUfsuac(Cgm)uacuuGfuUfucuuuacsa	167	UUUUUACCCAUUCACUUUAAUA	257

Duplex	Sense	Oligo Sequence	SEQ ID NO:	Antisense	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-597404	A-	gsasgug(Ahd)CfuAfuAfAaggaugcuaaL96	78	A-	VPusAFsacca(Tgm)ccuamAfAfufcacscasu	168	AUGAGUGACUAUAAGGAUGGUUA	258
AD-597409	A-	asesuau(Ahd)AfgGfAfUfgguaccuaaL96	79	A-	VPusAFsugau(Agm)aaccanCfuUfauguscса	169	UGACUAUAAGGAUGGUUACCAUA	259
AD-597410	A-	csusuaa(Ahd)GfgAfUfGfuguaaccauaL96	80	A-	VPusUfsaugg(Tgm)aaccanCfuUfuaugusc	170	GACUAUAAGGAUGGUUAACCAUG	260
AD-597417	A-	gsasuggg(Uhd)UfaCfCfAfAagaacuaaL96	81	A-	VPusAFsgau(Tgm)cuauaggUfaAfccacscsu	171	AGGAUGGUUACCAUAGAAACUUC	261
AD-597443	A-	asesuae(Uhd)AfcAfGfAfGfcuagacal96	82	A-	VPusGfscuaa(Ggm)cacuacGfuAfguugscsu	172	AGACUACUACAGAGUGCUAAGCU	262
AD-597455	A-	usgsuaa(Ahd)GfcUfGfCfAugugucuaaL96	83	A-	VPusAFsugac(Agm)caugcaGfcUfuaacscsu	173	AGUGCUAAGCUGCAUGUGUCAUC	263
AD-597459	A-	asasgcu(Ghd)CfaUfGfUfGfcuaucuaaL96	84	A-	VPusUfsaaga(Tgm)gacacaUfgCfagucisag	174	CUAAGCUGCAUGUGUCAUCUUAC	264
AD-597460	A-	asgsaug(Chd)AfmGfUfGfucuaucuaaL96	85	A-	VPusGfsguag(Agm)ugacacAfufGfcacuscua	175	UAAGCUGCAUGUGUCAUCUUACA	265
AD-597534	A-	csasgua(Uhd)AfuUfUfCfGaggaaguaaL96	86	A-	VPusAFsacuu(Tgm)ccuagaaAfuaAfuaucsuu	176	AACAGUAUAUUUCAGGAAGGUUA	266
AD-597569	A-	asasaac(Uhd)AfcCfUfAfAagcagcauaL96	87	A-	VPusAFsugcu(Ggm)cuuagGfuAfgaumisasa	177	UUAAAUCUACCUAAAAGCAGCAUA	267
AD-597861	A-	asgsuac(Uhd)AfgGfUfUfuaunungcaal96	88	A-	VPusUfsgcaal(Agm)auaaacCfuAfagacungsg	178	CCAGUCCUAGGUUUAUUUUGCAG	268
AD-597864	A-	csesuaa(Ghd)UfuUfAfUfufungcagacal96	89	A-	VPusGfsgucg(Cgm)aaanaAfAfCfuaaggsasc	179	GUCCUAGGUUAUUUUGCAGACU	269
AD-597894	A-	csesaaag(Uhd)UfaUfUfCfGagccuacuaaL96	90	A-	VPusUfsaaga(Ggm)gcugaaUfaAfCuauggsasa	180	UCCCAAAGUUAUUCAGCCUCAUAU	270
AD-597898	A-	gsusuaa(Uhd)CfaGfCfCfcauaugacal96	91	A-	VPusGfscuaa(Agm)ugaggCfUfaAuaacsuu	181	AAGUUAUUCAGCCUCAUAUGACU	271
AD-597899	A-	usisuaa(Uhd)AfgCfCfUfcauaugacuaL96	92	A-	VPusAFsguca(Tgm)augaggCfuGfaaanaescu	182	AGUUAUUCAGCCUCAUAUGACUC	272
AD-597900	A-	usasaac(Ahd)GfcCfUfCfuaugacuaaL96	93	A-	VPusGfsguc(Agm)uagaggGfcUfgaunusc	183	GUUAUUCAGCCUCAUAUGACUCC	273
AD-597925	A-	uscsagg(Uhd)UfuAfuAfCfCaagaaguaaL96	94	A-	VPusAFsacug(Tgm)uunguAfAfAfccagascsc	184	GGUCGGCUUUAACCAAACAGUUC	274
AD-597927	A-	gsgscuu(Uhd)AfcCfAfAfAacagucuaaL96	95	A-	VPusUfsgaac(Tgm)guuuugGfuAfagccsgsa	185	UCGGCUUUAACCAAACAGUUCAG	275
AD-597937	A-	asasaca(Ghd)UfuCfAfGfagugacuaaL96	96	A-	VPusAFsagug(Cgm)acucugAfAfCfugnuunusg	186	CAAAACAGUUAAGAGUGGACUUU	276
AD-597946	A-	asgsagu(Ghd)CfaCfUfUfuggacacaaL96	97	A-	VPusUfsguau(Ggm)ccaangUfgCfcaucungsa	187	UCAGAGUGCAUUUUGGCACACAA	277
AD-597972	A-	asascag(Ahd)AfcAfAfUfuauguguaaL96	98	A-	VPusAFsacca(Tgm)uagauGfuUfcaunuscsc	188	GGAACAGAACAAUCUAAUUGUG	278
AD-597974	A-	csasgaat(Chd)AfaUfUfUfuauguguaaL96	99	A-	VPusCfscaca(Cgm)auaagaUfuGfuaucsuu	189	AACAGAACAAUCUAAUUGUGGU	279

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-597984	A-1146652.1	usasag(Uhd)GfuGfGfUfugguuaucaL96	100	A-1146653.1	VpusGfsaaua(Cgm)caaacAfcAfcuaasgsa	190	UCUAAUGUGUGGUUUUGUAUUC	280
AD-597988	A-1146660.1	gsusag(Uhd)UfuUfGfGfuaucuaaL96	101	A-1146661.1	VpusCfsuag(Ugn)uaucaAfaCfcaasasu	191	AUGUGUGGUUUUGUAUUC	281
AD-597989	A-1146662.1	usgsag(Uhd)UfuGfGfUfaucaagL96	102	A-1146663.1	VpusAfsuag(Ugn)uaucaAfaAfcacasa	192	UGUGUGGUUUUGUAUUC	282
AD-595724.1	A-1142132.1	gsasag(Chd)AfgUfGfUfgguuuaaL96	463	A-1142133.1	VpusCfsuuaa(Cgm)accacaCfuGfucgsa	553	UCGACGACAGUGUGGUUAAGG	643
AD-595769.1	A-1142222.1	asusgaal(Ahd)GfgAfcUfuaaagcaL96	464	A-1142223.1	VpusGfscuu(Tgn)gaaguuCfcUfucausgsa	554	UCAUGAAAGGACUUUCAAGGCC	644
AD-595854.1	A-1142392.1	asasaga(Chd)GfgUfGfUfucuaaL96	465	A-1142393.1	VpusAfsaaua(Cgm)agaacaCfcCfuausug	555	CAAAAGAGGGUGUUCUCUAUGUA	645
AD-595855.1	A-1142394.1	asasgag(Chd)GfuGfUfucuaaL96	466	A-1142395.1	VpusUfscuu(Agn)gagaacAfcCfuausuu	556	AAAAGAGGGUGUUCUCUAUGUAG	646
AD-595866.1	A-1142416.1	csuscu(Uhd)GfuAfcGfGfuaaL96	467	A-1142417.1	VpusGfscuu(Cgm)gagcuAfcAfuaggsa	557	UUCUCUAUGUAGGCUCCAAAACC	647
AD-595926.1	A-1142536.1	asasga(Chd)AfaAfcGfAfcgaagL96	468	A-1142537.1	VpusGfsuac(Tgn)ugcuUfuGfucuu	558	AGAAAGACCAAGAGCAAGUGACA	648
AD-596096.1	A-1142876.1	ascsau(Chd)AfgGfCfUfuaaL96	469	A-1142877.1	VpusCfsuui(Cgm)auaagCfuCfuauscsa	559	UGACAAUGAGGCUUAUGAAAUGC	649
AD-596100.1	A-1142884.1	usgsag(Chd)UfuAfuGfuaaL96	470	A-1142885.1	VpusAfsagag(Agn)uuaaAfaGfucua	560	AAUGAGGCUUAUGAAAUGCCUUC	650
AD-596124.1	A-1142932.1	gsasag(Chd)GfuAfuCfuaaL96	471	A-1142933.1	VpusCfsguag(Tgn)cuuagAfcCfuausc	561	GAGGAAAGGUAUCAAGACUACGA	651
AD-596126.1	A-1142936.1	asasgag(Uhd)AfuCfAfcgaL96	472	A-1142937.1	VpusUfscuu(Agn)gucuuAfuAfcuu	562	GGAAAGGUAUCAAGACUACGAAC	652
AD-596127.1	A-1142938.1	asgsag(Uhd)UfcAfcGfuaaL96	473	A-1142939.1	VpusGfscuu(Tgn)ugcuUfuAfcuu	563	GAAAGGUAUCAAGACUACGAACC	653
AD-596128.1	A-1142940.1	gsasga(Uhd)CfaAfcGfAfcuaL96	474	A-1142941.1	VpusGfscuu(Cgm)uagcuUfuAfuacuu	564	AAGGGUAUCAAGACUACGAACCU	654
AD-596129.1	A-1142942.1	gsasuu(Chd)AfaGfAfcuaaL96	475	A-1142943.1	VpusAfsaguu(Cgm)uagcuUfuGfuausc	565	AGGGUAUCAAGACUACGAACCU	655
AD-596130.1	A-1142944.1	gsasuu(Chd)AfaGfAfcuaaL96	476	A-1142945.1	VpusCfsguu(Tgn)cuuagCfuUfguausc	566	GGGUAUCAAGACUACGAACCU	656
AD-596131.1	A-1142946.1	usasga(Chd)GfuAfcGfuaaL96	477	A-1142947.1	VpusUfscag(Tgn)cuuagUfcUfguausc	567	GGUAUCAAGACUACGAACCU	657
AD-596133.1	A-1142950.1	uscsag(Chd)CfuAfcGfuaaL96	478	A-1142951.1	VpusCfsuua(Cgm)uagcuAfgUfuausgsa	568	UAUCAAGACUACGAACCU	658
AD-596137.1	A-1142958.1	gsasuu(Chd)GfuAfcGfuaaL96	479	A-1142959.1	VpusUfscag(Tgn)cuuagUfcGfuausc	569	AAGACUACGAACCU	659
AD-596144.1	A-1142972.1	asascu(Chd)AfaGfCfuaaL96	480	A-1142973.1	VpusUfscuu(Cgm)uagcuUfuCfuausc	570	CGAACCUAAGGCUAAGAAU	660
AD-596147.1	A-1142978.1	csusga(Chd)CfcUfAfcuaaL96	481	A-1142979.1	VpusAfsaaua(Tgn)uuaaGfCfuausc	571	ACCUGAAGCCUAAAGAAU	661

Duplex	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD- 596168.1	A- 1143020.1	usgsnc(Chd)CtaGfUfUfUcugagaaL96	482	A- 1143021.1	VPusAfsrcnc(Agn)agaaacUfgGfgagcasasa	572	UUUGCUCCCAGUUUCUUUGAGAUC	662
AD- 596169.1	A- 1143022.1	gsencc(Chd)AfgUfUfUfUcugagaaL96	483	A- 1143023.1	VPusGfsrcnc(Cgm)aaagaaCfUfGfgagcsasa	573	UUGCUCCCAGUUUCUUUGAGAUCU	663
AD- 596170.1	A- 1143024.1	csuscc(Chd)GfnUfUfUfUcugagaaL96	484	A- 1143025.1	VPusAfsgaunc(Tgm)caagaaAfcUfggagcsasa	574	UGCUCACAGUUUCUUUGAGAUCUG	664
AD- 596171.1	A- 1143026.1	ussccac(Chd)UfnUfUfUfUcugagaaL96	485	A- 1143027.1	VPusCfsgaunc(Cgm)ucaagaAfaCfuggagsgsc	575	GCUCACAGUUUCUUUGAGAUCUGC	665
AD- 596172.1	A- 1143028.1	csescag(Uhd)UfnUfUfUfUcugagaaL96	486	A- 1143029.1	VPusGfscaga(Tgm)cucaagAfaAfcugggcsag	576	CUCCACAGUUUCUUUGAGAUCUGCU	666
AD- 596175.1	A- 1143034.1	asgsnuu(Chd)UfnGfAfGfauccugaaL96	487	A- 1143035.1	VPusUfscage(Agn)gauncAfaGfaauncsgsg	577	CCAGUUUCUUUGAGAUCUGCUGAC	667
AD- 596177.1	A- 1143038.1	usisnu(Chd)GfaGfAfUfauccugaaL96	488	A- 1143039.1	VPusUfsguca(Cgm)gauncUfaAfaagaaacsu	578	AGUUUCUUUGAGAUCUGCUGACAG	668
AD- 596215.1	A- 1143114.1	asgsngc(Uhd)CfaGfUfUfUfcaauugaaL96	489	A- 1143115.1	VPusGfscaca(Tgm)uggaaCfUfaGfcacuncsg	579	CAAGUGCUCAGUUCCAAGUGGCC	669
AD- 596231.1	A- 1143146.1	gsusgcc(Chd)AfgUfCfAfHgcaannuaL96	490	A- 1143147.1	VPusGfsaauu(Cgm)ucaucaCfUfGfgcacasau	580	AUGUGCCCAGUCAGACAUUUUCU	670
AD- 596235.1	A- 1143154.1	csesagu(Chd)AfnGfAfCfauuuncuaaL96	491	A- 1143155.1	VPusUfsgag(Agn)aauncAfnGfauccgsgsc	581	GCCCAGUCAGACAUUUUCUCAAA	671
AD- 596283.1	A- 1143250.1	csasnuca(Chd)CfaGfUfGfauugaaL96	492	A- 1143251.1	VPusUfscacu(Cgm)aaucacUfGfCfuaugsgsa	582	UCCAUCAGCAGUGAUUGAAGUAU	672
AD- 596319.1	A- 1143322.1	usisnuca(Chd)UfgAfAfGfugaauuaaL96	493	A- 1143323.1	VPusAfsgua(Tgm)ucaucuCfaGfugaacsag	583	CCUUUCACUGAAGUGAAUACAUG	673
AD- 596320.1	A- 1143324.1	ususcac(Uhd)GfaGfAfGfugaaucaagL96	494	A- 1143325.1	VPusCfsgaunc(Agn)ucaacuUfaAfgugaacsag	584	CUUUCACUGAAGUGAAUACAUGG	674
AD- 596322.1	A- 1143328.1	csasucg(Chd)AfgUfGfAfaucaungaaL96	495	A- 1143329.1	VPusAfscacu(Cgm)uaucacCfUfaCfugaacsasa	585	UUCACUGAAGUGAAUACAUGGUA	675
AD- 596323.1	A- 1143330.1	ascsuga(Chd)GfnGfAfAfuaucungaaL96	496	A- 1143331.1	VPusUfscaca(Tgm)gauncAfcUfuaucgsgsa	586	UCACUGAAGUGAAUACAUGGUAG	676
AD- 596325.1	A- 1143334.1	usgsaag(Uhd)GfaAfUfAfCauugaaL96	497	A- 1143335.1	VPusGfscuac(Cgm)augaaUfaAfcuacgsgsu	587	ACUGAAGUGAAUACAUGGUAGCA	677
AD- 596326.1	A- 1143336.1	gsasagu(Chd)AfaUfAfCfauugaaL96	498	A- 1143337.1	VPusUfsguca(Cgm)caugaaUfnCfauucgsag	588	CUGAAGUGAAUACAUGGUAGCAG	678
AD- 596362.1	A- 1143408.1	usgsagu(Uhd)UfnUfUfUfGfaucauaL96	499	A- 1143409.1	VPusGfsaung(Agn)agccacAfaAfaucacsasa	589	UGUGAUUUUGUGGCUUCAUCU	679
AD- 596390.1	A- 1143464.1	asasaa(Chd)AfcCfUfAfaguacuaL96	500	A- 1143465.1	VPusCfsgaunc(Cgm)acuaagGfnGfuuuuisasa	590	UUAAAAACACCUAAGUGACUACC	680
AD- 596391.1	A- 1143466.1	asasaac(Chd)CfcUfAfAfaguacuaL96	501	A- 1143467.1	VPusGfsguag(Tgm)acuaaGfgUfguuuuisasa	591	UAAAAACACCUAAGUGACUACCA	681
AD- 596392.1	A- 1143468.1	asasaca(Chd)CfuAfAfGfugaacuaaL96	502	A- 1143469.1	VPusUfsgguu(Cgm)ucaacuAfgGfuuuuisusu	592	AAAAACACCUAAGUGACUACCAC	682
AD- 596396.1	A- 1143476.1	ascsuac(Chd)GfnGfAfCfuaacuaaL96	503	A- 1143477.1	VPusUfsgaunc(Cgm)gauncAfcUfuaugsgsu	593	ACACCUAAGUGACUACCAUCUUAU	683

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-596402.1	A-1143488.1	gsusgac(Uhd)AfcCfAfCfuaunucuaalL96	504	A-1143489.1	VPusUfsagaa(Agn)uaagugGfuAfignucisusu	594	AAAGUGACUACCACUUAUUUCUAA	684
AD-596425.1	A-1143534.1	csusgmu(Ghd)UfuCfAfGfagugmuuaalL96	505	A-1143535.1	VPusUfsaaca(Agn)cucucugAfaCfacaagsca	595	UGCUGUUGUUACAGAAAGUUGUAG	685
AD-596426.1	A-1143536.1	usgsung(Uhd)UfcAfGfAfagugmuuaalL96	506	A-1143537.1	VPusCfsuuaa(Agn)acuucugGfaAfcaacagsgc	596	GCUGUUGUUCAGAAAGUUGUAGU	686
AD-596427.1	A-1143538.1	gsusugu(Uhd)CfaGfAfAfGmuugmuuaalL96	507	A-1143539.1	VPusAfsuuaa(Cgn)aacumcUfgAfacaacsasg	597	CUGUUGUUCAGAAAGUUGUUGUAGUG	687
AD-596431.1	A-1143546.1	ususcag(Ahd)AfgUfUfGfuaugmuuaalL96	508	A-1143547.1	VPusAfsauca(Cgn)uaacaaCfuUfucagascsa	598	UGUUCAGAAAGUUGUUGUAGUUAUU	688
AD-596436.1	A-1143556.1	asasgmu(Ghd)UfuAfGfUfgaunucuaalL96	509	A-1143557.1	VPusUfsagca(Agn)uacacuAfaCfacauniscu	599	AGAAAGUUGUUAAGUUAUUUGCUAU	689
AD-596469.1	A-1143622.1	usisuma(Ahd)UfgAfUfAfGugucuaalL96	510	A-1143623.1	VPusCfsuuaa(Agn)caguanCfaUfuaaasgsa	600	UCUUUUAAGUAUCUGUCUUAAGA	690
AD-596477.1	A-1143638.1	asusacu(Ghd)UfcUfAfAfgaauaungaalL96	511	A-1143639.1	VPusUfscannu(Agn)uucuaaGfaCfaguaniscsa	601	UGAUACUGUCUAAAGAAUAAUGAC	691
AD-596515.1	A-1143714.1	asgscau(Ghd)AfaAfCfUfangaacuaalL96	512	A-1143715.1	VPusUfsagau(Ggn)cauagUfuCfanguiscsa	602	UGAGCAUGAAACUUAUGCACCUAU	692
AD-596517.1	A-1143718.1	csasuga(Ahd)AfcUfAfUfGcaacuaalL96	513	A-1143719.1	VPusUfsuaua(Ggn)ugcuaaGfuUfucangscsu	603	AGCAUGAAACUUAUGCACCUAUAA	693
AD-596605.1	A-1143894.1	usisuaa(Ghd)CfcAfUfCfucacuaunuaalL96	514	A-1143895.1	VPusUfsuuaa(Ggn)ugagauGfGfGuaaasasa	604	UUUUUAUCCCAUCUCACUUAUUAAU	694
AD-596606.1	A-1143896.1	usisuaa(Ghd)CfaUfCfUfCfucuaunuaalL96	515	A-1143897.1	VPusAfsuuaa(Agn)ugagauUfgGfGuaaasasa	605	UUUUUAUCCCAUCUCACUUAUUAAU	695
AD-596609.1	A-1143902.1	uscacca(Uhd)CfuCfAfCfuaaunuaalL96	516	A-1143903.1	VPusAfsuuaa(Tgn)aaagugAfgAfugggasusa	606	UAUCCCAUCUCACUUAUUAAUAAU	696
AD-596709.1	A-1144102.1	asasaau(Ghd)GfaAfCfAfuaacccuaalL96	517	A-1144103.1	VPusUfsagau(Tgn)uaaungUfcCfuauniscu	607	AGAAAUGGAAACUUAUACCCUAC	697
AD-597019.1	A-1144722.1	asusug(Ghd)AfcAfUfAfuaagacuaalL96	518	A-1144723.1	VPusAfsugug(Cgn)uaaauaGfuGfuauniscu	608	ACAUUAGCACAUUAUAGCACAUU	698
AD-597232.1	A-1145148.1	uscuaa(Uhd)UfcAfGfGfagagacuaalL96	519	A-1145149.1	VPusUfsagau(Cgn)uucccuGfaAfagagasa	609	UUUCUUAUCCAGGGAAGAUUCUUAU	699
AD-597297.1	A-1145278.1	asasguc(Ahd)CfuAfGfUfagaagmuuaalL96	520	A-1145279.1	VPusAfsuuaa(Tgn)uucuaaAfgUfagucisusu	610	AAAAGUCACUAGUAGAAAGUUAU	700
AD-597298.1	A-1145280.1	asgsuca(Chd)UfaGfUfAfgaagmuuaalL96	521	A-1145281.1	VPusUfsuuaa(Tgn)uucuaaCfaGfugacisusu	611	AAAGUCACUAGUAGAAAGUUAUAA	701
AD-597325.1	A-1145334.1	csasgaau(Uhd)AfuUfCfUfagacuaalL96	522	A-1145335.1	VPusAfsuuaa(Ggn)uucuaaAfuAfuucugisusc	612	GACAGAAUUAUUCUAGACAUUGCUA	702
AD-597326.1	A-1145336.1	asgsaau(Ahd)UfuCfUfAfagacuaalL96	523	A-1145337.1	VPusUfsagca(Tgn)gucuaaAfaUfuauniscu	613	ACAGAAUUAUUCUAGACAUUGCUAG	703
AD-597327.1	A-1145338.1	gsasana(Uhd)UfcUfAfGfagacuaalL96	524	A-1145339.1	VPusCfsuuaa(Agn)ugucuaaGfaAfuuauniscu	614	CAGAAUUAUUCUAGACAUUGCUAGC	704
AD-597335.1	A-1145354.1	usasgac(Ahd)UfgCfUfAfGcagmuuaalL96	525	A-1145355.1	VPusAfsuuaa(Cgn)ugcuaaCfaUfignucisusa	615	UCUAGACAUUGCUAGCAGUUAUUA	705

Duplex	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD- 597397.1	A- 1145478.1	gsasggg(Ahd)UfgAtrGtUfgacuaaagaaL96	526	A- 1145479.1	VPusCfsmauu(Agm)gucacuCtaUfuccucsesu	616	AGAGGAUAUGAGUGACUAUAAGG	706
AD- 597398.1	A- 1145480.1	asgsaa(Uhd)GfaGfaGtUfGfacaiaaagaaL96	527	A- 1145481.1	VPusCfscuaa(Tgn)agucacUfcaAfmucucscsc	617	GGAGAAUGAGUGACUAUAAGGA	707
AD- 597404.1	A- 1145492.1	gsasngg(Ahd)CfuAfuAfgagnggmaaaL96	528	A- 1145493.1	VPusAfsacca(Tgn)ccuaauAfguUfcaucsesu	618	AUGAGUGACUAUAAGGAUGGUUA	708
AD- 597409.1	A- 1145502.1	ascsmau(Ahd)AfgGfaUfGfguaccuaaL96	529	A- 1145503.1	VPusAfsuagat(Agm)accacCfuUfuaugscsa	619	UGACUAUAAGGAUGGUUAACCAUA	709
AD- 597410.1	A- 1145504.1	csusaau(Ahd)GfgAfuUfGfgmuaccuaaL96	530	A- 1145505.1	VPusUfisaugg(Tgn)aaaccauCfcUfuaugscsc	620	GACUAUAAGGAUGGUUAACCAUAG	710
AD- 597417.1	A- 1145518.1	gsasngg(Uhd)UfgAtrCfAfaagaacuaaL96	531	A- 1145519.1	VPusAfsaguu(Tgn)cuauaggUfaAfccacsesu	621	AGGAUGGUUACCAUAGAAACUUC	711
AD- 597443.1	A- 1145570.1	ascsuac(Uhd)AfcAtrGfAfngucuaagcaL96	532	A- 1145571.1	VPusGfscuaa(Ggn)ccacucGfuAfnguaucsesu	622	AGACUAUACAGAGUGCUAAGCU	712
AD- 597455.1	A- 1145594.1	usgscaa(Ahd)GfcUfGfCfangucuaaL96	533	A- 1145595.1	VPusAfsuagat(Agm)caugcaGfcUfuaagascsu	623	AGUGCUAAGCUGCAUGUGUCAUC	713
AD- 597459.1	A- 1145602.1	asasgcu(Ghd)CtaUfGfUfngucuaaiaaL96	534	A- 1145603.1	VPusUfisaagat(Tgn)gacacaUfgCfagcuaisag	624	CUAAGCUGCAUGUGUGUCAUCUUAC	714
AD- 597460.1	A- 1145604.1	asgsngg(Chd)AfuGfuUfGfcauauaiaL96	535	A- 1145605.1	VPusGfsumaig(Agm)ugacacAfuGfcaucuisa	625	UAAGCUGCAUGUGUGUCAUCUUACA	715
AD- 597534.1	A- 1145752.1	csasgaa(Uhd)AfuUfUfCfaggaagumaL96	536	A- 1145753.1	VPusAfsacuu(Tgn)ccugaaAfuAfuaucngusu	626	AACAGUAUUUUCAGGAAGGUUA	716
AD- 597569.1	A- 1145822.1	asasuauc(Uhd)AfcCfuUfAfaagacuaaL96	537	A- 1145823.1	VPusAfsugcu(Ggn)cuuaagGfuAfgaumisasa	627	UUAAAUCUACCUAAAAGCAGCAUA	717
AD- 597861.1	A- 1146406.1	asgsuucc(Uhd)AfgGfuUfuaauungcaal96	538	A- 1146407.1	VPusUfsgcaat(Agm)auaataCfuAfgagucsgsg	628	CCAGUCCUAGGUUUUUUUUGCAG	718
AD- 597864.1	A- 1146412.1	csesuaig(Ghd)UfuUfAfuUfuuugcgacal96	539	A- 1146413.1	VPusGfscugc(Cgn)aaaaaAfaCfuaagsgasc	629	GUCCUAGGUUUUUUUUGCAGACU	719
AD- 597894.1	A- 1146472.1	csesaaig(Uhd)UfuUfUfUfCfagccuaaL96	540	A- 1146473.1	VPusUfisaugat(Ggn)gcuuaaUfaAfuaugsgsga	630	UCCCAAGUUUUUUCAGGCCUCAUAU	720
AD- 597898.1	A- 1146480.1	gsasuaui(Uhd)CfaGfCfCfcauaugcaal96	541	A- 1146481.1	VPusGfscuauc(Agm)ugaggeUfgAfauaucsesu	631	AAGUUUUUCAGCCUCAUAUGACU	721
AD- 597899.1	A- 1146482.1	ususaui(Chd)AfgCfCfUfcauaugacuaL96	542	A- 1146483.1	VPusAfsuacat(Tgn)auagaggCfuGfaaiaascsu	632	AGUUUUUCAGCCUCAUAUGACUC	722
AD- 597900.1	A- 1146484.1	usasauc(Ahd)GfcCfuUfCfauaugacuaL96	543	A- 1146485.1	VPusGfsgauc(Agm)uaugagGfcUfgaiaaasc	633	GUUUUUUCAGCCUCAUAUGACUCC	723
AD- 597925.1	A- 1146534.1	uscsggc(Uhd)UfuAtrCfCfaaacagumaL96	544	A- 1146535.1	VPusAfsacug(Tgn)uuuugaaAfaAfgccgascsc	634	GGUCGGCUUUACCAAAAACAGUUUC	724
AD- 597927.1	A- 1146538.1	gsagcuui(Uhd)AfcCfaAfaaagumaaL96	545	A- 1146539.1	VPusUfsgaac(Tgn)uuuuugGfuAfaagccsgsa	635	UCGGCUUUUACCAAAAACAGUUUCAG	725
AD- 597937.1	A- 1146558.1	asasaat(Ghd)UfuCfAtrGfagucuaaL96	546	A- 1146559.1	VPusAfsagug(Cgn)acucagAfaCfugiuusng	636	CAAAAACAGUUUCAGAGUGCACTUU	726
AD- 597946.1	A- 1146576.1	asgsagu(Ghd)CfaCfuUfuggcaacaaL96	547	A- 1146577.1	VPusUfsgugu(Ggn)ccaaagUfgCfcaucsgsa	637	UCAGAGUGCACTUUUGGCACACAA	727

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-597972.1	A-1146628.1	asascag(Ahd)AfcAfAfUfcuauguguaL96	548	A-1146629.1	VPusAfscaca(Tgn)uagauGfuUfcuugmuscsc	638	GGAACAGAACAAUCUAAUUGUGUG	728
AD-597974.1	A-1146632.1	csasgaal(Chd)AfaUfcUfuaugugugaaL96	549	A-1146633.1	VPusCfscaca(Cgn)auuagAUfcUfcuugususu	639	AACAGAACAAUCUAAUUGUGUGU	729
AD-597984.1	A-1146652.1	usasaug(Uhd)GfuGfuGfuUfcuuguaucuaL96	550	A-1146653.1	VPusGfscuu(Cgn)cauaccAfcAfcauuaasgsa	640	UCUAAUGUGUGGUUUUGGUUUUCC	730
AD-597988.1	A-1146660.1	gsusgug(Chd)UfuUfGfGfuaucuaagaaL96	551	A-1146661.1	VPusCfsmuag(Agn)auaccaAfaCfcauacasa	641	AUGUGUGGUUUUGGUUUUCCAAAGU	731
AD-597989.1	A-1146662.1	usgsuag(Uhd)UfuGfGfUfaucuaagaaL96	552	A-1146663.1	VPusAfscumg(Cgn)auuaccAfaAfcauacasa	642	UGUGUGGUUUUGGUUUUCCAAAGU	732
AD-464229.1	A-900784.1	asusgaagGfgAfCfUfuaucuaagaaL96	913	A-900785.1	VPusGfscuuUfuGfAfuaagUfcUfcuugmusc	1005	UC AUGA AAGGACUUUCAAAGGCC	1097
AD-464313.1	A-900952.1	asasagagGfgUfGfUfuaucuaagaaL96	914	A-900953.1	VPusAfscuuAfgAfGfaacaCfcCfucumusc	1006	CAAAAGAGGGUGUUUCUUAUGUA	1098
AD-464314.1	A-900954.1	asasagagGfuGfuUfUfcuuauguaaL96	915	A-900955.1	VPusUfsacaUfaGfAfgaacAfcCfucumusc	1007	AAAAGAGGGUGUUUCUUAUGUAG	1099
AD-464559.1	A-901440.1	usgsagagUfuAfUfGfuauguaaL96	916	A-901441.1	VPusAfscagCfaUfUfuaaAfaGfcauacasa	1008	AAUGAGGCUUAUGAAAUGGCCUUC	1100
AD-464585.1	A-901492.1	asasaggaUfuAfUfGfuauguaaL96	917	A-901493.1	VPusUfscugUfaGfUfcuagAfuAfccumusc	1009	GGAAAGGGUUAUCAAAGCUACGAAC	1101
AD-464586.1	A-901494.1	asgsagaaUfcAfAfGfuaucuaagaaL96	918	A-901495.1	VPusGfsmucGfuAfGfuaaGfaUfcauacasa	1010	GAAGGGUUAUCAAAGCUACGAAC	1102
AD-464590.1	A-901502.1	usasaagaGfuCfUfAfGfuaucuaagaaL96	919	A-901503.1	VPusUfscagGfuUfcuagUfcUfuaaascs	1011	GGUAUCAAGACUACGAACCUUGAA	1103
AD-464592.1	A-901506.1	usasaagaCfuAfCfGfuaucuaagaaL96	920	A-901507.1	VPusCfsmucAfgGfuUfcuagAfgUfcuagasa	1012	UAUCAAGACUACGAACCUUGAAGC	1104
AD-464603.1	A-901528.1	asascuagAfaGfCfCfuaagaauaaL96	921	A-901529.1	VPusUfscuuUfcUfUfagagCfuCfagmuscsg	1013	CGAACCUUGAAGCCUAAAGAAAUU	1105
AD-464606.1	A-901534.1	csusgaagCfcUfAfAfgaauuaucuaL96	922	A-901535.1	VPusAfsgauAfuUfUfuaaGfgCfuaucagsgu	1014	ACCUGAAGCCUAAAGAAAUUUCUU	1106
AD-464630.1	A-901582.1	usccagUfuUfCfUfuauguaaL96	923	A-901583.1	VPusCfscagUfcUfcuaagaAfaCfuaucagsg	1015	GCUCCAGUUUUCUUGAGAUUCUGC	1107
AD-464634.1	A-901590.1	asgsuucUfuGfAfGfuaucuaagaaL96	924	A-901591.1	VPusUfscagCfaGfAfuaaAfaGfaucagsg	1016	CCAGUUUCUUGAGAUUCUGUGAC	1108
AD-464636.1	A-901594.1	usuuuucGfaGfAfUfcuaguaaL96	925	A-901595.1	VPusUfsgucAfgCfAfuaaUfcAfagaascsu	1017	AGUUUCUUGAGAUUCUGUGUGACAG	1109
AD-464694.1	A-901710.1	cscsagucAfuGfAfCfuaucuaaL96	926	A-901711.1	VPusUfsguaGfaAfuaaAfuGfuaucagsg	1018	GCCCAGUUAUGACAUUUUCUAAA	1110
AD-464742.1	A-901806.1	csasucagCfaGfuUfGfuauguaaL96	927	A-901807.1	VPusUfscuuUfcAfAfuaaUfcCfuaucagsg	1019	UCCAUCAGCAGUUAUGAAGUAU	1111
AD-464778.1	A-901878.1	usuuuucUfgAfAfGfuaucuaaL96	928	A-901879.1	VPusAfsguuAfuUfcuagAfaGfuaucagsg	1020	CCUUUCACUGAAGUUAUGAUAUG	1112
AD-464779.1	A-901880.1	usuuuucGfaAfGfUfuaucuaaL96	929	A-901881.1	VPusCfscuuUfuUfuaaUfcAfuaucagsg	1021	CUUUACUCUGAAGUUAUGAUAUG	1113

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-464782.1	A-901886.1	ascnugaaGfuGfAfAfnacnugnaaL96	930	A-901887.1	VPusUfsaacAfuaGfuUfaunucAfefUfucnagsga	1022	UCACUGAAGUGAAUACAUGGUAG	1114
AD-464813.1	A-901948.1	ascscuaaGfuGfAfCfucnaccuaaL96	931	A-152515.1	VPusUfsaagUfgGfuUfagucAfefUfagugsgsu	1023	ACACCUAAGUGACUACCACUUAU	1115
AD-464814.1	A-901949.1	gsnugacuAfcCfAfCfuaunucuaaL96	932	A-152519.1	VPusUfsagaAfuaUfAfagugGfuAfugacscsu	1024	AAGUGACUACCACUUAUUUCUAA	1116
AD-464815.1	A-901950.1	usgsacuaCfcAfCfUfuaunucuaaL96	933	A-152535.1	VPusUfsuagAfuaUfUfaaguGfgUfagucascu	1025	AGUGACUACCACUUAUUUCUAAA	1117
AD-464856.1	A-902029.1	asasacacCfuAfAfGfugacuaaL96	934	A-902030.1	VPusUfsgguAfugUfCfuaunAfGfGfugunusuu	1026	AAAAACACCUAAGUGACUACCAC	1118
AD-464859.1	A-902035.1	csnscuaAfugUfGfAfCfuaacuaaL96	935	A-902036.1	VPusUfsaguGfgUfAfagucCfuUfagugsgsu	1027	AACACCUAAGUGACUACCACUUA	1119
AD-464884.1	A-902085.1	csnsgungUfuCfAfGfagunuguaaL96	936	A-902086.1	VPusUfsaacAfuaCfufucugAfafCfagacsga	1028	UGCUGUUGUUCAGAAAGUUGUAG	1120
AD-464885.1	A-902087.1	usgsunguUfcAfGfAfagunuguaaL96	937	A-902088.1	VPusCfsuaaCfuaAfCfucucGfuAfcaacsgsc	1029	GCUGUUGUUCAGAAAGUUGUAGU	1121
AD-464886.1	A-902089.1	gsnugunuCfaGfAfAfgnugunuaaL96	938	A-902090.1	VPusAfsuaaAfuaAfCfuaucUfgAfcaacsg	1030	CUGUUGUUCAGAAAGUUGUAGUG	1122
AD-464928.1	A-902173.1	usnsmuaUfgAfUfAfCfugucuaaL96	939	A-902174.1	VPusCfsuaaCfuaAfCfuaucUfgAfuaaasga	1031	UCUUUUAUGAUACUGUCUUAAGA	1123
AD-464936.1	A-902189.1	asusacugUfcUfAfAfagaauguaaL96	940	A-902190.1	VPusUfscuuUfuUfUfuaaGfuCfagunusca	1032	UGAUACUGUCUAAAGAAUUAUGAC	1124
AD-464977.1	A-902268.1	agsgaangAfuaAfCfUfagacuaaL96	941	A-902269.1	VPusUfsaggUfgCfAfuaaGfuCfagucscsa	1033	UGAGCAUGAAACUAGCACCUCUUA	1125
AD-464978.1	A-902270.1	csnugaaAfcUfAfUfagacuaaL96	942	A-902271.1	VPusUfsuaaGfgUfGfcaaaGfuUfuaugscsu	1034	AGCAUGAAACUAGCACCUCUUA	1126
AD-465064.1	A-902441.1	usnsmuaCfcAfUfCfuaacuaaL96	943	A-902442.1	VPusUfsuaaAfugUfGfaguuGfgGfuaaasasa	1035	UUUUUAUCCCAUCUCACUUUUAU	1127
AD-465065.1	A-902443.1	usnsmuaCfcAfUfCfuaacuaaL96	944	A-902444.1	VPusUfsuaaAfuaGfuUfagaaUfgGfuaaasasa	1036	UUUUUAUCCCAUCUCACUUUUAU	1128
AD-465068.1	A-902449.1	usnsmuaCfuCfAfCfuaaanaaL96	945	A-902450.1	VPusUfsuaaUfuAfAfagugAfGfUfagugsgsu	1037	UAUCCCAUCUCACUUUUAUUAU	1129
AD-465168.1	A-902649.1	asasaangGfuAfCfAfuaacuaaL96	946	A-902650.1	VPusUfsaggGfuUfAfaguuUfcCfuaunuscu	1038	AGAAAAGGAAACUUAACCCUAC	1130
AD-465691.1	A-903695.1	usnsmuaUfcAfGfGfagaaucuaaL96	947	A-903696.1	VPusUfsagaUfcUfUfcuuGfuAfagagasa	1039	UUUCUCUUUCAGGGAAGAUUAU	1131
AD-465756.1	A-903825.1	asagacacCfuAfGfUfagaanaaL96	948	A-903826.1	VPusAfsuaaUfuUfCfuaaAfGfUfagucunusu	1040	AAAAAGCACUAGUAGAAAGUUA	1132
AD-465757.1	A-903827.1	asgsuacUfaGfuUfAfagaanaaL96	949	A-903828.1	VPusUfsuaaCfuUfUfuaaUfaGfagucunusu	1041	AAAGUCACUAGUAGAAAGUUA	1133
AD-465760.1	A-903833.1	csnscuaUfaGfAfAfagaaanaaL96	950	A-903834.1	VPusAfsuaaUfuUfCfuaaUfaCfagugsgsc	1042	GUCACUAGUAGAAAGUUAUUAU	1134
AD-465784.1	A-903881.1	csnsgaauAfuUfCfUfagacuaaL96	951	A-903882.1	VPusAfsuaaUfuUfCfuaaUfaCfagucunusc	1043	GACAGAAUUAUUAUUAUUAUUA	1135

Duplex	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD- 465785.1	A- 903883.1	asgsaauUfuCfuAfAfgcaugcuuaal.96	952	A- 903884.1	VPusUfsgagAfuGfuUfcuagAfaUfamucsgsu	1044	ACAGAAUAUUCUAGACAUGCUCAG	1136
AD- 465794.1	A- 903901.1	usagacaUfgCfuUfAfagcauuaual.96	953	A- 903902.1	VPusAfsuaaAfUfGfucugCfuUfngcuasgsa	1045	UCUAGACAUGCUCUAGCAUGUUUAUA	1137
AD- 465876.1	A- 904065.1	gsaauagUfuCfuCfAfAfgaacaual.96	954	A- 904066.1	VPusAfsaguUfuCfuUfanguUfuAfcuacsesu	1046	AGGAUGGUUACCAUAGAAACUUC	1138
AD- 465918.1	A- 904149.1	asasgcugCfuUfGfuUfngcauuaal.96	955	A- 904150.1	VPusUfsgagAfuGfAfcaalUfgCfagcuasag	1047	CUAAGCUGCAUGUGUCAUCUCUAC	1139
AD- 465919.1	AD- 904151.1	asgsongcAfuGfuUfGfcauucuaal.96	956	A- 904152.1	VPusGfsuaaGfuUfGfcaacAfuGfagcuusua	1048	UAAGCUGCAUGUGUCAUCUCUACA	1140
AD- 466320.1	A- 904953.1	asgsuacuAfgGfuUfUfuaunugcaal.96	957	A- 904954.1	VPusUfsgcaAfaUfUfaaacCfuAfggacuysg	1049	CCAGUCCUAGGUUUUAUUUUGCAG	1141
AD- 466384.1	A- 905081.1	uscsgcuUfuAfCfCfhaacaguaual.96	958	A- 905082.1	VPusAfsacuGfuUfUfugguUfuAfcagcasesc	1050	GGUCGCUUUAACCAAAACAGUUC	1142
AD- 466386.1	A- 905085.1	gsgscumuAfcCfuAfAfaacaguaual.96	959	A- 905086.1	VPusUfsgaaCfuGfuUfuuugGfuAfaagccsgsa	1051	UCGGCUUUAACCAAAACAGUUCAG	1143
AD- 466443.1	A- 905199.1	usasauguGfuGfGfuUfugguuaual.96	960	A- 905200.1	VPusGfsaauAfcCfAfaaccAfcAfaumaasgsa	1052	UCUAAUUGUGUGGUUUGUAUUC	1144
AD- 475646.1	A- 919481.1	asusaacuCfuUfUfAfagcauguaual.96	961	A- 919482.1	VPusAfsuacAfuGfGfGfuuaaAfgAfuuguausuu	1053	AAUACAUUUUAGCCUAGGGAUG	1145
AD- 475661.1	A- 919511.1	gsgsauguGfuUfCfAfAfgaagagcaal.96	962	A- 919512.1	VPusGfsuuccUfuUfCfanguaAfcAfcuaccsasu	1054	AUGGAUGUGUUCAUAGAAAGGACU	1146
AD- 475663.1	A- 919515.1	asusaguUfcAfuUfGfaagagcaual.96	963	A- 919516.1	VPusAfsaguCfcUfUfucuaGfuAfcacauscsc	1055	GGAUGUGUUCAUAGAAAGGACUUU	1147
AD- 475666.1	A- 919521.1	usgsuacuUfgAfaAfAfgcauucuaal.96	964	A- 919522.1	VPusUfsgaaAfgUfCfcmuUfAfguacascsa	1056	UGUGUUCAUAGAAAGGACUUUCA	1148
AD- 475723.1	A- 919635.1	gsasuguccUfcUfAfuUfugagguccal.96	965	A- 919636.1	VPusGfsgaaCfcUfAfcanaGfuGfagcuuscsc	1057	GGGAGUCCUUAUGUAGGUUCCA	1149
AD- 475728.1	A- 919645.1	csuscuuGfuAfGfGfuuccaacaal.96	966	A- 919646.1	VPusGfsuuiuUfgGfAfaccuAfcAfuagagsgsa	1058	UCCUCUAUGUAGGUUCCAAAAACU	1150
AD- 475761.1	AD- 919709.1	usgsugmcAfuGfGfAfngacaacaal.96	967	A- 919710.1	VPusUfsgauGfuUfCfauccAfuGfcaaccsu	1059	AGUGGUUCUAGGAGUGACAAACAG	1151
AD- 475765.1	A- 919717.1	uscsauggAfgUfGfAfcaacaggaal.96	968	A- 919718.1	VPusCfseacUfgUfUfngucaCfuCfagcasasc	1060	GUUCAUGGAGUGACAACACAGUGGC	1152
AD- 475888.1	A- 901440.1	usgsaggeUfuAfuUfGfaaagccuaal.96	969	A- 919961.1	VPusAfsaggsCfuUfUfucuaAfaGfducacsusu	1061	AAUGAGGCUUAUGAAAUGGCCUUC	3601
AD- 475895.1	A- 919973.1	gsgsaucCfuGfGfAfngacugccal.96	970	A- 919974.1	VPusGfsgcaUfgUfCfmuccAfgGfmuccsusu	1062	AAGGAUCCUGGAAAGACAUGCCU	1153
AD- 475927.1	A- 920037.1	asgsuagGfcUfuUfAfgaanaagccal.96	971	A- 920038.1	VPusGfsgcaUfuUfCfauaaGfcCfuacuscsc	1063	GCAGUGAGGCUUAUGAAAUGCCU	1154
AD- 475929.1	A- 920041.1	asgsuacuAfuGfAfAfaugccuuaal.96	972	A- 920042.1	VPusUfsgaaGfgCfAfuuuicAfuAfgcuacsca	1064	UGAGGCUUAUGAAAUGCCUUCAG	1155
AD- 475930.1	A- 920044.1	gsgscuuaUfgAfaAfAfguccuagcal.96	973	A- 920044.1	VPusCfsgaaAfgCfcauunCfuUfagccsucsc	1065	GAGGCUUAUGAAAUGCCUUCAGA	1156

Duplex AD- AD-	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD- 475941.1	A- 920064.1	asusgcuUfcAfGfAfGgaagcuuaL96	974	A- 920065.1	VPusUfsagcCfuUfCfcuclGfaAfGcgausuu	1066	AAUUGCCUUCAGAGGAAGGCUAC	1157
AD- 475942.1	A- 920066.1	usgscumCfGfAfGfAfGgaagcuacL96	975	A- 920067.1	VPusGfsgagCfcUfUfCucUfAfGfagcgausuu	1067	AAUGCCUUCAGAGGAAGGCUACC	1158
AD- 475952.1	AD- 920086.1	gsgsaaggCfuAfCfCfGgaagcuagL96	976	A- 920087.1	VPusCfsguaGfuCfUfugguAfGfCmuccusuc	1068	GAGGAAGGCUACCAAGACUAUGA	1159
AD- 475953.1	A- 920088.1	gsasaggeUfaCfCfAfGagcuangaL96	977	A- 920089.1	VPusUfscuaAfGfUfCfmuaggUfaGfCmuccesu	1069	AGGAAGGCUACCAAGACUAUGAG	1160
AD- 475954.1	AD- 920090.1	asasgcuAfCfAfAfGagcuangaL96	978	A- 920091.1	VPusCfsguaUfaGfUfCfmuagGfuAfGcmuccesc	1070	GGAAGGCUACCAAGACUAUGAGC	1161
AD- 475955.1	AD- 920092.1	asgsguaCfCfAfAfGfGgaagcuacL96	979	A- 920093.1	VPusGfsgucAfAfAfGfCfucmGfGfUfagcguusc	1071	GAAGGUACCAAGACUAUGAGCC	1162
AD- 475966.1	A- 920114.1	ascsuuagAfGfCfCfUfGgaagcuuaL96	980	A- 920115.1	VPusUfsgagGfcUfUfCfagcCfuCfauagucsu	1072	AGACUAUGAGCCUAGAACCUAAG	1163
AD- 476025.1	AD- 920230.1	gscsuucmCfcAfUfGfGcguacaagL96	981	A- 920231.1	VPusCfsguagUfaCfGfCfccaGfGfAfagagcsag	1073	CUGCUCUCCAUUGGCGUACAAAGU	1164
AD- 476026.1	AD- 920232.1	csusuncCfAfUfGfGfGcuacagual96	982	A- 920233.1	VPusAfscumGfuAfCfGfccaUfGfGfagagcsa	1074	UGCUCUCCAUUGGCGUACAAAGUG	1165
AD- 476027.1	A- 920234.1	uscsuuccAfFuGfGfCfGcuacagual96	983	A- 920235.1	VPusCfscacUfGfUfAfGfagccAfFuGfagagsgsc	1075	GCUCUCCAUUGGCGUACAAAGUGC	1166
AD- 476029.1	A- 920238.1	ususscamGfGfCfGfUfGcuagcuacL96	984	A- 920239.1	VPusAfsgcaCfuUfGfGfucacCfcAfuggaasgsa	1076	UCUCCAUUGGCGUACAAAGUGCUUC	1167
AD- 476030.1	AD- 920240.1	uscscaugGfCfGfUfAfGcuagcuacL96	985	A- 920241.1	VPusGfsgagAfcUfUfGfuacGfCfGagagasaug	1077	CUUCCAUUGGCGUACAAAGUGCUCA	1168
AD- 476032.1	AD- 920244.1	csasuggcGfuAfCfAfAfagucuguaL96	986	A- 920245.1	VPusCfsgagGfcAfCfGfuagAfGfCgaugsgsa	1078	UCCAUGGCGUACAAAGUGCUCAGU	1169
AD- 476041.1	A- 920262.1	usgsguccCfGfGfUfCfGcuacuuuaL96	987	A- 920263.1	VPusAfsgagGfuCfAfGfagacUfGfGfGcuacisuu	1079	AAUGGCCCGAGUACUGAGCCUUUU	1170
AD- 476058.1	A- 920291.1	ascsuuumUfcUfCfAfGcuagcuacL96	988	A- 920292.1	VPusGfsgucAfGfCfUfGfagGfaAfGagagmsca	1080	UGACCUUUUCUCAAAGCUGUACA	1171
AD- 476061.1	A- 920297.1	usussuucCfAfAfAfGfGcuagcuacL96	989	A- 920298.1	VPusAfsguagUfaCfAfGfGcuUfGfAfgaagaasgs	1081	CCUUUUUCUCAAAGCUGUACAGUG	1172
AD- 476089.1	A- 920353.1	uscsuuccAfFuCfAfGfGcuagcuacL96	990	A- 920354.1	VPusCfsgauCfAfCfUfGfGcuAfFuGfGagagcsu	1082	AGUCUUCCAUCAGCAGUGAUCGG	1173
AD- 476146.1	A- 920466.1	csusugggAfFuAfUfUfGcuagguacL96	991	A- 920467.1	VPusAfsgcccAfcAfAfcaauAfFuCfGcagcsca	1083	UGCUGGGAUAUUGUUGUGGCUU	1174
AD- 476152.1	A- 902071.1	asasaacCfcUfAfAfGcuagcuacL96	992	A- 920475.1	VPusCfsguaGfuCfAfGfCfmaGfGfUfguuusasa	1084	UAAAAACACCUAAGUGACUACCA	1175
AD- 476192.1	A- 920548.1	gsasaacuUfaAfAfAfGcuagcuacL96	993	A- 920549.1	VPusAfscumAfGfGfUfGfuuuUfaAfGmuccisuu	1085	AAGAAAAUUAAAAACACCUAAGUG	1176
AD- 476198.1	A- 920560.1	usasaacAfCfCfUfAfGagcuacuaL96	994	A- 920561.1	VPusGfsguagUfcAfCfGfmuagGfuGfmuuasag	1086	CUUAAAAACCCUAAAGUGACUACC	1177
AD- 476306.1	A- 920771.1	asusaugUfGfAfGfCfGcuagcuacL96	995	A- 920772.1	VPusUfsaguCfuCfAfGfucnGfCfCfauaansuu	1087	AAUUUUGUGAGCAUGAGACUAU	1177

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-476309.1	A-920777.1	asusgagGfcAfuGfGfagacuaagcaL96	996	A-920778.1	VPusGfscuuAfgUfCfuaGfCfUfcaucisasa	1088	UUUAUGUGAGCAUGAGACUAUGCA	1178
AD-476311.1	A-920781.1	gsusgagcAfuGfAfgfagacacacal96	997	A-920782.1	VPusGfscuuAfuGfCfuaGfCfUfcaucisasa	1089	AUGUGAGCAUGAGACUAUGCACC	1179
AD-476312.1	A-920783.1	usgsagcaUfgAfgfAfcuaugacacal96	998	A-920784.1	VPusGfscuuGfCfAfgfCfuaGfCfUfcaucisasa	1090	UGUGAGCAUGAGACUAUGCACC	1180
AD-476313.1	A-920785.1	gsagcauGfAfgfAfcfuaugacacacal96	999	A-920786.1	VPusGfscuuGfCfAfgfCfuaGfCfUfcaucisasa	1091	GUGAGCAUGAGACUAUGCACC	1181
AD-476316.1	A-920789.1	asgsaugAfgAfcfUfagcaccuual96	1000	A-920790.1	VPusUfscagUfgCfAfuagCfUfcaucisasa	1092	UGAGCAUGAGACUAUGCACC	1182
AD-476317.1	A-920791.1	gsasuaGfAfcUfAfgcaccuual96	1001	A-920792.1	VPusUfscagGfCfAfuagCfUfcaucisasa	1093	GAGCAUGAGACUAUGCACC	1183
AD-476320.1	A-920797.1	usgsagacUfaUfgCfAfcuaaual96	1002	A-920798.1	VPusUfscuaUfaGfCfuaGfCfUfcaucisasa	1094	CAUGAGCAUGAGACUAUAAU	1184
AD-476321.1	A-920799.1	gsasgacuAfuGfCfAfcuaaual96	1003	A-920800.1	VPusUfscuaAfuAfgfCfuaGfCfUfcaucisasa	1095	AUGAGCAUGAGACUAUAAU	1185
AD-476344.1	A-920845.1	asusgugUfuUfaUfuaacungual96	1004	A-920846.1	VPusCfsacaAfgUfUfaaUfaAfcacacasa	1096	UGAUGUGUUUUUUAAACUUUGU	1186
AD-595768.1	A-1142220.1	csasuga(Ahd)AfgGfAfcfuaaaggaal96	1371	A-1142221.1	VPusCfscuu(Ggn)aaagCfUfcaucisasa	1460	UUCAUGAAAGGACUUUCAAAGGC	1549
AD-595769.2	A-1142222.1	asusgaat(Ahd)GfAfcUfuaaaggaal96	1372	A-1142223.1	VPusGfscuu(Tgn)aaagCfUfcaucisasa	1461	UCAUGAAAGGACUUUCAAAGGC	1550
AD-595770.1	A-1142224.1	usgsaaat(Ghd)GfAfcUfuaaaggaal96	1373	A-1142225.1	VPusGfscuu(Tgn)aaagCfUfcaucisasa	1462	CAUGAAAGGACUUUCAAAGGC	1551
AD-595771.1	A-1142226.1	gsasaag(Ghd)AfcUfUfcaaggaal96	1374	A-1142227.1	VPusUfsggac(Tgn)aaagCfUfcaucisasa	1463	AUGAAAGGACUUUCAAAGGC	1552
AD-595772.1	A-1142228.1	asasagg(Ahd)CfuUfUfcaaggaal96	1375	A-1142229.1	VPusUfsggac(Tgn)aaagCfUfcaucisasa	1464	UGAAAGGACUUUCAAAGGC	1553
AD-595773.1	A-1142230.1	asasggat(Chd)UfuUfCfAfaaggaal96	1376	A-1142231.1	VPusCfscuu(Ggn)aaagCfUfcaucisasa	1465	GAAAGGACUUUCAAAGGC	1554
AD-595774.1	A-1142232.1	asgsagac(Uhd)UfuUfCfAfaaggaal96	1377	A-1142233.1	VPusCfscuu(Ggn)aaagCfUfcaucisasa	1466	AAAGGACUUUCAAAGGC	1555
AD-595926.2	A-1142536.1	asasgac(Chd)AfaAfgfAfgcaggaal96	1378	A-1142537.1	VPusGfscuu(Tgn)aaagCfUfcaucisasa	1467	AGAAAGCACAAGAGCAAGUACA	1556
AD-595933.1	A-1142550.1	asasag(Chd)AfaGfUfGfacaangual96	1379	A-1142551.1	VPusUfscuu(Tgn)aaagCfUfcaucisasa	1468	CAAAAGCAAGAGCAAGUACA	1557
AD-595935.1	A-1142554.1	gsasgac(Ahd)GfuGfAfcfuaangual96	1380	A-1142555.1	VPusCfscuu(Agn)aaagCfUfcaucisasa	1469	AAGAGCAAGAGCAAGUACA	1558
AD-595936.1	A-1142556.1	asgsaat(Ghd)UfgAfcfAfaangual96	1381	A-1142557.1	VPusUfscuu(Ggn)aaagCfUfcaucisasa	1470	AGAGCAAGAGCAAGUACA	1559
AD-595937.1	A-1142558.1	gsasag(Uhd)GfaCfAfaangual96	1382	A-1142559.1	VPusCfscuu(Agn)aaagCfUfcaucisasa	1471	GAGCAAGAGCAAGUACA	1560
AD-595938.1	A-1142560.1	csasag(Uhd)AfcAfaangual96	1383	A-1142561.1	VPusCfscuu(Agn)aaagCfUfcaucisasa	1472	AGCAAGAGCAAGUACA	1561

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-596098.1	A-1142880.1	asasuga(Ghd)GfcUfUfAfugaangccaL96	1384	A-1142881.1	VPusGfsgcau(Tgn)ucauaaGfcCfcausnsg	1473	ACAAUGAGGCUUAUGAAAUGCCU	1562
AD-596099.1	A-1142882.1	asusgag(Ghd)CfuUfAfUfgaaugccaL96	1385	A-1142883.1	VPusAfsggca(Tgn)ucauaaAfgCfcausnsg	1474	CAAUGAGGCUUAUGAAAUGCCU	1563
AD-596100.2	A-1142884.1	usgsaag(Ghd)UfuUfUfGfaaangccaL96	1386	A-1142885.1	VPusAfsgagc(Agn)umcauAfaGfcaucasu	1475	AAUGAGGCUUAUGAAAUGCCU	1564
AD-596101.1	A-1142886.1	gsasgac(Uhd)UfaUfGfAfaugccaL96	1387	A-1142887.1	VPusGfsgaag(Cgn)umcauUfaAfgcucasu	1476	AUGAGGCUUAUGAAAUGCCU	1565
AD-596215.2	A-1143114.1	asgsugc(Uhd)CfaGfUfUfccaangccaL96	1388	A-1143115.1	VPusGfscaca(Tgn)uggaacUfgAfgcausnsg	1477	CAAGUGCUAGUUCCAAUGUGCC	1566
AD-596217.1	A-1143118.1	usgsnuc(Ahd)GfuUfCfCfaugccaL96	1389	A-1143119.1	VPusGfsggca(Cgn)uuggaaAfcUfgacacsu	1478	AGUGCUCAGUUCCAAUGUGCCCA	1567
AD-596276.1	A-1143236.1	asgsnuc(Uhd)CfcAfUfCfagcaggaL96	1390	A-1143237.1	VPusAfscnac(Tgn)gcugaaGfgAfgacacsu	1479	GAAUGUCUCCAUACAGCAGUAU	1568
AD-596326.2	A-1143336.1	gsasagu(Ghd)AfaUfAfCfanguagcaL96	1391	A-1143337.1	VPusUfsgcua(Cgn)caugaaUfuCfcaucacsu	1480	CUGAAGUGAAUACAUGGUAGCAG	1569
AD-596328.1	A-1143340.1	asgsuga(Ahd)UfaCfAfUfguagcaggaL96	1392	A-1143341.1	VPusCfscugc(Tgn)accagUfaUfcaucacsu	1481	GAAUGAAUACAUGGUAGCAGGG	1570
AD-596390.2	A-1143464.1	asasaat(Chd)AfcCfUfAfagugacuacalL96	1393	A-1143465.1	VPusGfsguag(Cgn)acuuaGfuGfuumusasa	1482	UUAAAAACACCUAAAGUGACUACC	1571
AD-596391.2	A-1143466.1	asasaac(Ahd)CfcUfAfAfgugacuacalL96	1394	A-1143467.1	VPusGfsguag(Tgn)acuuaGfgUfguumusasa	1483	UAAAAACACCUAAAGUGACUACCA	1572
AD-596392.2	A-1143468.1	asasaac(Chd)CfuAfaGfugacuacalL96	1395	A-1143469.1	VPusUfsguag(Ggn)ucauuAfgGfuguumusasa	1484	AAAAACACCUAAAGUGACUACCAC	1573
AD-596393.1	A-1143470.1	asasaac(Chd)UfaAfGfUfgacuacalL96	1396	A-1143471.1	VPusGfsguag(Agn)gucacuUfaGfuguumusasa	1485	AAAAACACCUAAAGUGACUACCACU	1574
AD-596394.1	A-1143472.1	asasaac(Uhd)AfaGfUfGfacuacalL96	1397	A-1143473.1	VPusAfsguag(Tgn)agucacUfuAfguguumusasa	1486	AAACACCUAAAGUGACUACCACU	1575
AD-596395.1	A-1143474.1	asasaac(Ahd)AfgUfGfAfcuacacalL96	1398	A-1143475.1	VPusAfsguag(Ggn)uagucCfuUfaguguumusasa	1487	AACACCUAAAGUGACUACCACUUA	1576
AD-596396.2	A-1143476.1	asasaac(Ahd)GfuGfAfcuacacalL96	1399	A-1143477.1	VPusUfsguag(Ggn)gucacAfcUfaguguumusasa	1488	ACACCUAAAGUGACUACCACUUAU	1577
AD-596397.1	A-1143478.1	asasaac(Ghd)UfgAfCfUfaccacalL96	1400	A-1143479.1	VPusAfsguag(Tgn)gucacCfuCfuaguguumusasa	1489	CACCUAAAGUGACUACCACUUAU	1578
AD-596398.1	A-1143480.1	asasaac(Uhd)GfaCfUfAfcacacalL96	1401	A-1143481.1	VPusAfsguag(Ggn)ugguagUfcAfcuaguguumusasa	1490	ACCUAAAGUGACUACCACUUAU	1579
AD-596401.1	A-1143486.1	asgsuga(Chd)UfaCfCfAfcuacacalL96	1402	A-1143487.1	VPusAfsguag(Tgn)uagugUfaGfcaucacalL96	1491	UAGUGACUACCACUUAUUAUUA	1580
AD-596402.2	A-1143488.1	gsusgac(Uhd)AfcCfAfcuacacalL96	1403	A-1143489.1	VPusUfsguag(Agn)uagugGfuAfgucacalL96	1492	AAGUGACUACCACUUAUUAUUA	1581
AD-596403.1	A-1143490.1	usgsacu(Ahd)CfcAfCfUfuumuacalL96	1404	A-1143491.1	VPusUfsguag(Agn)uagugGfgUfagucacalL96	1493	AGUGACUACCACUUAUUAUUA	1582
AD-596521.1	A-1143726.1	asasaac(Ahd)UfgCfAfcuacacalL96	1405	A-1143727.1	VPusUfsguag(Agn)uagugCfuUfagumucsa	1494	UGAAACUAGCACCACUUAUUAUUA	1583

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-596564.1	A-1143812.1	usugug(Uhd)UfuGfUfAfuuaaaggcaL96	1406	A-1143813.1	VPusCfscuu(Tgn)auuacAfafacaaagssu	1495	ACUUGUUGUUUGUAUAUAAAUGGU	1584
AD-689314.1	A-1142220.1	csasuga(Ahd)AfgGfAfCfuucaaaaggaL96	1407	A-900783.1	VPusCfscuuUfgAfafagucCfuUfucuaagasa	1496	UUC AUGAAAAGGACUUUCAAAGGC	1585
AD-689315.1	A-1142222.1	asusgaat(Ahd)GfgAfCfUfuucaaaaggcaL96	1408	A-900785.1	VPusGfscuuUfuGfAfaaguCfcUfuucausgsa	1497	UCAUGAAAAGGACUUUCAAAGGCC	1586
AD-689316.1	A-1142224.1	usgsaaat(Ghd)GfAfCfUfuucaaaaggcaL96	1409	A-900787.1	VPusGfsgccUfuUfgfaagUfcCfuucausug	1498	CAUGAAAAGGACUUUCAAAGGCCA	1587
AD-689317.1	A-1142226.1	gsasaag(Ghd)AfcUfUfUfcaaaaggcaL96	1410	A-900789.1	VPusUfsgccCfuUfUfgaaaGfuCfuucaasasu	1499	AUGAAAAGGACUUUCAAAGGCCAA	1588
AD-689318.1	A-1142228.1	asasagat(Ahd)CfuUfUfCfaaaggccaalL96	1411	A-152531.1	VPusUfsggcCfuUfUfgaaaAfgUfuucausasa	1500	UGAAAAGGACUUUCAAAGGCCAAG	1589
AD-689319.1	A-1142230.1	asasgga(Chd)UfuUfCfAfaagccaaggaL96	1412	A-900791.1	VPusCfsgugGfcCfUfuuagaAfafGfuucausasc	1501	GAAAAGGACUUUCAAAGGCCAAGG	1590
AD-689320.1	A-1142232.1	asgsagac(Uhd)UfuCfAfafaggccaaggaL96	1413	A-900793.1	VPusCfscuuGfCfCfuungAfafAfguucaususu	1502	AAAGGACUUUCAAAGGCCAAGGA	1591
AD-689452.1	A-1142536.1	asasagac(Chd)AfaAfGfAfgaaggaagcaL96	1414	A-901101.1	VPusGfscuuCfuUfGfuucauUfuGfuucauscsu	1503	AGAAAGCACCACAAAGACAAAGUGACA	1592
AD-689459.1	A-1142550.1	asasagat(Chd)AfaGfUfGfacaanguaL96	1415	A-901109.1	VPusAfsacaUfuUfGfuucauUfuGfuucausug	1504	CAAAAGCAAGUGACAAAUGUUG	1593
AD-689461.1	A-1142554.1	gsasagat(Ahd)GfuGfAfCfaaangunggaL96	1416	A-152527.1	VPusCfscacCfaUfUfuucauAfcUfuucaususu	1505	AAGAGCAAGUGACAAAUGUUGGA	1594
AD-689462.1	A-1142556.1	asgscaat(Ghd)UfgAfCfAfaangunggaL96	1417	A-901113.1	VPusUfscacAfcAfUfuucauCfaCfuungcsusu	1506	AGAGCAAGUGACAAAUGUUGGAG	1595
AD-689463.1	A-1142558.1	gsasagat(Uhd)GfAfCfAfangunggaL96	1418	A-901115.1	VPusCfscacAfaCfAfuungUfcAfcuucaususc	1507	GAGCAAGUGACAAAUGUUGGAGG	1596
AD-689464.1	A-1142560.1	csasagat(Ghd)AfcAfAfafangunggaL96	1419	A-901117.1	VPusCfscacCfaAfCfauuuGfuCfuungcsusu	1508	AGCAAGUGACAAAUGUUGGAGGA	1597
AD-689615.1	A-1142880.1	asasuga(Ghd)GfcUfUfAfugaangccaL96	1420	A-901437.1	VPusGfsgcaUfuUfGfuaaaGfcCfuucausgsu	1509	ACAAUGAGGCUUAUGAAAUGCCU	1598
AD-689616.1	A-1142882.1	asusgag(Ghd)CfuUfAfUfgaangccaL96	1421	A-901439.1	VPusAfsagccAfafUfuucauAfgCfuucausug	1510	CAAUGAGGCUUAUGAAAUGCCUU	1599
AD-689617.1	A-1142884.1	usgsagat(Chd)UfuAfUfGfaangccaL96	1422	A-901441.1	VPusAfsagccCfaUfUfuucauAfaGfuucaususu	1511	AAUGAGGCUUAUGAAAUGCCUUC	1600
AD-689618.1	A-1142886.1	gsasgac(Uhd)UfaUfGfAfangccaL96	1423	A-901443.1	VPusGfsaagGfcAfUfuucaUfaAfguucaususu	1512	AUGAGGCUUAUGAAAUGCCUUCU	1601
AD-689747.1	A-1143102.1	usgsuac(Ahd)AfgUfGfCfuucauucaL96	1424	A-1316021.1	VPusUfsggaAfcUfGfagcaCfuUfuucausag	1513	CCUGUACAAAGGUCUCAGUUCCAA	3602
AD-689748.1	A-1143104.1	gsusacat(Ahd)GfuGfCfUfcauucaL96	1425	A-1316022.1	VPusUfsggaAfaCfuUfgagcAfcUfuucausasa	1514	CUGUACAAAGUGUCUCAUUUCCAAU	3603
AD-689753.1	A-1143114.1	asgsuac(Uhd)CfaGfUfUfcaangungcaL96	1426	A-901671.1	VPusGfscacAfafUfGfagcaUfgAfguucausug	1515	CAAGUGUCAGUUCCAAUGUGCC	1602
AD-689755.1	A-1143118.1	usgsuac(Ahd)GfuUfCfAfaangungccaL96	1427	A-901675.1	VPusGfsggcAfcAfUfuucaUfcUfgagcauscu	1516	AGUGCUCAGUUCCAAUGUGCCCA	1603

Duplex	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD- 689786.1	A- 1143232.1	gsasagu(Chd)UfnCtCfAfhcagcagnal.96	1428	A- 1316023.1	VPusCfscuGfCfUfGfanguAfaGfacuucsasa	1517	UCGAAGCUUCCAUCAAGCAGUGA	3604
AD- 689787.1	A- 1143234.1	asasagu(Uhd)UfcCfAfUfCfagcagagnaal.96	1429	A- 1316024.1	VPusUfscacUfGfCUfGfanguGfAfGfacuucsasa	1518	CGAAGUUUCCAUCAAGCAGUGAU	3605
AD- 689788.1	A- 1143236.1	asgsuau(Uhd)CfcAfUfCfGcagcagnaal.96	1430	A- 901793.1	VPusAfscuaCfuGfCfGfanguGfAfGfaguususc	1519	GAAGUUCUCCAUCAAGCAGUGAUU	1604
AD- 689835.1	A- 1143336.1	gsasagu(Ghd)AfaUfAfCfanguagcaal.96	1431	A- 901893.1	VPusUfsgcuAfCfAfGfanguUfnCfacuucsasg	1520	CUGAAGUGAAUACAUGGUAGCAG	1605
AD- 689907.1	A- 1316093.1	usgsaag(Uhd)CfuUfCfCfauagcagcagnal.96	1432	A- 1316094.1	VPusAfscugCfuGfAfGfanguAfgAfacuucasasa	1521	UUUGAAAGUUCUCCAUCAAGCAGUG	1606
AD- 689925.1	A- 1143462.1	usasaa(Chd)CfaCfCfUfUfagngagcuaal.96	1433	A- 1316128.1	VPusUfsguGfAfCfUfGfanguUfGfUfnuunasasa	1522	AUUA AAAACACCUAAAGUGACUAC	3606
AD- 689926.1	A- 1143464.1	asasaa(Chd)AfCfCfUfAfGfagngacuacal.96	1434	A- 902026.1	VPusGfsguUfAfCfCfGfanguGfUfnuunusasa	1523	UUAAAAACACCUAAAGUGACUACC	1607
AD- 689927.1	A- 1143466.1	asasaac(Chd)CfcUfAfAfGfagngacuacal.96	1435	A- 902028.1	VPusGfsguafGfuCfAfCfuaaGfGfUfnuunusasa	1524	UAAAAACACCUAAAGUGACUACCA	1608
AD- 689928.1	A- 1143468.1	asasaca(Chd)CfuAfAfGfGfagngacuacal.96	1436	A- 902030.1	VPusUfsgguAfGfUfCfGfacuafGfGfugnuunusu	1525	AAAAACACCUAAAGUGACUACCAC	1609
AD- 689929.1	A- 1143470.1	asasac(Chd)UfaAfAfGfUfGfagngacuacal.96	1437	A- 902032.1	VPusGfsguGfUfaGfUfGfacuUfGfGfugnuunusu	1526	AAAACACCUAAAGUGACUACCACU	1610
AD- 689930.1	A- 1143472.1	asasacc(Uhd)AfAfGfUfGfagngacuacal.96	1438	A- 902034.1	VPusAfsguGfUfAfGfGfacuUfUfAfGfugnuunusu	1527	AAACACCUAAAGUGACUACCACUU	1611
AD- 689931.1	A- 1143474.1	asasacc(Chd)AfGfUfAfAfGfagngacuacal.96	1439	A- 902036.1	VPusAfsguGfGfUfAfGfGfacuCfuUfGfugngusu	1528	AACACCUAAAGUGACUACCACUUA	1612
AD- 689932.1	A- 1143476.1	ascsua(Chd)GfuAfAfGfAfGfagngacuacal.96	1440	A- 152515.1	VPusUfsguGfGfUfGfGfagucAfGfUfGfugngusu	1529	ACACCUAAAGUGACUACCACUUAU	1613
AD- 689933.1	A- 1143478.1	csasuaaf(Ghd)UfgAfCfUfAfGfagngacuacal.96	1441	A- 902038.1	VPusAfsguaGfUfGfGfGfagucCfuCfGfuaagsgsu	1530	CACCUAAGUGACUACCACUUAUU	1614
AD- 689934.1	A- 1143480.1	csuasag(Uhd)GfuCfUfAfAfGfagngacuacal.96	1442	A- 902040.1	VPusAfsguaAfGfUfGfGfGfagucUfCfAfGfuaagsgsu	1531	ACCUAAGUGACUACCACUUAUUU	1615
AD- 689935.1	A- 1143482.1	uasasagu(Ghd)AfCfUfAfCfGfagngacuacal.96	1443	A- 902042.1	VPusAfsgaafAfAfGfUfGfGfagucGfUfGfacuusgsg	1532	CCUAAGUGACUACCACUUAUUUC	1616
AD- 689936.1	A- 1143484.1	asasagug(Chd)CfuAfCfCfGfagngacuacal.96	1444	A- 902044.1	VPusGfsgaafUfaAfGfGfagucAfGfUfGfacuusgsg	1533	CUAAGUGACUACCACUUAUUUUU	1617
AD- 689937.1	A- 1143486.1	asgsuga(Chd)UfaCfGfCfAfCfGfagngacuacal.96	1445	A- 902046.1	VPusAfsgaaAfUfaAfGfGfagucUfaGfGfacuusasa	1534	UAAGUGACUACCACUUAUUUCUA	1618
AD- 689938.1	A- 1143488.1	gsusgac(Uhd)AfCfCfAfCfGfagngacuacal.96	1446	A- 152519.1	VPusUfsgagAfAfUfAfGfagucGfUfAfGfacuususu	1535	AAGUGACUACCACUUAUUUCUAA	1619
AD- 689939.1	A- 1143490.1	usgsacu(Chd)CfcAfCfUfUfGfagngacuacal.96	1447	A- 152535.1	VPusUfsgagAfAfUfAfGfagucGfUfGfagucscsu	1536	AGUGACUACCACUUAUUUCUAAA	1620
AD- 690068.1	A- 1143726.1	asasacu(Chd)UfgCfAfCfGfagngacuacal.96	1448	A- 902279.1	VPusUfsgauUfaUfaUfGfGfagucCfuUfGfagnuucsasa	1537	UGAAACUAGCACCACCUAUAUUUAC	1621
AD- 900079.1	A- 1316237.1	asusngug(Uhd)UfnUfAfUfGfagngacuacal.96	1449	A- 920846.1	VPusCfscacaAfGfUfUfGfagucAfAfGfacuucsasa	1538	UGAUGUGUUUAUUAAACUUGUGU	1622

Duplex Name	Sense Oligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA target sequence	SEQ ID NO:
AD-690080.1	A-1316238.1	usgsugr(Uhd)UfuAfUfUfaacungugal96	1450	A-920848.1	VPusAfscaeAfafGfUfuaauAfafAcacacusc	1539	GAUGUGUUUUUUUAACUUGUGUU	1623
AD-690092.1	A-1143812.1	usisugr(Uhd)UfuGfUfAfuaaauauggal96	1451	A-902360.1	VPusCfscauUfuAfUfauacAfafAcacacsgu	1540	ACUUGUGUUUGUAUAUAAAUGGU	1624
AD-691823.1	A-1143102.1	usgsuac(Ahd)AfgUfGfCfucagucuaal96	1452	A-1318409.1	VPusUfsgaa(Cgn)ugagcaCfuUfguacacag	1541	CCUGUACAAAGUGCUCAGUCCAA	3607
AD-691824.1	A-1143104.1	gsusaca(Ahd)GfuGfCfUfcagucuaal96	1453	A-1318428.1	VPusUfsgaa(Agn)ugagcaCfuUfguacacag	1542	CUGUACAAAGUGCUCAGUCCAAU	3608
AD-691843.1	A-1316093.1	usgsaag(Uhd)CfuUfCfCfancagcagual96	1454	A-1318430.1	VPusAfscae(Tgn)ganggaAfafAcacacasa	1543	UUUGAAGUCUUCCAUACGACAGUG	1625
AD-691844.1	A-1143232.1	gsasagr(Uhd)UfuCfCfAfucagcagual96	1455	A-1318429.1	VPusCfscau(Cgn)ugagcaCfuUfguacacasa	1544	UCGAAAGUCUUCCAUACGACAGUGA	3609
AD-691845.1	A-1143234.1	asasgr(Uhd)UfuCfCfAfucagcagual96	1456	A-1318460.1	VPusUfscacu(Ggn)ugagcaCfuUfguacacasa	1545	CGAAGUCUUCCAUACGACAGUAU	3610
AD-691875.1	A-1143462.1	usasaal(Ahd)CfaCfCfUfaagugacuaal96	1457	A-1318460.1	VPusUfscacu(Ggn)ugagcaCfuUfguacacasa	1546	AUUAAAACACCUAAAGUGACUAC	3611
AD-691953.1	A-1316237.1	asusgr(Uhd)UfuUfAfUfuaacungugal96	1458	A-1318538.1	VPusCfscau(Cgn)ugagcaCfuUfguacacasa	1547	UGAUGUGUUUUUAUAAACUUGUGU	1626
AD-691954.1	A-1316238.1	usgsugr(Uhd)UfuAfUfUfaacungugal96	1459	A-1318539.1	VPusAfscae(Agn)gmaauAfafAcacacusc	1548	GAUGUGUUUUUAUAAACUUGUGUU	1627

Table 3. Unmodified Sense and Antisense Strand Sequences of Human and Primate SNCA siRNAs.

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-595724	A-1142132.1	GACGACAG UGUGUGU AAAGA	NM_000345.3 231- 251_G21U s	231-251	283	A-1142133.1	UCUUUACA CCACACUG UCGUGCA	NM_000345.3 229- 251_C1A as	229-251	373
AD-595769	A-1142222.1	AUGAAAAGG ACUUUCAA AGGCA	NM_000345.3 276- 296_C21U s	276-296	284	A-1142223.1	UGCCUUTG AAAGUCCU UUCAUCA	NM_000345.3 274- 296_G1A as	274-296	374
AD-595854	A-1142392.1	AAAGAGGG UGUUCUCU AUGUA	NM_000345.3 363- 383_A21U s	363-383	285	A-1142393.1	UACAUAGA GAACACCC UCUUUUG	NM_000345.3 361- 383_U1A as	361-383	375
AD-595855	A-1142394.1	AAGAGGGU GUUCUCUA UGUAA	NM_000345.3 364- 384_G21U s	364-384	286	A-1142395.1	UUAUUAAG AGAACACC CUCUUUU	NM_000345.3 362- 384_C1A as	362-384	376
AD-595866	A-1142416.1	CUCUAUGU AGGCUCCA AAACA	NM_000345.3 375- 395_C21U s	375-395	287	A-1142417.1	UGUUUUGG AGCCUACA UAGAGAA	NM_000345.3 373- 395_G1A as	373-395	377
AD-595926	A-1142536.1	AAGACCAA AGAGCAAG UGACA	NM_000345.3 435- 455_A21U s	435-455	288	A-1142537.1	UGUACACTU GCUUUUG GUCUUUU	NM_000345.3 433- 455_U1A as	433-455	378

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-596096	A-1142876.1	ACAAUGAG GCUUAUGA AAUGA	NM_000345.3 _625- 645 C21U s	625-645	289	A-1142877.1	UCAUUUCA UAAGCCUC AUUGUCA	NM_000345.3 _623- 645 G1A as	623-645	379
AD-596100	A-1142884.1	UGAGGCUU AUGAAUG CCUUA	NM_000345.3 _629- 649 C21U s	629-649	290	A-1142885.1	UAAGGCAU UUCAUAAAG CCUCAUU	NM_000345.3 _627- 649 G1A as	627-649	380
AD-596124	A-1142932.1	GGAAGGGU AUCAAGAC UACGA	NM_000345.3 _653- 673 A21U s	653-673	291	A-1142933.1	UCGUAGTC UUGAUACC CUUCUC	NM_000345.3 _651- 673 U1A as	651-673	381
AD-596126	A-1142936.1	AAGGUAU CAAGACUA CGAAA	NM_000345.3 _655- 675 C21U s	655-675	292	A-1142937.1	UUUCGUAG UUUGAUUA CCCUUCC	NM_000345.3 _653- 675 G1A as	653-675	382
AD-596127	A-1142938.1	AGGUAUC AAGACUAC GAACA	NM_000345.3 _656- 676 C21U s	656-676	293	A-1142939.1	UGUUCGTA GUUUGAU ACCUUUC	NM_000345.3 _654- 676 G1A as	654-676	383
AD-596128	A-1142940.1	GGUAUCA AGACUACG AACCA	NM_000345.3 _657-677 s	657-677	294	A-1142941.1	UGUUCGTA GUUUGAU ACCUUUC	NM_000345.3 _655-677 as	655-677	384
AD-596129	A-1142942.1	GGUAUCA GACUACGA ACCUA	NM_000345.3 _658- 678 G21U s	658-678	295	A-1142943.1	UAGGUUCG UAGUCUUG AUACCUU	NM_000345.3 _656- 678 C1A as	656-678	385
AD-596130	A-1142944.1	GUAUCAAG ACUACGAA CCUGA	NM_000345.3 _659- 679 A21U s	659-679	296	A-1142945.1	UCAGGUTC GUAGUCUU GAUACCC	NM_000345.3 _657- 679 U1A as	657-679	386
AD-596131	A-1142946.1	UAUCAAGA CUACGAAC CUGAA	NM_000345.3 _660- 680 A21U s	660-680	297	A-1142947.1	UUCAGGTU CGUAGUCU UGAUACC	NM_000345.3 _658- 680 U1A as	658-680	387
AD-596133	A-1142950.1	UCAAGACU ACGAACCU GAAGA	NM_000345.3 _662- 682 C21U s	662-682	298	A-1142951.1	UCUUCAGG UUCGUAGU CUUGAUA	NM_000345.3 _660- 682 G1A as	660-682	388
AD-596137	A-1142958.1	GACUACGA ACCUGAAG CCUAA	NM_000345.3 _666- 686 A21U s	666-686	299	A-1142959.1	UUAAGGCTU CAGGUUCG UAGUCUU	NM_000345.3 _664- 686 U1A as	664-686	389
AD-596144	A-1142972.1	AACCUGAA GCCUAAGA AUAA	NM_000345.3 _673-693 s	673-693	300	A-1142973.1	UUAUUUCU UAGGCUUC AGGUUCG	NM_000345.3 _671-693 as	671-693	390
AD-596147	A-1142978.1	CUGAAGCC UAAGAAAU AUCUA	NM_000345.3 _676-696 s	676-696	301	A-1142979.1	UAGAUATU UCUUAGGC UUCAGGU	NM_000345.3 _674-696 as	674-696	391
AD-596168	A-1143020.1	UGCUCCA GUUCUUG AGAU	NM_000345.3 _697- 717 C21U s	697-717	302	A-1143021.1	UAUCUCA GAAACUGG GAGCAAA	NM_000345.3 _695- 717 G1A as	695-717	392
AD-596169	A-1143022.1	GCUCCCAG UUUCUUGA GAUCA	NM_000345.3 _698-718 s	698-718	303	A-1143023.1	UGAUCUCA AGAAACUG GGGCAA	NM_000345.3 _696-718 as	696-718	393

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-596170	A-1143024.1	CUCCAGU UUCUUGAG AUCUA	NM_000345.3 _69- 719 G21U s	699-719	304	A-1143025.1	UAGAUCTC AAGAAACU GGGAGCA	NM_000345.3 _697- 719 C1A as	697-719	394
AD-596171	A-1143026.1	UCCAGUU UCUUGAGA UCUGA	NM_000345.3 _700- 720 C21U s	700-720	305	A-1143027.1	UCAGAUUC CAAGAAAC UGGGAGC	NM_000345.3 _698- 720 G1A as	698-720	395
AD-596172	A-1143028.1	CCCAGUU CUUGAGAU CUGCA	NM_000345.3 _701-721 s	701-721	306	A-1143029.1	UGCAGATC UCAAGAAA CUGGGAG	NM_000345.3 _699-721 as	699-721	396
AD-596175	A-1143034.1	AGUUCUU GAGAUUCG CUGAA	NM_000345.3 _704- 724 C21U s	704-724	307	A-1143035.1	UUCAGCAG AUCUCAAG AAACUGG	NM_000345.3 _702- 724 G1A as	702-724	397
AD-596177	A-1143038.1	UUUCUUGA GAUCUGCU GACAA	NM_000345.3 _706- 726 G21U s	706-726	308	A-1143039.1	UGUCACGC AGAUUCUA AGAAACU	NM_000345.3 _704- 726 C1A as	704-726	398
AD-596215	A-1143114.1	AGUGCUCA GUUCCAAU GUGCA	NM_000345.3 _744- 764 C21U s	744-764	309	A-1143115.1	GGAAACUGA GCACUUG	NM_000345.3 _742- 764 G1A as	742-764	399
AD-596231	A-1143146.1	UUCACGCA GUGCCAG UUUCA	NM_000345.3 _760-780 s	760-780	310	A-1143147.1	UGAAAUUGU CAUGACUG GGCACAU	NM_000345.3 _758-780 as	758-780	400
AD-596235	A-1143154.1	CCAGUCAU GACAUUUC UCAAA	NM_000345.3 _764- 784 A21U s	764-784	311	A-1143155.1	UUUGAGAA AUCGCAUG ACUGGC	NM_000345.3 _762- 784 U1A as	762-784	401
AD-596283	A-1143250.1	CAUCAGCA GUGAUUGA AGUAA	NM_000345.3 _812-832 s	812-832	312	A-1143251.1	UUACUUA AUCACUGC UGAUGGA	NM_000345.3 _810-832 as	810-832	402
AD-596319	A-1143322.1	UUUCACUG AAGUGAAU ACAUA	NM_000345.3 _869- 889 G21U s	869-889	313	A-1143323.1	UAUGUATU CACUUCAG UGAAAGG	NM_000345.3 _867- 889 C1A as	867-889	403
AD-596320	A-1143324.1	UUCACUGA AGUGAAUA CAUGA	NM_000345.3 _870- 890 G21U s	870-890	314	A-1143325.1	UCAUGUAU UCACUUA GUGAAAG	NM_000345.3 _868- 890 C1A as	868-890	404
AD-596322	A-1143328.1	CACUGAAG UGAAUACA UGGUA	NM_000345.3 _872- 892 A21U s	872-892	315	A-1143329.1	UACCAUGU AUUCACUU CAGUGAA	NM_000345.3 _870- 892 U1A as	870-892	405
AD-596323	A-1143330.1	ACUGAAGU GAUACAU GGUAA	NM_000345.3 _873- 893 G21U s	873-893	316	A-1143331.1	UUACCATG UAUUCACU UCAGUGA	NM_000345.3 _871- 893 C1A as	871-893	406
AD-596325	A-1143334.1	UGAAGUGA AUACAUUG UAGCA	NM_000345.3 _875- 895 A21U s	875-895	317	A-1143335.1	UGCUACCA UGUAUUA CUUCAGU	NM_000345.3 _873- 895 U1A as	873-895	407
AD-596326	A-1143336.1	GAAGUGAA UACAUUGU AGCAA	NM_000345.3 _876- 896 G21U s	876-896	318	A-1143337.1	UUGCUACC AUGUAUUC ACUUCAG	NM_000345.3 _874- 896 C1A as	874-896	408

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-596362	A-1143408.1	UGGAUUUU GUGGCUUC AAUCA	NM_000345.3 _912-932_s	912-932	319	A-1143409.1	UGAUUGAA GCCACAAA AUCCACA	NM_000345.3 _910-932_as	910-932	409
AD-596390	A-1143464.1	AAAAACAC CUAAGUGA CUACA	NM_000345.3 _951- 971_C21U_s	951-971	320	A-1143465.1	UGUAGUCA CUUAGGUG UUUUUAA	NM_000345.3 _949- 971_G1A_as	949-971	410
AD-596391	A-1143466.1	AAACACCC UAAAGUGAC UACCA	NM_000345.3 _952- 972_A21U_s	952-972	321	A-1143467.1	UGGUAGTC ACUUAGGU GUUUUUA	NM_000345.3 _950- 972_U1A_as	950-972	411
AD-596392	A-1143468.1	AAACACCU AAGUGACU ACCAA	NM_000345.3 _953- 973_C21U_s	953-973	322	A-1143469.1	UUGGUAGU CACUUAGG UGUUUUU	NM_000345.3 _951- 973_G1A_as	951-973	412
AD-596396	A-1143476.1	ACCUAAGU GACUACCA CUUAA	NM_000345.3 _957-977_s	957-977	323	A-1143477.1	UUAGGUGG UAGUCACU UAGGUGU	NM_000345.3 _955-977_as	955-977	413
AD-596402	A-1143488.1	GUGACUAC CACUUUUU UCUAA	NM_000345.3 _963- 983_A21U_s	963-983	324	A-1143489.1	UUAGAAAU AAGUGGUA GUCACUU	NM_000345.3 _961- 983_U1A_as	961-983	414
AD-596425	A-1143534.1	CUGUUGUU CAGAAUUU GUUAA	NM_000345.3 _1005- 1025_G21U_s	1005-1025	325	A-1143535.1	UUACAAC UUCUGAAC AACAGCA	NM_000345.3 _1003- 1025_C1A_as	1003-1025	415
AD-596426	A-1143536.1	UGUUGUUC AGAAGUUG UUAGA	NM_000345.3 _1006-1026_s	1006-1026	326	A-1143537.1	UCUAACAA CUUCUGAA CAACAGC	NM_000345.3 _1004-1026_as	1004-1026	416
AD-596427	A-1143538.1	GUUGUUCA GAAGUUUG UAGUA	NM_000345.3 _1007- 1027_G21U_s	1007-1027	327	A-1143539.1	UACUAACA ACUUCUGA ACAACAG	NM_000345.3 _1005- 1027_C1A_as	1005-1027	417
AD-596431	A-1143546.1	UUCAGAAG UUGUUAGU GAUUA	NM_000345.3 _1011-1031_s	1011-1031	328	A-1143547.1	UAAUCACU AACAAACU CUGAACA	NM_000345.3 _1009-1031_as	1009-1031	418
AD-596436	A-1143556.1	AAGUUUUU AGUGAUUU GCUAA	NM_000345.3 _1016-1036_s	1016-1036	329	A-1143557.1	UAGCAAA UCACUAA AACUUCU	NM_000345.3 _1014-1036_as	1014-1036	419
AD-596469	A-1143622.1	UUUAAUUG AUACUGUC UAAGA	NM_000345.3 _1063- 1083_A21U_s	1063-1083	330	A-1143623.1	UCUUAGAC AGUAUCAU UAAAAGA	NM_000345.3 _1061- 1083_U1A_as	1061-1083	420
AD-596477	A-1143638.1	AUACUGUC UAAGAAUA AUGAA	NM_000345.3 _1071- 1091_C21U_s	1071-1091	331	A-1143639.1	UUCAUUUU UCUUAGAC AGUAUCA	NM_000345.3 _1069- 1091_G1A_as	1069-1091	421
AD-596515	A-1143714.1	AGCAUGAA ACUAGCA CCUAA	NM_000345.3 _1136-1156_s	1136-1156	332	A-1143715.1	UUAGGUGC AUAUUUUC AUGCUCA	NM_000345.3 _1134-1156_as	1134-1156	422
AD-596517	A-1143718.1	CAUGAAAC UAUGCACC UAUAA	NM_000345.3 _1138- 1158_A21U_s	1138-1158	333	A-1143719.1	UUUAGGU GCAUAGUU UCAUGCU	NM_000345.3 _1136- 1158_U1A_as	1136-1158	423

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-596605	A-1143894.1	UUUAUCC AUCUCACU UUAAA	NM_000345.3 _1269-1289_s	1269-1289	334	A-1143895.1	UUUAAAAGU GAGAUAGG AUAAAA	NM_000345.3 _1267-1289_as	1267-1289	424
AD-596606	A-1143896.1	UUUAUCCA UCUCACUU UAAUA	NM_000345.3 _1270- _1290_A2IU_s	1270-1290	335	A-1143897.1	UUUAAAAG UAGAUAGG GAUAAAA	NM_000345.3 _1268- _1290_U1A_as	1268-1290	425
AD-596609	A-1143902.1	UCCCAUCUC ACUUAAU AAUA	NM_000345.3 _1273- _1293_A2IU_s	1273-1293	336	A-1143903.1	UAUUAUTA AAGUGAGA UGGGAUA	NM_000345.3 _1271- _1293_U1A_as	1271-1293	426
AD-596709	A-1144102.1	AAAUUGGA ACAUUAA CCUAA	NM_000345.3 _1399- _1419_C2IU_s	1399-1419	337	A-1144103.1	UUAGGGTU AAUGUCC AUUUUCU	NM_000345.3 _1397- _1419_G1A_as	1397-1419	427
AD-597019	A-1144722.1	AUAGCAC AUUUAGC ACAU	NM_000345.3 _1850-1870_s	1850-1870	338	A-1144723.1	UAUGUCU AAUAGUG CUAAUGU	NM_000345.3 _1848-1870_as	1848-1870	428
AD-597232	A-1145148.1	UCUCUUC AGGGAAGA UCUAA	NM_000345.3 _2138-2158_s	2138-2158	339	A-1145149.1	UUAGAUCU UCCUGAA AGAGAAA	NM_000345.3 _2136-2158_as	2136-2158	429
AD-597297	A-1145278.1	AAGUCACU AGUAGAA GUAA	NM_000345.3 _2271- _2291_A2IU_s	2271-2291	340	A-1145279.1	UAUACUTU CUACUAGU GACUUU	NM_000345.3 _2269- _2291_U1A_as	2269-2291	430
AD-597298	A-1145280.1	AGUCACUA GUAGAAAG UAUAA	NM_000345.3 _2272- _2292_A2IU_s	2272-2292	341	A-1145281.1	UUUAUACTU UCUACUAG UGACUU	NM_000345.3 _2270- _2292_U1A_as	2270-2292	431
AD-597325	A-1145334.1	CAGAAU UCUAGACA UGCUA	NM_000345.3 _2301- _2321_A2IU_s	2301-2321	342	A-1145335.1	UAGCAUGU CUAGAAUA UUCUGUC	NM_000345.3 _2299- _2321_U1A_as	2299-2321	432
AD-597326	A-1145336.1	AGAAU CUAGACAU GCUAA	NM_000345.3 _2302- _2322_G2IU_s	2302-2322	343	A-1145337.1	UUAGCATG UCUAGAAU AUUCUGU	NM_000345.3 _2300- _2322_C1A_as	2300-2322	433
AD-597327	A-1145338.1	GAUUAU UAGACAU CUAGA	NM_000345.3 _2303- _2323_C2IU_s	2303-2323	344	A-1145339.1	UCUAGCAU GUUAGAA UAUUCUG	NM_000345.3 _2301- _2323_G1A_as	2301-2323	434
AD-597335	A-1145354.1	UAGACAUG CUAGCAGU UUUA	NM_000345.3 _2311- _2331_A2IU_s	2311-2331	345	A-1145355.1	UAUAAACU GCUAGCAU GUCUAGA	NM_000345.3 _2309- _2331_U1A_as	2309-2331	435
AD-597397	A-1145478.1	GAGGAU AGUGACUA UAAGA	NM_000345.3 _2381- _2401_G2IU_s	2381-2401	346	A-1145479.1	UCUUUAAG UCACUCAU UCCUCCU	NM_000345.3 _2379- _2401_C1A_as	2379-2401	436
AD-597398	A-1145480.1	AGGAU GUGACUAU AAGGA	NM_000345.3 _2382- _2402_A2IU_s	2382-2402	347	A-1145481.1	UCCUUAATA GUCACUCA UCCUCCU	NM_000345.3 _2380- _2402_U1A_as	2380-2402	437
AD-597404	A-1145492.1	GAGUGACU AUAAAGAU GGUUA	NM_000345.3 _2388- _2408_A2IU_s	2388-2408	348	A-1145493.1	UAACCATCC UUUAAGUC ACUCAU	NM_000345.3 _2386- _2408_U1A_as	2386-2408	438

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-597409	A-1145502.1	ACUUAAG GAUGGUUA CCAUA	NM_000345.3 _2393- 2413 A21U s	2393-2413	349	A-1145503.1	UAUGGUAA CCAUCUU UAUGUCA	NM_000345.3 _2391- 2413 UIA as	2391-2413	439
AD-597410	A-1145504.1	CUUAAGG AUGGUUAC CAUAA	NM_000345.3 _2394- 2414 G21U s	2394-2414	350	A-1145505.1	UUAUGGTA ACCAUCCU UAUAGUC	NM_000345.3 _2392- 2414 CIA as	2392-2414	440
AD-597417	A-1145518.1	GAUGGUUA CCAUAAGAA ACUUA	NM_000345.3 _2401- 2421 C21U s	2401-2421	351	A-1145519.1	UAAGUUTC UAUGGUAA CCAUCU	NM_000345.3 _2399- 2421 GIA as	2399-2421	441
AD-597443	A-1145570.1	ACUACUAC AGAGUGCU AAGCA	NM_000345.3 _2445-2465 s	2445-2465	352	A-1145571.1	UGCUUAGC ACUCUGUA GUAGUCU	NM_000345.3 _2443-2465 as	2443-2465	442
AD-597455	A-1145594.1	UGCUAAGC UGCAUGUG UCAUA	NM_000345.3 _2457- 2477 C21U s	2457-2477	353	A-1145595.1	UAUGACAC AUCGAGCU UAGCACU	NM_000345.3 _2455- 2477 GIA as	2455-2477	443
AD-597459	A-1145602.1	AAGCUGCA UGUGUCAU CUUAA	NM_000345.3 _2461- 2481 C21U s	2461-2481	354	A-1145603.1	UUAAGATG ACACAUGC AGCUUAG	NM_000345.3 _2459- 2481 GIA as	2459-2481	444
AD-597460	A-1145604.1	AGCUGCAU GUGUCAUC UUACA	NM_000345.3 _2462- 2482 A21U s	2462-2482	355	A-1145605.1	UGUAAGAU GACACAUG CAGCUUA	NM_000345.3 _2460- 2482 UIA as	2460-2482	445
AD-597534	A-1145752.1	CAGUAUUA UUCAGGAA GGUUA	NM_000345.3 _2553- 2573 A21U s	2553-2573	356	A-1145753.1	UAACCUCC UGAAUAU ACUGUU	NM_000345.3 _2551- 2573 UIA as	2551-2573	446
AD-597569	A-1145822.1	AAUUCUAC CUAAAGCA GCAUA	NM_000345.3 _2599- 2619 A21U s	2599-2619	357	A-1145823.1	UAUGCUGC UUUAGGUA GAUUUA	NM_000345.3 _2597- 2619 UIA as	2597-2619	447
AD-597861	A-1146406.1	AGUCCUAG GUUUUUU UGCAA	NM_000345.3 _2951- 2971 G21U s	2951-2971	358	A-1146407.1	UUGCAAAA UAAACCUA GGACUGG	NM_000345.3 _2949- 2971 CIA as	2949-2971	448
AD-597864	A-1146412.1	CCUAGGUU UAUUUUGC AGACA	NM_000345.3 _2954-2974 s	2954-2974	359	A-1146413.1	UGUCUGCA AAAUAAAC CUAGGAC	NM_000345.3 _2952-2974 as	2952-2974	449
AD-597894	A-1146472.1	CCAAGUUA UUCAGCCU CAUAA	NM_000345.3 _2984+3004 s	2984-3004	360	A-1146473.1	UUUAGGAG CUAGAUAA CUUGGGA	NM_000345.3 _2982-3004 as	2982-3004	450
AD-597898	A-1146480.1	GUUAUUA GCCUCAUA UGACA	NM_000345.3 _2988-3008 s	2988-3008	361	A-1146481.1	UGUCAUUA GAGGCUGA AUAAUUA	NM_000345.3 _2986-3008 as	2986-3008	451
AD-597899	A-1146482.1	UUUUAUUA CCUCAUAU GACUA	NM_000345.3 _2989- 3009 C21U s	2989-3009	362	A-1146483.1	UAUCATA UGAGGCUG AAUAAU	NM_000345.3 _2987- 3009 GIA as	2987-3009	452
AD-597900	A-1146484.1	UAUUCAGC CUCAUAUG ACUCA	NM_000345.3 _2990- 3010 C21U s	2990-3010	363	A-1146485.1	UGAGUCAU AUGAGGCU GAUUAAC	NM_000345.3 _2988- 3010 GIA as	2988-3010	453

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-597925	A-1146534.1	UCGGCUUU ACCAAAC AGUUA	NM_000345.3 _3015- 3035 C21U s	3015-3035	364	A-1146535.1	UAACTGTU UUGGUAAA GCCGACC	NM_000345.3 _3013- 3035 G1A as	3013-3035	454
AD-597927	A-1146538.1	GGCUUAC CAAAACAG UUCAA	NM_000345.3 _3017- 3037 G21U s	3017-3037	365	A-1146539.1	UUGAACTG UUUUGGUA AAGCCGA	NM_000345.3 _3015- 3037 C1A as	3015-3037	455
AD-597937	A-1146558.1	AAACAGUU CAGAGUGC ACUUA	NM_000345.3 _3027-3047 s	3027-3047	366	A-1146559.1	UAAAGUCA CUCUGAAC UGUUUUG	NM_000345.3 _3025-3047 as	3025-3047	456
AD-597946	A-1146576.1	AGAGUGCA CUUUGGCA CACAA	NM_000345.3 _3036- 3056 A21U s	3036-3056	367	A-1146577.1	UUGUGUGC CAAAGUGC ACUCUGA	NM_000345.3 _3034- 3056 U1A as	3034-3056	457
AD-597972	A-1146628.1	AACGAAC AAUCUAAU GUGUA	NM_000345.3 _3062- 3082 G21U s	3062-3082	368	A-1146629.1	UACACATU AGAUUGUU CUGUUGC	NM_000345.3 _3060- 3082 C1A as	3060-3082	458
AD-597974	A-1146632.1	CAGAACAA UCUAAUGU GUGGA	NM_000345.3 _3064-3084 s	3064-3084	369	A-1146633.1	UCCACACA UUAGAUGG UUCUGUU	NM_000345.3 _3062-3084 as	3062-3084	459
AD-597984	A-1146652.1	UAAUGUGU GGUUGGU AUUCA	NM_000345.3 _3074- 3094 C21U s	3074-3094	370	A-1146653.1	UGAAUACC AAACCACA CAUUAAGA	NM_000345.3 _3072- 3094 G1A as	3072-3094	460
AD-597988	A-1146660.1	GUGUGGUU UGGUAUUC CAAGA	NM_000345.3 _3078-3098 s	3078-3098	371	A-1146661.1	UCUUGGAA UACCAAAC CACACAU	NM_000345.3 _3076-3098 as	3076-3098	461
AD-597989	A-1146662.1	UGUGGUUU GGUUAUCC AAGUA	NM_000345.3 _3079- 3099 G21U s	3079-3099	372	A-1146663.1	UACUUGGA AUACCAAA CCACACA	NM_000345.3 _3077- 3099 C1A as	3077-3099	462
AD-595724.1	A-1142132.1	GACGACAG UGUGGUGU AAAGA	NM_000345.3 _231- 251 G21U s	231-251	733	A-1142133.1	UCUUUACA CCACACUG UCGUCGA	NM_000345.3 _229- 251 C1A as	229-251	823
AD-595769.1	A-1142222.1	AUGAAAGG ACUUUCAA AGGCA	NM_000345.3 _276- 296 C21U s	276-296	734	A-1142223.1	UGCCUUTG AAAGUCCU UUCAUGA	NM_000345.3 _274- 296 G1A as	274-296	824
AD-595854.1	A-1142392.1	AAAGAGGG UGUUCUCU AUGUA	NM_000345.3 _363- 383 A21U s	363-383	735	A-1142393.1	UACAUAGA GAACACCC UCUUUUUG	NM_000345.3 _361- 383 U1A as	361-383	825
AD-595855.1	A-1142394.1	AAGAGGGU GUUCUCUA UGUAA	NM_000345.3 _364- 384 G21U s	364-384	736	A-1142395.1	UUACAUAG AGAACACC CUCUUUUG	NM_000345.3 _362- 384 C1A as	362-384	826
AD-595866.1	A-1142416.1	CUCUAUGU AGGCUCCA AAACA	NM_000345.3 _375- 395 C21U s	375-395	737	A-1142417.1	UGUUUUGG AGCUUACA UAGAGAA	NM_000345.3 _373- 395 G1A as	373-395	827
AD-595926.1	A-1142536.1	AAGACCAA AGAGCAAG UGACA	NM_000345.3 _435- 455 A21U s	435-455	738	A-1142537.1	UGUACACTU GCUUCUUUG GUCUUUCU	NM_000345.3 _433- 455 U1A as	433-455	828

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AD-596096.1	A-1142876.1	ACAAUGAG GCUUAUGA AAUGA	NM_000345.3 _625- 645 C21U s	625-645	739	A-1142877.1	UCAUUUCA UAAGCCUC AUUGUCA	NM_000345.3 _623- 645 G1A as	623-645	829
AD-596100.1	A-1142884.1	UGAGGCUU AUGAAUG CCUUA	NM_000345.3 _629- 649 C21U s	629-649	740	A-1142885.1	UAAGGCAU UUCAAAG CCUCAUU	NM_000345.3 _627- 649 G1A as	627-649	830
AD-596124.1	A-1142932.1	GGAAGGGU AUCAGAC UACGA	NM_000345.3 _653- 673 A21U s	653-673	741	A-1142933.1	UCGUAGTC UUGAUACC CUUCUC	NM_000345.3 _651- 673 U1A as	651-673	831
AD-596126.1	A-1142936.1	AAGGUUAU CAAGACUA CGAAA	NM_000345.3 _655- 675 C21U s	655-675	742	A-1142937.1	UUUCGUAG UUUGAUUA CCCUUCC	NM_000345.3 _653- 675 G1A as	653-675	832
AD-596127.1	A-1142938.1	AGGUUAUC AAGACUAC GAACA	NM_000345.3 _656- 676 C21U s	656-676	743	A-1142939.1	UGUUCGTA GUUUGAU ACCUUUC	NM_000345.3 _654- 676 G1A as	654-676	833
AD-596128.1	A-1142940.1	GGUAUUA AGACUACG AACCA	NM_000345.3 _657-677 s	657-677	744	A-1142941.1	UGGUUCGU AGUCUUGA UACCCUU	NM_000345.3 _655-677 as	655-677	834
AD-596129.1	A-1142942.1	GGUAUCAA GACUACGA ACCUA	NM_000345.3 _658- 678 G21U s	658-678	745	A-1142943.1	UAGGUUCG UAGUCUUG AUACCCU	NM_000345.3 _656- 678 C1A as	656-678	835
AD-596130.1	A-1142944.1	GUAUCAAG ACUACGAA CCUGA	NM_000345.3 _659- 679 A21U s	659-679	746	A-1142945.1	UCAGGUTC GUAGUCUU GAUACCC	NM_000345.3 _657- 679 U1A as	657-679	836
AD-596131.1	A-1142946.1	UAUCAAGA CUACGAAC CUGAA	NM_000345.3 _660- 680 A21U s	660-680	747	A-1142947.1	UUCAGGTU CGUAGUCU UGAUACC	NM_000345.3 _658- 680 U1A as	658-680	837
AD-596133.1	A-1142950.1	UCAAGACU ACGAACCU GAAGA	NM_000345.3 _662- 682 C21U s	662-682	748	A-1142951.1	UCUUCAGG UUCGUAGU CUUGAUA	NM_000345.3 _660- 682 G1A as	660-682	838
AD-596137.1	A-1142958.1	GACUACGA ACCUGAAG CCUAA	NM_000345.3 _666- 686 A21U s	666-686	749	A-1142959.1	UUAAGGCTU CAGGUUCG UAGUCUU	NM_000345.3 _664- 686 U1A as	664-686	839
AD-596144.1	A-1142972.1	AACCUAGAA GCCUAGA AUAAA	NM_000345.3 _673-693 s	673-693	750	A-1142973.1	UUAUUUCU UAGGCUUC AGGUUCG	NM_000345.3 _671-693 as	671-693	840
AD-596147.1	A-1142978.1	CUGAAGCC UAAGAAAU AUCUA	NM_000345.3 _676-696 s	676-696	751	A-1142979.1	UAGAUATU UCUUAGGC UUCAGGU	NM_000345.3 _674-696 as	674-696	841
AD-596168.1	A-1143020.1	UGCUCCA GUUUCUUG AGAUU	NM_000345.3 _697- 717 C21U s	697-717	752	A-1143021.1	UUAUCUAA GAAACUGG GAGCAAA	NM_000345.3 _695- 717 G1A as	695-717	842
AD-596169.1	A-1143022.1	GCUCCCAG UUUCUUGA GAUCA	NM_000345.3 _698-718 s	698-718	753	A-1143023.1	UGAUCUCA AGAAACUG GGAGCAA	NM_000345.3 _696-718 as	696-718	843

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AD-596170.1	A-1143024.1	CUCCAGU UUCUUGAG AUCUA	NM_000345.3 NM_697-719 G21U s	699-719	754	A-1143025.1	UAGAUCTC AAGAAACU GGGAGCA	NM_000345.3 NM_697-719 C1A as	697-719	844
AD-596171.1	A-1143026.1	UCCAGUU UCUUGAGA UCUGA	NM_000345.3 NM_700-720 C21U s	700-720	755	A-1143027.1	UCAGAUUC CAAGAAAC UGGGAGC	NM_000345.3 NM_698-720 G1A as	698-720	845
AD-596172.1	A-1143028.1	CCCAGUU CUUGAGAU CUGCA	NM_000345.3 NM_701-721 s	701-721	756	A-1143029.1	UGCAGATC UCAAGAAA CUGGGAG	NM_000345.3 NM_699-721 as	699-721	846
AD-596175.1	A-1143034.1	AGUUCUU GAGAUUCG CUGAA	NM_000345.3 NM_704-724 C21U s	704-724	757	A-1143035.1	UUCAGCAG AUCUCAAG AAACUGG	NM_000345.3 NM_702-724 G1A as	702-724	847
AD-596177.1	A-1143038.1	UUUCUUGA GAUCUGCU GACAA	NM_000345.3 NM_706-726 G21U s	706-726	758	A-1143039.1	UUGUCAGC AGAUUCUA AGAAACU	NM_000345.3 NM_704-726 C1A as	704-726	848
AD-596215.1	A-1143114.1	AGUGCUCA GUUCCAAU GUGCA	NM_000345.3 NM_744-764 C21U s	744-764	759	A-1143115.1	GGAAACUGA GCACUUG	NM_000345.3 NM_742-764 G1A as	742-764	849
AD-596231.1	A-1143146.1	UUCGCCAG UCAUGACA UUUCA	NM_000345.3 NM_760-780 s	760-780	760	A-1143147.1	UGAAAUUGU CAUGACUG GGCACAU	NM_000345.3 NM_758-780 as	758-780	850
AD-596235.1	A-1143154.1	CCAGUCAU GACAUUUC UCAAA	NM_000345.3 NM_784-804 A21U s	764-784	761	A-1143155.1	UUUGAGAA AUCUCAUG ACUGGGC	NM_000345.3 NM_762-784 U1A as	762-784	851
AD-596283.1	A-1143250.1	CAUCAGCA GUGAUUGA AGUAA	NM_000345.3 NM_812-832 s	812-832	762	A-1143251.1	UUACUUA AUCACUGC UGAUGGA	NM_000345.3 NM_810-832 as	810-832	852
AD-596319.1	A-1143322.1	UUUCACUG AAGUGAAU ACAUA	NM_000345.3 NM_869-889 G21U s	869-889	763	A-1143323.1	UAUGUATU CACUUCAG UGAAAGG	NM_000345.3 NM_867-889 C1A as	867-889	853
AD-596320.1	A-1143324.1	UUCACUGA AGUGAAUA CAUGA	NM_000345.3 NM_870-890 G21U s	870-890	764	A-1143325.1	UCAUGUAU UCACUUA GUGAAAG	NM_000345.3 NM_868-890 C1A as	868-890	854
AD-596322.1	A-1143328.1	CACUGAAG UGAAUACA UGGUA	NM_000345.3 NM_872-892 A21U s	872-892	765	A-1143329.1	UACCAUGU AUUCACUU CAGUGAA	NM_000345.3 NM_870-892 U1A as	870-892	855
AD-596323.1	A-1143330.1	ACUGAAGU GAUACAU GGUAA	NM_000345.3 NM_873-893 G21U s	873-893	766	A-1143331.1	UUACCATG UAUUCACU UCAGUGA	NM_000345.3 NM_871-893 C1A as	871-893	856
AD-596325.1	A-1143334.1	UGAAGUGA AUACAUUG UAGCA	NM_000345.3 NM_875-895 A21U s	875-895	767	A-1143335.1	UGCUACCA UGUAUUA CUUCAGU	NM_000345.3 NM_873-895 U1A as	873-895	857
AD-596326.1	A-1143336.1	GAAGUGAA UACAUUGU AGCAA	NM_000345.3 NM_876-896 G21U s	876-896	768	A-1143337.1	UUGCUACC AUGUAUUC ACUUCAG	NM_000345.3 NM_874-896 C1A as	874-896	858

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-596362.1	A-1143408.1	UGGAUUUU GUGGCUUC AAUCA	NM_000345.3 _912-932_s	912-932	769	A-1143409.1	UGAUUGAA GCCACAAA AUCCACA	NM_000345.3 _910-932_as	910-932	859
AD-596390.1	A-1143464.1	AAAAACAC CUAAGUGA CUACA	NM_000345.3 _951- 971_C21U_s	951-971	770	A-1143465.1	UGUAGUCA CUUAGGUG UUUUUAA	NM_000345.3 _949- 971_G1A_as	949-971	860
AD-596391.1	A-1143466.1	AAACACCC UAAAGUGAC UACCA	NM_000345.3 _952- 972_A21U_s	952-972	771	A-1143467.1	UGGUAGTC ACUUAGGU GUUUUUA	NM_000345.3 _950- 972_U1A_as	950-972	861
AD-596392.1	A-1143468.1	AAACACCU AAGUGACU ACCAA	NM_000345.3 _953- 973_C21U_s	953-973	772	A-1143469.1	UUGGUAGU CACUUAGG UGUUUUU	NM_000345.3 _951- 973_G1A_as	951-973	862
AD-596396.1	A-1143476.1	ACCUAAGU GACUACCA CUUAA	NM_000345.3 _957-977_s	957-977	773	A-1143477.1	UUAGGUGG UAGUCACU UAGGUGU	NM_000345.3 _955-977_as	955-977	863
AD-596402.1	A-1143488.1	GUGACUAC CACUUUUU UCUAA	NM_000345.3 _963- 983_A21U_s	963-983	774	A-1143489.1	UUAGAAAU AAGUGGUA GUCACUU	NM_000345.3 _961- 983_U1A_as	961-983	864
AD-596425.1	A-1143534.1	CUGUUGUU CAGAAUUU GUUAA	NM_000345.3 _1005- 1025_G21U_s	1005-1025	775	A-1143535.1	UUAAACAAC UUCUGAAC AACAGCA	NM_000345.3 _1003- 1025_C1A_as	1003-1025	865
AD-596426.1	A-1143536.1	UGUUGUUC AGAAGUUG UUAGA	NM_000345.3 _1006-1026_s	1006-1026	776	A-1143537.1	UCUAACAA CUUCUGAA CAACAGC	NM_000345.3 _1004-1026_as	1004-1026	866
AD-596427.1	A-1143538.1	GUUGUUCA GAAGUUUG UAGUA	NM_000345.3 _1007- 1027_G21U_s	1007-1027	777	A-1143539.1	UACUAACA ACUUCUGA ACAACAG	NM_000345.3 _1005- 1027_C1A_as	1005-1027	867
AD-596431.1	A-1143546.1	UUCAGAAG UUGUUAGU GAUUA	NM_000345.3 _1011-1031_s	1011-1031	778	A-1143547.1	UAAUCACU AACAAACU CUGAACA	NM_000345.3 _1009-1031_as	1009-1031	868
AD-596436.1	A-1143556.1	AAGUUUUU AGUGUUUU GCUAA	NM_000345.3 _1016-1036_s	1016-1036	779	A-1143557.1	UUAGCAAA UCACUAA AACUUCU	NM_000345.3 _1014-1036_as	1014-1036	869
AD-596469.1	A-1143622.1	UUUUAUUG AUACUGUC UAAAG	NM_000345.3 _1063- 1083_A21U_s	1063-1083	780	A-1143623.1	UCUUAGAC AGUAUCAU UAAAAGA	NM_000345.3 _1061- 1083_U1A_as	1061-1083	870
AD-596477.1	A-1143638.1	AUACUGUC UAAGAAUA AUGAA	NM_000345.3 _1071- 1091_C21U_s	1071-1091	781	A-1143639.1	UUCAUUUU UCUUAGAC AGUAUCA	NM_000345.3 _1069- 1091_G1A_as	1069-1091	871
AD-596515.1	A-1143714.1	AGCAUGAA ACUAGGCA CCUAA	NM_000345.3 _1136-1156_s	1136-1156	782	A-1143715.1	UUAGGUGC AUAUUUUC AUGCUCA	NM_000345.3 _1134-1156_as	1134-1156	872
AD-596517.1	A-1143718.1	CAUGAAAC UAUGCACC UAUAA	NM_000345.3 _1138- 1158_A21U_s	1138-1158	783	A-1143719.1	UUUAAGGU GCAUAGUU UCAUGCU	NM_000345.3 _1136- 1158_U1A_as	1136-1158	873

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-596605.1	A-1143894.1	UUUAUCC AUCUCACU UUAAA	NM_000345.3 _1269-1289_s	1269-1289	784	A-1143895.1	UUUAAAAGU GAGAUAGG AUAAAA	NM_000345.3 _1267-1289_as	1267-1289	874
AD-596606.1	A-1143896.1	UUAUCCA UCUCACUU UAAUA	NM_000345.3 _1270- _1290_A2IU_s	1270-1290	785	A-1143897.1	UUUAAAAG UGAGAUAGG GAUAAAA	NM_000345.3 _1268- _1290_U1A_as	1268-1290	875
AD-596609.1	A-1143902.1	UCCCAUCUC ACUUAAU AAUA	NM_000345.3 _1273- _1293_A2IU_s	1273-1293	786	A-1143903.1	UAUUATA AAGUGAGA UGGGAUA	NM_000345.3 _1271- _1293_U1A_as	1271-1293	876
AD-596709.1	A-1144102.1	AAAUUGA ACAUUAC CCUAA	NM_000345.3 _1399- _1419_C2IU_s	1399-1419	787	A-1144103.1	UUAGGGTU AAUGUCC AUUUUCU	NM_000345.3 _1397- _1419_G1A_as	1397-1419	877
AD-597019.1	A-1144722.1	AUAGCAC AUUUAGC ACAU	NM_000345.3 _1850-1870_s	1850-1870	788	A-1144723.1	UAUGUCU AAUAGUG CUAAUGU	NM_000345.3 _1848-1870_as	1848-1870	878
AD-597232.1	A-1145148.1	UCUCUUC AGGGAAGA UCUAA	NM_000345.3 _2138-2158_s	2138-2158	789	A-1145149.1	UUAGAUCU UCCUGAA AGAGAA	NM_000345.3 _2136-2158_as	2136-2158	879
AD-597297.1	A-1145278.1	AAGUCACU AGUAGAA GUAA	NM_000345.3 _2271- _2291_A2IU_s	2271-2291	790	A-1145279.1	UAUACUTU CUACUAGU GACUUU	NM_000345.3 _2269- _2291_U1A_as	2269-2291	880
AD-597298.1	A-1145280.1	AGUCACUA GUAGAAAG UAUAA	NM_000345.3 _2272- _2292_A2IU_s	2272-2292	791	A-1145281.1	UUUAUACTU UCUACUAG UGACUU	NM_000345.3 _2270- _2292_U1A_as	2270-2292	881
AD-597325.1	A-1145334.1	CAGAAU UCUAGACA UGCUA	NM_000345.3 _2301- _2321_A2IU_s	2301-2321	792	A-1145335.1	UAGCAUGU CUAGAAUA UUCUGUC	NM_000345.3 _2299- _2321_U1A_as	2299-2321	882
AD-597326.1	A-1145336.1	AGAAU CUAGACAU GCUAA	NM_000345.3 _2302- _2322_G2IU_s	2302-2322	793	A-1145337.1	UUAGCATG UCUAGAAU AUUCUGU	NM_000345.3 _2300- _2322_C1A_as	2300-2322	883
AD-597327.1	A-1145338.1	GAUUAU UAGACAU CUAGA	NM_000345.3 _2303- _2323_C2IU_s	2303-2323	794	A-1145339.1	UCUAGCAU GUUAGAA UAUUCUG	NM_000345.3 _2301- _2323_G1A_as	2301-2323	884
AD-597335.1	A-1145354.1	UAGACAU CUAGCAGU UUUA	NM_000345.3 _2311- _2331_A2IU_s	2311-2331	795	A-1145355.1	UAUAAACU GCUAGCAU GUCUAGA	NM_000345.3 _2309- _2331_U1A_as	2309-2331	885
AD-597397.1	A-1145478.1	GAGGAUG AGUGACUA UAAGA	NM_000345.3 _2381- _2401_G2IU_s	2381-2401	796	A-1145479.1	UCUUUAAG UCACUCAU UCCUCU	NM_000345.3 _2379- _2401_C1A_as	2379-2401	886
AD-597398.1	A-1145480.1	AGGAUGA GUGACU AAGGA	NM_000345.3 _2382- _2402_A2IU_s	2382-2402	797	A-1145481.1	UCCUATA GUCACUCA UCCUCU	NM_000345.3 _2380- _2402_U1A_as	2380-2402	887
AD-597404.1	A-1145492.1	GAGUGACU AUAGGAU GGUUA	NM_000345.3 _2388- _2408_A2IU_s	2388-2408	798	A-1145493.1	UAACCATCC UUUAAGUC ACUCAU	NM_000345.3 _2386- _2408_U1A_as	2386-2408	888

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-597409.1	A-1145502.1	ACUUAAG GAUGGUUA CCAUA	NM_000345.3 _2393- 2413 A21U s	2393-2413	799	A-1145503.1	UAUGGUAA CCAUCUU AUAGUCA	NM_000345.3 _2391- 2413 UIA as	2391-2413	889
AD-597410.1	A-1145504.1	CUAUAAGG AUGGUUAC CAUAA	NM_000345.3 _2394- 2414 G21U s	2394-2414	800	A-1145505.1	UUAUGGTA ACCAUCCU UAUAGUC	NM_000345.3 _2392- 2414 CIA as	2392-2414	890
AD-597417.1	A-1145518.1	GAUGGUUA CCAUAAGAA ACUUA	NM_000345.3 _2401- 2421 C21U s	2401-2421	801	A-1145519.1	UAAGUUTC UAUGGUAA CCAUCU	NM_000345.3 _2399- 2421 GIA as	2399-2421	891
AD-597443.1	A-1145570.1	ACUACUAC AGAGUGCU AAGCA	NM_000345.3 _2445-2465 s	2445-2465	802	A-1145571.1	UGCUUAGC ACUCUGUA GUAGUCU	NM_000345.3 _2443-2465 as	2443-2465	892
AD-597455.1	A-1145594.1	UGCUAAGC UGCAUGUG UCAUA	NM_000345.3 _2457- 2477 C21U s	2457-2477	803	A-1145595.1	UAUGACAC AUCGAGCU UAGCACU	NM_000345.3 _2455- 2477 GIA as	2455-2477	893
AD-597459.1	A-1145602.1	AAGCUGCA UGUGUCAU CUUAA	NM_000345.3 _2461- 2481 C21U s	2461-2481	804	A-1145603.1	UUAAGATG ACACAUGC AGCUUAG	NM_000345.3 _2459- 2481 GIA as	2459-2481	894
AD-597460.1	A-1145604.1	AGCUGCAU GUGUCAUC UUACA	NM_000345.3 _2462- 2482 A21U s	2462-2482	805	A-1145605.1	UGUAAAGU GACACAUG CAGCUUA	NM_000345.3 _2460- 2482 UIA as	2460-2482	895
AD-597534.1	A-1145752.1	CAGUUAU UUCAGGAA GGUUA	NM_000345.3 _2553- 2573 A21U s	2553-2573	806	A-1145753.1	UAACCUCC UGAAUAU ACUGUU	NM_000345.3 _2551- 2573 UIA as	2551-2573	896
AD-597569.1	A-1145822.1	AAUUCUAC CUAAAGCA GCAUA	NM_000345.3 _2599- 2619 A21U s	2599-2619	807	A-1145823.1	UAUGCUGC UUUAGGUA GAUUUA	NM_000345.3 _2597- 2619 UIA as	2597-2619	897
AD-597861.1	A-1146406.1	AGUCCUAG GUUUUUU UGCAA	NM_000345.3 _2951- 2971 G21U s	2951-2971	808	A-1146407.1	UUGCAAAA UAAACCUA GGACUGG	NM_000345.3 _2949- 2971 CIA as	2949-2971	898
AD-597864.1	A-1146412.1	CCUAGGUU UAUUUUGC AGACA	NM_000345.3 _2954-2974 s	2954-2974	809	A-1146413.1	UGUCUGCA AAUAAAC CUAGGAC	NM_000345.3 _2952-2974 as	2952-2974	899
AD-597894.1	A-1146472.1	CCAAGUUA UUCAGCCU CAUAA	NM_000345.3 _2984-3004 s	2984-3004	810	A-1146473.1	UUUAGGAG CUAGAUAA CUUGGA	NM_000345.3 _2982-3004 as	2982-3004	900
AD-597898.1	A-1146480.1	GUUAUUA GCCUCAUA UGACA	NM_000345.3 _2988-3008 s	2988-3008	811	A-1146481.1	UGUCAUUA GAGGCUGA AUACCU	NM_000345.3 _2986-3008 as	2986-3008	901
AD-597899.1	A-1146482.1	UUUUCAG CCUCAUUA GACUA	NM_000345.3 _2989- 3009 C21U s	2989-3009	812	A-1146483.1	UAGUCATA UGAGGCUG AAUAAU	NM_000345.3 _2987- 3009 GIA as	2987-3009	902
AD-597900.1	A-1146484.1	UAUUCAGC CUCAUAUG ACUCA	NM_000345.3 _2990- 3010 C21U s	2990-3010	813	A-1146485.1	UGAGUCAU AUGAGGCU GAUAAAC	NM_000345.3 _2988- 3010 GIA as	2988-3010	903

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-597925.1	A-1146534.1	UCGGCUUU ACCAAAC AGUUA	NM_000345.3 _3015- 3035 C21U s	3015-3035	814	A-1146535.1	UAAUCGTU UUGGUAAA GCCGACC	NM_000345.3 _3013- 3035 G1A as	3013-3035	904
AD-597927.1	A-1146538.1	GGCUUAC CAAAACAG UUCAA	NM_000345.3 _3017- 3037 G21U s	3017-3037	815	A-1146539.1	UUGAACTG UUUUGGUA AAGCCGA	NM_000345.3 _3015- 3037 C1A as	3015-3037	905
AD-597937.1	A-1146558.1	AAACAGUU CAGAGUGC ACUUA	NM_000345.3 _3027-3047 s	3027-3047	816	A-1146559.1	UAAUGGCA CUCUGAAC UGUUUUG	NM_000345.3 _3025-3047 as	3025-3047	906
AD-597946.1	A-1146576.1	AGAGUGCA CUUUGGCA CACAA	NM_000345.3 _3036- 3056 A21U s	3036-3056	817	A-1146577.1	UUGUGUGC CAAAGUGC ACUCUGA	NM_000345.3 _3034- 3056 U1A as	3034-3056	907
AD-597972.1	A-1146628.1	AACAGAAC AAUCUAAU GUGUA	NM_000345.3 _3062- 3082 G21U s	3062-3082	818	A-1146629.1	UACACATU AGAUUGUU CUGUUCC	NM_000345.3 _3060- 3082 C1A as	3060-3082	908
AD-597974.1	A-1146632.1	CAGAACAA UCUAAUGU GUGGA	NM_000345.3 _3064-3084 s	3064-3084	819	A-1146633.1	UCCACACA UUAGAUG UUCUGUU	NM_000345.3 _3062-3084 as	3062-3084	909
AD-597984.1	A-1146652.1	UAUUGUGU GCUUUGGU AUUCA	NM_000345.3 _3074- 3094 C21U s	3074-3094	820	A-1146653.1	UGAAUACC AAACCACA CAUUAAG	NM_000345.3 _3072- 3094 G1A as	3072-3094	910
AD-597988.1	A-1146660.1	GUGUGGUU UGGUAUUC CAAGA	NM_000345.3 _3078-3098 s	3078-3098	821	A-1146661.1	UCUUGGAA UACCAAC CACACAU	NM_000345.3 _3076-3098 as	3076-3098	911
AD-597989.1	A-1146662.1	UGUGGUUU GGUAUUC AAGUA	NM_000345.3 _3079- 3099 G21U s	3079-3099	822	A-1146663.1	UACUUGGA AUACCAAA CCACACA	NM_000345.3 _3077- 3099 C1A as	3077-3099	912
AD-464229.1	A-900784.1	AUGAAAGG ACUUCAA AGGCA	NM_000345.3 _276- 296 C21U s	276-296	1187	A-900785.1	UGCCUUUG AAAGUCCU UUCAUGA	NM_000345.3 _274- 296 G1A as	274-296	1279
AD-464313.1	A-900952.1	AAAGAGGG UGUUCUCU AUGUA	NM_000345.3 _363-383 s	363-383	1188	A-900953.1	UACAUAGA GAACACCC UCUUUUG	NM_000345.3 _361-383 as	361-383	1280
AD-464314.1	A-900954.1	AAGAGGGU GUUCUCUA UGUAA	NM_000345.3 _364- 384 G21U s	364-384	1189	A-900955.1	UUACAUAG AGAACACC CUCUUUU	NM_000345.3 _362- 384 C1A as	362-384	1281
AD-464559.1	A-901440.1	UGAGGCUU AUGAAUG CCUUA	NM_000345.3 _629- 649 C21U s	629-649	1190	A-901441.1	UAGGGCAU UUCAUAG CCUCAU	NM_000345.3 _627- 649 G1A as	627-649	1282
AD-464585.1	A-901492.1	AAGGUUUA CAAGACUA CGAAA	NM_000345.3 _655- 675 C21U s	655-675	1191	A-901493.1	UUUCGUAG UCUUGAUA CCCUUCC	NM_000345.3 _653- 675 G1A as	653-675	1283
AD-464586.1	A-901494.1	AGGUUAUC AAGACUAC GAACA	NM_000345.3 _656- 676 C21U s	656-676	1192	A-901495.1	UGUUCGUA GUUUUGAU ACCCUUC	NM_000345.3 _654- 676 G1A as	654-676	1284

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-464590.1	A-901502.1	UAUCAAGA CUACGAAC CUGAA	NM_000345.3 _660-680_s	660-680	1193	A-901503.1	UUCAGGUU CGUAGUCU UGAUACC	NM_000345.3 _658-680_as	658-680	1285
AD-464592.1	A-901506.1	UCAAGACU ACGAACCU GAAGA	NM_000345.3 _662-682_C21U_s	662-682	1194	A-901507.1	UCUUCAGG UUCGUAGU CUUGAUA	NM_000345.3 _660-682_G1A_as	660-682	1286
AD-464603.1	A-901528.1	AACUGGAA GCCUAAGA AAUAA	NM_000345.3 _673-693_s	673-693	1195	A-901529.1	UUUUUUUU UAGGCUUC AGGUUUG	NM_000345.3 _671-693_as	671-693	1287
AD-464606.1	A-901534.1	CUGAAGCC UAAGAAAU AUCUA	NM_000345.3 _676-696_s	676-696	1196	A-901535.1	UAGUAUUU UCUUAGGC UUCAGGU	NM_000345.3 _674-696_as	674-696	1288
AD-464630.1	A-901582.1	UCCAGAGU UCUUGAGA UCUGA	NM_000345.3 _700-720_C21U_s	700-720	1197	A-901583.1	UCAGAUUU CAAGAAAC UGGGAGC	NM_000345.3 _698-720_G1A_as	698-720	1289
AD-464634.1	A-901590.1	AGUUUCUU GAGAUUCG CUGAA	NM_000345.3 _704-724_C21U_s	704-724	1198	A-901591.1	UUCAGCAG AUCUCAAG AAACUGG	NM_000345.3 _702-724_G1A_as	702-724	1290
AD-464636.1	A-901594.1	UUUCUUUA GAUCUGCU GACAA	NM_000345.3 _706-726_G21U_s	706-726	1199	A-901595.1	UUGUCAGC AGAUUCUA AGAAACU	NM_000345.3 _704-726_C1A_as	704-726	1291
AD-464694.1	A-901710.1	CCAGUCAU GACAUUUC UCAAA	NM_000345.3 _764-784_s	764-784	1200	A-901711.1	UUUGAGAA AUCACUGC ACUGGC	NM_000345.3 _762-784_as	762-784	1292
AD-464742.1	A-901806.1	CAUCAGCA GUGAUUGA AGUAA	NM_000345.3 _812-832_s	812-832	1201	A-901807.1	UUACUUAU AUCACUGC UGAUGGA	NM_000345.3 _810-832_as	810-832	1293
AD-464778.1	A-901878.1	UUUCACUG AAGUGAAU ACAUAA	NM_000345.3 _869-889_G21U_s	869-889	1202	A-901879.1	UAUGUAUU CACUUCAG UGAAAGG	NM_000345.3 _867-889_C1A_as	867-889	1294
AD-464779.1	A-901880.1	UUCACUGA AGUGAAUA CAUGA	NM_000345.3 _870-890_G21U_s	870-890	1203	A-901881.1	UCAUGUAU UCACUUAU GUGAAAG	NM_000345.3 _868-890_C1A_as	868-890	1295
AD-464782.1	A-901886.1	ACUGAAAGU GAUUAACU GGUAA	NM_000345.3 _873-893_G21U_s	873-893	1204	A-901887.1	UUACCAUG UAUUCACU UCAGUGA	NM_000345.3 _871-893_C1A_as	871-893	1296
AD-464813.1	A-901948.1	ACCUAAAGU GACUACCA CUUAA	NM_000345.3 _957-977_s	957-977	1205	A-152515.1	UUAAAGUGG UAGUCACU UAGGUGU	NM_007308.2 _869-890_as	955-977	1297
AD-464814.1	A-901949.1	GUGACUAC CACUUAUU UCUAA	NM_000345.3 _963-983_s	963-983	1206	A-152519.1	UUAGAAAU AAGUGGUA GUCACUU	NM_007308.2 _875-896_as	961-983	1298
AD-464815.1	A-901950.1	UGACUACC ACUUAUUU CUAAA	NM_000345.3 _964-984_s	964-984	1207	A-152535.1	UUUAGAAA UAAAGUGGU AGUCACU	NM_007308.2 _876-897_as	962-984	1299

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-464856.1	A-902029.1	AAACACCU AAGUGACU ACCAA	NM_000345.3 _953- 973 C21U s	953-973	1208	A-902030.1	UUGGUAGU CACUAGG UGUUUU	NM_000345.3 _951- 973 G1A as	951-973	1300
AD-464859.1	A-902035.1	CACCUAAG UGACUACC ACUUA	NM_000345.3 _956-976_s	956-976	1209	A-902036.1	UAAGUGGU AGUCACUU AGGUGUU	NM_000345.3 _954-976_as	954-976	1301
AD-464884.1	A-902085.1	CUGUUGUU CAGAAAGU GUUAA	NM_000345.3 _1005- 1025 G21U s	1005-1025	1210	A-902086.1	UUAACAAC UUCUGAAC AACAGCA	NM_000345.3 _1003- 1025 C1A as	1003-1025	1302
AD-464885.1	A-902087.1	UGUUGUUC AGAAAGUUG UUAGA	NM_000345.3 _1006-1026_s	1006-1026	1211	A-902088.1	UCUAAACA CUUCUGAA CAACAGC	NM_000345.3 _1004-1026_as	1004-1026	1303
AD-464886.1	A-902089.1	GUUGUUCA GAAGUUGU UAGUA	NM_000345.3 _1007- 1027 G21U s	1007-1027	1212	A-902090.1	ACUUAACA ACUUCUGA ACAACAG	NM_000345.3 _1005- 1027 C1A as	1005-1027	1304
AD-464928.1	A-902173.1	UUUUA AUG AUACUGUC UAAGA	NM_000345.3 _1063-1083_s	1063-1083	1213	A-902174.1	UCUUAGAC AGUAUCAU UAAAAGA	NM_000345.3 _1061-1083_as	1061-1083	1305
AD-464936.1	A-902189.1	AUACUGUC UAAGAAUA AUGAA	NM_000345.3 _1071- 1091 C21U s	1071-1091	1214	A-902190.1	UUCAUUU UCUUAGAC AGUAUCA	NM_000345.3 _1069- 1091 G1A as	1069-1091	1306
AD-464977.1	A-902268.1	AGCAUGAA ACU AUGCA CCUAA	NM_000345.3 _1136-1156_s	1136-1156	1215	A-902269.1	UUAGGUGC GCAUAGUU AUGCUC	NM_000345.3 _1134-1156_as	1134-1156	1307
AD-464978.1	A-902270.1	CAUGAAAC UAUGCACC UAUAA	NM_000345.3 _1138-1158_s	1138-1158	1216	A-902271.1	UUUAGGU GCAUAGUU UCAUGCU	NM_000345.3 _1136-1158_as	1136-1158	1308
AD-465064.1	A-902441.1	UUUAUCCC AUCUCACU UUAAA	NM_000345.3 _1269-1289_s	1269-1289	1217	A-902442.1	UUUAAAGU GAGAUGGG AUAAAA	NM_000345.3 _1267-1289_as	1267-1289	1309
AD-465065.1	A-902443.1	UUAUCCCA UCUCACUU UAAUA	NM_000345.3 _1270-1290_s	1270-1290	1218	A-902444.1	UUUAAAG UGAGAUGG GAUAAAA	NM_000345.3 _1268-1290_as	1268-1290	1310
AD-465068.1	A-902449.1	UCCCAUCUC ACUUUAU AAUA	NM_000345.3 _1273-1293_s	1273-1293	1219	A-902450.1	UAUUUUUA AAGUGAGA UGGGAUA	NM_000345.3 _1271-1293_as	1271-1293	1311
AD-465168.1	A-902649.1	AAAUUGGA ACAUU AAC CCUAA	NM_000345.3 _1399- 1419 C21U s	1399-1419	1220	A-902650.1	UUAGGGUU AAUGUCC AUUUUCU	NM_000345.3 _1397- 1419 G1A as	1397-1419	1312
AD-465691.1	A-903695.1	UCUCUUC AGGGAAGA UCUAA	NM_000345.3 _2138-2158_s	2138-2158	1221	A-903696.1	UUAGAUCU UCCUGAA AGAGAAA	NM_000345.3 _2136-2158_as	2136-2158	1313
AD-465756.1	A-903825.1	AAGUCACU AGUAGAAA GUAAU	NM_000345.3 _2271-2291_s	2271-2291	1222	A-903826.1	UUACUUU CUACUAGU GACUUUU	NM_000345.3 _2269-2291_as	2269-2291	1314

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-465757.1	A-903827.1	AGUCACUA GUAGAAAG UAUAA	NM_000345.3 _2272-2292_s	2272-2292	1223	A-903828.1	UUUAACUU UCUACUAG UGACUUU	NM_000345.3 _2270-2292_as	2270-2292	1315
AD-465760.1	A-903833.1	CACUAGUA GAAAGUAU AAUUA	NM_000345.3 _2275-2295_s	2275-2295	1224	A-903834.1	UAAUUAUA CUUUCUAC UAGUGAC	NM_000345.3 _2273-2295_as	2273-2295	1316
AD-465784.1	A-903881.1	CAGAAUUA UCUAGACA UGCUA	NM_000345.3 _2301-2321_s	2301-2321	1225	A-903882.1	UAGCAUGU CUAGAAUA UUCUGUC	NM_000345.3 _2299-2321_as	2299-2321	1317
AD-465785.1	A-903883.1	AGAAUAUU CUAGACAU GCUAA	NM_000345.3 _2302-2322_G2IU_s	2302-2322	1226	A-903884.1	UUAGCAUG UCUAGAAU AUUCUGU	NM_000345.3 _2300-2302_C1A_as	2300-2322	1318
AD-465794.1	A-903901.1	UAGACAUG CUAGCAGU UUUAU	NM_000345.3 _2311-2331_s	2311-2331	1227	A-903902.1	UUAAACUU GCUAGCAU GUCUAGA	NM_000345.3 _2309-2331_as	2309-2331	1319
AD-465876.1	A-904065.1	GAUGGUUA CCAUAGAA ACUUA	NM_000345.3 _2401-2421_C2IU_s	2401-2421	1228	A-904066.1	UAAAGUUC UAUGGUAA CCAUCUU	NM_000345.3 _2399-2421_G1A_as	2399-2421	1320
AD-465918.1	A-904149.1	AAGCUGCA UGUGUCAU CUUAA	NM_000345.3 _2461-2481_C2IU_s	2461-2481	1229	A-904150.1	UUAAAGUG ACACAUGC AGCUUAG	NM_000345.3 _2459-2481_G1A_as	2459-2481	1321
AD-465919.1	A-904151.1	AGUGCAU GUGUCAUC UUACA	NM_000345.3 _2462-2482_s	2462-2482	1230	A-904152.1	UGUAAGAU GACACAUG CAGCUUA	NM_000345.3 _2460-2482_as	2460-2482	1322
AD-466320.1	A-904953.1	AGUCCUAG GUUUAUUU UGCAA	NM_000345.3 _2951-2971_G2IU_s	2951-2971	1231	A-904954.1	UUGCAAAA UAAACCUA GGACUGG	NM_000345.3 _2949-2971_C1A_as	2949-2971	1323
AD-466384.1	A-905081.1	UCGGCUUU ACCAAAC AGUUA	NM_000345.3 _3015-3035_C2IU_s	3015-3035	1232	A-905082.1	UAAACUGUU UUGGUAAA GCCGACC	NM_000345.3 _3013-3035_G1A_as	3013-3035	1324
AD-466386.1	A-905085.1	GGCUUUAC CAAAACAG UUCAA	NM_000345.3 _3017-3037_G2IU_s	3017-3037	1233	A-905086.1	UUGAACUG UUUUGGUA AAGCCGA	NM_000345.3 _3015-3037_C1A_as	3015-3037	1325
AD-466443.1	A-905199.1	UAAUGUGU GGUUUGGU AUUCA	NM_000345.3 _3074-3094_C2IU_s	3074-3094	1234	A-905200.1	UGAAUACC AAACCACA CAUUAAGA	NM_000345.3 _3072-3094_G1A_as	3072-3094	1326
AD-475646.1	A-919481.1	AUACAUCU UUAGCCAU GGAUA	NM_00104245 _1.2_294-314_G2IU_s	294-314	1235	A-919482.1	UAUCUUGU GCUAAAGA UGUAUUU	NM_00104245 _1.2_292-314_C1A_as	292-314	1327
AD-475661.1	A-919511.1	GGAUGUGU UCAUGAAA GGACA	NM_00104245 _1.2_310-330_s	310-330	1236	A-919512.1	UGUCCUUU CAUGAACA CAUCCAU	NM_00104245 _1.2_308-330_as	308-330	1328
AD-475663.1	A-919515.1	AUGUGUUC AUGAAAGG ACTUA	NM_00104245 _1.2_312-332_s	312-332	1237	A-919516.1	UAAGUCCU UUCAUGAA CACAUCC	NM_00104245 _1.2_310-332_as	310-332	1329

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-475666.1	A-919521.1	UGUUCAG AAAGGACU UUCAA	NM_00104245 1.2_315-335_s	315-335	1238	A-919522.1	UUGAAAGU CCUUCAU GAACACA	NM_00104245 1.2_313-335 as	313-335	1330
AD-475723.1	A-919635.1	GAGUCCUC UAUGUAGG UUCCA	NM_00104245 1.2_414-434_s	414-434	1239	A-919636.1	UGGAACCU ACAAGAG GACUCCC	NM_00104245 1.2_412-434 as	412-434	1331
AD-475728.1	A-919645.1	CUCUAGU AGGUUCCA AAACA	NM_00104245 1.2_419-439_s	419-439	1240	A-919646.1	UGUUUGG AACCUACA UAGAGA	NM_00104245 1.2_417-439 as	417-439	1332
AD-475761.1	A-919709.1	UGGUCAU GGAGUGAC AACAA	NM_00104245 1.2_450-470 G21U_s	450-470	1241	A-919710.1	UGUUGUC ACUCCAUG AACCACU	NM_00104245 1.2_448-470 C1A as	448-470	1333
AD-475765.1	A-919717.1	UCAUGGAG UGACAACA GUGGA	NM_00104245 1.2_454-474 C21U_s	454-474	1242	A-919718.1	UCCACUGU UGUACACUC CAUGAAC	NM_00104245 1.2_452-474 G1A as	452-474	1334
AD-475888.1	A-901440.1	UGAGGCUU AUGAAUUG CCUUA	NM_000345.3 629-649 C21U_s	629-649	1243	A-919961.1	UAAAGGCAU UUAUUAAG CCUCACU	NM_00104245 1.2_671-693 G1A as	627-649	1335
AD-475895.1	A-919973.1	GGAUCCU GGAAGACA UGCCA	NM_00104245 1.2_638-658_s	638-658	1244	A-919974.1	UGGCAUGU CUUCCAGG AUUCCUU	NM_00104245 1.2_636-658 as	636-658	1336
AD-475927.1	A-920037.1	AGUGAGGC UUUUGAAA UGCCA	NM_00104245 1.2_671-691_s	671-691	1245	A-920038.1	UGGCAUUA CAUAAAGCC UCACUGC	NM_00104245 1.2_669-691 as	669-691	1337
AD-475929.1	A-920041.1	AGGCUUUA GAAUUGCC UUCAA	NM_00104245 1.2_675-695 G21U_s	675-695	1246	A-920042.1	UUGAAGGC AUUUCUA AGCCUCA	NM_00104245 1.2_673-695 C1A as	673-695	1338
AD-475930.1	A-920043.1	GGCUUAUG AAUUGCCU UCAGA	NM_00104245 1.2_676-696_s	676-696	1247	A-920044.1	UCUGAAGG CAUUAUUA AAGCCUC	NM_00104245 1.2_674-696 as	674-696	1339
AD-475941.1	A-920064.1	AUGCCUUC AGAGGAAG GCUAA	NM_00104245 1.2_686-706 C21U_s	686-706	1248	A-920065.1	UUAAGCCUU CCUCUGAA GGCAUUU	NM_00104245 1.2_684-706 G1A as	684-706	1340
AD-475942.1	A-920066.1	UGCCUUCA GAGGAAGG CUACA	NM_00104245 1.2_687-707 C21U_s	687-707	1249	A-920067.1	UGUAGCCU UCCUCUGA AGGCAUU	NM_00104245 1.2_685-707 G1A as	685-707	1341
AD-475952.1	A-920086.1	GGAAGGCU ACCAAGAC UAUGA	NM_00104245 1.2_697-717_s	697-717	1250	A-920087.1	UCAUAGUC UUGGUAGC CUUCCUC	NM_00104245 1.2_695-717 as	695-717	1342
AD-475953.1	A-920088.1	GAAGGCUA CCAAGACU AUGAA	NM_00104245 1.2_698-718 G21U_s	698-718	1251	A-920089.1	UUCUAAGU CUUGGUAG CCUUCUU	NM_00104245 1.2_696-718 C1A as	696-718	1343
AD-475954.1	A-920090.1	AAGGCUAC CAAGACUA UGAGA	NM_00104245 1.2_699-719 C21U_s	699-719	1252	A-920091.1	UCUCAUAG UCUUGGUA GCCUUCC	NM_00104245 1.2_697-719 G1A as	697-719	1344

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AD-475955.1	A-920092.1	AGGCUACC AAGACUUAU GAGCA	NM_00104245 1.2_700- 720 C21U s	700-720	1253	A-920093.1	UGCUCUA GUCUUGGU AGCCUUC	NM_00104245 1.2_698- 720 G1A as	698-720	1345
AD-475966.1	A-920114.1	ACUAUGAG CCUGAGGC CUAAA	NM_00104245 1.2_711- 731 G21U s	711-731	1254	A-920115.1	UUUAGGCU UACAGGCUC AUAGUCU	NM_00104245 1.2_709- 731 C1A as	709-731	1346
AD-476025.1	A-920230.1	GCUCUCC AUGGCGUA CAAGA	NM_00104245 1.2_769-789_s	769-789	1255	A-920231.1	UCUUGUAC GCCAUGGA AGAGCAG	NM_00104245 1.2_767- 789 as	767-789	1347
AD-476026.1	A-920232.1	CUCUCCCA UGGCGUAC AAGUA	NM_00104245 1.2_770- 790 G21U s	770-790	1256	A-920233.1	UACUUGUA CGCCAUUG AAGAGCA	NM_00104245 1.2_768- 790 C1A as	768-790	1348
AD-476027.1	A-920234.1	UCUCCAU GGCGUACA AGUA	NM_00104245 1.2_771- 791 C21U s	771-791	1257	A-920235.1	UACUUGU ACGCCAUG GAAGAGC	NM_00104245 1.2_769- 791 G1A as	769-791	1349
AD-476029.1	A-920238.1	UCCAUUGG CGUACAAG UGCUA	NM_00104245 1.2_773- 793 C21U s	773-793	1258	A-920239.1	UAGCACUU GUACGCCA UGGAAGA	NM_00104245 1.2_771- 793 G1A as	771-793	1350
AD-476030.1	A-920240.1	UCCAUUGG GUACAAGU GCUCA	NM_00104245 1.2_774-794_s	774-794	1259	A-920241.1	UGAGCACU UGUAGGCC AUGGAAG	NM_00104245 1.2_772- 794 as	772-794	1351
AD-476032.1	A-920244.1	CAUGGGGU ACAAAGUC UCAGA	NM_00104245 1.2_776-796_s	776-796	1260	A-920245.1	UCUGAGCA CUUGUACG CCACAUU	NM_00104245 1.2_774- 796 as	774-796	1352
AD-476041.1	A-920262.1	UGUGCCCA GUC AUGAC CUUUA	NM_00104245 1.2_802-822_s	802-822	1261	A-920263.1	UAAAGGUC AUGACUGG GCACAUU	NM_00104245 1.2_800- 822 as	800-822	1353
AD-476058.1	A-920291.1	ACCUUUC UCAAGCU GUACA	NM_00104245 1.2_816-836_s	816-836	1262	A-920292.1	UGUACAGC UUUGAGAA AAGGUCA	NM_00104245 1.2_814- 836 as	814-836	1354
AD-476061.1	A-920297.1	UUUUCUCA AAGCUGUA CAGUA	NM_00104245 1.2_819- 839 G21U s	819-839	1263	A-920298.1	UACUGUAC AGCUUUGA GAAAAGG	NM_00104245 1.2_817- 839 C1A as	817-839	1355
AD-476089.1	A-920353.1	UCUCCAU CAGCAGUG AUCGA	NM_00104245 1.2_850- 870 G21U s	850-870	1264	A-920354.1	UCGAUCAC UGCUGAUG GAAGACU	NM_00104245 1.2_848- 870 C1A as	848-870	1356
AD-476146.1	A-920466.1	CUGUGGAU AUUGUUGU GGCUA	NM_00104245 1.2_947-967_s	947-967	1265	A-920467.1	UAGCCACA ACAAUUAUC CACAGCA	NM_00104245 1.2_945- 967 as	945-967	1357
AD-476152.1	A-92027.1	AAACACC UAAAGUGAC UACCA	NM_000345.3 _952-972_s	952-972	1266	A-920475.1	UGGUAGUC ACUUAGGU GUUUUAA	NM_00104245 1.2_992- 1014 as	950-972	1358
AD-476192.1	A-920548.1	GAAACUUA AAACACCU AAGUA	NM_00104245 1.2_987- 1007 G21U s	987-1007	1267	A-920549.1	UACUUAGG UGUUUUAA GUUUUCU	NM_00104245 1.2_985- 1007 C1A as	985-1007	1359

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AD-476198.1	A-920560.1	UAAACAC CUAAGUGA CUACA	NM_00104245 1.2_993- 1013 C21U s	993-1013	1268	A-920561.1	UGUAGUCA CUUAGGUG UUUUAAG	NM_00104245 1.2_991- 1013 G1A as	991-1013	1360
AD-476306.1	A-920771.1	AUUAUGUG AGCAUGAG ACUAA	NM_00104245 1.2_1155- 1175 s	1155-1175	1269	A-920772.1	UUAGUCUC AUGUCAC AUAAUUU	NM_00104245 1.2_1153- 1175 as	1153-1175	1361
AD-476309.1	A-920777.1	AUGUGAGC AUGAGACU AUGCA	NM_00104245 1.2_1158- 1178 s	1158-1178	1270	A-920778.1	UGCAUAGU CUCAUGCU CACAUAA	NM_00104245 1.2_1156- 1178 as	1156-1178	1362
AD-476311.1	A-920781.1	GUGAGCAU GAGACUUA GCACA	NM_00104245 1.2_1160- 1180 C21U s	1160-1180	1271	A-920782.1	UGUGCAUA GUCUCAUG CUCACAU	NM_00104245 1.2_1158- 1180 G1A as	1158-1180	1363
AD-476312.1	A-920783.1	UGAGCAUG AGACUUAUG CACCA	NM_00104245 1.2_1161- 1181 s	1161-1181	1272	A-920784.1	UGUGGCAU AGUCUCAU GCUCACA	NM_00104245 1.2_1159- 1181 as	1159-1181	1364
AD-476313.1	A-920785.1	GAGCAUGA GACUAUGC ACCUA	NM_00104245 1.2_1162- 1182 s	1162-1182	1273	A-920786.1	UAGGUGCA UAGUCUCA UGCUCAC	NM_00104245 1.2_1160- 1182 as	1160-1182	1365
AD-476316.1	A-920789.1	AGCAUGAG ACUAUGCA CCUAA	NM_00104245 1.2_1163- 1183 s	1163-1183	1274	A-920790.1	UUAGGUGC UAGUCUC AUGCUCU	NM_00104245 1.2_1161- 1183 as	1161-1183	1366
AD-476317.1	A-920791.1	GCAUGAGA CUAUGCAC CUAUA	NM_00104245 1.2_1164- 1184 s	1164-1184	1275	A-920792.1	UUAUAGGUG CAUAGUCU CAUGCUC	NM_00104245 1.2_1162- 1184 as	1162-1184	1367
AD-476320.1	A-920797.1	UGAGACUA UGCACCUA UAAAA	NM_00104245 1.2_1167- 1187 s	1167-1187	1276	A-920798.1	UUUUAUAG GUGCAUAG UCUCAUG	NM_00104245 1.2_1165- 1187 as	1165-1187	1368
AD-476321.1	A-920799.1	GAGACUUA GCACCUUA AAAAA	NM_00104245 1.2_1168- 1188 s	1168-1188	1277	A-920800.1	UUAUUAUA GGUGCAUA GUCUCAU	NM_00104245 1.2_1166- 1188 as	1166-1188	1369
AD-476344.1	A-920845.1	AUGUGUUU UAUUAAAU UGUGA	NM_00104245 1.2_1216- 1236 s	1216-1236	1278	A-920846.1	UCACAAAGU UAAUAAAA CACAUCA	NM_00104245 1.2_1214- 1236 as	1214-1236	1370
AD-595768.1	A-1142220.1	CAUGAAAG GACUUUCA AAGGA	NM_000345.3 275- 295 C21U s	275-295	1628	A-1142221.1	UCCUUUGA AAGUCCUU UCAUGAA	NM_000345.3 273- 295 G1A as	273-295	1717
AD-595769.2	A-1142222.1	AUGAAAAG ACUUUCAA AGGCA	NM_000345.3 276- 296 C21U s	276-296	1629	A-1142223.1	UGCCUUTG AAAGUCCU UUCAUCA	NM_000345.3 274- 296 G1A as	274-296	1718
AD-595770.1	A-1142224.1	UGAAAGGA CUUUCAAA GGCCA	NM_000345.3 277- 297 A21U s	277-297	1630	A-1142225.1	UGGCCUTU GAAAGUCC UUUCAUG	NM_000345.3 275- 297 U1A as	275-297	1719
AD-595771.1	A-1142226.1	GAAAGGAC UUUCAAG GCCAA	NM_000345.3 278- 298 A21U s	278-298	1631	A-1142227.1	UUGGCCUTU UGAAAGUC CUUUCUAU	NM_000345.3 276- 298 U1A as	276-298	1720

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-595772.1	A-1142228.1	AAAGGACU UUCAAAGG CCAAA	NM_000345.3 _279- 299 G21U s	279-299	1632	A-1142229.1	UUUGGCCU UUGAAAGU CCUUUCA	NM_000345.3 _277- 299 C1A as	277-299	1721
AD-595773.1	A-1142230.1	AAGGACUU UCAAAGGC CAAGA	NM_000345.3 _280- 300 G21U s	280-300	1633	A-1142231.1	UUUUGGCC UUUGAAAG UCCUUUC	NM_000345.3 _278- 300 C1A as	278-300	1722
AD-595774.1	A-1142232.1	AGGACUUU CAAAGGCC AAGGA	NM_000345.3 _281- 301 A21U s	281-301	1634	A-1142233.1	UCCUUGGC CUUUGAAA GUCCUUU	NM_000345.3 _279- 301 U1A as	279-301	1723
AD-595926.2	A-1142536.1	AAGACCAA AGAGCAAG UGACA	NM_000345.3 _435- 455 A21U s	435-455	1635	A-1142537.1	UGUCACU GUCUUUG GUCUUUC	NM_000345.3 _433- 455 U1A as	433-455	1724
AD-595933.1	A-1142550.1	AAGACCAA GUGACAAA UGUUA	NM_000345.3 _442- 462 G21U s	442-462	1636	A-1142551.1	UAAACAUU GUACAUUG CUCUUUG	NM_000345.3 _440- 462 C1A as	440-462	1725
AD-595935.1	A-1142554.1	GACAAAGU GACAAAGU UUGGA	NM_000345.3 _444- 464 A21U s	444-464	1637	A-1142555.1	UCCAACAU UUGUCACU UGUCUUU	NM_000345.3 _442- 464 U1A as	442-464	1726
AD-595936.1	A-1142556.1	AGCAAGUG ACAAUGU UGGAA	NM_000345.3 _445- 465 G21U s	445-465	1638	A-1142557.1	UCCAACA UUUGUCAC UUGUCUU	NM_000345.3 _443- 465 C1A as	443-465	1727
AD-595937.1	A-1142558.1	GCAAGUGA CAAAUGUU GGAGA	NM_000345.3 _446- 466 G21U s	446-466	1639	A-1142559.1	UCUCCAAC AUUUGUCA CUUGCUC	NM_000345.3 _444- 466 C1A as	444-466	1728
AD-595938.1	A-1142560.1	CAAGUGAC AAUUGUUG GAGGA	NM_000345.3 _447- 467 A21U s	447-467	1640	A-1142561.1	UCCUCCAAC AUUUGUCA CUUGCU	NM_000345.3 _445- 467 U1A as	445-467	1729
AD-596098.1	A-1142880.1	AAUGAGGC UUAUGAAA UGCCA	NM_000345.3 _627-647 s	627-647	1641	A-1142881.1	UGGCAUTU CAUAAAGCC UCAUUGU	NM_000345.3 _625-647 as	625-647	1730
AD-596099.1	A-1142882.1	AUGAGGCU UAUGAAAU GCCUA	NM_000345.3 _628-648 s	628-648	1642	A-1142883.1	UAGGCATU UCAUAAAGC CUCAUUG	NM_000345.3 _626-648 as	626-648	1731
AD-596100.2	A-1142884.1	UGAGGCUU AUGAAUG CCUUA	NM_000345.3 _629- 649 C21U s	629-649	1643	A-1142885.1	UAAAGGCAU UUCAUAAAG CCUCAUU	NM_000345.3 _627- 649 G1A as	627-649	1732
AD-596101.1	A-1142886.1	GAGGCUUA UGAAUUGC CUUCA	NM_000345.3 _630-650 s	630-650	1644	A-1142887.1	UGAAGGCA UUUCAUAA GCCUCAU	NM_000345.3 _628-650 as	628-650	1733
AD-596215.2	A-1143114.1	AGUGCUCA GUUCCAAU GUGCA	NM_000345.3 _744- 764 C21U s	744-764	1645	A-1143115.1	UGCACATU GGAACUGA GCACUUG	NM_000345.3 _742- 764 G1A as	742-764	1734
AD-596217.1	A-1143118.1	UGCUCAGU UCCAAUGU GCCCA	NM_000345.3 _746- 766 A21U s	746-766	1646	A-1143119.1	UGGCACA UUGGAACU GAGCACU	NM_000345.3 _744- 766 U1A as	744-766	1735

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-596276.1	A-1143236.1	AGUCUUC AUCAGCAG UGAUA	NM_000345.3 _805-825_s	805-825	1647	A-1143237.1	UAUACCTGC UGAUGGAA GACUUC	NM_000345.3 _803-825_as	803-825	1736
AD-596326.2	A-1143336.1	GAAGUGAA UACAUUGU AGCAA	NM_000345.3 _876- 896_G21U_s	876-896	1648	A-1143337.1	UUGCUACC AUGUAUUC ACUUCAG	NM_000345.3 _874- 896_C1A_as	874-896	1737
AD-596328.1	A-1143340.1	AGUGAUA CAUGGUAG CAGGA	NM_000345.3 _878- 898_G21U_s	878-898	1649	A-1143341.1	UCCUGCTAC CAUGUAUU CACUUC	NM_000345.3 _876- 898_C1A_as	876-898	1738
AD-596390.2	A-1143464.1	AAAACAC CUAAGUGA CUACA	NM_000345.3 _951- 971_C21U_s	951-971	1650	A-1143465.1	UGUAGUCA CUUAGGUG UUUUUA	NM_000345.3 _949- 971_G1A_as	949-971	1739
AD-596391.2	A-1143466.1	AAAACAC UAAGUGAC UACCA	NM_000345.3 _952- 972_A21U_s	952-972	1651	A-1143467.1	UGUAGTGC ACUUAAGU GUUUUA	NM_000345.3 _950- 972_U1A_as	950-972	1740
AD-596392.2	A-1143468.1	AAACACU AAGUGACU ACCAA	NM_000345.3 _953- 973_G21U_s	953-973	1652	A-1143469.1	UUGUAGU CACUUAAG UGUUUU	NM_000345.3 _951- 973_G1A_as	951-973	1741
AD-596393.1	A-1143470.1	AACACCUA AGUGACUA CCACA	NM_000345.3 _954-974_s	954-974	1653	A-1143471.1	UGUGGUAG UCACUUAAG GUGUUU	NM_000345.3 _952-974_as	952-974	1742
AD-596394.1	A-1143472.1	ACACCUAA GUGACUAC CACUA	NM_000345.3 _955-975_s	955-975	1654	A-1143473.1	UAGUGGTA GUACUUUA GGUGUU	NM_000345.3 _953-975_as	953-975	1743
AD-596395.1	A-1143474.1	CACCUAAG UGACUACC ACUUA	NM_000345.3 _956- 976_A21U_s	956-976	1655	A-1143475.1	UAAGUGGU AGUCACUU AGGUGU	NM_000345.3 _954- 976_U1A_as	954-976	1744
AD-596396.2	A-1143476.1	ACCUAAGU GACUACCA CUUAA	NM_000345.3 _957-977_s	957-977	1656	A-1143477.1	UUAAGUGG UAGUCACU UAGGUGU	NM_000345.3 _955-977_as	955-977	1745
AD-596397.1	A-1143478.1	CCUAAAGU ACUACCAC UUUAU	NM_000345.3 _958-978_s	958-978	1657	A-1143479.1	UAUAAAGTG GUAGUCAC UUAGGUG	NM_000345.3 _956-978_as	956-978	1746
AD-596398.1	A-1143480.1	CUAAGUGA CUACCACU UAUUA	NM_000345.3 _959-979_s	959-979	1658	A-1143481.1	UAAUAAAGU GGUAGUCA CUUAGGU	NM_000345.3 _957-979_as	957-979	1747
AD-596401.1	A-1143486.1	AGUGACUA CCACUUAU UUCUA	NM_000345.3 _962- 982_A21U_s	962-982	1659	A-1143487.1	UAGAATA AGUGGUAG UCACUUA	NM_000345.3 _960- 982_U1A_as	960-982	1748
AD-596402.2	A-1143488.1	GUGACUAC CACUUAUU UCUAA	NM_000345.3 _963- 983_A21U_s	963-983	1660	A-1143489.1	UUAGAAU AAGUGGUA GUCACUU	NM_000345.3 _961- 983_U1A_as	961-983	1749
AD-596403.1	A-1143490.1	UGACUACC ACUUAUUU CUAAA	NM_000345.3 _964- 984_A21U_s	964-984	1661	A-1143491.1	UUUAGAAA UUAAGUGGU AGUCACU	NM_000345.3 _962- 984_U1A_as	962-984	1750

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-596521.1	A-1143726.1	AAACUAG CACCUAUA AAUAA	NM_000345.3 _1142- 1162 C21U s	1142-1162	1662	A-1143727.1	UUUUUUU AGGUGCAU AGUUUCA	NM_000345.3 _1140- 1162 G1A as	1140-1162	1751
AD-596564.1	A-1143812.1	UUGUGUU GUUAUAA AUGGA	NM_000345.3 _1204-1224_s	1204-1224	1663	A-1143813.1	UCCAUTA UAUACAAA CACAAU	NM_000345.3 _1202-1224_as	1202-1224	1752
AD-689314.1	A-1142220.1	CAUGAAG GACUUUCA AAGGA	NM_000345.3 _275- 295 C21U s	275-295	1664	A-900783.1	UCCUUUGA AAGUCCUU UCAUGAA	NM_000345.3 _273- 295 G1A as	273-295	1753
AD-689315.1	A-1142222.1	AUGAAAG ACUUCAA AGGCA	NM_000345.3 _276- 296 C21U s	276-296	1665	A-900785.1	UGCCUUUG AAGUCCUU UUCAUGA	NM_000345.3 _274- 296 G1A as	274-296	1754
AD-689316.1	A-1142224.1	UGAAAGGA CUUUCAAA GGCCA	NM_000345.3 _277- 297 A21U s	277-297	1666	A-900787.1	UGGCCUUU GAAAGUCC UUUCAUG	NM_000345.3 _275-297_as	275-297	1755
AD-689317.1	A-1142226.1	GAAAGGAC UUUCAAG GCCAA	NM_000345.3 _278- 298 A21U s	278-298	1667	A-900789.1	UUGGCCUU UGAAAGUC CUUCAU	NM_000345.3 _276-298_as	276-298	1756
AD-689318.1	A-1142228.1	AAAGGACU UUCAAGG CCAAA	NM_000345.3 _279- 299 G21U s	279-299	1668	A-152531.1	UUUGGCCU UUUGAAAG CCUUUCA	NM_007308.2 _275- 296 G21A as	277-299	1757
AD-689319.1	A-1142230.1	AAGGACUU UCAAGGC CAAGA	NM_000345.3 _280- 300 G21U s	280-300	1669	A-900791.1	UCUUGGCC UUUGAAAG UCCUUUC	NM_000345.3 _278- 300 C1A as	278-300	1758
AD-689320.1	A-1142232.1	AGGACUUU CAAGGCC AAGGA	NM_000345.3 _281- 301 A21U s	281-301	1670	A-900793.1	UCCUUGGC CUUUGAAA GUCCUUU	NM_000345.3 _279-301_as	279-301	1759
AD-689452.1	A-1142536.1	AAGACAA AGAGCAAG UGACA	NM_000345.3 _435- 455 A21U s	435-455	1671	A-901101.1	UGUCACUU GUCUUUG GUCUUUC	NM_000345.3 _433-455_as	433-455	1760
AD-689459.1	A-1142550.1	AAGACAA GUGACAAA UGUUA	NM_000345.3 _442- 462 G21U s	442-462	1672	A-901109.1	UAAACAUU GUCAUUUG CUCUUUG	NM_000345.3 _440- 462 C1A as	440-462	1761
AD-689461.1	A-1142554.1	GAGCAAGU GACAAAG UUGGA	NM_000345.3 _444- 464 A21U s	444-464	1673	A-152527.1	UCCAACAU UUUGACAC UUGCUUC	NM_007308.2 _440-461_as	442-464	1762
AD-689462.1	A-1142556.1	AGCAAGUG ACAAUGU UGGAA	NM_000345.3 _445- 465 G21U s	445-465	1674	A-901113.1	UCCAACA UUUGUCAC UUGCUUC	NM_000345.3 _443- 465 C1A as	443-465	1763
AD-689463.1	A-1142558.1	GCAAGUGA CAAAUGUU GGAGA	NM_000345.3 _446- 466 G21U s	446-466	1675	A-901115.1	UCUCCAAC AUUGUCA CUUGCUC	NM_000345.3 _444- 466 C1A as	444-466	1764
AD-689464.1	A-1142560.1	CAAGUGAC AAUUGUUG GAGGA	NM_000345.3 _447- 467 A21U s	447-467	1676	A-901117.1	UCCUCCAAC AUUGUCA CUUGCU	NM_000345.3 _445-467_as	445-467	1765

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-689615.1	A-1142880.1	AAUGAGGC UUAUGAAA UGCCA	NM_000345.3 _627-647_s	627-647	1677	A-901437.1	UGGCAUUU CAUAAGCC UCAUUGU	NM_000345.3 _625-647_as	625-647	1766
AD-689616.1	A-1142882.1	AUGAGGCU UAUGAAAU GCCUA	NM_000345.3 _628-648_s	628-648	1678	A-901439.1	UAGGCAUU UCAAAAGC CUCAUUG	NM_000345.3 _626-648_as	626-648	1767
AD-689617.1	A-1142884.1	UGAGGCUU AUGAAAU CCUUA	NM_000345.3 _629-649_C21U_s	629-649	1679	A-901441.1	UAAGGCAU UUCAAAG CCUCAU	NM_000345.3 _627-649_G1A_as	627-649	1768
AD-689618.1	A-1142886.1	GAGGCUUA UGAAAU CUUCA	NM_000345.3 _630-650_s	630-650	1680	A-901443.1	UGAAGGCA UUUCAUAA GCCUCAU	NM_000345.3 _628-650_as	628-650	1769
AD-689747.1	A-1143102.1	UGUACAAG UGCUCAGU UCCAA	NM_000345.3 _738-758_A21U_s	738-758	1681	A-1316021.1	UUGGAACU GAGCACUU GUACAA	XM_00555542 _0.2_905-927_as	736-758	1770
AD-689748.1	A-1143104.1	GUACAAGU GCUCAGUU CCAAA	NM_000345.3 _739-759_s	739-759	1682	A-1316022.1	UUUGGAAC UGAGCACU UGUACAA	XM_00555542 _0.2_906-928_as	737-759	1771
AD-689753.1	A-1143114.1	AGUGCUCA GUUCCAAU GUGCA	NM_000345.3 _744-764_C21U_s	744-764	1683	A-901671.1	UGCACAUU GGAACUGA GCACUUG	NM_000345.3 _742-764_G1A_as	742-764	1772
AD-689755.1	A-1143118.1	UGCUCAGU UCCAAUGU GCCCA	NM_000345.3 _746-766_A21U_s	746-766	1684	A-901675.1	UGGGCACA UUGGAACU GAGCACU	NM_000345.3 _744-766_as	744-766	1773
AD-689786.1	A-1143232.1	GAAGUCUU CCAUCAGC AGUGA	NM_000345.3 _803-823_A21U_s	803-823	1685	A-1316023.1	UCACUGCU GAUGGAAG ACUUCAA	XM_00555542 _0.2_970-992_as	801-823	1774
AD-689787.1	A-1143234.1	AAGUCUUC CAUCAGCA GUGAA	NM_000345.3 _804-824_s	804-824	1686	A-1316024.1	UUCACUGC UGAUGGAA GACUUCA	XM_00555542 _0.2_971-993_as	802-824	1775
AD-689788.1	A-1143236.1	AGUCUUC AUCAGCAG UGAUA	NM_000345.3 _805-825_s	805-825	1687	A-901793.1	UAUCACUG CUGAUGGA AGACUUC	NM_000345.3 _803-825_as	803-825	1776
AD-689835.1	A-1143336.1	GAAGUGAA UACAUGGU AGCAA	NM_000345.3 _876-896_G21U_s	876-896	1688	A-901893.1	UUGCUACC AUGUAUUC ACUUCAG	NM_000345.3 _874-896_C1A_as	874-896	1777
AD-689907.1	A-1316093.1	UGAAGUCU UCCAUCAG CAGUA	XM_00555542 _0.2_971-991_G21A_s	971-991	1689	A-1316094.1	UACUGCUG AUGGAAGA CUCAAA	XM_00555542 _0.2_969-991_C1U_as	969-991	1778
AD-689925.1	A-1143462.1	UAAAACA CCUAAUG ACUAA	NM_000345.3 _950-970_C21U_s	950-970	1690	A-1316128.1	UUAAGUCAC UUAGGUGU UUUUA	XM_00555542 _0.2_1117-1139_G1U_as	948-970	1779
AD-689926.1	A-1143464.1	AAAACAC CUAAGUGA CUACA	NM_000345.3 _951-971_C21U_s	951-971	1691	A-902026.1	UGUAGUCA CUAAGGUG UUUUUA	NM_000345.3 _949-971_G1A_as	949-971	1780

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-689927.1	A-1143466.1	AAACACC UAAAGUGAC UACCA	NM_000345.3 952- 972 A21U s	952-972	1692	A-902028.1	UGGUAGUC ACUUAGGU GUUUUA	NM_000345.3 950-972_as	950-972	1781
AD-689928.1	A-1143468.1	AAACACCU AAGUGACU ACCAA	NM_000345.3 953- 973 C21U s	953-973	1693	A-902030.1	UUGGUAGU CACUUAGG UGUUUU	NM_000345.3 951- 973 G1A as	951-973	1782
AD-689929.1	A-1143470.1	AACACCUA AGUGACUA CCACA	NM_000345.3 954-974 s	954-974	1694	A-902032.1	UGUGGUAG UCACUUAG GUGUUU	NM_000345.3 952-974 as	952-974	1783
AD-689930.1	A-1143472.1	ACACCUAA GUGACUAC CACUA	NM_000345.3 955-975 s	955-975	1695	A-902034.1	UAGUGGUA GUCACUUA GGUGUUU	NM_000345.3 953-975 as	953-975	1784
AD-689931.1	A-1143474.1	CACCUAAG UGACUACC ACUUA	NM_000345.3 956- 976 A21U s	956-976	1696	A-902036.1	UAAAGUGGU AGUCACUU AGGUGUU	NM_000345.3 954-976_as	954-976	1785
AD-689932.1	A-1143476.1	ACCUAAGU GACUACCA CUUAA	NM_000345.3 957-977 s	957-977	1697	A-152515.1	UUAAAGUGG UAGUCACU UAGGUGU	NM_007308.2 869-890_as	955-977	1786
AD-689933.1	A-1143478.1	CCUAAAGU ACUACCAC UUUAU	NM_000345.3 958-978 s	958-978	1698	A-902038.1	UUAAGUGG GUAGUCAC UUAGGUG	NM_000345.3 956-978_as	956-978	1787
AD-689934.1	A-1143480.1	CUAAGUGA CUACCACU UAUUA	NM_000345.3 959-979 s	959-979	1699	A-902040.1	UAAUAAGU GGUAGUCA CUUAGGU	NM_000345.3 957-979_as	957-979	1788
AD-689935.1	A-1143482.1	UAAGUGAC UACCACUU AUUUA	NM_000345.3 960- 980 C21U s	960-980	1700	A-902042.1	UAAUAAG UGGUAGUC ACUUAGG	NM_000345.3 958-980_as	958-980	1789
AD-689936.1	A-1143484.1	AAGUGACU ACCACUUA UUUCA	NM_000345.3 961-981 s	961-981	1701	A-902044.1	UGAAAUAA GUGGUAGU CACUUAG	NM_000345.3 959-981_as	959-981	1790
AD-689937.1	A-1143486.1	AGUGACUA CCACUUUA UUCUA	NM_000345.3 962- 982 A21U s	962-982	1702	A-902046.1	UAGAAAUU AGUGGUAG UCACUUA	NM_000345.3 960-982_as	960-982	1791
AD-689938.1	A-1143488.1	GUGACUAC CACUUUUU UCUAA	NM_000345.3 963- 983 A21U s	963-983	1703	A-152519.1	UUAGAAAU AAGUGGUA GUCACUU	NM_007308.2 875-896_as	961-983	1792
AD-689939.1	A-1143490.1	UGACUACC ACUUUUUU CUAAA	NM_000345.3 964- 984 A21U s	964-984	1704	A-152535.1	UUUAGAAA UAAUGGUG AGUCACU	NM_007308.2 876-897_as	962-984	1793
AD-690068.1	A-1143726.1	AAACUAAU CACCUAUA AAUAA	NM_000345.3 1142- 1162 C21U s	1142-1162	1705	A-902279.1	UUUUUUUU AGGUGCAU AGUUUCA	NM_000345.3 1140- 1162 G1A as	1140-1162	1794
AD-690079.1	A-1316237.1	AUGUGUUU UAUUAAAU UGUGA	XM_00555542 0.2 1358- 1378 s	1358-1378	1706	A-920846.1	UCACAAGU UAAUAAAA CACAUCA	NM_00104245 1.2 1214- 1236 as	1356-1378	1795

Duplex ID	sense name	sensetrans	Accession No.	Range	SEQ ID NO:	antisense name	antisense trans	Accession No.	Range	SEQ ID NO:
AD-690080.1	A-1316238.1	UGUGUUUU AUUAAUUU GUGUA	XM_00555542 0.2_1359- 1379 s	1359-1379	1707	A-920848.1	UACACAAG UUAAUAAA ACACAUC	NM_00104245 1.2_1215- 1237 as	1357-1379	1796
AD-690092.1	A-1143812.1	UUUGUUUU GUUAUAAA AUGGA	NM_000345.3 _1204-1224_s	1204-1224	1708	A-902360.1	UCCAUUUA UAUACAAA CACAAAG	NM_000345.3 _1202-1224_as	1202-1224	1797
AD-691823.1	A-1143102.1	UGUACAAG UGCUCAGU UCCAA	NM_000345.3 _738- 758_A21U s	738-758	1709	A-1318408.1	UUUGAACU GAGCACUU GUACAAG	XM_00555542 0.2_905- 927 as	736-758	1798
AD-691824.1	A-1143104.1	GUACAAGU GCUCAGUU CCAAA	NM_000345.3 _739-759 s	739-759	1710	A-1318409.1	UUUGAAC UAGCACU UGUACAA	XM_00555542 0.2_906- 928 as	737-759	1799
AD-691843.1	A-1316093.1	UGAAGUCU UCCAUCAG CAGUA	XM_00555542 0.2_971- 991_G21A s	971-991	1711	A-1318428.1	UACUGCTG AUGGAAGA CUUCAA	XM_00555542 0.2_969- 991_C1U as	969-991	1800
AD-691844.1	A-1143232.1	GAAUCUUU CCAUCAGC AGUA	NM_000345.3 _803- 823_A21U s	803-823	1712	A-1318429.1	UCACUGCU GAUGGAAG ACUCAA	XM_00555542 0.2_970- 992 as	801-823	1801
AD-691845.1	A-1143234.1	AAGUCUUC CAUCAGCA GUGAA	NM_000345.3 _804-824_s	804-824	1713	A-1318430.1	UUCACUGC UGAUGGAA GACUUCA	XM_00555542 0.2_971- 993 as	802-824	1802
AD-691875.1	A-1143462.1	UAAAAACA CCUAAAGU ACUAA	NM_000345.3 _950- 970_C21U s	950-970	1714	A-1318460.1	UUAGUCAC UUAGGUGU UUUUAAA	XM_00555542 0.2_1117- 1139_G1U as	948-970	1803
AD-691953.1	A-1316237.1	AUGUGUUU UAUUAAAU UGUGA	XM_00555542 0.2_1358- 1378 s	1358-1378	1715	A-1318538.1	UCACAAGU UAAUAAAA CACAUCA	XM_00555542 0.2_1356- 1378 as	1356-1378	1804
AD-691954.1	A-1316238.1	UGUGUUUU AUUAAUUU GUGUA	XM_00555542 0.2_1359- 1379 s	1359-1379	1716	A-1318539.1	UACACAAG UUAAUAAA ACACAUC	XM_00555542 0.2_1357- 1379 as	1357-1379	1805

Table 4. SNCA In Vitro Screen Performed by RNA-seq in BE(2)-C Cells.

Duplex ID (10 nM dose)	On target knock down (%)
AD-595724	-13.05%
AD-595769	-75.51%
AD-595854	-82.58%
AD-595855	-57.20%
AD-595866	-55.77%
AD-595926	-84.84%
AD-596096	-14.89%
AD-596100	-7.98%
AD-596124	-84.38%
AD-596126	-18.96%
AD-596127	-59.08%

Duplex ID (10 nM dose)	On target knock down (%)
AD-596128	-64.34%
AD-596129	-55.98%
AD-596130	-85.95%
AD-596131	-43.71%
AD-596133	-82.68%
AD-596137	-86.68%
AD-596144	-72.65%
AD-596147	-43.35%
AD-596168	-80.88%
AD-596169	-68.13%
AD-596170	-81.96%

Duplex ID (10 nM dose)	On target knock down (%)
AD-596171	-75.26%
AD-596172	-89.10%
AD-596175	-82.02%
AD-596177	-87.61%
AD-596215	-78.99%
AD-596231	-85.14%
AD-596235	-61.45%
AD-596283	-66.76%
AD-596319	-80.92%
AD-596320	-67.82%
AD-596322	-60.23%
AD-596323	-87.91%
AD-596325	-25.11%
AD-596326	-28.25%
AD-596362	-66.57%
AD-596390	-48.41%
AD-596391	-67.87%
AD-596392	-75.16%
AD-596396	-72.01%
AD-596402	-73.89%
AD-596425	-76.17%
AD-596426	-70.03%
AD-596427	-59.75%
AD-596431	-65.79%
AD-596436	-80.94%
AD-596469	-47.84%
AD-596477	-39.38%
AD-596515	-65.28%
AD-596517	-71.68%
AD-596605	-38.29%
AD-596606	-44.42%
AD-596609	-36.07%
AD-596709	2.38%
AD-597019	-11.57%

Duplex ID (10 nM dose)	On target knock down (%)
AD-597232	-10.43%
AD-597297	-28.11%
AD-597298	-20.19%
AD-597325	-17.38%
AD-597326	-29.27%
AD-597327	-15.39%
AD-597335	-32.70%
AD-597397	-26.07%
AD-597398	-36.26%
AD-597404	-30.07%
AD-597409	16.73%
AD-597410	-7.55%
AD-597417	-4.79%
AD-597443	-22.35%
AD-597455	-1.69%
AD-597459	-34.53%
AD-597460	-24.46%
AD-597534	-17.19%
AD-597569	-20.02%
AD-597861	-8.34%
AD-597864	-16.26%
AD-597894	-42.84%
AD-597898	-25.02%
AD-597899	9.74%
AD-597900	0.69%
AD-597925	-12.17%
AD-597927	-10.96%
AD-597937	-19.23%
AD-597946	-11.95%
AD-597972	-26.16%
AD-597974	-25.23%
AD-597984	-30.85%
AD-597988	-10.49%
AD-597989	-17.11%

Table 5. SNCA Knock-Down Assessed by qPCR and RNA-seq in BE(2)-C cells.

DuplexID	% of Message Remaining			Average	STD
	Passage 1	Passage 2	Passage 3		
AD-596477.1	47	69	58	58	11.01992
AD-596235.1	33	50	36	40	9.269913
AD-597232.1	61	99	75	78	19.29934
AD-597298.1	67	80	63	70	8.825857

DuplexID	% of Message Remaining				Average	STD
	Passage 1	Passage 2	Passage 3			
AD-596171.1	28	35	19		27	8.130847
AD-597925.1	61	83	73		72	10.78871
AD-597927.1	74	78	79		77	2.519625
AD-596319.1	20	25	20		22	3.215917
AD-596396.1	29	41	29		33	6.936593
AD-596402.1	26	39	27		31	7.3094
AD-597459.1	63	84	75		74	10.58517
AD-596131.1	39	54	45		46	7.784137
AD-596320.1	34	48	33		38	8.408126
AD-596517.1	26	40	27		31	7.905545
AD-596606.1	52	80	65		66	14.14451
AD-596609.1	59	84	59		67	14.7158
AD-597297.1	69	90	72		77	11.20186
AD-597417.1	62	85	68		72	11.85658
AD-596100.1	66	81	71		73	7.790383
AD-596172.1	20	31	17		23	7.374681
AD-596425.1	25	36	24		29	6.681592
AD-596427.1	30	45	29		34	8.806158
AD-596515.1	22	38	26		29	8.173514
AD-596605.1	51	69	54		58	9.276456
AD-597325.1	72	90	68		77	11.41825
AD-597326.1	67	92	68		76	13.75651
AD-597335.1	64	94	70		76	16.07252
AD-597460.1	64	101	79		81	18.54527
AD-597984.1	63	92	71		75	14.71759
AD-595854.1	23	33	19		25	7.324429
AD-595855.1	35	46	35		39	6.328028
AD-596126.1	126	83	1946		718	1063.644
AD-596127.1	44	64	41		50	12.77985
AD-596133.1	25	35	18		26	8.279378
AD-596144.1	24	36	26		29	6.505101
AD-596147.1	39	72	51		54	16.82907
AD-596175.1	21	31	25		26	4.630111
AD-596177.1	19	30	18		22	6.563827
AD-596283.1	29	48	45		41	10.09666
AD-596323.1	20	32	18		23	7.852572
AD-596392.1	25	37	22		28	7.888691
AD-596426.1	30	42	30		34	7.000756
AD-596469.1	46	65	53		55	9.591057
AD-596709.1	106	122	98		109	12.03926
AD-595769.1	22	38	23		27	8.923867
AD-597861.1	71	94	84		83	11.82668
AD-597937.1	70	98	78		82	14.10247
AD-64543.7*	66	94	84		81	13.81149
AD-597988.1	74	93	81		82	9.744747

DuplexID	% of Message Remaining				Passage 3	Average	STD
	Passage 1	Passage 2	Passage 3	Passage 4			
AD-597989.1	62	83	79		75	11.5116	
AD-596129.1	32	49	44		42	8.432036	
AD-596170.1	21	31	19		24	6.210674	
AD-596322.1	41	68	49		38	16.32933	
AD-596390.1	32	52	46		43	10.17705	
AD-596391.1	26	38	27		31	6.732695	
AD-596436.1	24	36	27		29	6.453891	
AD-597019.1	63	84	78		75	10.74946	
AD-595724.1	63	79	85		76	11.66526	
AD-597404.1	63	80	83		75	10.98295	
AD-597409.1	67	94	102		88	18.29244	
AD-597410.1	66	99	80		82	16.35816	
AD-597864.1	66	98	76		80	16.31143	
AD-597946.1	61	90	72		74	15.02109	
AD-597972.1	83	87	74		81	6.890878	
AD-597974.1	70	95	78		81	12.69742	
AD-595866.1	26	42	35		34	7.742897	
AD-596128.1	28	35	84		49	30.52729	
AD-596137.1	17	26	18		20	4.83207	
AD-596215.1	18	32	20		23	7.6555	
AD-596326.1	45	69	64		59	12.6858	
AD-597327.1	62	83	81		75	11.18543	
AD-597569.1	58	87	88		77	17.01053	
AD-597894.1	64	86	77		76	11.04145	
AD-597899.1	74	97	121		97	23.53896	
AD-597900.1	73	95	101		90	14.8509	
AD-595926.1	24	30	21		25	4.467998	
AD-596168.1	21	31	19		24	6.44147	
AD-596169.1	29	39	29		32	6.03107	
AD-596231.1	19	31	19		23	6.895029	
AD-596362.1	30	42	33		35	6.325971	
AD-58643.17	42	54	45		47	6.360314	
AD-597398.1	75	94	85		85	9.515257	
AD-597443.1	68	82	76		75	6.898931	
AD-597534.1	69	94	83		82	12.47207	
mock	74	103	90		89	14.74418	
AD-596096.1	63	86	73		74	11.67158	
AD-596124.1	26	35	27		29	5.345602	
AD-596130.1	22	30	21		24	5.05537	
AD-596325.1	48	69	64		60	11.16311	
AD-596431.1	27	40	34		34	6.512177	
mock	78	99	113		97	17.23253	
AD-597397.1	62	87	75		75	12.38764	
AD-597455.1	63	94	92		83	17.36572	
AD-597898.1	131	89	84		101	26.05352	

DuplexID	% of Message Remaining				Average	STD
	Passage 1	Passage 2	Passage 3	Passage 4		
mock	74	98	95	89		12.99399
mock	233	100	104	146		75.6163

* No KD for TMP, since TMP does not express in Be(2)C

Table 6. Knockdown of SNCA in HeLa and B16F10 Cells Assessed *Via* Branched DNA Method, Relative to GAPDH.

Duplex ID	shOP	HeLa				B16F10			
		10 nM	StDev	0.1 nM	StDev	10 nM	StDev	0.1 nM	StDev
AD-690092.1	12.5	48.1	7.8	83.4	4.8	15.8	1.9	78.0	2.3
AD-596564.1	12.5	71.0	7.1	97.1	6.4	22.7	10.4	85.7	4.7
AD-689461.1	15.4	15.9	5.6	97.8	13.0	18.5	2.4	109.2	4.1
AD-595935.1	15.4	40.1	3.6	109.4	5.0	42.8	1.2	90.6	22.4
AD-596401.1	19.5	20.5	1.1	44.4	14.2	15.0	3.2	69.5	4.6
AD-689937.1	19.5	23.6	1.4	45.2	6.8	15.4	2.7	40.9	4.5
AD-689936.1	23	23.4	2.7	27.1	3.3	19.6	4.5	48.6	8.1
AD-689463.1	23.9	10.6	0.1	92.4	8.8	14.6	1.1	106.9	8.8
AD-595937.1	23.9	15.0	1.5	103.6	10.3	18.6	4.0	105.3	11.7
AD-690080.1	27.1	57.8	9.6	90.2	5.6	16.4	1.7	78.1	9.7
AD-691954.1	27.1	71.4	12.1	108.2	7.0	15.9	1.4	89.2	10.6
AD-689464.1	28	13.6	2.1	92.8	23.9	18.5	2.0	145.3	29.1
AD-595938.1	28	48.1	3.0	105.8	9.4	58.6	3.3	122.5	25.3
AD-689753.1	30.4	10.4	0.4	76.5	3.0	16.3	1.6	90.0	11.7
AD-596215.2	30.4	13.8	0.9	98.2	7.9	17.1	5.2	91.0	17.4
AD-689935.1	32.5	21.8	2.9	76.1	6.2	13.6	1.5	75.7	5.4
AD-690079.1	33.7	43.0	10.3	82.0	1.4	15.0	2.5	59.1	1.8
AD-691953.1	33.7	89.4	2.2	104.9	7.1	19.1	3.9	82.9	2.8
AD-689938.1	38.5	19.9	0.9	41.6	5.3	17.8	3.2	37.5	5.4
AD-596402.2	38.5	23.6	0.8	84.2	7.2	21.3	1.4	90.7	5.6
AD-595768.1	38.6	50.3	4.3	61.1	22.2	63.9	13.7	101.3	2.8
AD-689314.1	38.6	18.5	2.5	82.8	8.1	22.7	3.3	101.2	3.7
AD-689459.1	40.7	8.3	1.0	59.9	4.7	11.8	2.8	84.2	4.3
AD-595933.1	40.7	25.0	3.0	98.6	2.8	24.6	2.1	87.9	8.5
AD-689462.1	46.7	11.4	1.4	82.1	13.6	14.7	0.8	113.5	5.9
AD-595936.1	46.7	71.0	9.6	103.9	11.7	67.7	6.2	107.1	12.0
AD-689934.1	51.3	24.3	1.1	59.5	3.3	16.7	2.1	86.7	8.1
AD-596398.1	51.3	76.3	3.2	105.2	12.5	49.0	8.4	93.5	4.0
AD-690068.1	57.9	25.5	2.0	72.0	7.2	14.2	3.3	67.6	4.3
AD-596521.1	57.9	44.7	2.3	106.0	9.9	40.9	5.4	89.1	5.1
AD-595769.2	63.8	10.3	1.5	72.5	5.9	21.6	2.2	96.3	12.9
AD-689315.1	63.8	12.8	0.9	73.5	5.1	20.3	4.3	115.4	6.3
AD-689615.1	65.7	11.5	1.4	85.5	2.0	19.0	3.4	98.9	3.5
AD-596098.1	65.7	59.2	2.4	99.5	3.6	81.7	12.6	88.5	4.0
AD-689939.1	65.8	24.9	6.9	53.2	7.7	17.0	2.1	46.0	4.4
AD-596403.1	65.8	26.3	3.3	80.0	3.9	23.7	3.3	79.7	3.7

Duplex ID	shOP	HeLa			B16F10		
		10 nM	StDev	0.1 nM	10 nM	StDev	0.1 nM
AD-596328.1	67.6	49.7	5.4	103.5	107.9	9.2	92.0
AD-689316.1	69.2	22.2	4.8	96.2	39.0	10.9	90.0
AD-595770.1	69.2	15.8	4.3	96.8	23.5	7.1	95.2
AD-689748.1	71.5	7.0	0.5	48.9	10.0	1.9	37.5
AD-691824.1	71.5	11.4	1.1	81.7	18.7	3.4	77.3
AD-689933.1	73.2	27.4	4.7	86.7	37.2	4.0	87.3
AD-596397.1	73.2	19.8	3.8	90.3	18.6	3.5	95.4
AD-689747.1	75.6	14.9	4.2	48.8	13.8	0.3	42.5
AD-691823.1	75.6	31.8	6.8	84.4	29.0	1.5	103.9
AD-689788.1	75.7	29.8	2.3	91.4	20.6	1.0	95.0
AD-596276.1	75.7	66.1	2.4	105.0	42.6	7.9	104.9
AD-596100.2	76.6	93.7	6.8	83.8	91.5	3.5	114.4
AD-689617.1	76.6	83.1	4.1	95.4	99.2	4.8	118.5
AD-689452.1	81.4	11.7	6.1	76.2	15.6	2.4	97.8
AD-689616.1	81.4	45.0	6.9	94.4	77.2	3.7	107.6
AD-595926.2	81.4	15.6	2.4	98.5	23.1	4.7	89.5
AD-596099.1	81.4	48.6	3.3	105.0	78.4	5.2	104.3
AD-689929.1	84.2	34.5	2.4	63.8	17.7	1.0	70.6
AD-596393.1	84.2	30.9	5.2	68.8	30.9	4.3	91.9
AD-691845.1	85.1	86.0	24.9	92.0	49.4	7.9	85.1
AD-689787.1	85.1	35.4	5.1	97.6	25.2	3.7	93.1
AD-689926.1	88.2	25.5	1.9	71.6	22.8	1.0	65.8
AD-596390.2	88.2	50.8	19.0	93.7	35.4	6.7	83.6
AD-595771.1	89.3	102.8	8.2	99.0	80.3	5.8	86.8
AD-689317.1	89.3	61.6	8.5	107.8	71.2	13.5	99.0
AD-689835.1	89.9	17.7	3.5	93.9	77.2	3.8	102.6
AD-596326.2	89.9	61.3	4.9	109.9	102.8	4.8	94.6
AD-691843.1	90.1	15.0	1.6	73.2	19.1	5.2	91.8
AD-689907.1	90.1	12.0	2.4	87.2	12.2	2.5	104.3
AD-689755.1	90.2	13.6	1.3	86.2	16.6	2.6	88.3
AD-596217.1	90.2	15.1	1.9	89.0	16.8	2.1	74.7
AD-689928.1	90.6	29.1	3.4	61.1	18.3	2.4	69.4
AD-596392.2	90.6	31.2	1.6	71.1	19.1	0.9	69.6
AD-596394.1	92.8	29.5	4.4	74.5	28.9	4.7	100.6
AD-689930.1	92.8	21.5	2.1	87.4	23.1	2.3	79.3
AD-689925.1	93	36.0	5.3	51.5	18.4	1.9	64.1
AD-691875.1	93	26.1	2.6	66.8	25.1	2.7	83.8
AD-691844.1	93.8	14.6	3.0	88.7	15.7	1.5	84.1
AD-689786.1	93.8	12.2	1.9	91.5	11.2	6.3	79.5
AD-689320.1	95.4	22.2	1.9	86.2	60.4	8.6	105.4
AD-595774.1	95.4	18.6	2.3	88.9	37.9	10.4	94.6
AD-689927.1	96.1	31.6	2.6	76.1	17.7	0.7	69.0
AD-596391.2	96.1	22.9	1.2	95.4	27.4	2.3	89.4
AD-689318.1	96.5	21.8	2.2	93.4	33.5	10.2	99.3
AD-596396.2	96.5	19.3	6.9	93.9	26.2	6.9	101.7

Duplex ID	shOP	HeLa			B16F10		
		10 nM	StDev	0.1 nM	10 nM	StDev	0.1 nM
AD-689932.1	96.5	26.4	2.1	98.6	37.9	6.1	87.6
AD-595772.1	96.5	90.0	24.0	106.3	89.1	4.3	96.4
AD-689618.1	96.8	54.1	9.2	95.6	55.4	5.1	105.9
AD-596101.1	96.8	82.6	10.2	109.6	81.6	5.3	96.8
AD-596395.1	97.2	22.1	1.4	81.1	17.6	3.4	87.0
AD-689931.1	97.2	22.3	2.2	83.8	22.6	3.0	72.8
AD-689319.1	98.1	16.6	2.1	91.8	43.0	5.3	104.2
AD-595773.1	98.1	9.0	0.3	93.9	22.6	3.3	85.1

Table 7. Knockdown of SNCA in Human BE(2)-C Cells Assessed *Via* qPCR, and Observed Inhibition of SNCA Expressed *Via* Dual-Luciferase psiCHECK2 Vector in Cos-7 Cells.

Duplex ID	human BE(2)C qPCR				human Dual-Luc				mouse Dual-Luc			
	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD
AD-476320	17.8	5.5	48.7	16.3	15.3	4.0	103.8	3.2	43.1	7.3	100.6	8.4
AD-464778	18.9	3.0	46.1	16.8	18.2	3.1	102.4	10.0	100.3	7.9	94.4	5.9
AD-464314	19.2	1.6	30.7	6.0	8.9	2.1	56.5	6.1	74.9	5.7	80.9	2.8
AD-464782	19.3	6.0	57.0	7.5	18.1	3.8	83.7	5.6	101.1	17.8	97.6	10.9
AD-476089	19.4	1.6	51.3	8.7	62.0	3.5	98.0	3.2	60.3	15.3	106.5	12.6
AD-464694	20.0	2.4	23.8	5.3	19.6	2.9	101.6	9.0	87.8	12.2	90.0	7.7
AD-475661	20.8	6.2	62.3	3.5	16.4	3.5	79.3	8.4	34.4	6.7	89.4	10.2
AD-464630	22.0	2.6	33.4	5.6	50.2	6.6	85.7	8.3	99.5	19.0	90.5	9.2
AD-476317	23.0	0.5	44.9	7.2	21.4	3.0	80.9	7.2	45.2	6.2	107.0	8.4
AD-464313	23.4	4.5	63.1	14.1	23.5	3.6	83.6	8.8	74.4	7.1	93.2	6.4
AD-464634	23.5	6.9	29.8	11.8	17.4	1.4	76.0	5.1	79.0	16.2	96.8	10.8
AD-476041	23.7	4.8	85.3	5.7	43.5	7.8	108.8	11.7	39.6	6.4	103.4	13.9
AD-475930	23.8	6.9	86.2	11.8	98.6	8.1	89.5	5.5	96.6	4.2	100.5	7.2
AD-464779	24.2	5.1	47.0	10.5	18.2	0.3	82.5	9.5	104.0	10.5	103.1	18.9
AD-475927	24.7	4.8	105.9	14.4	119.1	9.5	92.1	8.8	89.3	11.2	97.5	14.7
AD-464590	24.7	4.4	53.4	12.4	38.5	4.9	88.3	10.9	104.3	11.8	106.0	6.7
AD-464585	25.2	5.5	63.6	10.8	76.6	12.4	89.0	7.1	98.4	7.1	87.9	10.2
AD-464636	25.8	9.1	37.8	8.6	15.6	2.8	77.6	5.3	93.4	9.6	93.2	7.4
AD-464977	25.8	8.1	34.3	7.1	21.4	4.7	79.2	4.1	26.3	8.5	78.8	11.2
AD-476313	26.5	4.7	62.9	6.2	18.8	4.3	89.2	5.7	39.9	10.3	102.2	19.9
AD-475728	26.5	9.9	94.0	13.4	11.4	2.1	86.4	5.8	29.1	4.7	88.9	12.5
AD-464603	26.5	11.0	50.2	5.8	19.4	1.1	78.4	4.2	51.4	5.6	95.1	9.6
AD-476306	26.8	8.0	69.3	13.9	27.1	3.0	93.7	8.0	20.5	3.0	90.3	14.0
AD-464886	27.0	8.0	32.6	5.8	11.1	1.7	77.0	7.8	96.3	9.5	105.1	15.4
AD-476316	27.5	1.8	54.9	15.9	18.9	3.3	83.0	6.2	41.0	9.0	94.1	2.4
AD-464606	27.7	4.9	78.1	7.6	26.3	9.2	80.4	8.6	84.9	8.4	100.9	8.9
AD-475723	28.2	6.0	85.4	13.9	20.9	2.4	88.7	1.2	68.8	6.0	94.8	5.0
AD-464229	28.4	9.9	65.7	3.2	14.9	3.9	75.3	14.6	32.7	3.7	85.9	5.9

Duplex ID	human BE(2)C qPCR				human Dual-Luc				mouse Dual-Luc			
	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD
AD-464742	28.4	9.2	43.2	8.2	11.7	2.6	77.5	11.3	75.1	12.1	94.4	11.4
AD-476311	29.8	2.7	89.9	14.3	54.1	2.0	86.0	6.5	52.4	8.6	99.1	3.2
AD-476312	31.1	7.5	77.2	13.4	35.6	5.3	86.0	17.1	55.6	1.7	110.0	16.9
AD-464978	31.1	10.2	39.6	8.3	23.8	5.4	92.9	7.0	46.6	9.9	89.0	12.4
AD-464814	32.3	9.6	27.3	3.0	36.7	4.0	69.7	1.4	22.9	0.6	68.7	4.6
AD-476198	32.8	5.2	63.0	15.0	36.7	4.0	96.9	13.3	41.1	3.8	93.1	11.1
AD-476321	33.0	7.2	43.7	7.0	15.0	1.6	81.6	3.6	21.8	3.1	78.6	8.4
AD-464815	33.4	7.1	48.0	6.9	15.2	1.8	70.6	13.0	25.0	2.6	69.4	5.6
AD-464936	33.7	5.3	32.0	4.5	30.8	7.4	91.1	12.8	93.2	9.2	90.5	15.1
AD-476152	35.2	8.2	77.4	13.7	72.0	8.1	99.3	8.1	77.3	7.2	91.6	11.7
AD-475929	35.7	5.5	89.1	22.7	145.1	12.3	104.6	16.1	103.9	16.3	91.3	15.9
AD-475895	35.7	2.6	93.2	3.9	123.5	3.7	98.3	4.2	108.9	11.3	101.7	11.1
AD-464884	35.8	10.6	32.3	4.0	11.8	0.9	78.9	11.1	71.3	10.4	91.0	2.6
AD-464928	36.7	9.9	47.1	5.6	11.2	1.2	55.7	5.5	87.2	12.7	98.6	10.8
AD-464885	37.9	5.2	61.7	9.9	13.5	2.4	85.2	8.9	99.0	9.0	99.5	15.7
AD-464859	38.5	9.2	61.1	10.1	28.9	3.0	91.2	11.1	54.1	3.1	89.0	10.0
AD-476032	39.6	9.1	84.8	14.5	86.3	10.0	108.8	8.7	43.8	4.7	99.9	11.8
AD-464586	41.3	10.3	108.5	23.4	56.3	6.8	101.8	9.5	97.8	5.6	106.0	10.7
AD-476146	41.5	4.4	108.9	17.7	90.1	5.5	99.6	1.7	43.6	6.0	95.9	7.1
AD-464856	41.7	12.9	50.5	17.3	25.5	4.0	99.8	4.4	42.1	4.4	99.4	8.3
AD-476344	42.8	11.8	81.9	10.6	23.9	1.2	83.5	9.1	9.1	2.6	48.0	8.0
AD-475966	43.0	8.2	96.4	9.7	63.6	7.0	91.4	13.2	65.1	10.7	101.3	5.2
AD-475666	44.9	10.4	72.2	7.1	24.3	4.0	75.5	10.6	18.6	2.5	77.9	9.5
AD-464592	53.1	16.6	119.9	25.1	62.8	5.4	94.9	15.3	80.9	2.7	92.7	9.2
AD-464813	53.2	4.5	92.1	21.7	59.7	9.4	98.0	13.6	71.0	6.3	96.0	5.5
AD-475663	61.0	8.9	93.0	6.3	43.1	4.5	89.0	6.0	57.6	8.1	89.8	7.8
AD-475765	63.8	9.7	102.6	18.3	98.8	6.0	100.3	8.0	73.7	6.3	106.0	12.3
AD-476309	67.4	12.7	87.8	4.7	70.1	5.1	91.1	4.7	70.9	6.1	94.3	15.3
AD-476029	68.2	3.0	78.4	6.7	78.3	5.3	94.0	9.4	38.1	2.5	107.4	7.6
AD-465065	68.3	12.5	60.5	8.7	73.8	10.7	79.5	9.1	101.8	9.7	88.9	9.0
AD-466386	73.5	8.1	64.2	11.0	77.2	4.4	91.3	8.5	106.6	8.3	90.2	10.3
AD-465064	75.8	11.7	77.1	15.0	71.0	3.2	95.3	7.4	98.3	8.6	90.7	3.3
AD-476026	80.7	9.5	109.7	20.4	112.1	18.3	111.8	3.5	70.3	7.5	95.3	10.8
AD-465068	81.9	16.9	78.5	21.0	80.2	11.1	90.1	13.7	108.7	8.7	102.3	5.5
AD-476025	84.6	3.5	102.2	5.8	100.8	4.3	94.8	6.8	93.6	10.5	107.8	3.9
AD-476027	88.6	3.1	117.3	10.9	109.5	20.6	93.8	11.1	80.1	5.7	102.7	4.5
AD-475953	89.7	7.4	95.5	13.6	100.6	7.7	98.2	8.1	93.4	4.8	110.5	11.4
AD-475942	92.5	3.4	97.0	16.9	129.1	10.0	101.1	11.4	126.0	10.1	97.4	5.9
AD-476030	92.8	2.7	107.2	10.7	103.8	10.8	97.9	8.7	63.9	8.1	101.7	11.2
AD-465760	92.9	5.3	72.5	13.6	73.6	9.4	91.9	5.7	89.6	12.9	83.0	8.1
AD-466384	94.1	12.0	75.8	14.8	61.3	6.9	94.5	10.2	89.9	16.9	90.9	10.0
AD-475941	94.6	9.2	115.1	8.7	116.2	5.2	100.1	13.2	110.8	9.1	99.9	3.1
AD-475952	95.8	13.5	89.8	11.8	118.0	4.3	108.0	15.3	90.7	11.4	103.0	7.7

Duplex ID	human BE(2)C qPCR				human Dual-Luc				mouse Dual-Luc			
	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD	10nM % Message Remaining	STD	0.1nM % Message Remaining	STD
AD-475954	96.9	12.2	87.9	12.3	118.4	6.4	90.5	4.5	93.9	18.0	95.2	13.3
AD-475888	97.2	16.5	80.5	13.3	100.1	7.8	89.9	8.9	94.4	16.8	103.3	22.8
AD-475955	104.8	21.4	80.9	13.1	101.3	8.7	98.1	11.8	83.0	3.1	89.2	7.8
AD-465757	106.5	15.0	67.5	14.5	93.7	9.8	91.9	16.0	105.8	7.0	105.2	6.4
AD-465691	109.1	9.2	68.9	14.5	99.2	1.1	99.4	7.8	98.9	22.0	94.3	9.1
AD-465918	109.3	7.2	92.0	26.8	85.1	11.6	92.4	7.3	96.2	8.6	90.1	13.1
AD-465876	110.7	25.5	97.4	11.6	83.4	12.9	102.9	9.9	80.1	4.1	98.2	13.6
AD-466443	113.2	16.5	111.0	26.1	57.9	0.9	98.6	5.1	98.7	12.8	95.2	9.4
AD-475646	116.5	27.4	100.7	9.6	117.7	21.4	96.3	8.7	37.9	5.5	92.1	12.2
AD-465784	118.8	8.0	109.4	30.2	91.8	8.4	110.0	11.8	105.4	1.7	94.9	7.6
AD-465168	120.6	33.0	108.7	24.8	73.1	5.5	93.7	13.3	102.7	16.0	95.9	9.9
AD-464559	122.2	17.6	106.8	12.7	93.4	11.6	91.8	9.4	83.9	6.2	89.1	12.8
AD-475761	125.8	25.8	116.8	9.6	89.2	14.2	94.9	8.7	58.3	7.9	103.6	13.8
AD-476058	131.7	10.3	114.8	18.4	59.7	9.8	100.3	4.7	41.0	5.3	97.1	13.5
AD-465785	135.4	10.8	123.3	28.8	107.0	8.2	109.9	5.4	83.6	5.2	89.6	8.7
AD-465919	136.8	23.8	107.3	24.2	91.1	10.8	93.2	10.3	93.4	18.3	91.0	3.7
AD-465756	137.5	19.4	107.6	8.6	95.0	17.0	108.3	15.6	100.3	6.7	95.4	6.1
AD-476061	142.2	18.5	123.1	10.8	87.3	5.9	90.1	9.4	22.4	2.4	75.2	3.7
AD-465794	145.7	20.9	118.6	30.0	100.8	6.9	100.0	4.1	111.9	1.7	97.2	7.8
AD-466320	151.5	15.4	116.2	15.8	85.3	8.8	90.4	8.9	95.9	18.8	102.1	7.5
AD-476192	157.9	27.5	122.1	3.2	100.6	5.4	92.1	7.3	70.6	11.2	104.4	6.1

Table 8. *In Vivo* Evaluation of SNCA RNAi Agents in Human SNCA AAV-Transduced Mice (see FIG. 1)

Duplex ID	PBS control (in 3'UTR expt)	AD- 464778	AD- 464782	AD- 464694	AD- 464634	AD- 464779	PBS control (in CDS expt)	AD- 464590	AD- 464313	AD- 464314	AD- 464585	AD- 464586	AD- 464592
Target Sequence	-	3'UTR	3'UTR	3'UTR	3'UTR	3'UTR	-	CDS	CDS	CDS	CDS	CDS	CDS
Average transcript remaining	1	0.3458	0.3031	0.1705	0.1703	0.4016	1	0.86	0.7	0.27	0.655	0.7075	0.7575
SD	0.3905	0.1237	0.05679	0.04853	0.03625	0.1588	0.3201	0.5602	0.1219	0.07118	0.1698	0.2002	0.1513

Table 9. Modified Duplex Sequences Dosed to Mice.

Duplex Id	Oligo Id	Strand	Oligonucleotide Sequence	SEQ ID NO
AD-464634	A-901590	sense	asgsuuucUfuGfAfGfaucugcugaaL96	1821
	A-901591	antisense	VPusUfscagCfaGfAfucucAfaGfaaacusgsg	1822
AD-464314	A-900954	sense	asasgaggGfuGfUfUfcucuauguaaL96	1823
	A-900955	antisense	VPusUfsacaUfaGfAfgaacAfcCfcucuususu	1824

Table 10. Mouse *In Vivo* SNCA Knockdown Results, at Days 7 and 14, at 3 mg/kg and 10 mg/kg Duplex Dosage. (see FIG. 3)

Duplex	siRNA treatment	% Message Remaining	SD	Sample
PBS	Day 7	100.00	24.96	Liver
Naïve	Day 7	108.10	21.00	Liver
3'UTR AD-464634	Dosed at 3 mg/kg; Measured at Day 7	18.43	7.30	Liver
3'UTR AD-464634	Dosed at 10 mg/kg; Measured at Day 7	17.72	10.28	Liver
CDS AD-464314	Dosed at 3 mg/kg; Measured at Day 7	31.26	4.80	Liver
CDS AD-464314	Dosed at 10 mg/kg; Measured at Day 7	5.94	3.07	Liver
PBS	Day 14	100.00	4.83	Liver
Naïve	Day 14	96.37	13.39	Liver
3'UTR AD-464634	Dosed at 3 mg/kg; Measured at Day 14	36.04	8.31	Liver
3'UTR AD-464634	Dosed at 10 mg/kg; Measured at Day 14	17.02	6.08	Liver
CDS AD-464314	Dosed at 3 mg/kg; Measured at Day 14	36.63	5.77	Liver
CDS AD-464314	Dosed at 10 mg/kg; Measured at Day 14	24.01	12.75	Liver

Table 11. Mouse/Rat Cross-Reactivity of SNCA RNAi Agents in Rat SNCA-AAV Overexpressing Mice (see FIG. 5)

Duplex ID	PBS control	AD-476344	AD-475666	AD-476306	AD-476061	AD-464814	AD-475728	AD-464229
n	3	4	4	4	4	4	4	4
Average transcript remaining	1.0000	0.7400	0.7035	0.6834	0.3006	0.3913	0.3790	0.5237
SD	0.4991	0.09166	0.1783	0.3062	0.1151	0.07808	0.1154	0.3044

Table 12. Further SNCA-Targeting Duplex Sequences, Modified.

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1548843.1	A-2860862	gsacga(Chd)agUfGfUfgguguaagaaL96	1825	A-2860863	VPusdCsuudTadCaccadCaCfugucgucsgsa	2180	UCGACGACAGUGUGGUGUAAAAGG	2535
AD-1548844.1	A-2860864	ascsgac(Ahd)guGfUfGfguguaaagaaL96	1826	A-2860865	VPusdCsuudTudAcaccdAcAfcugucgucsgsa	2181	CGACGACAGUGUGGUGUAAAAGG	2536
AD-1548845.1	A-2860866	csgsaca(Ghd)ngUfGfGfguguaaagaaL96	1827	A-2860867	VPusdTsccdTudTaccadCaCfugucgucsgsa	2182	GACGACAGUGUGGUGUAAAAGG	2537
AD-1548851.1	A-2860878	usgsugg(Uhd)guAfaAfAfggaaucaaaL96	1828	A-2860879	VPusdAsugdAadTuccu dTuaAfcacacacscsu	2183	AGUGUGGUGUAAAAGG	2538
AD-1548854.1	A-2860884	gsgsugu(Ahd)aaGfGfAfaucuaaagaaL96	1829	A-2860885	VPusdCsuadAudGaaau dCcUfuaacacacsc	2184	GUGGUGUAAAAGG	2539
AD-1548869.1	A-2860914	asusug(Chd)caUfGfGfauguaaucaaaL96	1830	A-2860915	VPusdTsgadAudAcanc dCaUfggcuaaagsga	2185	UCAUUAGCCCAUGG	2540
AD-1548870.1	A-2860916	usugac(Chd)auGfGfAfaucuaaagaaL96	1831	A-2860917	VPusdAsugdAadTaccu dCcAfcugcuaaagsg	2186	CAUUAGCCCAUGG	2541
AD-1548876.1	A-2860928	asusgga(Uhd)guAfaUfUfcaugaaagaaL96	1832	A-2860929	VPusdCsuudTudCauga dAuAfcacacacscsu	2187	CCAUGGAUGUAUU CAUGAAAAGG	2542
AD-1548884.1	A-2860944	asusuca(Uhd)gaAfaUfGfgaaucaaaL96	1833	A-2860945	VPusdTsgadAudAgucc dTuaUfcaugaauaasc	2188	GUAUUCAUGAAAAG	2543
AD-1548886.1	A-2860948	uscsaug(Ahd)aaGfGfAfaucuaaagaaL96	1834	A-2860949	VPusdCsuudTgdAaagu dCcUfuaacacacsc	2189	AUUCUAAAAGG	2544
AD-1548887.1	A-2860950	csasuga(Ahd)agGfAfaUfuaaagaaL96	1835	A-2860951	VPusdCsuudTudGaaag dTcCfuaacacacsc	2190	UUCAUAAAAGG	2545

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-154888.1	A-2860952	asusgaa(Ahd)ggAfCfUfucuaaggaL96	1836	A-2860953	VPusdGscdTudTgaadGuCfucuaagga	2191	UCAUGAAAAGGACU UUCAAGGCC	2546
AD-154897.1	A-2861126	asgsagg(Ghd)ugUfCfCfucuauguaL96	1837	A-2861127	VPusdCsuadCadTagag dAaCfaccucucusu	2192	AAAGAGGGUGUUC UCUAUGUAGG	2547
AD-154897.1	A-2861128	gsasggg(Uhd)guUfCfUfucuauguaL96	1838	A-2861129	VPusdCscudAcidAuaga dCaAfaccucucusu	2193	AAGAGGGUGUUCU CUAUGUAGGC	2548
AD-154897.1	A-2861132	gsasggg(Uhd)guUfCfUfucuauguaL96	1839	A-2861133	VPusdAsgcdCudAcaua dGaCfaccucucusu	2194	GAGGGUGUUCU AUGUAGGCUC	2549
AD-154903.1	A-2861250	usgsagc(Ghd)agAfAfGfaccuaaggaL96	1840	A-2861251	VPusdCscudTudTgguc dTuCfucagccscsu	2195	AGUGGUGAGAAAG ACCAAAGAGC	2550
AD-154903.1	A-2861252	gsasggg(Uhd)guUfCfUfucuauguaL96	1841	A-2861253	VPusdGscdCudTuggu dCuUfucagccscsu	2196	GUGGUGAGAAAG CCAAAGAGCA	2551
AD-154904.1	A-2861264	gsasggg(Uhd)guUfCfUfucuauguaL96	1842	A-2861265	VPusdTscadCudTgcud TuUfugucucucsu	2197	GAGAAGACCAAAG AGCAAAGAGC	2552
AD-154905.1	A-2861280	asgsagg(Ghd)aaGfUfGfaccuaaggaL96	1843	A-2861281	VPusdAsacdAudTuguc dAcUfugucucucsu	2198	CAAAGAGCAAAGUG ACAAUGUUG	2553
AD-154905.1	A-2861282	asgsagg(Ghd)aaGfUfGfaccuaaggaL96	1844	A-2861283	VPusdCsaadCadTuugu dCaCfugucucucsu	2199	AAAGAGCAAAGUG CAAUGUUGG	2554
AD-154905.1	A-2861284	gsasggg(Uhd)guUfCfUfucuauguaL96	1845	A-2861285	VPusdCscadAcidAuung dTcAfcugucucucsu	2200	AAGAGCAAAGUGAC AAAUGUUGA	2555
AD-154905.1	A-2861286	asgsagg(Ghd)ugAfCfAfaaunguaL96	1846	A-2861287	VPusdTscadAadCaunu dGuCfucagccscsu	2201	AGAGCAAAGUGACA AAUGUUGAG	2556
AD-154920.1	A-2861596	usgsagc(Ghd)aaGfUfGfaccuaaggaL96	1847	A-2861597	VPusdCsaadAadGcuc dAuUfugucaggaL96	2202	GAUCCUGACAAUG AGGCUUAUGA	2557
AD-154921.1	A-2861598	csasagg(Ghd)aaUfGfAfaaunguaL96	1848	A-2861599	VPusdTscadTadAgcud CaUfugucaggaL96	2203	AUCCUGACAAUGA GGUUAUGAA	2558
AD-154921.1	A-2861600	csasagg(Ghd)aaUfGfAfaaunguaL96	1849	A-2861601	VPusdTscadAudAagcc dTcAfcugucaggaL96	2204	UCCUGACAAUGAG GCUUAUGAA	2559
AD-154921.1	A-2861608	csasagg(Ghd)aaUfGfAfaaunguaL96	1850	A-2861609	VPusdGscadTudTcaud AgCfucuaaggaL96	2205	GACAAUGAGGCUU AUGAAAUGCC	2560
AD-154921.1	A-2861610	asasagg(Ghd)gcUfUfUfucuaaggaL96	1851	A-2861611	VPusdGsgcdAudTucau dAaGfucuaaggaL96	2206	ACAAUGAGGCUUA UGAAAUGCCU	2561
AD-154922.1	A-2861620	gsasggg(Uhd)ugAfAfAfaaunguaL96	1852	A-2861621	VPusdCsaadAadGcuc dTuCfuaaaggaL96	2207	GAGGCUUAUGAAA UGCUCUCUGA	2562
AD-154922.1	A-2861624	csasagg(Ghd)aaGfUfGfaccuaaggaL96	1853	A-2861625	VPusdCscudAadAagcc dAuUfucuaaggaL96	2208	GGCUUAUGAAAUG CCUUCUGAGG	2563

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1549225.1	A-2861626	usuaug(Ahd)aaUfGfCfucuaaggaL96	1854	A-2861627	VPusdCscudCadGaaggdCaUfucuaaagsc	2209	GUUUAUGAAAUGC CUUCUGAGGA	2564
AD-1549245.1	A-2861666	asaggg(Uhd)auCfAfAfgacuagaaL96	1855	A-2861667	VPusdTsudGudAgucudTgAfuaccuuscsc	2210	GGAAGGGUAUCAAGACUACGAAC	2565
AD-1549246.1	A-2861668	asgsggu(Ahd)ucAfAfGfacuacgaL96	1856	A-2861669	VPusdGsuudCgdTtagucdTUGfuaaccuusc	2211	GAAGGGUAUCAAGACUACGAAC	2566
AD-1549249.1	A-2861674	gsusauc(Ahd)agAfCfUfagacuaccgaL96	1857	A-2861675	VPusdCsaadGudTcgua dGuCfuagauaccsc	2212	GGUAUCAAGACUACGAAC	2567
AD-1549264.1	A-2861704	ascscug(Ahd)agCfCfUfagaaauaL96	1858	A-2861705	VPusdAsaadTudTcuaa dGgCfuaaccuusc	2213	GAACCUGAAGCCUUAAGAAUUCU	2568
AD-1549265.1	A-2861706	cscsuga(Ahd)gcCfUfAfagaaauaL96	1859	A-2861707	VPusdGsaadAndTucuu dAgGfuaaccuusc	2214	AACCUGAAGCCUUAAGAAUUCU	2569
AD-1549266.1	A-2861708	csusga(Ahd)ccUfAfAfagaaauaL96	1860	A-2861709	VPusdAsaadTadTucuu dTaGfuaaccuusc	2215	ACCUGAAGCCUUAAGAAUUCU	2570
AD-1549267.1	A-2861710	usgsaag(Chd)cuAfAfGfuaaauaL96	1861	A-2861711	VPusdAsaadAndTucuu dTaGfuaaccuusc	2216	CCUGAAGCCUUAAGAAUUCU	2571
AD-1549268.1	A-2861712	gsasagc(Chd)uaAfGfAfagaaauaL96	1862	A-2861713	VPusdAsaadGadTucuu dCuUfuaaccuusc	2217	CUGAAGCCUUAAGAAUUCU	2572
AD-1549269.1	A-2861714	asagcc(Uhd)aaGfAfAfagaaauaL96	1863	A-2861715	VPusdCsaadAgdAuauu dTcUfuaaccuusc	2218	UGAAGCCUUAAGAAUUCU	2573
AD-1549270.1	A-2861716	asgscu(Ahd)agAfAfAfuaucuaL96	1864	A-2861717	VPusdGsaadAadGauau dTuCfuaaccuusc	2219	GAAGCCUUAAGAAUUAUCUUCU	2574
AD-1549271.1	A-2861718	gscscua(Ahd)gaAfAfUfuaucuaL96	1865	A-2861719	VPusdAsaadAadAgaua dTuUfuaaccuusc	2220	AAGCCUUAAGAAUUAUCUUCU	2575
AD-1549272.1	A-2861720	cscsuaa(Chd)aaAfUfAfuaucuaL96	1866	A-2861721	VPusdGsaadCadAagau dAuUfuaaccuusc	2221	AGCCUUAAGAAUUAUCUUCU	2576
AD-1549280.1	A-2861736	asusauc(Uhd)uuGfCfUfuaucuaL96	1867	A-2861737	VPusdGsaadAadTggga dGcAfaagauaL96	2222	AAUAUCUUCUUCUCCCAGUUUCU	2577
AD-1549281.1	A-2861738	usasauc(Uhd)ugCfUfCfuaucuaL96	1868	A-2861739	VPusdAsaadAadCuggg dAgCfaagauaL96	2223	AAUAUCUUCUUCUCCCAGUUUCU	2578
AD-1549282.1	A-2861740	asuscua(Chd)gcUfCfCfuaucuaL96	1869	A-2861741	VPusdAsaadAadCuggg dGcAfaagauaL96	2224	AAUAUCUUCUUCUCCCAGUUUCU	2579
AD-1549283.1	A-2861742	uscsuuu(Chd)cuCfCfCfuaucuaL96	1870	A-2861743	VPusdCsaadGadAacug dGgAfgaagauaL96	2225	UAUCUUCUUCUCCCAGUUUCU	2580
AD-1549284.1	A-2861744	csusung(Chd)ucCfCfAfuaucuaL96	1871	A-2861745	VPusdTsaadAadAaacu dGgGfagaaagauaL96	2226	AUCUUCUUCUCCCAGUUUCU	2581

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1549285.1	A-2861746	usugc(Uhd)ccCfAfGfuuuugagL96	1872	A-2861747	VPusdCsuadAadGaaacdTgGfagcaasgsa	2227	UCUUUGCUCCAGUUUUCUUGAGA	2582
AD-1549290.1	A-2861756	uscscga(Ghd)uuUfCfUfugagaucaL96	1873	A-2861757	VPusdCsuadAadCucadCaAfucaggagsg	2228	GCUCCAGUUUCUUGAGAUUGC	2583
AD-1549293.1	A-2861762	csasguu(Uhd)uuUfGfAfgauucugagL96	1874	A-2861763	VPusdCsuadCadGaucu dCaAfgaauucgsg	2229	CCCAGUUUCUUGAGAUCUGUGA	2584
AD-1549333.1	A-2861842	asasguu(Ghd)ucAfGfUfuccaauugagL96	1875	A-2861843	VPusdCsuadAadTggaa dCuGfagcauugsu	2230	ACAAAGUCUCAGUUCCAAUGUC	2585
AD-1549334.1	A-2861844	asgsu(Ghd)caGfUfUfcauugagL96	1876	A-2861845	VPusdGsuadCadTugga dAcUfagcauucsg	2231	CAAGUCUCAGUUCCAAUGGCC	2586
AD-1549351.1	A-2861878	usgscc(Ghd)guCfAfUfgacauuualL96	1877	A-2861879	VPusdAsgadAadTguca dTgAfcuaggagsg	2232	UGUCCAGUCAGUACAUUUUC	2587
AD-1549352.1	A-2861880	gsccga(Ghd)ucAfUfGfacaauuualL96	1878	A-2861881	VPusdGsuadAadAuguc dAuGfagcauucsg	2233	GUGCCAGUCAGUACAUUUUCA	2588
AD-1549353.1	A-2861882	csccag(Ghd)caUfGfAfcuauuualL96	1879	A-2861883	VPusdTsagadGadAangu dCaUfagcauucsg	2234	UGCCAGUCAGUACAUUUUCA	2589
AD-1549354.1	A-2861884	csccag(Ghd)auGfAfCfauuucuaaL96	1880	A-2861885	VPusdTsagadAadAangu dTcAfcuaggagsg	2235	GCCAGUCAGUACAUUUUCA	2590
AD-1549357.1	A-2861890	gsu(Ghd)acAfUfUfucuaaagL96	1881	A-2861891	VPusdAsgadTudGagaa dAuGfagcauucsg	2236	CAGUCAGUACAUUUUCA	2591
AD-1549359.1	A-2861894	csasga(Ghd)auUfUfCfucuaaagL96	1882	A-2861895	VPusdAsgadCudTugag dAaAfcuaggagsg	2237	GUCAUGACAUUUUCUCAAAGUUU	2592
AD-1549391.1	A-2861958	uscsgaa(Ghd)ucUfUfCfcauagagL96	1883	A-2861959	VPusdCsuadCudGaugg dAaGfagcauucsg	2238	UCUCGAGUCUUC CAUCAGAGU	2593
AD-1549397.1	A-2861970	uscuu(Ghd)auCfAfGfcauagagL96	1884	A-2861971	VPusdCsuadTcdAcugc dTgAfcuaggagsg	2239	AGUCUCCAGUACAGUGAUUGA	2594
AD-1549400.1	A-2861976	uscsgaa(Ghd)agCfAfGfugaagagL96	1885	A-2861977	VPusdCsuadCadAucac dTgCfugaagagsg	2240	CUCCAGUCAGAGUUGAUUGAGU	2595
AD-1549401.1	A-2861978	csccau(Ghd)gcAfGfUfcauagagL96	1886	A-2861979	VPusdAsgadTcdAucac dCuGfagcauucsg	2241	UUCCAGUCAGAGU GAUUGAGUA	2596
AD-1549403.1	A-2861982	asuscag(Ghd)agUfGfAfuagagagL96	1887	A-2861983	VPusdAsgadCudTcau dCaCfugaagagsg	2242	CCAUCAGCAGUGA UUGAAGUAGU	2597
AD-1549406.1	A-2861988	asgsag(Ghd)gaUfUfGfagaauuualL96	1888	A-2861989	VPusdCsuadAadAcuuc dAaUfagcauucsg	2243	UCAGCAGUGAUUGAAGUAGUUGU	2598
AD-1549407.1	A-2861990	gsccag(Ghd)auUfGfAfgauuualL96	1889	A-2861991	VPusdAsgadGadTacu dCaAfcuaggagsg	2244	CAGCAGUGAUUGA AGUAGUUGA	2599

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1549412.1	A-2862000	gsasug(Ahd)agUfAfUfcuguaacuaL96	1890	A-2862001	VPsdCsgdGudAcagadTaCfucuaacsasc	2245	GUGAUUGAAGUAUUGUACUG	2600
AD-1549425.1	A-2862026	ususcgg(Uhd)gcUfUfCfcucuaacuaL96	1891	A-2862027	VPsdAsgdGadAagggdAaGfcaccgaasasu	2246	AUUUCGGUGCUUCUUUACUG	2601
AD-1549426.1	A-2862028	uscsggu(Ghd)cuUfCfCfcuuaacuaL96	1892	A-2862029	VPsdCsgdTgdAaaggdGaAfcaccgaasasa	2247	UUUCGGUGCUUCCUUUACUGA	2602
AD-1549432.1	A-2862040	csusucc(Chd)uuUfCfAfcugaaguaL96	1893	A-2862041	VPsdTscadCudTcagudGaAfcagggaagsca	2248	UGCUUCCCUUCAUGAAAGUGAA	2603
AD-1549438.1	A-2862052	ususua(Chd)ugAfAfGfuguaacuaL96	1894	A-2862053	VPsdAsugdTadTucacdTuCfagugaaasgsg	2249	CCUUUCACUGAAGUGAAUACAU	2604
AD-1549439.1	A-2862054	ususcac(Uhd)gaAfGfUfgaaucauaL96	1895	A-2862055	VPsdCsaudGudAuaucdCuUfcagugaasag	2250	CUUUCACUGAAGUGAAUACAU	2605
AD-1549441.1	A-2862058	csascug(Ahd)agUfGfAfauacunguaL96	1896	A-2862059	VPsdAscedAudGuaauCdCaCfucagugasa	2251	UUCACUGAAGUGAUAUACAU	2606
AD-1549442.1	A-2862060	ascsga(Ahd)guGfAfAfuaucunguaL96	1897	A-2862061	VPsdTscadCadTguaudTcAfcuacugsga	2252	UCACUGAAGUGAUAUACAU	2607
AD-1549443.1	A-2862062	csusga(Chd)ugAfAfUfacaunguaL96	1898	A-2862063	VPsdCsuadCcdAuguadTuCfucuaacugsg	2253	CACUUAUUUCCACUUAUUU	2608
AD-1549517.1	A-2862210	csusaag(Uhd)gaCfUfAfccacuuaualL96	1899	A-2862211	VPsdAsaudAadGuggdAgUfcacuuaagsgsu	2254	ACCUAAGUGACUACACUUAUUU	2609
AD-1549518.1	A-2862212	usasagu(Ghd)acUfAfCfcacuuaualL96	1900	A-2862213	VPsdAsaadTadAagggdTcAfcuacuuaasgsg	2255	CCUUAAGUGACUACACUUAUUU	2610
AD-1549519.1	A-2862214	asasgug(Ahd)cuAfCfCfcacuuaualL96	1901	A-2862215	VPsdGsaadAudAagugdGuAfcuacuuaasag	2256	CUAAGUGACUACCUUAUUU	2611
AD-1549520.1	A-2862216	asgsuga(Chd)uaCfCfAfcuuaauualL96	1902	A-2862217	VPsdAsgadAadTaagudGgUfcagucacusa	2257	UAAGUGACUACCUUAUUU	2612
AD-1549521.1	A-2862218	gsusgac(Uhd)acCfAfCfcuuaauualL96	1903	A-2862219	VPsdTsgadAadAuaagdTGfugagucacsusu	2258	AAGUGACUACCUUAUUU	2613
AD-1549522.1	A-2862220	usgsacu(Ahd)ccAfCfUfcuuaauualL96	1904	A-2862221	VPsdTsuadGadAuaadGGuGfugagucacsusu	2259	AGUGACUACCUUAUUU	2614
AD-1549524.1	A-2862224	ascsuac(Chd)acUfUfAfuaauuaualL96	1905	A-2862225	VPsdAsumdTadGaaauDaaGfugagucacsusa	2260	UGACUACCUUAUUU	2615
AD-1549525.1	A-2862226	csusacc(Ahd)cuUfAfUfuaauuaualL96	1906	A-2862227	VPsdGsaudTudAgaaadTaAfcagugagusc	2261	GACUACCUUAUUU	2616
AD-1549527.1	A-2862230	ascscac(Uhd)uaUfUfUfuaauuaualL96	1907	A-2862231	VPsdAsggdAudTuagadAaUfaagugugusag	2262	CUACCUUAUUU	2617

Duplex Name	SenseOligo Name	Oligo Sequence	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1549541.1	A-2862258	usugcu(Ghd)uuGfUfUfcaagauaalL96	A-2862259	VPusdCsaadCudTcuagadAcAfaacagacasa	2263	2618	UGUUGCUGUUGUU CAGAAAGUUUGU	2618
AD-1549542.1	A-2862260	usgcu(Ghd)ugUfUfCfagaaguuualL96	A-2862261	VPusdAsaadAcadTucugdAaCfaacagacasc	2264	2619	GUUGCUGUUGUUC AGAAGUUUGU	2619
AD-1549543.1	A-2862262	gscsugu(Uhd)guUfCfAfgaaguuuaalL96	A-2862263	VPusdAsaadAadCuucudGaAfaacagacasa	2265	2620	UUGCUGUUGUUCA GAAAGUUUGUA	2620
AD-1549544.1	A-2862264	csusgu(Ghd)uuCfAfGfaaguuuaalL96	A-2862265	VPusdTsaadCadAcuucdTgAfaacagacasa	2266	2621	UGCUGUUGUUCAG AAGUUUGUAG	2621
AD-1549545.1	A-2862266	usgsuug(Uhd)ucAfGfAfaguuuaalL96	A-2862267	VPusdCsuadAcadAacuuTuCfugaacacasa	2267	2622	GCUGUUGUUCAGAGUUGUUAGU	2622
AD-1549547.1	A-2862270	gsusugu(Uhd)caGfAfGfuuuaalL96	A-2862269	VPusdAsaadAadCaacudTcUfgaacaacasa	2268	2623	CUGUUGUUCAGAA GUUGUUAGUG	2623
AD-1549548.1	A-2862272	usgsuug(Uhd)ucAfGfAfaguuuaalL96	A-2862271	VPusdCsaadTadAcaacdTuCfugaacacasa	2269	2624	UGUUGUUCAGAAAGUUGUUAGU	2624
AD-1549552.1	A-2862280	csasga(Ghd)uuGfUfUfaguuuaalL96	A-2862281	VPusdCsaadAudCacua dAcAfaacacacasa	2271	2626	UUCAGAAAGUUUGU AGUAGUUUGC	2626
AD-1549554.1	A-2862284	gsasagu(Uhd)guUfAfGfuuuaalL96	A-2862285	VPusdAsaadAadAucacdTgAfaacacacasa	2272	2627	CAGAAAGUUUGUAGUGAUUUGCUA	2627
AD-1549555.1	A-2862286	asgsuug(Uhd)uuAfGfUfaguuuaalL96	A-2862287	VPusdTsaadCadAauca dCuAfaacacacasa	2273	2628	AGAAAGUUUGUUGU GAUUUGCUAU	2628
AD-1549556.1	A-2862288	asgsuug(Uhd)uuAfGfUfaguuuaalL96	A-2862289	VPusdAsaadGcdAaau dAcUfaacacacasa	2274	2629	GAAAGUUUGUUGUAG AUUUGCUAUC	2629
AD-1549595.1	A-2862366	gsasuac(Uhd)guCfUfAfaguuuaalL96	A-2862367	VPusdCsaadTadTucuu dAgAfaacacacasa	2275	2630	AUGAUACUGUCUA AGAAUAAUGA	2630
AD-1549596.1	A-2862368	asusacu(Ghd)ucUfAfAfgaauuaalL96	A-2862369	VPusdTsaadTudAuuu dTgAfaacacacasa	2276	2631	UGAUACUGUCUAA GAAUAAUGAC	2631
AD-1549615.1	A-2862406	asesgu(Uhd)ugUfGfAfaguuuaalL96	A-2862407	VPusdTsaadCadAauu dCaCfaacacacasa	2277	2632	UGACGUAUUGUGA AAUUUGUUA	2632
AD-1549628.1	A-2862432	usasugu(Ghd)agCfAfUfgaauuaalL96	A-2862433	VPusdCsaadAgdTuuca dTgCfucacacasa	2278	2633	AAUUGUGAGAGCAU GAAACUAUGC	2633
AD-1549630.1	A-2862436	usgsuag(Ghd)caUfGfAfaguuuaalL96	A-2862437	VPusdTsaadAudAuuu dCaUfgcucacasa	2279	2634	UAUGUGAGCAUGA AACUAUAGCAC	2634
AD-1549639.1	A-2862454	gsasaac(Uhd)uuGfCfAfaguuuaalL96	A-2862455	VPusdAsaadTadTaggu dGcAfaacacacasa	2280	2635	AUGAAACUAUGCA CCUAUAAUA	2635

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1549640.1	A-2862456	asasacut(Ahd)ugCfAfCfcuaaauaalL96	1926	A-2862457	VPusdTsaundTudAuaggdTgCfaaaguuuscsa	2281	UGAAACUAUGCACCUAAUAAUAC	2636
AD-1549641.1	A-2862458	asascua(Uhd)gcAfCfCfcuaaauaalL96	1927	A-2862459	VPusdGsuadTudTauagdTGuGfcauaguuuscsa	2282	GAAACUAUGCACCUAAUAAUACU	2637
AD-1549642.1	A-2862460	ascsuau(Ghd)caCfCfCUfaaauaauaalL96	1928	A-2862461	VPusdAsgndAudTuaaagdGgUfcauaguuuscsa	2283	AAACUAUGCACCUAAUAAUACU	2638
AD-1549643.1	A-2862462	csusaug(CHd)acCfUfAfaaauaauaalL96	1929	A-2862463	VPusdTsgdTadTuaudAgGfugaauaguuuscsa	2284	AAACUAUGCACCUAAUAAUACU	2639
AD-1549682.1	A-2862540	csusugu(Ghd)uuUfGfUfaaauaauaalL96	1930	A-2862541	VPusdCsaundTudAuuaadCaAfacaacaguuuscsa	2285	CACUUGUGUUUGUAUAAUAAUACU	2640
AD-1549683.1	A-2862542	usugug(Uhd)uuGfUfAfaaauaauaalL96	1931	A-2862543	VPusdCsaundTudAuuaadCaAfacaacaguuuscsa	2286	ACUUGUGUUUGUAUAAUAAUACU	2641
AD-1549684.1	A-2862544	usgsugu(Ghd)uuUfAfUfaaauaauaalL96	1932	A-2862545	VPusdAscdAudTuaaadTaCfaaacaacaguuuscsa	2287	CUUGUGUUUGUAUAAUAAUACU	2642
AD-1549685.1	A-2862546	gsusguu(Uhd)uuAfUfAfaaauaauaalL96	1933	A-2862547	VPusdCsaundTudAuuaadCaAfacaacaguuuscsa	2288	UUGUGUUUGUAUAAUAAUACU	2643
AD-1549686.1	A-2862548	usgsugu(Ghd)uuUfAfUfaaauaauaalL96	1934	A-2862549	VPusdTsaundTudAuuaadTaCfaaacaacaguuuscsa	2289	UGUGUUUGUAUAAUAAUACU	2644
AD-1549726.1	A-2862628	usascu(CHd)uuCfUfCfcuaaauaalL96	1935	A-2862629	VPusdTsaundTudAuuaadTaCfaaacaacaguuuscsa	2290	UUUUAUCCCAUUCUCAUUUAAUAAU	2645
AD-1549727.1	A-2862630	usascu(CHd)uuCfUfCfcuaaauaalL96	1936	A-2862631	VPusdTsaundTudAuuaadTaCfaaacaacaguuuscsa	2291	UUUUAUCCCAUUCUCAUUUAAUAAU	2646
AD-1549728.1	A-2862632	usascu(CHd)uuCfUfCfcuaaauaalL96	1937	A-2862633	VPusdAsuudAudTaaagdTaCfaaacaacaguuuscsa	2292	UUUUAUCCCAUUCUCAUUUAAUAAU	2647
AD-1549729.1	A-2862634	usascu(CHd)uuCfUfCfcuaaauaalL96	1938	A-2862635	VPusdTsaundTudAuuaadTaCfaaacaacaguuuscsa	2293	UUUUAUCCCAUUCUCAUUUAAUAAU	2648
AD-1550292.1	A-2863760	gscsaca(Uhd)uuUfAfGfcuaaauaalL96	1939	A-2863761	VPusdTsaundTudAuuaadTaCfaaacaacaguuuscsa	2294	UAGCACAUUUUAGUUUAAUAAU	2649
AD-1550346.1	A-2863868	asusauu(CHd)gcAfCfAfaaauaauaalL96	1940	A-2863869	VPusdAsgndAudTuaaagdGgUfcauaguuuscsa	2295	ACAUUUUAGCACUUUAAUAAU	2650
AD-1550458.1	A-2864092	usascag(Ghd)aaAfUfGfcuaaauaalL96	1941	A-2864093	VPusdGsuadTudAuuaadCaAfacaacaguuuscsa	2296	UUUUAUCCCAUUCUCAUUUAAUAAU	2651
AD-1550459.1	A-2864094	ascsagg(CHd)aaUfGfCfcuaaauaalL96	1942	A-2864095	VPusdTsgdTadTuaaagdCaUfuccuaguuuscsa	2297	UUUUAUCCCAUUCUCAUUUAAUAAU	2652
AD-1550647.1	A-2864470	csusuuu(CHd)uuGfUfUfccaauaalL96	1943	A-2864471	VPusdAsuadTudTggcaadCaAfuuuaaaguuuscsa	2298	UUUUAUCCCAUUCUCAUUUAAUAAU	2653

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1550648.1	A-2864472	usuuu(Ahd)ugUfUfGfcaauuuuL96	1944	A-2864473	VPudTtsaudAudTuggc dAaCfaunuaasgsg	2299	CCUUUAAAUGUUG CCAAAUUAU	2654
AD-1550656.1	A-2864488	usugcc(Ahd)aaUfAfUfanguuuuL96	1945	A-2864489	VPudAsgadAudTcaua dTaUfuugccaascsa	2300	UGUUGCCAAAUU AUGAAUUCUA	2655
AD-1550657.1	A-2864490	usgsc(Ahd)auAfUfAfugauuuuL96	1946	A-2864491	VPudTtsagdAadTucan dAuAfuunugccasac	2301	GUUGCCAAAUUA UGAAUUCUAG	2656
AD-1550658.1	A-2864492	gscsaa(Ahd)uaUfAfUfgaauuuuL96	1947	A-2864493	VPudCsuadGadAuica dTaUfuunugccasac	2302	UGCCAAAUUAU AUUUCUAGG	2657
AD-1550659.1	A-2864494	cscsaa(Uhd)auAfUfGfauuuuL96	1948	A-2864495	VPudCscudAgaAauuc dAuAfuunugccsca	2303	UGCCAAAUUAU GAAUUCUAGG	2658
AD-1550660.1	A-2864496	csasaau(Ahd)uaUfGfAfauuuL96	1949	A-2864497	VPudTscddTadGaanud CaUfaunuuugsgsc	2304	GCCAAAUUAUGA AUUCUAGGAU	2659
AD-1550661.1	A-2864498	asasau(Uhd)auGfAfAfuuuuL96	1950	A-2864499	VPudAsudCudAgaau dTcAfuuaunuuugsg	2305	CCAAAUUAUGAA UUCUAGGAU	2660
AD-1550755.1	A-2864686	usuuu(Ahd)ggAfAfGfauuuuL96	1951	A-2864687	VPudTtsuadAudAgauc dTuCfcuugaaasgsa	2306	UUCUUCAGGGAAG AUUCUUAAC	2661
AD-1550756.1	A-2864688	ususcag(Ghd)gaAfGfAfuaauuL96	1952	A-2864689	VPudGsuadAadTagau dCuUfcccuaasgsa	2307	CUUCAGGGAAGA UCUUAUAACU	2662
AD-1550757.1	A-2864690	uscsagg(Ghd)aaGfAfUfcuaauuL96	1953	A-2864691	VPudAsgudTadAuaga dTcUfcccuaasgsa	2308	UUCAGGGAAGAUC UAUUAACUCC	2663
AD-1550758.1	A-2864692	uscsagg(Ahd)agAfUfCfuaauuL96	1954	A-2864693	VPudGsgadTudAauag dAuCfuuccuaggsa	2309	UUCAGGGAAGAUC UAUUAACUCC	2664
AD-1550869.1	A-2864914	uscsacu(Ahd)guAfGfAfauuuL96	1955	A-2864915	VPudAsuudAudAcuuu dCuAfcuagugascsu	2310	AGUCACUAGUAGA AAGUAUAUU	2665
AD-1550871.1	A-2864918	csuasgu(Ahd)gaAfAfGfuaauuL96	1956	A-2864919	VPudGsaadAudTauac dTuUfcuacuaugsg	2311	CACUAGUAGAAAG UAUUAUUUCA	2666
AD-1550887.1	A-2864950	usuuu(Ahd)acAfGfAfauuuL96	1957	A-2864951	VPudCsuadGadAuauu dCuGfuucuaasgsa	2312	AUUUCAAGACAGA AUUUCUAGA	2667
AD-1550888.1	A-2864952	uscsaag(Ahd)caGfAfAfuuuuL96	1958	A-2864953	VPudTtsuadAgaAauu dTcUfcccuaasgsa	2313	UUUCAAGACAGAA UAUUCUAGAC	2668
AD-1550949.1	A-2865074	usuuu(Ahd)agAfCfAfugauuL96	1959	A-2865075	VPudCsuadGadAuauu dCuGfuucuaasgsa	2314	AAUUAUUCUAGACA UGCUAGAGU	2669
AD-1550954.1	A-2865084	usagac(Ahd)ugCfUfAfcaguuuL96	1960	A-2865085	VPudAfuadAudCugcu dAgCfauguaugsg	2315	UCUAGACAGUCUA GCAGUUUAU	2670
AD-1550955.1	A-2865086	asgsaca(Uhd)gcUfAfGfcauuuL96	1961	A-2865087	VPudTtsaudAadAcugc dTaGfcauguaugsg	2316	CUAGACAUUCUAG CAGUUUAU	2671

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1550956.1	A-2865088	gsascau(Ghd)cuAfGfC faguuuaualL96	1962	A-2865089	VPusdAsuadTadAacug dCuAfcuagucsesa	2317	UAGACAUGCUGAGC AGUUUAUUG	2672
AD-1550957.1	A-2865090	ascsaug(CHd)uaGfCfA fguuaualL96	1963	A-2865091	VPusdCsandAudAaacu dGcUfagcaugscsu	2318	AGACAUGCUGAGC GUUUUAUUG	2673
AD-1550958.1	A-2865092	csasugc(Uhd)agCfAfG fuuaualL96	1964	A-2865093	VPusdAscadTadTaaacd TgCfuagcaugsc	2319	GACAUGCUGAGC GUUUUAUUG	2674
AD-1550959.1	A-2865094	asusgcu(Ahd)gcAfGf UfuuaualL96	1965	A-2865095	VPusdTscadAudAuaaa dCuGfcuagcaugscsu	2320	ACAUGCUGAGCAGU UUAUAUUG	2675
AD-1550960.1	A-2865096	usgscua(Ghd)caGfUf UfuuaualL96	1966	A-2865097	VPusdAsuadCadTaaad dAcUfagcaugscsu	2321	CAUGCUGAGCAGU UUAUAUUG	2676
AD-1550961.1	A-2865098	gscsuag(CHd)agUfUf UfaualL96	1967	A-2865099	VPusdAsandAadAuaaa dAaCfugcaugscsu	2322	AUGCUGAGCAGU UUAUAUUG	2677
AD-1550963.1	A-2865102	usasgca(Ghd)uuUfAf UfaualL96	1968	A-2865103	VPusdTsgadAudAcaaa dTaAfcuagcaugsc	2323	GCUAGCAGUUUAU AUGUAUUG	2678
AD-1550964.1	A-2865104	asgscag(Uhd)uuAfUf AfuguaualL96	1969	A-2865105	VPusdAsugdAadTaaau dAuAfaucgcaugscsu	2324	CUAGCAGUUUAU AUGUAUUG	2679
AD-1550965.1	A-2865106	gscsagu(Uhd)uaUfAf UfuaualL96	1970	A-2865107	VPusdCsandGadAuaaa dTaUfaaagcaugscsu	2325	UAGCAGUUUAU AUGUAUUG	2680
AD-1550984.1	A-2865144	asgsuaa(Uhd)guGfAf UfaualL96	1971	A-2865145	VPusdCsadAudAuaaa dTcAfcuagcaugscsu	2326	UGAGUAAUGUGAGU AUUAUUGG	2681
AD-1551066.1	A-2865308	gsasgga(Ahd)ugAfGf UfguaualL96	1972	A-2865309	VPusdCsundAudAguca dCuCfauuagcaugscsu	2327	AGGAGGAAUGAGU GACUAUAGG	2682
AD-1551067.1	A-2865310	asgsaga(Uhd)gaGfUf GfauuaualL96	1973	A-2865311	VPusdCsudTadTaaacd AcUfauuagcaugscsu	2328	GGAGGAAUGAGUG ACUAUAGG	2683
AD-1551068.1	A-2865312	gsasau(Ghd)agUfGf AfuaualL96	1974	A-2865313	VPusdTscadTadAuaau dCaCfuaucgcaugscsu	2329	GAGGAAUGAGUG CUAUAGG	2684
AD-1551069.1	A-2865314	gsasau(Ghd)guGfAf CfuuaualL96	1975	A-2865315	VPusdAsudCudTaaag dTcAfcuagcaugscsu	2330	AGGAAUGAGUGAGU UUAUAGG	2685
AD-1551070.1	A-2865316	asasuga(Ghd)ugAfCf UfaualL96	1976	A-2865317	VPusdCsandCedTuaaa dGuCfuaucgcaugscsu	2331	GGAAUGAGUGAGU AUUAUAGG	2686
AD-1551073.1	A-2865322	gsasgug(Ahd)cuAfUf AfaggaualL96	1977	A-2865323	VPusdAsandCadTccuu dAuAfcuagcaugscsu	2332	AUGAGUGAGUUA AGGAUUG	2687
AD-1551076.1	A-2865328	usgsacu(Ahd)uaAfGf GfuaualL96	1978	A-2865329	VPusdGsgudAadCcauc dCuUfuaugcaugscsu	2333	AGUGACUUAAGG AUGGUUACCA	2688
AD-1551077.1	A-2865330	gsascau(Uhd)aaGfGfA fuguuaualL96	1979	A-2865331	VPusdTsggdTadAcauu dCcUfuaugcaugscsu	2334	GUGACUUAAGG UGUUUAUUG	2689

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1551078.1	A-2865332	ascuau(Ahd)agGfAfUfguuaacaaL96	1980	A-2865333	VPusdAsagdGudAacca dTcCfuuaagucsa	2335	UGACUUAUAGGAU GGUAACCAUA	2690
AD-1551086.1	A-2865348	gsasagg(Uhd)uaCfCfAfuagaacuaL96	1981	A-2865349	VPusdAsagdGudTcuau dGgUfaaccacscs	2336	AGGAUGGUUACCA UAGAAACUUC	2691
AD-1551090.1	A-2865356	gsusuae(Chd)auAfGfAfacuucuaL96	1982	A-2865357	VPusdAsagdGadAguuu dCuAfuagucacscs	2337	UGGUUACCAUAGA AACUCCUUU	2692
AD-1551091.1	A-2865358	ususacc(Ahd)uaGfAfAfacuucuaL96	1983	A-2865359	VPusdAsaadGgdAguuu dTcUfaugguuascsc	2338	GGUUAACCAUAGAA ACUCCUUU	2693
AD-1551164.1	A-2865504	usascua(Chd)agAfGfUfguagcuaL96	1984	A-2865505	VPusdCsgadCudTagca dCuCfuuaagucsu	2339	ACUACUACAGAGU GCUAAGCUGC	2694
AD-1551170.1	A-2865516	asgsagu(Ghd)cuAfAfGfucgauguaL96	1985	A-2865517	VPusdCscadAudGcagc dTuAfgcacucsgsu	2340	ACAGAGUGCUAAG CUGCAUGUGU	2695
AD-1551171.1	A-2865518	gsasgug(Chd)uaAfGfCfugcuauguaL96	1986	A-2865519	VPusdAscadCadTgcag dCuUfagcacucsu	2341	CAGAGUGCUAAGC UGCAUGUGUC	2696
AD-1551177.1	A-2865530	usasagc(Uhd)gcAfUfGfucuaucuaL96	1987	A-2865531	VPusdAsagdAudGacac dAuGfcagcucsgsc	2342	GCUAAGCUGCAUG UGUCAUCUUA	2697
AD-1551180.1	A-2865536	gsesguc(Ahd)ugUfGfUfcaucuaacaaL96	1988	A-2865537	VPusdTsgudAadGauga dCaCfaugcagcsu	2343	AAGCUGCAUGUGU CAUCUUAACAC	2698
AD-1551181.1	A-2865538	csusgca(Uhd)guGfUfCfaucaacaaL96	1989	A-2865539	VPusdGsgudTadAgaug dAcAfcagcagcsu	2344	AGCUGCAUGUGUC AUCUUAACAU	2699
AD-1551182.1	A-2865540	usgscau(Ghd)ugUfCfAfucuaacuaL96	1990	A-2865541	VPusdAsagdGudAagau dGaCfagcagcsu	2345	GCUGCAUGUGUCA UCUAACAU	2700
AD-1551251.1	A-2865678	usasgag(Ahd)gaAfAfUfgguuaguuL96	1991	A-2865679	VPusdAsaadCudTaccad TuUfcucucuaugsu	2346	ACUAGAGAGAGAAU GGUAGUUUC	2701
AD-1551253.1	A-2865682	gsasgag(Ahd)aaUfGfGfuaguuuaL96	1992	A-2865683	VPusdAsgadAadCuuaac dCaUfucucucsu	2347	UAGAGAGAGAAUGG UAAAGUUUCU	2702
AD-1551254.1	A-2865684	asgsaga(Ahd)auGfGfUfaaguuuaL96	1993	A-2865685	VPusdAsagdAadAcuaa dCcAfuucucucsu	2348	AGAGAGAGAAUGGU AAGUUUCUUG	2703
AD-1551255.1	A-2865686	gsasgaa(Ahd)ugGfUfAfaguucuaL96	1994	A-2865687	VPusdCsaadGadAacuu dAcCfaucucucsu	2349	GAGAGAGAAUGGUA AGUUUCUUGU	2704
AD-1551256.1	A-2865688	asgsaaa(Uhd)ggUfAfAfguuucuaL96	1995	A-2865689	VPusdAcsadAgdAaacu dTaCfcauucucsu	2350	AGAGAGAAUGGUAA GUUUUCUUGU	2705
AD-1551257.1	A-2865690	gsasaau(Ghd)guAfAfGfuucuaL96	1996	A-2865691	VPusdAsaadAadGaacc dTuAfcacucucsu	2351	GAGAGAAUGGUAAG UUUUCUUGU	2706
AD-1551258.1	A-2865692	asasaug(Ghd)uaAfGfUfucuauguaL96	1997	A-2865693	VPusdAsaadCadAgaau dCuUfaceauucsu	2352	AGAGAAUGGUAAGU UUCUUUGUUU	2707

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1551346.1	A-2865868	usasuuG(Ahd)acAfGfUfaauuuuacagAL96	1998	A-2865869	VPusdCsgadAadAuauadCuGfuuuacagAL96	2353	GUUUAUUGAACAGUUAUUAUUACAGG	2708
AD-1551347.1	A-2865870	asusuga(Ahd)caGfUfAfuaauuacagAL96	1999	A-2865871	VPusdCscudGadAuauadCuUfuuuacagAL96	2354	UUUAUUGAACAGUAUUAUUACAGGA	2709
AD-1551353.1	A-2865882	csasgna(Uhd)auUfUfCfaggaagguuAL96	2000	A-2865883	VPusdAsadCudTccngdAaAfuaucugusuuAL96	2355	AACAGUAUAUUUCAGGAAGGUUA	2710
AD-1551392.1	A-2865960	csusacc(Uhd)aaAfGfCfagcauuuAL96	2001	A-2865961	VPusdAsaadTadTgngdCuUfuaagguagsuuAL96	2356	AUCUACCUAAAGCAGCAUUAUUU	2711
AD-1551566.1	A-2866308	asasguu(Ghd)ngAfCfCfagaauuuAL96	2002	A-2866309	VPusdTsaadAudTcaugdGnUcfacaucuuAL96	2357	GAAAGUUUGUAGACCUGAAUUUUA	2712
AD-1551588.1	A-2866352	asusuaa(Uhd)guGfGfAfuaaauuAL96	2003	A-2866353	VPusdGsaadTudTguauUdCuAfaauaauuAL96	2358	GGAUUUAUGUGGAUACAAAUUCU	2713
AD-1551589.1	A-2866354	usuuuu(Ghd)ngGfAfUfacaauuuAL96	2004	A-2866355	VPusdAsgadAudTuguaUdCcfacaauaauuAL96	2359	GAUUUAUGUGGAUACAAAUUCU	2714
AD-1551590.1	A-2866356	usuuuu(Ghd)ngGfAfUfacaauuuAL96	2005	A-2866357	VPusdGsgadAadTuguUdCuAfaauaauuAL96	2360	AUUUAUGUGGAUACAAAUUCU	2715
AD-1551592.1	A-2866360	asusug(Ghd)auAfCfAfaauuuAL96	2006	A-2866361	VPusdAsggdAadAauuuUdGnUcfacaauuAL96	2361	UUUAUGUGGAUACAAAUUCU	2716
AD-1551646.1	A-2866468	gsgsuaa(Chd)aaAfUfUfcauuuuAL96	2007	A-2866469	VPusdTsuadAadGgagaUdAuUfuuuauuAL96	2362	GUGGAUACAAAUUCUCCUUUA	2717
AD-1551648.1	A-2866472	asusaca(Ahd)auUfCfUfcauuuuAL96	2008	A-2866473	VPusdCsuadTadAaggaUdGaAfuuuauuAL96	2363	GGAUACAAAUUCUCCUUUAAGU	2718
AD-1551649.1	A-2866474	usascaaa(Ahd)uuCfUfCfcauuuuAL96	2009	A-2866475	VPusdAscudTudAaaggUdAgAfaauuauuAL96	2364	GAUACAAAUUCUCCUUUAAGU	2719
AD-1551650.1	A-2866476	ascsaaa(Uhd)ucUfCfCfuuuuuAL96	2010	A-2866477	VPusdCscadTudTaaagdGaGfaauuauuAL96	2365	AUACAAAUUCUCCUUUAAGU	2720
AD-1551651.1	A-2866478	csasaau(Uhd)cuCfCfUfuuuuuAL96	2011	A-2866479	VPusdAscudTudTaaagdGgAfaauuauuAL96	2366	UACAAAUUCUCCUUUAAGU	2721
AD-1551653.1	A-2866482	asauuu(Uhd)ccUfUfUfuaagguuAL96	2012	A-2866483	VPusdAsaadCadCuuaaUdAaGfagaauuAL96	2367	CAAAUUCUCCUUUAAGU	2722
AD-1551655.1	A-2866486	ususcuc(Chd)uuUfAfAfagguuuuAL96	2013	A-2866487	VPusdAsgadAadCacuuUdTaAfaaggaauuAL96	2368	AAUUCUCCUUUAAGU	2723
AD-1551656.1	A-2866488	uscsucc(Uhd)uuAfAfAfugguuuuAL96	2014	A-2866489	VPusdAsaadAadAcacuUdTuAfaaggaauuAL96	2369	AUUCUCCUUUAAGUGUUUUCU	2724
AD-1551657.1	A-2866490	csusccu(Uhd)uaAfAfGfuuuuuAL96	2015	A-2866491	VPusdGsaadGadAaacUdTuUfaaaggaauuAL96	2370	UUCUCCUUUAAGUGUUUUCU	2725

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1551658.1	A-2866492	uscscuu(Uhd)aaAfGfUfguuuuccaL96	2016	A-2866493	VPsdGsgdAadAaaca dCuUfuaaaggagsga	2371	UCUCCUUUAAAAGU GUUUUUUUCCC	2726
AD-1551659.1	A-2866494	cscsuuu(Ahd)aaGfUfGfuuuuccaL96	2017	A-2866495	VPsdGsgdAadGaaac dAcUfuaaaggagsg	2372	CUCCUUUAAAAGU GUUUUUUUCCC	2727
AD-1551661.1	A-2866498	usuuuaa(Ahd)guGfUfUfuuuuccaL96	2018	A-2866499	VPsdAsadGgdAagaa dAcAfcuuuaasgsg	2373	CCUUUAAAAGUGUU UUUUUUUUUUU	2728
AD-1551665.1	A-2866506	asasguu(Uhd)uuCfUfUfcccuaaL96	2019	A-2866507	VPsdTsaadTadAggga dAgAfaaacaacusa	2374	UAAAAGUGUUUUUU CCCUUUUUUUU	2729
AD-1551666.1	A-2866508	asgsugu(Uhd)ucUfUfCfcuaaL96	2020	A-2866509	VPsdAsaadTudAaggg dAaGfaaacaacusa	2375	AAAGUGUUUUUUUU CCUUUUUUUUUU	2730
AD-1551667.1	A-2866510	gsusguu(Uhd)cuUfCfCfcuaaL96	2021	A-2866511	VPsdAsaadTadAaggg dGafgaacaacusa	2376	AAGUGUUUUUUUU CCUUUUUUUUUU	2731
AD-1551668.1	A-2866512	gsusguu(Uhd)ucCfCfUfuaaL96	2022	A-2866513	VPsdTsaadAadAuaaa dGgGfaaacaacusa	2377	GUGUUUUUUUUUUU UAAUUUUUUUU	2732
AD-1551670.1	A-2866516	ususcuu(Chd)ccUfUfUfuaaL96	2023	A-2866517	VPsdGsaadAadAuaau dAaGfagaacaacusa	2378	GUUUUUUUUUUUU AUUUUUUUUU	2733
AD-1551672.1	A-2866520	csusucc(Chd)uuAfAfUfaaL96	2024	A-2866521	VPsdCsgadAadAuaaa dTuAfaggaagagasa	2379	UUCUUUUUUUUUUU AUUUUUUUUU	2734
AD-1552052.1	A-2867280	csusucc(Chd)uuCfUfUfuaaL96	2025	A-2867281	VPsdAsaadAadTuggg dAgAfaaacaacusa	2380	GACUUACAUUUCUC CCAAGUUUUUU	2735
AD-1552053.1	A-2867282	ususaaca(Uhd)ucUfCfUfuaaL96	2026	A-2867283	VPsdAsaadAadCuugg dGafgaacaacusa	2381	ACUUACAUUUCUCC CAAGUUUUUU	2736
AD-1552054.1	A-2867284	usascuu(Uhd)cuCfCfUfuaaL96	2027	A-2867285	VPsdGsaadTadAcuug dGgAfaaacaacusa	2382	CUUACAUUUCUCCC AAGUUUUUUU	2737
AD-1552055.1	A-2867286	ascsuuu(Chd)ucCfCfUfuaaL96	2028	A-2867287	VPsdTsgadAadAuaaa dGgGfaaacaacusa	2383	UUACAUUUCUCCC AGUUUUUUUU	2738
AD-1552056.1	A-2867288	csasuuu(Uhd)ccCfAfUfuaaL96	2029	A-2867289	VPsdCsgadAadTaaau dTgGfagaagagusa	2384	UACAUUUCUCCCAG GUUUUUUUUU	2739
AD-1552057.1	A-2867290	asusuuu(Chd)ccAfAfUfuaaL96	2030	A-2867291	VPsdGscudAadAuaac dTuGfagaagagusa	2385	ACAUUUCUCCCAG GUUUUUUUUU	2740
AD-1552065.1	A-2867306	asasguu(Chd)uuCfAfUfuaaL96	2031	A-2867307	VPsdCsaadAadGaggg dTgAfaaacaacusa	2386	CCAAGUUUUUUUUU CCUCAUUUUU	2741
AD-1552066.1	A-2867308	asgsuuu(Uhd)ucAfGfUfuaaL96	2032	A-2867309	VPsdTsaadTadTgaggg CuGfaaacaacusa	2387	CAAGUUUUUUUUU CUCUAUUUUU	2742
AD-1552067.1	A-2867310	gsusuuu(Uhd)caGfCfUfuaaL96	2033	A-2867311	VPsdGscudAadAugag dGcUfagaacaacusa	2388	AAGUUUUUUUUUUU UCAUUUUUUU	2743

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1552158.1	A-2867492	ascasgu(Uhd)caGfAfG fugacauuugaL96	2034	A-2867493	VPusdCsaadAadTgcac dTcUfugaacugususu	2389	AAACAGUUCAGAG UGCACUUUGG	2744
AD-1552159.1	A-2867494	csasgu(Chd)agAfGf UfugaacuggaL96	2035	A-2867495	VPusdCsaadAadGugca dCuCfugaacugususu	2390	AACAGUUCAGAGU GCACUUUGG	2745
AD-1552161.1	A-2867498	gsusuca(Chd)agUfGf CfagaucuggaL96	2036	A-2867499	VPusdTsgcdCadAagug dCaCfugaacugususu	2391	CAGUUCAGAGUGC ACUUUGGCAC	2746
AD-1552169.1	A-2867514	usgsac(Uhd)uuGfGf CfagaacuggaL96	2037	A-2867515	VPusdCsaadTudGugug dCcAfaagugcascsu	2392	AGUGCACUUUGGC ACACAAUUGG	2747
AD-1552191.1	A-2867558	asascag(Ahd)acAfAfU fcauaguguaL96	2038	A-2867559	VPusdAscadCadTuaga dTcUfugaacugususu	2393	GGACACAGAACAAU CUAAUGUGUG	2748
AD-1552192.1	A-2867560	ascsga(Ahd)caAfUfC fuauguguaL96	2039	A-2867561	VPusdCsaadAadAuuag dAuUfugaacugususu	2394	GAACAGAACAAUC UAAUGUGUG	2749
AD-1552193.1	A-2867562	csasga(Chd)aaUfCfU fauguguguaL96	2040	A-2867563	VPusdCsaadCadCauna dGaUfugaacugususu	2395	AACAGAACAAUCU AAUGUGUGU	2750
AD-1552244.1	A-2867664	asgsaac(Ahd)auCfUfA fauguguguaL96	2041	A-2867665	VPusdAscadAadAcauu dAgAfuugugususu	2396	ACAGAACAAUCUA AUGUGUGUU	2751
AD-1552247.1	A-2867670	ascsaau(Chd)uaAfUfG fuguguguaL96	2042	A-2867671	VPusdCsaadAadCacacd AuUfugaacugususu	2397	GAACAAUCUAAUG UGUGUGUUUG	2752
AD-1552248.1	A-2867672	csasauc(Uhd)aaUfGfU fuguguguaL96	2043	A-2867673	VPusdCsaadAadCcaad CaUfugaacugususu	2398	AACAAUCUAAUGU GUGGUUUGU	2753
AD-1552249.1	A-2867674	asasuc(Uhd)auGfUf GfuguguguaL96	2044	A-2867675	VPusdAscadAadAccac dAcAfuugugususu	2399	ACAAUCUAAUGUG UGGUUUUGUA	2754
AD-1552250.1	A-2867676	asuscua(Ahd)ugUfGf UfuguguguaL96	2045	A-2867677	VPusdTsaadCadAaccad CaCfaucugususu	2400	CAUCUAAUGUGU GGUUUGUAU	2755
AD-1552251.1	A-2867678	uscuaa(Uhd)guGfUf GfuguguguaL96	2046	A-2867679	VPusdAsuadCcdAaacc dAcAfaucugususu	2401	AAUCUAAUGUGUG GUUUUGUAU	2756
AD-1552253.1	A-2867682	usasau(Uhd)guGfGf UfuguguguaL96	2047	A-2867683	VPusdGsaadTadCcaad CcAfaucugususu	2402	UCUAAUGUGUGUGU UUGUAUUC	2757
AD-1552254.1	A-2867684	asasugu(Chd)ugGfUf UfuguguguaL96	2048	A-2867685	VPusdGsgadAadAccaa dAcCfaucugususu	2403	CUAAUGUGUGUGU UGGUUUUGUA	2758
AD-1552255.1	A-2867686	asusgu(Uhd)ggUfUf UfuguguguaL96	2049	A-2867687	VPusdTsgadAadTaccad AaCfagaacugususu	2404	UAAUGUGUGUGUU GGUAUUC	2759
AD-1552257.1	A-2867690	gsusgu(Chd)uuUfGf GfuaucuguaL96	2050	A-2867691	VPusdCsuadGgdAaacc dCaAfaucugususu	2405	AUGUGUGUGUGUG UAUUCCAAU	2760
AD-1571164.1	A-1142146	gsusgu(Chd)UfGfUfA fAfaucuguaL96	2051	A-2901262	VPusUfsgadAu(Tgn)cc uuuAfaCfagaacugususu	2406	CAGUGUGUGUGUAA AGGAUUCAU	2761

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1571165.1	A-1142150	gsusggg(Ghd)UfaAfA fGfgaaucauaL96	2052	A-2901263	VPusAfsadGa(Agn)uu ccuuUfaCfaccacsasc	2407	GUGUGGUGUAAAAG GAAUUAUAU	2762
AD-1571166.1	A-1142190	asgscca(Uhd)GfgAfUf GfuaucagaalL96	2053	A-2901264	VPusUfscadTg(Agn)au acuuCfcAfuggcusa	2408	UUAAGCCAUUGGAUG UAUUCAUGAA	2763
AD-1571167.1	A-1142200	usgsgru(Ghd)UfaUfUf CfauagaagaaL96	2054	A-2901265	VPusUfscadTu(Tgn)ca ugaUfaCfauccasug	2409	CAUGGAUGUAUUC AUGAAAGGAC	2764
AD-1571168.1	A-1142214	asusuca(Uhd)GfaAfAf GfgacuuaaaL96	2055	A-2901266	VPusUfsgdAa(Agn)gu ccuuUfcAfugaasasc	2410	GUUAUUAUGAAAAG GACUUUCAA	2765
AD-1571169.1	A-1142222	asusga(Ahd)GfgAfCf UfucaaaagaaL96	2056	A-2901267	VPusGfscdTu(Tgn)ga aaguCfcUfmucausga	2411	UCAUGAAAAGGACU UUCAAGGCC	2766
AD-1571170.1	A-1142224	usgsaaa(Ghd)GfaCfUf UfucaaaagaaL96	2057	A-2901268	VPusGfsgcdCu(Tgn)ug aaagUfcCfuucasug	2412	CAUGAAAAGGACUU UCAAAAGGCA	2767
AD-1571171.1	A-1142402	gsusgug(Uhd)UfcUfCf UfaugaagaaL96	2058	A-2901269	VPusAfsadCu(Agn)ca uagaGfaAfaccacsusc	2413	GAGGUGUUCUCU AUGUAGGCU	2768
AD-1571172.1	A-1142522	gsusgug(Ahd)GfaAfGf AfcaaaagaaL96	2059	A-2901270	VPusGfscdCu(Tgn)ug gucuUfcUfcagccsasc	2414	GUGGUCUGAGAAGA CCAAAGAGCA	2769
AD-1571173.1	A-1142534	gsasaga(Chd)CfaAfAf GfagaagaaL96	2060	A-2901271	VPusUfscadCu(Tgn)gc ucuUfGfufmucaususc	2415	GAGAAAGACCAAAG AGCAAAGGAC	2770
AD-1571174.1	A-1142868	csusuga(Chd)AfaUfGf AfggcuuaaaL96	2061	A-2901272	VPusUfscadTa(Agn)gc cucaUfuGfucaggsasu	2416	AUCCUGACAAUGA GGUUAUGAA	2771
AD-1571175.1	A-1142878	csasang(Ahd)GfgCfUf UfaugaagaaL96	2062	A-2901273	VPusGfscadTu(Tgn)ca uaagCfcUfcauugususc	2417	GACAAUGAGGCUU AUGAAAUGCC	2772
AD-1571176.1	A-1142880	asasuga(Ghd)GfcUfUf AfugaagaaL96	2063	A-2901274	VPusGfsgcdAu(Tgn)uc auaaGfcCfuauggsu	2418	ACAAUGAGGCUUA UGAAAUGCCU	2773
AD-1571177.1	A-1142902	usgsaaa(Uhd)GfcCfUf UfcugagaagaL96	2064	A-2901275	VPusCfsuudCc(Tgn)ca gaagGfcAfmucaususa	2419	UAUGAAAUGCCUU CUGAGGAAGG	2774
AD-1571178.1	A-1142936	asasggg(Uhd)AfuCfAf AfgaucagaalL96	2065	A-2901276	VPusUfscdGu(Agn)gu cuugAfuAfccuiscusc	2420	GGAAGGGUAUCAA GACUACGAAC	2775
AD-1571179.1	A-1142938	asgsgru(Ahd)UfcAfAf GfacuacagaalL96	2066	A-2901277	VPusGfsuudCg(Tgn)ag ucuUfGfUfaccuiscusc	2421	GAAGGGUAUCAAG ACUACGAACC	2776
AD-1571180.1	A-1142974	ascsug(Ahd)AfgCfCf UfaagaauaaL96	2067	A-2901278	VPusAfsadTu(Tgn)cu uaagCfcUfcaugususc	2422	GAACCCUGAAGCCU AAGAAUAUC	2777
AD-1571181.1	A-1142978	csusga(Ghd)CfcUfAf AfgaauaauaL96	2068	A-2901279	VPusUfsgadTa(Tgn)uu cuuaGfgCfuicaggsu	2423	ACCUGAAGCCUAA GAAUAUUCU	2778
AD-1571182.1	A-1142982	gsasagc(Chd)UfaAfGf AfauaucauaL96	2069	A-2901280	VPusAfsadGa(Tgn)au uuUfGfGfmucausasc	2424	CUGAAGCCUAAAGA AAUAUCUUUG	2779

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1571183.1	A-1142992	csusaag(Ahd)AfaUfAfUfcuunguccaL96	2070	A-2901281	VPusGfsadGc(Agn)aa gaaUfuUfcuungsgsc	2425	GCCUAAAGAAUAU CUUUGCUCC	2780
AD-1571184.1	A-1143006	asusac(Uhd)UfuGfCfUfccaguucaL96	2071	A-2901282	VPusGfsadAc(Tgn)gg gacAfaAfgauausu	2426	AAUAUCUUUGCU CCCAGUUUCU	2781
AD-1571185.1	A-1143018	ususgc(Uhd)CfcAfGfUfcuungagaaL96	2072	A-2901283	VPusUfscudCa(Agn)ga aacuGfGfagcaasag	2427	CUUUGCUCCAGU UUUCUUGAGAU	2782
AD-1571186.1	A-1143020	usgsc(Uhd)CfaGfUfUfcuungagaaL96	2073	A-2901284	VPusAfsudTc(Agn)ag aaacUfgGfagcasasa	2428	UUUGCUCCAGUU UCUUGAGAU	2783
AD-1571187.1	A-1143100	csusgaa(Chd)AfaGfUfGfucaguucaL96	2074	A-2901285	VPusGfsadAc(Tgn)ga gcacUfuGfucagsgsa	2429	UCCUGUACAAUG CUCAGUUCCA	2784
AD-1571188.1	A-1143104	gsusaca(Ahd)GfuGfCfUfcaguucaL96	2075	A-2901286	VPusUfsgdGa(Agn)cu gagcAfcUfuguaacsag	2430	CUGUACAAAGUG CAGUUCCAAU	2785
AD-1571189.1	A-1143154	csusgaa(Chd)AfuGfAfCfaunucuaaL96	2076	A-2901287	VPusUfsgdAg(Agn)aa ungUfuGfucagsgsc	2431	GCCCAGUCAUGAC AUUUCUCAA	2786
AD-1571190.1	A-1143240	uscsuuc(Chd)AfuCfAfGfcaguucaL96	2077	A-2901288	VPusCfsadTc(Agn)cu gcugAfuGfagaaacsu	2432	AGUCUCCAUUCAG CAGUGAUUGA	2787
AD-1571191.1	A-1143244	usucca(Uhd)CfaGfCfAfcuungaaL96	2078	A-2901289	VPusUfsgdAa(Tgn)ca cugcUfgAfcuungsgsa	2433	UCUCCAUUCAGCA GUGAUUGAAG	2788
AD-1571192.1	A-1143248	csusac(Uhd)GfcAfGfUfcuungaaL96	2079	A-2901290	VPusAfsudTc(Agn)au cacUfuGfagaaacsu	2434	UCCAUUCAGCAGU GAUUGAAUGA	2789
AD-1571193.1	A-1143252	asusac(Uhd)AfuGfUfAfcuungaaL96	2080	A-2901291	VPusAfsudCu(Tgn)ca aucaCfuGfcuungsgsg	2435	CCAUUCAGCAGUGA UUGAAUGAUC	2790
AD-1571194.1	A-1143260	gscsagu(Chd)AfuUfGfAfaguucaL96	2081	A-2901292	VPusAfsadGa(Tgn)ac uucaAfuCfagucsu	2436	CAGCAGUGAUUGA AGUAUCUGUA	2791
AD-1571195.1	A-1143310	csusucc(Chd)UfuUfCfAfcuungaaL96	2082	A-2901293	VPusUfscadCu(Tgn)ca gugaAfaGfagaaacsu	2437	UGCUUCCUUUCA CUGAAUGGAA	2792
AD-1571196.1	A-1143324	ususcac(Uhd)GfaAfGfUfgaaacaL96	2083	A-2901294	VPusCfsadGu(Agn)uu cacUfcAfcuungaaacsag	2438	CUUUCACUGAAGU GAAUACAUGG	2793
AD-1571197.1	A-1143326	uscsacu(Chd)AfaGfUfGfaaacaL96	2084	A-2901295	VPusCfsadTg(Tgn)au ucaCfuCfagucgasa	2439	UUUCACUGAAGUG AAUAUCAUGU	2794
AD-1571198.1	A-1143330	ascsgaa(Chd)GfuGfAfAfcuungaaL96	2085	A-2901296	VPusUfscadCa(Tgn)gu auucAfcUfcuungsgsa	2440	UCACUGAAGUGAA UACAUGGUAG	2795
AD-1571199.1	A-1143496	csusacc(Uhd)CfuUfAfUfcuuaaL96	2086	A-2901297	VPusGfsadTu(Agn)ga aaauAfcUfcuungsgsc	2441	GACUACACUUAU UUCUAAAUC	2796
AD-1571200.1	A-1143498	usascac(Chd)UfuAfUfUfcuuaaL96	2087	A-2901298	VPusGfsadTu(Tgn)ag aaauAfaGfuguaacsu	2442	ACUACACUUAU UCUAAAUCU	2797

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1571201.1	A-1143502	cscsacu(Uhd)AfuUfUfCfuaaauccuaL96	2088	A-2901299	VPusGfsagdGa(Tgn)uuagaaAfuAfaaguggsusa	2443	UACCACUUUAUUUCUAAAUCUCA	2798
AD-1571202.1	A-1143558	asgsung(Uhd)UfaGfUfGfaauugcuuaL96	2089	A-2901300	VPusAfsnadGc(Agn)aaucacUfaAfaacausc	2444	GAAGUUGUUAGUGAUUUGCUAUC	2799
AD-1571203.1	A-1143638	asusacu(Ghd)UfcUFAfAfagaauaagaL96	2090	A-2901301	VPusUfiscadTu(Agn)uucuaGfaCfagauusesa	2445	UGAUACUGUCUAA	2800
AD-1571204.1	A-1143700	asusaug(Uhd)GfaGfCfAfagaauaualL96	2091	A-2901302	VPusAfsnadGu(Tgn)ucaugcUfcAfaacausu	2446	GAAUAAUGAC	2801
AD-1571205.1	A-1143702	usasugu(Ghd)AfgCfAfUfgaauaualL96	2092	A-2901303	VPusCfsaudAg(Tgn)uucangCfuCfacaauuscu	2447	AAUUAUGUGAGCAUUGAAACUAUG	2802
AD-1571206.1	A-1143706	usgsuga(Ghd)CfaUfGfAfaacuaualL96	2093	A-2901304	VPusUfsgcdAu(Agn)guuucalUfgCfucacausa	2448	AAUUAUGUGAGCAUUGAAACUAUG	2803
AD-1571207.1	A-1143728	asascua(Uhd)GfcAfCfCfuaaauaualL96	2094	A-2901305	VPusGfsnadTu(Tgn)uagguGfcAfaagunuscu	2449	GAAACUAUGCACC	2804
AD-1571208.1	A-1143732	csusaug(CHD)AfcCfUfAfuaaauaualL96	2095	A-2901306	VPusUfsgadTa(Tgn)uuaugGfuGfcauagsusu	2450	UAUAAUAUCU	2805
AD-1571209.1	A-1143818	usgsuuu(Ghd)UfaUfaUfaaauugugaalL96	2096	A-2901307	VPusUfiscadCc(Agn)uuuaualUfaCfaaacacsa	2451	UUAUAAUAUA	2806
AD-1571210.1	A-1143904	cscscacu(CHD)UfcAfCfUfuuaaauaualL96	2097	A-2901308	VPusUfiscadTa(Tgn)uaagguGfaGfauggggsasu	2452	UUAUAAUAUA	2807
AD-1571211.1	A-1144738	asusauu(Ahd)GfcAfCfAfuaaaggcuL96	2098	A-2901309	VPusAfsagdCu(Tgn)gauguGfcUfaaauagsu	2453	ACAUAUUAGCACA	2808
AD-1571212.1	A-1145040	csusuuu(Ahd)AfuGfUfUfgcaauaualL96	2099	A-2901310	VPusAfsnadTu(Tgn)ggcaacAfuUfaaagggsa	2454	UCCUUUAAAUGUU	2809
AD-1571213.1	A-1145068	asasaua(Uhd)AfuGfAfAfuaaaggauL96	2100	A-2901311	VPusAfsnadCu(Agn)gaauucAfuAfaauuusgg	2455	GCCAAUAUA	2810
AD-1571214.1	A-1145152	uscsuuu(CHD)AfgGfGfAfagaauaualL96	2101	A-2901312	VPusAfsaudAg(Agn)ucaucCfuGfaaagggsa	2456	UUCUAGGCU	2811
AD-1571215.1	A-1145338	gsasaua(Uhd)UfcUFAfGfagaugcuagaL96	2102	A-2901313	VPusCfsnadGc(Agn)ugucuaGfaAfaauuscu	2457	ACAUGCUAGC	2812
AD-1571216.1	A-1145344	usasuuu(CHD)AfgAfCfAfugaagcagaL96	2103	A-2901314	VPusCfsugdCu(Agn)gcanguCfuAfaaauuscu	2458	AAUUAUUUCUAGACA	2813
AD-1571217.1	A-1145352	csusaga(CHD)AfuGfCfUfagcaguuuaL96	2104	A-2901315	VPusUfiscadAc(Tgn)gcuaagcAfuGfuaaggsa	2459	UGCUAGCAU	2814
AD-1571218.1	A-1145366	usgsuau(CHD)CfaGfUfUfuuaaauaualL96	2105	A-2901316	VPusAfsnadCa(Tgn)uuaacUfgCfuaagcasu	2460	AGCAGUUUAU	2815

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1571219.1	A-1145368	gscsuag(Chd)AfgUfUfUfUfaugauguaaL96	2106	A-2901317	VPusAfsadAc(Agn)uaaauaCfuGfuaagcsasu	2461	AUGCUAGCAGUUUUAUGUAUUC	2816
AD-1571220.1	A-1145378	csasgu(Uhd)AfuAfUfGfuaucagaaL96	2107	A-2901318	VPusUfscadTg(Agn)auacauAfuAfaucgcsu	2462	AGCAGUUUAUGUAUUCAGAG	2817
AD-1571221.1	A-1145398	gsusaui(Chd)AfuGfAfGfuauguaaL96	2108	A-2901319	VPusAfsadAc(Agn)uuacucAfuGfuaucgsasu	2463	AUGUAUUCAGAGUAUUGUAUA	2818
AD-1571222.1	A-1145484	gsasaug(Ahd)GfuGfAfCfuaaaggaaL96	2109	A-2901320	VPusAfsadCu(Tgn)auagucAfcUfcauucscsu	2464	AGGAUAGAGUGACUAUAAAGGAG	2819
AD-1571223.1	A-1145492	gsasgu(Ahd)CfuAfUfAfagaagaaL96	2110	A-2901321	VPusAfsadCa(Tgn)ccuuauAfgUfcaucgsasu	2465	AUGAGUGACUAUAAGGAGGUUA	2820
AD-1571224.1	A-1145500	gsascua(Uhd)AfaGfGfAfugguacaaL96	2111	A-2901322	VPusUfsggdTa(Agn)ccauccUfuAfuagucscsu	2466	GUGACUAUAAGGAGGUUAACCAU	2821
AD-1571225.1	A-1145510	usasagg(Ahd)UfgGfUfUfacaagaaL96	2112	A-2901323	VPusUfscadTa(Tgn)gguaacCfaUfcauuausa	2467	UAUAAGGAGUGGUUAACCAUAGAA	2822
AD-1571226.1	A-1145518	gsasugg(Uhd)UfaCfCfAfuaagaacuaL96	2113	A-2901324	VPusAfsagdTu(Tgn)cuauugUfaAfcuacscsu	2468	AGGAGUGGUUACCAUAGAAACUUC	2823
AD-1571227.1	A-1145520	asusggu(Uhd)AfcCfAfUfagaacuaL96	2114	A-2901325	VPusGfsaadGu(Tgn)ucuaugGfuAfaacauusc	2469	GGAUGGUUACCAUAGAAACUUC	2824
AD-1571228.1	A-1145526	gsusnac(Chd)AfuAfGfAfaacuaL96	2115	A-2901326	VPusAfsagdGa(Agn)guuuuAfuGfuaacscsa	2470	UGGUUACCAUAGAAACUUCUUU	2825
AD-1571229.1	A-1145528	ususaac(Ahd)UfaGfAfAfaucuaL96	2116	A-2901327	VPusAfsaadGg(Agn)aguuuUfaUfaguuascsc	2471	GGUUAACCAUAGAAACUUCUUU	2826
AD-1571230.1	A-1145572	csusaui(Ahd)CfaGfAfGfugaagaaL96	2117	A-2901328	VPusAfsagdTu(Agn)gcacucUfgUfaguuascsc	2472	GACUACUACAGAGUGCUAAGCUG	2827
AD-1571231.1	A-1145594	usgsua(Ahd)GfcUfGfCfagauguaaL96	2118	A-2901329	VPusAfsadAc(Agn)caugcaGfcUfuaagcsasu	2473	AGUGCUAAGCUGCAUGUGUCAUC	2828
AD-1571232.1	A-1145610	usgscau(Ghd)UfgUfCfAfucuaaL96	2119	A-2901330	VPusAfsagdGu(Agn)agauaCfaCfaugcagsc	2474	GCUGCAUGUGUCAUCUUAACUA	2829
AD-1571233.1	A-1145648	usasgag(Ahd)GfaAfAfUfguaaguaaL96	2120	A-2901331	VPusAfsadCu(Tgn)accauuUfcUfcauagcsu	2475	ACUAGAGAGAAAUUGGUAAGUUUC	2830
AD-1571234.1	A-1145650	asgsaga(Ghd)AfaAfUfGfuaaguucaL96	2121	A-2901332	VPusGfsaadAc(Tgn)uaaccauUfuCfucucag	2476	CUAGAGAGAAAUUGUAAGUUUCU	2831
AD-1571235.1	A-1145742	usugaa(Chd)AfgUfAfUfaucagaaL96	2122	A-2901333	VPusUfscadTg(Agn)aaauaCfuGfuaacsa	2477	UAUUGAACAGUAUAUUUCAGAA	2832
AD-1571236.1	A-1145752	csasgna(Uhd)AfuUfUfCfagaagaaL96	2123	A-2901334	VPusAfsadCu(Tgn)ccugaaAfuAfuacugcsu	2478	AACAGUAUAUUUCAGGAGGUUA	2833

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1571237.1	A-1145972	gsgaaa(Ghd)UfuGfUfGfaccagaauaL96	2124	A-2901335	VPusAfsuudCa(Tgn)ggueacAfaCfuucccsusa	2479	UAGGAAAGUUGUGACCAUGAAUU	2834
AD-1571238.1	A-1146022	asusuaa(Ghd)GfuGfGfAfuacaauuacalL96	2125	A-2901336	VPusGfsadTu(Tgn)guauccAfcAfuauaascsc	2480	GGAUUUUGUGGUAUACAAUUUU	2835
AD-1571239.1	A-1146028	usasugu(Ghd)GfaUfAfCfaaauuuccalL96	2126	A-2901337	VPusGfsadGa(Agn)uuguaUfcCfacaatasa	2481	UUUUGUGGAUACAAUUCUU	2836
AD-1571240.1	A-1146050	asasaui(Chd)UfcCfUfUfuuaaguguaL96	2127	A-2901338	VPusAfsadAc(Tgn)uuuaagGfaGfaauuugsu	2482	ACAAAUUCUCCUUUAAAGUGUU	2837
AD-1571241.1	A-1146054	asusueu(Chd)CfuUfUfAfaaguguaL96	2128	A-2901339	VPusGfsadAc(Agn)cuuaaaAfgGfagaauusu	2483	AAUUCUCCUUUAAGUGUUUU	2838
AD-1571242.1	A-1146062	uscsuui(Uhd)AfaAfGfUfguuuuccalL96	2129	A-2901340	VPusGfsadAg(Agn)aacacuUfuAfaagsgsa	2484	UCUCCUUUAAAGUGUUUUUUUUUU	2839
AD-1571243.1	A-1146066	csusuaa(Ahd)AfgUfGfUfuuuuccuL96	2130	A-2901341	VPusAfsadGa(Agn)gaacacCfuUfuuaagsgsa	2485	UCCUUUAAAGUGUUUUUUUUUU	2840
AD-1571244.1	A-1146068	ususuua(Ahd)GfuGfUfUfuuuuccuL96	2131	A-2901342	VPusAfsadGg(Agn)agaacacAfcUfuuaaagsg	2486	CCUUUAAAGUGUUUUUUUUUU	2841
AD-1571245.1	A-1146450	csusuac(Ahd)UfuCfUfCfcaaguuuaL96	2132	A-2901343	VPusAfsuudAc(Tgn)ugggagAfaUfguaagusc	2487	GACUUACAUUCUCUCCAAUUUU	2842
AD-1571246.1	A-1146460	asusueu(Chd)CfcAfAfGfuuaucagcaL96	2133	A-2901344	VPusGfsuudGa(Agn)uaacuuGfgGfagaauusg	2488	ACAUUCUCCCAAGUUUUUACGCC	2843
AD-1571247.1	A-1146482	ususuui(Chd)AfgCfCfUfcauagacuaL96	2134	A-2901345	VPusAfsuudCa(Tgn)auaggCfuGfauuaascu	2489	AGUUUUUACAGCCUUAUUGACUC	2844
AD-1571248.1	A-1146634	asgsaac(Ahd)AfuCfUfAfauguguguaL96	2135	A-2901346	VPusAfsuudAc(Agn)cauuagAfuUfguuucsgsu	2490	ACAGAACAAUUCUAUGUGUGUU	2845
AD-1571249.1	A-1146638	asascua(Uhd)CfuAfAfUfguguguaL96	2136	A-2901347	VPusAfsuudCc(Agn)cauuuAfgAfuuguuucsu	2491	AGAACAAUUCUAAUGUGUGUUU	2846
AD-1571250.1	A-1146654	asasugu(Chd)UfgGfUfUfuguaucalL96	2137	A-2901348	VPusGfsadAu(Agn)ccaaacCfaCfacaauasg	2492	CUAAUGUGUGUGUUUGUAUUAUCCA	2847
AD-1571251.1	A-1146656	asusngu(Uhd)GfuUfUfUfguuaucalL96	2138	A-2901349	VPusUfsgdAa(Tgn)acaaacCfcAfcacausa	2493	UAAUGUGUGUUUUGUAUUAUCCA	2848
AD-1571252.1	A-1146660	gsusngu(Chd)UfuUfGfGfuaucacagaL96	2139	A-2901350	VPusCfsuudGg(Agn)auaccaAfaCfcaacasa	2494	AUGUGUGUUUUGUAUUAUCCA	2849
AD-1571253.1	A-1142114	usgscc(Ahd)UfuCfGfAfcagacuguaL96	2140	A-2901351	VPusAfsadCu(G2p)ucguccAfaUfgccacscu	2495	AGUGGCCAUUCGACACAGUG	2850
AD-1571254.1	A-1142132	gsasega(Chd)AfgUfGfUfgguuaaagaL96	2141	A-2901352	VPusCfsuudTa(C2p)accacaCfuGfucgucsgsa	2496	UCGACGACAGUGUGUGUAAAGG	2851

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1571255.1	A-1142192	gscscat(Ghd)GfaUfGfUfaucuaagaaL96	2142	A-2901353	VPusUfscdAu(G2p)aa uacaUfcCfaugcgsusa	2497	UAGCCAUGGAUGU AUUCAUGAAA	2852
AD-1571256.1	A-1142198	asusga(Uhd)GfuAfUfUfcaugaagaaL96	2143	A-2901354	VPusCfsudTu(C2p)au ggauAfcAfuccaugg	2498	CCAUGGAUGUAU CAUGAAAAGA	2853
AD-1571257.1	A-1142400	asgsgr(Ghd)UfuCUfCfuauguaagaaL96	2144	A-2901355	VPusGfscdTa(C2p)au agagAfaCfaccucsu	2499	AGAGGUGUUCUC UAUGUAGGCU	2854
AD-1571258.1	A-1142546	csasaag(Ahd)GfcAfAfGfugacaaagaaL96	2145	A-2901356	VPusCfsudTu(G2p)uc acuuGfcUfcuuugsgsu	2500	ACCAAGAGCAAG UGACAAAUGU	2855
AD-1571259.1	A-1142556	asgscaat(Ghd)UfgAfCfAfaunguagaaL96	2146	A-2901357	VPusUfscdAa(C2p)au unguCfaCfmgucsu	2501	AGAGCAAUGACAA AUUGUUGGAG	2856
AD-1571260.1	A-1142876	ascsaau(Ghd)AfgGfCfUfuaugaaagaaL96	2147	A-2901358	VPusCfsudTu(C2p)au aagcCfuCfauugscsa	2502	UGACAAUGAGGCU UAUGAAAUGC	2857
AD-1571261.1	A-1143032	csasgru(Uhd)CfuUfGfAfgaucugaaL96	2148	A-2901359	VPusCfsagCa(G2p)au cucaAfgAfaacugsgsg	2503	CCCAGUUUCUUGA GAUCUGCUGA	2858
AD-1571262.1	A-1143102	usgsuac(Ahd)AfgUfGfCfucaguucaaaL96	2149	A-2901360	VPusUfsggdAa(C2p)ug agcaCfuUfguacsgsg	2504	CCUGUACAAGUGC UCAGUUCCA	2859
AD-1571263.1	A-1143110	csasagr(Ghd)CfuCfAfGfuccaagaaL96	2150	A-2901361	VPusUfscdTu(G2p)ga acugAfgCfucugcsusa	2505	UACAAAGUCUCAG UUCCAAUGUG	2860
AD-1571264.1	A-1143160	gsuscau(Ghd)AfcAfUfUfucuaagaaL96	2151	A-2901362	VPusUfscdTu(G2p)ag aaauGfuCfauagcsusg	2506	CAGUCAUGACAUU UCUCAAAAGU	2861
AD-1571265.1	A-1143228	uscsgr(Ghd)UfcUfUfCfcaucagaaL96	2152	A-2901363	VPusCfsgdCu(G2p)au ggaaGfaCfmcagsgsa	2507	UCUCGAAGUCUUC CAUCAGCAGU	2862
AD-1571266.1	A-1143256	csasgr(Ghd)UfgAfUfUfgaagaaL96	2153	A-2901364	VPusUfsgdTa(C2p)uu caauCfaCfugcgsasu	2508	AUCAGCAGUGAUU GAAGUUUCUG	2863
AD-1571267.1	A-1143308	gscsuuc(Chd)CfuUfUfCfucagaaL96	2154	A-2901365	VPusUfscdTu(C2p)ag ugaaAfgGfagagcsasc	2509	GUGCUUCCCUUUC ACUGAAAGUGA	2864
AD-1571268.1	A-1143328	csascug(Ahd)AfgUfGfAfaucagaaL96	2155	A-2901366	VPusUfscdAu(G2p)ua uucaCfuUfcagugsa	2510	UUCACUGAAGUGA AUACAUGGUA	2865
AD-1571269.1	A-1143334	usgsaag(Uhd)GfaAfUfAfaucagaaL96	2156	A-2901367	VPusGfscdAc(C2p)au gnaUfCfAfcuacsgsu	2511	ACUGAAGUGAAUA CAUGGUAGCA	2866
AD-1571270.1	A-1143480	csusaag(Uhd)GfaCfUfAfcacuaaaL96	2157	A-2901368	VPusUfscdAa(G2p)ug guagUfscAfcuagsgsu	2512	ACCUAAGUGACUA CCACUUUUUU	2867
AD-1571271.1	A-1143494	ascsuac(Chd)AfcUfUfAfinuuaaaL96	2158	A-2901369	VPusUfscdTa(G2p)aa auaaGfuGfuaugscsa	2513	UGACUACCACUUA UUUUAAAUC	2868
AD-1571272.1	A-1143704	asusgru(Ahd)GfcAfUfGfaaauagaaL96	2159	A-2901370	VPusGfscdTa(G2p)uu ucuGfcUfcacaaasu	2514	AUAUGGAGCAUG AAACUAUGCA	2869

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1571273.1	A-1144184	ascsacU(Ghd)CfcAfGf AfaguguuuaL96	2160	A-2901371	VPusAfsaadCa(C2p)ac uncuGfgCfagugusug	2515	CAACACUGCCAGA AGUGUGUUU	2870
AD-1571274.1	A-1145066	csasaau(Ahd)UfaUfGf AfanucuaagaaL96	2161	A-2901372	VPusUfscdTa(G2p)aa uucaUfaUfauuugsgsc	2516	GCCAAAUAUAUGA AUUCUAGGAU	2871
AD-1571275.1	A-1145282	gsuscac(Uhd)AfgUfAf GfaaguuuaaL96	2162	A-2901373	VPusUfscdTa(C2p)uu ucuCfuAfgugacsusu	2517	AAGUCACUAGUAG AAAAGUAUAU	2872
AD-1571276.1	A-1145324	csasaga(Chd)AfgAfAf UfaucuaagaaL96	2163	A-2901374	VPusGfsudTa(G2p)aa uauuUfaUfagugacsusu	2518	UUCAAGACAGAAU AUUCUAGACA	2873
AD-1571277.1	A-1145370	csusagc(Ahd)GfuUfUf AfuaguuuaaL96	2164	A-2901375	VPusGfsaadTa(C2p)uu auaaAfcUfguagcsa	2519	UGCUAGCAGUUUA UAUGUAUAUA	2874
AD-1571278.1	A-1145498	usgsacu(Ahd)UfaUfGf GfaguuuaaL96	2165	A-2901376	VPusGfsudAa(C2p)ca ucuUfaUfagucacsu	2520	AGUGACUAUAAGG AUGGUUACCA	2875
AD-1571279.1	A-1145524	gsgsuua(Chd)CfaUfAf GfaaacuuuaL96	2166	A-2901377	VPusAfsagdAa(G2p)uu ucuUfgGfuaacsasu	2521	AUGGUUACCAUAG AAACUUCCUU	2876
AD-1571280.1	A-1145600	usasagc(Uhd)GfcAfUf GfuguaucuaL96	2167	A-2901378	VPusAfsagdAu(G2p)ac acuuGfcAfguuagsc	2522	GCUAAGCUGCAUG UGUCAUCUUA	2877
AD-1571281.1	A-1145606	gscsugc(Ahd)UfgUfGf UfcuucuaaL96	2168	A-2901379	VPusUfsgudAa(G2p)uu gacaCfaUfgcagcsusu	2523	AAGCUGCAUGUGU CAUCUUAACAC	2878
AD-1571282.1	A-1145750	ascsagu(Ahd)UfaUfUf UfcaggaagaaL96	2169	A-2901380	VPusAfsadTu(C2p)cu gaaaUfaUfagugusuc	2524	GAACAGUAUAUUU CAGGAAGGUU	2879
AD-1571283.1	A-1145828	uscsuac(Chd)UfaUfAf GfcagcauuaL96	2170	A-2901381	VPusAfsaadAu(G2p)cu gcuUfaUfguagacsusu	2525	AAUCUACCUAAAAG CAGCAUAUUU	2880
AD-1571284.1	A-1146032	usgsugg(Ahd)UfaUfAf AfanucuuuaL96	2171	A-2901382	VPusAfsagdGa(G2p)aa uuugUfaUfcaacasua	2526	UAUGUGGAUACAA AUUCUCCUUU	2881
AD-1571285.1	A-1146038	gsgsuua(Chd)AfaUfUf UfcuucuuuaL96	2172	A-2901383	VPusUfscdAa(G2p)ga gaauUfuGfuaacsasu	2527	GUGGAUACAAAUU CUCCUUUAAA	2882
AD-1571286.1	A-1146052	asasunc(Uhd)CfcUfUf UfaaguuuaL96	2173	A-2901384	VPusAfsaadCa(C2p)uu uaaaGfgAfgaauusug	2528	CAAAUUCUCCUUU AAAAGUUAUC	2883
AD-1571287.1	A-1146056	ususcuc(Chd)UfuUfAf AfaguuuuuaL96	2174	A-2901385	VPusAfsagdAa(C2p)ac muuaAfaGfgagaausu	2529	AAUUCUCCUUUAA AGUGUUUUCU	2884
AD-1571289.1	A-1146074	asasagu(Chd)UfuUfUf UfuccuuuaaL96	2175	A-2901387	VPusAfsudAa(G2p)gg aagaAfaCfacuuusasa	2530	UAAAAGUGUUUUCU UCCUUUAAUA	2885
AD-1571290.1	A-1146584	usgsac(Chd)UfuUfGf CfcacaaugaL96	2176	A-2901388	VPusCfsaadTu(G2p)ug ugccAfaAfgugacsusu	2531	AGUGCACUUUGGC ACACAAUUGG	2886
AD-1571291.1	A-1146636	gsasaca(Ahd)UfcUfAf AfuguguuuaL96	2177	A-2901389	VPusAfsadCa(C2p)ac auuaGfaUfugucacsu	2532	CAGAACAUAUCUAA UGUGUGGUUU	2887

Duplex Name	SenseOligo Name	Oligo Sequence	SEQ ID NO:	Antisense Oligo Name	Oligo Sequence	SEQ ID NO:	mRNA Target Sequence	SEQ ID NO:
AD-1571292.1	A-1146650	csusaau(Ghd)UfgUfgGfGfuungguauaL96	2178	A-2901390	VPusAfsaudAc(C2p)aaaccaCfaCfaunagsasu	2533	AUCUAAUGUGUGG UUUUGUAUUC	2888
AD-1571293.1	A-1146652	usasaug(Uhd)GfuGfGfUfngguaucaL96	2179	A-2901391	VPusGfsadTa(C2p)caaaccAfcAfcuaaagsa	2534	UCUAAUGUGUGGU UUGGUAUUC	2889

Table 13. Further SNCA-Targeting Duplex Sequences, Unmodified.

Duplex Name	Sense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)	Antisense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)
AD-1548843.1	A-2860862	GACGACAGUGUGGU GUAAAGA	2890	193-213	A-2860863	UCUUTACACACACA CUGUCGUCGA	3245	191-213
AD-1548844.1	A-2860864	ACGACAGUGUGGUG UAAAGGA	2891	194-214	A-2860865	UCCUTUACACCCAC ACUGUCGUCG	3246	192-214
AD-1548845.1	A-2860866	CGACAGUGUGGUGU AAAGGAA	2892	195-215	A-2860867	UTCCTUTACACCA CACUGUCGUC	3247	193-215
AD-1548851.1	A-2860878	UGUGGUGUAAAGGA AUUCAUA	2893	201-221	A-2860879	UAUGAATUCCUTU ACACCCACAU	3248	199-221
AD-1548854.1	A-2860884	GGUGUAAAGGAAU CAUUAGA	2894	204-224	A-2860885	UCUAAUGAAUUC CUUUACACCCAC	3249	202-224
AD-1548869.1	A-2860914	AUAGCCAUUGGAUG UAUUCA	2895	219-239	A-2860915	UTGAUACAUC AUUGCUAAUGA	3250	217-239
AD-1548870.1	A-2860916	TUAGCCAUUGGAUG AUUCAUA	2896	220-240	A-2860917	UAUGAATACAU CAUGGCUAAUG	3251	218-240
AD-1548876.1	A-2860928	AUGGAUGAUUCAU GAAAGGA	2897	226-246	A-2860929	UCCUTUCAUGAA UACAUCCAUGG	3252	224-246
AD-1548884.1	A-2860944	AUUCAUAGAAAGGAC UUUCAAA	2898	234-254	A-2860945	UTUGAAAAGUCCTU UCAUGAAUAC	3253	232-254
AD-1548886.1	A-2860948	UCAUGAAAGGACUU UCAAAAGA	2899	236-256	A-2860949	UCUUTGAAAGUC CUUUCAUGAAU	3254	234-256
AD-1548887.1	A-2860950	CAUGAAAGGACUUU CAAAGGA	2900	237-257	A-2860951	UCCUTUGAAAAGTC CUUUCAUGAA	3255	235-257
AD-1548888.1	A-2860952	AUGAAAGGACUUUC AAAAGGA	2901	238-258	A-2860953	UGCCTUTGAAAGU CCUUUCAUGA	3256	236-258

Duplex Name	Sense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)	Antisense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)
AD-1548975.1	A-2861126	AGAGGGUGUUCUCU AUGUAGA	2902	327-347	A-2861127	UCUACATAGAGA ACACCCUUCUU	3257	325-347
AD-1548976.1	A-2861128	GAGGUGUUCUCUA UGUAGGA	2903	328-348	A-2861129	UCCUACAUAGAG AACACCCUUCU	3258	326-348
AD-1548978.1	A-2861132	GGGUGUUCUCUAUG UAGGCCUA	2904	330-350	A-2861133	UAGCCUACAUAG AGAACACCCUC	3259	328-350
AD-1549037.1	A-2861250	UGGCUAGAGAACACC AAAGAGA	2905	389-409	A-2861251	UCUCTUTGGUCTU CUCAGCCACU	3260	387-409
AD-1549038.1	A-2861252	GGCUGAGAAAGACCA AAAGAGCA	2906	390-410	A-2861253	UGCUCUTUGGUC UUCUCAGCCAC	3261	388-410
AD-1549044.1	A-2861264	GAAGACCAAGAGAGC AAGUGAA	2907	396-416	A-2861265	UTCACUTGCUCTU UGGUCUUCUC	3262	394-416
AD-1549052.1	A-2861280	AAGAGCAAGUGACA AAUGUUA	2908	404-424	A-2861281	UAACAUTUGUCA CUUGCUCUUG	3263	402-424
AD-1549053.1	A-2861282	AGAGCAAGUGACAA AUGUUGA	2909	405-425	A-2861283	UCAACATUUGUC ACUUGCUCUU	3264	403-425
AD-1549054.1	A-2861284	GAGCAAGUGACAAA UGUUGGA	2910	406-426	A-2861285	UCCACAUAUUGTC ACUUGCUCUU	3265	404-426
AD-1549055.1	A-2861286	AGCAAGUGACAAAU GUUGGAA	2911	407-427	A-2861287	UTCCAACAUAUUG UCACUUGCUCU	3266	405-427
AD-1549210.1	A-2861596	UCCUGACAAUGAGG CUUAUGA	2912	582-602	A-2861597	UCAUAAGCCUCA UUGUCAGGAUC	3267	580-602
AD-1549211.1	A-2861598	CCUGACAAUGAGGC UUAUGAA	2913	583-603	A-2861599	UTCATAAGCCUCA UUGUCAGGAU	3268	581-603
AD-1549212.1	A-2861600	CUGACAAUGAGGCU UAUGAAA	2914	584-604	A-2861601	UTUCAUAAGCCTC AUUGUCAGGA	3269	582-604
AD-1549216.1	A-2861608	CAAUGAGGCUUAUG AAUUGCA	2915	588-608	A-2861609	UGCATUTCAUAAG CCUCAUUGUC	3270	586-608
AD-1549217.1	A-2861610	AAUGAGGCUUAUGA AAUGCCA	2916	589-609	A-2861611	UGGCAUTUCAUA AGCCUCAUUGU	3271	587-609
AD-1549222.1	A-2861620	GGCUUAUGAAAUGC CUUCUGA	2917	594-614	A-2861621	UCAGAAAGGCAUT UCAUAAGCCUC	3272	592-614
AD-1549224.1	A-2861624	CUUAUGAAAUGCCU UCUGAGA	2918	596-616	A-2861625	UCUCAGAAAGGCA UUAUCAUAAAGCC	3273	594-616
AD-1549225.1	A-2861626	UUAUGAAAUGCCUU CUGAGGA	2919	597-617	A-2861627	UCCUCAGAAAGGC AUUUCAUAAAGC	3274	595-617

Duplex Name	Sense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)	Antisense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)
AD-1549245.1	A-2861666	AAGGUUAUCAAGAC UACGAAA	2920	617-637	A-2861667	UTUCGUAGUCUTG AUACCCUUCC	3275	615-637
AD-1549246.1	A-2861668	AGGUUAUCAAGACU ACGAACA	2921	618-638	A-2861669	UGUUCGTAGUCTU GAUACCCUUC	3276	616-638
AD-1549249.1	A-2861674	GUUCAAAGACUACG AACCUGA	2922	621-641	A-2861675	UCAGGUTCUGUAG UCUUUAUACCC	3277	619-641
AD-1549264.1	A-2861704	ACCUGAAGCCUAAAG AAAUAAU	2923	636-656	A-2861705	UAUATUTCUUAG GCUUCAGGUUC	3278	634-656
AD-1549265.1	A-2861706	CCUGAAGCCUAAAGA AAUAUCA	2924	637-657	A-2861707	UGAUAUTUCUUA GGCUUCACGGU	3279	635-657
AD-1549266.1	A-2861708	CUGAAGCCUAAAGAA AUUCUA	2925	638-658	A-2861709	UAGATATUUCUTA GGCUUCACGGU	3280	636-658
AD-1549267.1	A-2861710	UGAAGCCUAAAGAAA UAUCUUA	2926	639-659	A-2861711	UAAGAUUUUUCT UAGGCUUCACGG	3281	637-659
AD-1549268.1	A-2861712	GAAGCCUAAAGAAU AUCUUUA	2927	640-660	A-2861713	UAAAGATAUUUC UUAGGCUUCACG	3282	638-660
AD-1549269.1	A-2861714	AAGCCUAAAGAAUA UCUUUGA	2928	641-661	A-2861715	UCAAAGAUUUUT CUUAGGCUUCA	3283	639-661
AD-1549270.1	A-2861716	AGCCUAAAGAAUAU CUUUUGCA	2929	642-662	A-2861717	UGCAAAGAUUUT UCUUAGGCUUC	3284	640-662
AD-1549271.1	A-2861718	GCCUAAAGAAUAUC UUUGCUA	2930	643-663	A-2861719	UAGCAAAGAUAT UUUUUAGGCUU	3285	641-663
AD-1549272.1	A-2861720	CCUAAAGAAUAUCU UUUCUCA	2931	644-664	A-2861721	UGAGCAAAGAUUA UUUUUAGGCUU	3286	642-664
AD-1549280.1	A-2861736	AUAUUUUUGCUCCC AGUUUCA	2932	652-672	A-2861737	UGAAACTGGGAG CAAAAGAUUUU	3287	650-672
AD-1549281.1	A-2861738	UAUUUUUGCUCCCC GUUUUCA	2933	653-673	A-2861739	UAGAAACUGGGG GCAAAGAUUUU	3288	651-673
AD-1549282.1	A-2861740	AUCUUUGCUCCCCAG UUUCUUA	2934	654-674	A-2861741	UAAGAAACUGGG AGCAAAGAUUU	3289	652-674
AD-1549283.1	A-2861742	UCUUUGCUCCCCAGU UUUCUUGA	2935	655-675	A-2861743	UCAAGAAACUGG GAGCAAAGAUUA	3290	653-675
AD-1549284.1	A-2861744	CUUUUGCUCCCCAGU UCUUUGAA	2936	656-676	A-2861745	UTCAAGAAACUG GGAGCAAAGAU	3291	654-676
AD-1549285.1	A-2861746	UUUGCUCCCCAGUUU CUUGAGA	2937	657-677	A-2861747	UCUCAAGAAACT GGGAGCAAAGA	3292	655-677

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AD-1549293.1	A-2861762	CAGUUUCUUGAGAU CUGCUGA	2939	665-685	A-2861763	UCAGCAGAUUC AAGAAACUGGG	3294	663-685
AD-1549333.1	A-2861842	AAGUGCUCAGUUCC AAUGUGA	2940	705-725	A-2861843	UCACAUTGGAAC UGAGCACUUGU	3295	703-725
AD-1549334.1	A-2861844	AGUGCUCAGUCCA AUGUGCA	2941	706-726	A-2861845	UGCACATUGGAA CUGAGCACUUG	3296	704-726
AD-1549351.1	A-2861878	UGCCCAGUCAUGAC AUUUCUA	2942	723-743	A-2861879	UAGAAATGUCAT GACUGGGCACA	3297	721-743
AD-1549352.1	A-2861880	GCCCAGUCAUGACA UUUCUCA	2943	724-744	A-2861881	UGAGAAAUGUCA UGACUGGGCAC	3298	722-744
AD-1549353.1	A-2861882	CCCAGUCAUGACAU UUCUCA	2944	725-745	A-2861883	UTGAGAAAUGUC AUGACUGGGCA	3299	723-745
AD-1549354.1	A-2861884	CCAGUCAUGACAUU UCUCAA	2945	726-746	A-2861885	UTUGAGAAAUGT CAUGACUGGGC	3300	724-746
AD-1549357.1	A-2861890	GUCAUGACAUUUCU CAAAAGUA	2946	729-749	A-2861891	UACUTUGAGAAA UGUCAUGACUG	3301	727-749
AD-1549359.1	A-2861894	CAUGACAUUUCUCA AAGUUUA	2947	731-751	A-2861895	UAAACUTUGAGA AAGUCAUGAC	3302	729-751
AD-1549391.1	A-2861958	UCGAAAGUCUCCAU CAGCAGA	2948	763-783	A-2861959	UCUGCUGAUGGA AGACUUCGAGA	3303	761-783
AD-1549397.1	A-2861970	UCUCCAUACAGCAG UGAUUGA	2949	769-789	A-2861971	UCAATCACUGCTG AUGGAAGACU	3304	767-789
AD-1549400.1	A-2861976	UCCAUCAGCAGUGA UUUGAAGA	2950	772-792	A-2861977	UCUCAAUACACTG CUGAUGGAAG	3305	770-792
AD-1549401.1	A-2861978	CCAUCAGCAGUGAU UGAAGUA	2951	773-793	A-2861979	UACUTCAAUACACU GCUGAUGGAA	3306	771-793
AD-1549403.1	A-2861982	AUCAGCAGUGAUUG AAGUUA	2952	775-795	A-2861983	UAUACUTCAAUC ACUGCUGAUGG	3307	773-795
AD-1549406.1	A-2861988	AGCAGUGAUUGAAG UAUCUGA	2953	778-798	A-2861989	UCAGAUACUUA AUCACUGCUGA	3308	776-798
AD-1549407.1	A-2861990	GCAGUGAUUGAAGU AUCUGUA	2954	779-799	A-2861991	UACAGATACUUC AAUCACUGCUG	3309	777-799

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AD-1549425.1	A-2862026	UUCGGUGCUUCCCU UUCACUA	2956	818-838	A-2862027	UAGUGAAAAGGA AGACCGAAAU	3311	816-838
AD-1549426.1	A-2862028	UCGGUGCUUCCCUU UCACUGA	2957	819-839	A-2862029	UCAGTGAAGGG AAGCACCAGAA	3312	817-839
AD-1549432.1	A-2862040	CUUCCCUUUCACUG AAGUGAA	2958	825-845	A-2862041	UTCACUTCAGUGA AAGGGAAGCA	3313	823-845
AD-1549438.1	A-2862052	UUUCACUGAAGUGA AUACAUA	2959	831-851	A-2862053	UAUGTATUCACU CAGUGAAAGG	3314	829-851
AD-1549439.1	A-2862054	UUCACUGAAGUGAA UACAUGA	2960	832-852	A-2862055	UCAUGUAUUCAC UUCAGUGAAAG	3315	830-852
AD-1549441.1	A-2862058	CACUGAAGUGAAUA CAUGGUA	2961	834-854	A-2862059	UACCAUGUAUUC ACUUCAGUGAA	3316	832-854
AD-1549442.1	A-2862060	ACUGAAGUGAAUAC AUGGUA	2962	835-855	A-2862061	UTACCATGUAUTC ACUUCAGUGA	3317	833-855
AD-1549443.1	A-2862062	CUGAAGUGAAUACA UGGUGA	2963	836-856	A-2862063	UCUACCAUGUAT UCACUUCAGUG	3318	834-856
AD-1549517.1	A-2862210	CUAAGUGACUACCA CUUAUUA	2964	921-941	A-2862211	UAAUAAAGUGUA GUCACUUAGGU	3319	919-941
AD-1549518.1	A-2862212	UAAGUGACUACCA UUUAUUA	2965	922-942	A-2862213	UAAATAAGUGGT AGUCACUUAGG	3320	920-942
AD-1549519.1	A-2862214	AAGUGACUACCAU UAUUUA	2966	923-943	A-2862215	UGAAAUAAAGUG UAGUCACUUAG	3321	921-943
AD-1549520.1	A-2862216	AGUGACUACCAU AUUUUA	2967	924-944	A-2862217	UAGAAATAAGUG GUAGUCACUUA	3322	922-944
AD-1549521.1	A-2862218	GUGACUACCAUUA UUUCUAA	2968	925-945	A-2862219	UTAGAAAUAAAGT GGUAGUCACUU	3323	923-945
AD-1549522.1	A-2862220	UGACUACCAUUAU UUUCUAA	2969	926-946	A-2862221	UTUAGAAAUAAAG UGGUAGUCACU	3324	924-946
AD-1549524.1	A-2862224	ACUACCAUUAUUU CUAAUA	2970	928-948	A-2862225	UAUUTAGAAUA AGUGGUAGUCA	3325	926-948
AD-1549525.1	A-2862226	CUACCAUUAUUUC UAAAUCA	2971	929-949	A-2862227	UGAUTUAGAAAT AAGUGGUAGUC	3326	927-949

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AD-1549541.1	A-2862258	UUGCUGUUGUUCAG AAGUUGA	2973	964-984	A-2862259	UACAACUUCUAGC AACAGCAACA	3328	962-984
AD-1549542.1	A-2862260	UGCUGUUGUUCAGA AGUUGUA	2974	965-985	A-2862261	UACAACUUCUAGC AACAGCAACA	3329	963-985
AD-1549543.1	A-2862262	GCUGUUGUUCAGAA GUUGUUA	2975	966-986	A-2862263	UACAACUUCUAGC AACAGCAACA	3330	964-986
AD-1549544.1	A-2862264	CUGUUGUUCAGAAAG UUUUA	2976	967-987	A-2862265	UTAAACAACUUCG AACAGCAACA	3331	965-987
AD-1549545.1	A-2862266	UGUUGUUCAGAAAGU UGUUA	2977	968-988	A-2862267	UCUACAACUUC UGAACAAACAGC	3332	966-988
AD-1549546.1	A-2862268	GUUGUUCAGAAAGU GUUAGUA	2978	969-989	A-2862269	UACUACAACUUC UGAACAAACAGC	3333	967-989
AD-1549547.1	A-2862270	UUUGUUCAGAAAGU UUAGUA	2979	970-990	A-2862271	UCACTAACCACTU CUGAACAAACA	3334	968-990
AD-1549548.1	A-2862272	UGUUCAGAAAGUUGU UAGUGAA	2980	971-991	A-2862273	UTCACUACAACU UCUGAACAAAC	3335	969-991
AD-1549552.1	A-2862280	CAGAAGUUGUUAAGU GAUUUA	2981	975-995	A-2862281	UCAAUUCACUAA CAACUUCUGAA	3336	973-995
AD-1549554.1	A-2862284	GAAGUUGUUAAGUA UUUGCUA	2982	977-997	A-2862285	UAGCAAAUACACT AACAAACUUCUG	3337	975-997
AD-1549555.1	A-2862286	AAGUUGUUAAGUAU UUUCUAA	2983	978-998	A-2862287	UTAGCAAAUACAC UAAACAACUUCU	3338	976-998
AD-1549556.1	A-2862288	AGUUGUUAAGUAU UGCUAUA	2984	979-999	A-2862289	UAUAGCAAAUACA CUAACAAACUUC	3339	977-999
AD-1549595.1	A-2862366	GAUACUGUCUAAAGA AUAAUGA	2985	1032-1052	A-2862367	UCAUTATUCUUAG ACAGUAUACAU	3340	1030-1052
AD-1549596.1	A-2862368	AUACUGUCUAAAGAA UAAUGAA	2986	1033-1053	A-2862369	UTCATUAUUCUTA GACAGUAUCA	3341	1031-1053
AD-1549615.1	A-2862406	ACGUAAUUGUGAAAU UUUGUUA	2987	1052-1072	A-2862407	UTAAACAAAUUUC ACAAUACGUGA	3342	1050-1072
AD-1549628.1	A-2862432	UAUGUGAGCAUGAA ACUAUGA	2988	1092-1112	A-2862433	UCAUAGTUUCATG CUCACAUAAU	3343	1090-1112

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AD-1549639.1	A-2862454	GAAACUAGCACCU AUAAAUA	2990	1103-1123	A-2862455	UAUUTATAGGUG CAUAGUUUCAU	3345	1101-1123
AD-1549640.1	A-2862456	AAACUAGCACCUA UAAAUAA	2991	1104-1124	A-2862457	UTAUTUAUAGGTG CAUAGUUUCA	3346	1102-1124
AD-1549641.1	A-2862458	AACUAGCACCUAU AAAUACA	2992	1105-1125	A-2862459	UGUATUTAUAGG UGCAUAGUUUC	3347	1103-1125
AD-1549642.1	A-2862460	ACUAGCACCUAUA AAUACUA	2993	1106-1126	A-2862461	UAGUAUTUAUAG GUGCAUAGUUU	3348	1104-1126
AD-1549643.1	A-2862462	CUAGCACCUAUA AUACUAA	2994	1107-1127	A-2862463	UTAGTATUUUAG GUGCAUAGUUU	3349	1105-1127
AD-1549682.1	A-2862540	CUUGUGUUUGUAUA UAAAUGA	2995	1165-1185	A-2862541	UCAUTUAUAUAC AAACACAAGUG	3350	1163-1185
AD-1549683.1	A-2862542	UUGUGUUUGUAUA AAAUGGA	2996	1166-1186	A-2862543	UCCATUTAUUAAC AAACACAAGU	3351	1164-1186
AD-1549684.1	A-2862544	UGUGUUUGUAUA AAUGGUA	2997	1167-1187	A-2862545	UACCAUTUAUATA CAAACACAAG	3352	1165-1187
AD-1549685.1	A-2862546	GUGUUUGUAUAUA AUGGUGA	2998	1168-1188	A-2862547	UCACCATUUUAUA UACAAACACAA	3353	1166-1188
AD-1549686.1	A-2862548	UGUUUGUAUAUAAA UGGUGAA	2999	1169-1189	A-2862549	UTCACCAUUUATA UACAAACACA	3354	1167-1189
AD-1549726.1	A-2862628	UAUCCCAUCUCACU UUAAUAA	3000	1233-1253	A-2862629	UTAUTAAAAGUGA GAUGGGUAUAAA	3355	1231-1253
AD-1549727.1	A-2862630	AUCCCAUCUCACUU UAAUAAA	3001	1234-1254	A-2862631	UTUATUAAAAGUG AGAUGGUAUAA	3356	1232-1254
AD-1549728.1	A-2862632	UCCCAUCUCACUUU AAUAAUA	3002	1235-1255	A-2862633	UAUUAUTAAAGT GAGAUGGGAUA	3357	1233-1255
AD-1549729.1	A-2862634	CCCAUCUCACUUUA AUAAUAA	3003	1236-1256	A-2862635	UTAUTATUAAAAGU GAGAUGGGAU	3358	1234-1256
AD-1550292.1	A-2863760	GCACAUUUAGCAC AUUCAA	3004	1816-1836	A-2863761	UTUGAATGUGCTA AUUUGUCUA	3359	1814-1836
AD-1550346.1	A-2863868	AUAUUAGCACAUUC AAGGCUA	3005	1820-1840	A-2863869	UAGCCUTGAAUG UGCUAAUAUUGU	3360	1818-1840

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AD-1550459.1	A-2864094	ACAGGAAAUGCCUU UAAACAA	3007	1958-1978	A-2864095	UTGTUAAAAGGC AUUCCUGUAA	3362	1956-1978
AD-1550647.1	A-2864470	CUUAAAUGUUGCC AAUUAUA	3008	2046-2066	A-2864471	UAUATUTGGCAAC AUUAAAAGGA	3363	2044-2066
AD-1550648.1	A-2864472	UUUAAAUGUUGCCA AAUUAUA	3009	2047-2067	A-2864473	UTAUAUTUGGCA ACAUUAAAAGG	3364	2045-2067
AD-1550656.1	A-2864488	UUGCCAAAUAUAUG AAUUCUA	3010	2055-2075	A-2864489	UAGAAUTCAUAT AUUUGGCAACA	3365	2053-2075
AD-1550657.1	A-2864490	UGCCAAAUAUAUGA AUUCUAA	3011	2056-2076	A-2864491	UTAGAAATUCAUA UAUUGGCAAC	3366	2054-2076
AD-1550658.1	A-2864492	GCCAAAUAUAUGAA UUCUAGA	3012	2057-2077	A-2864493	UCUAGAAUUCAT AUUUGGCAAC	3367	2055-2077
AD-1550659.1	A-2864494	CCAAAUAUAUGAAU UCUAGGA	3013	2058-2078	A-2864495	UCCUAGAAUUCUA UAUUAUUUGGCA	3368	2056-2078
AD-1550660.1	A-2864496	CAAAUAUAUGAAU CUAGGAA	3014	2059-2079	A-2864497	UTCCTAGAAUUCUA UAUUAUUUGGC	3369	2057-2079
AD-1550661.1	A-2864498	AAAUUAUAUGAAU UAGGAUA	3015	2060-2080	A-2864499	UAUCCUAGAAUUT CAUAUAUUUGG	3370	2058-2080
AD-1550755.1	A-2864686	UUUCAGGGAAGAU UAUUAUA	3016	2104-2124	A-2864687	UTUAAUAUAUUT UCCUUGAAAGA	3371	2102-2124
AD-1550756.1	A-2864688	UUCAGGGAAGAU AUUAACA	3017	2105-2125	A-2864689	UGUUAATAGAU UCCUUGAAAG	3372	2103-2125
AD-1550757.1	A-2864690	UCAGGGAAGAU UUAACUA	3018	2106-2126	A-2864691	UAGUTAAUAUAT CUUCCUUGAAA	3373	2104-2126
AD-1550758.1	A-2864692	CAGGGAAGAU UAACUCA	3019	2107-2127	A-2864693	UGAGTUAUAUAGA UCUCCUUGAA	3374	2105-2127
AD-1550869.1	A-2864914	UCACUAGUAGAAAG UAUUAUA	3020	2236-2256	A-2864915	UAUUAUAUUAU UACUAGUGACU	3375	2234-2256
AD-1550871.1	A-2864918	CUAGUAGAAAGUAU AAUUAUA	3021	2239-2259	A-2864919	UGAAAUTAUACT UUCUACUAGUG	3376	2237-2259
AD-1550887.1	A-2864950	UUCAGACAGAAUA UUCUAGA	3022	2256-2276	A-2864951	UCUAGAAUAUUC UGUCUUGAAAU	3377	2254-2276
AD-1550888.1	A-2864952	UCAAGACAGAAUAU UCUAGAA	3023	2257-2277	A-2864953	UTCUAGAAUAU UGUCUUGAAAU	3378	2255-2277

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AD-1550954.1	A-2865084	UAGACAUAGCUAGCA GUUUAUA	3025	2273-2293	A-2865085	UAUAAAACUGCUA GCAUGUCUAGA	3380	2271-2293
AD-1550955.1	A-2865086	AGACAUAGCUAGCAG UUUAUAA	3026	2274-2294	A-2865087	UTAUAAAACUGCTA GCAUGUCUAG	3381	2272-2294
AD-1550956.1	A-2865088	GACAUAGCUAGCAGU UUUAUA	3027	2275-2295	A-2865089	UAUATAAACUGC UAGCAUGUCUA	3382	2273-2295
AD-1550957.1	A-2865090	ACAUGCUAGCAGUU UAUAUGA	3028	2276-2296	A-2865091	UCAUAAAACUG CUAGCAUGUCU	3383	2274-2296
AD-1550958.1	A-2865092	CAUGCUAGCAGUUU AUUAUGA	3029	2277-2297	A-2865093	UACATATAAACTG CUAGCAUGUC	3384	2275-2297
AD-1550959.1	A-2865094	AUGCUAGCAGUUUA UAUGUAA	3030	2278-2298	A-2865095	UTACAUAAUAAAC UGCUAGCAUGU	3385	2276-2298
AD-1550960.1	A-2865096	UGCUAGCAGUUUAU AUGUAUA	3031	2279-2299	A-2865097	UAUACATAUAAA CUGCUAGCAUG	3386	2277-2299
AD-1550961.1	A-2865098	GCUAGCAGUUUAUA UGUAUUA	3032	2280-2300	A-2865099	UAUACAUUAUA ACUGCUAGCAU	3387	2278-2300
AD-1550963.1	A-2865102	UAGCAGUUUAUAUG UAUUCAA	3033	2282-2302	A-2865103	UTGAUUAACAUAT AAACUGCUAGC	3388	2280-2302
AD-1550964.1	A-2865104	AGCAGUUUAUAUGU AUUCAUA	3034	2283-2303	A-2865105	UAUGAAATACAU UAAAACUGCUAG	3389	2281-2303
AD-1550965.1	A-2865106	GCAGUUUAUAUGUA UUCAUGA	3035	2284-2304	A-2865107	UCAUGAAUACAT AUAAAACUGCUA	3390	2282-2304
AD-1550984.1	A-2865144	AGUAAUGUGAUUA UAUUUGA	3036	2304-2324	A-2865145	UCCAAUUAUUAAT CACAUUACUCA	3391	2302-2324
AD-1551066.1	A-2865308	GAGAAUGAGUGAC UAUAAGA	3037	2343-2363	A-2865309	UCUUAUAGUCAC UCAUUCUCCU	3392	2341-2363
AD-1551067.1	A-2865310	AGGAUUGAGUGACU AUAAAGG	3038	2344-2364	A-2865311	UCCUTATAGUCAC UCAUUCUCCU	3393	2342-2364
AD-1551068.1	A-2865312	GGAAUGAGUGACUA UAAGGAA	3039	2345-2365	A-2865313	UTCCTUAUAGUCA CUCAUUCUCCU	3394	2343-2365
AD-1551069.1	A-2865314	GAAUGAGUGACUAU AAGGAUA	3040	2346-2366	A-2865315	UAUCCUTAUAGTC ACUCAUUCUCCU	3395	2344-2366

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AD-1551073.1	A-2865322	GAGUGACUAUAAGG AUGGUUA	3042	2350-2370	A-2865323	UAACCATCCUAU AGUCACUCAU	3397	2348-2370
AD-1551076.1	A-2865328	UGACUAUAAGGAUG GUUACCA	3043	2353-2373	A-2865329	UGGUAAACCAUCC UUUAUAGUCACU	3398	2351-2373
AD-1551077.1	A-2865330	GACUAUAAGGAUGG UUACCAA	3044	2354-2374	A-2865331	UTGGTAACCAUCC UUUAUAGUCAC	3399	2352-2374
AD-1551078.1	A-2865332	ACUAUAAGGAUGGU UACCAUA	3045	2355-2375	A-2865333	UAUGGUAACCAT CCUUAUAGUCA	3400	2353-2375
AD-1551086.1	A-2865348	GAUGGUUACCAUAG AAACUUA	3046	2363-2383	A-2865349	UAAGTUTCUAUG GUAAACCAUCCU	3401	2361-2383
AD-1551090.1	A-2865356	GUUACCAUAGAAAC UUCCUUA	3047	2367-2387	A-2865357	UAAGGAAGUUUC UAUGGUAACCA	3402	2365-2387
AD-1551091.1	A-2865358	UUACCAUAGAAACU UCCUUUA	3048	2368-2388	A-2865359	UAAAGGAAGUUT CUAUGGUAACC	3403	2366-2388
AD-1551164.1	A-2865504	UACUACAGAGUGCU AAGCUGA	3049	2409-2429	A-2865505	UCAGCUTAGCACU CUGUAGUAGU	3404	2407-2429
AD-1551170.1	A-2865516	AGAGUGCUAAGCUG CAUGUGA	3050	2415-2435	A-2865517	UCACAUGCAGCTU AGCACUCUGU	3405	2413-2435
AD-1551171.1	A-2865518	GAGUGCUAAGCUGC AUGUGUA	3051	2416-2436	A-2865519	UACACATGCAGCU UAGCACUCUG	3406	2414-2436
AD-1551177.1	A-2865530	UAAGCUGCAUGUGU CAUCUUA	3052	2422-2442	A-2865531	UAAGAUGACACA UGCAGCUUAGC	3407	2420-2442
AD-1551180.1	A-2865536	GCUGCAUGUGUCAU CUUACAA	3053	2425-2445	A-2865537	UTGUAAGAUGAC ACAUGCAGCUU	3408	2423-2445
AD-1551181.1	A-2865538	CUGCAUGUGUCAUC UUACACA	3054	2426-2446	A-2865539	UGUGTAAGAUGA CACAUUGCAGCU	3409	2424-2446
AD-1551182.1	A-2865540	UGCAUGUGUCAUCU UACACUA	3055	2427-2447	A-2865541	UAGUGUAAGAUG ACACAUGCAGC	3410	2425-2447
AD-1551251.1	A-2865678	UAGAGAGAAAUGGU AAGUUUA	3056	2446-2466	A-2865679	UAAAACUTACCATU UCUCUCUAGU	3411	2444-2466
AD-1551253.1	A-2865682	GAGAGAAUUGGUAA GUUUCUA	3057	2448-2468	A-2865683	UAGAAACUUACC AUUUCUCUCA	3412	2446-2468
AD-1551254.1	A-2865684	AGAGAAAUGGUAA UUUCUUA	3058	2449-2469	A-2865685	UAAGAAAACUUAC CAUUUCUCUCU	3413	2447-2469

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AD-1551255.1	A-2865686	GAGAAUUGGUAAGU UUCUUGA	3059	2450-2470	A-2865687	UCAAAGAAACUUA CCAUUUCUCUC	3414	2448-2470
AD-1551256.1	A-2865688	AGAAUUGGUAAGUU UCUUGA	3060	2451-2471	A-2865689	UACAAGAAACUT ACCAUUUCUCU	3415	2449-2471
AD-1551257.1	A-2865690	GAAUUGGUAAGUUU CUUGUUA	3061	2452-2472	A-2865691	UAACAAGAAACT UACCAUUUCUC	3416	2450-2472
AD-1551258.1	A-2865692	AAUUGGUAAGUUUC UUGUUUA	3062	2453-2473	A-2865693	UAAACAAGAAAC UUACCAUUUCU	3417	2451-2473
AD-1551346.1	A-2865868	UAUUGAACAGUAUA UUUCAGA	3063	2508-2528	A-2865869	UCUGAAAUUAAC UGUJCAAUUAC	3418	2506-2528
AD-1551347.1	A-2865870	AUUGAACAGUAUAU UUCAGGA	3064	2509-2529	A-2865871	UCCUGAAAUUA CUGUJCAAUUA	3419	2507-2529
AD-1551353.1	A-2865882	CAGUAUAUUUCAGG AAGGUUA	3065	2515-2535	A-2865883	UAACCUCCUGAA AUUAUCUGUU	3420	2513-2535
AD-1551392.1	A-2865960	CUACUAAAGCAGC AUUUUA	3066	2565-2585	A-2865961	UAAATATGUGCU UUAGGUAGAU	3421	2563-2585
AD-1551566.1	A-2866308	AAGUUGUGACCAUG AAUUUA	3067	2673-2693	A-2866309	UTAAAUCAUGG UCACAACUUUC	3422	2671-2693
AD-1551588.1	A-2866352	AUUUAUGUGGAUAC AAAUUCA	3068	2696-2716	A-2866353	UGAATUTGUAUCC ACAUAAUUC	3423	2694-2716
AD-1551589.1	A-2866354	UUUAUGUGGAUACA AAUUCUA	3069	2697-2717	A-2866355	UAGAAUTUGUAT CCACAUAUUA	3424	2695-2717
AD-1551590.1	A-2866356	UUUAUGUGGAUACA AUUCUCA	3070	2698-2718	A-2866357	UGAGAATUUGUA UCCACAUAUUA	3425	2696-2718
AD-1551592.1	A-2866360	AUGUGGAUACAAAU UCUCCUA	3071	2700-2720	A-2866361	UAGGAGAAUUUG UAUCCACAUA	3426	2698-2720
AD-1551646.1	A-2866468	GGAUACAAAUUCUC CUUUAAA	3072	2704-2724	A-2866469	UTUAAAAGGAGAA UUUGUAUCCAC	3427	2702-2724
AD-1551648.1	A-2866472	AUACAAAUUCUCCU UUAAAAG	3073	2706-2726	A-2866473	UCUUTAAAGGAG AAUUUGUAUCC	3428	2704-2726
AD-1551649.1	A-2866474	UACAAAUUCUCCUU UAAAAGUA	3074	2707-2727	A-2866475	UACUTUAAAAGGA GAAUUUGUAUC	3429	2705-2727
AD-1551650.1	A-2866476	ACAAAUUCUCCUUU AAAGUA	3075	2708-2728	A-2866477	UACCTUTAAAAGGA GAAUUUGUAU	3430	2706-2728

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AD-1551653.1	A-2866482	AAUUCUCCUUUAAA GUGUUUA	3077	2711-2731	A-2866483	UAAACACUUUAA AGGAGAAUUUG	3432	2709-2731
AD-1551655.1	A-2866486	UUCUCCUUUAAAAGU GUUUCUA	3078	2713-2733	A-2866487	UAGAAAACACUUT AAAGGAGAAUU	3433	2711-2733
AD-1551656.1	A-2866488	UCUCCUUUAAAAGUG UUUCUUA	3079	2714-2734	A-2866489	UAGAAAACACUT UAAAGGAGAAU	3434	2712-2734
AD-1551657.1	A-2866490	CUCCUUUAAAAGUGU UUCUUA	3080	2715-2735	A-2866491	UGAAGAAAACACT UUAAAAGGAGAA	3435	2713-2735
AD-1551658.1	A-2866492	UCCUUUAAAAGUGUU UCUUCCA	3081	2716-2736	A-2866493	UGGAAGAAAACAC UUUAAAGGAGA	3436	2714-2736
AD-1551659.1	A-2866494	CCUUUAAAAGUGUUU CUUCCCA	3082	2717-2737	A-2866495	UGGAAGAAAACA CUUUAAAAGGAG	3437	2715-2737
AD-1551661.1	A-2866498	UUUAAAAGUGUUUCU UCCCUUA	3083	2719-2739	A-2866499	UAAGGGAAGAAA CACUUUAAAAGG	3438	2717-2739
AD-1551665.1	A-2866506	AAGUUUUUUUCCCU UUAAUUA	3084	2723-2743	A-2866507	UTAUTAAGGGAA GAAACACUUUA	3439	2721-2743
AD-1551666.1	A-2866508	AGUGUUUUUUUCCCU UAAUAUA	3085	2724-2744	A-2866509	UAUATUAAAGGGA AGAAACACUUU	3440	2722-2744
AD-1551667.1	A-2866510	GUGUUUUUUUCCCUU AAUAUUA	3086	2725-2745	A-2866511	UAUAUTAAAGGG AAGAAACACUU	3441	2723-2745
AD-1551668.1	A-2866512	GUUUCUCCCUUAA UAUUUA	3087	2727-2747	A-2866513	UTAAAUUUUAAAG GGAGAAACAC	3442	2725-2747
AD-1551670.1	A-2866516	UUCUCCCUUAAUA UUUAUCA	3088	2729-2749	A-2866517	UGAUAAAUUUUA AGGGAAGAAAC	3443	2727-2749
AD-1551672.1	A-2866520	CUUCCCUUAAUAU UAUCUGA	3089	2731-2751	A-2866521	UCAGAUAAAUAT UAAAGGGAAGAA	3444	2729-2751

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AD-1552053.1	A-2867282	UUACAUUCUCCCAAGUUUA	3091	2936-2956	A-2867283	UAUAACTUGGGA GAUUAAGUC	3446	2934-2956
AD-1552054.1	A-2867284	UACAUUCUCCCAAGUUUA	3092	2937-2957	A-2867285	UGAATAACUUGG GAGAAUGUAAG	3447	2935-2957
AD-1552055.1	A-2867286	ACAUUCUCCCAAGUUUA	3093	2938-2958	A-2867287	UTGAUUAACUUG GGAGAAUGUAA	3448	2936-2958
AD-1552056.1	A-2867288	CAUUCUCCCAAGUUUA	3094	2939-2959	A-2867289	UCUGAATAACUTG GGAGAAUGUA	3449	2937-2959
AD-1552057.1	A-2867290	AUUCUCCCAAGUUUA	3095	2940-2960	A-2867291	UGCUGAAUAACT UGGGAGAAUGU	3450	2938-2960
AD-1552065.1	A-2867306	AAGUUAUUCAGCCU CAUUA	3096	2948-2968	A-2867307	UCAUAUGAGGCT GAAUAACUUGG	3451	2946-2968
AD-1552066.1	A-2867308	AGUUAUUCAGCCU CAUUA	3097	2949-2969	A-2867309	UTCATATGAGGCU GAAUAACUUG	3452	2947-2969
AD-1552067.1	A-2867310	GUUAUUCAGCCU CAUUA	3098	2950-2970	A-2867311	UGUCAUAUGAGG CUGAAUAACU	3453	2948-2970
AD-1552158.1	A-2867492	ACAGUUCAGAGUGC ACUUA	3099	2991-3011	A-2867493	UCAAAGTGCACTC UGAACUGUUU	3454	2989-3011
AD-1552159.1	A-2867494	CAGUUCAGAGUGC ACUUA	3100	2992-3012	A-2867495	UCCAAAAGUGCAC UCUGAACUGUU	3455	2990-3012
AD-1552161.1	A-2867498	GUUCAGAGUGCACU UUGGCA	3101	2994-3014	A-2867499	UTGCCAAAAGUGC ACUCUGAACUG	3456	2992-3014
AD-1552169.1	A-2867514	UGCACUUUGGCACA CAAUUA	3102	3002-3022	A-2867515	UCAATUGUGUGC CAAAAGUGCACU	3457	3000-3022
AD-1552191.1	A-2867558	AACAGAACAAUCUA AUGUGA	3103	3024-3044	A-2867559	UACACATUAAGATU GUUCUGUUCC	3458	3022-3044
AD-1552192.1	A-2867560	ACAGAACAAUCUA AUGUGA	3104	3025-3045	A-2867561	UCACACAUUAGA UUGUUCUGUUC	3459	3023-3045
AD-1552193.1	A-2867562	CAGAACAAUCUAUG GUGUGA	3105	3026-3046	A-2867563	UCCACACAUUAG AUUGUUCUGUU	3460	3024-3046
AD-1552244.1	A-2867664	AGAACAAUCUAUG GUGUGA	3106	3027-3047	A-2867665	UACCACACAUUA GAUUGUUCUGU	3461	3025-3047
AD-1552247.1	A-2867670	ACAAUCUAAUGUGU GGUUUA	3107	3030-3050	A-2867671	UCAAACCCACACA UUAAGAUUGUUC	3462	3028-3050

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AD-1552249.1	A-2867674	AAUCUAAUGUGUGG UUUUGGUA	3109	3032-3052	A-2867675	UACCAAACCCACAC AUUAGAUGUU	3464	3030-3052
AD-1552250.1	A-2867676	AUCUAAUGUGUGGU UUGGUAA	3110	3033-3053	A-2867677	UTACCAAACCCACA CAUUAGAUGU	3465	3031-3053
AD-1552251.1	A-2867678	UCUAAUGUGUGGUU UGGUAUA	3111	3034-3054	A-2867679	UAUACCAAACCA CACAUUAGAUA	3466	3032-3054
AD-1552253.1	A-2867682	UAAUGUGUGGUUUG GUUAUCA	3112	3036-3056	A-2867683	UGAATACCAAACCC ACACAUUAGA	3467	3034-3056
AD-1552254.1	A-2867684	AAUGUGUGGUUUUGG UAUUCCA	3113	3037-3057	A-2867685	UGGAUUAACCAAA CCACACAUUAG	3468	3035-3057
AD-1552255.1	A-2867686	AUGUGUGGUUUUGGU AUUCCAA	3114	3038-3058	A-2867687	UTGGAATACCAAAA CCACACAUUA	3469	3036-3058
AD-1552257.1	A-2867690	GUGUGGUUUUGGUUA UCCAAGA	3115	3040-3060	A-2867691	UCUUGGAUUAACC AAACCCACACAU	3470	3038-3060
AD-1571164.1	A-1142146	GUGUGGUUAAGG AAUUCAA	3116	200-220	A-2901262	UUGAAUUCUUU ACACCCACACUG	3471	198-220
AD-1571165.1	A-1142150	GUGUGUAAAGGAA UUCAUUA	3117	202-222	A-2901263	UAAUGAAUUCUU UUAACCCACAC	3472	200-222
AD-1571166.1	A-1142190	AGCCAUUGGAUGUAU UCAUGAA	3118	222-242	A-2901264	UUCATGAUUAACA UCCAUGGCUAA	3473	220-242
AD-1571167.1	A-1142200	UGGAUGUAUUC AUG AAAGGAA	3119	227-247	A-2901265	UUCCTUTCAUGAA UACAUCCAUG	3474	225-247
AD-1571168.1	A-1142214	AUUCAUAGAAAGGAC UUUUCAA	3120	234-254	A-2901266	UUUGAAAAGUCCU UUCAUGAAUAC	3475	232-254
AD-1571169.1	A-1142222	AUGAAAGGACUUUC AAAGGCA	3121	238-258	A-2901267	UGCCTUTGAAAGU CCUUUCAUGA	3476	236-258
AD-1571170.1	A-1142224	UGAAAGGACUUUCA AAGGCCA	3122	239-259	A-2901268	UGGCCUTUGAAA GUCCUUUCAUG	3477	237-259
AD-1571171.1	A-1142402	GGGUGUUCUUAUG UAGGCUA	3123	330-350	A-2901269	UAGCCUACAUAG AGAACACCCUC	3478	328-350
AD-1571172.1	A-1142522	GGCUGAGAAAGACCA AAGAGCA	3124	390-410	A-2901270	UGCUCUTUGGUC UUCUCAGCCAC	3479	388-410

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AD-1571174.1	A-1142868	CCUGACAAUGAGGC UUAUGAA	3126	583-603	A-2901272	UUCATAAGCCUCA UUGUCAGGAU	3481	581-603
AD-1571175.1	A-1142878	CAUAGAGGCUUAUG AAUUGCA	3127	588-608	A-2901273	UGCATUTCAUAAAG CCUCAUUGUC	3482	586-608
AD-1571176.1	A-1142880	AAUGAGGCUUAUGA AAUGCCA	3128	589-609	A-2901274	UGGCAUTUCAUA AGCCUCAUUGU	3483	587-609
AD-1571177.1	A-1142902	UGAAAUGCCUUCUG AGGAAGA	3129	600-620	A-2901275	UCUCCCTCAGAAAG GCAUUUCAUA	3484	598-620
AD-1571178.1	A-1142936	AAGGUAUCAAAGAC UACGAAA	3130	617-637	A-2901276	UUUCGUAGUCUU GAUACCCUUC	3485	615-637
AD-1571179.1	A-1142938	AGGUAUCAAGACU ACGAACA	3131	618-638	A-2901277	UGUUCGTAGUCU UGAUACCCUUC	3486	616-638
AD-1571180.1	A-1142974	ACCUGAAGCCUAAAG AAAUUA	3132	636-656	A-2901278	UAUATUTCUUAG GCUUCAGGUUC	3487	634-656
AD-1571181.1	A-1142978	CUGAAGCCUAAAGAA AUUCUA	3133	638-658	A-2901279	UAGATATUUCUU AGGCUUCAGGU	3488	636-658
AD-1571182.1	A-1142982	GAAGCCUAAAGAAU AUCUUUA	3134	640-660	A-2901280	UAAAGATAUUUC UUAGGCUUCAG	3489	638-660
AD-1571183.1	A-1142992	CUAAGAAUAUCUU UGCUCCA	3135	645-665	A-2901281	UGGAGCAAAGAU AUUUCUUAGGC	3490	643-665
AD-1571184.1	A-1143006	AUAUCUUUUCUCCC AGUUUCA	3136	652-672	A-2901282	UGAAACTGGGAG CAAGAUAUUU	3491	650-672
AD-1571185.1	A-1143018	UUGCUCACAGUUUC UUGAGAA	3137	658-678	A-2901283	UUCUCAAGAAAC UGGGAGCAAAG	3492	656-678
AD-1571186.1	A-1143020	UGCUCACAGUUUCU UGAGAU	3138	659-679	A-2901284	UAUCTCAAGAAA CUGGGAGCAAA	3493	657-679
AD-1571187.1	A-1143100	CUGUACAAAGUGCUC AGUUCCA	3139	699-719	A-2901285	UGGAACCTGAGCA CUUGUACAGGA	3494	697-719
AD-1571188.1	A-1143104	GUACAAAGUGCUCAG UUCGAAA	3140	701-721	A-2901286	UUUGGAACUGAG CACUUGUACAG	3495	699-721
AD-1571189.1	A-1143154	CCAGUCAUGACAUU UCUCAAA	3141	726-746	A-2901287	UUUGAGAAAUUGU CAUGACUGGGC	3496	724-746
AD-1571190.1	A-1143240	UCUCCCAUCAGCAG UGAUUGA	3142	769-789	A-2901288	UCAATCACUGCUG AUGGAAGACU	3497	767-789

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AD-1571192.1	A-1143248	CCAUCAGCAGUGAU UGAAGUA	3144	773-793	A-2901290	UACUTCAAUCACU GCUGAUGGAA	3499	771-793
AD-1571193.1	A-1143252	AUCAGCAGUGAUUG AAGUAUA	3145	775-795	A-2901291	UAUACUTCACUAC ACUGCUGAUGG	3500	773-795
AD-1571194.1	A-1143260	GCAGUGAUUGAAGU AUCUGUA	3146	779-799	A-2901292	UACAGATACUUC AAUCACUCUG	3501	777-799
AD-1571195.1	A-1143310	CUCCCCUUCACUG AAGUGAA	3147	825-845	A-2901293	UUCACUTCAGUG AAAGGGAAGCA	3502	823-845
AD-1571196.1	A-1143324	UUCACUGAAGUGAA UACAUGA	3148	832-852	A-2901294	UCAUGUAUUCAC UUCAGUGAAAG	3503	830-852
AD-1571197.1	A-1143326	UCACUGAAGUGAAU ACAUGGA	3149	833-853	A-2901295	UCCATGTAAUUCAC UUCAGUGAAA	3504	831-853
AD-1571198.1	A-1143330	ACUGAAGUGAAUAC AUGGUAA	3150	835-855	A-2901296	UUACCATGUAUU CACUUCAGUGA	3505	833-855
AD-1571199.1	A-1143496	CUACCACUUAUUUC UAAAUCA	3151	929-949	A-2901297	UGAUTUAGAAAU AAGUGGUAGUC	3506	927-949
AD-1571200.1	A-1143498	UACCACUUAUUUCU AAUCCA	3152	930-950	A-2901298	UGGATUTAGAAA UAAUGGUAGU	3507	928-950
AD-1571201.1	A-1143502	CCACUUAUUUCUAA AUCCUCA	3153	932-952	A-2901299	UGAGGATUUAGA AAUAGUGGUA	3508	930-952
AD-1571202.1	A-1143558	AGUUGUUAGUGAUU UGCUAUA	3154	979-999	A-2901300	UAUAGCAAAUCA CUAACAACUUC	3509	977-999
AD-1571203.1	A-1143638	AUACUGUCUAAAGAA UAAUGAA	3155	1033-1053	A-2901301	UUCATUAUUCUU AGACAGUAUCA	3510	1031-1053
AD-1571204.1	A-1143700	AUUGUGAGCAUGA AACUAUA	3156	1091-1111	A-2901302	UAUAGUTUCAUG CUCACAUUUU	3511	1089-1111
AD-1571205.1	A-1143702	UAUGUGAGCAUGAA ACUAUGA	3157	1092-1112	A-2901303	UCAUAGTUUCAU GCUCACAUUUU	3512	1090-1112
AD-1571206.1	A-1143706	UGUGAGCAUGAAAC UAUGCAA	3158	1094-1114	A-2901304	UUGCAUAGUUUC AUGCUCACAAU	3513	1092-1114
AD-1571207.1	A-1143728	AACUAUGCACCUAU AAAUACA	3159	1105-1125	A-2901305	UGUATUTAUAGG UGCAUAGUUUC	3514	1103-1125

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AD-1571209.1	A-1143818	UGUUUGUAUUA UGGUGAA	3161	1169-1189	A-2901307	UUCACCAUUUAU AUACAAACACA	3516	1167-1189
AD-1571210.1	A-1143904	CCCAUCUCACUUUA AUAAUAA	3162	1236-1256	A-2901308	UUATATUAAAG UGAGAUUGGGAU	3517	1234-1256
AD-1571211.1	A-1144738	AUAUAGCACAUUC AAGGCUA	3163	1820-1840	A-2901309	UAGCCUTGAAUG UGCUAAUUGU	3518	1818-1840
AD-1571212.1	A-1145040	CUUAAAUGUUGCC AAAUAA	3164	2046-2066	A-2901310	UAUATUTGGCAAC AUUAAAAGGA	3519	2044-2066
AD-1571213.1	A-1145068	AAAUUAUGAAUUC UAGGAUA	3165	2060-2080	A-2901311	UAUCCUAGAAU CAUAUUAUUGG	3520	2058-2080
AD-1571214.1	A-1145152	UCUUUCAGGGAAGA UCUAUUA	3166	2102-2122	A-2901312	UAUAGAUCUUC CCUGAAAGAGA	3521	2100-2122
AD-1571215.1	A-1145338	GAAUUAUCUAGACA UGCUAGA	3167	2265-2285	A-2901313	UCUAGCAUGUCU AGAAUUAUUCUG	3522	2263-2285
AD-1571216.1	A-1145344	UAUUCUAGACAUGC UAGCAGA	3168	2268-2288	A-2901314	UCUGCUAGCAUG UCUAGAAUUAU	3523	2266-2288
AD-1571217.1	A-1145352	CUAGACAUUCUAGC AGUUUAA	3169	2272-2292	A-2901315	UUAACTGCUAG CAUGUCUAGAA	3524	2270-2292
AD-1571218.1	A-1145366	UGCUAGCAGUUUAU AUGUAUA	3170	2279-2299	A-2901316	UAUACATAUAAA CUGCUAGCAUG	3525	2277-2299
AD-1571219.1	A-1145368	GCUAGCAGUUUAU UGUAUUA	3171	2280-2300	A-2901317	UAUACAUUAUA ACUGCUAGCAU	3526	2278-2300
AD-1571220.1	A-1145378	CAGUUUAUUGUAU UCAUGAA	3172	2285-2305	A-2901318	UUCATGAAUACA UAUAAACUGCU	3527	2283-2305
AD-1571221.1	A-1145398	GUAUUCUAGAGUAA UGUGAUA	3173	2295-2315	A-2901319	UAUCACAUUAU CAUGAAUACAU	3528	2293-2315
AD-1571222.1	A-1145484	GAAUGAGUGACUAU AAGGAUA	3174	2346-2366	A-2901320	UAUCCUTAUAGU CACUCAUUCU	3529	2344-2366
AD-1571223.1	A-1145492	GAGUACUAUAAAG AUGGUUA	3175	2350-2370	A-2901321	UAACCATCCUUAU AGUCACUCAU	3530	2348-2370
AD-1571224.1	A-1145500	GACUAUAAAGGAUGG UUACCAA	3176	2354-2374	A-2901322	UUGGTAACCAUCC UUUAUAGUCAC	3531	2352-2374

Duplex Name	Sense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)	Antisense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)
AD-1571225.1	A-1145510	UAAGGAUGGUUACC AUAGAA	3177	2359-2379	A-2901323	UUUCTATGUAAC CAUCCUUAUA	3532	2357-2379
AD-1571226.1	A-1145518	GAUGGUUACCAUAG AAACUUA	3178	2363-2383	A-2901324	UAAGTUTCUAUG GUAACCAUCCU	3533	2361-2383
AD-1571227.1	A-1145520	AUGGUUACCAUAGA AACUUA	3179	2364-2384	A-2901325	UGAAGUTUCUAU GGUAACCAUCC	3534	2362-2384
AD-1571228.1	A-1145526	GUUACCAUAGAAAC UUCUUA	3180	2367-2387	A-2901326	UAAGGAAGUUUC UAUAGUAACCA	3535	2365-2387
AD-1571229.1	A-1145528	UUACCAUAGAAACU UCCUUA	3181	2368-2388	A-2901327	UAAAGGAAGUUU CUAUGGUAACC	3536	2366-2388
AD-1571230.1	A-1145572	CUACUACAGAGUGC UAAGCUA	3182	2408-2428	A-2901328	UAGCTUAGCACUC UGUAGUAGUC	3537	2406-2428
AD-1571231.1	A-1145594	UGCUAAGCUGCAUG UGUCAUA	3183	2419-2439	A-2901329	UAUGACACAUGC AGCUUAGCACU	3538	2417-2439
AD-1571232.1	A-1145610	UGCAUGUGUCAUCU UACACUA	3184	2427-2447	A-2901330	UAGUGUAAGAUG ACACAUGCAGC	3539	2425-2447
AD-1571233.1	A-1145648	UAGAGAGAAAUGGU AAGUUUA	3185	2446-2466	A-2901331	UAAACUTACCAU UUCUCUCUAGU	3540	2444-2466
AD-1571234.1	A-1145650	AGAGAGAAAUGGUA AGUUUCA	3186	2447-2467	A-2901332	UGAAACTUACCA UUUCUCUCUAG	3541	2445-2467
AD-1571235.1	A-1145742	UUGAACAGUAUAUU UCAGGAA	3187	2510-2530	A-2901333	UUCCTGAAUAUU ACUGUUCAAUA	3542	2508-2530
AD-1571236.1	A-1145752	CAGUAUAUUUCAGG AAGGUUA	3188	2515-2535	A-2901334	UAACCUCCUGAA AUUAUCUGUU	3543	2513-2535
AD-1571237.1	A-1145972	GGAAAGUUGGACC AUGAAUA	3189	2670-2690	A-2901335	UAUUCATGGUCA CAACUUUCCUA	3544	2668-2690
AD-1571238.1	A-1146022	AUUUAUGUGGAUAC AAAUUA	3190	2696-2716	A-2901336	UGAATUTGUAUCC ACAUAUAUCC	3545	2694-2716
AD-1571239.1	A-1146028	UAUGUGGAUACAAA UUCUCCA	3191	2699-2719	A-2901337	UGGAGAAUUUGU AUCCACAUAUA	3546	2697-2719
AD-1571240.1	A-1146050	AAAUUCUCCUUUAA AGUGUUA	3192	2710-2730	A-2901338	UAACACTUUAAA GGAGAAUUUGU	3547	2708-2730
AD-1571241.1	A-1146054	AUUCUCCUUUAAAAG UGUUUCA	3193	2712-2732	A-2901339	UGAAACACUUUA AAGGAGAAUUU	3548	2710-2732

Duplex Name	Sense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)	Antisense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)
AD-1571242.1	A-1146062	UCCUUUAAAAGUGUU UCUCCA	3194	2716-2736	A-2901340	UGGAAGAAAACAC UUUAAAAGGAGA	3549	2714-2736
AD-1571243.1	A-1146066	CUUUAAAAGUGUUUC UUCCCUA	3195	2718-2738	A-2901341	UAGGGAAGAAAAC ACUUAAAAGGA	3550	2716-2738
AD-1571244.1	A-1146068	UUUAAAAGUGUUUCU UCCCUUA	3196	2719-2739	A-2901342	UAAGGGAAGAAA CACUUUAAAAGG	3551	2717-2739
AD-1571245.1	A-1146450	CUUACAUUCUCCCA AGUUUAU	3197	2935-2955	A-2901343	UAUAACTTUGGGA GAAUGUAAGUC	3552	2933-2955
AD-1571246.1	A-1146460	AUUCUCCCAAGUUA UUCAGCA	3198	2940-2960	A-2901344	UGCUGAAUAAACU UGGGAAGAAUGU	3553	2938-2960
AD-1571247.1	A-1146482	UUAUUCAGCCUCAU AUGACUA	3199	2951-2971	A-2901345	UAGUCATAUGAG GCUGAAUAAACU	3554	2949-2971
AD-1571248.1	A-1146634	AGAACAAUCUAAUG UGUGGUA	3200	3027-3047	A-2901346	UACCACACAUUA GAUUGUUCUGU	3555	3025-3047
AD-1571249.1	A-1146638	AACAAUCUAAUGUG UGGUUUA	3201	3029-3049	A-2901347	UAAACCACACAU UAGAUUGUUCU	3556	3027-3049
AD-1571250.1	A-1146654	AAUGUGUGUUUGG UAUCCA	3202	3037-3057	A-2901348	UGGAUUAACCAA CCACACAUUAG	3557	3035-3057
AD-1571251.1	A-1146656	AUGUGUGUUUGGU AUUCCA	3203	3038-3058	A-2901349	UUGGAATACCAA ACCACACAUUA	3558	3036-3058
AD-1571252.1	A-1146660	GUUGGUUUUGGUU UCCAAGA	3204	3040-3060	A-2901350	UCUUGGAUUAAC AAACCACACAU	3559	3038-3060
AD-1571253.1	A-1142114	UGGCCAUUCGACGA CAGUGUA	3205	184-204	A-2901351	UACACUGUCGUC GAUUGGCCACU	3560	182-204
AD-1571254.1	A-1142132	GACGACAGUGUGGU GUAAGA	3206	193-213	A-2901352	UCUUTACACCACA CUGUCGUGCA	3561	191-213
AD-1571255.1	A-1142192	GCCAUUGGAUUAU CAUGAAA	3207	223-243	A-2901353	UUUCAUGAAUAC AUCCAUGGCUA	3562	221-243
AD-1571256.1	A-1142198	AUGGAUGUAUUAU GAAAGGA	3208	226-246	A-2901354	UCCUTUCAUGAA UACAUCUCCAU	3563	224-246
AD-1571257.1	A-1142400	AGGUGUUCUCUAU GUAGGCA	3209	329-349	A-2901355	UGCCTACAUAGA GAACACCCUUCU	3564	327-349
AD-1571258.1	A-1142546	CAAGAGCAAGUGA CAAAUGA	3210	402-422	A-2901356	UCAUTUGUCACU UGCUCUUUGGU	3565	400-422

Duplex Name	Sense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)	Antisense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)
AD-1571259.1	A-1142556	AGCAAGUGACAAAU GUUGGAA	3211	407-427	A-2901357	UCCAACAUAUUU UACUUUGUCUCU	3566	405-427
AD-1571260.1	A-1142876	ACAAUGAGGCUUAU GAAUUA	3212	587-607	A-2901358	UCAUTUCAUAAG CCUCAUUGUCA	3567	585-607
AD-1571261.1	A-1143032	CAGUUUCUUGAGAU CUGCUGA	3213	665-685	A-2901359	UCAGCAGAUUC AAGAAACUGGG	3568	663-685
AD-1571262.1	A-1143102	UGUACAAAGUCUCA GUUCCAA	3214	700-720	A-2901360	UUGGAACUGAGC ACUUGUACAGG	3569	698-720
AD-1571263.1	A-1143110	CAAGUGCUCAGUUC CAAUGUA	3215	704-724	A-2901361	UACATUGGAACU GAGCACUUUGA	3570	702-724
AD-1571264.1	A-1143160	GUCAUGACAUUUCU CAAGUA	3216	729-749	A-2901362	UACUTUGAGAAA UGUCAUGACUG	3571	727-749
AD-1571265.1	A-1143228	UCGAAGUCUCCAU CAGCAGA	3217	763-783	A-2901363	UCUGCUGAUGGA AGACUUCGAGA	3572	761-783
AD-1571266.1	A-1143256	CAGCAGUGAUUGAA GUUUCUA	3218	777-797	A-2901364	UAGATACUUCAA UCACUGCUGAU	3573	775-797
AD-1571267.1	A-1143308	GCUUCCUUUCACU GAAGUGA	3219	824-844	A-2901365	UCACTUCAGUGA AAGGGAAGCAC	3574	822-844
AD-1571268.1	A-1143328	CACUGAAGUGAAUA CAUGGUA	3220	834-854	A-2901366	UACCAUGUAUUC ACUUCAGUGAA	3575	832-854
AD-1571269.1	A-1143334	UGAAGUGAAUACAU GGUAGCA	3221	837-857	A-2901367	UGCACCAUGUA UUCACUUUCAGU	3576	835-857
AD-1571270.1	A-1143480	CUAAGUGACUACCA CUUUAUA	3222	921-941	A-2901368	UAAUAAAGUGUA GUCACUUAGGU	3577	919-941
AD-1571271.1	A-1143494	ACUACCACUUUAUU CUAAAUA	3223	928-948	A-2901369	UAUUTAGAAAUA AGUGGUAGUCA	3578	926-948
AD-1571272.1	A-1143704	AUGUGAGCAUGAAA CUAUGCA	3224	1093-1113	A-2901370	UGCATAUUUUCA UGGUCACAUUA	3579	1091-1113
AD-1571273.1	A-1144184	ACACUGCCAGAAAGU GUGUUUA	3225	1402-1422	A-2901371	UAAACACACUUC UGGCAGUGUUG	3580	1400-1422
AD-1571274.1	A-1145066	CAAAUUAUUGAAUU CUAGGAA	3226	2059-2079	A-2901372	UUCCTAGAAUUC AUUAUUUUGGC	3581	2057-2079
AD-1571275.1	A-1145282	GUCACUAGUAGAAA GUUUAUA	3227	2235-2255	A-2901373	UUUATACUUUCU ACUAGUGACUU	3582	2233-2255
AD-1571276.1	A-1145324	CAAGACAGAAUUAU CUAGACA	3228	2258-2278	A-2901374	UGUCTAGAAUUA UCUGUCUUUGAA	3583	2256-2278

Duplex Name	Sense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)	Antisense Oligo Name	Trans Sequence	SEQ ID NO:	Range (NM_000345.4)
AD-1571277.1	A-1145370	CUAGCAGUUUAUUAU GUUUUA	3229	2281-2301	A-2901375	UGAATACAUUA AAACUGCUAGCA	3584	2279-2301
AD-1571278.1	A-1145498	UGACUUAAGGAUG GUUACCA	3230	2353-2373	A-2901376	UGGUAACCAUCC UUUAAGUCACU	3585	2351-2373
AD-1571279.1	A-1145524	GGUUAACCAUAGAAA CUUCCUA	3231	2366-2386	A-2901377	UAGGAAGUUUCU AUGGUAACCAU	3586	2364-2386
AD-1571280.1	A-1145600	UAGGCUGCAUGUGU CAUCUUA	3232	2422-2442	A-2901378	UAGAUGACACA UGCAGCUUAGC	3587	2420-2442
AD-1571281.1	A-1145606	GCUGCAUGUGUCAU CUUACAA	3233	2425-2445	A-2901379	UUGUAAGAUGAC ACAUGCAGCUU	3588	2423-2445
AD-1571282.1	A-1145750	ACAGUUAUUUCAG GAAGGUA	3234	2514-2534	A-2901380	UACCTUCCUGAAA UAUACUGUUC	3589	2512-2534
AD-1571283.1	A-1145828	UCUACCUAAGCAG CAUAUUA	3235	2564-2584	A-2901381	UAUAUGCUGCU UUAGGUAGAUU	3590	2562-2584
AD-1571284.1	A-1146032	UGUGGAUACAAAUU CUCCUUA	3236	2701-2721	A-2901382	UAAGGAGAAUUU GUUCCACAUUA	3591	2699-2721
AD-1571285.1	A-1146038	GGUAACAAUUCUC CUUAAA	3237	2704-2724	A-2901383	UUUAAAAGGAGAA UUUGUAUCCAC	3592	2702-2724
AD-1571286.1	A-1146052	AAUUCUCCUUUAAA GUGUUUA	3238	2711-2731	A-2901384	UAAACACUUUAA AGGAGAAUUUG	3593	2709-2731
AD-1571287.1	A-1146056	UUCUCCUUUAAAAGU GUUUUA	3239	2713-2733	A-2901385	UAGAAAACACUUU AAAAGGAGAAUU	3594	2711-2733
AD-1571289.1	A-1146074	AAAGUGUUUUCUCC CUUAAUA	3240	2722-2742	A-2901387	UAUUAAAGGGAAG AAACACUUUAA	3595	2720-2742
AD-1571290.1	A-1146584	UGCACUUUGGCACA CAAUUGA	3241	3002-3022	A-2901388	UCAATUGUGUC CAAAAGUGCACU	3596	3000-3022
AD-1571291.1	A-1146636	GAACAAUCUAAUUGU GUGGUUA	3242	3028-3048	A-2901389	UAACCCACACAUU AGAUUGUUCUG	3597	3026-3048
AD-1571292.1	A-1146650	CUAAUGUGUGGUUU GGUAUUA	3243	3035-3055	A-2901390	UAAUACCAAAACC ACACAUUAGAU	3598	3033-3055
AD-1571293.1	A-1146652	UAAUGUGUGGUUUG GUUUUA	3244	3036-3056	A-2901391	UGAATACCAAAACC ACACAUUAGA	3599	3034-3056

Table 14. Knockdown of SNCA in Be(2)C Cells, *in vitro*.

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1nm_Fit
AD-1549052.1	11.7	4.1	17.1	2.9	24.1	3.3	16.5
AD-1549359.1	13.6	2.8	13.4	3.5	27.4	3.6	16.8
AD-1549054.1	10.7	2.0	18.1	5.6	29.6	5.7	17.2
AD-1571262.1	14.9	2.0	15.6	2.0	21.9	1.1	17.3
AD-1549333.1	13.5	3.7	22.2	3.1	20.6	6.3	17.7
AD-1549407.1	14.8	1.5	21.3	1.4	18.5	1.4	18.0
AD-1548854.1	11.5	2.1	19.7	2.2	27.8	4.9	18.3
AD-1549403.1	14.0	4.9	20.1	2.2	24.5	5.3	18.4
AD-1549283.1	17.0	4.9	18.2	4.5	22.8	0.7	18.6
AD-1549641.1	15.0	1.5	20.4	3.3	21.6	3.8	18.6
AD-1549267.1	12.3	2.5	18.7	3.4	30.8	6.6	18.8
AD-1548851.1	15.7	1.9	17.1	2.1	27.2	4.5	19.2
AD-1548869.1	11.4	2.1	22.3	3.4	30.2	6.4	19.4
AD-1549272.1	19.1	6.2	16.8	2.0	26.3	5.4	19.8

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mM_Fit
AD-1571164.1	11.8	1.3	25.8	2.1	29.4	7.6	20.0
AD-1549354.1	13.0	2.8	24.5	5.4	26.0	2.6	20.0
AD-1571188.1	16.4	1.9	21.1	2.2	23.8	4.7	20.1
AD-1549401.1	10.9	1.2	26.1	4.7	32.9	8.4	20.9
AD-1548886.1	11.3	1.5	24.9	5.7	33.2	2.6	20.9
AD-1571191.1	14.3	4.3	22.8	5.7	33.2	8.8	21.3
AD-1571193.1	18.5	3.3	20.8	3.9	27.5	1.9	21.8
AD-1548884.1	12.4	1.5	21.7	2.8	40.3	9.2	21.8
AD-1571187.1	16.8	2.3	22.7	3.5	29.1	3.7	22.0
AD-1549357.1	15.8	3.6	24.9	3.9	28.3	4.5	22.1
AD-1571194.1	16.2	4.3	23.9	3.0	32.0	7.3	22.5
AD-1549285.1	17.0	3.0	21.0	2.5	33.4	6.3	22.7
AD-1549266.1	14.7	2.3	24.9	2.4	32.2	2.7	22.7
AD-1549351.1	13.8	1.5	22.7	3.3	40.8	11.6	23.0
AD-1548870.1	17.3	2.7	20.4	2.9	36.0	4.3	23.2
AD-1549245.1	14.8	3.2	24.5	2.4	35.7	4.9	23.2
AD-1549334.1	16.8	2.3	22.1	3.3	35.1	3.7	23.4
AD-1549397.1	21.5	4.8	20.9	2.9	30.5	6.3	23.6
AD-1549290.1	17.9	2.7	22.0	2.9	35.3	1.9	23.6
AD-1549525.1	22.7	3.9	21.5	3.9	27.8	2.4	23.6

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mM_Fit
AD-1549406.1	17.4	1.1	23.6	3.7	33.1	5.7	23.8
AD-1549284.1	15.7	4.0	28.2	7.0	32.6	4.9	23.8
AD-1549439.1	20.3	2.8	26.0	4.7	27.2	5.6	23.8
AD-1549269.1	16.5	3.4	21.9	1.8	39.2	3.9	24.0
AD-1549518.1	22.5	2.9	25.6	2.9	24.6	4.6	24.0
AD-1549628.1	20.5	1.1	24.5	2.8	27.5	3.3	24.1
AD-1571199.1	18.5	0.4	29.0	3.1	26.0	4.8	24.1
AD-1549442.1	17.2	2.5	26.1	2.1	32.5	4.6	24.3
AD-1549596.1	23.2	2.3	23.2	3.8	27.6	5.6	24.3
AD-1549400.1	16.1	2.8	24.4	3.1	40.8	9.8	24.8
AD-1549280.1	20.6	6.3	20.8	1.2	38.2	4.2	24.9
AD-1549441.1	18.7	1.2	25.6	3.2	33.5	3.3	25.0
AD-1549556.1	22.5	3.4	24.3	2.8	31.4	7.2	25.3
AD-1571202.1	18.8	2.3	27.1	2.8	33.0	7.0	25.3
AD-1549271.1	21.0	5.7	24.1	4.6	34.0	3.0	25.4
AD-1549517.1	21.8	2.1	24.0	2.8	32.7	3.5	25.5
AD-1549293.1	18.1	3.4	28.1	2.4	34.0	5.0	25.5
AD-1549639.1	22.6	3.7	24.1	3.0	31.6	3.8	25.7
AD-1549443.1	17.8	2.1	27.6	2.7	36.6	2.9	26.1
AD-1571195.1	17.7	3.1	28.4	5.8	37.2	6.2	26.2

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1549595.1	24.7	3.7	27.8	3.7	27.1	2.1	26.2
AD-1549546.1	23.9	6.8	30.9	5.5	26.3	2.0	26.4
AD-1549246.1	15.5	1.1	28.6	4.4	42.9	3.8	26.6
AD-1571192.1	21.9	5.1	28.5	6.0	33.4	5.3	27.0
AD-1571165.1	16.8	2.5	27.6	0.8	44.6	8.6	27.1
AD-1549270.1	19.2	3.9	28.3	5.0	39.9	7.2	27.4
AD-1549521.1	25.9	3.5	29.6	1.0	27.4	5.6	27.4
AD-1549541.1	26.7	6.1	30.6	5.6	27.2	2.9	27.6
AD-1549552.1	24.2	2.7	30.9	3.9	30.2	4.5	28.1
AD-1549522.1	30.4	5.6	27.4	3.6	28.2	4.9	28.3
AD-1549545.1	26.8	4.5	30.1	2.5	28.5	3.0	28.3
AD-1549519.1	24.8	4.5	30.1	4.8	32.9	8.4	28.4
AD-1549630.1	24.6	2.9	29.7	3.3	32.2	2.2	28.4
AD-1549353.1	16.9	1.4	31.1	6.8	44.9	3.6	28.4
AD-1549544.1	26.7	1.5	26.1	3.8	33.7	4.7	28.5
AD-1549642.1	26.3	1.8	29.1	3.0	31.6	3.0	28.9
AD-1549438.1	24.2	4.9	28.1	3.3	36.9	3.5	29.0
AD-1549412.1	21.0	4.8	25.4	2.2	44.9	5.3	29.0
AD-1571198.1	19.2	2.4	34.3	6.6	37.9	4.0	29.0
AD-1571258.1	24.6	3.9	28.5	3.3	35.8	2.9	29.1

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1571201.1	28.4	6.5	29.5	2.9	30.6	4.6	29.2
AD-1549640.1	27.2	3.1	28.5	2.8	33.7	2.3	29.5
AD-1571266.1	26.3	5.7	28.9	4.4	35.4	1.1	29.7
AD-1571172.1	16.2	3.2	24.8	4.6	63.6	5.1	29.7
AD-1549527.1	26.5	4.6	28.0	4.7	36.5	7.4	29.7
AD-1549547.1	26.2	2.6	31.2	5.5	33.2	3.2	29.8
AD-1549037.1	17.5	1.5	32.2	7.1	49.1	5.0	29.8
AD-1571205.1	25.5	0.6	32.9	1.1	33.3	6.0	30.1
AD-1549053.1	19.2	6.2	32.4	5.2	47.8	7.8	30.3
AD-1571264.1	25.4	4.8	34.6	4.2	32.8	3.6	30.3
AD-1571186.1	22.3	1.1	27.6	4.5	46.7	6.7	30.4
AD-1571204.1	26.8	1.6	30.1	2.2	35.5	3.1	30.5
AD-1549555.1	26.8	1.3	33.8	5.0	31.4	5.0	30.5
AD-1548887.1	15.5	2.7	38.7	4.8	51.5	5.2	30.6
AD-1549426.1	24.5	6.2	27.6	3.0	44.5	7.1	30.7
AD-1548844.1	28.1	4.7	28.6	1.8	36.3	2.7	30.7
AD-1549520.1	27.5	3.1	35.7	2.4	29.7	2.3	30.7
AD-1549543.1	28.1	2.1	31.7	4.1	33.7	5.4	30.9
AD-1549548.1	27.7	4.3	33.8	6.1	34.4	5.1	31.4
AD-1571206.1	25.0	2.8	33.2	5.0	38.8	3.4	31.6

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1549210.1	16.5	1.2	34.8	1.3	56.0	8.0	31.9
AD-1571200.1	27.0	2.1	34.1	4.5	35.9	5.6	31.9
AD-1571207.1	29.1	2.1	31.2	5.7	37.2	1.4	32.4
AD-1549542.1	30.1	7.5	37.8	6.2	31.9	4.2	32.4
AD-1549211.1	20.9	6.4	27.9	5.8	62.7	6.9	32.4
AD-1571263.1	32.3	3.8	33.4	3.8	32.3	4.3	32.5
AD-1549391.1	23.5	5.1	27.8	4.2	54.6	6.6	32.5
AD-1549212.1	19.6	3.3	34.9	5.6	54.5	9.7	32.9
AD-1549268.1	21.9	6.7	33.8	3.4	51.2	3.6	33.2
AD-1549352.1	25.9	4.0	31.7	8.0	48.4	6.4	33.5
AD-1571261.1	30.3	2.4	34.6	6.2	36.7	3.0	33.6
AD-1549044.1	20.5	3.2	32.5	1.9	60.8	7.3	34.1
AD-1549554.1	32.5	4.1	33.9	5.8	37.3	2.7	34.1
AD-1548975.1	23.6	6.7	33.2	3.6	54.0	7.9	34.3
AD-1549432.1	21.9	1.7	40.3	11.2	49.0	3.1	34.6
AD-1549524.1	35.6	6.1	33.3	2.9	38.0	9.4	34.9
AD-1549643.1	26.5	5.1	41.7	8.8	40.3	3.4	35.2
AD-1571196.1	30.3	3.8	33.1	4.8	45.1	4.3	35.4
AD-1571203.1	32.6	2.1	35.5	7.2	40.1	3.9	35.5
AD-1549425.1	28.1	4.2	30.4	0.4	49.8	8.2	35.6

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1549264.1	18.9	3.3	40.1	3.4	64.5	10.5	36.0
AD-1549249.1	23.5	6.7	36.2	6.9	61.5	14.4	36.3
AD-1571257.1	32.8	8.8	35.0	2.6	43.8	4.6	36.4
AD-1549265.1	22.3	7.2	42.7	4.1	53.2	3.8	36.4
AD-1548843.1	31.6	4.0	42.4	11.3	39.1	6.2	36.6
AD-1548845.1	24.7	1.8	43.4	9.3	47.9	8.7	36.6
AD-1571256.1	33.6	5.6	35.3	5.7	42.5	4.3	36.6
AD-1571255.1	28.1	3.4	45.5	4.5	39.8	6.3	36.8
AD-1571174.1	20.8	3.1	34.8	5.2	71.5	11.1	36.8
AD-1571173.1	23.5	8.5	36.4	3.8	67.4	11.4	37.5
AD-1548876.1	21.9	6.4	44.6	5.3	57.2	6.9	37.8
AD-1549615.1	33.2	0.7	38.7	4.9	43.1	4.0	38.0
AD-1571166.1	24.2	1.6	42.1	6.0	54.5	1.7	38.3
AD-1571269.1	32.7	6.2	37.6	3.6	48.2	3.2	38.7
AD-1548976.1	18.9	1.8	37.0	4.1	86.5	20.6	38.9
AD-1549038.1	26.0	7.2	37.2	4.4	65.2	10.7	38.9
AD-1571167.1	23.8	4.4	40.9	4.4	63.8	3.6	39.2
AD-1571170.1	23.9	6.2	39.1	6.1	69.4	11.1	39.6
AD-1548888.1	27.0	4.9	43.5	7.4	55.1	3.5	39.7
AD-1571189.1	25.6	4.9	47.4	7.0	56.8	12.5	40.5

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1571259.1	42.2	3.1	46.6	1.5	33.7	5.7	40.5
AD-1549224.1	22.4	2.7	44.7	7.2	73.5	12.2	41.5
AD-1571208.1	37.7	7.7	42.4	7.2	48.0	2.7	42.2
AD-1549222.1	20.5	2.8	54.0	10.3	70.9	14.6	42.7
AD-1571268.1	35.4	1.5	40.6	4.0	57.9	3.9	43.4
AD-1571270.1	39.7	6.7	45.6	7.9	47.9	10.0	43.7
AD-1549217.1	27.7	3.7	53.3	5.3	58.3	3.5	43.9
AD-1571184.1	29.8	3.4	41.0	4.1	76.0	15.1	44.8
AD-1571271.1	41.1	10.3	45.0	7.3	51.5	5.2	45.0
AD-1571272.1	43.6	11.8	45.5	9.0	49.8	3.8	45.3
AD-1571190.1	37.4	7.1	47.0	9.4	62.4	4.8	47.2
AD-1549055.1	27.2	5.0	51.9	9.1	79.7	3.7	47.7
AD-1571169.1	42.5	7.6	41.0	4.8	75.0	15.2	49.5
AD-1571265.1	36.5	7.2	57.9	4.9	59.6	5.8	49.6
AD-1571267.1	48.2	2.5	44.3	6.1	65.2	8.4	51.4
AD-1549686.1	48.6	8.1	50.5	7.4	60.7	2.9	52.5
AD-1549225.1	30.6	7.6	56.2	12.2	97.3	17.3	53.6
AD-1549683.1	46.4	5.6	57.4	7.8	59.5	4.7	53.7
AD-1571183.1	38.8	4.7	55.9	7.2	76.7	18.2	54.2
AD-1549682.1	43.4	3.8	55.3	10.4	68.4	9.7	54.2

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1nm_Fit
AD-1571185.1	39.4	4.7	58.8	6.7	79.0	12.8	56.1
AD-1571232.1	61.0	8.4	54.1	8.5	56.0	4.7	56.6
AD-1571260.1	50.8	9.0	56.2	2.6	65.4	6.1	56.8
AD-1549684.1	54.7	6.9	61.2	11.4	58.0	7.5	57.4
AD-1571253.1	44.4	4.8	60.9	8.5	72.9	3.4	57.8
AD-1571181.1	36.9	4.3	75.2	9.9	72.8	5.1	58.2
AD-1571182.1	46.4	5.9	54.7	4.5	80.6	4.3	58.7
AD-1571197.1	54.0	5.2	61.1	8.3	63.1	11.3	58.7
AD-1551648.1	57.6	4.2	61.8	14.0	63.9	16.0	59.7
AD-1549216.1	39.0	5.1	78.3	6.7	73.4	6.7	60.4
AD-1550657.1	92.2	18.7	52.5	8.0	52.0	3.5	62.2
AD-1552192.1	67.3	1.9	74.8	9.7	54.9	4.9	65.2
AD-1549685.1	66.3	8.5	67.0	13.5	71.8	8.1	67.4
AD-1571254.1	63.1	6.1	71.7	7.1	70.3	10.8	67.8
AD-1550869.1	73.2	2.5	61.4	2.7	71.0	4.9	67.9
AD-1548978.1	43.1	7.1	76.6	13.7	98.1	11.2	68.2
AD-1571180.1	45.7	1.2	86.0	14.4	91.8	19.3	70.3
AD-1549281.1	49.2	11.2	74.7	13.2	102.9	10.6	71.3
AD-1550757.1	83.5	7.8	62.5	8.0	73.3	5.2	72.1
AD-1550958.1	69.4	5.3	66.0	4.7	82.5	5.3	72.6

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mM_Fit
AD-1551177.1	81.3	7.1	66.8	4.4	76.5	9.0	74.4
AD-1550755.1	77.4	1.8	77.8	18.1	75.8	9.7	75.9
AD-1550756.1	79.2	7.7	82.4	5.1	67.7	9.5	76.0
AD-1551665.1	94.1	11.4	66.5	13.7	79.0	19.0	76.8
AD-1551069.1	88.7	4.6	66.6	7.8	79.3	11.6	77.3
AD-1551656.1	72.6	11.0	64.4	4.9	99.5	24.7	77.6
AD-1571289.1	71.1	10.4	84.4	4.2	80.2	11.0	77.7
AD-1550758.1	89.8	6.8	56.4	7.9	87.7	7.2	78.0
AD-1549728.1	66.2	11.4	85.9	8.5	86.2	12.1	78.0
AD-1551649.1	89.2	21.9	78.8	6.7	70.9	6.6	78.3
AD-1551067.1	81.7	8.0	77.7	10.8	78.9	4.7	79.0
AD-1551651.1	71.9	6.2	81.1	11.0	86.5	9.5	79.0
AD-1571287.1	64.1	19.0	80.1	7.3	105.6	16.5	79.7
AD-1551661.1	72.3	6.1	81.1	16.0	88.9	3.2	79.7
AD-1551181.1	78.6	5.8	80.4	6.9	82.4	7.0	80.2
AD-1551655.1	81.8	10.9	73.0	13.8	89.5	7.9	80.2
AD-1571178.1	65.6	7.6	93.8	11.1	86.7	17.6	80.2
AD-1552054.1	96.9	18.8	93.5	24.6	61.0	7.2	80.9
AD-1549726.1	65.7	5.6	96.6	21.3	84.5	10.1	80.9
AD-1571220.1	81.0	16.3	79.2	6.3	87.4	16.0	81.4

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mM_Fit
AD-1571179.1	57.1	1.6	97.0	8.8	96.7	17.9	81.5
AD-1551588.1	95.8	23.0	81.1	9.2	74.7	15.2	81.8
AD-1551657.1	80.8	15.9	74.9	15.6	96.0	5.6	82.1
AD-1552053.1	74.5	15.1	92.0	22.1	85.1	5.5	82.2
AD-1549727.1	79.2	16.0	96.5	15.5	76.4	12.8	82.2
AD-1552249.1	73.9	8.8	87.9	13.0	88.6	6.6	82.4
AD-1551070.1	88.6	8.4	81.8	8.1	82.1	6.8	83.8
AD-1550964.1	85.4	8.0	78.1	2.6	88.6	5.6	83.8
AD-1571293.1	67.0	10.4	87.8	6.0	103.0	16.2	83.8
AD-1550887.1	97.5	5.1	84.2	7.8	74.4	10.4	84.5
AD-1551666.1	86.6	17.9	86.0	22.6	88.5	15.3	84.7
AD-1571209.1	71.6	6.4	92.0	9.0	94.1	10.6	85.0
AD-1551086.1	87.1	18.1	88.8	15.6	83.6	4.2	85.4
AD-1571215.1	89.9	11.3	94.1	8.4	75.9	14.0	85.5
AD-1571290.1	73.8	19.8	90.2	10.2	98.5	5.2	85.7
AD-1571175.1	78.4	7.2	104.2	13.0	78.4	5.7	85.8
AD-1550956.1	87.2	8.4	88.4	15.2	85.8	11.6	86.2
AD-1550659.1	82.8	11.7	83.0	13.4	96.8	6.9	86.6
AD-1550871.1	89.6	5.6	86.8	8.5	85.6	12.5	86.6
AD-1571280.1	84.4	17.1	86.0	5.9	95.3	21.1	86.7

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1550656.1	94.4	7.1	82.3	1.0	84.9	10.1	86.8
AD-1551347.1	88.3	14.3	99.6	17.1	77.8	11.5	87.0
AD-1550959.1	78.9	3.9	90.0	7.6	93.6	9.0	87.0
AD-1551658.1	80.8	4.0	94.4	15.2	88.8	7.4	87.2
AD-1550954.1	84.7	8.1	100.2	7.5	80.2	11.8	87.4
AD-1551171.1	82.8	7.6	90.4	13.2	93.4	13.0	88.0
AD-1552191.1	80.0	14.0	86.0	9.3	102.7	4.7	88.3
AD-1571283.1	47.4	4.2	119.8	18.1	117.5	8.4	88.3
AD-1550960.1	77.5	8.3	104.8	8.1	87.1	10.0	88.5
AD-1552253.1	86.8	5.2	83.9	7.9	96.7	13.1	88.5
AD-1571224.1	92.1	16.5	84.4	17.3	94.5	16.2	88.7
AD-1571222.1	103.3	9.8	86.9	8.1	79.4	9.2	89.0
AD-1549729.1	82.5	5.0	97.4	5.3	89.6	14.8	89.0
AD-1571282.1	55.4	16.6	113.8	19.6	116.8	14.6	89.0
AD-1551078.1	91.4	15.0	84.2	7.4	93.5	5.8	89.1
AD-1550660.1	91.5	14.5	94.9	6.2	83.7	6.0	89.3
AD-1571238.1	87.3	4.0	86.7	8.3	97.4	15.6	89.6
AD-1551650.1	90.2	25.0	100.8	4.1	85.0	10.8	90.0
AD-1571242.1	87.3	12.5	83.0	15.9	103.7	6.4	90.0
AD-1551253.1	94.8	17.0	94.9	6.5	82.4	1.3	90.1

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1549282.1	72.7	20.4	101.0	26.4	108.3	11.2	90.3
AD-1551180.1	95.5	9.7	88.1	4.1	89.0	7.4	90.6
AD-1571244.1	87.7	11.7	85.5	27.7	111.1	30.2	90.8
AD-1551667.1	87.5	12.6	92.2	13.3	97.0	18.8	91.0
AD-1552066.1	88.0	7.7	94.9	16.5	92.8	11.0	91.0
AD-1552065.1	90.1	19.9	88.0	12.8	101.7	25.2	91.1
AD-1551255.1	97.6	4.7	82.3	5.7	95.0	8.6	91.1
AD-1571229.1	93.0	13.6	85.6	7.5	96.3	3.4	91.1
AD-1552251.1	90.4	8.3	94.3	12.1	90.9	11.0	91.3
AD-1571251.1	90.4	8.6	87.4	4.3	97.5	6.9	91.4
AD-1571221.1	84.3	12.9	101.7	7.6	91.8	10.0	91.7
AD-1552169.1	100.5	22.8	89.9	17.7	89.8	3.6	91.8
AD-1552244.1	94.4	16.6	90.4	5.8	92.4	4.0	91.9
AD-1551066.1	92.4	7.8	97.4	8.3	87.7	3.5	92.2
AD-1571211.1	82.1	9.4	104.2	15.4	94.4	16.3	92.2
AD-1550292.1	99.9	15.2	86.7	7.4	91.9	4.9	92.2
AD-1551090.1	85.1	12.5	91.7	12.4	103.0	8.6	92.5
AD-1552052.1	97.0	24.2	88.3	4.8	96.6	8.9	92.8
AD-1571233.1	105.1	16.4	90.0	17.8	88.7	16.5	92.8
AD-1571228.1	99.2	11.5	90.2	9.3	91.5	6.8	93.0

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1571243.1	96.7	17.0	93.1	16.7	93.1	10.3	93.2
AD-1551091.1	106.0	9.4	86.9	6.6	90.2	8.6	93.7
AD-1550888.1	103.7	6.9	103.2	8.5	77.8	17.2	93.7
AD-1571247.1	89.4	9.1	89.5	10.3	105.1	12.1	93.8
AD-1571176.1	67.4	12.9	102.8	8.0	120.8	11.5	94.0
AD-1551566.1	102.7	8.4	107.9	18.2	81.7	19.0	94.0
AD-1552161.1	94.4	17.1	105.4	5.6	85.8	8.9	94.1
AD-1571279.1	84.5	16.5	108.4	26.7	98.4	16.2	94.5
AD-1571210.1	90.0	14.7	97.6	17.3	100.7	12.3	94.9
AD-1551258.1	100.9	13.1	90.0	4.0	96.2	4.8	95.2
AD-1551659.1	81.2	8.6	108.1	16.3	101.0	10.1	95.3
AD-1550963.1	92.8	12.2	99.3	10.9	98.1	21.9	95.3
AD-1551670.1	112.3	16.3	82.5	20.5	102.2	30.3	95.4
AD-1571236.1	94.8	7.7	100.1	16.3	93.3	7.1	95.4
AD-1571246.1	92.4	2.5	98.3	7.6	96.7	9.9	95.5
AD-1550661.1	91.1	11.0	105.7	11.3	93.1	12.2	95.8
AD-1571214.1	97.7	3.5	97.8	6.9	93.7	16.1	95.8
AD-1571218.1	83.6	9.3	116.2	18.2	92.3	8.9	95.9
AD-1571252.1	91.3	14.8	103.2	17.7	96.6	7.2	96.0
AD-1571168.1	84.4	14.1	91.7	14.4	119.1	22.0	96.1

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1571213.1	89.9	15.1	106.6	12.9	95.3	12.1	96.1
AD-1552193.1	88.9	10.5	98.7	13.7	104.6	14.1	96.3
AD-1571286.1	94.8	10.7	100.4	2.6	95.3	10.8	96.4
AD-1551073.1	103.1	11.4	99.8	9.2	88.8	10.2	96.6
AD-1571177.1	90.8	11.6	119.3	28.8	86.7	9.1	96.6
AD-1571240.1	91.8	10.8	102.6	14.9	101.1	21.1	97.0
AD-1571216.1	113.7	8.5	98.5	17.0	83.5	8.4	97.0
AD-1571241.1	102.3	12.0	89.9	7.7	102.5	9.1	97.2
AD-1571231.1	99.5	15.6	90.5	9.5	105.0	14.0	97.3
AD-1551346.1	115.2	7.9	88.0	5.5	91.7	9.5	97.4
AD-1552247.1	108.7	23.9	88.0	16.7	102.5	12.3	97.9
AD-1550957.1	91.3	9.7	109.6	4.4	95.1	10.2	97.9
AD-1552248.1	106.1	8.9	96.7	13.3	94.5	14.9	98.0
AD-1551590.1	94.6	14.0	100.5	6.8	101.9	18.5	98.1
AD-1571225.1	102.6	21.2	101.3	8.7	93.2	7.8	98.1
AD-1550984.1	92.5	7.9	96.5	10.2	108.3	10.6	98.4
AD-1551653.1	99.2	7.9	94.3	5.4	103.2	6.0	98.6
AD-1552257.1	94.9	4.9	97.3	9.8	104.9	5.5	98.7
AD-1571171.1	85.5	5.1	107.8	9.6	105.6	8.6	98.7
AD-1571237.1	102.6	7.0	111.8	2.5	85.3	11.5	98.8

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mM_Fit
AD-1551646.1	110.7	15.7	96.7	12.5	95.2	21.8	99.2
AD-1550647.1	94.4	9.1	110.7	12.5	96.0	9.8	99.6
AD-1550949.1	109.2	16.9	105.2	17.0	88.4	7.7	99.7
AD-1552255.1	109.5	6.7	102.1	11.7	90.4	10.5	99.8
AD-1571273.1	99.5	8.8	97.0	10.3	105.4	11.7	100.1
AD-1551668.1	104.8	6.7	93.2	8.0	105.1	15.5	100.2
AD-1571235.1	112.5	20.7	94.1	14.9	99.7	18.8	100.3
AD-1552250.1	91.8	9.1	106.4	3.0	104.8	10.0	100.5
AD-1571281.1	90.6	7.1	103.9	7.5	109.5	8.6	100.9
AD-1550955.1	117.3	6.5	95.3	9.3	94.7	17.3	101.0
AD-1551256.1	118.3	18.2	96.8	11.2	92.7	13.9	101.2
AD-1571223.1	98.7	15.0	114.9	16.0	93.9	4.7	101.3
AD-1551170.1	100.9	6.1	97.3	12.2	108.5	6.9	101.3
AD-1571292.1	94.7	11.8	105.2	23.9	108.5	9.9	101.4
AD-1571248.1	96.1	16.7	97.1	8.9	114.9	12.4	101.5
AD-1551076.1	109.2	11.6	98.9	14.5	99.9	13.6	101.6
AD-1552055.1	109.2	5.0	110.5	3.8	87.4	8.5	101.6
AD-1550965.1	104.9	6.2	102.0	5.5	101.5	17.1	102.1
AD-1551589.1	97.8	14.7	95.3	11.3	116.8	12.5	102.2
AD-1571226.1	118.1	19.4	94.7	5.7	99.6	14.1	102.9

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1nm_Fit
AD-1571217.1	107.1	12.2	108.1	11.8	97.2	15.6	103.1
AD-1571291.1	92.0	12.0	112.6	18.3	109.4	14.7	103.5
AD-1571219.1	106.4	6.8	100.0	12.3	111.7	27.6	104.1
AD-1551077.1	115.4	14.9	106.4	8.2	93.6	7.2	104.3
AD-1551182.1	121.0	15.5	95.7	5.9	100.1	7.5	104.6
AD-1571278.1	95.2	3.7	103.3	11.9	117.7	8.3	104.6
AD-1571230.1	118.6	9.9	98.6	9.6	99.1	5.4	104.9
AD-1551254.1	112.5	16.4	103.2	13.4	101.7	4.7	105.0
AD-1551353.1	107.7	4.9	100.8	11.1	108.5	9.6	105.3
AD-1551672.1	108.4	11.5	101.5	10.3	110.1	12.1	105.5
AD-1552056.1	113.2	5.9	102.3	10.2	102.9	5.0	105.7
AD-1571249.1	103.0	7.1	104.0	10.8	111.8	4.9	105.9
AD-1571212.1	103.0	6.2	113.7	8.7	107.7	19.2	106.1
AD-1551068.1	113.9	13.5	110.2	7.8	98.7	15.7	106.6
AD-1550459.1	112.3	11.1	121.1	13.7	91.5	8.1	107.0
AD-1552158.1	95.9	9.4	111.2	8.6	117.7	10.4	107.5
AD-1550658.1	99.0	14.9	113.9	12.5	113.6	16.2	107.6
AD-1552057.1	123.3	25.2	104.7	10.8	100.5	8.8	107.9
AD-1571245.1	108.0	23.5	116.7	15.9	107.4	31.2	108.3
AD-1550648.1	111.7	16.3	109.7	15.1	110.9	28.9	108.6

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1mm_Fit
AD-1571274.1	105.3	23.6	109.5	20.2	118.3	26.8	108.6
AD-1550961.1	108.2	17.7	110.4	11.1	112.3	20.5	108.9
AD-1550458.1	114.5	6.9	123.3	31.3	97.0	15.4	109.2
AD-1571227.1	106.7	12.6	111.0	6.2	119.3	16.8	111.5
AD-1552067.1	101.4	5.9	111.6	12.8	124.0	10.6	111.5
AD-1551592.1	108.7	19.8	112.9	8.5	119.8	14.4	112.7
AD-1571275.1	99.9	6.3	121.1	14.7	119.5	13.6	112.9
AD-1571285.1	111.1	12.4	126.9	17.3	107.9	9.0	114.3
AD-1571250.1	105.9	7.0	130.9	10.6	108.8	9.3	115.2
AD-1571276.1	111.0	2.7	117.9	10.9	119.0	13.7	115.6
AD-1571234.1	126.1	14.8	106.2	9.3	120.0	21.5	116.0
AD-1552254.1	120.5	5.0	118.9	9.4	112.8	12.7	117.0
AD-1551251.1	130.0	16.3	113.0	16.5	116.9	17.4	118.5
AD-1550346.1	108.1	12.9	132.9	27.7	119.6	17.0	119.4
AD-1571239.1	114.0	23.5	113.1	10.5	135.6	21.3	119.5
AD-1551164.1	124.4	6.8	126.1	9.6	118.8	12.7	122.7
AD-1552159.1	116.2	6.2	131.5	12.5	129.0	3.4	125.1
AD-1571277.1	124.2	3.9	125.1	21.4	131.6	19.1	125.5
AD-1551392.1	126.2	10.3	129.8	19.8	126.2	11.1	126.6
AD-1551257.1	130.9	11.8	131.2	19.7	123.3	6.2	127.6

Duplex Name	10nM	STDEV	1nM	STDEV	0.1nM	STDEV	1nm_Fit
AD-1571284.1	131.6	24.8	135.8	7.0	129.3	10.1	130.8

INFORMAL SEQUENCE LISTING

SEQ ID NO: 1

LOCUS NM_007308 3312 bp mRNA linear PRI 31-AUG-2020
 DEFINITION Homo sapiens synuclein alpha (SNCA), transcript variant 4,
 mRNA. VERSION NM_007308.3

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Reverse complement of SEQ ID NO: 1

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SEQ ID NO: 3

LOCUS XM_005555421 2955 bp mRNA linear PRI 25-JAN-2016

DEFINITION PREDICTED: *Macaca fascicularis* synuclein alpha (SNCA),
 transcript variant X7, mRNA.

VERSION XM_005555421.2

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SEQ ID NO: 4

Reverse complement of SEQ ID NO: 3

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312

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SEQ ID NO: 7

LOCUS NM_019169 1176 bp mRNA linear ROD 23-AUG-2020
 DEFINITION Rattus norvegicus synuclein alpha (Snca), mRNA.
 VERSION NM_019169.2

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SEQ ID NO: 8

Reverse complement of SEQ ID NO: 7

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SEQ ID NO: 1806

LOCUS XM_535656 1493 bp mRNA linear MAM

06-JAN-2021

DEFINITION PREDICTED: Canis lupus familiaris synuclein alpha (SNCA),
transcript variant X12, mRNA.

ACCESSION XM_535656

VERSION XM_535656.7

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SEQ ID NO: 3600

Reverse complement of SEQ ID NO: 1806

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EQUIVALENTS

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of SNCA, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO: 1, or a nucleotide sequence having at least 90% nucleotide sequence identity to a portion of the nucleotide sequence of SEQ ID NO: 1, and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 2, or a nucleotide sequence having at least 90% nucleotide sequence identity to a portion of the nucleotide sequence of SEQ ID NO: 2.
2. A double stranded ribonucleic acid (RNAi) agent for inhibiting expression of a SNCA gene, wherein the RNAi agent comprises a sense strand and an antisense strand, and wherein the antisense strand comprises a region of complementarity comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from an antisense sequence selected from the group consisting of the antisense sequences of **Tables 2, 3, 12 and 13**.
3. The dsRNA agent of claim 1 or claim 2, wherein the sense strand or the antisense strand is conjugated to one or more lipophilic moieties.
4. The dsRNA agent of any one of claims 1-3, wherein the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO: 1, and the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 2, such that the sense strand is complementary to the at least 17 contiguous nucleotides in the antisense strand.
5. The dsRNA agent of any one of claims 1-4, wherein the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO: 1, and the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0 or 1 mismatches, of the

corresponding portion of the nucleotide sequence of SEQ ID NO: 2, such that the sense strand is complementary to the at least 19 contiguous nucleotides in the antisense strand.

6. The dsRNA agent of any one of claims 1-5, wherein the sense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0 or 1 mismatches, of a portion of the nucleotide sequence of SEQ ID NO: 1, and the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0 or 1 mismatches, of the corresponding portion of nucleotide sequence of SEQ ID NO: 2, such that the sense strand is complementary to the at least 21 contiguous nucleotides in the antisense strand.

7. The dsRNA agent of any one of claims 1-6, wherein the sense strand or the antisense strand is a sense strand or an antisense strand selected from the group consisting of any of the sense strands and antisense strands in any one of **Tables 2, 3, 12 and 13**.

8. The dsRNA agent of any one of claims 1-7, wherein both the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

9. The dsRNA agent of claim 2, wherein the lipophilic moiety is conjugated to one or more positions in the double stranded region of the dsRNA agent.

10. The dsRNA agent of claim 8 or 9, wherein the lipophilic moiety is conjugated via a linker or a carrier.

11. The dsRNA agent of any one of claims 8-10, wherein lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

12. The dsRNA agent of any one of claims 1-11, wherein the hydrophobicity of the double-stranded RNAi agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNAi agent, exceeds 0.2.

13. The dsRNA agent of claim 12, wherein the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

14. The dsRNA agent of any one of claims 1-13, wherein the dsRNA agent comprises at least one modified nucleotide.

15. The dsRNA agent of claim 14, wherein no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides.

16. The dsRNA agent of claim 14, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

17. The dsRNA agent of any one of claims 14-16, wherein at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofuran-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

18. The dsRNA agent of claim 17, wherein the modified nucleotide is selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxy-thymine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

19. The dsRNA agent of claim 17, wherein the modified nucleotide comprises a short sequence of 3'-terminal deoxy-thymine nucleotides (dT).

20. The dsRNA agent of claim 17, wherein the modifications on the nucleotides are 2'-O-methyl, GNA and 2'fluoro modifications.
21. The dsRNA agent of claim 17, further comprising at least one phosphorothioate internucleotide linkage.
22. The dsRNA agent of claim 21, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.
23. The dsRNA agent of any one of claims 1-22, wherein each strand is no more than 30 nucleotides in length.
24. The dsRNA agent of any one of claims 1-23, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.
25. The dsRNA agent of any one of claims 1-23, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.
26. The dsRNA agent of any one of claims 1-25, wherein the double stranded region is 15-30 nucleotide pairs in length.
27. The dsRNA agent of claim 26, wherein the double stranded region is 17-23 nucleotide pairs in length.
28. The dsRNA agent of claim 26, wherein the double stranded region is 17-25 nucleotide pairs in length.
29. The dsRNA agent of claim 26, wherein the double stranded region is 23-27 nucleotide pairs in length.
30. The dsRNA agent of claim 26, wherein the double stranded region is 19-21 nucleotide pairs in length.
31. The dsRNA agent of claim 26, wherein the double stranded region is 21-23 nucleotide pairs in length.

32. The dsRNA agent of any one of claims 1-31, wherein each strand has 19-30 nucleotides.
33. The dsRNA agent of any one of claims 1-31, wherein each strand has 19-23 nucleotides.
34. The dsRNA agent of any one of claims 1-31, wherein each strand has 21-23 nucleotides.
35. The dsRNA agent of any one of claims 8-34, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.
36. The dsRNA agent of claim 35, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand via a linker or carrier.
37. The dsRNA agent of claim 36, wherein the internal positions include all positions except the terminal two positions from each end of the at least one strand.
38. The dsRNA agent of claim 36, wherein the internal positions include all positions except the terminal three positions from each end of the at least one strand.
39. The dsRNA agent of claim 36-38, wherein the internal positions exclude a cleavage site region of the sense strand.
40. The dsRNA agent of claim 39, wherein the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.
41. The dsRNA agent of claim 39, wherein the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.
42. The dsRNA agent of claim 36-38, wherein the internal positions exclude a cleavage site region of the antisense strand.
43. The dsRNA agent of claim 42, wherein the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.
44. The dsRNA agent of claim 36-38, wherein the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.

45. The dsRNA agent of any one of claims 1-44, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5' end of each strand.
46. The dsRNA agent of claim 45, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5' end of each strand.
47. The dsRNA agent of claim 9, wherein the positions in the double stranded region exclude a cleavage site region of the sense strand.
48. The dsRNA agent of any one of claims 1-47, wherein the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.
49. The dsRNA agent of claim 48, wherein the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.
50. The dsRNA agent of claim 48, wherein the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.
51. The dsRNA agent of claim 48, wherein the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.
52. The dsRNA agent of claim 48, wherein the lipophilic moiety is conjugated to position 16 of the antisense strand.
53. The dsRNA agent of any one of claims 1-52, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.
54. The dsRNA agent of claim 53, wherein the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric

acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

55. The dsRNA agent of claim 54, wherein the lipophilic moiety contains a saturated or unsaturated C₄-C₃₀ hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

56. The dsRNA agent of claim 55, wherein the lipophilic moiety contains a saturated or unsaturated C₆-C₁₈ hydrocarbon chain.

57. The dsRNA agent of claim 55, wherein the lipophilic moiety contains a saturated or unsaturated C₁₆ hydrocarbon chain.

58. The dsRNA agent of claim 57, wherein the saturated or unsaturated C₁₆ hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

59. The dsRNA agent of any one of claims 1-56, wherein the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

60. The dsRNA agent of claim 59, wherein the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalanyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

61. The dsRNA agent of any one of claims 1-56, wherein the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

62. The double-stranded iRNA agent of any one of claims 1-61, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

63. The dsRNA agent of any one of claims 1-62, wherein the lipophilic moiety or targeting ligand is conjugated via a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.
64. The dsRNA agent of any one of claims 1-63, wherein the 3' end of the sense strand is protected via an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.
65. The dsRNA agent of any one of claims 1-64, further comprising a targeting ligand that targets a liver tissue.
66. The dsRNA agent of claim 65, wherein the targeting ligand is a GalNAc conjugate.
67. The dsRNA agent of any one of claims 1-66 further comprising:
a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, or
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.
68. The dsRNA agent of any one of claims 1-66 further comprising:
a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, or
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

69. The dsRNA agent of any one of claims 1-66 further comprising:
- a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
 - a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, or
 - a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.
70. The dsRNA agent of any one of claims 1-66 further comprising:
- a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
 - a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration,
 - a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, or
 - a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.
71. The dsRNA agent of any one of claims 1-66 further comprising:
- a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
 - a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, or
 - a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.
72. The dsRNA agent of any one of claims 1-71, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.
73. The dsRNA agent of claim 72, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

74. The dsRNA agent of any one of claims 1-71, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an A:U base pair.
75. The dsRNA agent of any one of claims 1-71, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.
76. A cell containing the dsRNA agent of any one of claims 1-75.
77. A pharmaceutical composition for inhibiting expression of a gene encoding SNCA, comprising the dsRNA agent of any one of claims 1-75.
78. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-75 and a lipid formulation.
79. A method of inhibiting expression of a SNCA gene in a cell, the method comprising:
- (a) contacting the cell with the dsRNA agent of any one of claims 1-75, or the pharmaceutical composition of claim 77 or 78; and
 - (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the SNCA gene, thereby inhibiting expression of the SNCA gene in the cell.
80. The method of claim 79, wherein the cell is within a subject.
81. The method of claim 80, wherein the subject is a human.
82. The method of any one of claims 79-81, wherein the expression of SNCA is inhibited by at least 50%.
83. The method of claim 81, wherein the subject meets at least one diagnostic criterion for a SNCA-associated disease.
84. The method of claim 81, wherein the subject has been diagnosed with a SNCA-associated disease.

85. The method of claim 84, wherein the SNCA-associated disease is a synucleinopathy, optionally a disease selected from the group consisting of PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

86. A method of treating a subject diagnosed with a SNCA-associated neurodegenerative disease, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-75 or the pharmaceutical composition of claim 77 or 78, thereby treating the subject.

87. The method of claim 86, wherein treating comprises amelioration of at least one sign or symptom of the disease.

88. The method of claim 86, where treating comprises prevention of progression of the disease.

89. The method of claim 86, wherein the SNCA-associated disease is characterized by one or more symptoms selected from the group consisting of tremors, slowed movement (bradykinesia), rigid muscles, impaired posture and balance, loss of automatic movements, speech changes, writing changes, visual, auditory, olfactory, or tactile hallucinations, poor regulation of body functions (autonomic nervous systems) such as dizziness, falls and bowel issues, cognitive problems such as confusion, poor attention, visual-spatial problems and memory loss, sleep difficulties such as rapid eye movement (REM) sleep behavior disorder (in which dreams are physically acted out while asleep), fluctuating attention including episodes of drowsiness, long periods of staring into space, long naps during the day or disorganized speech, depression, and apathy, orthostatic hypotension (a sudden drop in blood pressure that occurs when a person stands up, causing a person to feel dizzy and lightheaded, and the need to sit, squat, or lie down in order to prevent fainting), clumsiness or incoordination, bladder control problems, contractures (chronic shortening of muscles or tendons around joints, which prevents the joints from moving freely) in

the hands or limbs, Pisa syndrome (an abnormal posture in which the body appears to be leaning to one side), antecollis (in which the neck bends forward and the head drops down), and involuntary and uncontrollable sighing or gasping.

90. The method of claim 86, wherein the SNCA-associated neurodegenerative disease is selected from the group consisting of a synucleinopathy, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

91. A method of preventing development of a SNCA-associated neurodegenerative disease in a subject meeting at least one diagnostic criterion for a SNCA-associated neurodegenerative disease, the method comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-75 or the pharmaceutical composition of claim 77 or 78, thereby preventing the development of a SNCA-associated neurodegenerative disease in the subject meeting at least one diagnostic criterion for a SNCA-associated neurodegenerative disease.

92. The method of any one of claims 86-91, wherein the subject is human.

93. The method of claim 91, wherein the subject has been diagnosed with a SNCA-associated disease.

94. The method of claim 93, wherein the SNCA-associated disease is selected from the group consisting of a synucleinopathy, such as PD, multiple system atrophy, Lewy body dementia (LBD), pure autonomic failure (PAF), Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar

degeneration, Alzheimer's disease, Huntington's disease, Down's syndrome, psychosis, schizophrenia and Creutzfeldt-Jakob disease.

95. The method of any one of claims 80-94, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

96. The method of any one of claims 80-95, wherein the dsRNA agent is administered to the subject intrathecally.

97. The method of any one of claims 80-96, further comprising administering to the subject an additional agent or a therapy suitable for treatment or prevention of a SNCA-associated disease or disorder.

98. A modified double stranded ribonucleic acid (RNAi) agent for inhibiting expression of a SNCA gene as listed in **Tables 2, 9, or 12**, wherein the 3'-terminus of each sense strand is optionally modified by both (i) removing the 3'-terminal L96 ligand and (ii) replacing the two phosphodiester internucleotide linkages between the three 3'-terminal nucleotides with phosphorothioate internucleotide linkages.