siRNA COMPOSITIONS AND METHODS TARGETING ALPHA-SYNUCLEIN NUCLEIC ACIDS

1. SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on September 27, 2023, is named "51436-042WO2_Sequence_Listing_9_27_23" and is 820,156 bytes in size.

2. BACKGROUND

[0002] Expression of the alpha-synuclein (SNCA) gene produces the protein alpha-synuclein. While the alpha-synuclein protein is a soluble monomer normally localized at the presynaptic region of axons, the protein can form filamentous aggregates that are the major component of intracellular inclusions in neurodegenerative synucleinopathies. For example, mutations in the SNCA gene and SNCA gene multiplications have been linked to the formation of the filamentous aggregates that are a hallmark of familial Parkinson's disease. Additional neurodegenerative synucleinopathies associated with alpha-synuclein aggregates include sporadic Parkinson's disease, Alzheimer's disease, multiple system atrophy, and Lewy body dementia. Currently there are limited treatment options available for neurodegenerative synucleinopathies. Accordingly, there remains a need for therapeutics that can selectively diminish SNCA activity in a manner that provides effective treatment for neurodegenerative synucleinopathies.

3. SUMMARY

[0003] The instant application is directed to single- or double-stranded interfering RNA molecules (e.g., siRNA molecules) that target an SNCA gene. The interfering RNA molecules may contain specific patterns of nucleoside modifications and internucleoside linkage modifications. The disclosure also features pharmaceutical compositions including the same. The siRNA molecules may be branched siRNA molecules, such as di-branched, tri-branched, or tetra-branched siRNA molecules. The disclosed siRNA molecules may further feature a 5' phosphorus stabilizing moiety and/or a hydrophobic moiety. Additionally, the disclosure provides methods for delivering the siRNA molecule of the disclosure to the central nervous system of a subject, such as a subject identified as having a synucleinopathy. In certain

embodiments, an interfering RNA molecule of the present disclosure is a di-branched siRNA molecule. In certain embodiments, the di-branched siRNA molecules of the present disclosure comprise:

a) a sense strand comprising the sequence (mU)#(mA)#(mC)(fC)(mA)(fC)(mU)(fU)(mA)(fU)(mU)(mU)(mC)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 841) and an antisense strand comprising the sequence V(mU)#(fU)#(mA)(fG)(fA)(fA)(mA)(fU)(mA)(fA)(mG)(fU)(mG)(fG)(mU)(fA)#(mG)#(mU)#(mC)#(mA)#(mC) (SEQ ID NO: 842);

b) a sense strand comprising the sequence (mC)#(mA)#(mA)(fG)(mU)(fG)(mC)(fU)(mC)(fA)(mG)(mU)(mU)(fC)#(mC)# (mA)-DIO (SEQ ID NO: 843) and an antisense strand comprising the sequence V(mU)#(fG)#(mG)(fA)(fA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)(mU)(fG)#(mU)#(mA)#(mC)#(mA)#(mG) (SEQ ID NO: 844);

c) a sense strand comprising the sequence (mA)#(mG)#(mU)(fG)(mG)(fU)(mG)(fC)(mA)(fU)(mG)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 845) and an antisense strand comprising the sequence V(mU)#(fA)#(mC)(fA)(fC)(fC)(mA)(fU)(mG)(fC)(mA)(fC)(mC)(fA)(mC)(fU)#(mC)#(mC)#(mC)#(mU)#(mC) (SEQ ID NO: 846).

d) a sense strand comprising the sequence (mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC)(fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 848);

e) a sense strand comprising the sequence (mU)#(mC)#(mA)(fG)(mU)(fU)(mC)(fC)(mA)(fA)(mU)(mG)(mU)(fG)#(mC)#(mA)-DIO (SEQ ID NO: 849) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 850).

f) a sense strand comprising the sequence (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)

(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 851) and an antisense strand comprising the sequence V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU)(mG)(fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852); or

g) a sense strand comprising the sequence (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 853) and an antisense strand comprising the sequence V(mU)#(fG)#(mU)(fU)(fU)(fU)(mA)(fA)(mC)(fA)(mU)(fC)(mG)(fU)(mA)(fG)#(mA)#(mU)#(mU)#(mG)#(mA) (SEQ ID NO: 854);

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate.

[0004] In some embodiments, the siRNA molecule comprises:

a) a sense strand comprising the sequence (mU)#(mA)#(mC)(fC)(mA)(fC)(mU)(fU)(mA)(fU)(mU)(mU)(mC)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 841) and an antisense strand comprising the sequence V(mU)#(fU)#(mA)(fG)(fA)(fA)(mA)(fU)(mA)(fA)(mG)(fU)(mG)(fG)(mU)(fA)#(mG)#(mU)#(mC)#(mA)#(mC) (SEQ ID NO: 842);

b) a sense strand comprising the sequence (mC)#(mA)#(mA)(fG)(mU)(fG)(mC)(fU)(mC)(fA)(mG)(mU)(mU)(fC)#(mC)# (mA)-DIO (SEQ ID NO: 843) and an antisense strand comprising the sequence V(mU)#(fG)#(mG)(fA)(fA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)(mU)(fG)#(mU)#(mA)#(mC)#(mA)#(mG) (SEQ ID NO: 844);

c) a sense strand comprising the sequence (mA)#(mG)#(mU)(fG)(mG)(fU)(mG)(fC)(mA)(fU)(mG)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 845) and an antisense strand comprising the sequence V(mU)#(fA)#(mC)(fA)(fC)(fC)(mA)(fU)(mG)(fC)(mA)(fC)(mC)(fA)(mC)(fU)#(mC)#(mC)#(mC)#(mU)#(mC) (SEQ ID NO: 846).

d) a sense strand comprising the sequence (mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC)(fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847) and an antisense

strand comprising the sequence V(mU)#(fU)#(mC)(fA)(fU)(fA)(mA)(fG)(mC)(fC)(mU)(fC)(mA)(fU)(mU)(fG)#(mU)#(mC)#(mA)#(mG)#(mG) (SEQ ID NO: 855)

e) a sense strand comprising the sequence (mA)#(mG)#(mU)(fG)(mC)(fU)(mC)(fA)(mG)(fU)(mU)(mC)(mC)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 856) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 850).

f) a sense strand comprising the sequence (mU)#(mC)#(mA)(fG)(mU)(fU)(mC)(fC)(mA)(fA)(mU)(mG)(mU)(fG)#(mC)#(mA)-DIO (SEQ ID NO: 857) and an antisense strand comprising the sequence V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU)(mG)(fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852); or

g) a sense strand comprising the sequence (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 853) and an antisense strand comprising the sequence V(mU)#(fG)#(mU)(fU)(fU)(fU)(mA)(fA)(mC)(fA)(mU)(fC)(mG)(fU)(mA)(fG)#(mA)#(mU)#(mU)#(mG)#(mA) (SEQ ID NO: 854);

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate.

[0005] In another aspect, the disclosure features a small interfering RNA (siRNA) molecule comprising an antisense strand and sense strand having complementarity to the antisense strand. The antisense strand may be, e.g., from 10 to 30 nucleotides in length and may have complementarity sufficient to hybridize to a region within an alpha-synuclein (*SNCA*) mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0006] In some embodiments, the antisense strand has at least 70% complementarity to a region of 21 contiguous nucleobases within the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In some embodiments, the antisense strand has at least 75% complementarity to a region of 21 contiguous nucleobases within the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In some embodiments, the antisense strand has at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

99%, or 100% complementarity to the region within the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID Nos: 421-840.

[0007] In some embodiments, the antisense strand comprises at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0008] In some embodiments, the antisense strand comprises from 10 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0009] In some embodiments, the antisense strand comprises from 12 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0010] In some embodiments, the antisense strand comprises from 15 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0011] In some embodiments, the antisense strand comprises from 18 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0012] In some embodiments, the antisense strand comprises from 21 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0013] In some embodiments, the antisense strand comprises from 24 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0014] In some embodiments, the antisense strand comprises 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the

region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0015] In some embodiments, the antisense strand comprises 9 or fewer nucleotide mismatches relative to a region of 21 contiguous nucleobases of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In some embodiments, the antisense strand comprises 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or only 1 mismatch relative to the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0016] In some embodiments, the region of the *SNCA* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 459, 535, 551, 599, 631, 663, 664, 666, 667, 671, 748, 750, 751, 752, 760, 762, and 777.

[0017] In some embodiments, the region of the *SNCA* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 535, 599, 664, 666, 671, 750, 752, 760, and 762.

[0018] In some embodiments, the antisense strand has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

[0019] In some embodiments, the antisense strand has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

[0020] In some embodiments, the antisense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 1-420. In some embodiments, the antisense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

[0021] In some embodiments, the antisense strand has the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

[0022] In some embodiments, the nucleic acid sequence is any one of SEQ ID NOs: 39, 115, 131, 179, 211, 243, 244, 246, 247, 251, 328, 330, 331, 332, 340, 342, and 357.

[0023] In some embodiments, the nucleic acid sequence is any one of SEQ ID NOs: 115, 179, 244, 246, 251, 330, 332, 340, and 342.

[0024] In some embodiments, the sense strand has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0025] In some embodiments, the sense strand has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0026] In some embodiments, the sense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 421-840. In some embodiments, the

sense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0027] In some embodiments, the sense strand has the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0028] In some embodiments, the nucleic acid sequence is any one of SEQ ID NOs: 459, 535, 551, 599, 631, 663, 664, 666, 667, 671, 748, 750, 751, 752, 760, 762, and 777.

[0029] In some embodiments, the nucleic acid sequence is any one of SEQ ID NOs: 535, 599, 664, 666, 671, 750, 752, 760, and 762.

[0030] In some embodiments, the antisense strand comprises a structure represented by Formula I, wherein Formula I is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C'\text{-}P^1)_k\text{-}C'$$

Formula I;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;
each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7.

[0031] In some embodiments, the antisense strand comprises a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0032] In some embodiments, the antisense strand comprises a structure represented by Formula II, wherein Formula II is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula II;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;
each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7.

[0033] In some embodiments, the antisense strand comprises a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-A-S-A

Formula A2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0034] In some embodiments, the sense strand comprises a structure represented by Formula III, wherein Formula III is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}F$$

Formula III;

wherein E is represented by the formula $(C\text{-}P^1)_2$;

F is represented by the formula $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;

A', C, D, P^1, and P^2 are as defined in Formula II; and

m is an integer from 1 to 7.

[0035] In some embodiments, the sense strand comprises a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-A

Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0036] In some embodiments, the sense strand comprises a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-A

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0037] In some embodiments, the sense strand comprises a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-B

Formula S3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0038] In some embodiments, the sense strand comprises a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-B

Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0039] In some embodiments, the antisense strand comprises a structure represented by Formula IV, wherein Formula IV is, in the 5'-to-3' direction:

$$A\text{-}(A')_j\text{-}C\text{-}P^2\text{-}B\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula IV;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D\text{-}P^1$;
each C is a 2'-O-Me ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7.

[0040] In some embodiments, the antisense strand comprises a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B-S-A-S-A-S-A

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0041] In some embodiments, the sense strand comprises a structure represented by Formula V, wherein Formula V is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}C\text{-}P^2\text{-}F$$

Formula V;

wherein E is represented by the formula $(C\text{-}P^1)_2$;
F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;
A', C, D, P^1 and P^2 are as defined in Formula IV; and
m is an integer from 1 to 7.

[0042] In some embodiments, the sense strand comprises a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A

Formula S5;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0043] In some embodiments, the sense strand comprises a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A

Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0044] In some embodiments, the sense strand comprises a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B

Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0045] In some embodiments, the sense strand comprises a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B

Formula S8;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0046] In some embodiments, the antisense strand comprises a structure represented by Formula VI, wherein Formula VI is, in the 5'-to-3' direction:

$$A\text{-}B_j\text{-}E\text{-}B_k\text{-}E\text{-}F\text{-}G_l\text{-}D\text{-}P^1\text{-}C'$$

Formula VI;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each B is represented by the formula $C\text{-}P^2$;

each C is a 2'-O-Me ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each E is represented by the formula $D\text{-}P^2\text{-}C\text{-}P^2$;

F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1$;

each G is represented by the formula $C\text{-}P^1$;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7;

k is an integer from 1 to 7; and

l is an integer from 1 to 7.

[0047] In some embodiments, the antisense strand comprises a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:

A-S-B-S-A-O-A-O-A-O-B-O-A-O-A-O-A-O-A-O-A-O-A-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0048] In some embodiments, the sense strand comprises a structure represented by Formula VII, wherein Formula VII is, in the 5'-to-3' direction:

$$H\text{-}B_m\text{-}I_n\text{-}A'\text{-}B_o\text{-}H\text{-}C$$

Formula VII;

wherein A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

each H is represented by the formula $(C\text{-}P^1)_2$;

each I is represented by the formula $(D\text{-}P^2)$;

B, C, D, P^1 and P^2 are as defined in Formula VI;

m is an integer from 1 to 7;

n is an integer from 1 to 7; and

o is an integer from 1 to 7.

[0049] In some embodiments, the sense strand comprises a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:

A-S-A-S-A-O-A-O-A-O-B-O-B-O-B-O-A-O-B-O-A-O-A-O-A-O-A-S-A-S-A

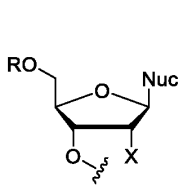
Formula S9;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

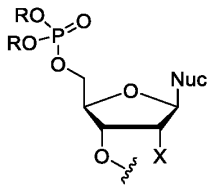
[0050] In some embodiments, the antisense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the antisense strand.

[0051] In some embodiments, the sense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the sense strand.

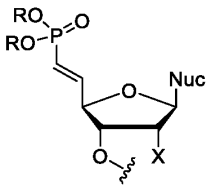
[0052] In some embodiments, each 5' phosphorus stabilizing moiety is, independently, represented by any one of Formulas IX-XVI:



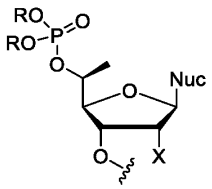
Formula IX



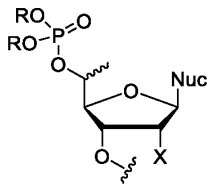
Formula X



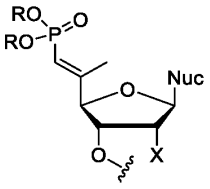
Formula XI



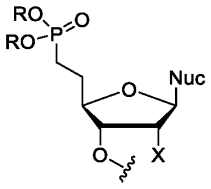
Formula XII



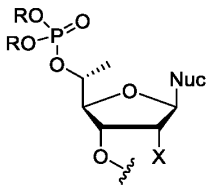
Formula XIII



Formula XIV



Formula XV



Formula XVI

wherein Nuc represents a nucleobase selected from the group consisting of adenine, uracil, guanine, thymine, and cytosine, and R represents an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, phenyl, benzyl, hydroxy, or hydrogen.

[0053] In some embodiments, the nucleobase is an adenine, uracil, guanine, thymine, or cytosine.

[0054] In some embodiments, the 5' phosphorus stabilizing moiety is (E)-vinylphosphonate represented by Formula XI.

[0055] In some embodiments, the siRNA molecule further comprises a hydrophobic moiety at the 5' or the 3' end of the siRNA molecule.

[0056] In some embodiments, the hydrophobic moiety is selected from a group consisting of cholesterol, vitamin D, or tocopherol.

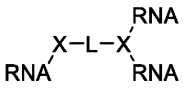
[0057] In some embodiments, the length of the sense strand is between 12 and 30 nucleotides.

[0058] In some embodiments, the siRNA molecule is a branched siRNA molecule.

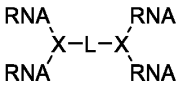
[0059] In some embodiments, the branched siRNA molecule is di-branched, tri-branched, or tetra-branched.

[0060] In some embodiments, the siRNA molecule is a di-branched siRNA molecule. In some embodiments, the di-branched siRNA molecule is represented by any one of Formulas XVII-XIX:

Formula XVII;



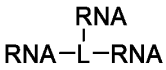
Formula XVIII;



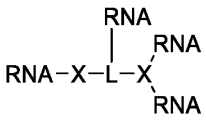
Formula XIX;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

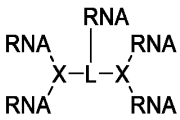
[0061] In some embodiments, the siRNA molecule is a tri-branched siRNA molecule, optionally wherein the tri-branched siRNA molecule is represented by any one of Formulas XX-XXIII:



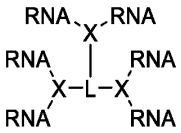
Formula XX;



Formula XXI;



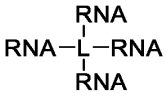
Formula XXII;

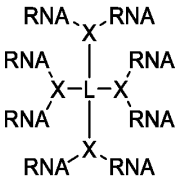


Formula XXIII;

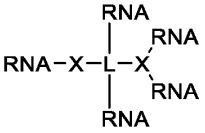
wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

[0062] In some embodiments, the siRNA molecule is a tetra-branched siRNA molecule, optionally wherein the tetra-branched siRNA molecule is represented by any one of Formulas XXIV-XXVIII:

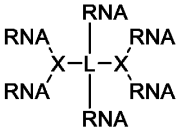




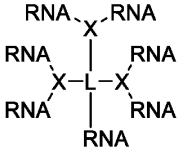
Formula XXIV;



Formula XXV;



Formula XXVI;



Formula XXVII; Formula XXVIII;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

[0063] In some embodiments, the linker is selected from a group consisting of one or more contiguous subunits of an ethylene glycol, alkyl, carbohydrate, block copolymer, peptide, RNA, and DNA.

[0064] In some embodiments, the one or more contiguous subunits is 2 to 20 contiguous subunits.

[0065] In another aspect, the disclosure features a pharmaceutical composition comprising the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, in combination with a pharmaceutically acceptable excipient, carrier, or diluent.

[0066] In another aspect, the disclosure features a method of delivering an siRNA molecule to a subject diagnosed as having a synucleinopathy, the method comprising administering to the subject a therapeutically effective amount of the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, optionally in combination with a pharmaceutically acceptable excipient, carrier, or diluent.

[0067] In another aspect, the disclosure features a method of treating a synucleinopathy in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, optionally in combination with a pharmaceutically acceptable excipient, carrier, or diluent.

[0068] In some embodiments, the synucleinopathy is Parkinson's disease. In some embodiments, the synucleinopathy is Alzheimer's disease. In some embodiments, the synucleinopathy is Lewy body dementia. In some embodiments, the synucleinopathy is a multiple symptom atrophy.

[0069] In another aspect, the disclosure features a method of reducing *SNCA* expression in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, optionally in combination with a pharmaceutically acceptable excipient, carrier, or diluent.

[0070] In some embodiments, the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intracerebroventricular, intrastriatal, intraparenchymal, or intrathecal injection. In some embodiments, the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intravenous, intramuscular, or subcutaneous injection.

[0071] In some embodiments, the subject is a human.

[0072] In a further aspect, the disclosure features a kit comprising (a) the siRNA molecule of any of the foregoing aspects or embodiments of the disclosure, optionally in combination with a pharmaceutically acceptable excipient, carrier, or diluent, and (b) a package insert. In some embodiments, the package insert instructs a user of the kit to perform the method of any of the above aspects or embodiments of the disclosure.

4. BRIEF DESCRIPTION OF THE FIGURES

[0073] FIG. 1 is a graph showing reduction in *SNCA* mRNA in hSNCA transgenic mice that were administered an siRNA molecule of the disclosure with a sense strand having SEQ ID No.: 664 and an antisense strand having SEQ ID No.: 244. mRNA was quantified in frontal cortex (fCTx), striatum (Cpu), hippocampus (Hp), temporal cortex (tCTx), midbrain, pons, medulla, and cerebellum (Cb), at a timepoint of 1 month, 2 months, 3 months, or 4 months following di-siRNA treatment at a dose level of 30 nmol.

[0074] FIG. 2 is a graph showing reduction in *SNCA* mRNA in hSNCA transgenic mice that were administered an siRNA molecule of the disclosure with a sense strand having SEQ ID No.: 664 and an antisense strand having SEQ ID No.: 244. mRNA was quantified in cervical spinal cord (SC-C), thoracic spinal cord (SC-T), and lumbar spinal cord (SC-L), at a timepoint of 1 month, 2 months, 3 months, or 4 months following di-siRNA treatment at a dose level of 30 nmol.

[0075] FIG. 3 is a graph showing reduction in human SNCA protein in hSNCA transgenic mice that were administered an siRNA molecule of the disclosure with a sense strand having SEQ ID No.: 664 and an antisense strand having SEQ ID No.: 244. Protein was quantified in frontal cortex (fCTx), striatum (Cpu), hippocampus (Hp), temporal cortex (tCTx), midbrain, and cerebellum (Cb), at a timepoint of 1 month, 2 months, 3 months, or 4 months following di-siRNA treatment at a dose level of 30 nmol.

[0076] FIG. 4 is a graph showing reduction in human SNCA protein in hSNCA transgenic mice that were administered an siRNA molecule of the disclosure with a sense strand having SEQ ID No.: 664 and an antisense strand having SEQ ID No.: 244. Protein was quantified in cervical spinal cord (SC-C), thoracic spinal cord (SC-T), and lumbar spinal cord (SC-L), at a timepoint of 1 month, 2 months, 3 months, or 4 months following di-siRNA treatment at a dose level of 30 nmol.

[0077] FIG. 5 is a graph showing reduction in mouse *Snca* mRNA in hSNCA transgenic mice that were administered an siRNA molecule of the disclosure with a sense strand having SEQ ID No.: 664 and an antisense strand having SEQ ID No.: 244. mRNA was quantified in

frontal cortex, striatum, hippocampus, and temporal cortex, 3 months or 4 months following di-siRNA treatment at 2.5 nmol, 5 nmol, 15 nmol, or 20 nmol dose levels.

[0078] FIG. 6 is a graph showing reduction in human *SNCA* mRNA in hSNCA transgenic mice that were administered an siRNA molecule of the disclosure with a sense strand having SEQ ID No.: 664 and an antisense strand having SEQ ID No.: 244. mRNA was quantified in frontal cortex, striatum, hippocampus, and temporal cortex, 3 months or 4 months following di-siRNA treatment at 2.5 nmol, 5 nmol, 15 nmol, or 20 nmol dose levels.

[0079] FIG. 7 is a graph showing reduction in human SNCA protein in hSNCA transgenic mice that were administered an siRNA molecule of the disclosure with a sense strand having SEQ ID No.: 664 and an antisense strand having SEQ ID No.: 244. Protein was quantified in frontal cortex, striatum, hippocampus, and temporal cortex, 3 months or 4 months following di-siRNA treatment at 2.5 nmol, 5 nmol, 15 nmol, or 20 nmol dose levels.

5. DETAILED DESCRIPTION

[0080] The instant application is directed to single- or double-stranded interfering RNA molecules (e.g., siRNA) targeting an SNCA gene. The interfering RNA molecules may contain specific patterns of nucleoside modifications and internucleoside linkage modifications, as pharmaceutical compositions including the same. The siRNA molecules may be branched siRNA molecules, such as di-branched, tri-branched, or tetra-branched siRNA molecules. The disclosed siRNA molecules may further feature a 5' phosphorus stabilizing moiety and/or a hydrophobic moiety. Additionally, the disclosure provides methods for delivering the siRNA molecule of the disclosure to the central nervous system of a subject, such as a subject identified as having a synucleinopathy.

5.1. Definitions

[0081] Unless otherwise defined herein, scientific, and technical terms used herein have the meanings that are commonly understood by those of ordinary skill in the art. In the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of "or" means "and/or" unless stated otherwise. The use of the term "including," as well as other forms, such as "includes" and "included," is not limiting.

[0082] As used herein, the term "nucleic acids" refers to RNA or DNA molecules consisting of a chain of ribonucleotides or deoxyribonucleotides, respectively. As used herein, the term "therapeutic nucleic acid" refers to a nucleic acid molecule (e.g., ribonucleic acid) that has partial or complete complementarity to, and interacts with, a disease-associated target mRNA and mediates silencing of expression of the mRNA.

[0083] As used herein, the term "carrier nucleic acid" refers to a nucleic acid molecule (e.g., ribonucleic acid) that has sequence complementarity with, and hybridizes with, a therapeutic nucleic acid. As used herein, the term "3' end" refers to the end of the nucleic acid that contains an unmodified hydroxyl group at the 3' carbon of the ribose ring.

[0084] As used herein, the term "nucleoside" refers to a molecule made up of a heterocyclic base and its sugar.

[0085] As used herein, the term "nucleotide" refers to a nucleoside having a phosphate group on its 3' or 5' sugar hydroxyl group.

[0086] As used herein, the term "siRNA" refers to small interfering RNA duplexes that induce the RNA interference (RNAi) pathway. siRNA molecules can vary in length (generally, between 18 and 30 base pairs) and contain varying degrees of complementarity to their target mRNA. The term "siRNA" includes duplexes of two separate strands, as well as single strands that optionally form hairpin structures including a duplex region.

[0087] As used herein, the term "antisense strand" refers to the strand of the siRNA duplex that contains some degree of complementarity to the target gene.

[0088] As used herein, the term "sense strand" refers to the strand of the siRNA duplex that contains complementarity to the antisense strand.

[0089] As used herein, the term "chemically modified nucleotide" refers to a non-standard nucleotide, including non-naturally occurring ribonucleotides or deoxyribonucleotides. Exemplary chemically modified nucleotides are modified at any position so as to alter certain chemical properties of the nucleotide yet retain the ability of the chemically modified nucleotide to perform its intended function.

[0090] As used herein, the term "metabolically stabilized" refers to RNA molecules that contain ribonucleotides that have been chemically modified from 2'-hydroxyl groups to 2'-O-methyl groups, 2' fluoro groups, or other modifications known in the art to stabilized RNA to enzymatic and/or non-enzymatic degradation.

[0091] As used herein, the term "phosphorothioate" refers to a phosphate group of a nucleotide that is modified by substituting one or more of the oxygens of the phosphate group with sulfur.

[0092] As used herein, the term "ethylene glycol chain" refers to a carbon chain with the formula $((CH_2OH)_2)$.

[0093] As used herein, "alkyl" refers to a saturated hydrocarbon group. Alkyl groups may be acyclic or cyclic and contain only C and H when unsubstituted. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "butyl" is meant to include n-butyl, sec-butyl, and iso-butyl. Examples of alkyl include ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. In some embodiments, alkyl may be substituted. Suitable substituents that may be introduced into an alkyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

[0094] As used herein, "alkenyl" refers to an acyclic or cyclic unsaturated hydrocarbon group having at least one site of olefinic unsaturation (i.e., having at least one moiety of the formula C=C). Alkenyl groups contain only C and H when unsubstituted. When an alkenyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "butenyl" is meant to include n-butenyl, sec-butenyl, and iso-butenyl. Examples of alkenyl include $–CH=CH_2$, $–CH_2-CH=CH_2$, and $–CH_2-CH=CH-CH=CH_2$. In some embodiments, alkenyl may be substituted. Suitable substituents that may be introduced into an alkenyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

[0095] As used herein, "alkynyl" refers to an acyclic or cyclic unsaturated hydrocarbon group having at least one site of acetylenic unsaturation (i.e., having at least one moiety of the formula C≡C). Alkynyl groups contain only C and H when unsubstituted. When an alkynyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "pentynyl" is meant to include n-pentynyl, sec-pentynyl, iso-pentynyl, and tert-pentynyl. Examples of alkynyl include $–C≡CH$ and $–C≡C-CH_3$. In some embodiments, alkynyl may be substituted. Suitable substituents that may be introduced into an alkynyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

[0096] As used herein the term "phenyl" denotes a monocyclic arene in which one hydrogen atom from a carbon atom of the ring has been removed. A phenyl group can be unsubstituted or substituted with one or more suitable substituents, wherein the substituent replaces an H of the phenyl group.

[0097] As used herein, the term “benzyl” refers to monovalent radical obtained when a hydrogen atom attached to the methyl group of toluene is removed. A benzyl generally has the formula of phenyl-CH_2-.

[0098] A benzyl group can be unsubstituted or substituted with one or more suitable substituents. For example, the substituent may replace an H of the phenyl component and/or an H of the methylene (-CH_2-) component.

[0099] As used herein, the term "amide" refers to an alkyl, alkenyl, alkynyl, or aromatic group that is attached to an amino-carbonyl functional group.

[0100] As used herein, the term "internucleoside" and "internucleotide" refer to the bonds between nucleosides and nucleotides, respectively.

[0101] As used herein, the term "triazol" refers to heterocyclic compounds with the formula ($C_2H_3N_3$), having a five-membered ring of two carbons and three nitrogens, the positions of which can change resulting in multiple isomers.

[0102] As used herein, the term "terminal group" refers to the group at which a carbon chain or nucleic acid ends.

[0103] As used herein, the term "lipophilic amino acid" refers to an amino acid including a hydrophobic moiety (e.g., an alkyl chain or an aromatic ring).

[0104] As used herein, the term "target of delivery" refers to the organ or part of the body that is desired to deliver the branched oligonucleotide compositions to.

[0105] As used herein, the term “branched siRNA” refers to a compound containing two or more double-stranded siRNA molecules covalently bound to one another. Branched siRNA molecules may be “di-branched,” also referred to herein as “di-siRNA,” wherein the siRNA molecule includes 2 siRNA molecules covalently bound to one another, e.g., by way of a linker. Branched siRNA molecules may be “tri-branched,” also referred to herein as “tri-siRNA,” wherein the siRNA molecule includes 3 siRNA molecules covalently bound to one another, e.g., by way of a linker. Branched siRNA molecules may be “tetra-branched,” also referred to herein as “tetra-siRNA,” wherein the siRNA molecule includes 4 siRNA molecules covalently bound to one another, e.g., by way of a linker.

[0106] As used herein, the term “branch point moiety” refers to a chemical moiety of a branched siRNA structure of the disclosure that may be covalently linked to a 5’ end or a 3’ end of an antisense strand or a sense strand of an siRNA molecule and which may support the attachment of additional single- or double-stranded siRNA molecules. Non-limiting examples of branch point moieties suitable for use in conjunction with the disclosed methods and

compositions include, e.g., phosphoroamidite, tosylated solketal, 1,3-diaminopropanol, pentaerythritol, and any one of the branch point moieties described in US 10,478,503.

[0107] As used herein, the term "5′ phosphorus stabilizing moiety" refers to a terminal phosphate group that includes phosphates as well as modified phosphates (e.g., phosphorothioates, phosphodiesters, phosphonates). The phosphate moiety can be located at either terminus, e.g., at the 5′-terminal nucleoside. In one aspect, the terminal phosphate is unmodified having the formula –O–P(=O)(OH)OH. In another aspect, the terminal phosphate is modified such that one or more of the O and OH groups are replaced with H, O, S, N(R'), or alkyl where R' is H, an amino protecting group, or unsubstituted or substituted alkyl. In some embodiments, the 5′ and or 3′ terminal group can include from 1 to 3 phosphate moieties that are each, independently, unmodified (di- or tri-phosphates) or modified.

[0108] As used herein, the term "between X and Y" is inclusive of the values of X and Y. For example, "between X and Y" refers to the range of values between the value of X and the value of Y, as well as the value of X and the value of Y.

[0109] As used herein, an "amino acid" refers to a molecule containing amine and carboxyl functional groups and a side chain specific to the amino acid.

[0110] In some embodiments the amino acid is chosen from the group of proteinogenic amino acids. In some embodiments, the amino acid is an L-amino acid or a D-amino acid. In some embodiments, the amino acid is a synthetic amino acid (e.g., a beta-amino acid).

[0111] It is understood that certain internucleoside linkages provided herein, including, e.g., phosphodiester and phosphorothioate, include a formal charge of -1 at physiological pH, and that said formal charge will be balanced by a cationic moiety, e.g., an alkali metal such as sodium or potassium, an alkali earth metal such as calcium or magnesium, or an ammonium or guanidinium ion.

[0112] The phosphate group of the nucleotide may also be modified, e.g., by substituting one or more of the oxygens of the phosphate group with sulfur (e.g., phosphorothioates), or by making other substitutions which allow the nucleotide to perform its intended function such as described in, for example, Eckstein, *Antisense Nucleic Acid Drug Dev.* 10:117-21, 2000; Rusckowski et al., *Antisense Nucleic Acid Drug Dev.* 10:333-45, 2000; Stein, *Antisense Nucleic Acid Drug Dev.* 11:317-25, 2001; Vorobjev et al., *Antisense Nucleic Acid Drug Dev.* 11:77-85, 2001; and US 5,684,143. Certain of the above-referenced modifications (e.g., phosphate group modifications) can decrease the rate of hydrolysis of, for example, polynucleotides including said modifications in vivo or in vitro.

[0113] As used herein, the term "complementary" refers to two nucleotides that form canonical Watson-Crick base pairs. For the avoidance of doubt, Watson-Crick base pairs in the context of the present disclosure include adenine-thymine, adenine-uracil, and cytosine-guanine base pairs. A proper Watson-Crick base pair is referred to in this context as a "match," while each unpaired nucleotide, and each incorrectly paired nucleotide, is referred to as a "mismatch." Alignment for purposes of determining percent nucleic acid sequence complementarity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software.

[0114] "Percent (%) sequence complementarity" with respect to a reference polynucleotide sequence is defined as the percentage of nucleic acids in a candidate sequence that are complementary to the nucleic acids in the reference polynucleotide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence complementarity. A given nucleotide is considered to be "complementary" to a reference nucleotide as described herein if the two nucleotides form canonical Watson-Crick base pairs. For the avoidance of doubt, Watson-Crick base pairs in the context of the present disclosure include adenine-thymine, adenine-uracil, and cytosine-guanine base pairs. A proper Watson-Crick base pair is referred to in this context as a "match," while each unpaired nucleotide, and each incorrectly paired nucleotide, is referred to as a "mismatch." Alignment for purposes of determining percent nucleic acid sequence complementarity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal complementarity over the full length of the sequences being compared. As an illustration, the percent sequence complementarity of a given nucleic acid sequence, A, to a given nucleic acid sequence, B, (which can alternatively be phrased as a given nucleic acid sequence, A that has a certain percent complementarity to a given nucleic acid sequence, B) is calculated as follows:

100 multiplied by (the fraction X/Y)

where X is the number of complementary base pairs in an alignment (e.g., as executed by computer software, such as BLAST) in that program's alignment of A and B, and where Y is the total number of nucleic acids in B. It will be appreciated that where the length of nucleic acid sequence A is not equal to the length of nucleic acid sequence B, the percent sequence

complementarity of A to B will not equal the percent sequence complementarity of B to A. As used herein, a query nucleic acid sequence is considered to be "completely complementary" to a reference nucleic acid sequence if the query nucleic acid sequence has 100% sequence complementarity to the reference nucleic acid sequence.

[0115] The term "gene silencing" refers to the suppression of gene expression, e.g., transgene, heterologous gene and/or endogenous gene expression, which may be mediated through processes that affect transcription and/or through processes that affect post-transcriptional mechanisms. In some embodiments, gene silencing occurs when an RNAi molecule initiates the inhibition or degradation of the mRNA transcribed from a gene of interest in a sequence-specific manner via RNA interference, thereby preventing translation of the gene's product.

[0116] The phrase "overactive disease driver gene," as used herein, refers to a gene having increased activity and/or expression that contributes to or causes a disease state in a subject (e.g., a human). The disease state may be caused or exacerbated by the overactive disease driver gene directly or by way of an intermediate gene(s).

[0117] The term "negative regulator," as used herein, refers to a gene that negatively regulates (e.g., reduces or inhibits) the expression and/or activity of another gene or set of genes.

[0118] The term "positive regulator," as used herein, refers to a gene that positively regulates (e.g., increases or saturates) the expression and/or activity of another gene or set of genes.

[0119] The term "phosphate moiety" as used herein, refers to a terminal phosphate group that includes phosphates as well as modified phosphates. The phosphate moiety can be located at either terminus, e.g., at the 5′-terminal nucleoside. In one aspect, the terminal phosphate is unmodified having the formula —O—P(═O)(OH)OH. In another aspect, the terminal phosphate is modified such that one or more of the O and OH groups are replaced with H, O, S, N(R') or alkyl where R' is H, an amino protecting group or unsubstituted or substituted alkyl. In some embodiments, the 5′ and or 3′ terminal group can include from 1 to 3 phosphate moieties that are each, independently, unmodified (di or tri-phosphates) or modified.

[0120] In the context of this disclosure, the term "oligonucleotide" refers to an oligomer or polymer of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or other nucleic acids. The term includes oligonucleotides composed of naturally-occurring nucleobases, sugars and covalent internucleoside (backbone) linkages as well as oligonucleotides having non-naturally-occurring (e.g., chemically modified) portions that function similarly. Such chemically modified oligonucleotides can exhibit desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

[0121] The term "treatment" refers to clinical intervention designed to alter the natural course of the patient or cell being treated during the course of clinical pathology. Desirable effects of treatment include decreasing the rate of disease progression, ameliorating or palliating the disease state, and remission or improved prognosis. For example, a patient is successfully "treated" if one or more symptoms associated with a synucleinopathy described herein are mitigated or eliminated, including, but are not limited to, decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, and/or prolonging survival of patients.

[0122] The term "delaying progression" of a disease refers to deferring, hindering, slowing, retarding, stabilizing, and/or postponing development of a cancer described herein. This delay can be of varying lengths of time, depending on the history of the synucleinopathy and/or patient being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the patient does not develop a synucleinopathy or relapse.

5.2. Anti-Alpha-Synuclein siRNAs

[0123] The instant application is directed to single- or double-stranded interfering RNA molecules (e.g., siRNA) targeting an SNCA gene. For example, but not by way of limitation, siRNA molecules targeting an SNCA gene can be designed to target an SNCA mRNA sequence.

[0124] In certain embodiments, the SNCA gene targeted by an siRNA of the instant disclosure expresses a mRNA comprising the sequence of NM_000345.3 (Homo sapiens synuclein, alpha (non A4 component of amyloid precursor) (SNCA), transcript variant 1, mRNA). The NM_000345.3 is: AGGAGAAGGAGAAGGAGGAGGACTAGGAGGAGGAGGACGG CGACGACCAGAAGGGGCCCAAGAGAGGGGGCGAGCGACCGAGCGCCGCGACGC GGAAGTGAGGTGCGTGCGGGCTGCAGCGCAGACCCCGGCCCGGCCCCTCCGAGA GCGTCCTGGGCGCTCCCTCACGCCTTGCCTTCAAGCCTTCTGCCTTTCCACCCTCG TGAGCGGAGAACTGGGAGTGGCCATTCGACGACAGTGTGGTGTAAAGGAATTCA TTAGCCATGGATGTATTCATGAAAGGACTTTCAAAGGCCAAGGAGGGAGTTGTG GCTGCTGCTGAGAAAACCAAACAGGGTGTGGCAGAAGCAGCAGGAAAGACAAA AGAGGGTGTTCTCTATGTAGGCTCCAAAACCAAGGAGGGAGTGGTGCATGGTGT GGCAACAGTGGCTGAGAAGACCAAAGAGCAAGTGACAAATGTTGGAGGAGCAG TGGTGACGGGTGTGACAGCAGTAGCCCAGAAGACAGTGGAGGGAGCAGGGAGC

ATTGCAGCAGCCACTGGCTTTGTCAAAAAGGACCAGTTGGGCAAGAATGAAGAA
GGAGCCCCACAGGAAGGAATTCTGGAAGATATGCCTGTGGATCCTGACAATGAG
GCTTATGAAATGCCTTCTGAGGAAGGGTATCAAGACTACGAACCTGAAGCCTAA
GAAATATCTTTGCTCCCAGTTTCTTGAGATCTGCTGACAGATGTTCCATCCTGTAC
AAGTGCTCAGTTCCAATGTGCCCAGTCATGACATTTCTCAAAGTTTTTACAGTGT
ATCTCGAAGTCTTCCATCAGCAGTGATTGAAGTATCTGTACCTGCCCCCACTCAG
CATTTCGGTGCTTCCCTTTCACTGAAGTGAATACATGGTAGCAGGGTCTTTGTGTG
CTGTGGATTTTGTGGCTTCAATCTACGATGTTAAAACAAATTAAAAACACCTAAG
TGACTACCACTTATTTCTAAATCCTCACTATTTTTTTGTTGCTGTTGTTCAGAAGTT
GTTAGTGATTTGCTATCATATATTATAAGATTTTTAGGTGTCTTTTAATGATACTG
TCTAAGAATAATGACGTATTGTGAAATTTGTTAATATATATAATACTTAAAAATA
TGTGAGCATGAAACTATGCACCTATAAATACTAAATATGAAATTTTACCATTTTG
CGATGTGTTTTATTCACTTGTGTTTGTATATAAATGGTGAGAATTAAAATAAAAC
GTTATCTCATTGCAAAAATATTTTATTTTTATCCCATCTCACTTTAATAATAAAAA
TCATGCTTATAAGCAACATGAATTAAGAACTGACACAAAGGACAAAAATATAAA
GTTATTAATAGCCATTTGAAGAAGGAGGAATTTTAGAAGAGGTAGAGAAAATGG
AACATTAACCCTACACTCGGAATTCCCTGAAGCAACACTGCCAGAAGTGTGTTTT
GGTATGCACTGGTTCCTTAAGTGGCTGTGATTAATTATTGAAAGTGGGGTGTTGA
AGACCCCAACTACTATTGTAGAGTGGTCTATTTCTCCCTTCAATCCTGTCAATGTT
TGCTTTACGTATTTTGGGGAACTGTTGTTTGATGTGTATGTGTTTATAATTGTTAT
ACATTTTTAATTGAGCCTTTTATTAACATATATTGTTATTTTTGTCTCGAAATAATT
TTTTAGTTAAAATCTATTTTGTCTGATATTGGTGTGAATGCTGTACCTTTCTGACA
ATAAATAATATTCGACCATGAATAAAAAAAAAAAAAAAGTGGGTTCCCGGGAAC
TAAGCAGTGTAGAAGATGATTTTGACTACACCCTCCTTAGAGAGCCATAAGACA
CATTAGCACATATTAGCACATTCAAGGCTCTGAGAGAATGTGGTTAACTTTGTTT
AACTCAGCATTCCTCACTTTTTTTTTTTAATCATCAGAAATTCTCTCTCTCTCTC
TCTTTTTCTCTCGCTCTCTTTTTTTTTTTTTTTTACAGGAAATGCCTTTAAACATC
GTTGGAACTACCAGAGTCACCTTAAAGGAGATCAATTCTCTAGACTGATAAAAA
TTTCATGGCCTCCTTTAAATGTTGCCAAATATATGAATTCTAGGATTTTTCCTTAG
GAAAGGTTTTTCTCTTTCAGGGAAGATCTATTAACTCCCCATGGGTGCTGAAAAT
AAACTTGATGGTGAAAAACTCTGTATAAATTAATTTAAAAATTATTTGGTTTCTCT
TTTTAATTATTCTGGGGCATAGTCATTTCTAAAAGTCACTAGTAGAAAGTATAAT
TTCAAGACAGAATATTCTAGACATGCTAGCAGTTTATATGTATTCATGAGTAATG
TGATATATATTGGGCGCTGGTGAGGAAGGAAGGAGGAATGAGTGACTATAAGGA

TGGTTACCATAGAAACTTCCTTTTTTACCTAATTGAAGAGAGACTACTACAGAGT
GCTAAGCTGCATGTGTCATCTTACACTAGAGAGAAATGGTAAGTTTCTTGTTTTA
TTTAAGTTATGTTTAAGCAAGGAAAGGATTTGTTATTGAACAGTATATTTCAGGA
AGGTTAGAAAGTGGCGGTTAGGATATATTTTAAATCTACCTAAAGCAGCATATTT
TAAAAATTTAAAAGTATTGGTATTAAATTAAGAAATAGAGGACAGAACTAGACT
GATAGCAGTGACCTAGAACAATTTGAGATTAGGAAAGTTGTGACCATGAATTTA
AGGATTTATGTGGATACAAATTCTCCTTTAAAGTGTTTCTTCCCTTAATATTTATC
TGACGGTAATTTTTGAGCAGTGAATTACTTTATATATCTTAATAGTTTATTTGGGA
CCAAACACTTAAACAAAAAGTTCTTTAAGTCATATAAGCCTTTTCAGGAAGCTTG
TCTCATATTCACTCCCGAGACATTCACCTGCCAAGTGGCCTGAGGATCAATCCAG
TCCTAGGTTTATTTTGCAGACTTACATTCTCCCAAGTTATTCAGCCTCATATGACT
CCACGGTCGGCTTTACCAAAACAGTTCAGAGTGCACTTTGGCACACAATTGGGA
ACAGAACAATCTAATGTGTGGTTTGGTATTCCAAGTGGGGTCTTTTTCAGAATCT
CTGCACTAGTGTGAGATGCAAACATGTTTCCTCATCTTTCTGGCTTATCCAGTATG
TAGCTATTTGTGACATAATAAATATATACATATATGAAAATA (SEQ ID NO: 858).

[0125] In certain embodiments, the SNCA gene targeted by an siRNA of the present disclosure expresses a mRNA comprising the sequence of NM_001146054.1 (Homo sapiens synuclein, alpha (non A4 component of amyloid precursor) (SNCA), transcript variant 2, mRNA). The NM_001146054.1 sequence is: GCCATTCGACGACAGGTTAGCGGGTTTGCCTCCCACT
CCCCCAGCCTCGCGTCGCCGGCTCACAGCGGCCTCCTCTGGGGACAGTCCCCCCC
GGGTGCCGCCTCCGCCCTTCCTGTGCGCTCCTTTTCCTTCTTCTTTCCTATTAAATA
TTATTTGGGAATTGTTTAAATTTTTTTTTTAAAAAAAGAGAGAGGCGGGGAGGAG
TCGGAGTTGTGGAGAAGCAGAGGGACTCAGTGTGGTGTAAAGGAATTCATTAGC
CATGGATGTATTCATGAAAGGACTTTCAAAGGCCAAGGAGGGAGTTGTGGCTGC
TGCTGAGAAAACCAAACAGGGTGTGGCAGAAGCAGCAGGAAAGACAAAAGAGG
GTGTTCTCTATGTAGGCTCCAAAACCAAGGAGGGAGTGGTGCATGGTGTGGCAA
CAGTGGCTGAGAAGACCAAAGAGCAAGTGACAAATGTTGGAGGAGCAGTGGTG
ACGGGTGTGACAGCAGTAGCCCAGAAGACAGTGGAGGGAGCAGGGAGCATTGC
AGCAGCCACTGGCTTTGTCAAAAAGGACCAGTTGGGCAAGAATGAAGAAGGAGC
CCCACAGGAAGGAATTCTGGAAGATATGCCTGTGGATCCTGACAATGAGGCTTA
TGAAATGCCTTCTGAGGAAGGGTATCAAGACTACGAACCTGAAGCCTAAGAAAT
ATCTTTGCTCCCAGTTTCTTGAGATCTGCTGACAGATGTTCCATCCTGTACAAGTG
CTCAGTTCCAATGTGCCCAGTCATGACATTTCTCAAAGTTTTTACAGTGTATCTCG
AAGTCTTCCATCAGCAGTGATTGAAGTATCTGTACCTGCCCCCACTCAGCATTTC

GGTGCTTCCCTTTCACTGAAGTGAATACATGGTAGCAGGGTCTTTGTGTGCTGTG
GATTTTGTGGCTTCAATCTACGATGTTAAAACAAATTAAAAACACCTAAGTGACT
ACCACTTATTTCTAAATCCTCACTATTTTTTTGTTGCTGTTGTTCAGAAGTTGTTAG
TGATTTGCTATCATATATTATAAGATTTTTAGGTGTCTTTTAATGATACTGTCTAA
GAATAATGACGTATTGTGAAATTTGTTAATATATATAATACTTAAAAATATGTGA
GCATGAAACTATGCACCTATAAATACTAAATATGAAATTTTACCATTTTGCGATG
TGTTTTATTCACTTGTGTTTGTATATAAATGGTGAGAATTAAAATAAAACGTTATC
TCATTGCAAAAATATTTTATTTTTATCCCATCTCACTTTAATAATAAAAATCATGC
TTATAAGCAACATGAATTAAGAACTGACACAAAGGACAAAAATATAAAGTTATT
AATAGCCATTTGAAGAAGGAGGAATTTTAGAAGAGGTAGAGAAAATGGAACATT
AACCCTACACTCGGAATTCCCTGAAGCAACACTGCCAGAAGTGTGTTTTGGTATG
CACTGGTTCCTTAAGTGGCTGTGATTAATTATTGAAAGTGGGGTGTTGAAGACCC
CAACTACTATTGTAGAGTGGTCTATTTCTCCCTTCAATCCTGTCAATGTTTGCTTT
ACGTATTTTGGGGAACTGTTGTTTGATGTGTATGTGTTTATAATTGTTATACATTT
TTAATTGAGCCTTTTATTAACATATATTGTTATTTTTGTCTCGAAATAATTTTTTAG
TTAAAATCTATTTTGTCTGATATTGGTGTGAATGCTGTACCTTTCTGACAATAAAT
AATATTCGACCATGAATAAAAAAAAAAAAAAAGTGGGTTCCCGGGAACTAAGCA
GTGTAGAAGATGATTTTGACTACACCCTCCTTAGAGAGCCATAAGACACATTAGC
ACATATTAGCACATTCAAGGCTCTGAGAGAATGTGGTTAACTTTGTTTAACTCAG
CATTCCTCACTTTTTTTTTTTAATCATCAGAAATTCTCTCTCTCTCTCTCTTTTTC
TCTCGCTCTCTTTTTTTTTTTTTTTTTACAGGAAATGCCTTTAAACATCGTTGGAAC
TACCAGAGTCACCTTAAAGGAGATCAATTCTCTAGACTGATAAAAATTTCATGGC
CTCCTTTAAATGTTGCCAAATATATGAATTCTAGGATTTTTCCTTAGGAAAGGTTT
TTCTCTTTCAGGGAAGATCTATTAACTCCCCATGGGTGCTGAAAATAAACTTGAT
GGTGAAAAACTCTGTATAAATTAATTTAAAAATTATTTGGTTTCTCTTTTTAATTA
TTCTGGGGCATAGTCATTTCTAAAAGTCACTAGTAGAAAGTATAATTTCAAGACA
GAATATTCTAGACATGCTAGCAGTTTATATGTATTCATGAGTAATGTGATATATA
TTGGGCGCTGGTGAGGAAGGAAGGAGGAATGAGTGACTATAAGGATGGTTACCA
TAGAAACTTCCTTTTTTACCTAATTGAAGAGAGACTACTACAGAGTGCTAAGCTG
CATGTGTCATCTTACACTAGAGAGAAATGGTAAGTTTCTTGTTTTATTTAAGTTAT
GTTTAAGCAAGGAAAGGATTTGTTATTGAACAGTATATTTCAGGAAGGTTAGAA
AGTGGCGGTTAGGATATATTTTAAATCTACCTAAAGCAGCATATTTTAAAAATTT
AAAAGTATTGGTATTAAATTAAGAAATAGAGGACAGAACTAGACTGATAGCAGT
GACCTAGAACAATTTGAGATTAGGAAAGTTGTGACCATGAATTTAAGGATTTATG

TGGATACAAATTCTCCTTTAAAGTGTTTCTTCCCTTAATATTTATCTGACGGTAAT
TTTTGAGCAGTGAATTACTTTATATATCTTAATAGTTTATTTGGGACCAAACACTT
AAACAAAAAGTTCTTTAAGTCATATAAGCCTTTTCAGGAAGCTTGTCTCATATTC
ACTCCCGAGACATTCACCTGCCAAGTGGCCTGAGGATCAATCCAGTCCTAGGTTT
ATTTTGCAGACTTACATTCTCCCAAGTTATTCAGCCTCATATGACTCCACGGTCGG
CTTTACCAAAACAGTTCAGAGTGCACTTTGGCACACAATTGGGAACAGAACAAT
CTAATGTGTGGTTTGGTATTCCAAGTGGGGTCTTTTTCAGAATCTCTGCACTAGTG
TGAGATGCAAACATGTTTCCTCATCTTTCTGGCTTATCCAGTATGTAGCTATTTGT
GACATAATAAATATATACATATATGAAAATA (SEQ ID NO: 859).

[0126] In certain embodiments, the SNCA gene targeted by an siRNA of the present disclosure expresses a mRNA comprising the sequence of NM_001146055.1 (Homo sapiens synuclein, alpha (non A4 component of amyloid precursor) (SNCA), transcript variant 3, mRNA). The NM_001146055.1sequence is:

ATTCTGGTGTGATCCAGGAACAGCTGTCTTCCAGCTCTG
AAAGAGTGTGGTGTAAAGGAATTCATTAGCCATGGATGTATTCATGAAAGGACT
TTCAAAGGCCAAGGAGGGAGTTGTGGCTGCTGCTGAGAAAACCAAACAGGGTGT
GGCAGAAGCAGCAGGAAAGACAAAAGAGGGTGTTCTCTATGTAGGCTCCAAAAC
CAAGGAGGGAGTGGTGCATGGTGTGGCAACAGTGGCTGAGAAGACCAAAGAGC
AAGTGACAAATGTTGGAGGAGCAGTGGTGACGGGTGTGACAGCAGTAGCCCAGA
AGACAGTGGAGGGAGCAGGGAGCATTGCAGCAGCCACTGGCTTTGTCAAAAAGG
ACCAGTTGGGCAAGAATGAAGAAGGAGCCCCACAGGAAGGAATTCTGGAAGAT
ATGCCTGTGGATCCTGACAATGAGGCTTATGAAATGCCTTCTGAGGAAGGGTATC
AAGACTACGAACCTGAAGCCTAAGAAATATCTTTGCTCCCAGTTTCTTGAGATCT
GCTGACAGATGTTCCATCCTGTACAAGTGCTCAGTTCCAATGTGCCCAGTCATGA
CATTTCTCAAAGTTTTTACAGTGTATCTCGAAGTCTTCCATCAGCAGTGATTGAAG
TATCTGTACCTGCCCCCACTCAGCATTTCGGTGCTTCCCTTTCACTGAAGTGAATA
CATGGTAGCAGGGTCTTTGTGTGCTGTGGATTTTGTGGCTTCAATCTACGATGTTA
AAACAAATTAAAAACACCTAAGTGACTACCACTTATTTCTAAATCCTCACTATTT
TTTTGTTGCTGTTGTTCAGAAGTTGTTAGTGATTTGCTATCATATATTATAAGATT
TTTAGGTGTCTTTTAATGATACTGTCTAAGAATAATGACGTATTGTGAAATTTGTT
AATATATATAATACTTAAAAATATGTGAGCATGAAACTATGCACCTATAAATACT
AAATATGAAATTTTACCATTTTGCGATGTGTTTTATTCACTTGTGTTTGTATATAA
ATGGTGAGAATTAAAATAAAACGTTATCTCATTGCAAAAATATTTTATTTTTATC
CCATCTCACTTTAATAATAAAAATCATGCTTATAAGCAACATGAATTAAGAACTG

ACACAAAGGACAAAAATATAAAGTTATTAATAGCCATTTGAAGAAGGAGGAATT
TTAGAAGAGGTAGAGAAAATGGAACATTAACCCTACACTCGGAATTCCCTGAAG
CAACACTGCCAGAAGTGTGTTTTGGTATGCACTGGTTCCTTAAGTGGCTGTGATT
AATTATTGAAAGTGGGGTGTTGAAGACCCCAACTACTATTGTAGAGTGGTCTATT
TCTCCCTTCAATCCTGTCAATGTTTGCTTTACGTATTTTGGGGAACTGTTGTTTGA
TGTGTATGTGTTTATAATTGTTATACATTTTTAATTGAGCCTTTTATTAACATATAT
TGTTATTTTTGTCTCGAAATAATTTTTTAGTTAAAATCTATTTTGTCTGATATTGGT
GTGAATGCTGTACCTTTCTGACAATAAATAATATTCGACCATGAATAAAAAAAAA
AAAAAAGTGGGTTCCCGGGAACTAAGCAGTGTAGAAGATGATTTTGACTACACC
CTCCTTAGAGAGCCATAAGACACATTAGCACATATTAGCACATTCAAGGCTCTGA
GAGAATGTGGTTAACTTTGTTTAACTCAGCATTCCTCACTTTTTTTTTTTAATCATC
AGAAATTCTCTCTCTCTCTCTCTCTTTTTCTCTCGCTCTCTTTTTTTTTTTTTTTTA
CAGGAAATGCCTTTAAACATCGTTGGAACTACCAGAGTCACCTTAAAGGAGATC
AATTCTCTAGACTGATAAAAATTTCATGGCCTCCTTTAAATGTTGCCAAATATAT
GAATTCTAGGATTTTTCCTTAGGAAAGGTTTTTCTCTTTCAGGGAAGATCTATTAA
CTCCCCATGGGTGCTGAAAATAAACTTGATGGTGAAAAACTCTGTATAAATTAAT
TTAAAAATTATTTGGTTTCTCTTTTTAATTATTCTGGGGCATAGTCATTTCTAAAA
GTCACTAGTAGAAAGTATAATTTCAAGACAGAATATTCTAGACATGCTAGCAGTT
TATATGTATTCATGAGTAATGTGATATATATTGGGCGCTGGTGAGGAAGGAAGG
AGGAATGAGTGACTATAAGGATGGTTACCATAGAAACTTCCTTTTTTACCTAATT
GAAGAGAGACTACTACAGAGTGCTAAGCTGCATGTGTCATCTTACACTAGAGAG
AAATGGTAAGTTTCTTGTTTTATTTAAGTTATGTTTAAGCAAGGAAAGGATTTGTT
ATTGAACAGTATATTTCAGGAAGGTTAGAAAGTGGCGGTTAGGATATATTTTAAA
TCTACCTAAAGCAGCATATTTTAAAAATTTAAAAGTATTGGTATTAAATTAAGAA
ATAGAGGACAGAACTAGACTGATAGCAGTGACCTAGAACAATTTGAGATTAGGA
AAGTTGTGACCATGAATTTAAGGATTTATGTGGATACAAATTCTCCTTTAAAGTG
TTTCTTCCCTTAATATTTATCTGACGGTAATTTTTGAGCAGTGAATTACTTTATAT
ATCTTAATAGTTTATTTGGGACCAAACACTTAAACAAAAAGTTCTTTAAGTCATA
TAAGCCTTTTCAGGAAGCTTGTCTCATATTCACTCCCGAGACATTCACCTGCCAA
GTGGCCTGAGGATCAATCCAGTCCTAGGTTTATTTTGCAGACTTACATTCTCCCA
AGTTATTCAGCCTCATATGACTCCACGGTCGGCTTTACCAAAACAGTTCAGAGTG
CACTTTGGCACACAATTGGGAACAGAACAATCTAATGTGTGGTTTGGTATTCCAA
GTGGGGTCTTTTTCAGAATCTCTGCACTAGTGTGAGATGCAAACATGTTTCCTCAT

CTTTCTGGCTTATCCAGTATGTAGCTATTTGTGACATAATAAATATATACATATAT
GAAAATA (SEQ ID NO: 860)

[0127] In certain embodiments, the SNCA gene targeted by an siRNA of the present disclosure expresses a mRNA comprising the sequence of NM_007308.2 (Homo sapiens synuclein, alpha (non A4 component of amyloid precursor) (SNCA), transcript variant 4, mRNA). NM_007308.2 sequence is:

GCCATTCGACGACAGGTTAGCGGGTTTGCCTCCCACTCCCCCAGCCTC
GCGTCGCCGGCTCACAGCGGCCTCCTCTGGGGACAGTCCCCCCCGGGTGCCGCCT
CCGCCCTTCCTGTGCGCTCCTTTTCCTTCTTCTTTCCTATTAAATATTATTTGGGAA
TTGTTTAAATTTTTTTTTTAAAAAAAGAGAGAGGCGGGGAGGAGTCGGAGTTGTG
GAGAAGCAGAGGGACTCAGTGTGGTGTAAAGGAATTCATTAGCCATGGATGTAT
TCATGAAAGGACTTTCAAAGGCCAAGGAGGGAGTTGTGGCTGCTGCTGAGAAAA
CCAAACAGGGTGTGGCAGAAGCAGCAGGAAAGACAAAAGAGGGTGTTCTCTAT
GTAGGCTCCAAAACCAAGGAGGGAGTGGTGCATGGTGTGGCAACAGTGGCTGAG
AAGACCAAAGAGCAAGTGACAAATGTTGGAGGAGCAGTGGTGACGGGTGTGAC
AGCAGTAGCCCAGAAGACAGTGGAGGGAGCAGGGAGCATTGCAGCAGCCACTG
GCTTTGTCAAAAAGGACCAGTTGGGCAAGGAAGGGTATCAAGACTACGAACCTG
AAGCCTAAGAAATATCTTTGCTCCCAGTTTCTTGAGATCTGCTGACAGATGTTCC
ATCCTGTACAAGTGCTCAGTTCCAATGTGCCCAGTCATGACATTTCTCAAAGTTTT
TACAGTGTATCTCGAAGTCTTCCATCAGCAGTGATTGAAGTATCTGTACCTGCCC
CCACTCAGCATTTCGGTGCTTCCCTTTCACTGAAGTGAATACATGGTAGCAGGGT
CTTTGTGTGCTGTGGATTTTGTGGCTTCAATCTACGATGTTAAAACAAATTAAAA
ACACCTAAGTGACTACCACTTATTTCTAAATCCTCACTATTTTTTTGTTGCTGTTG
TTCAGAAGTTGTTAGTGATTTGCTATCATATATTATAAGATTTTTAGGTGTCTTTT
AATGATACTGTCTAAGAATAATGACGTATTGTGAAATTTGTTAATATATATAATA
CTTAAAAATATGTGAGCATGAAACTATGCACCTATAAATACTAAATATGAAATTT
TACCATTTTGCGATGTGTTTTATTCACTTGTGTTTGTATATAAATGGTGAGAATTA
AAATAAAACGTTATCTCATTGCAAAAATATTTTATTTTTATCCCATCTCACTTTAA
TAATAAAAATCATGCTTATAAGCAACATGAATTAAGAACTGACACAAAGGACAA
AAATATAAAGTTATTAATAGCCATTTGAAGAAGGAGGAATTTTAGAAGAGGTAG
AGAAAATGGAACATTAACCCTACACTCGGAATTCCCTGAAGCAACACTGCCAGA
AGTGTGTTTTGGTATGCACTGGTTCCTTAAGTGGCTGTGATTAATTATTGAAAGTG
GGGTGTTGAAGACCCCAACTACTATTGTAGAGTGGTCTATTTCTCCCTTCAATCCT
GTCAATGTTTGCTTTACGTATTTTGGGGAACTGTTGTTTGATGTGTATGTGTTTAT

AATTGTTATACATTTTTAATTGAGCCTTTTATTAACATATATTGTTATTTTTGTCTC
GAAATAATTTTTTAGTTAAAATCTATTTTGTCTGATATTGGTGTGAATGCTGTACC
TTTCTGACAATAAATAATATTCGACCATGAATAAAAAAAAAAAAAAAAGTGGGTT
CCCGGGAACTAAGCAGTGTAGAAGATGATTTTGACTACACCCTCCTTAGAGAGC
CATAAGACACATTAGCACATATTAGCACATTCAAGGCTCTGAGAGAATGTGGTT
AACTTTGTTTAACTCAGCATTCCTCACTTTTTTTTTTTAATCATCAGAAATTCTCTC
TCTCTCTCTCTCTTTTTCTCTCGCTCTCTTTTTTTTTTTTTTTTTACAGGAAATGCCT
TTAAACATCGTTGGAACTACCAGAGTCACCTTAAAGGAGATCAATTCTCTAGACT
GATAAAAATTTCATGGCCTCCTTTAAATGTTGCCAAATATATGAATTCTAGGATT
TTTCCTTAGGAAAGGTTTTTCTCTTTCAGGGAAGATCTATTAACTCCCCATGGGTG
CTGAAAATAAACTTGATGGTGAAAAACTCTGTATAAATTAATTTAAAAATTATTT
GGTTTCTCTTTTTAATTATTCTGGGGCATAGTCATTTCTAAAAGTCACTAGTAGAA
AGTATAATTTCAAGACAGAATATTCTAGACATGCTAGCAGTTTATATGTATTCAT
GAGTAATGTGATATATATTGGGCGCTGGTGAGGAAGGAAGGAGGAATGAGTGAC
TATAAGGATGGTTACCATAGAAACTTCCTTTTTTACCTAATTGAAGAGAGACTAC
TACAGAGTGCTAAGCTGCATGTGTCATCTTACACTAGAGAGAAATGGTAAGTTTC
TTGTTTTATTTAAGTTATGTTTAAGCAAGGAAAGGATTTGTTATTGAACAGTATAT
TTCAGGAAGGTTAGAAAGTGGCGGTTAGGATATATTTTAAATCTACCTAAAGCAG
CATATTTTAAAAATTTAAAAGTATTGGTATTAAATTAAGAAATAGAGGACAGAA
CTAGACTGATAGCAGTGACCTAGAACAATTTGAGATTAGGAAAGTTGTGACCAT
GAATTTAAGGATTTATGTGGATACAAATTCTCCTTTAAAGTGTTTCTTCCCTTAAT
ATTTATCTGACGGTAATTTTTGAGCAGTGAATTACTTTATATATCTTAATAGTTTA
TTTGGGACCAAACACTTAAACAAAAAGTTCTTTAAGTCATATAAGCCTTTTCAGG
AAGCTTGTCTCATATTCACTCCCGAGACATTCACCTGCCAAGTGGCCTGAGGATC
AATCCAGTCCTAGGTTTATTTTGCAGACTTACATTCTCCCAAGTTATTCAGCCTCA
TATGACTCCACGGTCGGCTTTACCAAAACAGTTCAGAGTGCACTTTGGCACACAA
TTGGGAACAGAACAATCTAATGTGTGGTTTGGTATTCCAAGTGGGGTCTTTTTCA
GAATCTCTGCACTAGTGTGAGATGCAAACATGTTTCCTCATCTTTCTGGCTTATCC
AGTATGTAGCTATTTGTGACATAATAAATATATACATATATGAAAATA (SEQ ID
NO: 861).

[0128] In certain embodiments, the present disclosure is directed to an siRNA molecule comprising an antisense strand and sense strand having complementarity to the antisense strand, wherein the antisense strand is from 10 to 30 nucleotides in length and has complementarity sufficient to hybridize to a region within an SNCA mRNA transcript having

the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand has at least 70% complementarity to a region of 21 contiguous nucleobases within the SNCA mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand has at least 75% complementarity to a region of 21 contiguous nucleobases within the SNCA mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. For example, but not by way of limitation, the antisense strand can have at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementarity to the region within the SNCA mRNA transcript having the nucleic acid sequence of any one of SEQ ID Nos: 421-840.

[0129] In certain embodiments, the antisense strand comprises at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand comprises from 10 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand comprises from 12 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand comprises from 15 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand comprises from 18 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand comprises from 21 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand comprises from 24 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the SNCA RNA

transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. In certain embodiments, the antisense strand comprises 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0130] In certain embodiments, the antisense strand comprises 9 or fewer nucleotide mismatches relative to a region of 21 contiguous nucleobases of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840. For example, but not by way of limitation, the antisense strand can comprise 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or only 1 mismatch relative to the region of the SNCA RNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

[0131] In certain embodiments, the siRNA molecule of the present disclosure targets a region of an SNCA RNA transcript that has the nucleic acid sequence of any one of SEQ ID NOs: 459, 535, 551, 599, 631, 663, 664, 666, 667, 671, 748, 750, 751, 752, 760, 762, and 777.

[0132] In certain embodiments, the present disclosure is directed to an siRNA molecule comprising a sense strand comprising an unmodified sense strand of Table 1A. In certain embodiments, the present disclosure is directed to an siRNA molecule comprising an antisense strand comprising an unmodified antisense strand of Table 1A. In certain embodiments the sense strand is UACCACUUAUUUCUAA (SEQ ID NO: 760) and the antisense strand is UUAGAAAUAAGUGGUAGUCAC (SEQ ID NO: 340). In certain embodiments the sense strand is CAAGUGCUCAGUUCCA (SEQ ID NO: 664) and the antisense strand is UGGAACUGAGCACUUGUACAG (SEQ ID NO: 244). In certain embodiments the sense strand is AGUGGUGCAUGGUGUA (SEQ ID NO: 535) and the antisense strand is UACACCAUGCACCACUCCCUC (SEQ ID NO: 115). In certain embodiments the sense strand is CAAUGAGGCUUAUGAA (SEQ ID NO: 599) and the antisense strand is UUCAUAAGCCUCAUUGUCAGG (SEQ ID NO: 179). In certain embodiments the sense strand is AGUGCUCAGUUCCAAA (SEQ ID NO: 666) and the antisense strand is UUUGGAACUGAGCACUUGUAC (SEQ ID NO: 246). In certain embodiments the sense strand is UCAGUUCCAAUGUGCA (SEQ ID NO: 671) and the antisense strand is UGCACAUUGGAACUGAGCACU (SEQ ID NO: 251). In certain embodiments the sense strand is CUACGAUGUUAAAACA (SEQ ID NO: 748) and the antisense strand is UGUUUUAACAUCGUAGAUUGA (SEQ ID NO: 328).

[0133] In certain embodiments, the present disclosure is directed to an siRNA molecule comprising a sense strand comprising a modified sense strand of Table 1B. In certain

embodiments, the present disclosure is directed to an siRNA molecule comprising an antisense strand comprising a modified antisense strand of Table 1B. In certain embodiments the sense strand is (mU)#(mA)#(mC)(fC)(mA)(fC)(mU)(fU)(mA)(fU)(mU)(mU)(mC)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 841) and the antisense strand is V(mU)#(fU)#(mA)(fG)(fA)(fA)(mA)(fU)(mA)(fA) (mG)(fU)(mG)(fG)(mU)(fA)#(mG)#(mU)#(mC)#(mA)#(mC) (SEQ ID NO: 842) (where m = 2'Ome; f = 2'F; # = phosphorothioate; -DIO = a divalent oligonucleotide (DIO) linker; V = vinyl phosphonate . In certain embodiments the sense strand is (mC)#(mA)#(mA)(fG)(mU)(fG)(mC)(fU) (mC)(fA)(mG)(mU)(mU)(fC)#(mC)#(mA)-DIO (SEQ ID NO: 843) and the antisense strand is V(mU)#(fG)#(mG)(fA)(fA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)(mU)(fG)#(mU)#(mA) #(mC)#(mA)#(mG) (SEQ ID NO: 844). In certain embodiments the sense strand is (mA)#(mG)#(mU) (fG)(mG)(fU)(mG)(fC)(mA)(fU)(mG)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 845) and the antisense strand is V(mU)#(fA)#(mC)(fA)(fC)(fC)(mA)(fU)(mG)(fC)(mA)(fC)(mC)(fA)(mC)(fU)#(mC)# (mC)#(mC)#(mU)#(mC) (SEQ ID NO: 846). In certain embodiments the sense strand is (mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC)(fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847) and the antisense strand is V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA) (mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 848). In certain embodiments the sense strand is (mU)#(mC)#(mA)(fG)(mU)(fU)(mC)(fC)(mA)(fA)(mU)(mG)(mU)(fG)#(mC)#(mA)-DIO (SEQ ID NO: 849) and the antisense strand is V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA) (mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 850). In certain embodiments the sense strand is (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 851) and the antisense strand is V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU) (mG)(fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852). In certain embodiments the sense strand is (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 853) and the antisense strand is

V(mU)#(fG)#(mU)(fU)(fU)(fU)(mA)(fA)(mC)(fA)(mU)(fC)(mG)(fU)
(mA)(fG)#(mA)#(mU)#(mU)#(mG)#(mA) (SEQ ID NO: 854). In certain embodiments, the sense strand is (mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC)
(fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847) and the antisense strand is
V(mU)#(fU)#(mC)(fA)(fU)(fA)(mA)(fG)(mC)(fC)(mU)(fC)(mA)(fU)(mU)(fG)#(mU)#(mC)
#(mA)#(mG)#(mG) (SEQ ID NO: 855). In certain embodiments, the sense strand is
(mA)#(mG)#(mU)(fG)(mC)(fU) (mC)(fA)(mG)(fU)(mU)(mC)(mC)(fA)#(mA)#(mA)-DIO
(SEQ ID NO: 856) and the antisense strand is
V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)#(mU)#(mG)
#(mU)#(mA)#(mC) (SEQ ID NO: 850). In certain embodiments, the sense strand is
(mU)#(mC)#(mA)(fG)(mU) (fU)(mC)(fC)(mA)(fA)(mU)(mG)(mU)(fG)#(mC)#(mA)-DIO
(SEQ ID NO: 857) and the antisense strand is
V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU)(mG)
(fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852).

Table 1A.

Position name	AT numbers	mRNA target sequence	Unmodified 16mer sense	Unmodified 21mer antisense
SNCA_963	AT4512-4509	GUGACUACCACUUAUUUCUAA (SEQ ID NO: 862)	UACCACUUAUUUCUAA (SEQ ID NO: 760)	UUAGAAAUAAGUGGUAGUCAC (SEQ ID NO: 340)
SNCA_737	AT4511-4514	CUGUACAAGUGCUCAGUUCCA (SEQ ID NO: 863)	CAAGUGCUCAGUUCCA (SEQ ID NO: 644)	UGGAACUGAGCACUUGUACAG (SEQ ID NO: 244)
SNCA_399	AT4524-4521	GAGGGAGUGGUGCAUGGUGUG (SEQ ID NO: 864)	AGUGGUGCAUGGUGUA (SEQ ID NO: 535)	UACACCAUGCACCACUCCCUC (SEQ ID NO: 115)
SNCA_621	AT4547-4546	CCUGACAAUGAGGCUUAUGAA (SEQ ID NO: 865)	CAAUGAGGCUUAUGAA (SEQ ID NO: 599)	UUCAUAAGCCUCAUUGUCAGG (SEQ ID NO: 179)
SNCA_739	AT4516-4513	GUACAAGUGCUCAGUUCCAAU (SEQ ID NO: 866)	AGUGCUCAGUUCCAAA (SEQ ID NO: 666)	UUUGGAACUGAGCACUUGUAC (SEQ ID NO: 246)
SNCA_744	AT4555-4554	AGUGCUCAGUUCCAAUGUGCC (SEQ ID NO: 867)	UCAGUUCCAAUGUGCA (SEQ ID NO 671)	UGCACAUUGGAACUGAGCACU (SEQ ID NO: 251)
SNCA_926	AT4520-4517	UCAAUCUACGAUGUUAAAACA (SEQ ID NO: 868)	CUACGAUGUUAAAACA (SEQ ID NO: 748)	UGUUUUAACAUCGUAGAUUGA (SEQ ID NO: 328)

Table 1B.

Position name	AT numbers	Modified 16mer sense	Modified 21mer antisense
SNCA_963	AT4512-4509	(mU)#(mA)#(mC)(fC)(mA)(fC)(mU)(fU)(mA)(fU)(mU)(mU)(mC)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 841)	V(mU)#(fU)#(mA)(fG)(fA)(fA)(mA)(fU)(mA)(fA)(mG)(fU)(mG)(fG)(mU)(fA)#(mG)#(mU)#(mC)#(mA)#(mC) (SEQ ID NO: 842)
SNCA_737	AT4511-4514	(mC)#(mA)#(mA)(fG)(mU)(fG)(mC)(fU)(mC)(fA)(mG)(mU)(mU)(fC)#(mC)#(mA)-DIO (SEQ ID NO: 843)	V(mU)#(fG)#(mG)(fA)(fA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)(mU)(fG)#(mU)#(mA)#(mC)#(mA)#(mG) (SEQ ID NO: 844)
SNCA_399	AT4524-4521	(mA)#(mG)#(mU)(fG)(mG)(fU)(mG)(fC)(mA)(fU)(mG)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 845)	V(mU)#(fA)#(mC)(fA)(fC)(fC)(mA)(fU)(mG)(fC)(mA)(fC)(mC)(fA)(mC)(fU)#(mC)#(mC)#(mC)#(mU)#(mC) (SEQ ID NO: 846)
SNCA_621	AT4547-4546	(mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC)(fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847)	V(mU)#(fU)#(mC)(fA)(fU)(fA)(mA)(fG)(mC)(fC)(mU)(fC)(mA)(fU)(mU)(fG)#(mU)#(mC)#(mA)#(mG)#(mG) (SEQ ID NO: 855)

SNCA_739	AT4516-4513	(mA)#(mG)#(mU)(fG)(mC)(fU)(mC)(fA)(mG)(fU)(mU)(mC)(mC)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 856)	V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 850)
SNCA_744	AT4555-4554	(mU)#(mC)#(mA)(fG)(mU)(fU)(mC)(fC)(mA)(fA)(mU)(mG)(fU)(mG)#(mC)#(mA)-DIO (SEQ ID NO: 857)	V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU)(mG)(fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852)
SNCA_926	AT4520-4517	(mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)(fU)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 853)	V(mU)#(fG)#(mU)(fU)(fU)(mA)(fA)(mC)(fA)(mU)(fC)(mG)(fU)(mA)(fG)#(mA)#(mU)#(mU)#(mG)#(mA) (SEQ ID NO: 854)

Note: m = 2'Ome; f = 2'F; # = phosphorothioate; -DIO = a divalent oligonucleotide (DIO) linker; V = vinyl phosphonate.

5.3. siRNA Structure

[0134] The siRNA molecules of the disclosure may be in the form of a single-stranded (ss) or double-stranded (ds) oligonucleotide structure. In some embodiments, the siRNA molecules may be di-branched, tri-branched, or tetra-branched molecules. Furthermore, the siRNA molecules of the disclosure may contain one or more phosphodiester internucleoside linkages and/or an analog thereof, such as a phosphorothioate internucleoside linkage. The siRNA molecules of the disclosure may further contain chemically modified nucleosides having 2' sugar modifications.

[0135] The simplest siRNAs consist of a ribonucleic acid, including a ss- or ds- structure, formed by a first strand (i.e., antisense strand), and in the case of a ds-siRNA, a second strand (i.e., sense strand). The first strand includes a stretch of contiguous nucleotides that is at least partially complementary to a target nucleic acid. The second strand also includes a stretch of contiguous nucleotides where the second stretch is at least partially identical to a target nucleic acid. The first strand and said second strand may be hybridized to each other to form a double-stranded structure. The hybridization typically occurs by Watson Crick base pairing.

[0136] Depending on the sequence of the first and second strand, the hybridization or base pairing is not necessarily complete or perfect, which means that the first and second strand are not 100% base-paired due to mismatches. One or more mismatches may also be present within the duplex without necessarily impacting the siRNA RNAi activity.

[0137] The first strand contains a stretch of contiguous nucleotides which is essentially complementary to a target nucleic acid. Typically, the target nucleic acid sequence is, in accordance with the mode of action of interfering ribonucleic acids, a ss-RNA, e.g., an mRNA. Such hybridization occurs most likely through Watson Crick base pairing but is not necessarily limited thereto. The extent to which the first strand has a complementary stretch of contiguous nucleotides to a target nucleic acid sequence may be between 80% and 100%, e.g., 80%, 85%, 90%, 95%, or 100% complementary.

[0138] The siRNA molecules described herein may employ modifications to the nucleobase, phosphate backbone, ribose core, 5′- and 3′-ends, and branching, wherein multiple strands of siRNA may be covalently linked.

[0139] The siRNA molecules described herein may contain one or more phosphodiester internucleoside linkages and/or an analog thereof, such as a phosphorothioate internucleoside linkage, in which oxyanion moieties are electrostatically neutralized by ionic bonding to a

divalent metal cation, such as Ba^{2+}, Be^{2+}, Ca^{2+}, Cu^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, or Zn^{2+}. In certain embodiments, the one or more divalent cations includes Ca^{2+} and Mg^{2+}, optionally wherein the ratio of Ca^{2+} to Mg^{2+} is from 1:100 to 100:1 (e.g., 1:75, 1:50, 1:25, 1:10, 1:5, 1:1, 5:1, 10:1, 25:1. 50:1, 75:1, or 100:1). In certain embodiments, the Ca^{2+} and Mg^{2+} are present in a 1:1 ratio. In certain embodiments, the one or more divalent cations displace water from a cationic binding site of the siRNA molecule. In certain embodiments, the degree of saturation of the cationic binding sites by the one or more divalent cations is from about 10% to about 100% (e.g., from about 20% to about 100%, from about 30% to about 100%, from about 40% to about 100%, from about 50% to about 100%, from about 60% to about 100%, from about 70% to about 100%, from about 80% to about 100%, or from about 90% to about 100%). In certain embodiments, the cationic binding site is located within an internucleoside linkage, such as a phosphodiester linkage and/or a phosphorothioate linkage. For example, the cationic binding site may be an oxyanion moiety within a phosphodiester linage or phosphorothioate linkage. In certain embodiments, the one or more divalent cations are characterized as having an ionic radius ranging from about 30 picometers to about 150 picometers (e.g., from about 30 picometers to about 140 picometers, from about 40 picometers to about 130 picometers, from about 50 picometers to about 120 picometers, from about 60 picometers to about 110 picometers, from about 60 picometers to about 100 picometers, or from about 60 picometers to about 90 picometers).

5.3.1. Lengths of siRNA Molecules

[0140] It is within the scope of the disclosure that any length, known and previously unknown in the art, may be employed for the current invention. As described herein, potential lengths for an antisense strand of the siRNA molecules of the present disclosure is between 10 and 30 nucleotides (e.g., 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), 15 and 25 nucleotides (e.g., 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, or 25 nucleotides), or 18 and 23 nucleotides (e.g., 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, or 23 nucleotides). In some embodiments, the antisense strand is 20 nucleotides. In some embodiments, the antisense strand is 21 nucleotides. In some

embodiments, the antisense strand is 22 nucleotides. In some embodiments, the antisense strand is 23 nucleotides. In some embodiments, the antisense strand is 24 nucleotides. In some embodiments, the antisense strand is 25 nucleotides. In some embodiments, the antisense strand is 26 nucleotides. In some embodiments, the antisense strand is 27 nucleotides. In some embodiments, the antisense strand is 28 nucleotides. In some embodiments, the antisense strand is 29 nucleotides. In some embodiments, the antisense strand is 30 nucleotides.

[0141] In some embodiments, the sense strand of the siRNA molecules of the present disclosure is between 12 and 30 nucleotides (e.g., 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), or 14 and 23 nucleotides (e.g., 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, or 23 nucleotides). In some embodiments, the sense strand is 15 nucleotides. In some embodiments, the sense strand is 16 nucleotides. In some embodiments, the sense strand is 17 nucleotides. In some embodiments, the sense strand is 18 nucleotides. In some embodiments, the sense strand is 19 nucleotides. In some embodiments, the sense strand is 20 nucleotides. In some embodiments, the sense strand is 21 nucleotides. In some embodiments, the sense strand is 22 nucleotides. In some embodiments, the sense strand is 23 nucleotides. In some embodiments, the sense strand is 24 nucleotides. In some embodiments, the sense strand is 25 nucleotides. In some embodiments, the sense strand is 26 nucleotides. In some embodiments, the sense strand is 27 nucleotides. In some embodiments, the sense strand is 28 nucleotides. In some embodiments, the sense strand is 29 nucleotides. In some embodiments, the sense strand is 30 nucleotides.

5.3.2. 2' Sugar Modifications

[0142] The present disclosure may include ss- and ds- siRNA molecule compositions including at least one (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or more) nucleosides having 2' sugar modifications. Possible 2′-modifications include all possible orientations of 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 may be substituted or unsubstituted C1 to C10 alkyl or C2 to C10 alkenyl and alkynyl. In some embodiments, the modification includes a 2'-O-methyl (2'-O-Me) modification. Other potential sugar substituent groups include: C1 to C10 lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3,

OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. In some embodiments, the modification includes 2′-methoxyethoxy (2′-O-$CH_2CH_2OCH_3$, also known as 2′-O-(2-methoxyethyl) or 2′-MOE). In some embodiments, the modification includes 2′-dimethylaminooxyethoxy, i.e., a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2′-DMAOE, and 2′-dimethylaminoethoxyethoxy (also known in the art as 2′-O-dimethylamino-ethoxy-ethyl or 2′-DMAEOE), i.e., 2′-O-$CH_2OCH_2N(CH_3)_2$. Other potential sugar substituent groups include, e.g., aminopropoxy (-$OCH_2CH_2CH_2NH_2$), allyl (-CH_2-$CH=CH_2$), -O-allyl (-O-CH_2-$CH=CH_2$) and fluoro (F). 2′-sugar substituent groups may be in the arabino (up) position or ribo (down) position. In some embodiments, the 2′-arabino modification is 2′-F. Similar modifications may also be made at other positions on the siRNA molecule, particularly the 3′ position of the sugar on the 3′ terminal nucleoside or in 2′-5′ linked oligonucleotides and the 5′ position of 5′ terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar.

5.3.3. Nucleobase Modifications

[0143] The siRNA molecules of the disclosure may also include nucleosides or other surrogate or mimetic monomeric subunits that include a nucleobase (often referred to in the art simply as "base" or "heterocyclic base moiety"). The nucleobase is another moiety that has been extensively modified or substituted and such modified and or substituted nucleobases are amenable to the present disclosure. 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). Chemically modified nucleobases also referred herein as heterocyclic base moieties 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 (-C=C-CH3) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 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, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in US 3,687,808, those disclosed in Kroschwitz, J.I., ed. *The Concise Encyclopedia of Polymer Science and Engineering,* New York, John Wiley & Sons, 1990, pp. 858-859; those disclosed by Englisch et al., *Angewandte Chemie,* International Edition 30:613, 1991; and those disclosed by Sanghvi, Y.S., Chapter 16, *Antisense Research and Applications,* CRC Press, Gait, M.J. ed., 1993, pp. 289-302. The siRNA molecules of the present disclosure may also include polycyclic heterocyclic compounds in place of one or more heterocyclic base moieties. A number of tricyclic heterocyclic compounds have been previously reported. These compounds are routinely used in antisense applications to increase the binding properties of the modified strand to a target strand.

[0144] Representative cytosine analogs that make three hydrogen bonds with a guanosine in a second strand include 1,3-diazaphenoxazine-2-one (Kurchavov *et al., Nucleosides and Nucleotides,* 16:1837-46, 1997), 1,3-diazaphenothiazine-2-one (Lin et al. *Am. Chem. Soc.,* 117:3873-4, 1995), and 6,7,8,9-tetrafluoro-l,3-diazaphenoxazine-2-one (Wang et al., *Tetrahedron Lett.,* 39:8385-8, 1998). Incorporated into oligonucleotides, these base modifications were shown to hybridize with complementary guanine and the latter was also shown to hybridize with adenine and to enhance helical thermal stability by extended stacking interactions (also see US 10/155,920 and US 10/013,295, both of which are herein incorporated by reference in their entirety). Further helix-stabilizing properties have been observed when a cytosine analog/substitute has an aminoethoxy moiety attached to the rigid 1,3-diazaphenoxazine-2-one scaffold (Lin et al., *Am. Chem. Soc.,* 120:8531-2, 1998).

5.3.4. Internucleoside Linkage Modifications

[0145] Another variable in the design of the present disclosure is the internucleoside linkage making up the phosphate backbone of the siRNA molecule. Although the natural RNA phosphate backbone may be employed here, derivatives thereof may be used which enhance desirable characteristics of the siRNA molecule. In certain embodiments, the siRNA molecule will be modified to exhibit reduced hydrolysis relative to the unmodified siRNA. One example

of a modification that decreases the rate of hydrolysis is phosphorothioates. Any portion or the whole of the backbone may contain phosphate substitutions (e.g., phosphorothioates). For instance, the internucleoside linkages may be between 0 and 100% phosphorothioate, e.g., between 0 and 100%, 10 and 100%, 20 and 100%, 30 and 100%, 40 and 100%, 50 and 100%, 60 and 100%, 70 and 100%, 80 and 100%, 90 and 100%, 0 and 90%, 0 and 80%, 0 and 70%, 0 and 60%, 0 and 50%, 0 and 40%, 0 and 30%, 0 and 20%, 0 and 10%, 10 and 90%, 20 and 80%, 30 and 70%, 40 and 60%, 10 and 40%, 20 and 50%, 30 and 60%, 40 and 70%, 50 and 80%, or 60 and 90% phosphorothioate linkages. Similarly, the internucleoside linkages may be between 0 and 100% phosphodiester linkages, e.g., between 0 and 100%, 10 and 100%, 20 and 100%, 30 and 100%, 40 and 100%, 50 and 100%, 60 and 100% 70 and 100%, 80 and 100%, 90 and 100%, 0 and 90%, 0 and 80%, 0 and 70%, 0 and 60%, 0 and 50%, 0 and 40%, 0 and 30%, 0 and 20%, 0 and 10%, 10 and 90%, 20 and 80%, 30 and 70%, 40 and 60%, 10 and 40%, 20 and 50%, 30 and 60%, 40 and 70%, 50 and 80%, or 60 and 90% phosphodiester linkages.

[0146] Specific examples of some potential siRNA molecules useful in this invention include oligonucleotides containing modified e.g., non-naturally occurring internucleoside linkages. As defined in this specification, oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom and internucleoside linkages that do not have a phosphorus atom. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. An exemplary phosphorus containing modified internucleoside linkage is the phosphorothioate internucleoside linkage. In some embodiments, the modified oligonucleotide backbones containing a phosphorus atom therein include, for example, phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkyl-phosphonates, thionoalkylphosphotriesters, selenophosphates, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Exemplary U.S. patents describing the preparation of phosphorus-containing linkages include but are not limited to, U.S. Pat. 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 U.S. Pat. RE39464, the entire contents of each of which are hereby incorporated herein by reference.

[0147] In some embodiments, the modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom 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; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts. Non-limiting examples of U.S. patents that teach the preparation of non-phosphorus backbones include, but are not limited to, U.S. Pat. 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.

5.4. Patterns of Modifications of siRNA Molecules

[0148] The following section provides a set of exemplary scaffolds into which the siRNA molecules of the disclosure may be incorporated.

[0149] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula I, wherein Formula I is, in the 5'-to-3' direction

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C'\text{-}P^1)_k\text{-}C'$$

Formula I;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$; each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$; B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$; each C is a 2'-O-methyl (2'-

O-Me) ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside; each D is a 2'-F ribonucleoside; each P^1 is a phosphorothioate internucleoside linkage; each P^2 is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 4. In some embodiments, k is 4. In some embodiments, j is 4 and k is 4. The antisense is complementary (e.g., fully or partially complementary) to a target nucleic acid sequence.

[0150] In some embodiments, the antisense strand includes a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0151] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula II, wherein Formula II is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula II;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$; each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$; B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$; each C is a 2'-O-methyl (2'-O-Me) ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside; each D is a 2'-F ribonucleoside; each P^1 is a phosphorothioate internucleoside linkage; each P^2 is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 4. In some embodiments, k is 4. In some embodiments, j is 4 and k is 4. The antisense is complementary (e.g., fully or partially complementary) to a target nucleic acid sequence.

[0152] In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-A-S-A

Formula A2;

[0153] wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0154] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula III, wherein Formula III is, in the 5'-to-3' direction:

$E\text{-}(A')_m\text{-}F$

Formula III;

wherein E is represented by the formula $(C\text{-}P^1)_2$; F is represented by the formula $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$; A', C, D, P^1, and P^2 are as defined in Formula I; and m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 4. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

[0155] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-A

Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0156] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-A

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0157] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-B

Formula S3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0158] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-B

Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0159] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula IV, wherein Formula IV is, in the 5'-to-3' direction:

$$A\text{-}(A')_j\text{-}C\text{-}P^2\text{-}B\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula IV;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$; each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$; B is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D\text{-}P^1$; each C is a 2'-O-Me ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside; each D is a 2'-F ribonucleoside; each P^1 is a phosphorothioate internucleoside linkage; each P^2 is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 6. In some

embodiments, k is 4. In some embodiments, j is 6 and k is 4. The antisense strand is complementary (e.g., fully or partially complementary) to a target nucleic acid.

[0160] In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B-S-A-S-A-S-A

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0161] In some embodiments of the disclosure, the siRNA of the disclosure may have a sense strand represented by Formula V, wherein Formula V is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}C\text{-}P^2\text{-}F$$

Formula V;

[0162] wherein E is represented by the formula $(C\text{-}P^1)_2$; F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$; A', C, D, P^1, and P^2 are as defined in Formula IV; and m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 5. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

[0163] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A

Formula S5;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0164] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A

Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0165] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B

Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0166] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B

Formula S8;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0167] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula VI, wherein Formula VI is, in the 5'-to-3' direction:

2- B_j-E-B_k-E-F-G_l-D-P^1-C'

Formula VI;

wherein A is represented by the formula C-P^1-D-P^1; each B is represented by the formula C-P^2; each C is a 2'-O-Me ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside; each D is a 2'-F ribonucleoside; each E is represented by the formula

D-P^2-C-P^2; F is represented by the formula D-P^1-C-P^1; each G is represented by the formula C-P^1; each P^1 is a phosphorothioate internucleoside linkage; each P^2 is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and l is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 3. In some embodiments, k is 6. In some embodiments, l is 2. In some embodiments, j is 3, k is 6, and l is 2. The antisense strand is complementary (e.g., fully or partially complementary) to a target nucleic acid.

[0168] In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:

A-S-B-S-A-O-A-O-A-O-B-O-A-O-A-O-A-O-A-O-A-O-A-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0169] In some embodiments of the disclosure, the siRNA may contain a sense strand including a region represented by Formula VII, wherein Formula VII is, in the 5'-to-3' direction:

$H\text{-}B_m\text{-}I_n\text{-}A'\text{-}B_o\text{-}H\text{-}C$

Formula VII;

wherein A' is represented by the formula C-P^2-D-P^2; each H is represented by the formula (C-P^1)$_2$; each I is represented by the formula (D-P^2); B, C, D, P^1, and P^2 are as defined in Formula VI; m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); n is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and o is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 3. In some embodiments, n is 3. In some embodiments, o is 3. In some embodiments, m is 3, n is 3, and o is 3. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

[0170] In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:

A-S-A-S-A-O-A-O-A-O-B-O-B-O-B-O-A-O-B-O-A-O-A-O-A-O-A-S-A-S-A

Formula S9;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

[0171] In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region that is represented by Formula VIII:

$$Z\text{-}((A\text{-}P\text{-})_n(B\text{-}P\text{-})_m)_q;$$

Formula VIII

wherein Z is a 5' phosphorus stabilizing moiety; each A is a 2'-O-methyl (2′-O-Me) ribonucleoside; each B is a 2′-fluoro-ribonucleoside; each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage; n is an integer from 1 to 5 (e.g., 1, 2, 3, 4, or 5); m is an integer from 1 to 5 (e.g., 1, 2, 3, 4, or 5); and q is an integer between 1 and 30 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30).

5.5. Methods of siRNA Synthesis

[0172] The siRNA molecules of the disclosure 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.

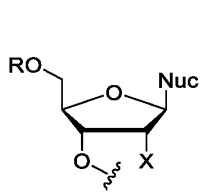
[0173] The siRNA agent can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide including unnatural or chemically modified nucleotides can be easily prepared. siRNA molecules of the disclosure can be prepared using solution-phase or solid-phase organic synthesis or both.

[0174] Further, it is contemplated that for any siRNA agent disclosed herein, further optimization could be achieved by systematically either adding or removing linked nucleosides to generate longer or shorter sequences. Further still, such optimized sequences can be adjusted by, e.g., the introduction of chemically modified nucleosides, and/or modified internucleoside linkages as described herein or as known in the art, including alternative nucleosides, alternative sugar moieties, and/or alternative internucleoside linkages as known in the art

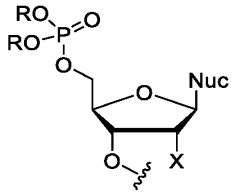
and/or discussed herein to further optimize the molecule (e.g., increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, and/or targeting to a particular location or cell type).

5.6. 5′ Phosphorus Stabilizing Moieties

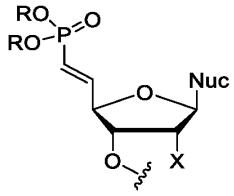
[0175] To further protect the siRNA molecules of this disclosure from degradation, a 5′-phosphorus stabilizing moiety may be employed. A 5′-phosphorus stabilizing moiety replaces the 5′-phosphate to prevent hydrolysis of the phosphate. Hydrolysis of the 5′-phosphate prevents binding to RISC, a necessary step in gene silencing. Any replacement for phosphate that does not impede binding to RISC is contemplated in this disclosure. In some embodiments, the replacement for the 5′-phosphate is also stable to *in vivo* hydrolysis. Each strand of a siRNA molecule may independently and optionally employ any suitable 5′-phosphorus stabilizing moiety.



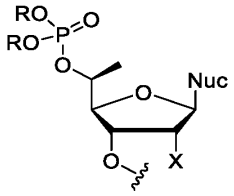
Formula IX



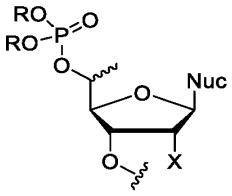
Formula X



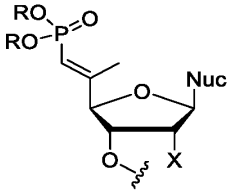
Formula XI



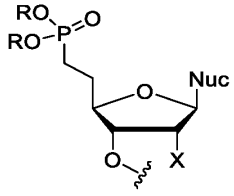
Formula XII



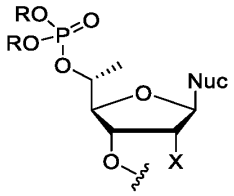
Formula XIII



Formula XIV



Formula XV



Formula XVI

[0176] Some exemplary endcaps are demonstrated in Formulas IX-XVI. Nuc in Formulas IX-XVI represents a nucleobase or nucleobase derivative or replacement as described herein. X in formula IX-XVI represents a 2'-modification as described herein. Some embodiments employ hydroxy as in Formula IX, phosphate as in Formula X, vinylphosphonates as in Formula XI and XIV, 5'-methyl-substitued phosphates as in Formula XII, XIII, and XVI, methylenephosphonates as in Formula XV, or vinyl 5′-vinylphsophonate as a 5′-phosphorus stabilizing moiety as demonstrated in Formula XI.

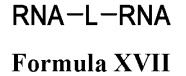
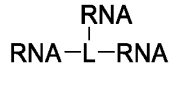
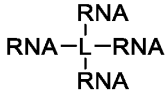
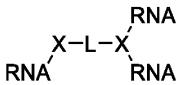
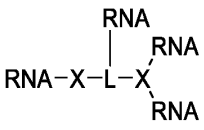
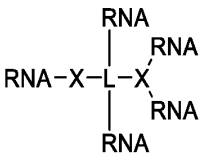
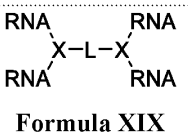
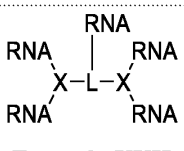
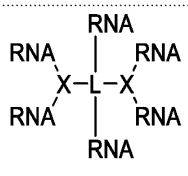
[0177] The present disclosure further provides siRNA molecules having one or more hydrophobic moieties attached thereto. The hydrophobic moiety may be covalently attached to the 5' end or the 3' end of the siRNA molecules of the disclosure. Non-limiting examples of hydrophobic moieties suitable for use with the siRNA molecules of the disclosure may include cholesterol, vitamin D, tocopherol, phosphatidylcholine (PC), docosahexaenoic acid, docosanoic acid, PC-docosanoic acid, eicosapentaenoic acid, lithocholic acid or any combination of the aforementioned hydrophobic moieties with PC.

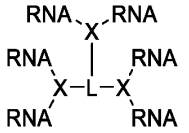
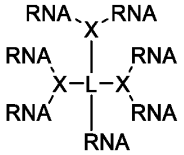
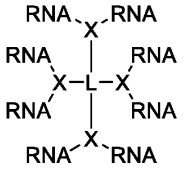
5.7. siRNA Branching

[0178] The siRNA molecules of the disclosure may be branched. For example, the siRNA molecules of the disclosure may have one of several branching patterns, as described herein.

[0179] According to the present disclosure, the siRNA molecules disclosed herein may be branched siRNA molecules. The siRNA molecule may not be branched, or may be di-branched, tri-branched, or tetra-branched, connected through a linker. Each main branch may be further branched to allow for 2, 3, 4, 5, 6, 7, or 8 separate RNA single- or double-strands. The branch points on the linker may stem from the same atom, or separate atoms along the linker. Some exemplary embodiments are listed in Table 2.

Table 2. Branched siRNA structures

Di-branched	Tri-branched	Tetra-branched
 **Formula XVII**	 **Formula XX**	 **Formula XXIV**
 **Formula XVIII**	 **Formula XXI**	 **Formula XXV**
 **Formula XIX**	 **Formula XXII**	 **Formula XXVI**

	 Formula XXIII	 Formula XXVII
		 Formula XXVIII

[0180] In some embodiments, the siRNA molecule is a branched siRNA molecule. In some embodiments, the branched siRNA molecule is di-branched, tri-branched, or tetra-branched. In some embodiments, the di-branched siRNA molecule is represented by any one of Formulas XVII-XIX, wherein each RNA, independently, is an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety (e.g., phosphoroamidite, tosylated solketal, 1,3-diaminopropanol, pentaerythritol, or any one of the branch point moieties described in US 10,478,503).

[0181] In some embodiments, the tri-branched siRNA molecule represented by any one of Formulas XX-XXIII, wherein each RNA, independently, is an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

[0182] In some embodiments, the tetra-branched siRNA molecule represented by any one of Formulas XXIV-XXVIII, wherein each RNA, independently, is an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

[0183] Multiple strands of siRNA described herein may be covalently attached by way of a linker. The effect of this branching improves, *inter alia*, cell permeability allowing better access into cells (e.g., neurons or glial cells) in the CNS. Any linking moiety may be employed which is not incompatible with the siRNAs of the present invention. Linkers include ethylene glycol chains of 2 to 10 subunits (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 subunits), alkyl chains, carbohydrate chains, block copolymers, peptides, RNA, DNA, and others. In some embodiments, any carbon or oxygen atom of the linker is optionally replaced with a nitrogen atom, bears a hydroxyl substituent, or bears an oxo substituent. In some embodiments, the linker is a poly-ethylene glycol (PEG) linker. The PEG linkers suitable for use with the

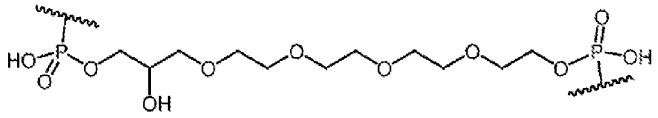
disclosed compositions and methods include linear or non-linear PEG linkers. Examples of non-linear PEG linkers include branched PEGs, linear forked PEGs, or branched forked PEGs.

[0184] PEG linkers of various weights may be used with the disclosed compositions and methods. For example, the PEG linker may have a weight that is between 5 and 500 Daltons. In some embodiments, a PEG linker having a weight that is between 500 and 1,000 Dalton may be used. In some embodiments, a PEG linker having a weight that is between 1,000 and 10,000 Dalton may be used. In some embodiments, a PEG linker having a weight that is between 200 and 20,000 Dalton may be used. In some embodiments, the linker is covalently attached to a sense strand of the siRNA. In some embodiments, the linker is covalently attached to an antisense strand of the siRNA. In some embodiments, the PEG linker is a triethylene glycol (TrEG) linker. In some embodiments, the PEG linker is a tetraethylene glycol (TEG) linker.

[0185] In some embodiments, the linker is an alkyl chain linker. In some embodiments, the linker is a peptide linker. In some embodiments, the linker is an RNA linker. In some embodiments, the linker is a DNA linker.

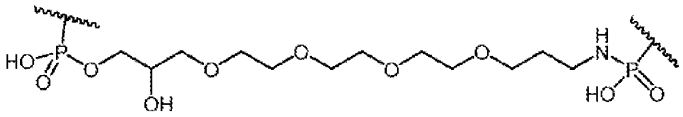
[0186] Linkers may covalently link 2, 3, 4, or 5 unique siRNA strands. The linker may covalently bind to any part of the siRNA oligomer. In some embodiments, the linker attaches to the 3′ end of nucleosides of each siRNA strand. In some embodiments, the linker attaches to the 5′ end of nucleosides of each siRNA strand. In some embodiments, the linker attaches to a nucleoside of an siRNA strand (e.g., sense or antisense strand) by way of a covalent bond-forming moiety. In some embodiments, the covalent-bond-forming moiety is selected from the group consisting of an alkyl, ester, amide, carbonate, carbamate, triazole, urea, formacetal, phosphonate, phosphate, and phosphate derivative (e.g., phosphorothioate, phosphoramidate, etc.). In certain embodiments the linker is a divalent oligonucleotide (DIO) linker.

[0187] In some embodiments, the linker has a structure of Formula L1:



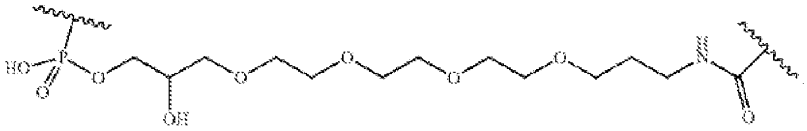
(Formula L1)

[0188] In some embodiments, the linker has a structure of Formula L2:



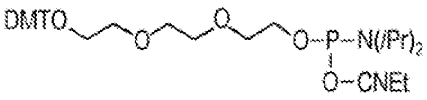
(**Formula L2**)

[0189] In some embodiments, the linker has a structure of Formula L3:



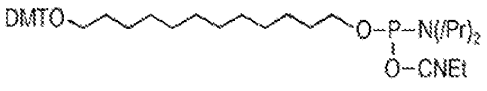
(**Formula L3**)

[0190] In some embodiments, the linker has a structure of Formula L4:



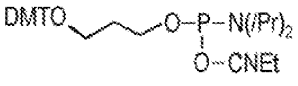
(**Formula L4**)

[0191] In some embodiments, the linker has a structure of Formula L5:



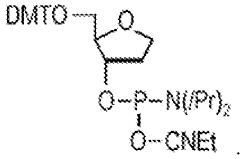
(**Formula L5**)

[0192] In some embodiments, the linker has a structure of Formula L6:



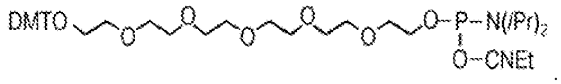
(**Formula L6**)

[0193] In some embodiments, the linker has a structure of Formula L7, as is shown below:



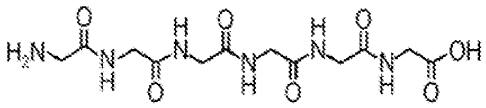
(**Formula L7**)

[0194] In some embodiments, the linker has a structure of Formula L8:



(Formula L8)

[0195] In some embodiments, the linker has a structure of Formula L9:



(Formula L9)

[0196] In some embodiments, the selection of a linker for use with one or more of the branched siRNA molecules disclosed herein may be based on the hydrophobicity of the linker, such that, e.g., desirable hydrophobicity is achieved for the one or more branched siRNA molecules of the disclosure. For example, a linker containing an alkyl chain may be used to increase the hydrophobicity of the branched siRNA molecule as compared to a branched siRNA molecule having a less hydrophobic linker or a hydrophilic linker.

[0197] The siRNA agents disclosed herein may be synthesized and/or modified by methods well established in the art, such as those described in Beaucage, S. L. et al. (edrs.), *Current Protocols in Nucleic Acid Chemistry*, John Wiley & Sons, Inc., New York, N.Y., 2000, which is hereby incorporated herein by reference.

5.8. Methods of Treatment

[0198] The *SNCA*-targeting siRNA molecules of the disclosure may be delivered to a subject, thereby treating a synucleinopathy. In certain embodiments, the synucleinopathy is Parkinson's disease, Alzheimer's disease, Lewy body dementia, multiple symptom atrophy, or any other medical risk(s) associated with the *SNCA* gene. For example, the siRNA molecules may be delivered to a subject, thereby treating a synucleinopathy and/or mitigating synucleinopathy associated phenotypes. Exemplary synucleinopathies include Parkinson's disease, Alzheimer's disease, Lewy body dementia, multiple symptom atrophy, or any other medical risk(s) associated with the *SNCA* gene. Furthermore, the siRNA molecules of the disclosure may also be delivered to a subject having a variant of the *SNCA* gene for which siRNA-mediated gene silencing of the *SNCA* variant gene reduces the expression level of *SNCA* transcript, thereby treating a synucleinopathy, e.g., Parkinson's disease, Alzheimer's disease, Lewy body dementia, multiple symptom atrophy, or any other medical risk(s) associated with the *SNCA* gene.

[0199] The disclosure provides methods of treating a subject by way of *SNCA* gene silencing with one or more of the siRNA molecules described herein. The gene silencing may be performed in a subject to silence wild type *SNCA* transcripts, mutant *SNCA* transcripts, splice isoforms of *SNCA* transcripts, and/or overexpressed *SNCA* transcripts thereof, relative to a healthy subject. The method may include delivering to the CNS or affected tissues of the subject (e.g., a human) the siRNA molecules of the disclosure or a pharmaceutical composition containing the same by any appropriate route of administration (e.g., intracerebroventricular, intrathecal injection, intrastriatal injection, intra-cisterna magna injection by catheterization, intraparenchymal injection, intravenous injection, subcutaneous injection, or intramuscular injection). The active compound can be administered in any suitable dose. The actual dosage amount of a composition of the present disclosure administered to a patient can be determined by physical and physiological factors such as body weight, severity of condition, previous or concurrent therapeutic interventions, idiopathy of the patient and on the route of administration. Depending upon the dosage and the route of administration, the number of administrations of an exemplary dosage and/or an effective amount may vary according to the response of the subject. The practitioner responsible for administration will, in any event, determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject. Administration may occur any suitable number of times per day, and for as long as necessary. Subjects may be adult or pediatric humans, with or without comorbid diseases.

5.8.1. Selection of Subjects

[0200] Subjects that may be treated with the siRNA molecules disclosed herein are subjects in need of treatment of, for example, a synucleinopathy. In certain embodiments, the synucleinopathy is Parkinson's disease, Alzheimer's disease, Lewy body dementia, multiple symptom atrophy, or any other medical risk(s) associated with the *SNCA* gene. Subjects that may be treated with the siRNA molecules disclosed herein may include, for example, humans, monkeys, rats, mice, pigs, and other mammals containing at least one orthologous copy of the *SNCA* gene. Subjects may be adult or pediatric humans, with or without comorbid diseases.

5.8.2. Pharmaceutical Compositions

[0201] The siRNA molecules in the present disclosure may be formulated into a pharmaceutical composition for administration to a subject in a biologically compatible form suitable for administration *in vivo*. Accordingly, the present disclosure provides a

pharmaceutical composition containing a siRNA molecule of the disclosure in admixture with a suitable diluent, carrier, or excipient. The siRNA molecules may be administered, for example, directly into the CNS or affected tissues of the subject (e.g., by way of intracerebroventricular, intrastriatally, intrathecal injection, intra-cisterna magna injection by catheterization, intraparenchymal injection, intravenous injection, subcutaneous injection, or intramuscular injection).

[0202] Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington, J.P. *The Science and Practice of Pharmacy*, Easton, PA. Mack Publishers, 2012, 22nd ed. and in The United States Pharmacopeial Convention, *The National Formulary*, United States Pharmacopeial, 2015, USP 38 NF 33).

[0203] Under ordinary conditions of storage and use, a pharmaceutical composition may contain a preservative, e.g., to prevent the growth of microorganisms. Pharmaceutical compositions may include sterile aqueous solutions, dispersions, or powders, e.g., for the extemporaneous preparation of sterile solutions or dispersions. In all cases the form may be sterilized using techniques known in the art and may be fluidized to the extent that may be easily administered to a subject in need of treatment.

[0204] A pharmaceutical composition may be administered to a subject, e.g., a human subject, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which may be determined by the solubility and/or chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

5.8.3. Dosing Regimens

[0205] A physician having ordinary skill in the art can readily determine an effective amount of the siRNA molecule for administration to a mammalian subject (e.g., a human) in need thereof. For example, a physician could start prescribing doses of one the siRNA molecules of the disclosure at levels lower than that required to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. Alternatively, a physician may begin a treatment regimen by administering one of the siRNA molecules of the disclosure at a high dose and subsequently administer progressively lower doses until reaching a minimal dosage at which a therapeutic effect is achieved (e.g., a reduction in expression of a target gene sequence). In general, a suitable daily dose of one of the siRNA molecules of the disclosure

will be an amount of the siRNA molecule which is the lowest dose effective to produce a therapeutic effect. The ss- or ds-siRNA molecules of the disclosure may be administered by injection, e.g., intrathecally, intracerebroventricularly, by intra-cisterna magna injection by catheterization, intraparenchy-mally, intravenously, subcutaneously, or intramuscularly. A daily dose of a therapeutic composition of the siRNA molecules of the disclosure may be administered as a single dose or as two, three, four, five, six or more doses administered separately at appropriate intervals throughout the day, week, month, or year, optionally, in unit dosage forms. While it is possible for the siRNA molecules of the disclosure to be administered alone, it may also be administered as a pharmaceutical formulation in combination with excipients, carriers, and optionally, additional therapeutic agents.

5.8.4. Routes of Administration

[0206] The method of the disclosure contemplates any route of administration tolerated by the therapeutic composition. Some embodiments of the method include injection intrathecally, intracerebroventricularly, intrastriatally, intraparenchymally, or by intra-cisterna magna injection by catheterization.

[0207] Intrathecal injection is the direct injection into the spinal column or subarachnoid space. By injecting directly into the CSF of the spinal column the siRNA molecules of the disclosure have direct access to cells (e.g., neurons and glial cells) in the spinal column and a route to access the cells in the brain by bypassing the blood brain barrier.

[0208] Intracerebroventricular (ICV) injection is a method to directly inject into the CSF of the cerebral ventricles. Similar to intrathecal injection, ICV is a method of injection which bypasses the blood brain barrier. Using ICV allows the advantage of access to the cells of the brain and spinal column without the danger of the therapeutic being degraded in the blood.

[0209] Intrastriatal injection is the direct injection into the striatum, or corpus striatum. The striatum is an area in the subcortical basal ganglia in the brain. Injecting into the striatum bypasses the blood brain barrier and the pharmacokinetic challenges of injection into the blood stream and allows for direct access to the cells of the brain.

[0210] Intraparenchymal administration is the direct injection into the parenchyma (e.g., the brain parenchyma). Injection into the brain parenchyma allows for injection directly into brain regions affected by a disease or disorder while bypassing the blood brain barrier.

[0211] Intra-cisterna magna injection by catheterization is the direct injection into the cisterna magna. The cisterna magna is the area of the brain located between the cerebellum and the

dorsal surface of the medulla oblongata. Injecting into the cisterna magna results in more direct delivery to the cells of the cerebellum, brainstem, and spinal cord.

[0212] In some embodiments of the methods described herein, the therapeutic composition may be delivered to the subject by way of systemic administration, e.g., intravenously, intramuscularly, or subcutaneously.

[0213] Intravenous (IV) injection is a method to directly inject into the bloodstream of a subject. The IV administration may be in the form of a bolus dose or by way of continuous infusion, or any other method tolerated by the therapeutic composition.

[0214] Intramuscular (IM) injection is injection into a muscle of a subject, such as the deltoid muscle or gluteal muscle. IM may allow for rapid absorption of the therapeutic composition.

[0215] Subcutaneous injection is injection into subcutaneous tissue. Absorption of compositions delivered subcutaneously may be slower than IV or IM injection, which may be beneficial for compositions requiring continuous absorption.

6. ENUMERATED EMBODIMENTS OF THE DISCLOSURE

[0216] The compositions, methods, and kits described herein include the following non-limiting, exemplary, enumerated embodiments of the disclosure. In some embodiments, the disclosure provides:

Embodiment 1. A small interfering RNA (siRNA) molecule comprising an antisense strand and sense strand having complementarity to the antisense strand, wherein the antisense strand is from 10 to 30 nucleotides in length and has complementarity sufficient to hybridize to a region within an alpha-synuclein (*SNCA*) mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 2. The siRNA molecule of embodiment 1, wherein the antisense strand has at least 70% complementarity to a region of 21 contiguous nucleobases within the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 3. The siRNA molecule of embodiment 2, wherein the antisense strand has at least 75% complementarity to a region of 21 contiguous nucleobases within the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840, optionally wherein the antisense strand has at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementarity to the region within the 421-840 mRNA transcript having the nucleic acid sequence of any one of SEQ ID Nos: 421-840.

Embodiment 4. The siRNA molecule of any one of embodiments 1-3, wherein the antisense strand comprises at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 5. The siRNA molecule of embodiment 4, wherein the antisense strand comprises from 10 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 6. The siRNA molecule of embodiment 5, wherein the antisense strand comprises from 12 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 7. The siRNA molecule of embodiment 6, wherein the antisense strand comprises from 15 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 8. The siRNA molecule of embodiment 7, wherein the antisense strand comprises from 18 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 9. The siRNA molecule of embodiment 8, wherein the antisense strand comprises from 21 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 10. The siRNA molecule of any one of embodiments 1-9, wherein the antisense strand comprises from 24 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 11. The siRNA molecule of embodiment 10, wherein the antisense strand comprises 30 contiguous nucleotides that are fully complementary to a contiguous

polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 12. The siRNA molecule of any one of embodiments 1-11, wherein the antisense strand comprises 9 or fewer nucleotide mismatches relative to a region of 21 contiguous nucleobases of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840, optionally wherein the antisense strand comprises 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or only 1 mismatch relative to the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 13. The siRNA molecule of any one of embodiments 1-12, wherein the region of the *SNCA* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 459, 535, 551, 599, 631, 663, 664, 666, 667, 671, 748, 750, 751, 752, 760, 762, and 777.

Embodiment 14. The siRNA molecule of embodiment 13, wherein the region of the *SNCA* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 535, 599, 664, 666, 671, 750, 752, 760, and 762.

Embodiment 15. The siRNA molecule of any one of embodiments 1-14, wherein the antisense strand has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

Embodiment 16. The siRNA molecule of embodiment 15, wherein the antisense strand has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

Embodiment 17. The siRNA molecule of embodiment 16, wherein the antisense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 1-420, optionally wherein the antisense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

Embodiment 18. The siRNA molecule of embodiment 17, wherein the antisense strand has the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

Embodiment 19. The siRNA molecule of any one of embodiments 15-18, wherein the nucleic acid sequence is any one of SEQ ID NOs: 39, 115, 131, 179, 211, 243, 244, 246, 247, 251, 328, 330, 331, 332, 340, 342, and 357.

Embodiment 20. The siRNA molecule of embodiment 19, wherein the nucleic acid sequence is any one of SEQ ID NOs: 115, 179, 244, 246, 251, 330, 332, 340, and 342.

Embodiment 21. The siRNA molecule of any one of embodiments 1-20, wherein the sense strand has a nucleic acid sequence that is at least 85% identical to the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 22. The siRNA molecule of embodiment 21, wherein the sense strand has a nucleic acid sequence that is at least 90% identical to the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 23. The siRNA molecule of embodiment 22, wherein the sense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 421-840, optionally wherein the sense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 24. The siRNA molecule of embodiment 23, wherein the sense strand has the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

Embodiment 25. The siRNA molecule of any one of embodiments 21-24, wherein the nucleic acid sequence is any one of SEQ ID NOs: 459, 535, 551, 599, 631, 663, 664, 666, 667, 671, 748, 750, 751, 752, 760, 762, and 777.

Embodiment 26. The siRNA molecule of embodiment 25, wherein the nucleic acid sequence is any one of SEQ ID NOs: 535, 599, 664, 666, 671, 750, 752, 760, and 762.

Embodiment 27. The siRNA molecule of any one of embodiments 1-26, wherein the antisense strand comprises a structure represented by Formula I, wherein Formula I is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C'\text{-}P^1)_k\text{-}C'$$

Formula I;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;

each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7; and

k is an integer from 1 to 7.

Embodiment 28. The siRNA molecule of embodiment 27, wherein the antisense strand comprises a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 29. The siRNA molecule of any one of embodiments 1-26, wherein the antisense strand comprises a structure represented by Formula II, wherein Formula II is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula II;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;

each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7; and

k is an integer from 1 to 7.

Embodiment 30. The siRNA molecule of embodiment 29, wherein the antisense strand comprises a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-A-S-A

Formula A2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 31. The siRNA molecule of any one of embodiments 1-30, wherein the sense strand comprises a structure represented by Formula III, wherein Formula III is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}F$$

Formula III;

wherein E is represented by the formula $(C\text{-}P^1)_2$;

F is represented by the formula $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $(C\text{-}P^2)_3\text{-}D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $(C\text{-}P^2)_3\text{-}D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;

A', C, D, P^1, and P^2 are as defined in Formula II; and

m is an integer from 1 to 7.

Embodiment 32. The siRNA molecule of embodiment 31, wherein the sense strand comprises a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-A

Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 33. The siRNA molecule of embodiment 31, wherein the sense strand comprises a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-A

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 34. The siRNA molecule of embodiment 31, wherein the sense strand comprises a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-B

Formula S3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 35. The siRNA molecule of embodiment 31, wherein the sense strand comprises a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-B

Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 36. The siRNA molecule of any one of embodiments 1-26 and 31-35, wherein the antisense strand comprises a structure represented by Formula IV, wherein Formula IV is, in the 5'-to-3' direction:

$A\text{-}(A')_j\text{-}C\text{-}P^2\text{-}B\text{-}(C\text{-}P^1)_k\text{-}C'$

Formula IV;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;

B is represented by the formula D-P^1-C-P^1-D-P^1;

each C is a 2'-O-Me ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7; and

k is an integer from 1 to 7.

Embodiment 37. The siRNA molecule of embodiment 36, wherein the antisense strand comprises a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B-S-A-S-A-S-A

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 38. The siRNA molecule of any one of embodiments 1-30, 36, and 37, wherein the sense strand comprises a structure represented by Formula V, wherein Formula V is, in the 5'-to-3' direction:

E-(A')$_m$-C-P^2-F

Formula V;

wherein E is represented by the formula (C-P^1)$_2$;

F is represented by the formula D-P^1-C-P^1-C, D-P^2-C-P^2-C, D-P^1-C-P^1-D, or D-P^2-C-P^2-D;

A', C, D, P^1 and P^2 are as defined in Formula IV; and

m is an integer from 1 to 7.

Embodiment 39. The siRNA molecule of embodiment 38, wherein the sense strand comprises a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A

Formula S5;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 40. The siRNA molecule of embodiment 38, wherein the sense strand comprises a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A

Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 41. The siRNA molecule of embodiment 38, wherein the sense strand comprises a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B

Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 42. The siRNA molecule of embodiment 38, wherein the sense strand comprises a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B

Formula S8;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 43. The siRNA molecule of any one of embodiments 1-26, 31-35 and 38-42, wherein the antisense strand comprises a structure represented by Formula VI, wherein Formula VI is, in the 5'-to-3' direction:

$$A\text{-}B_j\text{-}E\text{-}B_k\text{-}E\text{-}F\text{-}G_l\text{-}D\text{-}P^1\text{-}C'$$

Formula VI;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;

each B is represented by the formula $C\text{-}P^2$;

each C is a 2'-O-Me ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each E is represented by the formula $D\text{-}P^2\text{-}C\text{-}P^2$;

F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1$;

each G is represented by the formula $C\text{-}P^1$;

each P^1 is a phosphorothioate internucleoside linkage;

each P^2 is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7;

k is an integer from 1 to 7; and

l is an integer from 1 to 7.

Embodiment 44. The siRNA molecule of embodiment 43, wherein the antisense strand comprises a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:

A-S-B-S-A-O-A-O-A-O-B-O-A-O-A-O-A-O-A-O-A-O-A-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

Embodiment 45. The siRNA molecule of any one of embodiments 1-30, 36, 37, 43, and 44, wherein the sense strand comprises a structure represented by Formula VII, wherein Formula VII is, in the 5'-to-3' direction:

$$H\text{-}B_m\text{-}I_n\text{-}A'\text{-}B_o\text{-}H\text{-}C$$

Formula VII;

wherein A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
each H is represented by the formula $(C\text{-}P^1)_2$;
each I is represented by the formula $(D\text{-}P^2)$;
B, C, D, P^1 and P^2 are as defined in Formula VI;
m is an integer from 1 to 7;
n is an integer from 1 to 7; and
o is an integer from 1 to 7.

Embodiment 46. The siRNA molecule of embodiment 45, wherein the sense strand comprises a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:

A-S-A-S-A-O-A-O-A-O-B-O-B-O-B-O-A-O-B-O-A-O-A-O-A-O-A-S-A-S-A

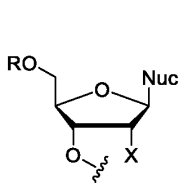
Formula S9;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

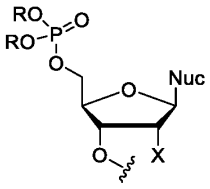
Embodiment 47. The siRNA molecule of any one of embodiments 1-46, wherein the antisense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the antisense strand.

Embodiment 48. The siRNA molecule of any one of embodiments 1-47, wherein the sense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the sense strand.

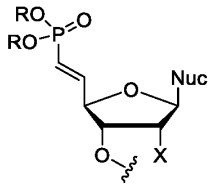
Embodiment 49. The siRNA molecule of embodiment 47 or 48, wherein each 5' phosphorus stabilizing moiety is, independently, represented by any one of Formulas IX-XVI:



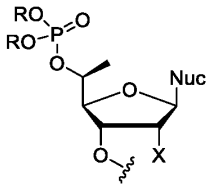
Formula IX



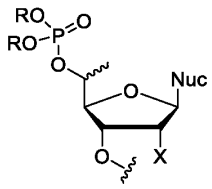
Formula X



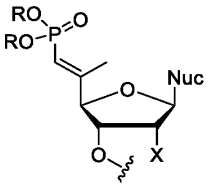
Formula XI



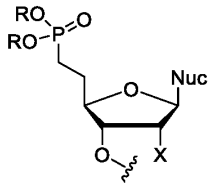
Formula XII



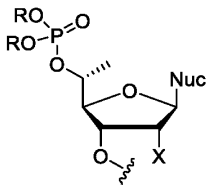
Formula XIII



Formula XIV



Formula XV



Formula XVI

wherein Nuc represents a nucleobase selected from the group consisting of adenine, uracil, guanine, thymine, and cytosine, and R represents an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, phenyl, benzyl, hydroxy, or hydrogen.

Embodiment 50. The siRNA molecule of embodiment 49, wherein the nucleobase is an adenine, uracil, guanine, thymine, or cytosine.

Embodiment 51. The siRNA molecule of any one of embodiments 47-50, wherein the 5' phosphorus stabilizing moiety is (E)-vinylphosphonate represented by Formula XI.

Embodiment 52. The siRNA molecule of any one of embodiments 1-51, wherein the siRNA molecule further comprises a hydrophobic moiety at the 5' or the 3' end of the siRNA molecule.

Embodiment 53. The siRNA molecule of embodiment 52, wherein the hydrophobic moiety is selected from a group consisting of cholesterol, vitamin D, or tocopherol.

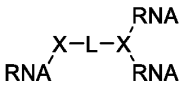
Embodiment 54. The siRNA molecule of any one of embodiments 1-53, wherein the length of the sense strand is between 12 and 30 nucleotides.

Embodiment 55. The siRNA molecule of any one of embodiments 1-54, wherein the siRNA molecule is a branched siRNA molecule.

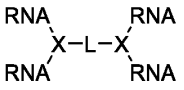
Embodiment 56. The siRNA molecule of embodiment 55, wherein the branched siRNA molecule is di-branched, tri-branched, or tetra-branched.

Embodiment 57. The siRNA molecule of embodiment 56, wherein the siRNA molecule is a di-branched siRNA molecule, optionally wherein the di-branched siRNA molecule is represented by any one of Formulas XVII-XIX:

Formula XVII;



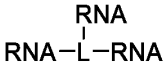
Formula XVIII;



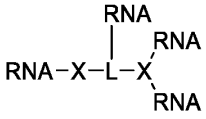
Formula XIX;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

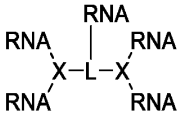
Embodiment 58. The siRNA molecule of embodiment 56, wherein the siRNA molecule is a tri-branched siRNA molecule, optionally wherein the tri-branched siRNA molecule is represented by any one of Formulas XX-XXIII:



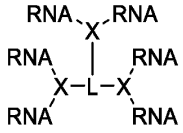
Formula XX;



Formula XXI;



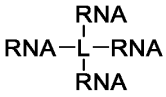
Formula XXII;

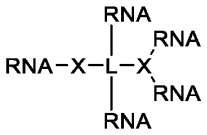


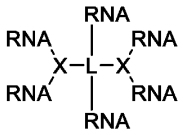
Formula XXIII;

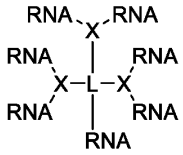
wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

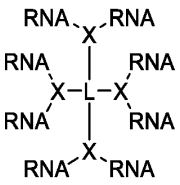
Embodiment 59. The siRNA molecule of embodiment 56, wherein the siRNA molecule is a tetra-branched siRNA molecule, optionally wherein the tetra-branched siRNA molecule is represented by any one of Formulas XXIV-XXVIII:











Formula XXIV; **Formula XXV;** **Formula XXVI;** **Formula XXVII;** **Formula XXVIII;**

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

Embodiment 60. The siRNA molecule of any one of embodiments 57-59, wherein the linker is selected from a group consisting of one or more contiguous subunits of an ethylene glycol, alkyl, carbohydrate, block copolymer, peptide, RNA, and DNA.

Embodiment 61. The siRNA molecule of embodiment 60, wherein the one or more contiguous subunits is 2 to 20 contiguous subunits.

Embodiment 62. An siRNA molecule comprising:

(I)

a) a sense strand comprising the sequence (mU)#(mA)#(mC)(fC)(mA)(fC)(mU)(fU)(mA)(fU)(mU)(mU)(mC)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 841) and an antisense strand comprising the sequence V(mU)#(fU)#(mA)(fG)(fA)(fA)(mA)(fU)(mA)(fA)(mG)(fU)(mG)(fG)(mU)(fA)#(mG)#(mU)#(mC)#(mA)#(mC) (SEQ ID NO: 842);

b) a sense strand comprising the sequence (mC)#(mA)#(mA)(fG)(mU)(fG)(mC)(fU)(mC)(fA)(mG)(mU)(mU)(fC)#(mC)# (mA)-DIO (SEQ ID NO: 843) and an antisense strand comprising the sequence V(mU)#(fG)#(mG)(fA)(fA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)(mU)(fG)#(mU)#(mA)#(mC)#(mA)#(mG) (SEQ ID NO: 844);

c) a sense strand comprising the sequence (mA)#(mG)#(mU)(fG)(mG)(fU)(mG)(fC)(mA)(fU)(mG)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 845) and an antisense strand comprising the sequence V(mU)#(fA)#(mC)(fA)(fC)(fC)(mA)(fU)(mG)(fC)(mA)(fC)(mC)(fA)(mC)(fU)#(mC)#(mC)#(mC)#(mU)#(mC) (SEQ ID NO: 846).

d) a sense strand comprising the sequence (mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC)(fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 848);

e) a sense strand comprising the sequence (mU)#(mC)#(mA)(fG)(mU)(fU)(mC)(fC)(mA)(fA)(mU)(mG)(mU)(fG)#(mC)#(mA)-DIO (SEQ ID NO: 849) and an antisense strand comprising the sequence

V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)
(fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 850).

f) a sense strand comprising the sequence
(mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)
(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 851) and an antisense strand comprising the sequence
V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU)(mG)
(fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852); or

g) a sense strand comprising the sequence
(mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)
(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 853) and an antisense strand comprising the sequence
V(mU)#(fG)#(mU)(fU)(fU)(fU)(mA)(fA)(mC)(fA)(mU)(fC)(mG)(fU)
(mA)(fG)#(mA)#(mU)#(mU)#(mG)#(mA) (SEQ ID NO: 854);

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate; or

(II)

a) a sense strand comprising the sequence
(mU)#(mA)#(mC)(fC)(mA)(fC)(mU)(fU)(mA)
(fU)(mU)(mU)(mC)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 841) and an antisense strand comprising the sequence
V(mU)#(fU)#(mA)(fG)(fA)(fA)(mA)(fU)(mA)(fA)(mG)(fU)(mG)(fG)
(mU)(fA)#(mG)#(mU)#(mC)#(mA)#(mC) (SEQ ID NO: 842);

b) a sense strand comprising the sequence (mC)#(mA)#(mA)(fG)(mU)(fG)(mC)(fU)
(mC)(fA)(mG)(mU)(mU)(fC)#(mC)# (mA)-DIO (SEQ ID NO: 843) and an antisense strand comprising the sequence
V(mU)#(fG)#(mG)(fA)(fA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)(mU)
(fG)#(mU)#(mA)#(mC)#(mA)#(mG) (SEQ ID NO: 844);

c) a sense strand comprising the sequence
(mA)#(mG)#(mU)(fG)(mG)(fU)(mG)(fC)(mA)
(fU)(mG)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 845) and an antisense strand comprising the sequence

V(mU)#(fA)#(mC)(fA)(fC)(fC)(mA)(fU)(mG)(fC)(mA)(fC)(mC)(fA)(mC)(fU)#(mC)#(mC)#(mC)#(mU)#(mC) (SEQ ID NO: 846).

d) a sense strand comprising the sequence (mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC)(fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847) and an antisense strand comprising the sequence V(mU)#(fU)#(mC)(fA)(fU)(fA)(mA)(fG)(mC)(fC)(mU)(fC)(mA)(fU)(mU)(fG)#(mU)#(mC)#(mA)#(mG)#(mG) (SEQ ID NO: 855)

e) a sense strand comprising the sequence (mA)#(mG)#(mU)(fG)(mC)(fU)(mC)(fA)(mG)(fU)(mU)(mC)(mC)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 856) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 850).

f) a sense strand comprising the sequence (mU)#(mC)#(mA)(fG)(mU)(fU)(mC)(fC)(mA)(fA)(mU)(mG)(mU)(fG)#(mC)#(mA)-DIO (SEQ ID NO: 857) and an antisense strand comprising the sequence V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU)(mG)(fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852); or

g) a sense strand comprising the sequence (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 853) and an antisense strand comprising the sequence V(mU)#(fG)#(mU)(fU)(fU)(fU)(mA)(fA)(mC)(fA)(mU)(fC)(mG)(fU)(mA)(fG)#(mA)#(mU)#(mU)#(mG)#(mA) (SEQ ID NO: 854);

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate

Embodiment 63. A pharmaceutical composition comprising the siRNA molecule of any one of embodiments 1-62 and a pharmaceutically acceptable excipient, carrier, or diluent.

Embodiment 64. A method of delivering an siRNA molecule to a subject diagnosed as having an , the method comprising administering a therapeutically effective amount of the siRNA molecule of any one of embodiments 1-62 or the pharmaceutical composition of embodiment 63 to the subject.

Embodiment 65. A method of treating a synucleinopathy in a subject in need thereof, the method comprising administering a therapeutically effective amount of the siRNA molecule of any one of embodiments 1-62 or the pharmaceutical composition of embodiment 63 to the subject.

Embodiment 66. The method of embodiment 65, wherein the synucleinopathy is Parkinson's disease.

Embodiment 67. The method of embodiment 65, wherein the synucleinopathy is Alzheimer's disease.

Embodiment 68. The method of embodiment 65, wherein the synucleinopathy is Lewy body dementia.

Embodiment 69. The method of embodiment 65, wherein the synucleinopathy is a multiple symptom atrophy.

Embodiment 70. A method of reducing *SNCA* expression in a subject in need thereof, the method comprising administering a therapeutically effective amount of the siRNA molecule of any one of embodiments 1-62 or the pharmaceutical composition of embodiment 63 to the subject.

Embodiment 71. The method of any one of embodiments 64-70, wherein the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intracerebroventricular, intrastriatal, intraparenchymal, or intrathecal injection.

Embodiment 72. The method of any one of embodiments 64-71, wherein the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intravenous, intramuscular, or subcutaneous injection.

Embodiment 73. The method of any one of embodiments 64-72, wherein the subject is a human.

Embodiment 74. A kit comprising the siRNA molecule of any one of embodiments 1-62, or the pharmaceutical composition of embodiment 63, and a package insert, wherein the package insert instructs a user of the kit to perform the method of any one of embodiments 64-73.

7. EXAMPLES

[0217] The following examples are put forth so as to provide those of ordinary skill in the art with a description of how the compositions and methods described herein may be used, made, and evaluated, and are intended to be purely exemplary of the disclosure and are not intended to limit the scope of what the inventors regard as their disclosure

Example 1. In Vitro Screening

[0218] In vitro screening was performed using human MeWo cells in a 96-well format. Briefly, cholesterol-conjugated, mono-siRNA was passively administered to cells in culture for 72 hours at 2 uM or 0.5 uM concentrations (single point format) or at serial 1:2.5 dilutions from 3 uM to 0.00196608 uM (IC50 format). Cells were lysed using the Cells-to-Ct kit (Thermo) and quantitative reverse transcriptase polymerase change reaction (QRT-PCR) was performed to assess target (SNCA) gene expression relative to housekeeping (ATP5B) gene expression using TaqMan primer/probes and Fast Advanced master mix (Thermo). Data are presented as mean % SNCA target expression (N=2-3 biological replicates, 2 technical replicates each) relative to untreated control cells, where 100% represents no knockdown and 0% represents complete target knockdown.

Table 2. ***In Vitro*** **Screening**

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_166	166	UAGGCUUGAAG GCAAGGCGUG	1	CUUGCCUUCA AGCCUA	421	AT1146-1147	60.79	0.65	86.06	1.65	
SNCA_171	171	UGCAGAAGGCU UGAAGGCAAG	2	CUUCAAGCCU UCUGCA	422	AT1148-1149	90.93	5.08	108.60	6.30	
SNCA_173	173	UAGGCAGAAGG CUUGAAGGCA	3	UCAAGCCUUC UGCCUA	423	AT1150-1151	85.96	1.71	108.24	2.21	
SNCA_174	174	UAAGGCAGAAG GCUUGAAGGC	4	CAAGCCUUCU GCCUUA	424	AT1098-1099	34.26	1.08			
SNCA_175	175	UAAAGGCAGAA GGCUUGAAGG	5	AAGCCUUCUG CCUUUA	425	AT1152-1153	93.45	0.11	120.23	1.66	
SNCA_176	176	UGAAAGGCAGA AGGCUUGAAG	6	AGCCUUCUGC CUUUCA	426	AT1154-1155	205.29	2.58	111.23	2.90	
SNCA_178	178	UUGGAAAGGCA GAAGGCUUGA	7	CCUUCUGCCU UUCCAA	427	AT1156-1157	94.92	2.50	90.56	0.32	
SNCA_179	179	UGUGGAAAGGC AGAAGGCUUG	8	CUUCUGCCUU UCCACA	428	AT1100-1101	56.88	0.11			
SNCA_187	187	UUCACGAGGGU GGAAAGGCAG	9	UUUCCACCCU CGUGAA	429	AT1102-1103	69.08	1.96			
SNCA_189	189	UGCUCACGAGG GUGGAAAGGC	10	UCCACCCUCG UGAGCA	430	AT1158-1159	94.08	1.55	104.85	0.21	
SNCA_217	217	UGUCGUCGAAU GGCCACUCCC	11	UGGCCAUUCG ACGACA	431	AT1160-1161	65.34	0.43	92.52	2.97	
SNCA_234	234	UUUCCUUUACA CCACACUGUC	12	UGUGGUGUA AAGGAAA	432	AT1162-1163	23.57	0.09	57.33	0.85	716
SNCA_235	235	UAUUCCUUUAC ACCACACUGU	13	GUGGUGUAA AGGAAUA	433	AT2116-2117	106.19	4.42	105.07	5.23	
SNCA_236	236	UAAUUCCUUUA CACCACACUG	14	UGGUGUAAA GGAAUUA	434	AT2118-2119	47.75	2.11	72.51	6.30	
SNCA_239	239	UAUGAAUUCCU UUACACCACA	15	UGUAAAGGA AUUCAUA	435	AT2120-2121	64.98	6.66	77.69	9.36	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_240	240	UAAUGAAUUCC UUUACACCAC	16	GUAAAGGAA UUCAUUA	436	AT2122-2123	48.02	3.20	71.47	9.83	
SNCA_241	241	UUAAUGAAUUC CUUUACACCA	17	UAAAGGAAU UCAUUAA	437	AT1164-1165	35.89	1.58	58.00	1.56	
SNCA_242	242	UCUAAUGAAUU CCUUUACACC	18	AAAGGAAUU CAUUAGA	438	AT1166-1167	21.20	0.14	47.77	0.27	457
SNCA_243	243	UGCUAAUGAAU UCCUUUACAC	19	AAGGAAUUC AUUAGCA	439	AT2124-2125	63.15	6.66	96.76	0.17	
SNCA_244	244	UGGCUAAUGAA UUCCUUUACA	20	AGGAAUUCA UUAGCCA	440	AT2126-2127	75.07	6.61	92.32	15.47	
SNCA_245	245	UUGGCUAAUGA AUUCCUUUAC	21	GGAAUUCAU UAGCCAA	441	AT2128-2129	77.66	4.49	95.06	8.84	
SNCA_246	246	UAUGGCUAAUG AAUUCCUUUA	22	GAAUUCAUU AGCCAUA	442	AT1650-1651	58.23	0.66	90.15	1.29	
SNCA_249	249	UUCCAUGGCUA AUGAAUUCCU	23	UUCAUUAGC CAUGGAA	443	AT1168-1169	63.13	0.70	79.57	1.16	
SNCA_250	250	UAUCCAUGGCU AAUGAAUUCC	24	UCAUUAGCCA UGGAUA	444	AT1170-1171	54.85	1.88	85.68	0.63	
SNCA_253	253	UUACAUCCAUG GCUAAUGAAU	25	UUAGCCAUG GAUGUAA	445	AT2130-2131	64.82	6.79	93.12	15.20	
SNCA_254	254	UAUACAUCCAU GGCUAAUGAA	26	UAGCCAUGG AUGUAUA	446	AT2132-2133	66.27	5.24	87.78	0.06	
SNCA_255	255	UAAUACAUCCA UGGCUAAUGA	27	AGCCAUGGA UGUAUUA	447	AT2134-2135	116.47	0.80	105.35	11.75	
SNCA_256	256	UGAAUACAUCC AUGGCUAAUG	28	GCCAUGGAUG UAUUCA	448	AT2136-2137	119.83	5.61	106.24	12.00	
SNCA_257	257	UUGAAUACAUC CAUGGCUAAU	29	CCAUGGAUG UAUUCAA	449	AT1104-1105	40.90	1.33			
SNCA_258	258	UAUGAAUACAU CCAUGGCUAA	30	CAUGGAUGU AUUCAUA	450	AT2138-2139	46.61	0.29	74.07	2.07	
SNCA_259	259	UCAUGAAUACA UCCAUGGCUA	31	AUGGAUGUA UUCAUGA	451	AT2140-2141	136.51	1.61	112.33	6.00	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_260	260	UUCAUGAAUAC AUCCAUGGCU	32	UGGAUGUAU UCAUGAA	452	AT1172-1173	31.88	0.22	50.79	0.08	
SNCA_261	261	UUUCAUGAAUA CAUCCAUGGC	33	GGAUGUAUU CAUGAAA	453	AT1106-1107	50.77	2.25			
SNCA_262	262	UUUUCAUGAAU ACAUCCAUGG	34	GAUGUAUUC AUGAAAA	454	AT2142-2143	100.59	2.74	67.02	1.17	
SNCA_266	266	UGUCCUUUCAU GAAUACAUCC	35	UAUUCAUGA AAGGACA	455	AT2144-2145	37.55	1.05	98.53	1.33	
SNCA_267	267	UAGUCCUUUCA UGAAUACAUC	36	AUUCAUGAA AGGACUA	456	AT2146-2147	59.67	0.53	104.29	2.02	
SNCA_268	268	UAAGUCCUUUC AUGAAUACAU	37	UUCAUGAAA GGACUUA	457	AT2148-2149	81.69	0.62	105.51	4.50	
SNCA_269	269	UAAAGUCCUUU CAUGAAUACA	38	UCAUGAAAG GACUUUA	458	AT1174-1175	25.70	0.08	45.89	0.62	708
SNCA_270	270	UGAAAGUCCUU UCAUGAAUAC	39	CAUGAAAGG ACUUUCA	459	AT1602-1603	14.69	0.57	60.98	0.58	628
SNCA_273	273	UUUUGAAAGUC CUUUCAUGAA	40	GAAAGGACU UUCAAAA	460	AT1604-1605	57.37	0.00	78.50	0.22	
SNCA_274	274	UCUUUGAAAGU CCUUUCAUGA	41	AAAGGACUU UCAAAGA	461	AT2150-2151	86.36	4.36	114.74	6.41	
SNCA_275	275	UCCUUUGAAAG UCCUUUCAUG	42	AAGGACUUU CAAAGGA	462	AT2152-2153	102.04	3.18	114.68	10.27	
SNCA_276	276	UGCCUUUGAAA GUCCUUUCAU	43	AGGACUUUC AAAGGCA	463	AT2154-2155	133.52	1.90	106.61	11.42	
SNCA_277	277	UGGCCUUUGAA AGUCCUUUCA	44	GGACUUUCA AAGGCCA	464	AT1630-1631	88.34	0.35	100.13	2.14	
SNCA_278	278	UUGGCCUUUGA AAGUCCUUUC	45	GACUUUCAA AGGCCAA	465	AT2156-2157	119.41	6.64	100.60	8.08	
SNCA_279	279	UUUGGCCUUUG AAAGUCCUUU	46	ACUUUCAAA GGCCAAA	466	AT1632-1633	66.81	1.50	85.78	0.42	
SNCA_280	280	UCUUGGCCUUU GAAAGUCCUU	47	CUUUCAAAG GCCAAGA	467	AT2158-2159	95.46	0.28	104.10	2.86	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_281	281	UCCUUGGCCUU UGAAAGUCCU	48	UUUCAAAGG CCAAGGA	468	AT2160-2161	116.94	0.49	107.85	16.32	
SNCA_282	282	UUCCUUGGCCU UUGAAAGUCC	49	UUCAAAGGCC AAGGAA	469	AT1176-1177	96.59	0.28	82.66	2.56	
SNCA_283	283	UCUCCUUGGCC UUUGAAAGUC	50	UCAAAGGCCA AGGAGA	470	AT1108-1109	108.76	3.86			
SNCA_284	284	UCCUCCUUGGC CUUUGAAAGU	51	CAAAGGCCAA GGAGGA	471	AT2162-2163	140.69	0.97	115.22	8.74	
SNCA_285	285	UCCCUCCUUGG CCUUUGAAAG	52	AAAGGCCAAG GAGGGA	472	AT2164-2165	185.56	7.86	143.88	11.73	
SNCA_286	286	UUCCCUCCUUG GCCUUUGAAA	53	AAGGCCAAGG AGGGAA	473	AT2166-2167	110.71	0.62	105.21	11.12	
SNCA_287	287	UCUCCCUCCUU GGCCUUUGAA	54	AGGCCAAGGA GGGAGA	474	AT1634-1635	107.71	0.58	85.74	1.09	
SNCA_288	288	UACUCCCUCCU UGGCCUUUGA	55	GGCCAAGGAG GGAGUA	475	AT2168-2169	106.40	5.58	135.71	0.13	
SNCA_289	289	UAACUCCCUCC UUGGCCUUUG	56	GCCAAGGAGG GAGUUA	476	AT2170-2171	96.56	1.04	133.40	6.01	
SNCA_290	290	UCAACUCCCUC CUUGGCCUUU	57	CCAAGGAGGG AGUUGA	477	AT1606-1607	48.85	0.83	92.41	0.81	
SNCA_291	291	UACAACUCCCU CCUUGGCCUU	58	CAAGGAGGGA GUUGUA	478	AT2172-2173	80.42	2.58	124.00	2.22	
SNCA_292	292	UCACAACUCCC UCCUUGGCCU	59	AAGGAGGGA GUUGUGA	479	AT2174-2175	108.17	1.72	137.72	0.84	
SNCA_293	293	UCCACAACUCC CUCCUUGGCC	60	AGGAGGGAG UUGUGGA	480	AT2176-2177	96.88	2.94	134.51	7.84	
SNCA_294	294	UGCCACAACUC CCUCCUUGGC	61	GGAGGGAGU UGUGGCA	481	AT2178-2179	59.87	4.59	108.13	12.66	
SNCA_295	295	UAGCCACAACU CCCUCCUUGG	62	GAGGGAGUU GUGGCUA	482	AT2180-2181	97.08	0.02	118.65	11.58	
SNCA_296	296	UCAGCCACAAC UCCCUCCUUG	63	AGGGAGUUG UGGCUGA	483	AT2182-2183	104.02	5.15	114.71	5.20	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_297	297	UGCAGCCACAA CUCCCUCCUU	64	GGGAGUUGU GGCUGCA	484	AT2184-2185	74.38	5.15	117.53	4.32	
SNCA_298	298	UAGCAGCCACA ACUCCCUCCU	65	GGAGUUGUG GCUGCUA	485	AT1178-1179	40.32	0.22	64.27	2.23	
SNCA_299	299	UCAGCAGCCAC AACUCCCUCC	66	GAGUUGUGG CUGCUGA	486	AT2186-2187	83.82	1.70	102.30	19.14	
SNCA_300	300	UGCAGCAGCCA CAACUCCCUC	67	AGUUGUGGC UGCUGCA	487	AT1180-1181	70.62	1.19	90.22	1.33	
SNCA_301	301	UAGCAGCAGCC ACAACUCCCU	68	GUUGUGGCU GCUGCUA	488	AT2188-2189	77.56	8.86	119.96	11.48	
SNCA_302	302	UCAGCAGCAGC CACAACUCCC	69	UUGUGGCUG CUGCUGA	489	AT2190-2191	87.50	7.88	121.88	14.18	
SNCA_303	303	UUCAGCAGCAG CCACAACUCC	70	UGUGGCUGC UGCUGAA	490	AT2192-2193	49.26	3.64	96.78	5.83	695
SNCA_304	304	UCUCAGCAGCA GCCACAACUC	71	GUGGCUGCU GCUGAGA	491	AT1608-1609	93.46	0.57	99.24	3.63	
SNCA_305	305	UUCUCAGCAGC AGCCACAACU	72	UGGCUGCUGC UGAGAA	492	AT2194-2195	118.36	9.27	143.32	0.11	
SNCA_306	306	UUUCUCAGCAG CAGCCACAAC	73	GGCUGCUGCU GAGAAA	493	AT2196-2197	88.32	1.45	123.83	6.95	
SNCA_307	307	UUUUCUCAGCA GCAGCCACAA	74	GCUGCUGCUG AGAAAA	494	AT1610-1611	37.30	0.71	75.14	1.14	
SNCA_309	309	UGUUUUCUCAG CAGCAGCCAC	75	UGCUGCUGA GAAAACA	495	AT2198-2199	84.47	6.37	116.01	16.74	
SNCA_310	310	UGGUUUUCUCA GCAGCAGCCA	76	GCUGCUGAGA AAACCA	496	AT1182-1183	57.16	0.04	85.79	0.89	
SNCA_311	311	UUGGUUUUCUC AGCAGCAGCC	77	CUGCUGAGA AAACCAA	497	AT1184-1185	72.29	0.68	77.04	0.49	
SNCA_312	312	UUUGGUUUUCU CAGCAGCAGC	78	UGCUGAGAA AACCAAA	498	AT1636-1637	123.35	6.80	91.92	0.09	
SNCA_313	313	UUUUGGUUUUC UCAGCAGCAG	79	GCUGAGAAA ACCAAAA	499	AT1186-1187	34.99	0.95	66.13	1.19	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_314	314	UGUUUGGUUUU CUCAGCAGCA	80	CUGAGAAAAC CAAACA	500	AT2200-2201	85.71	0.50	112.04	10.25	
SNCA_315	315	UUGUUUGGUUU UCUCAGCAGC	81	UGAGAAAACC AAACAA	501	AT1188-1189	24.68	0.55	83.60	0.88	59500
SNCA_316	316	UCUGUUUGGUU UUCUCAGCAG	82	GAGAAAACCA AACAGA	502	AT1190-1191	49.23	2.88	79.77	0.13	
SNCA_317	317	UCCUGUUUGGU UUUCUCAGCA	83	AGAAAACCAA ACAGGA	503	AT2202-2203	71.67	7.80	95.59	11.99	
SNCA_318	318	UCCCUGUUUGG UUUUCUCAGC	84	GAAAACCAAA CAGGGA	504	AT2204-2205	69.74	5.84	95.32	1.47	
SNCA_324	324	UGCCACACCCU GUUUGGUUUU	85	CAAACAGGGU GUGGCA	505	AT1192-1193	60.09	0.35	74.69	1.87	
SNCA_325	325	UUGCCACACCC UGUUUGGUUU	86	AAACAGGGU GUGGCAA	506	AT2206-2207	121.83	6.95	131.25	1.25	
SNCA_326	326	UCUGCCACACC CUGUUUGGUU	87	AACAGGGUG UGGCAGA	507	AT2208-2209	111.67	4.13	120.59	13.95	
SNCA_327	327	UUCUGCCACAC CCUGUUUGGU	88	ACAGGGUGU GGCAGAA	508	AT1194-1195	48.13	5.53	72.80	1.86	
SNCA_328	328	UUUCUGCCACA CCCUGUUUGG	89	CAGGGUGUG GCAGAAA	509	AT2210-2211	103.50	4.11	107.86	2.43	
SNCA_341	341	UUCUUUCCUGC UGCUUCUGCC	90	AAGCAGCAGG AAAGAA	510	AT1196-1197	94.67	2.25	103.83	0.76	
SNCA_347	347	UCUUUUGUCUU UCCUGCUGCU	91	CAGGAAAGAC AAAAGA	511	AT2212-2213	99.20	2.50	104.16	0.18	
SNCA_348	348	UUCUUUUGUCU UUCCUGCUGC	92	AGGAAAGAC AAAAGAA	512	AT2214-2215	96.36	0.57	103.60	6.70	
SNCA_349	349	UCUCUUUUGUC UUUCCUGCUG	93	GGAAAGACA AAAGAGA	513	AT1198-1199	23.99	0.14	59.54	1.15	721
SNCA_350	350	UCCUCUUUUGU CUUUCCUGCU	94	GAAAGACAA AAGAGGA	514	AT2216-2217	63.26	0.14	88.33	1.84	
SNCA_351	351	UCCCUCUUUUG UCUUUCCUGC	95	AAAGACAAA AGAGGGA	515	AT2218-2219	75.11	5.81	114.33	10.69	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_352	352	UACCCUCUUUUGUCUUUCCUG	96	AAGACAAAAGAGGGUA	516	AT2220-2221	105.91	3.04	106.42	7.35	
SNCA_354	354	UACACCCUCUUUUGUCUUUCC	97	GACAAAAGAGGGUGUA	517	AT2222-2223	71.70	0.16	97.99	5.66	
SNCA_355	355	UAACACCCUCUUUUGUCUUUC	98	ACAAAAGAGGGUGUUA	518	AT1200-1201	22.37	0.20	49.96	2.04	394
SNCA_356	356	UGAACACCCUCUUUUGUCUUU	99	CAAAAGAGGGUGUUCA	519	AT2224-2225	34.44	1.66	71.19	7.02	
SNCA_357	357	UAGAACACCCUCUUUUGUCUU	100	AAAAGAGGGUGUUCUA	520	AT2226-2227	34.50	0.86	70.23	3.70	
SNCA_369	369	UGAGCCUACAUAGAGAACACC	101	UCUCUAUGUAGGCUCA	521	AT2228-2229	94.35	0.67	102.82	15.41	
SNCA_370	370	UGGAGCCUACAUAGAACACAC	102	CUCUAUGUAGGCUCCA	522	AT2230-2231	118.81	4.08	112.56	0.08	
SNCA_371	371	UUGGAGCCUACAUAGAACACA	103	UCUAUGUAGGCUCCAA	523	AT1202-1203	78.33	0.46	95.33	1.48	
SNCA_372	372	UUUGGAGCCUACAUAGAACAC	104	CUAUGUAGGCUCCAAA	524	AT1204-1205	35.36	1.56	71.23	1.03	
SNCA_373	373	UUUUGGAGCCUACAUAGAACA	105	UAUGUAGGCUCCAAAA	525	AT2232-2233	125.42	1.29	109.09	18.57	
SNCA_375	375	UGUUUUGGAGCCUACAUAGAG	106	UGUAGGCUCCAAAACA	526	AT2234-2235	137.15	1.41	108.07	16.93	
SNCA_380	380	UCCUUGGUUUUUGGAGCCUACA	107	GCUCCAAAACCAAGGA	527	AT2236-2237	109.37	2.55	102.44	5.29	
SNCA_381	381	UUCCUUGGUUUUGGAGCCUAC	108	CUCCAAAACCAAGGAA	528	AT2238-2239	132.79	2.25	104.19	12.20	
SNCA_382	382	UCUCCUUGGUUUUGGAGCCUA	109	UCCAAAACCAAGGAGA	529	AT1206-1207	47.41	1.14	72.46	1.78	
SNCA_383	383	UCCUCCUUGGUUUUGGAGCCU	110	CCAAAACCAAGGAGGA	530	AT2240-2241	77.22	0.32	98.42	0.92	
SNCA_384	384	UCCCUCCUUGGUUUUGGAGCC	111	CAAAACCAAGGAGGGA	531	AT2242-2243	111.43	2.38	112.37	1.57	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_389	389	UCCACUCCCUC CUUGGUUUUUG	112	CCAAGGAGGG AGUGGA	532	AT2244-2245	87.32	5.00	102.25	8.66	
SNCA_397	397	UACCAUGCACC ACUCCCUCCU	113	GGAGUGGUG CAUGGUA	533	AT2246-2247	95.66	3.35	112.02	3.24	
SNCA_398	398	UCACCAUGCAC CACUCCCUCC	114	GAGUGGUGC AUGGUGA	534	AT2248-2249	65.99	0.06	95.82	9.68	
SNCA_399	399	UACACCAUGCA CCACUCCCUC	115	AGUGGUGCA UGGUGUA	535	AT1208-1209	19.38	0.10	57.90	0.20	1380
SNCA_400	400	UCACACCAUGC ACCACUCCCU	116	GUGGUGCAU GGUGUGA	536	AT2250-2251	117.38	2.85	114.61	11.72	
SNCA_401	401	UCCACACCAUG CACCACUCCC	117	UGGUGCAUG GUGUGGA	537	AT2252-2253	85.46	3.87	101.55	14.24	
SNCA_405	405	UGUUGCCACAC CAUGCACCAC	118	GCAUGGUGU GGCAACA	538	AT2254-2255	57.98	0.98	96.07	9.43	
SNCA_406	406	UUGUUGCCACA CCAUGCACCA	119	CAUGGUGUG GCAACAA	539	AT2256-2257	48.00	2.52	82.00	4.16	
SNCA_407	407	UCUGUUGCCAC ACCAUGCACC	120	AUGGUGUGG CAACAGA	540	AT1210-1211	46.24	0.61	74.39	2.11	
SNCA_408	408	UACUGUUGCCA CACCAUGCAC	121	UGGUGUGGC AACAGUA	541	AT2258-2259	102.83	1.26	99.08	5.63	
SNCA_409	409	UCACUGUUGCC ACACCAUGCA	122	GGUGUGGCA ACAGUGA	542	AT2260-2261	97.41	1.65	100.50	15.82	
SNCA_413	413	UCAGCCACUGU UGCCACACCA	123	UGGCAACAG UGGCUGA	543	AT2262-2263	93.29	4.84	103.94	6.85	
SNCA_414	414	UUCAGCCACUG UUGCCACACC	124	GGCAACAGUG GCUGAA	544	AT2264-2265	111.86	6.60	111.96	12.79	
SNCA_415	415	UCUCAGCCACU GUUGCCACAC	125	GCAACAGUGG CUGAGA	545	AT1212-1213	40.83	0.23	66.73	0.08	
SNCA_416	416	UUCUCAGCCAC UGUUGCCACA	126	CAACAGUGGC UGAGAA	546	AT2266-2267	62.18	0.59	94.75	8.26	
SNCA_417	417	UUUCUCAGCCA CUGUUGCCAC	127	AACAGUGGC UGAGAAA	547	AT2268-2269	94.25	0.25	117.57	4.61	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_418	418	UCUUCUCAGCC ACUGUUGCCA	128	ACAGUGGCUG AGAAGA	548	AT1612-1613	19.17	0.03	61.99	0.23	2130
SNCA_419	419	UUCUUCUCAGC CACUGUUGCC	129	CAGUGGCUGA GAAGAA	549	AT1214-1215	45.86	0.95	79.74	1.09	
SNCA_420	420	UGUCUUCUCAG CCACUGUUGC	130	AGUGGCUGA GAAGACA	550	AT2270-2271	37.73	1.65	70.07	7.05	
SNCA_421	421	UGGUCUUCUCA GCCACUGUUG	131	GUGGCUGAG AAGACCA	551	AT1638-1639	28.96	0.86	81.19	1.35	1810
SNCA_422	422	UUGGUCUUCUC AGCCACUGUU	132	UGGCUGAGA AGACCAA	552	AT1640-1641	57.17	1.91	74.20	1.02	
SNCA_423	423	UUUGGUCUUCU CAGCCACUGU	133	GGCUGAGAA GACCAAA	553	AT2272-2273	103.56	4.49	94.20	10.60	
SNCA_424	424	UUUUGGUCUUC UCAGCCACUG	134	GCUGAGAAG ACCAAAA	554	AT2274-2275	75.69	0.54	93.94	20.60	
SNCA_425	425	UCUUUGGUCUU CUCAGCCACU	135	CUGAGAAGAC CAAAGA	555	AT2276-2277	81.93	4.29	109.95	7.78	
SNCA_426	426	UUCUUUGGUCU UCUCAGCCAC	136	UGAGAAGACC AAAGAA	556	AT1642-1643	31.25	0.20	68.81	0.79	1360
SNCA_427	427	UCUCUUUGGUC UUCUCAGCCA	137	GAGAAGACCA AAGAGA	557	AT1216-1217	37.55	0.36	77.93	1.33	
SNCA_428	428	UGCUCUUUGGU CUUCUCAGCC	138	AGAAGACCAA AGAGCA	558	AT2278-2279	57.44	2.59	88.01	5.11	
SNCA_430	430	UUUGCUCUUUG GUCUUCUCAG	139	AAGACCAAAG AGCAAA	559	AT1218-1219	25.55	0.29	58.58	0.74	
SNCA_431	431	UCUUGCUCUUU GGUCUUCUCA	140	AGACCAAAGA GCAAGA	560	AT2280-2281	117.42	2.24	119.05	9.12	
SNCA_432	432	UACUUGCUCUU UGGUCUUCUC	141	GACCAAAGAG CAAGUA	561	AT1220-1221	37.41	0.91	62.89	0.85	
SNCA_433	433	UCACUUGCUCU UUGGUCUUCU	142	ACCAAAGAGC AAGUGA	562	AT2282-2283	108.85	4.56	103.56	19.33	
SNCA_434	434	UUCACUUGCUC UUUGGUCUUC	143	CCAAAGAGCA AGUGAA	563	AT2284-2285	30.01	3.32	59.42	3.43	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_438	438	UUUUGUCACUU GCUCUUUGGU	144	AGAGCAAGU GACAAAA	564	AT2286-2287	48.55	3.36	58.16	10.29	628
SNCA_439	439	UAUUUGUCACU UGCUCUUUGG	145	GAGCAAGUG ACAAAUA	565	AT2288-2289	69.36	2.82	67.47	3.92	
SNCA_440	440	UCAUUUGUCAC UUGCUCUUUG	146	AGCAAGUGAC AAAUGA	566	AT2290-2291	103.25	3.57	77.33	5.42	
SNCA_441	441	UACAUUUGUCA CUUGCUCUUU	147	GCAAGUGACA AAUGUA	567	AT1222-1223	27.41	0.56	44.61	0.27	
SNCA_442	442	UAACAUUUGUC ACUUGCUCUU	148	CAAGUGACAA AUGUUA	568	AT1224-1225	14.67	0.46	36.24	0.38	483
SNCA_443	443	UCAACAUUUGU CACUUGCUCU	149	AAGUGACAA AUGUUGA	569	AT2292-2293	53.20	1.45	84.49	10.68	
SNCA_444	444	UCCAACAUUUG UCACUUGCUC	150	AGUGACAAA UGUUGGA	570	AT1644-1645	30.43	2.55	72.82	0.19	1110
SNCA_445	445	UUCCAACAUUU GUCACUUGCU	151	GUGACAAAU GUUGGAA	571	AT2294-2295	97.37	2.79	115.22	1.92	
SNCA_446	446	UCUCCAACAUU UGUCACUUGC	152	UGACAAAUG UUGGAGA	572	AT2296-2297	74.90	0.88	87.49	3.67	
SNCA_447	447	UCCUCCAACAU UUGUCACUUG	153	GACAAAUGU UGGAGGA	573	AT2298-2299	101.08	1.14	119.59	3.40	
SNCA_462	462	UCCCGUCACCA CUGCUCCUCC	154	AGCAGUGGU GACGGGA	574	AT1652-1653	81.52	0.18	103.29	0.79	
SNCA_473	473	UCUGCUGUCAC ACCCGUCACC	155	CGGGUGUGAC AGCAGA	575	AT1226-1227	64.77	0.24	77.39	0.67	
SNCA_476	476	UCUACUGCUGU CACACCCGUC	156	GUGUGACAGC AGUAGA	576	AT1228-1229	67.35	0.61	86.62	0.02	
SNCA_483	483	UUUCUGGGCUA CUGCUGUCAC	157	AGCAGUAGCC CAGAAA	577	AT1230-1231	98.33	1.26	97.34	1.80	
SNCA_484	484	UCUUCUGGGCU ACUGCUGUCA	158	GCAGUAGCCC AGAAGA	578	AT1232-1233	70.36	2.21	98.95	0.21	
SNCA_494	494	UCCUCCACUGU CUUCUGGGCU	159	AGAAGACAG UGGAGGA	579	AT2300-2301	84.02	0.76	109.70	10.82	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_495	495	UCCCUCCACUG UCUUCUGGGC	160	GAAGACAGU GGAGGGA	580	AT2302-2303	163.41	4.20	108.67	9.02	
SNCA_496	496	UUCCCUCCACU GUCUUCUGGG	161	AAGACAGUG GAGGGAA	581	AT2304-2305	183.89	12.29	119.75	9.94	
SNCA_497	497	UCUCCCUCCAC UGUCUUCUGG	162	AGACAGUGG AGGGAGA	582	AT2306-2307	113.54	5.06	104.13	7.04	
SNCA_498	498	UGCUCCCUCCA CUGUCUUCUG	163	GACAGUGGA GGGAGCA	583	AT2308-2309	116.30	1.34	96.30	4.18	
SNCA_507	507	UAUGCUCCCUG AGCAUA	164	GGGAGCAGGG AGCAUA	584	AT2310-2311	99.38	4.60	85.16	1.90	
SNCA_510	510	UGCAAUGCUCC CUGCUCCCUC	165	AGCAGGGAGC AUUGCA	585	AT2312-2313	117.69	5.33	107.80	1.64	
SNCA_511	511	UUGCAAUGCUC CCUGCUCCCU	166	GCAGGGAGCA UUGCAA	586	AT2314-2315	24.99	1.34	46.38	3.46	503
SNCA_556	556	UUUCAUUCUUG CCCAACUGGU	167	UUGGGCAAG AAUGAAA	587	AT1110-1111	97.32	1.12			
SNCA_557	557	UCUUCAUUCUU GCCCAACUGG	168	UGGGCAAGA AUGAAGA	588	AT1234-1235	82.37	0.32	95.72	0.02	
SNCA_559	559	UUUCUUCAUUC UUGCCCAACU	169	GGCAAGAAU GAAGAAA	589	AT1236-1237	120.54	0.77	90.36	0.37	
SNCA_585	585	UUCCAGAAUUC CUUCCUGUGG	170	GGAAGGAAU UCUGGAA	590	AT2316-2317	69.74	0.96	82.28	2.70	
SNCA_586	586	UUUCCAGAAUU CCUUCCUGUG	171	GAAGGAAUU CUGGAAA	591	AT2318-2319	91.73	3.19	98.89	12.59	
SNCA_594	594	UGGCAUAUCUU CCAGAAUUCC	172	UCUGGAAGA UAUGCCA	592	AT2320-2321	94.61	1.30	95.67	7.47	
SNCA_598	598	UCACAGGCAUA UCUUCCAGAA	173	GAAGAUAUG CCUGUGA	593	AT1238-1239	92.83	0.62	89.11	0.03	
SNCA_611	611	UCAUUGUCAGG AUCCACAGGC	174	UGGAUCCUG ACAAUGA	594	AT1240-1241	90.13	1.97	79.05	0.80	
SNCA_613	613	UCUCAUUGUCA GGAUCCACAG	175	GAUCCUGACA AUGAGA	595	AT1242-1243	73.28	1.55	109.41	3.09	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_614	614	UCCUCAUUGUC AGGAUCCACA	176	AUCCUGACAA UGAGGA	596	AT1244-1245	81.61	0.72	115.01	0.10	
SNCA_619	619	UAUAAGCCUCA UUGUCAGGAU	177	GACAAUGAG GCUUAUA	597	AT2322-2323	112.50	7.58	96.31	6.27	
SNCA_620	620	UCAUAAGCCUC AUUGUCAGGA	178	ACAAUGAGGC UUAUGA	598	AT1246-1247	77.40	1.74	101.73	3.14	
SNCA_621	621	UUCAUAAGCCU CAUUGUCAGG	179	CAAUGAGGC UUAUGAA	599	AT1654-1655	18.55	0.05	63.43	0.73	109
SNCA_622	622	UUUCAUAAGCC UCAUUGUCAG	180	AAUGAGGCU UAUGAAA	600	AT1656-1657	28.80	0.18	56.07	5.18	
SNCA_623	623	UUUUCAUAAGC CUCAUUGUCA	181	AUGAGGCUU AUGAAAA	601	AT2324-2325	57.62	1.34	76.96	2.72	
SNCA_624	624	UAUUUCAUAAG CCUCAUUGUC	182	UGAGGCUUA UGAAAUA	602	AT2326-2327	31.06	1.74	60.18	3.42	
SNCA_625	625	UCAUUUCAUAA GCCUCAUUGU	183	GAGGCUUAU GAAAUGA	603	AT2328-2329	110.24	10.33	106.19	3.75	
SNCA_626	626	UGCAUUUCAUA AGCCUCAUUG	184	AGGCUUAUG AAAUGCA	604	AT1248-1249	107.25	4.15	112.46	2.44	
SNCA_627	627	UGGCAUUUCAU AAGCCUCAUU	185	GGCUUAUGA AAUGCCA	605	AT2330-2331	103.65	5.43	103.01	14.07	
SNCA_628	628	UAGGCAUUUCA UAAGCCUCAU	186	GCUUAUGAA AUGCCUA	606	AT2332-2333	104.43	2.87	104.03	8.30	
SNCA_629	629	UAAGGCAUUUC AUAAGCCUCA	187	CUUAUGAAA UGCCUUA	607	AT2334-2335	106.81	0.86	108.29	8.27	
SNCA_630	630	UGAAGGCAUUU CAUAAGCCUC	188	UUAUGAAAU GCCUUCA	608	AT1614-1615	105.43	2.44	92.48	0.71	
SNCA_633	633	UUCAGAAGGCA UUUCAUAAGC	189	UGAAAUGCC UUCUGAA	609	AT2336-2337	78.98	0.52	100.46	7.28	
SNCA_634	634	UCUCAGAAGGC AUUUCAUAAG	190	GAAAUGCCU UCUGAGA	610	AT1658-1659	76.73	0.95	104.01	2.91	
SNCA_637	637	UUUCCUCAGAA GGCAUUUCAU	191	AUGCCUUCU GAGGAAA	611	AT1250-1251	101.17	0.52	108.02	0.11	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_648	648	UUCUUGAUACC CUUCCUCAGA	192	GGAAGGGUA UCAAGAA	612	AT1252-1253	72.11	0.03	95.93	0.33	
SNCA_649	649	UGUCUUGAUAC CCUUCCUCAG	193	GAAGGGUAU CAAGACA	613	AT1112-1113	84.62	1.29			
SNCA_662	662	UCUUCAGGUUC GUAGUCUUGA	194	ACUACGAACC UGAAGA	614	AT1254-1255	111.64	1.43	105.70	0.26	
SNCA_663	663	UGCUUCAGGUU CGUAGUCUUG	195	CUACGAACCU GAAGCA	615	AT1256-1257	53.28	0.59	86.66	0.85	
SNCA_664	664	UGGCUUCAGGU UCGUAGUCUU	196	UACGAACCUG AAGCCA	616	AT1258-1259	106.42	0.67	112.79	2.44	
SNCA_668	668	UCUUAGGCUUC AGGUUCGUAG	197	AACCUGAAGC CUAAGA	617	AT2338-2339	116.64	3.09	103.71	3.84	
SNCA_669	669	UUCUUAGGCUU CAGGUUCGUA	198	ACCUGAAGCC UAAGAA	618	AT1260-1261	69.33	1.21	96.46	1.55	
SNCA_669	669	UUCUUAGGCUU CAGGUUCGUA	199	ACCUGAAGCC UAAGAA	619	AT2340-2341	94.55	3.06	98.46	1.71	
SNCA_670	670	UUUCUUAGGCU UCAGGUUCGU	200	CCUGAAGCCU AAGAAA	620	AT1262-1263	29.27	0.24	58.37	1.06	
SNCA_671	671	UUUUCUUAGGC UUCAGGUUCG	201	CUGAAGCCUA AGAAAA	621	AT2342-2343	72.19	2.90	84.19	1.75	
SNCA_672	672	UAUUUCUUAGG CUUCAGGUUC	202	UGAAGCCUA AGAAAUA	622	AT2344-2345	31.24	1.69	60.26	4.85	
SNCA_673	673	UUAUUUCUUAG GCUUCAGGUU	203	GAAGCCUAAG AAAUAA	623	AT2346-2347	40.00	0.79	74.05	4.77	
SNCA_675	675	UGAUAUUUCUU AGGCUUCAGG	204	AGCCUAAGAA AUAUCA	624	AT2348-2349	92.34	2.40	111.65	5.14	
SNCA_676	676	UAGAUAUUUCU UAGGCUUCAG	205	GCCUAAGAAA UAUCUA	625	AT2350-2351	49.09	0.73	90.99	4.17	
SNCA_677	677	UAAGAUAUUUC UUAGGCUUCA	206	CCUAAGAAA UAUCUUA	626	AT1264-1265	27.50	0.60	52.84	0.88	
SNCA_678	678	UAAAGAUAUUU CUUAGGCUUC	207	CUAAGAAAU AUCUUUA	627	AT1266-1267	39.96	0.68	70.02	1.05	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_679	679	UCAAAGAUAUU UCUUAGGCUU	208	UAAGAAAUA UCUUUGA	628	AT2352-2353	52.17	2.73	97.22	7.78	
SNCA_680	680	UGCAAAGAUAU UUCUUAGGCU	209	AAGAAAUAU CUUUGCA	629	AT2354-2355	77.61	2.38	104.48	2.48	
SNCA_681	681	UAGCAAAGAUA UUUCUUAGGC	210	AGAAAUAUC UUUGCUA	630	AT1268-1269	27.87	0.67	37.13	1.00	
SNCA_682	682	UGAGCAAAGAU AUUUCUUAGG	211	GAAAUAUCU UUGCUCA	631	AT1270-1271	18.24	0.13	49.56	0.43	554
SNCA_683	683	UGGAGCAAAGA UAUUUCUUAG	212	AAAUAUCUU UGCUCCA	632	AT2356-2357	75.29	2.75	101.82	5.89	
SNCA_684	684	UGGGAGCAAAG AUAUUUCUUA	213	AAUAUCUUU GCUCCCA	633	AT2358-2359	100.11	0.76	116.00	6.34	
SNCA_693	693	UCAAGAAACUG GGAGCAAAGA	214	GCUCCCAGUU UCUUGA	634	AT1272-1273	78.60	1.02	87.69	2.63	
SNCA_694	694	UUCAAGAAACU GGGAGCAAAG	215	CUCCCAGUUU CUUGAA	635	AT2360-2361	114.92	2.06	105.73	9.44	
SNCA_695	695	UCUCAAGAAAC UGGGAGCAAA	216	UCCCAGUUUC UUGAGA	636	AT2362-2363	70.02	2.88	84.15	5.15	
SNCA_696	696	UUCUCAAGAAA CUGGGAGCAA	217	CCCAGUUUCU UGAGAA	637	AT1274-1275	32.00	0.42	48.23	0.74	
SNCA_697	697	UAUCUCAAGAA ACUGGGAGCA	218	CCAGUUUCU UGAGAUA	638	AT1114-1115	31.18	1.36			
SNCA_698	698	UGAUCUCAAGA AACUGGGAGC	219	CAGUUUCUU GAGAUCA	639	AT2364-2365	43.76	0.21	76.39	1.50	
SNCA_699	699	UAGAUCUCAAG AAACUGGGAG	220	AGUUUCUUG AGAUCUA	640	AT2366-2367	29.88	0.15	43.85	1.67	
SNCA_701	701	UGCAGAUCUCA AGAAACUGGG	221	UUUCUUGAG AUCUGCA	641	AT1276-1277	54.94	0.85	66.08	1.02	
SNCA_705	705	UGUCAGCAGAU CUCAAGAAAC	222	UUGAGAUCU GCUGACA	642	AT2368-2369	33.46	0.57	74.92	1.10	
SNCA_706	706	UUGUCAGCAGA UCUCAAGAAA	223	UGAGAUCUG CUGACAA	643	AT2370-2371	33.52	1.08	74.88	4.38	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_707	707	UCUGUCAGCAG AUCUCAAGAA	224	GAGAUCUGC UGACAGA	644	AT1660-1661	24.05	0.16	65.00	0.32	362
SNCA_708	708	UUCUGUCAGCA GAUCUCAAGA	225	AGAUCUGCU GACAGAA	645	AT1278-1279	43.36	0.76	70.25	1.01	
SNCA_709	709	UAUCUGUCAGC AGAUCUCAAG	226	GAUCUGCUG ACAGAUA	646	AT2372-2373	68.28	2.59	101.23	4.91	
SNCA_710	710	UCAUCUGUCAG CAGAUCUCAA	227	AUCUGCUGAC AGAUGA	647	AT2374-2375	55.83	0.83	91.80	3.53	
SNCA_711	711	UACAUCUGUCA GCAGAUCUCA	228	UCUGCUGACA GAUGUA	648	AT2376-2377	36.90	2.66	62.99	2.67	
SNCA_715	715	UUGGAACAUCU GUCAGCAGAU	229	CUGACAGAU GUUCCAA	649	AT2378-2379	39.67	1.77	79.44	1.75	
SNCA_716	716	UAUGGAACAUC UGUCAGCAGA	230	UGACAGAUG UUCCAUA	650	AT2380-2381	30.77	2.62	53.24	3.75	
SNCA_717	717	UGAUGGAACAU CUGUCAGCAG	231	GACAGAUGU UCCAUCA	651	AT1662-1663	24.71	1.01	52.32	0.41	553
SNCA_718	718	UGGAUGGAACA UCUGUCAGCA	232	ACAGAUGUU CCAUCCA	652	AT2382-2383	54.63	2.70	77.52	4.46	
SNCA_719	719	UAGGAUGGAAC AUCUGUCAGC	233	CAGAUGUUCC AUCCUA	653	AT2384-2385	47.82	2.86	74.84	9.26	
SNCA_720	720	UCAGGAUGGAA CAUCUGUCAG	234	AGAUGUUCC AUCCUGA	654	AT1116-1117	52.35	1.04			
SNCA_721	721	UACAGGAUGGA ACAUCUGUCA	235	GAUGUUCCA UCCUGUA	655	AT2386-2387	36.14	2.35	86.93	4.85	
SNCA_722	722	UUACAGGAUGG AACAUCUGUC	236	AUGUUCCAU CCUGUAA	656	AT2388-2389	68.12	2.05	103.87	10.60	
SNCA_725	725	UUUGUACAGGA UGGAACAUCU	237	UUCCAUCCUG UACAAA	657	AT1664-1665	56.71	0.40	101.80	0.32	
SNCA_730	730	UAGCACUUGUA CAGGAUGGAA	238	UCCUGUACAA GUGCUA	658	AT1280-1281	30.16	0.29	40.60	0.93	
SNCA_732	732	UUGAGCACUUG UACAGGAUGG	239	CUGUACAAG UGCUCAA	659	AT1666-1667	18.73	0.16	40.49	0.10	208

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_733	733	UCUGAGCACUU GUACAGGAUG	240	UGUACAAGU GCUCAGA	660	AT1282-1283	33.73	5.36	56.91	3.29	
SNCA_734	734	UACUGAGCACU UGUACAGGAU	241	GUACAAGUG CUCAGUA	661	AT2390-2391	46.73	1.60	79.08	8.22	
SNCA_735	735	UAACUGAGCAC UUGUACAGGA	242	UACAAGUGC UCAGUUA	662	AT2392-2393	45.36	0.79	81.46	6.20	
SNCA_736	736	UGAACUGAGCA CUUGUACAGG	243	ACAAGUGCUC AGUUCA	663	AT1646-1647	30.52	0.75	43.27	1.70	164
SNCA_737	737	UGGAACUGAGC ACUUGUACAG	244	CAAGUGCUCA GUUCCA	664	AT1648-1649	25.01	0.04	26.76	0.23	90.5
SNCA_738	738	UUGGAACUGAG CACUUGUACA	245	AAGUGCUCA GUUCCAA	665	AT2394-2395	35.16	4.26	74.06	8.85	507
SNCA_739	739	UUUGGAACUGA GCACUUGUAC	246	AGUGCUCAG UUCCAAA	666	AT2396-2397	22.34	0.28	33.18	2.24	94
SNCA_740	740	UAUUGGAACUG AGCACUUGUA	247	GUGCUCAGU UCCAAUA	667	AT1284-1285	23.68	3.33	41.78	0.37	213
SNCA_741	741	UCAUUGGAACU GAGCACUUGU	248	UGCUCAGUU CCAAUGA	668	AT2398-2399	64.53	2.99	84.95	5.41	
SNCA_742	742	UACAUUGGAAC UGAGCACUUG	249	GCUCAGUUCC AAUGUA	669	AT2400-2401	50.50	5.16	71.67	3.30	
SNCA_743	743	UCACAUUGGAA CUGAGCACUU	250	CUCAGUUCCA AUGUGA	670	AT2402-2403	43.06	2.83	71.45	2.17	
SNCA_744	744	UGCACAUUGGA ACUGAGCACU	251	UCAGUUCCAA UGUGCA	671	AT1286-1287	22.19	2.66	33.39	0.25	136
SNCA_745	745	UGGCACAUUGG AACUGAGCAC	252	CAGUUCCAAU GUGCCA	672	AT2404-2405	36.09	0.76	71.89	7.40	
SNCA_746	746	UGGGCACAUUG GAACUGAGCA	253	AGUUCCAAU GUGCCCA	673	AT2406-2407	46.81	3.22	83.75	1.33	
SNCA_747	747	UUGGGCACAUU GGAACUGAGC	254	GUUCCAAUG UGCCCAA	674	AT2408-2409	48.24	3.85	84.90	7.63	
SNCA_748	748	UCUGGGCACAU UGGAACUGAG	255	UUCCAAUGU GCCCAGA	675	AT1288-1289	42.67	1.51	82.36	1.71	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_749	749	UACUGGGCACA UUGGAACUGA	256	UCCAAUGUGC CCAGUA	676	AT2410-2411	57.51	1.78	89.15	9.51	
SNCA_750	750	UGACUGGGCAC AUUGGAACUG	257	CCAAUGUGCC CAGUCA	677	AT1290-1291	44.08	1.04	99.78	0.87	
SNCA_751	751	UUGACUGGGCA CAUUGGAACU	258	CAAUGUGCCC AGUCAA	678	AT1292-1293	88.30	2.24	99.97	2.62	
SNCA_752	752	UAUGACUGGGC ACAUUGGAAC	259	AAUGUGCCCA GUCAUA	679	AT1294-1295	118.93	1.22	123.64	0.44	
SNCA_755	755	UGUCAUGACUG GGCACAUUGG	260	GUGCCCAGUC AUGACA	680	AT1296-1297	83.75	0.20	88.63	0.41	
SNCA_758	758	UAAUGUCAUGA CUGGGCACAU	261	CCCAGUCAUG ACAUUA	681	AT1298-1299	89.23	0.27	96.17	0.19	
SNCA_759	759	UAAAUGUCAUG ACUGGGCACA	262	CCAGUCAUGA CAUUUA	682	AT1300-1301	67.00	1.05	113.12	0.17	
SNCA_760	760	UGAAAUGUCAU GACUGGGCAC	263	CAGUCAUGAC AUUUCA	683	AT1302-1303	97.42	2.79	103.79	2.21	
SNCA_763	763	UUGAGAAAUGU CAUGACUGGG	264	UCAUGACAU UUCUCAA	684	AT1304-1305	322.29	2.83	129.19	4.10	
SNCA_764	764	UUUGAGAAAUG UCAUGACUGG	265	CAUGACAUU UCUCAAA	685	AT1306-1307	51.38	0.02	47.85	0.36	
SNCA_765	765	UUUUGAGAAAU GUCAUGACUG	266	AUGACAUUU CUCAAAA	686	AT2412-2413	27.57	0.38	48.03	6.40	
SNCA_766	766	UCUUUGAGAAA UGUCAUGACU	267	UGACAUUUC UCAAAGA	687	AT1308-1309	24.66	0.30	30.18	0.17	151
SNCA_767	767	UACUUUGAGAA AUGUCAUGAC	268	GACAUUUCU CAAAGUA	688	AT1310-1311	72.62	0.33	58.66	1.32	
SNCA_787	787	UCUUCGAGAUA CACUGUAAAA	269	CAGUGUAUC UCGAAGA	689	AT2414-2415	41.76	0.71	64.88	10.93	
SNCA_788	788	UACUUCGAGAU ACACUGUAAA	270	AGUGUAUCU CGAAGUA	690	AT2416-2417	30.50	1.67	50.80	3.22	
SNCA_789	789	UGACUUCGAGA UACACUGUAA	271	GUGUAUCUC GAAGUCA	691	AT1312-1313	36.89	0.97	55.63	1.92	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_790	790	UAGACUUCGAG AUACACUGUA	272	UGUAUCUCG AAGUCUA	692	AT1118-1119	40.72	0.83			
SNCA_791	791	UAAGACUUCGA GAUACACUGU	273	GUAUCUCGA AGUCUUA	693	AT2418-2419	24.63	0.65	42.23	0.25	327
SNCA_792	792	UGAAGACUUCG AGAUACACUG	274	UAUCUCGAA GUCUUCA	694	AT1314-1315	119.37	0.37	108.03	2.17	
SNCA_796	796	UGAUGGAAGAC UUCGAGAUAC	275	UCGAAGUCU UCCAUCA	695	AT2420-2421	47.19	0.74	63.35	3.93	616
SNCA_797	797	UUGAUGGAAGA CUUCGAGAUA	276	CGAAGUCUUC CAUCAA	696	AT2422-2423	54.87	1.38	68.42	4.62	
SNCA_798	798	UCUGAUGGAAG ACUUCGAGAU	277	GAAGUCUUCC AUCAGA	697	AT1316-1317	105.24	1.89	96.39	1.85	
SNCA_799	799	UGCUGAUGGAA GACUUCGAGA	278	AAGUCUUCCA UCAGCA	698	AT1318-1319	38.66	1.23	57.82	0.96	
SNCA_800	800	UUGCUGAUGGA AGACUUCGAG	279	AGUCUUCCA UCAGCAA	699	AT1616-1617	129.88	1.72	87.01	2.05	
SNCA_801	801	UCUGCUGAUGG AAGACUUCGA	280	GUCUUCCAUC AGCAGA	700	AT1320-1321	71.81	0.69	78.75	1.98	
SNCA_802	802	UACUGCUGAUG GAAGACUUCG	281	UCUUCCAUCA GCAGUA	701	AT1322-1323	104.53	3.64	97.58	1.47	
SNCA_803	803	UCACUGCUGAU GGAAGACUUC	282	CUUCCAUCAG CAGUGA	702	AT2424-2425	79.55	0.12	84.25	6.39	
SNCA_804	804	UUCACUGCUGA UGGAAGACUU	283	UUCCAUCAGC AGUGAA	703	AT2426-2427	74.67	4.48	79.98	3.02	
SNCA_805	805	UAUCACUGCUG AUGGAAGACU	284	UCCAUCAGCA GUGAUA	704	AT1324-1325	87.39	0.20	91.28	0.66	
SNCA_806	806	UAAUCACUGCU GAUGGAAGAC	285	CCAUCAGCAG UGAUUA	705	AT1326-1327	81.50	1.45	92.99	1.52	
SNCA_807	807	UCAAUCACUGC UGAUGGAAGA	286	CAUCAGCAGU GAUUGA	706	AT2428-2429	33.69	3.40	49.66	0.32	
SNCA_808	808	UUCAAUCACUG CUGAUGGAAG	287	AUCAGCAGU GAUUGAA	707	AT1328-1329	119.29	1.41	105.24	1.02	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_809	809	UUUCAAUCACU GCUGAUGGAA	288	UCAGCAGUG AUUGAAA	708	AT1330-1331	42.00	0.00	48.80	1.65	
SNCA_810	810	UCUUCAAUCAC UGCUGAUGGA	289	CAGCAGUGA UUGAAGA	709	AT2430-2431	39.99	0.25	59.24	1.92	
SNCA_811	811	UACUUCAAUCA CUGCUGAUGG	290	AGCAGUGAU UGAAGUA	710	AT1332-1333	59.66	2.17	74.75	0.99	
SNCA_812	812	UUACUUCAAUC ACUGCUGAUG	291	GCAGUGAUU GAAGUAA	711	AT2432-2433	34.59	0.75	61.10	2.83	
SNCA_813	813	UAUACUUCAAU CACUGCUGAU	292	CAGUGAUUG AAGUAUA	712	AT2434-2435	26.73	1.39	43.03	5.13	
SNCA_820	820	UGGUACAGAUA CUUCAAUCAC	293	UGAAGUAUC UGUACCA	713	AT2436-2437	57.48	7.43	81.70	1.40	
SNCA_821	821	UAGGUACAGAU ACUUCAAUCA	294	GAAGUAUCU GUACCUA	714	AT2438-2439	40.15	2.94	71.31	4.03	
SNCA_822	822	UCAGGUACAGA UACUUCAAUC	295	AAGUAUCUG UACCUGA	715	AT1668-1669	25.79	0.44	57.75	0.07	
SNCA_823	823	UGCAGGUACAG AUACUUCAAU	296	AGUAUCUGU ACCUGCA	716	AT1334-1335	78.38	0.90	97.50	2.27	
SNCA_824	824	UGGCAGGUACA GAUACUUCAA	297	GUAUCUGUA CCUGCCA	717	AT2440-2441	103.97	8.12	94.20	3.65	
SNCA_825	825	UGGGCAGGUAC AGAUACUUCA	298	UAUCUGUAC CUGCCCA	718	AT1336-1337	95.03	0.77	96.62	0.71	
SNCA_846	846	UAAGCACCGAA AUGCUGAGUG	299	AGCAUUUCG GUGCUUA	719	AT1338-1339	66.95	1.87	104.26	3.12	
SNCA_847	847	UGAAGCACCGA AAUGCUGAGU	300	GCAUUUCGG UGCUUCA	720	AT1340-1341	83.57	0.42	116.71	1.29	
SNCA_851	851	UAAGGGAAGCA CCGAAAUGCU	301	UUCGGUGCU UCCCUUA	721	AT1342-1343	60.19	0.59	105.33	2.09	
SNCA_852	852	UAAAGGGAAGC ACCGAAAUGC	302	UCGGUGCUUC CCUUUA	722	AT1344-1345	86.27	1.63	119.57	0.43	
SNCA_854	854	UUGAAAGGGAA GCACCGAAAU	303	GGUGCUUCCC UUUCAA	723	AT1346-1347	91.22	1.94	126.94	1.53	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_855	855	UGUGAAAGGGA AGCACCGAAA	304	GUGCUUCCCU UUCACA	724	AT1348-1349	89.48	2.34	105.49	1.18	
SNCA_856	856	UAGUGAAAGGG AAGCACCGAA	305	UGCUUCCCUU UCACUA	725	AT1120-1121	81.59	0.08			
SNCA_858	858	UUCAGUGAAAG GGAAGCACCG	306	CUUCCCUUUC ACUGAA	726	AT1350-1351	87.75	1.15	119.57	0.28	
SNCA_861	861	UACUUCAGUGA AAGGGAAGCA	307	CCCUUUCACU GAAGUA	727	AT1352-1353	74.26	0.16	109.87	0.84	
SNCA_866	866	UUAUUCACUUC AGUGAAAGGG	308	UCACUGAAG UGAAUAA	728	AT2442-2443	81.32	1.85	69.80	2.04	
SNCA_867	867	UGUAUUCACUU CAGUGAAAGG	309	CACUGAAGU GAAUACA	729	AT1354-1355	59.72	3.20	111.30	2.21	
SNCA_869	869	UAUGUAUUCAC UUCAGUGAAA	310	CUGAAGUGA AUACAUA	730	AT2444-2445	39.30	4.01	60.37	5.73	
SNCA_870	870	UCAUGUAUUCA CUUCAGUGAA	311	UGAAGUGAA UACAUGA	731	AT2446-2447	35.87	1.93	61.59	0.03	
SNCA_871	871	UCCAUGUAUUC ACUUCAGUGA	312	GAAGUGAAU ACAUGGA	732	AT1356-1357	28.58	0.24	75.21	0.14	
SNCA_872	872	UACCAUGUAUU CACUUCAGUG	313	AAGUGAAUA CAUGGUA	733	AT2448-2449	38.42	0.63	59.34	1.27	
SNCA_873	873	UUACCAUGUAU UCACUUCAGU	314	AGUGAAUAC AUGGUAA	734	AT2450-2451	37.95	0.33	61.84	1.11	
SNCA_880	880	UACCCUGCUAC CAUGUAUUCA	315	ACAUGGUAG CAGGGUA	735	AT1358-1359	97.33	1.96	115.54	1.36	
SNCA_888	888	UACACAAAGAC CCUGCUACCA	316	GCAGGGUCU UUGUGUA	736	AT1360-1361	78.77	2.42	122.58	5.97	
SNCA_900	900	UAAAAUCCACA GCACACAAAG	317	UGUGCUGUG GAUUUUA	737	AT1362-1363	81.77	1.82	140.27	1.63	
SNCA_902	902	UACAAAAUCCA CAGCACACAA	318	UGCUGUGGA UUUUGUA	738	AT1364-1365	95.72	3.22	136.78	4.66	
SNCA_915	915	UGUAGAUUGAA GCCACAAAAU	319	GUGGCUUCA AUCUACA	739	AT2452-2453	31.78	0.81	61.78	3.03	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_916	916	UCGUAGAUUGA AGCCACAAAA	320	UGGCUUCAA UCUACGA	740	AT1366-1367	73.27	0.27	113.24	2.17	
SNCA_917	917	UUCGUAGAUUG AAGCCACAAA	321	GGCUUCAAUC UACGAA	741	AT1368-1369	47.76	0.46	99.67	1.14	
SNCA_918	918	UAUCGUAGAUU GAAGCCACAA	322	GCUUCAAUC UACGAUA	742	AT1122-1123	28.06	0.93			
SNCA_919	919	UCAUCGUAGAU UGAAGCCACA	323	CUUCAAUCU ACGAUGA	743	AT2454-2455	27.85	0.12	33.77	1.61	
SNCA_920	920	UACAUCGUAGA UUGAAGCCAC	324	UUCAAUCUA CGAUGUA	744	AT1670-1671	21.28	0.46	28.37	1.17	110
SNCA_921	921	UAACAUCGUAG AUUGAAGCCA	325	UCAAUCUACG AUGUUA	745	AT1370-1371	44.82	0.64	95.05	0.79	
SNCA_922	922	UUAACAUCGUA GAUUGAAGCC	326	CAAUCUACGA UGUUAA	746	AT1124-1125	33.29	0.46			
SNCA_923	923	UUUAACAUCGU AGAUUGAAGC	327	AAUCUACGA UGUUAAA	747	AT2456-2457	29.92	0.91	35.17	0.65	
SNCA_926	926	UGUUUUAACAU CGUAGAUUGA	328	CUACGAUGU UAAAACA	748	AT1372-1373	13.44	0.18	32.54	0.47	74.2
SNCA_952	952	UGGUAGUCACU UAGGUGUUUU	329	ACCUAAGUG ACUACCA	749	AT1618-1619	33.58	0.91	70.83	3.23	579
SNCA_953	953	UUGGUAGUCAC UUAGGUGUUU	330	CCUAAGUGAC UACCAA	750	AT1620-1621	23.56	0.03	43.15	1.17	247
SNCA_954	954	UGUGGUAGUCA CUUAGGUGUU	331	CUAAGUGAC UACCACA	751	AT1622-1623	20.93	0.37	34.84	0.91	141
SNCA_955	955	UAGUGGUAGUC ACUUAGGUGU	332	UAAGUGACU ACCACUA	752	AT1624-1625	27.96	0.34	36.13	0.35	72.3
SNCA_956	956	UAAGUGGUAGU CACUUAGGUG	333	AAGUGACUA CCACUUA	753	AT2458-2459	68.87	1.92	78.83	3.69	
SNCA_957	957	UUAAGUGGUAG UCACUUAGGU	334	AGUGACUACC ACUUAA	754	AT1626-1627	93.33	2.05	102.73	2.09	
SNCA_958	958	UAUAAGUGGUA GUCACUUAGG	335	GUGACUACCA CUUAUA	755	AT1374-1375	95.43	1.75	114.63	1.06	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_959	959	UAAUAAGUGGU AGUCACUUAG	336	UGACUACCAC UUAUUA	756	AT1376-1377	96.25	1.41	111.52	0.07	
SNCA_960	960	UAAAUAAGUGG UAGUCACUUA	337	GACUACCACU UAUUUA	757	AT1628-1629	73.53	3.28	84.17	3.74	
SNCA_961	961	UGAAAUAAGUG GUAGUCACUU	338	ACUACCACUU AUUUCA	758	AT1378-1379	83.34	2.00	104.40	0.48	
SNCA_962	962	UAGAAAUAAGU GGUAGUCACU	339	CUACCACUUA UUUCUA	759	AT1380-1381	72.93	2.89	114.57	3.37	
SNCA_963	963	UUAGAAAUAAG UGGUAGUCAC	340	UACCACUUA UUUCUAA	760	AT2460-2461	44.68	0.02	39.85	1.73	86.4
SNCA_964	964	UUUAGAAAUAA GUGGUAGUCA	341	ACCACUUAU UUCUAAA	761	AT1126-1127	35.34	0.72			
SNCA_966	966	UAUUUAGAAAU AAGUGGUAGU	342	CACUUAUUU CUAAAUA	762	AT2462-2463	47.56	0.96	49.14	5.00	101
SNCA_967	967	UGAUUUAGAAA UAAGUGGUAG	343	ACUUAUUUC UAAAUCA	763	AT1382-1383	26.20	0.84	45.91	1.00	
SNCA_969	969	UAGGAUUUAGA AAUAAGUGGU	344	UUAUUUCUA AAUCCUA	764	AT1384-1385	80.64	1.42	109.50	1.99	
SNCA_997	997	UUCUGAACAAC AGCAACAAAA	345	UUGCUGUUG UUCAGAA	765	AT1128-1129	64.08	0.03			
SNCA_998	998	UUUCUGAACAA CAGCAACAAA	346	UGCUGUUGU UCAGAAA	766	AT1386-1387	37.03	0.07	62.31	1.95	
SNCA_999	999	UCUUCUGAACA ACAGCAACAA	347	GCUGUUGUU CAGAAGA	767	AT1388-1389	29.00	0.23	63.19	0.67	
SNCA_1000	1000	UACUUCUGAAC AACAGCAACA	348	CUGUUGUUC AGAAGUA	768	AT2464-2465	40.60	1.62	54.75	2.72	
SNCA_1001	1001	UAACUUCUGAA CAACAGCAAC	349	UGUUGUUCA GAAGUUA	769	AT1390-1391	35.90	0.38	54.07	2.10	
SNCA_1002	1002	UCAACUUCUGA ACAACAGCAA	350	GUUGUUCAG AAGUUGA	770	AT1392-1393	35.69	0.41	44.16	1.66	
SNCA_1003	1003	UACAACUUCUG AACAACAGCA	351	UUGUUCAGA AGUUGUA	771	AT1394-1395	39.47	1.37	52.07	1.07	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_1004	1004	UAACAACUUCU GAACAACAGC	352	UGUUCAGAA GUUGUUA	772	AT1396-1397	107.18	0.05	119.74	1.03	
SNCA_1005	1005	UUAACAACUUC UGAACAACAG	353	GUUCAGAAG UUGUUAA	773	AT1398-1399	36.17	0.16	51.16	0.08	
SNCA_1006	1006	UCUAACAACUU CUGAACAACA	354	UUCAGAAGU UGUUAGA	774	AT1400-1401	41.80	0.30	63.67	0.99	
SNCA_1007	1007	UACUAACAACU UCUGAACAAC	355	UCAGAAGUU GUUAGUA	775	AT2466-2467	38.02	2.79	69.95	3.05	
SNCA_1008	1008	UCACUAACAAC UUCUGAACAA	356	CAGAAGUUG UUAGUGA	776	AT2468-2469	30.58	2.69	37.78	4.01	
SNCA_1009	1009	UUCACUAACAA CUUCUGAACA	357	AGAAGUUGU UAGUGAA	777	AT1402-1403	24.90	0.13	40.45	1.21	60.2
SNCA_1010	1010	UAUCACUAACA ACUUCUGAAC	358	GAAGUUGUU AGUGAUA	778	AT2470-2471	31.73	2.33	36.31	1.09	
SNCA_1011	1011	UAAUCACUAAC AACUUCUGAA	359	AAGUUGUUA GUGAUUA	779	AT1404-1405	26.83	0.14	58.18	0.51	
SNCA_1012	1012	UAAAUCACUAA CAACUUCUGA	360	AGUUGUUAG UGAUUUA	780	AT1406-1407	103.49	0.54	108.04	1.06	
SNCA_1013	1013	UCAAAUCACUA ACAACUUCUG	361	GUUGUUAGU GAUUUGA	781	AT1408-1409	29.85	0.81	47.56	1.26	
SNCA_1014	1014	UGCAAAUCACU AACAACUUCU	362	UUGUUAGUG AUUUGCA	782	AT1410-1411	35.44	1.06	56.37	3.08	
SNCA_1015	1015	UAGCAAAUCAC UAACAACUUC	363	UGUUAGUGA UUUGCUA	783	AT2472-2473	32.24	3.11	36.17	1.38	
SNCA_1016	1016	UUAGCAAAUCA CUAACAACUU	364	GUUAGUGAU UUGCUAA	784	AT2474-2475	34.74	1.68	42.34	0.19	
SNCA_1017	1017	UAUAGCAAAUC ACUAACAACU	365	UUAGUGAUU UGCUAUA	785	AT1130-1131	55.62	0.45			
SNCA_1018	1018	UGAUAGCAAAU CACUAACAAC	366	UAGUGAUUU GCUAUCA	786	AT2476-2477	42.69	1.00	51.40	0.10	
SNCA_1019	1019	UUGAUAGCAAA UCACUAACAA	367	AGUGAUUUG CUAUCAA	787	AT2478-2479	42.74	3.67	58.63	2.36	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_1020	1020	UAUGAUAGCAA AUCACUAACA	368	GUGAUUUGC UAUCAUA	788	AT1412-1413	44.21	0.80	50.67	0.63	
SNCA_1054	1054	UUAUCAUUAAA AGACACCUAA	369	UGUCUUUUA AUGAUAA	789	AT1414-1415	41.41	1.36	70.73	2.44	
SNCA_1055	1055	UGUAUCAUUAA AAGACACCUA	370	GUCUUUUAA UGAUACA	790	AT1416-1417	47.30	0.27	68.37	0.66	
SNCA_1056	1056	UAGUAUCAUUA AAAGACACCU	371	UCUUUUAAU GAUACUA	791	AT1418-1419	37.09	0.11	53.92	0.26	
SNCA_1057	1057	UCAGUAUCAUU AAAAGACACC	372	CUUUUAAUG AUACUGA	792	AT1420-1421	92.38	0.83	110.68	1.08	
SNCA_1058	1058	UACAGUAUCAU UAAAAGACAC	373	UUUUAAUGA UACUGUA	793	AT1422-1423	46.20	0.05	60.28	2.14	
SNCA_1059	1059	UGACAGUAUCA UUAAAAGACA	374	UUUAAUGAU ACUGUCA	794	AT2480-2481	58.92	1.05	79.18	12.25	
SNCA_1069	1069	UAUUAUUCUUA GACAGUAUCA	375	CUGUCUAAG AAUAAUA	795	AT1424-1425	92.94	1.46	96.26	2.16	
SNCA_1071	1071	UUCAUUAUUCU UAGACAGUAU	376	GUCUAAGAA UAAUGAA	796	AT1426-1427	26.53	1.87	50.90	5.02	
SNCA_1072	1072	UGUCAUUAUUC UUAGACAGUA	377	UCUAAGAAU AAUGACA	797	AT1428-1429	31.92	0.55	44.71	8.69	
SNCA_1073	1073	UCGUCAUUAUU CUUAGACAGU	378	CUAAGAAUA AUGACGA	798	AT2482-2483	32.94	1.58	45.31	0.44	
SNCA_1074	1074	UACGUCAUUAU UCUUAGACAG	379	UAAGAAUAA UGACGUA	799	AT1430-1431	32.58	0.30	37.05	2.37	
SNCA_1075	1075	UUACGUCAUUA UUCUUAGACA	380	AAGAAUAAU GACGUAA	800	AT1132-1133	44.54	0.52			
SNCA_1077	1077	UAAUACGUCAU UAUUCUUAGA	381	GAAUAAUGA CGUAUUA	801	AT1432-1433	121.47	12.96	99.74	6.77	
SNCA_1079	1079	UACAAUACGUC AUUAUUCUUA	382	AUAAUGACG UAUUGUA	802	AT1434-1435	31.62	0.09	59.80	1.11	
SNCA_1080	1080	UCACAAUACGU CAUUAUUCUU	383	UAAUGACGU AUUGUGA	803	AT2484-2485	32.80	3.53	35.19	0.03	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_1081	1081	UUCACAAUACG UCAUUAUUCU	384	AAUGACGUA UUGUGAA	804	AT2486-2487	34.91	0.71	42.38	0.04	
SNCA_1086	1086	UAAAUUUCACA AUACGUCAUU	385	CGUAUUGUG AAAUUUA	805	AT1436-1437	94.26	4.12	132.12	6.66	
SNCA_1087	1087	UCAAAUUUCAC AAUACGUCAU	386	GUAUUGUGA AAUUUGA	806	AT1134-1135	39.56	0.27			
SNCA_1088	1088	UACAAAUUUCA CAAUACGUCA	387	UAUUGUGAA AUUUGUA	807	AT1136-1137	40.04	0.27			
SNCA_1126	1126	UGUUUCAUGCU CACAUAUUUU	388	AUGUGAGCA UGAAACA	808	AT2488-2489	46.59	3.78	66.85	6.05	
SNCA_1127	1127	UAGUUUCAUGC UCACAUAUUU	389	UGUGAGCAU GAAACUA	809	AT2490-2491	38.29	0.00	60.84	0.66	
SNCA_1128	1128	UUAGUUUCAUG CUCACAUAUU	390	GUGAGCAUG AAACUAA	810	AT1438-1439	48.00	1.87	95.90	1.83	469
SNCA_1129	1129	UAUAGUUUCAU GCUCACAUAU	391	UGAGCAUGA AACUAUA	811	AT1440-1441	29.70	0.89	58.69	0.78	
SNCA_1130	1130	UCAUAGUUUCA UGCUCACAUA	392	GAGCAUGAA ACUAUGA	812	AT2492-2493	64.05	7.10	81.28	7.32	
SNCA_1131	1131	UGCAUAGUUUC AUGCUCACAU	393	AGCAUGAAAC UAUGCA	813	AT2494-2495	74.33	1.24	87.78	10.54	
SNCA_1132	1132	UUGCAUAGUUU CAUGCUCACA	394	GCAUGAAAC UAUGCAA	814	AT1138-1139	39.83	0.68			
SNCA_1133	1133	UGUGCAUAGUU UCAUGCUCAC	395	CAUGAAACU AUGCACA	815	AT1442-1443	87.10	2.13	134.13	0.17	
SNCA_1134	1134	UGGUGCAUAGU UUCAUGCUCA	396	AUGAAACUA UGCACCA	816	AT1444-1445	33.57	1.20	74.13	1.02	
SNCA_1135	1135	UAGGUGCAUAG UUUCAUGCUC	397	UGAAACUAU GCACCUA	817	AT1446-1447	31.14	0.11	60.86	0.58	
SNCA_1136	1136	UUAGGUGCAUA GUUUCAUGCU	398	GAAACUAUG CACCUAA	818	AT1448-1449	40.52	0.24	79.10	2.18	
SNCA_1137	1137	UAUAGGUGCAU AGUUUCAUGC	399	AAACUAUGC ACCUAUA	819	AT1450-1451	101.53	3.24	125.31	3.05	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_1138	1138	UUAUAGGUGCA UAGUUUCAUG	400	AACUAUGCAC CUAUAA	820	AT2496-2497	76.10	5.24	81.07	3.00	
SNCA_1140	1140	UUUUAUAGGUG CAUAGUUUCA	401	CUAUGCACCU AUAAAA	821	AT1452-1453	110.34	1.93	124.30	1.26	
SNCA_1142	1142	UUAUUUAUAGG UGCAUAGUUU	402	AUGCACCUAU AAAUAA	822	AT2498-2499	49.81	3.27	71.26	4.92	
SNCA_1144	1144	UAGUAUUUAUA GGUGCAUAGU	403	GCACCUAUAA AUACUA	823	AT1454-1455	89.46	0.68	110.34	1.33	
SNCA_1168	1168	UGCAAAAUGGU AAAAUUUCAU	404	AUUUUACCA UUUUGCA	824	AT1456-1457	57.72	1.34	85.91	4.51	
SNCA_1172	1172	UCAUCGCAAAA UGGUAAAAUU	405	UACCAUUUU GCGAUGA	825	AT1672-1673	75.12	1.35	92.30	1.76	
SNCA_1174	1174	UCACAUCGCAA AAUGGUAAAA	406	CCAUUUUGC GAUGUGA	826	AT1140-1141	68.16	2.50			
SNCA_1175	1175	UACACAUCGCA AAAUGGUAAA	407	CAUUUUGCG AUGUGUA	827	AT1458-1459	103.81	0.71	140.57	1.75	
SNCA_1176	1176	UAACACAUCGC AAAAUGGUAA	408	AUUUUGCGA UGUGUUA	828	AT1460-1461	74.14	1.04	96.32	2.23	
SNCA_1177	1177	UAAACACAUCG CAAAAUGGUA	409	UUUUGCGAU GUGUUUA	829	AT1462-1463	70.60	0.63	88.29	0.20	
SNCA_1178	1178	UAAAACACAUC GCAAAAUGGU	410	UUUGCGAUG UGUUUUA	830	AT1142-1143	75.63	1.22			
SNCA_1179	1179	UUAAAACACAU CGCAAAAUGG	411	UUGCGAUGU GUUUUAA	831	AT1464-1465	110.49	0.02	121.81	0.49	
SNCA_1182	1182	UGAAUAAAACA CAUCGCAAAA	412	CGAUGUGUU UUAUUCA	832	AT1466-1467	118.45	0.57	128.71	0.40	
SNCA_1183	1183	UUGAAUAAAAC ACAUCGCAAA	413	GAUGUGUUU UAUUCAA	833	AT1468-1469	72.48	1.26	84.16	1.21	
SNCA_1184	1184	UGUGAAUAAAA CACAUCGCAA	414	AUGUGUUUU AUUCACA	834	AT1470-1471	103.14	1.32	83.83	0.65	
SNCA_1186	1186	UAAGUGAAUAA AACACAUCGC	415	GUGUUUUAU UCACUUA	835	AT1472-1473	100.14	0.34	104.22	0.04	

Name	Position in NM_00345.3	21mer antisense sequence	SEQ ID NO.	16mer sense sequence	SEQ ID NO.	In vitro duplex ID#	% UNT SNCA mRNA expression @ 2uM	ST DEV	% UNT SNCA mRNA expression @ 0.5uM	ST DEV	IC50 (nM)
SNCA_1187	1187	UCAAGUGAAUA AAACACAUCG	416	UGUUUUAUU CACUUGA	836	AT1474-1475	57.23	1.09	68.81	0.55	
SNCA_1188	1188	UACAAGUGAAU AAAACACAUC	417	GUUUUAUUC ACUUGUA	837	AT1476-1477	64.08	0.34	88.53	3.23	
SNCA_1189	1189	UCACAAGUGAA UAAAACACAU	418	UUUUAUUCA CUUGUGA	838	AT1478-1479	60.96	1.89	82.93	0.01	
SNCA_1205	1205	UACCAUUUAUA UACAAACACA	419	UUGUAUAUA AAUGGUA	839	AT1144-1145	97.07	1.76			
SNCA_1207	1207	UUCACCAUUUA UAUACAAACA	420	GUAUAUAAA UGGUGAA	840	AT1480-1481	84.43	0.16	110.16	1.70	

Example 2. *In Vivo* Screening

[0219] *In vivo* screening was performed using 12 week old hSNCA transgenic mice. Briefly, PBS or divalent siRNA was administered via bilateral stereotactic ICV injection at a dose of 1 nmol or 5 nmol in a total volume of 5 uL. One week after compound administration, animals were euthanized, perfused, and the brain was sliced into 1mm thick cortical slices. Biopsy punches (1-2mm diameter) were taken of the relevant brain regions (Striatum = Cpu, hippocampus = HP, temporal cortex = tCTx) and were snap frozen. Tissue punches were homogenized in Trizol (Invitrogen) using a Qiagen TissueLyser and total RNA was isolated the RNeasy kit (Qiagen). Quantitative reverse transcriptase polymerase change reaction (QRT-PCR) was performed to assess target (human SNCA) gene expression relative to housekeeping (mouse ATP5B) gene expression using TaqMan primer/probes and Fast Advanced master mix (Thermo). Data are presented as % SNCA target knockdown (N=8 animals, 4 male, 4 female, 2 technical replicates each) relative to PBS treated control animals, where 100% represents complete target knockdown and 0% represents no target knockdown.

Table 3. *In Vivo* Screening

				% SNCA Knock-Down					
				Cpu		HP		tCTx	
Position	21mer antisense sequence	16mer sense sequence	In vitro duplex ID	5 nmol	1 nmol	5 nmol	1 nmol	5 nmol	1 nmol
SNCA_737	UGGAACUGAGCACU UGUACAG (SEQ ID NO: 244)	CAAGUGCUCAGUU CCA (SEQ ID NO: 664)	AT4511-4514	60	30.9	67.2	33.1	65.8	42.8
SNCA_955	UAGUGGUAGUCACU UAGGUGU (SEQ ID NO: 332)	UAAGUGACUACCA CUA (SEQ ID NO: 752)	AT4507-4510	51.2	20.1	60.7	14.3	58.7	39.6
SNCA_1009	UUCACUAACAACUUC UGAACA (SEQ ID NO: 357)	AGAAGUUGUUAG UGAA (SEQ ID NO: 777)	AT4518-4515	33.5	18.9	14.2	-9.5	20.1	-9.5
SNCA_926	UGUUUUAACAUCGU AGAUUGA (SEQ ID NO: 328)	CUACGAUGUUAA AACA (SEQ ID NO: 748)	AT4520-4517	62.6	20.2	77.8	-5.9	50.8	-46.4
SNCA_963	UUAGAAAUAAGUGG UAGUCAC (SEQ ID NO: 340)	UACCACUUAUUUC UAA (SEQ ID NO: 760)	AT4512-4509	77	32.9	61.7	47.2	60.8	-13.8
SNCA_739	UUUGGAACUGAGCA CUUGUAC (SEQ ID NO: 246)	AGUGCUCAGUUCC AAA (SEQ ID NO: 666)	AT4516-4513	47.1	24.5	63.3	54.6	41.4	-7.7
SNCA_421	UGGUCUUCUCAGCCA CUGUUG (SEQ ID NO: 131)	GUGGCUGAGAAG ACCA (SEQ ID NO: 551)	AT4522-4519	-2	31.8	10.7	16.8	-147.7	-36.2
SNCA_399	UACACCAUGCACCAC UCCCUC (SEQ ID NO: 115)	AGUGGUGCAUGG UGUA (SEQ ID NO: 535)	AT4524-4521	71.6	41.6	79.9	34.9	47.7	-5.8
SNCA_621	UUCAUAAGCCUCAUU GUCAGG (SEQ ID NO: 179)	CAAUGAGGCUUA UGAA (SEQ ID NO: 599)	AT4547-4546	48.5	48.5	50	41	35.8	17.7
SNCA_966	UAUUUAGAAAUAAG UGGUAGU (SEQ ID NO: 342)	CACUUAUUUCUAA AUA (SEQ ID NO: 762)	AT4563-4562	54	29.7	58.6	37.6	47.1	7.5
SNCA_744	UGCACAUUGGAACU GAGCACU	UCAGUUCCAAUGU GCA	AT4555-4554	52.2	43.5	67.5	40.7	23.5	-7.2

	(SEQ ID NO: 251)	(SEQ ID NO: 671)								
SNCA_270	UGAAAGUCCUUUCA UGAAUAC (SEQ ID NO: 39)	CAUGAAAGGACU UUCA (SEQ ID NO: 459)	AT4543-4542	35.7	25.7	52.7	20.2	24.2		7.1
SNCA_740	UAUUGGAACUGAGC ACUUGUA (SEQ ID NO: 247)	GUGCUCAGUUCCA AUA (SEQ ID NO: 667)	AT4553-4552	22.8	26.6	39.5	26.5	-6.6		4.3
SNCA_953	UUGGUAGUCACUUA GGUGUUU (SEQ ID NO: 330)	CCUAAGUGACUAC CAA (SEQ ID NO: 750)	AT4559-4558	55	29.5	64.3	46.5	28.8		-3
SNCA_682	UGAGCAAAGAUAUU UCUUAGG (SEQ ID NO: 211)	GAAAUAUCUUUG CUCA (SEQ ID NO: 631)	AT4549-4548	38.9	19.1	53.7	43.7	22.9		17.7
SNCA_736	UGAACUGAGCACUU GUACAGG (SEQ ID NO: 243)	ACAAGUGCUCAGU UCA (SEQ ID NO: 663)	AT4551-4550	55	32.9	67.8	12.5	43.7		-16.6
SNCA_954	UGUGGUAGUCACUU AGGUGUU (SEQ ID NO: 331)	CUAAGUGACUACC ACA (SEQ ID NO: 751)	AT4561-4560	60.4	20.7	61	31.5	21.7		-33

Example 3. *In vivo* inhibition of SNCA gene expression using a di-siRNA sequence in mouse

Objective

[0220] This Example describes the results of a series of experiments undertaken to investigate the ability of an siRNA molecule complementary to a specific region within a human *SNCA* transcript to effectuate reduced expression of the *SNCA* gene.

In vivo administration of di-siRNA

[0221] An siRNA molecule of the disclosure was synthesized as a di-branched siRNA molecule having the structure of Formula XVII. The sense strand had the sequence of SEQ ID No.: 664 and had a pattern of chemical modifications having the broad structure of Formula III and the specific structure of Formula S1. The antisense strand had the sequence of SEQ ID No.: 244 and had a pattern of chemical modifications having the broad structure of Formula II and the specific structure of Formula A2. The antisense strand further included a 5' vinyl phosphonate moiety of Formula XI.

[0222] *In vivo* durability was assessed in mouse using similar methods as described in Example 2. Briefly, PBS or the di-branched siRNA molecule described above was administered via bilateral stereotactic intracerebroventricular (ICV) injection at a dose of 30 nmol in a total volume of 10 μL.

[0223] One month, two months, three months, or four months after compound administration, animals were euthanized, perfused, and the brain was sliced into 1 mm thick cortical slices. Biopsy punches (1-2 mm diameter) were taken of the relevant brain regions (frontal cortex = fCTx, striatum = Cpu, hippocampus = HP, temporal cortex = tCTx, midbrain = Mb, pons = Pons, medulla = Med, cerebellum = CB, cervical spinal cord = SC-C, thoracic spinal cord = SC-T, and lumbar spinal cord = SC-L) and snap frozen.

RNA quantification analysis

[0224] mRNA quantification was performed as described in Example 2. Comparative analysis was performed for relative SNCA mRNA quantitation against samples taken from time-matched PBS control mice. Results are shown in **Figure 1 and Figure 2**.

Protein expression analysis

[0225] Human α-synuclein protein knockdown was quantified by colorimetric sandwich ELISA (Invitrogen KHB0061). Biological samples were lysed using tissue lysis buffer (CST

Cell Lysis Buffer #9803) and bead-beater homogenization on a Qiagen Tissuelyser II. The ELISA was performed using the tissue lysates in accordance with the manufacturer's instructions. The ELISA utilizes a target-specific antibody-coated immunoassay plate to bind to the analyte which in turn binds to the capture antibody. An HRP conjugated secondary detection antibody is used in conjunction with a substrate to generate the measurable signal which is read on a colorimetric plate reader. Data are presented as % SNCA target knockdown (N=8 animals, 4 male, 4 female, 2 technical replicates each), with each siRNA treatment group normalized to time-matched PBS control animals. Results are shown in **Figure 3 and Figure 4.**

Statistical assessment

[0226] Statistical analysis was Mann-Whitney test, two-tailed. **** = $p<0.0001$, *** = $p<0.001$, ** = $p<0.01$, * = $p<0.05$. BQL = values below the limit of quantification but above the limit of detection in the ELISA; values were included in the graph.

Conclusion

[0227] The results in this example demonstrate that an siRNA molecule of the disclosure, with a sense strand having SEQ ID No.: 664 and an antisense strand having SEQ ID No.: 244, successfully reduced *SNCA* expression *in vivo*.

Example 4: Dose response of SNCA knockdown *in vivo*

Objective

[0228] This Example describes the results of a series of experiments undertaken to investigate the *in vivo* dose response of an siRNA molecule complementary to a specific region within an *SNCA* transcript to effectuate reduced expression of the *SNCA* gene.

Materials and Methods

[0229] *In vivo* dose response was assessed in mouse using similar methods as described in Example 3. Briefly, PBS or the di-branched siRNA molecule described in Example 3 was administered via bilateral stereotactic ICV injection at a dose of 2.5 nmol, 5 nmol, 10 nmol, 15 nmol, or 20 nmol in a total volume of 10 µL. Three months after compound administration, animals were euthanized and tissue harvest, mRNA quantification (human and mouse *Snca*), and protein quantitation (human SNCA) were performed as described in Example 2 and Example 3.

Results

[0230] Statistical analysis was two-way ANOVA with Dunnett's multiple comparisons test. **** = $p<0.0001$, *** = $p<0.001$, ** = $p<0.01$, * = $p<0.05$. Results are shown in **Figures 5, 6, and 7.**

Conclusion

[0231] The results reported in this example demonstrate that an siRNA molecule of the disclosure successfully silences *SNCA* in a dose-dependent manner in various regions of the brain.

WHAT IS CLAIMED IS:

1. A small interfering RNA (siRNA) molecule comprising an antisense strand and sense strand having complementarity to the antisense strand, wherein the antisense strand is from 10 to 30 nucleotides in length and has complementarity sufficient to hybridize to a region within an alpha-synuclein (*SNCA*) mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840, wherein the antisense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 1-420.

2. The siRNA molecule of claim 1, wherein the antisense strand comprises at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

3. The siRNA molecule of claim 1 or 2, wherein the antisense strand comprises from 15 to 30 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840, optionally wherein the antisense strand comprises 18, 19, 20, 21, 22, 23, 24, or 25 contiguous nucleotides that are fully complementary to a contiguous polynucleotide segment of equal length within the region of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

4. The siRNA molecule of any one of claims 1-3, wherein the antisense strand comprises 3 or fewer nucleotide mismatches relative to a region of 21 contiguous nucleobases of the *SNCA* mRNA transcript having the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

5. The siRNA molecule of any one of claims 1-4, wherein the region of the *SNCA* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 459, 535, 551, 599, 631, 663, 664, 666, 667, 671, 748, 750, 751, 752, 760, 762, and 777.

6. The siRNA molecule of claim 5, wherein the region of the *SNCA* mRNA transcript has the nucleic acid sequence of any one of SEQ ID NOs: 535, 599, 664, 666, 671, 750, 752, 760, and 762.

7. The siRNA molecule of any one of claims 1-6, wherein the antisense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 1-420.

8. The siRNA molecule of any one of claims 1-7, wherein the sense strand has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence of SEQ ID NOs: 421-840, optionally wherein the sense strand has a nucleic acid sequence that is at least 96%, 97%, 98%, 99%, or 100% identical to the nucleic acid sequence of any one of SEQ ID NOs: 421-840.

9. The siRNA molecule of any one of claims 1-8, wherein the antisense strand comprises:

(a) a structure represented by Formula I, wherein Formula I is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C'\text{-}P^1)_k\text{-}C'$$

Formula I;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;
each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7,

optionally wherein the antisense strand comprises a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(b) a structure represented by Formula II, wherein Formula II is, in the 5'-to-3' direction:

$$A\text{-}B\text{-}(A')_j\text{-}C\text{-}P^2\text{-}D\text{-}P^1\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula II;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2\text{-}D\text{-}P^2$;
each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7,

optionally wherein the antisense strand comprises a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-A-S-A

Formula A2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(c) a structure represented by Formula IV, wherein Formula IV is, in the 5'-to-3' direction:

$$A\text{-}(A')_j\text{-}C\text{-}P^2\text{-}B\text{-}(C\text{-}P^1)_k\text{-}C'$$

Formula IV;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
B is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D\text{-}P^1$;
each C is a 2'-O-Me ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;
each D is a 2'-F ribonucleoside;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7; and
k is an integer from 1 to 7,

optionally wherein the antisense strand comprises a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

A-S-B-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B-S-A-S-A-S-A

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage; or

(d) a structure represented by Formula VI, wherein Formula VI is, in the 5'-to-3' direction:

$$A\text{-}B_j\text{-}E\text{-}B_k\text{-}E\text{-}F\text{-}G_l\text{-}D\text{-}P^1\text{-}C'$$

Formula VI;

wherein A is represented by the formula $C\text{-}P^1\text{-}D\text{-}P^1$;
each B is represented by the formula $C\text{-}P^2$;

each C is a 2'-O-Me ribonucleoside;
each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;
each D is a 2'-F ribonucleoside;
each E is represented by the formula D-P^2-C-P^2;
F is represented by the formula D-P^1-C-P^1;
each G is represented by the formula C-P^1;
each P^1 is a phosphorothioate internucleoside linkage;
each P^2 is a phosphodiester internucleoside linkage;
j is an integer from 1 to 7;
k is an integer from 1 to 7; and
l is an integer from 1 to 7,

optionally wherein the antisense strand comprises a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:

A-S-B-S-A-O-A-O-A-O-B-O-A-O-A-O-A-O-A-O-A-O-A-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

10. The siRNA molecule of any one of claims 1-9, wherein the sense strand comprises:

(a) a structure represented by Formula III, wherein Formula III is, in the 5'-to-3' direction:

E-$(A')_m$-F

Formula III;

wherein E is represented by the formula $(C\text{-}P^1)_2$;
F is represented by the formula $(C\text{-}P^2)_3$-D-P^1-C-P^1-C, $(C\text{-}P^2)_3$-D-P^2-C-P^2-C, $(C\text{-}P^2)_3$-D-P^1-C-P^1-D, or $(C\text{-}P^2)_3$-D-P^2-C-P^2-D;
A', C, D, P^1, and P^2 are as defined in Formula II; and
m is an integer from 1 to 7,

optionally wherein:

(i) the sense strand comprises a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-A

Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(ii) the sense strand comprises a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-A

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(iii) the sense strand comprises a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-S-A-S-B

Formula S3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage; or

(iv) the sense strand comprises a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A-O-A-O-B-O-A-O-B

Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(b) a structure represented by Formula V, wherein Formula V is, in the 5'-to-3' direction:

$$E\text{-}(A')_m\text{-}C\text{-}P^2\text{-}F$$

Formula V;

wherein E is represented by the formula $(C\text{-}P^1)_2$;
F is represented by the formula $D\text{-}P^1\text{-}C\text{-}P^1\text{-}C$, $D\text{-}P^2\text{-}C\text{-}P^2\text{-}C$, $D\text{-}P^1\text{-}C\text{-}P^1\text{-}D$, or $D\text{-}P^2\text{-}C\text{-}P^2\text{-}D$;
A', C, D, P^1 and P^2 are as defined in Formula IV; and
m is an integer from 1 to 7,

optionally wherein:

(i) the sense strand comprises a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A

Formula S5;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(ii) the sense strand comprises a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-A

Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage;

(iii) the sense strand comprises a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-B

Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage; or

(iv) the sense strand comprises a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:

A-S-A-S-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B

Formula S8;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage; or

(c) a structure represented by Formula VII, wherein Formula VII is, in the 5'-to-3' direction:

$H\text{-}B_m\text{-}I_n\text{-}A'\text{-}B_o\text{-}H\text{-}C$

Formula VII;

wherein A' is represented by the formula $C\text{-}P^2\text{-}D\text{-}P^2$;
each H is represented by the formula $(C\text{-}P^1)_2$;
each I is represented by the formula $(D\text{-}P^2)$;
B, C, D, P^1 and P^2 are as defined in Formula VI;
m is an integer from 1 to 7;
n is an integer from 1 to 7; and
o is an integer from 1 to 7,

optionally wherein the sense strand comprises a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:

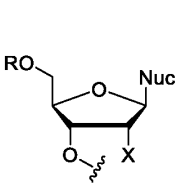
A-S-A-S-A-O-A-O-A-O-B-O-B-O-B-O-A-O-B-O-A-O-A-O-A-O-A-S-A-S-A

Formula S9;

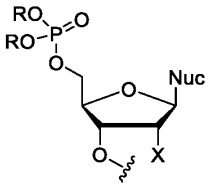
wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

11. The siRNA molecule of any one of claims 1-10, wherein the antisense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the antisense strand and/or the sense strand further comprises a 5' phosphorus stabilizing moiety at the 5' end of the sense strand.

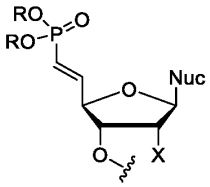
12. The siRNA molecule of claim 11, wherein each 5' phosphorus stabilizing moiety is, independently, represented by any one of Formulas IX-XVI:



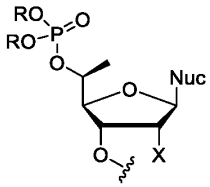
Formula IX



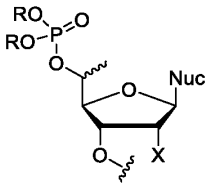
Formula X



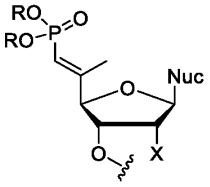
Formula XI



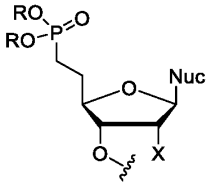
Formula XII



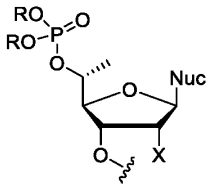
Formula XIII



Formula XIV



Formula XV

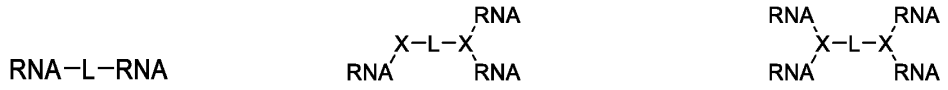


Formula XVI

wherein Nuc represents a nucleobase selected from the group consisting of adenine, uracil, guanine, thymine, and cytosine, and R represents an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, phenyl, benzyl, hydroxy, or hydrogen.

13. The siRNA molecule of any one of claims 1-12, wherein the siRNA molecule is a branched siRNA molecule.

14. The siRNA molecule of claim 13, wherein the branched siRNA molecule is a di-branched siRNA molecule, optionally wherein the di-branched siRNA molecule is represented by any one of Formulas XVII-XIX:



Formula XVII; **Formula XVIII**; **Formula XIX**;

wherein each RNA is, independently, an siRNA molecule, L is a linker, and each X, independently, represents a branch point moiety.

15. An siRNA molecule comprising:

(I)

a) a sense strand comprising the sequence (mU)#(mA)#(mC)(fC)(mA)(fC)(mU)(fU)(mA) (fU)(mU)(mU)(mC)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 841) and an antisense strand comprising the sequence V(mU)#(fU)#(mA)(fG)(fA)(fA)(mA)(fU)(mA)(fA)(mG)(fU)(mG)(fG) (mU)(fA)#(mG)#(mU)#(mC)#(mA)#(mC) (SEQ ID NO: 842);

b) a sense strand comprising the sequence (mC)#(mA)#(mA)(fG)(mU)(fG)(mC)(fU) (mC)(fA)(mG)(mU)(mU)(fC)#(mC)# (mA)-DIO (SEQ ID NO: 843) and an antisense strand comprising the sequence V(mU)#(fG)#(mG)(fA)(fA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)(mU) (fG)#(mU)#(mA)#(mC)#(mA)#(mG) (SEQ ID NO: 844);

c) a sense strand comprising the sequence (mA)#(mG)#(mU)(fG)(mG)(fU)(mG)(fC)(mA) (fU)(mG)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 845) and an antisense strand comprising the sequence V(mU)#(fA)#(mC)(fA)(fC)(fC)(mA)(fU)(mG)(fC)(mA)(fC)(mC)(fA)(mC) (fU)#(mC)#(mC)#(mC)#(mU)#(mC) (SEQ ID NO: 846).

d) a sense strand comprising the sequence (mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC) (fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC) (fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 848);

e) a sense strand comprising the sequence (mU)#(mC)#(mA)(fG)(mU)(fU)(mC)(fC)(mA) (fA)(mU)(mG)(mU)(fG)#(mC)#(mA)-DIO (SEQ ID NO: 849) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC) (fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 850).

f) a sense strand comprising the sequence (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU) (fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 851) and an antisense strand comprising the sequence V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU)(mG) (fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852); or

g) a sense strand comprising the sequence (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU) (fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 853) and an antisense strand comprising the sequence V(mU)#(fG)#(mU)(fU)(fU)(fU)(mA)(fA)(mC)(fA)(mU)(fC)(mG)(fU) (mA)(fG)#(mA)#(mU)#(mU)#(mG)#(mA) (SEQ ID NO: 854);

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate; or

(II)

a) a sense strand comprising the sequence (mU)#(mA)#(mC)(fC)(mA)(fC)(mU)(fU)(mA) (fU)(mU)(mU)(mC)(fU)#(mA)#(mA)-DIO (SEQ ID NO: 841) and an antisense strand comprising the sequence V(mU)#(fU)#(mA)(fG)(fA)(fA)(mA)(fU)(mA)(fA)(mG)(fU)(mG)(fG) (mU)(fA)#(mG)#(mU)#(mC)#(mA)#(mC) (SEQ ID NO: 842);

b) a sense strand comprising the sequence (mC)#(mA)#(mA)(fG)(mU)(fG)(mC)(fU) (mC)(fA)(mG)(mU)(mU)(fC)#(mC)# (mA)-DIO (SEQ ID NO: 843) and an antisense strand comprising the sequence V(mU)#(fG)#(mG)(fA)(fA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)(mU) (fG)#(mU)#(mA)#(mC)#(mA)#(mG) (SEQ ID NO: 844);

c) a sense strand comprising the sequence (mA)#(mG)#(mU)(fG)(mG)(fU)(mG)(fC)(mA)(fU)(mG)(mG)(mU)(fG)#(mU)#(mA)-DIO (SEQ ID NO: 845) and an antisense strand comprising the sequence V(mU)#(fA)#(mC)(fA)(fC)(fC)(mA)(fU)(mG)(fC)(mA)(fC)(mC)(fA)(mC)(fU)#(mC)#(mC)#(mC)#(mU)#(mC) (SEQ ID NO: 846).

d) a sense strand comprising the sequence (mC)#(mA)#(mA)(fU)(mG)(fA)(mG)(fG)(mC)(fU)(mU)(mA)(mU)(fG)#(mA)#(mA)-DIO (SEQ ID NO: 847) and an antisense strand comprising the sequence V(mU)#(fU)#(mC)(fA)(fU)(fA)(mA)(fG)(mC)(fC)(mU)(fC)(mA)(fU)(mU)(fG)#(mU)#(mC)#(mA)#(mG)#(mG) (SEQ ID NO: 855)

e) a sense strand comprising the sequence (mA)#(mG)#(mU)(fG)(mC)(fU)(mC)(fA)(mG)(fU)(mU)(mC)(mC)(fA)#(mA)#(mA)-DIO (SEQ ID NO: 856) and an antisense strand comprising the sequence V(mU)#(fU)#(mU)(fG)(fG)(fA)(mA)(fC)(mU)(fG)(mA)(fG)(mC)(fA)(mC)(fU)#(mU)#(mG)#(mU)#(mA)#(mC) (SEQ ID NO: 850).

f) a sense strand comprising the sequence (mU)#(mC)#(mA)(fG)(mU)(fU)(mC)(fC)(mA)(fA)(mU)(mG)(mU)(fG)#(mC)#(mA)-DIO (SEQ ID NO: 857) and an antisense strand comprising the sequence V(mU)#(fG)#(mC)(fA)(fC)(fA)(mU)(fU)(mG)(fG)(mA)(fA)(mC)(fU)(mG)(fA)#(mG)#(mC)#(mA)#(mC)#(mU) (SEQ ID NO: 852); or

g) a sense strand comprising the sequence (mC)#(mU)#(mA)(fC)(mG)(fA)(mU)(fG)(mU)(fU)(mA)(mA)(mA)(fA)#(mC)#(mA)-DIO (SEQ ID NO: 853) and an antisense strand comprising the sequence V(mU)#(fG)#(mU)(fU)(fU)(fU)(mA)(fA)(mC)(fA)(mU)(fC)(mG)(fU)(mA)(fG)#(mA)#(mU)#(mU)#(mG)#(mA) (SEQ ID NO: 854);

wherein m represents a 2'-O-Me ribonucleoside, f represents a 2'-F ribonucleoside, # represents a phosphorothioate internucleoside linkage, -DIO represents a divalent oligonucleotide (DIO) linker; and V represents a vinyl phosphonate.

16. A pharmaceutical composition comprising the siRNA molecule of any one of claims 1-15 and a pharmaceutically acceptable excipient, carrier, or diluent.

17. A method of treating a synucleinopathy in a human subject in need thereof, the method comprising administering a therapeutically effective amount of the siRNA molecule of any one of claims 1-15 or the pharmaceutical composition of claim 16 to the subject.

18. The method of claim 17, wherein the synucleinopathy is Parkinson's disease, Alzheimer's disease, Lewy body dementia, or a multiple symptom atrophy.

19. The method of claim 17 or 18, wherein the siRNA molecule or the pharmaceutical composition is administered to the subject by way of intracerebroventricular, intrastriatal, intraparenchymal, or intrathecal injection.

20. A kit comprising the siRNA molecule of any one of claims 1-15, or the pharmaceutical composition of claim 16, and a package insert, wherein the package insert instructs a user of the kit to perform the method of any one of claims 17-19.