

CLAIMS

1. An RNAi oligonucleotide for reducing *SNCA* gene expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a *SNCA* mRNA target sequence of any one of SEQ ID NOs: 1846, 1683-1845, and 1847-2066, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.
2. The RNAi oligonucleotide of claim 1, wherein the sense strand is 15 to 50 nucleotides in length, optionally wherein the sense strand is 18 to 36 nucleotides in length, and/or wherein the antisense strand is 15 to 30 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length and wherein antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length, optionally at least 20 nucleotides in length, and/or wherein the region of complementarity is at least 19 contiguous nucleotides in length; optionally at least 20 contiguous nucleotides in length.
3. An RNAi oligonucleotide for reducing *SNCA* gene expression, the oligonucleotide comprising:
 - (i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *SNCA* mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 2230, 2067-2229, and 2231-2450, and
 - (ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.
4. The RNAi oligonucleotide of any one of claims 1-3, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L

forms a loop between S1 and S2 of 3-5 nucleotides in length, optionally wherein L is a triloop or a tetraloop; optionally wherein the tetraloop comprises the sequence 5'-GAAA-3'.

5. The RNAi oligonucleotide of claim 4, wherein the S1 and S2 are 1-10 nucleotides in length and have the same length; optionally wherein S1 and S2 are 6 nucleotides in length optionally wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 1680).

6. The RNAi oligonucleotide of any one of claims 1-3, wherein the oligonucleotide comprises a blunt end; optionally wherein the blunt end comprises the 3' end of the sense strand; further optionally wherein the sense strand is 20-22 nucleotides.

7. The RNAi oligonucleotide of any one of claims 1 to 6, wherein the antisense strand comprises a 3' overhang sequence of one or more nucleotides in length; optionally wherein the overhang comprises purine nucleotides, and/or wherein the 3' overhang sequence is 2 nucleotides in length; optionally wherein the 3' overhang is selected from AA, GG, AG, and GA; further optionally wherein the overhang is GG.

8. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide; optionally wherein the modified nucleotide comprises a 2'-modification, and/or wherein the 2'-modification is a modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro- β -d-arabinonucleic acid; optionally wherein the modification is a 2'-modification selected from 2'-fluoro and 2'-O-methyl.

9. The RNAi oligonucleotide of claim 8, wherein about 18% to about 23%, or 18%, 19%, 20%, 21%, 22% or 23% of the nucleotides of the sense strand comprise the 2'-fluoro modification, or wherein about 38% to about 43%, or 38%, 39%, 40%, 41%, 42% or 43% of the nucleotides of the sense strand comprise the 2'-fluoro modification, and/or

wherein about 25% to about 35%, or 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprise the 2'-fluoro modification, and/or wherein about 25% to about 35%, or 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the oligonucleotide comprise the 2'-fluoro modification, and/or wherein about 35-45%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44% or 45% of the nucleotides of the oligonucleotide comprise the 2'-fluoro modification.

10. The RNAi oligonucleotide of claim 8 or 9, wherein the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3', wherein each of positions 3, 5, 8, 10, 12, 13, 15, and 17 comprise the 2'-fluoro modification, or wherein the sense strand comprises 20 nucleotides with positions 1-20 from 5' to 3', wherein each of positions 3, 5, 8, 10, 12, 13, 15, and 17 comprise the 2'-fluoro modification, and/or wherein the antisense strand comprises 22 nucleotides with positions 1-22 from 5' to 3', and wherein each of positions 2, 3, 4, 5, 7, 10, 14, 16 and 19 comprise the 2'-fluoro modification, and/or wherein the remaining nucleotides comprise the 2'-O-methyl modification.

11. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage; optionally wherein the at least one modified internucleotide linkage is a phosphorothioate linkage, optionally wherein the antisense strand comprises the phosphorothioate linkage (i) between positions 1 and 2, and between positions 2 and 3; or (ii) between positions 1 and 2, between positions 2 and 3, and between positions 3 and 4, and wherein positions are numbered 1-4 from 5' to 3', and/or wherein the antisense strand is 22 nucleotides in length, and wherein the antisense strand comprises the phosphorothioate linkage between positions 20 and 21 and between positions 21 and 22, and wherein positions are numbered 1-22 from 5' to 3', and/or wherein the sense strand comprises the phosphorothioate linkage between positions 1 and 2, and wherein positions are numbered 1-2 from 5' to 3', and/or wherein the sense strand is 20 nucleotides in length, wherein the sense strand comprises the phosphorothioate linkage between positions between positions 1 and 2, between positions 18 and 19 and between positions 19 and 20, and wherein positions are numbered 1-20 from 5' to 3'.

12. The RNAi oligonucleotide of any one of the preceding claims, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, optionally wherein the phosphate analog is oxymethyl phosphonate, vinyl phosphonate or malonyl phosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 4'-oxymethylphosphonate.

13. The RNAi oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands; optionally wherein each targeting ligand comprises a carbohydrate, amino sugar, lipid, cholesterol, or polypeptide.

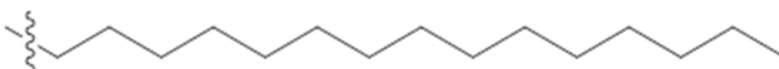
14. The RNAi oligonucleotide of any one of claims 4, 5 and 7-13, wherein the stem-loop comprises one or more targeting ligands conjugated to one or more nucleotides of the stem-loop; optionally wherein the one or more targeting ligands is conjugated to one or more nucleotides of the loop (L); optionally wherein the loop (L) comprises 4 nucleotides numbered 1-4 from 5' to 3', wherein nucleotides at positions 2, 3, and 4 each comprise one or more targeting ligands, and wherein the targeting ligands are the same or different.

15. The RNAi oligonucleotide of claim 14, wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety; optionally wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety; optionally wherein up to 4 nucleotides of loop (L) of the stem-loop are each conjugated to a monovalent GalNAc moiety.

16. The RNAi oligonucleotide of any one of claims 6-13, wherein the one or more targeting ligands is a lipid moiety; optionally wherein the lipid moiety is conjugated to the 5'terminal nucleotide of the sense strand; optionally wherein the lipid moiety is a hydrocarbon chain; optionally wherein the hydrocarbon chain is a C₈-C₃₀ hydrocarbon chain; optionally wherein the

hydrocarbon chain is a C₁₆ hydrocarbon chain; optionally wherein the C₁₆ hydrocarbon chain is

represented by:



17. The RNAi oligonucleotide of claim 16, wherein the lipid moiety is conjugated to the 2' carbon of the ribose ring of the 5' terminal nucleotide.

18. The RNAi oligonucleotide of any one of claims 1-17, wherein the region of complementarity is fully complementary to the SNCA mRNA target sequence at nucleotide positions 2-8 of the antisense strand, and wherein nucleotide positions are numbered 5' to 3', and/or

wherein the region of complementarity is fully complementary to the SNCA mRNA target sequence at nucleotide positions 2-11 of the antisense strand, and wherein nucleotide positions are numbered 5' to 3'.

19. The RNAi oligonucleotide of any one of claims 1 to 18, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 1551, 1537, 1538, 1539, 1540, 1541, 1542, 1543, 1544, 1545, 1546, 1547, 1548, 1549, 1550, 1552, 1553, 1554, 1555, 1556, 1557, 1558, 1559, 1560, 1561, 1562, 1563, 1564, 1565, 1566, 1567, 1568, 1569, 1570, 1571 and 1681, and/or wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 1586, 1572, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1583, 1584, 1585, 1587, 1588, 1589, 1590, 1591, 1592, 1593, 1594, 1595, 1596, 1597, 1598, 1599, 1600, 1601, 1602, 1603, 1604, 1605, -and 1606.

20. The RNAi oligonucleotide of any one of claims 1 to 19, wherein the sense strand and the antisense strand comprise nucleotide sequences selected from the group consisting of:

- a) SEQ ID NOs: 1551 and 1586, respectively;
- b) SEQ ID NOs: 1537 and 1572, respectively;
- c) SEQ ID NOs: 1538 and 1573, respectively;
- d) SEQ ID NOs: 1539 and 1574, respectively;

e) SEQ ID NOs: 1540 and 1575, respectively;
f) SEQ ID NOs: 1541 and 1576, respectively;
g) SEQ ID NOs: 1542 and 1577, respectively;
h) SEQ ID NOs: 1543 and 1578, respectively;
i) SEQ ID NOs: 1544 and 1579, respectively;
j) SEQ ID NOs: 1545 and 1580, respectively;
k) SEQ ID NOs: 1546 and 1581, respectively;
l) SEQ ID NOs: 1547 and 1582, respectively;
m) SEQ ID NOs: 1548 and 1583, respectively;
n) SEQ ID NOs: 1549 and 1584, respectively;
o) SEQ ID NOs: 1550 and 1585, respectively;
p) SEQ ID NOs: 1552 and 1587, respectively;
q) SEQ ID NOs: 1553 and 1588, respectively;
r) SEQ ID NOs: 1554 and 1589, respectively;
s) SEQ ID NOs: 1555 and 1590, respectively;
t) SEQ ID NOs: 1556 and 1591, respectively;
u) SEQ ID NOs: 1557 and 1592, respectively;
v) SEQ ID NOs: 1558 and 1593, respectively;
w) SEQ ID NOs: 1559 and 1594, respectively;
x) SEQ ID NOs: 1560 and 1595, respectively;
y) SEQ ID NOs: 1561 and 1596, respectively;
z) SEQ ID NOs: 1562 and 1597, respectively;
aa) SEQ ID NOs: 1563 and 1598, respectively;
bb) SEQ ID NOs: 1564 and 1599, respectively;
cc) SEQ ID NOs: 1565 and 1600, respectively;
dd) SEQ ID NOs: 1566 and 1601, respectively;
ee) SEQ ID NOs: 1567 and 1602, respectively;
ff) SEQ ID NOs: 1568 and 1603, respectively;
gg) SEQ ID NOs: 1569 and 1604, respectively;
hh) SEQ ID NOs: 1570 and 1605, respectively;
ii) SEQ ID NOs: 1571 and 1606, respectively; and

jj) SEQ ID NOs: 1681 and 1586, respectively.

21. The RNAi oligonucleotide of any one of claims 1-18, wherein the sense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 1621, 1607, 1608, 1609, 1610, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1619, 1620, 1622, 1623, 1624, 1625, 1626, 1627, 1628, 1629, 1630, 1631, 1632, 1633, 1634, 1635, 1636, 1637, 1638, 1639, 1640, 1641, and 1682, and/or wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 1656, 1642, 1643, 1644, 1645, 1646, 1647, 1648, 1649, 1650, 1651, 1652, 1653, 1654, 1655, 1657, 1658, 1659, 1660, 1661, 1662, 1663, 1664, 1665, 1666, 1667, 1668, 1669, 1670, 1671, 1672, 1673, 1674, 1675, and 1676.

22. The RNAi oligonucleotide of any one of claims 1-18, wherein the sense strand and the antisense strand comprise nucleotide sequences selected from the group consisting of:

- a) SEQ ID NOs: 1621 and 1656, respectively;
- b) SEQ ID NOs: 1607 and 1642, respectively;
- c) SEQ ID NOs: 1608 and 1643, respectively;
- d) SEQ ID NOs: 1609 and 1644, respectively;
- e) SEQ ID NOs: 1610 and 1645, respectively;
- f) SEQ ID NOs: 1611 and 1646, respectively;
- g) SEQ ID NOs: 1612 and 1647, respectively;
- h) SEQ ID NOs: 1613 and 1648, respectively;
- i) SEQ ID NOs: 1614 and 1649, respectively;
- j) SEQ ID NOs: 1615 and 1650, respectively;
- k) SEQ ID NOs: 1616 and 1651, respectively;
- l) SEQ ID NOs: 1617 and 1652, respectively;
- m) SEQ ID NOs: 1618 and 1653, respectively;
- n) SEQ ID NOs: 1619 and 1654, respectively;
- o) SEQ ID NOs: 1620 and 1655, respectively;
- p) SEQ ID NOs: 1622 and 1657, respectively;
- q) SEQ ID NOs: 1623 and 1658, respectively;
- r) SEQ ID NOs: 1624 and 1659, respectively;

s) SEQ ID NOs: 1625 and 1660, respectively;
t) SEQ ID NOs: 1626 and 1661, respectively;
u) SEQ ID NOs: 1627 and 1662, respectively;
v) SEQ ID NOs: 1628 and 1663, respectively;
w) SEQ ID NOs: 1629 and 1664, respectively;
x) SEQ ID NOs: 1630 and 1665, respectively;
y) SEQ ID NOs: 1631 and 1666, respectively;
z) SEQ ID NOs: 1632 and 1667, respectively;
aa) SEQ ID NOs: 1633 and 1668, respectively;
bb) SEQ ID NOs: 1634 and 1669, respectively;
cc) SEQ ID NOs: 1635 and 1670, respectively;
dd) SEQ ID NOs: 1636 and 1671, respectively;
ee) SEQ ID NOs: 1637 and 1672, respectively;
ff) SEQ ID NOs: 1638 and 1673, respectively;
gg) SEQ ID NOs: 1639 and 1674, respectively;
hh) SEQ ID NOs: 1640 and 1675, respectively;
ii) SEQ ID NOs: 1641 and 1676, respectively; and
jj) SEQ ID NOs: 1682 and 1656, respectively.

23. A pharmaceutical composition comprising the RNAi oligonucleotide of any one of claims 1 to 22, and a pharmaceutically acceptable carrier, delivery agent, or excipient.

24. Use of the RNAi oligonucleotide of any one of claims 1 to 22, or the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating a subject having a disease, disorder, or condition associated with *SNCA* gene expression, optionally wherein the disease, disorder, or condition associated with *SNCA* gene expression is multiple system atrophy, dementia with Lewy bodies, or Parkinson disease.

25. An *in vitro* method for reducing *SNCA* gene expression in a cell, or a population of cells, the method comprising the steps of:

contacting the cell or the population of cells with the RNAi oligonucleotide of any one of claims 1 to 22, or the pharmaceutical composition of claim 23; optionally wherein reducing *SNCA* gene expression comprises reducing an amount or level of *SNCA* mRNA, an amount or level of *SNCA* protein, a *SNCA* activity/function, or a combination thereof.

26. Use of the RNAi oligonucleotide of any one of claims 1 to 22, or the pharmaceutical composition of claim 23, in the manufacture of a medicament for reducing *SNCA* gene expression in a subject; optionally wherein reducing *SNCA* gene expression comprises reducing an amount or level of *SNCA* mRNA, an amount or level of *SNCA* protein, a *SNCA* activity/function, or a combination thereof.

27. The use of claim 26, wherein the subject has a disease, disorder, or condition associated with *SNCA* gene expression; optionally wherein the disease, disorder, or condition associated with *SNCA* gene expression is multiple system atrophy, dementia with Lewy bodies, or Parkinson disease.

28. The use of any one of claims 24, 26, and 27, wherein *SNCA* gene expression is reduced in tissue of one or more regions of the central nervous system (CNS), and wherein the tissue is associated with Parkinson disease; optionally wherein tissue associated with Parkinson disease is selected from: putamen, midbrain tegmentum, substantia nigra, pons, and medulla; and/or wherein *SNCA* gene expression is reduced in tissue of one or more regions of the central nervous system (CNS), and wherein the tissue is associated with multiple system atrophy; optionally wherein tissue associated with multiple system atrophy is selected from: caudate nucleus, putamen, midbrain tegmentum, substantia nigra, pons, cerebellar cortex, cerebellar white matter, medulla, cervical spinal cord, thoracic spinal cord, and lumbar spinal cord; and/or

wherein *SNCA* gene expression is reduced in one or more regions of the central nervous system (CNS) selected from: cervical spinal cord, thoracic spinal cord, lumbar spinal cord, frontal cortex, temporal cortex, cerebellum, midbrain, occipital cortex, parietal cortex, hippocampus, caudate nucleus, thalamus, brainstem, motor cortex, globus pallidus, midbrain tegmentum, substantia nigra, pons, cerebellar white matter, and cerebellar dentate nucleus.

29. The use of any one of Claims 24 and 26 to 28, wherein said medicament is to be administered in combination with a second composition or therapeutic agent.

30. The RNAi oligonucleotide of any one of claims 1 to 22, or the pharmaceutical composition of claim 23, for use as a medicament.

31. A kit comprising the RNAi oligonucleotide of any one of claims 1 to 22, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder, or condition associated with *SNCA* gene expression; optionally wherein the disease, disorder, or condition associated with *SNCA* gene expression is multiple system atrophy, dementia with Lewy bodies, and Parkinson disease.