

CLAIMS

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of LRRK2, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 2.

2. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of LRRK2, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding LRRK2, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2.

3. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of LRRK2, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding LRRK2, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 3, 4, 6 or 7.

4. The dsRNA agent of any one of claims 1-3, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 3383-3403, 2105-2125, 2356-2376, 5413-5433, 2603-2623, 3563-3583, 2192-2212, 3088-3108, 3105-3125, 2203-2223, 7348-7368, 7097-7117, 6319-6339, 3886-3906, 5190-5210, 3964-3984, 5138-5158, 1254-1274, 7098-7118, 7048-7068, 7050-7070, 2764-2784, 3087-3107, 7526-7546, 4849-4869, 5272-5292, 468-488, 7520-7540, 3720-3740, 4016-4036, 7792-7812, 2515-2535, 2286-2306, 4014-4034, 3721-3741, 2284-2304, 1896-1916, 3876-3896, 7788-7808, 4013-4033, 1275-1295, 7527-7547, 3606-3626, 7525-7545, 468-488, 1254-1274, 2105-2125, 2192-2212, 2203-2223, 2603-2623, 2764-2784, 3087-3107, 3088-3108, 3383-3403, 3563-3583, 3876-3896, 3886-3906, 3964-3984, 4849-4869, 5138-5158, 5190-5210, 5272-5292, 6319-6339, 7097-7117, 7098-7118, and 7348-

7368 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 2.

5. The dsRNA agent of any one of claims 1-4, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-601140.1, AD-599927.1, AD-612673.1, AD-615420.1, AD-600406.1, AD-601294.1, AD-600013.1, AD-600853.1, AD-613382.1, AD-600024.1, AD-604701.1, AD-604452.1, AD-603747.1, AD-601616.1, AD-602766.1, AD-601694.1, AD-602734.1, AD-599139.1, AD-604453.1, AD-616783.1, AD-616785.1, AD-600566.1, AD-600852.1, AD-617239.1, AD-602466.1, AD-602848.1, AD-598424.1, AD-617233.1, AD-613965.1, AD-614239.1, AD-617466.1, AD-612820.1, AD-612611.1, AD-614237.1, AD-613966.1, AD-612609.1, AD-612246.1, AD-601606.1, AD-617462.1, AD-614236.1, AD-611650.1, AD-617240.1, AD-613851.1, AD-617238.1, AD-1335323.1, AD-1335325.1, AD-1335324.1, AD-1508169, AD-1508884, AD-1509672, AD-1509758, AD-1509769, AD-1510151, AD-1510311, AD-1510597, AD-1510598, AD-1510885, AD-1511039, AD-1511351, AD-1511361, AD-1511439, AD-1512211, AD-1512479, AD-1512511, AD-1512593, AD-1513492, AD-1514197, AD-1514198 and AD-1514446.

6. The dsRNA agent of claim 1 or 2, wherein the nucleotide sequence of the sense and antisense strand comprise any one of the sense and antisense strand nucleotide sequences in any one of Tables 3, 4, 6 or 7.

7. The dsRNA agent of any one of claims 1-6, wherein the sense strand, the antisense strand, or both the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

8. The dsRNA agent of claim 7, wherein the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent.

9. The dsRNA agent of claim 7 or 8, wherein the lipophilic moiety is conjugated via a linker or carrier.

10. The dsRNA agent of any one of claims 7-9, wherein lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

11. The dsRNA agent of any one of claims 1-10, wherein the hydrophobicity of the double-stranded RNA agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNA agent, exceeds 0.2.

12. The dsRNA agent of claim 11, wherein the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.
13. The dsRNA agent of any one of claims 1-12, wherein the dsRNA agent comprises at least one modified nucleotide.
14. The dsRNA agent of claim 13, wherein no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides
15. The dsRNA agent of claim 13, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.
16. The dsRNA agent of any one of claims 13-15, wherein at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3'-terminal deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxy-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofuran-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.
17. The dsRNA agent of claim 16, wherein the modified nucleotide is selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxythymidine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

18. The dsRNA agent of claim 16, wherein the modified nucleotide comprises a short sequence of 3'-terminal deoxythymidine nucleotides (dT).
19. The dsRNA agent of claim 16, wherein the modifications on the nucleotides are 2'-O-methyl, GNA and 2'fluoro modifications.
20. The dsRNA agent of any one of claims 1-19, further comprising at least one phosphorothioate internucleotide linkage.
21. The dsRNA agent of claim 20, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.
22. The dsRNA agent of any one of claims 1-21, wherein each strand is no more than 30 nucleotides in length.
23. The dsRNA agent of any one of claims 1-22, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.
24. The dsRNA agent of any one of claims 1-23, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.
25. The dsRNA agent of any one of claims 1-24, wherein the double stranded region is 15-30 nucleotide pairs in length.
26. The dsRNA agent of claim 25, wherein the double stranded region is 17-23 nucleotide pairs in length.
27. The dsRNA agent of claim 25, wherein the double stranded region is 17-25 nucleotide pairs in length.
28. The dsRNA agent of claim 25, wherein the double stranded region is 23-27 nucleotide pairs in length.
29. The dsRNA agent of claim 25, wherein the double stranded region is 19-21 nucleotide pairs in length.

30. The dsRNA agent of claim 25, wherein the double stranded region is 21-23 nucleotide pairs in length.
31. The dsRNA agent of any one of claims 1-30, wherein each strand has 19-30 nucleotides.
32. The dsRNA agent of any one of claims 1-30, wherein each strand has 19-23 nucleotides.
33. The dsRNA agent of any one of claims 1-30, wherein each strand has 21-23 nucleotides.
34. The dsRNA agent of any one of claims 8-33, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.
35. The dsRNA agent of claim 34, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand via a linker or carrier.
36. The dsRNA agent of claim 35, wherein the internal positions include all positions except the terminal two positions from each end of the at least one strand.
37. The dsRNA agent of claim 35, wherein the internal positions include all positions except the terminal three positions from each end of the at least one strand.
38. The dsRNA agent of claim 35-37, wherein the internal positions exclude a cleavage site region of the sense strand.
39. The dsRNA agent of claim 38, wherein the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.
40. The dsRNA agent of claim 38, wherein the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.
41. The dsRNA agent of claim 35-37, wherein the internal positions exclude a cleavage site region of the antisense strand.
42. The dsRNA agent of claim 41, wherein the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.

43. The dsRNA agent of claim 35-37, wherein the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.
44. The dsRNA agent of any one of claims 8-43, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5' end of each strand.
45. The dsRNA agent of claim 44, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand.
46. The dsRNA agent of claim 8, wherein the internal positions in the double stranded region exclude a cleavage site region of the sense strand.
47. The dsRNA agent of any one of claims 7-46, wherein the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.
48. The dsRNA agent of claim 47, wherein the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.
49. The dsRNA agent of claim 47, wherein the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.
50. The dsRNA agent of claim 47, wherein the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.
51. The dsRNA agent of claim 47, wherein the lipophilic moiety is conjugated to position 16 of the antisense strand.
52. The dsRNA agent of any one of claims 7-51, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

53. The dsRNA agent of claim 52, wherein the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl) lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

54. The dsRNA agent of claim 52, wherein the lipophilic moiety contains a saturated or unsaturated C4-C30 hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

55. The dsRNA agent of claim 54, wherein the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

56. The dsRNA agent of claim 54, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

57. The dsRNA agent of claim 56, wherein the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

58. The dsRNA agent of any one of claims 7-57, wherein the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

59. The dsRNA agent of claim 58, wherein the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3] dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyll; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

60. The dsRNA agent of any one of claims 7-57, wherein the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

61. The double-stranded iRNA agent of any one of claims 7-60, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

62. The dsRNA agent of any one of claims 7-61, wherein the lipophilic moiety or targeting ligand is conjugated via a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

63. The dsRNA agent of any one of claims 7-62, wherein the 3' end of the sense strand is protected via an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3] dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

64. The dsRNA agent of any one of claims 7-61, further comprising a targeting ligand that targets a liver tissue.

65. The dsRNA agent of any one of claims 7-61, further comprising a targeting ligand that targets a neuronal cell.

66. The dsRNA agent of any one of claims 7-61, further comprising a targeting ligand that targets any ocular cell.

67. The dsRNA agent of claim 64, wherein the targeting ligand is a GalNAc conjugate.

68. The dsRNA agent of any one of claims 1-67 further comprising
a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.

69. The dsRNA agent of any one of claims 1-67 further comprising
a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and

a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

70. The dsRNA agent of any one of claims 1-67 further comprising
a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

71. The dsRNA agent of any one of claims 1-67 further comprising
a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration,
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

72. The dsRNA agent of any one of claims 1-67 further comprising
a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,
a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and
a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

73. The dsRNA agent of any one of claims 1-72, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

74. The dsRNA agent of claim 73, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

75. The dsRNA agent of any one of claims 1-72, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

76. The dsRNA agent of any one of claims 1-72, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.
77. A cell containing the dsRNA agent of any one of claims 1-76.
78. A pharmaceutical composition for inhibiting expression of a gene encoding **LRRK2**, comprising the dsRNA agent of any one of claims 1-76.
79. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-76 and a lipid formulation.
80. The pharmaceutical composition of claim 78 or 79, wherein dsRNA agent is in an unbuffered solution.
81. The pharmaceutical composition of claim 80, wherein the unbuffered solution is saline or water.
82. The pharmaceutical composition of claim 78 or 79, wherein said dsRNA agent is in a buffer solution.
83. The pharmaceutical composition of claim 82, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.
84. The pharmaceutical composition of claim 82, wherein the buffer solution is phosphate buffered saline (PBS).
85. A method of inhibiting expression of a **LRRK2** gene in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-76, or the pharmaceutical composition of any one of claims 78-84, thereby inhibiting expression of the **LRRK2** gene in the cell.
86. The method of claim 85, wherein the cell is within a subject.
87. The method of claim 86, wherein the subject is a human.
88. The method of claim 87, wherein the subject has a **LRRK2**-associated disorder.

89. The method of claim 88, wherein the LRRK2-associated disorder is a neurodegenerative disorder.
90. The method of claim 89, wherein the neurodegenerative disorder is a familial disorder.
91. The method of claim 89, wherein the neurodegenerative disorder is a sporadic disorder.
92. The method of claim 90 or 91, wherein the neurodegenerative disorder is Parkinson's disease.
93. The method of claim 88, wherein the LRRK2-associated disorder is an ocular disorder.
94. The method of any one of claims 85-93, wherein contacting the cell with the dsRNA agent inhibits the expression of LRRK2 by at least about 25%.
95. The method of any one of claims 85-94, wherein inhibiting expression of LRRK2 decreases LRRK2 protein level in serum of the subject by at least about 25%.
96. A method of treating a subject having a disorder that would benefit from reduction in LRRK2 expression, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-76, or the pharmaceutical composition of any one of claims 78-84, thereby treating the subject having the disorder that would benefit from reduction in LRRK2 expression.
97. A method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in LRRK2 expression, comprising administering to the subject a prophylactically effective amount of the dsRNA agent of any one of claims 1-76, or the pharmaceutical composition of any one of claims 78-84, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in LRRK2 expression.
98. The method of claim 96 or 97, wherein the disorder is a LRRK2-associated disorder.
99. The method of claim 98, wherein the LRRK2-associated disorder is selected from the group consisting of Parkinson's disease, and ocular disorders.
100. The method of any one of claims 97-99, wherein the subject is human.
101. The method of claim 100, wherein the administration of the agent to the subject causes a decrease in LRRK2 protein accumulation.

102. The method of any one of claims 96-101, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.
103. The method of any one of claims 96-102, wherein the dsRNA agent is administered to the subject intrathecally.
104. The method of any one of claims 96-103, further comprising determining the level of LRRK2 in a sample(s) from the subject.
105. The method of claim 104, wherein the level of LRRK2 in the subject sample(s) is a Lrrk2 protein level in a blood, serum, or cerebrospinal fluid sample(s).
106. The method of any one of claims 96-105, further comprising administering to the subject an additional therapeutic agent.
107. A kit comprising the dsRNA agent of any one of claims 1-76 or the pharmaceutical composition of any one of claims 78-84.
108. A vial comprising the dsRNA agent of any one of claims 1-76 or the pharmaceutical composition of any one of claims 78-84.
109. A syringe comprising the dsRNA agent of any one of claims 1-76 or the pharmaceutical composition of any one of claims 78-84.
110. An intrathecal pump comprising the dsRNA agent of any one of claims 1-76 or the pharmaceutical composition of any one of claims 78-84.