What is Claimed

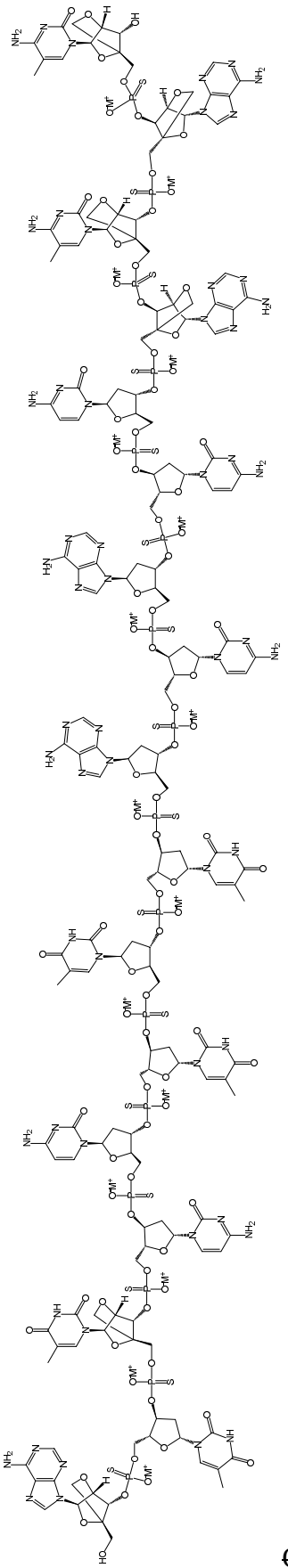
1. An antisense oligonucleotide (ASO) comprising~~, consisting essentially of, or consisting of~~ the contiguous nucleotide sequence of AtTcctttacaccACAC (SEQ ID NO: 4), wherein the upper letter is beta-D-oxy-LNA and the lower letter is DNA.

2. The ASO of claim 1, which comprises an internucleotide linkage selected from the group consisting of a phosphodiester linkage, a phosphotriester linkage, a methylphosonate linkage, a phosphoramidate linkage, a phosphorothioate linkage, and combinations thereof.

3. The ASO of claim 2, wherein the internucleotide linkage is a phosphorothioate linkage.

4. The ASO of claim 1, wherein the contiguous nucleotide sequence is OxyAs DNAts OxyTs DNAcs DNAcs DNAts DNAts DNAts DNAas DNAcs DNAas DNAcs DNAcs OxyAs OxyMCs OxyAs OxyMC, wherein OxyA, OxyT, and Oxy MC are adenine beta D-oxy-LNA, thymine beta D-oxy-LNA, and methyl cytosine beta D-oxy-LNA, respectively, wherein DNAt, DNAc, and DNAa are thymine DNA, cytosine DNA, and adenine DNA, respectively, and wherein s is a phosphorothioate linkage between two nucleotides.

5. The ASO of ~~any one of~~ claim~~s~~ 1~~ to 4~~, comprising~~ a molecular formula of~~ the structure:



~~$C_{171}H_{214}N_{56}O_{90}P_{16}S_{16}$ and a structure as shown in FIG. 1B~~,

wherein M^+ is a counterion.

6. The ASO of claim 5, wherein the counterion is selected from the group consisting of H^+, Na^+, $NH4^+$, and any combination thereof.

7. The ASO of claim 6, wherein the counterion is Na^+.

8. A conjugate comprising the ASO of ~~any one of~~ claim~~s~~ 1~~ to 7~~, wherein the ASO is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

9. The conjugate of claim 8, wherein the non-nucleotide or non-polynucleotide moiety comprises a protein, a fatty acid chain, a sugar residue, a glycoprotein, a polymer, or any combinations thereof.

10. A pharmaceutical composition comprising the ASO of ~~any one~~ claim~~s~~ 1~~ to 7 or the conjugate of claim 8 or 9~~ and a pharmaceutically acceptable carrier.

11. The composition of claim 10, which further comprises a therapeutic agent.

12. The composition of claim 11, wherein the therapeutic agent is an alpha-synuclein antagonist.

13. A kit comprising the ASO of ~~any one~~ claim~~s~~ 1~~ to 7, the conjugate of claim 8 or 9, or the composition of any one of claims 10 to 12,~~ and instructions for use.

~~14. A diagnostic kit comprising the ASO of any one claims 1 to 7, the conjugate of claim 8 or 9, or the composition of any one of claims 10 to 12, and instructions for use.~~

14~~15~~. Use of the ASO of claim 1 for the manufacture of a medicament for ~~A method of~~ inhibiting or reducing expression of SNCA mRNA and/or SNCA protein ~~expression~~ in a cell, ~~the method comprising administering the ASO of any one claims 1 to 7, the conjugate of claim 8 or 9, or the composition of any one of claims 10 to 12~~ wherein the medicament is to be administered to the cell expressing SNCA mRNA and/or SNCA protein~~, wherein the SNCA protein expression in the cell is~~ to inhibit~~ed~~ or reduce~~d after the administration~~ the expression of SNCA mRNA and/or SCNA protein in the cell.

~~16. The method of claim 15, wherein the ASO inhibits or reduces expression of *SNCA* mRNA in the cell after the administration.~~

~~17. The method of claim 15 or 16, wherein the expression of *SNCA* mRNA is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% after the administration compared to a cell not exposed to the ASO.~~

~~18. The method of any one of claims 15 to 17, wherein the ASO reduces expression of SNCA protein in the cell after the administration by at least about 60%, at least about 70%, at least about 80%, or at least about 90% compared to a cell not exposed to the ASO.~~

~~19. The method of any one of claims 15 to 18, wherein the cell is a neuron.~~

~~20. A method for treating a synucleinopathy in a subject in need thereof, comprising administering an effective amount of the ASO of any one claims 1 to 7, the conjugate of claim 8 or 9, or the composition of any one of claims 10 to 12 to the subject.~~

~~21. Use of the ASO of any one claims 1 to 7, the conjugate of claim 8 or 9, or the composition of any one of claims 10 to 12 for the manufacture of a medicament.~~

15~~22~~. Use of the ASO of ~~any one~~ claim~~s~~ 1 ~~to 7, the conjugate of claim 8 or 9, or the composition of any one of claims 10 to 12~~ for the manufacture of a medicament for the treatment of a synucleinopathy in a subject in need thereof, wherein an effective amount of the medicament is to be administered to the subject.

17~~23~~. The ASO ~~of any one~~ of claim~~s~~ 1 ~~to 7, the conjugate of claim 8 or 9, or the composition of any one of claims 10 to 12~~ for use in therapy.

18. The ASO of claim 1 for use in therapy of inhibiting or reducing expression of SNCA mRNA and/or SNCA protein in a cell, wherein the ASO is to be administered to the cell expressing SNCA mRNA and/or SNCA protein to inhibit or reduce the expression of SNCA mRNA and/or SCNA protein in the cell.

19~~24~~. The ASO of ~~any one~~ claim~~s~~ 1 ~~to 7, the conjugate of claim 8 or 9, or the composition of any one of claims 10 to 12~~ for use in therapy of a synucleinopathy in a subject in need thereof.

20~~25~~. The ~~method of claim 20, the~~ use of claim 15~~21 or 22,~~ or the ASO for use of claim 19~~23 or 24~~, wherein the synucleinopathy is selected from the group consisting of Parkinson's

disease, Parkinson's Disease Dementia (PDD), multiple system atrophy, dementia with Lewy bodies, and any combinations thereof.

21. A pharmaceutical composition comprising the ASO of any one claims 3 to 5 or 7 and a pharmaceutically acceptable carrier.

~~26. The method of claim 20 or 25, the use of any one of claims 21, 22, and 25, or the ASO for use of any one of claims 23 to 25, wherein the subject is a human.~~

~~27. The method of any one of claims 20, 25, and 26 , the use of any one of claims 21, 22, 25, and 26, or the ASO for use of any one of claims 23 to 26, wherein the ASO, the conjugate, or the composition is administered orally, parenterally, intrathecally, intra-cerebroventricularly, pulmonarily, topically, or intraventricularly.~~