CLAIMS

1. A fusion protein comprising a zinc finger protein (ZFP) domain and a transcription repressor domain, wherein the ZFP domain binds to a target region of a human alpha-synuclein gene (*SNCA* gene).

2. The fusion protein of claim 1, wherein the target region is within 1 kb of a transcription start site (TSS) in the *SNCA* gene.

3. The fusion protein of claim 2, wherein the TSS is TSS1, 2a, or 2b.

4. The fusion protein of claim 3, wherein the target region is within 500 bps upstream of TSS 1, within 500 bps downstream of TSS 1, within 500 bps upstream of TSS 2a, and/or within 500 bps downstream of TSS 2b, of the *SNCA* gene.

5. The fusion protein of any one of the preceding claims, wherein the ZFP domain comprises six zinc fingers and the fusion protein optionally represses expression of the *SNCA* gene by at least about 40%, 75%, 90%, 95%, or 99% with no or minimal detectable off-target binding or activity.

6. The fusion protein of any one of the preceding claims, wherein the transcription repressor domain comprises a KRAB domain amino acid sequence from human KOX1.

7. The fusion protein of any one of the preceding claims, wherein the ZFP domain is linked to the transcription repressor through a peptide linker.

8. The fusion protein of any one of the preceding claims, wherein the ZFP domain comprises a DNA-binding recognition helix sequence shown in Table 1.

9. The fusion protein of any one of the preceding claims, wherein the ZFP domain comprises the DNA-binding recognition helix sequences as shown in a single row of Table 1.

10. A nucleic acid construct comprising a coding sequence for the fusion protein of any one of claims 1-9, wherein the coding sequence is linked operably to a transcription regulatory element.

11. The nucleic acid construct of claim 10, wherein the transcription regulatory element is a mammalian promoter that is constitutively active or inducible in a brain cell, and wherein the promoter is optionally a human synapsin I promoter.

12. A recombinant virus comprising the nucleic acid construct of claim 10 or 11.

13. The recombinant virus of claim 12, wherein the recombinant virus is an adeno-associated viral vector, an adenoviral vector, or a lentiviral vector.

14. A pharmaceutical composition comprising the nucleic acid construct of claim 10 or 11, or the recombinant virus of claim 12 or 13, and a pharmaceutically acceptable carrier.

15. A host cell comprising the nucleic acid construct of claim 10 or 11, or the recombinant virus of claim 12 or 13.

16. The host cell of claim 15, wherein the host cell is a human cell.

17. The host cell of claim 15, wherein the host cell is a brain cell or a pluripotent stem cell, wherein the stem cell is optionally an embryonic stem cell or an inducible pluripotent stem cell (iPSC).

18. A method of inhibiting expression of alpha-synuclein in a human brain cell, comprising introducing into the cell a fusion protein of any one of claims 1-9, optionally through introduction of a nucleic acid construct of claim 10 or 11 or a recombinant virus of claim 12 or 13, thereby inhibiting the expression of alpha-synuclein in the cell.

19. The method of claim 18, wherein the human brain cell is a neuron, a glial cell, an ependymal cell, or a neuroepithelial cell.

20. The method of claim 18 or 19, wherein the cell is in the brain of a patient suffering from or at risk of developing Parkinson's disease, Lewy body dementia, Alzheimer's disease, multiple system atrophy, or another synucleinopathy.

21. The method of any one of claims 18-20, comprising introducing into the cell a recombinant virus that expresses the fusion protein.

22. The method of claim 21, wherein the recombinant virus is an adeno-associated virus (AAV), optionally of serotype 9.

23. Use of a recombinant AAV encoding a fusion protein of any one of claims 1-9 in the manufacture of a medicament for treating a synucleinopathy in a patient, wherein said recombinant AAV encoding said fusion protein is to be administered to the patient.

24. The use of claim 23, wherein the AAV is introduced to the patient via intravenous, intrathecal, intracerebroventricular, intra-cisternal magna, intrastriatal, or intranigral injection, or injection into any brain region.

25. The use of claim 23 or 24, wherein the synucleinopathy is Parkinson's disease, Lewy body dementia, Alzheimer's disease, or multiple system atrophy.

26. A fusion protein of any one of claims 1-9, a nucleic acid construct of claim 10 or 11, a recombinant virus of claim 12 or 13, or a pharmaceutical composition of claim 14 for use in the method of any one of claims 18-22.

27. Use of a fusion protein of any one of claims 1-9, a nucleic acid construct of claim 10 or 11, or a recombinant virus of claim 12 or 13 for the manufacture of a medicament in the method of any one of claims 18-22.