

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 microtubule-associated protein tau (*MAPT*) gene.
2. The fusion protein of claim 1, wherein the target region is within 1.5 kb of a transcription start site (TSS) in the *MAPT* gene.
3. The fusion protein of claim 2, wherein the target region is within 1000 bps upstream of the TSS, and/or within 500 bps downstream of the TSS of the *MAPT* gene.
4. The fusion protein of any one of the preceding claims, wherein the fusion protein represses expression of the *MAPT* gene by at least about 40%, 75%, 90%, 95%, or 99% with no or minimal detectable off-target binding or activity.
5. The fusion protein of any one of the preceding claims, wherein the transcription repressor domain comprises a KRAB domain, wherein the KRAB domain optionally is from a human KOX1 protein.
6. The fusion protein of any one of the preceding claims, wherein the DNA-binding domain is linked to the transcription repressor through a peptide linker.
7. The fusion protein of any one of the preceding claims, wherein the ZFP domain comprises a DNA-binding recognition helix sequence shown in FIG. 14 or FIG. 16.
8. 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 FIG. 14 or FIG. 16.
9. The fusion protein of claim any one of the preceding claims, wherein the ZFP domain of the fusion protein

comprises four, five, or six zinc fingers;
binds to a target sequence shown in FIG. 14 or FIG. 16;
comprises the DNA-binding recognition helix sequences of a ZFP
transcription factor shown in FIG. 15 or FIG. 17;
comprises the DNA-binding recognition helix sequences linked as shown in
FIG. 14, FIG. 15, FIG. 16, or FIG. 17; and/or
comprises an amino acid sequence selected from SEQ ID NOs: 89-196, 197-
248 and 267-307.

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, wherein the construct is optionally a recombinant viral construct.

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 or 16, 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 tau 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, a recombinant virus of claim 12 or 13, or a pharthereby inhibiting the expression of tau in the cell.
19. The method of claim 18, wherein the human brain cell is a neuron, a glial cell, an ependymal cell, a neuroepithelial cell, an endothelial cell, or an oligodendrocyte.
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 Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, traumatic brain injury (TBI), seizure disorders, corticobasal degeneration (CBD), chronic traumatic encephalopathy (CTE), or another tauopathy.
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 or a pseudotype derived from AAV9.
23. A method of treating a tauopathy in a patient in need thereof, comprising administering to the patient a recombinant AAV or a nucleic acid construct encoding a fusion protein of any one of claims 1-9.
24. The method of claim 23, wherein the AAV or nucleic acid construct is introduced to the patient via an intravenous, intrathecal, intracerebral, intracerebroventricular, intra-cisternal magna, intrahippocampal, intrathalamic, or intraparenchymal route.
25. The method of claim 23 or 24, wherein the tauopathy is Alzheimer's disease, or frontotemporal dementia, progressive supranuclear palsy, traumatic brain injury (TBI), seizure disorders, corticobasal degeneration (CBD), or chronic traumatic encephalopathy (CTE).

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 18-25.

27. Use of a fusion protein of any one of claims 1-9, or a nucleic acid construct of claim 10 or 11, or a recombinant virus of claim 12 or 13, for the manufacture of a medicament for use in the method of any one of claims 18-25.