

\CLAIMS

1. — ~~A method of treating, preventing and/or curing a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of one or more viral vectors comprising a transgene encoding retromer core protein VPS35 and at least one transgene encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.~~

2. — ~~A method of treating, preventing and/or curing a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of one or more compositions comprising at least one viral vector comprising a transgene encoding retromer core protein VPS35 and at least one transgene encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.~~

31. ~~A method of treating, preventing and/or curing a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of~~Use of ~~one or more compositions comprising a nucleic acid encoding retromer core protein VPS35 and at least one nucleic acid encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof, in the manufacture of a medicament for treating, preventing and/or curing a neurogenerative disease or disorder in a subject.~~

4. — ~~A method of alleviating one or more symptoms of a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of the one or more viral vectors comprising a transgene encoding retromer core protein VPS35 and at least one transgene encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.~~

5. — ~~A method of alleviating one or more symptoms of a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of one or more compositions comprising at least one viral vector comprising a~~

~~transgene encoding retromer core protein VPS35 and at least one transgene encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.~~

~~6. — A method of alleviating one or more symptoms of a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of one or more compositions comprising a nucleic acid encoding retromer core protein VPS35 and at least nucleic acid encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.~~

2. The use of claim 1, wherein the nucleic acid encoding retromer core protein VPS35 and the at least one nucleic acid encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof, are provided in one or more viral vectors.

73. The method use of any of claims 2 and 5~~claim 2~~, wherein ~~a therapeutically effective amount of a~~ the one or more compositions comprise a first composition comprising at least one viral vector comprising a transgene encoding retromer core protein VPS35 is administered to a subject, and a therapeutically effective amount of and a second composition comprising at least one viral vector comprising a transgene encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof is administered to the subject.

84. The method use of claim 73, wherein a therapeutically effective amount of a third composition comprising at least one viral vector comprising a transgene encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof is administered to the subject.

95. The method use of claim 73, wherein the first and second composition are administered sequentially.

106. The method use of claim 73, wherein the first and second composition are administered simultaneously.

~~117.~~ The ~~method-use~~ of claim ~~84~~, wherein the first, second and third composition are administered sequentially.

~~128.~~ The ~~method-use~~ of claim ~~84~~, wherein the first, second and third composition are administered simultaneously.

~~139.~~ The ~~method-use~~ of any one of claims ~~2, 3, 5, and 6~~1-8, wherein the one or more compositions further comprises a pharmaceutical carrier.

~~1410.~~ The ~~method-use~~ of any one of claims ~~1-13~~1-9, wherein the neurodegenerative disease or disorder is chosen from the group consisting of Alzheimer's disease (AD), Parkinson's disease, neuronal ceroid lipofuscinosis (NCL), transmissible spongiform encephalopathies (TSEs or prion disease), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), frontotemporal lobar dementia linked to chromosome 17q21-22 and its subtypes (FTLD-17/FTLD-Tau), Lewy Body Disease (LBD), amyotrophic lateral sclerosis (ALS), frontal-temporal degeneration (FTD), ALS-FTD, and chronic traumatic encephalopathy (CTE).

~~1511.~~ A viral vector comprising at least one transgene encoding retromer core protein VPS35 and encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.

~~16.~~—The vector of claim ~~15~~, wherein the retromer core protein VPS35 encoded by the transgene has an amino acid sequence that is at least 85% identical to the amino acid sequence of VPS35 (SEQ ID NO: 1).

~~17~~12. The vector of claim ~~15~~11, wherein the retromer core protein VPS35 encoded by the transgene has the amino acid sequence of VPS35 (SEQ ID NO: 1).

~~18.~~—The vector of claim ~~15~~, wherein the transgene encoding the retromer core protein Vps35 comprises human Vps35 (SEQ ID NO: 1).

~~19. The vector of claim 15, wherein the transgene has a nucleic acid sequence that is at least 70% identical to the nucleic acid sequence encoding VPS35 (SEQ ID NO: 1).~~

~~20~~13. The vector of claim ~~15~~11, wherein the transgene has the nucleic acid sequence of SEQ ID NO: 10.

~~21. The vector of claim 15, wherein the retromer core protein VPS26a encoded by the transgene has an amino acid sequence that is at least 85% identical to the amino acid sequence of VPS26a (SEQ ID NO: 2).~~

~~22~~14. The vector of claim ~~15~~11, wherein the retromer core protein Vps26a encoded by the transgene has the amino acid sequence of VPS26a (SEQ ID NO: 2).

~~23. The vector of claim 15, wherein the transgene encoding the retromer core protein Vps35 comprises human VPS26a (SEQ ID NO: 2).~~

~~24. The vector of claim 15, wherein the transgene has a nucleic acid sequence that is at least 70% identical to the nucleic acid sequence encoding VPS26a (SEQ ID NO: 2).~~

~~25. The vector of claim 15, wherein the retromer core protein VPS26b encoded by the transgene has an amino acid sequence that is at least 85% identical to the amino acid sequence of VPS26b (SEQ ID NO: 3).~~

~~26~~15. The vector of claim ~~15~~11, wherein the retromer core protein VPS26b encoded by the transgene has the amino acid sequence of VPS26b (SEQ ID NO: 3).

~~27. The vector of claim 15, wherein the transgene encoding the retromer core protein VPS35 comprises human VPS26b (SEQ ID NO: 3).~~

~~28. The vector of claim 15, wherein the transgene has a nucleic acid sequence that is at least 70% identical to the nucleic acid sequence encoding VPS26b (SEQ ID NO: 3).~~

~~29~~16. The vector of any one of claims ~~1-28~~2-15, wherein the vector is selected from the group consisting of adeno-associated virus (AAV), adenovirus, lentivirus, retrovirus, poxvirus, baculovirus, herpes simplex virus, vaccinia virus, and a synthetic virus.

~~30.~~—The vector of claim 29, wherein the viral vector is an AAV.

~~31.~~—The vector of claim 30, wherein the AAV is an AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, and AAVrh10.

~~32.~~—The vector of claim 30, wherein the AAV is chosen from the group consisting of AAV9 and AAV2/9.

~~33.~~—The vector of any one of claims ~~1-32~~, wherein the transgene is operably linked to a promoter that induces expression of the transgene in a neural cell.

~~34.~~—The vector of any one of claims ~~1-33~~, wherein the transgene is operably linked to an enhancer that induces expression of the transgene in a neural cell.

~~35~~17. A composition comprising at least one viral vector comprising a transgene encoding retromer core protein VPS35 and a transgene encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.

~~36.~~—The composition of claim ~~35~~, wherein the retromer core protein VPS35 encoded by the transgene has an amino acid sequence that is at least 85% identical to the amino acid sequence of VPS35 (SEQ ID NO: 1).

~~37~~18. The composition of claim ~~35~~17, wherein the retromer core protein VPS35 encoded by the transgene has the amino acid sequence of VPS35 (SEQ ID NO: 1).

~~38.~~—The composition of claim ~~35~~, wherein the transgene encoding the retromer core protein VPS35 comprises human VPS35 (SEQ ID NO: 1).

~~39. The composition of claim 35, wherein the transgene has a nucleic acid sequence that is at least 70% identical to the nucleic acid sequence encoding VPS35 (SEQ ID NO: 1).~~

~~40~~19. The composition of claim ~~35~~17, wherein the transgene has the nucleic acid sequence of SEQ ID NO: 10.

~~41. The composition of claim 35, wherein the retromer core protein VPS26a encoded by the transgene has an amino acid sequence that is at least 85% identical to the amino acid sequence of VPS26a (SEQ ID NO: 2).~~

~~42~~20. The composition of claim ~~35~~17, wherein the retromer core protein VPS26a encoded by the transgene has the amino acid sequence of VPS26a (SEQ ID NO: 2).

~~43. The composition of claim 35, wherein the transgene encoding the retromer core protein Vps35 comprises human VPS26a (SEQ ID NO: 2).~~

~~44. The composition of claim 35, wherein the transgene has a nucleic acid sequence that is at least 70% identical to the nucleic acid sequence encoding VPS26a (SEQ ID NO: 2).~~

~~45. The composition of claim 35, wherein the retromer core protein VPS26b encoded by the transgene has an amino acid sequence that is at least 85% identical to the amino acid sequence of VPS26b (SEQ ID NO: 3).~~

~~46~~21. The composition of claim ~~35~~17, wherein the retromer core protein VPS26b encoded by the transgene has the amino acid sequence of VPS26b (SEQ ID NO: 3).

~~47. The composition of claim 35, wherein the transgene encoding the retromer core protein VPS35 comprises human VPS26b (SEQ ID NO: 3).~~

~~48. The composition of claim 35, wherein the transgene has a nucleic acid sequence that is at least 70% identical to the nucleic acid sequence encoding VPS26b (SEQ ID NO: 3).~~

~~49~~22. The composition of claim ~~35~~17, wherein the vector is selected from the group consisting of adeno-associated virus (AAV), adenovirus, lentivirus, retrovirus, poxvirus, baculovirus, herpes simplex virus, vaccinia virus, and a synthetic virus.

~~50. The composition of claim 49, wherein the viral vector is an AAV.~~

~~51. The composition of claim 50, wherein the AAV is an AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, and AAVrh10.~~

~~52. The composition of claim 50, wherein the AAV is chosen from the group consisting of AAV9 and AAV2/9.~~

~~53. The composition of any one of claims 35-52, wherein the transgene is operably linked to a promoter that induces expression of the transgene in a neural cell.~~

~~54. The composition of any one of claims 35-52, wherein the transgene is operably linked to an enhancer that induces expression of the transgene in a neural cell.~~

~~55. The composition of claim 35, further comprising a pharmaceutical carrier.~~

~~56. A composition comprising at least one nucleic acid encoding VPS35 and a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.~~

~~57. The composition of claim 56, comprising a first nucleic acid encoding VPS35 and a second nucleic acid encoding a retromer core protein chosen from the group consisting of VPS26a, VPS26b, and combinations thereof.~~

~~58. A kit comprising the composition of any of claims 35-57.~~