

WHAT IS CLAIMED IS:

1. Use of a WW domain-containing oxidoreductase (WWOX) wild type gene, or a functional derivative thereof, under control of a regulatory element that results in expression of WWOX in the brain, in the manufacture of a medicament for the treatment of a WWOX-associated CNS disease, wherein the WWOX wild type gene, or the functional derivative thereof, under control of the regulatory element that results in expression of WWOX in the brain, is to be administered to the brain of a patient in need of such treatment.
2. The use of claim 1, wherein the WWOX-associated CNS disease is selected from WWOX-related epileptic encephalopathy (WOREE) syndrome; spinocerebellar ataxia, autosomal recessive, 12 (SCAR12), Alzheimer's disease, West syndrome, autism, multiple sclerosis and disorder of sexual development (DSD).
3. The use of claim 2, wherein the WWOX-associated CNS disease is WOREE syndrome or SCAR12.
4. The use of any one of claims 1 to 3, wherein the patient has compound heterozygous mutations of WWOX.
5. The use of any one of claims 1 to 4, wherein the regulatory element is a promoter that directs expression of the WWOX gene in neurons.
6. The use of claim 5, wherein the promoter is a universal promoter.
7. The use of claim 6, wherein the promoter is CMV promoter, E2F1 promoter, and U1snRNA promoter, or a derivative thereof.
8. The use of claim 5, wherein the regulatory element is a promoter that is expressed specifically in neurons.
9. The use of claim 8, wherein the promoter is selected from synapsin I promoter, CamKII promoter, MeCP2 promoter, NSE promoter, and Hb9 promoter, or a derivative thereof.
10. The use of claim 8 or 9, wherein the promoter is not expressed or is expressed at a lower level in glial cells.

11. The use of claim 10, wherein the promoter is not expressed or is expressed at a lower level in oligodendrocytes and/or astrocytes.
12. The use of any one of claims 8 to 11, wherein the regulatory element is a synapsin I promoter, or derivative thereof.
13. The use of any one of claims 1 to 4, wherein the regulatory element is a promoter that directs expression of the WWOX gene in oligodendrocytes.
14. The use of claim 13, wherein the promoter is selected from MBP promoter, PLP1 promoter, and CNP promoter, or a derivative thereof.
15. The use of any one of claims 1 to 4, wherein the regulatory element is a promoter that directs expression of the WWOX gene in astrocytes.
16. The use of claim 15, wherein the promoter is GFAP promoter or S100b promoter, or a derivative thereof.
17. The use of any one of claims 5 to 16, wherein the promoter further comprises one or more enhancer sequences.
18. The use of any one of claims 1 to 17, wherein the WWOX gene comprises untranslated sequences that enhance mRNA stability.
19. The use of any one of claims 1 to 17, wherein the WWOX wild type gene is delivered with one or more detectable labels.
20. The use of claim 19, wherein the detectable label is an encoded fluorescent protein.
21. The use of any one of claims 1 to 20, wherein the WWOX wild type gene or functional derivative thereof is delivered using polymeric nanoparticles, inorganic nanoparticles, liponanoparticles, or exosomes.
22. The use of any one of claims 1 to 21, wherein the WWOX wild type gene or functional derivative thereof is delivered with a Cas enzyme or polynucleotide encoding a Cas enzyme, and gRNA or polynucleotide encoding the gRNA, to direct insertion of the WWOX wild type gene or portion thereof.

23. The use of any one of claims 1 to 22, wherein the WWOX wild type gene or functional derivative thereof is delivered by a viral vector.
- 5 24. The use of claim 23, wherein the viral vector is an adeno-associated virus (AAV) delivery system.
25. The use of claim 24, wherein the AAV delivery system is AAV9.
- 10 26. The use of any one of claims 1 to 25, wherein the WWOX wild type gene encodes the amino acid sequence of SEQ ID NO: 2.
27. The use of claim 26, wherein the WWOX wild type gene comprises one or more introns.
- 15 28. The use of claim 26, wherein the WWOX wild type gene is a cDNA.
29. The use of claim 28, wherein the WWOX wild type gene, or a functional derivative thereof, under control of a regulatory element comprises the nucleotide sequence substantially as set forth in SEQ ID NO: 1 or 3.
- 20 30. The use of any one of claims 1 to 29, wherein the administration is by a route selected from direct injection into the parenchyma, injection into the cerebrospinal fluid via the intracerebroventricular, and by intrathecal (cisternal or lumbar) route.
- 25 31. The use of any one of claims 1 to 30, wherein the individual is a pediatric or neonatal patient.
32. The use of any one of claims 1 to 31, wherein the individual is an adult patient.
- 30 33. The use of claim 31 or 32, wherein the patient exhibits one or more symptoms selected from growth impairment, epileptic episodes, impairment of cognitive function, impairment of social function, impairment of fertility, ataxia, retinopathy, mental retardation, and microcephaly.
- 35 34. The use of any one of claims 1 to 33, wherein there are no more than three administration episodes.
35. The use of claim 34, wherein there are no more than two administration episodes.

36. The use of claim 34, wherein there is one administration episode.
37. Use of an AAV9 gene delivery system comprising a WWOX wild type gene under control of a synapsin-1 promoter, in the manufacture of a medicament for the treatment of WOREE syndrome or SCAR12, wherein the AAV9 gene delivery system is to be administered to the brain of a patient in need of such treatment.
38. The use of claim 37, wherein the AAV9 delivery system comprising the nucleotide sequence substantially as set forth in SEQ ID NO: 1 or SEQ ID NO: 3.
39. An expression construct, comprising a WWOX wild type gene, or a functional derivative thereof, under the expression control of a neuron-specific promotor.
40. The expression construct of claim 39, wherein the promoter is selected from synapsin 1 promoter, CamKII promoter, MeCP2 promoter, NSE promoter, and Hb9 promoter, or a derivative thereof.
41. The expression construct of claim 40, wherein the promoter is synapsin 1 or derivative thereof.
42. The expression construct of claim 41, comprising the nucleotide sequence substantially as set forth in SEQ ID NO: 1, 3, 4, or 5.
43. The expression construct of any one of claims 39 to 42, wherein the expression construct is a viral vector.
44. The expression construct of claim 43, wherein the viral vector is adeno-associated virus (AAV).
45. The expression construct of claim 44, wherein the AAV is AAV9.
46. A pharmaceutical composition for direct administration into the brain comprising the expression construct of any one of claims 39 to 45, and a pharmaceutically acceptable carrier suitable for direct injection to the brain.

47. The pharmaceutical composition of claim 46 for use in treating WOREE syndrome or SCAR12.

48. Use of the pharmaceutical composition of claim 46 in the manufacture of a medicament
5 for the treatment of WOREE or SCAR12.