CLAIMS

What is claimed is

1. A recombinant nucleic acid construct comprising a mini-promoter operably linked to a coding sequence for a TCF4 polypeptide.

2. The recombinant nucleic acid of claim 1, further comprising one or more transcription factor binding motifs.

3. The recombinant nucleic acid of claim 2, wherein the one or more transcription factor binding motifs are microE5 motifs.

4. The recombinant nucleic acid of claim 3, wherein the recombinant nucleic acid comprises from 1 to 15 microE5 motifs.

5. The recombinant nucleic acid of claim 4, wherein the recombinant nucleic acid comprises at least 5 microE5 motifs.

6. The recombinant nucleic acid of claim 4, wherein the recombinant nucleic acid comprises at least 10 microE5 motifs.

7. The recombinant nucleic acid of claim 4, wherein the recombinant nucleic acid comprises 12 microE5 motifs.

8. The recombinant nucleic acid of claim 4, having a general structure of: $microE5_n$-minipromoter-TCF4 coding sequence, wherein n is an integer in the range of 5 to 15.

9. The recombinant nucleic acid of any one of claims 4 to 8, wherein the microE5 motif comprises the nucleotide sequence of SEQ ID NO:10.

10. The recombinant nucleic acid of any one of claims 1 to 9, wherein the TCF4 polypeptide is TCF4-B.

11. The recombinant nucleic acid of claim 10, wherein the TCF4 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 2.

12. The recombinant nucleic acid of claim 11, wherein the TCF4 polypeptide comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:2.

13. The recombinant nucleic acid of claim 11, wherein the TCF4 polypeptide comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO:2.

14. The recombinant nucleic acid of claim 11, wherein the TCF4 polypeptide comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO:2.

15. The recombinant nucleic acid of any one of claims 1 to 14, wherein the TCF4 coding sequence comprises a nucleotide sequence that is at least 80% identical to SEQ ID NO:1.

16. The recombinant nucleic acid of claim 15, wherein the TCF4 coding sequence comprises a nucleotide sequence that is at least 85% identical to SEQ ID NO:1.

17. The recombinant nucleic acid of claim 16, wherein the TCF4 coding sequence comprises a nucleotide sequence that is at least 90% identical to SEQ ID NO:1.

18. The recombinant nucleic acid of claim 16, wherein the TCF4 coding sequence comprises a nucleotide sequence that is at least 95% identical to SEQ ID NO:1.

19. The recombinant nucleic acid of any one of claims 1 to 18, wherein the mini-promoter comprises a core promoter.

20. The recombinant nucleic acid of claim 19, wherein the mini-promoter comprises a nucleotide sequence that has at least 70% sequence identity to SEQ ID NO:3.

21. The recombinant nucleic acid of claim 19, wherein the mini-promoter comprises a nucleotide sequence that has at least 80% sequence identity to SEQ ID NO:3.

22. The recombinant nucleic acid of claim 19, wherein the mini-promoter comprises a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO:3.

23. The recombinant nucleic acid of claim 19, wherein the mini-promoter comprises the nucleotide sequence of SEQ ID NO:3, optionally with from 1 to 5 nucleotide modifications independently selected from deletions, insertions, and substitutions.

24. The recombinant nucleic acid of any one of claims 1 to 23, wherein the nucleic acid construct comprises a nucleotide sequence that is at least 80% identical to any one of SEQ ID Nos: 4, 5, 6, 7 or 8.

25. A vector comprising a recombinant nucleic acid of any one of claims 1 to 24.

26. The vector of claim 25, wherein the vector is a viral vector.

27. The vector of claim 26, wherein the viral vector is a retroviral vector.

28. The vector of claim 25, wherein the vector is an adeno-associated virus (AAV) vector, lentiviral vector or gamma-retroviral vector.

29. The vector of claim 28, wherein the vector is an AAV9 vector.

30. A recombinant cell comprising the recombinant nucleic acid of any one of claims 1 to 24 or the vector of any one of claims 25 to 28.

31. A pharmaceutical composition comprising a vector of any one of claims 25 to 29.

32. Use of a recombinant nucleic acid of any one of claims 1 to 24 or a vector of any one of claims 25 to 39, or a pharmaceutical composition of claim 31 in the manufacture of a medicament for the treatment of a neurological or neurodevelopmental disease or disorder related in a subject, wherein the medicament is to be administered to the subject to cause a neuron of the subject to be transformed with the recombinant nucleic acid.

33. The use of claim 32, wherein the neurological or neurodevelopmental disease or disorder is Pitt-Hopkins Syndrome, schizophrenia, autism, autism spectrum disorder, or 18q syndrome.

34. The use of claim 32, wherein the neurological or neurodevelopmental disease or disorder is Pitt-Hopkins Syndrome, and is associated with TCF4 haploinsufficiency.

35. The use of any one of claims 32 to 34, wherein the subject has one or more single nucleotide polymorphisms in a TCF4 gene.

36. The use of any one of claims 32 to 34, wherein the subject has a chromosomal deletion including at least a portion of a TCF4 gene.

37. The use of claim 36, wherein the subject has a complete deletion of a TCF4 gene.

38. The use of any one of claims 32 to 34, wherein the subject has a chromosomal translocation comprising at least a portion of a TCF4 gene, or wherein the subject has a translocation, frameshift, or non-sense mutation in a TCF4 gene.

39. The use of any one of claims 32 to 38, wherein the subject is an infant or pediatric subject.

40. The use of claim 39, wherein the subject is about 16 years of age or less, or about 12 years of age or less, or about 8 years of age

or less, or about 5 years of age or less, or about 2 years of age or less.

41. The use of any one of claims 32 to 38, wherein the subject is an adult subject.

42. Use of a recombinant nucleic acid expressing TCF4-B polypeptide in the manufacture of a medicament for the treatment of a neurological or neurodevelopmental disease or disorder related to TCF4 haploinsuffiency in a subject, wherein the medicament is to be administered to the subject to cause increasing expression of one or more of SOX3 and SOX4 in neurons of the subject.

43. The use of claim 42, wherein the recombinant nucleic acid comprises a mini-promoter operably linked to a coding sequence for the TCF4-B polypeptide.

44. The use of claim 43, wherein the recombinant nucleic acid further comprises one or more transcription factor binding motifs.

45. The use of claim 44, wherein the one or more transcription factor binding motifs are microE5 motifs.

46. The use of claim 45, wherein the recombinant nucleic acid comprises from 1 to 15 microE5 motifs.

47. The use of claim 46, wherein the recombinant nucleic acid comprises at least 5 microE5 motifs, or at least 10 microE5 motifs, or 12 microE5 motifs.

48. The use of claim 46, wherein the one or more transcription factor binding motifs have a general structure of: microE5n-minipromoter-TCF4 coding sequence, wherein n is an integer in the range of 5 to 15.

49. The use of any one of claims 45 to 48, wherein the microE5 motif comprises the nucleotide sequence of SEQ ID NO:10.

50. The use of any one of claims 42 to 49, wherein the recombinant nucleic acid expressing TCF4-B polypeptide is to be delivered to said subject with a viral vector.

51. The use of claim 50, wherein the viral vector is a retroviral vector.

52. The use of claim 50, wherein the viral vector is an adeno-associated virus (AAV) vector, lentiviral vector or gamma-retroviral vector.

53. The use of claim 52, wherein the viral vector is an AAV9 vector.

54. The use of any one of claims 42 to 53, wherein the neurological or neurodevelopmental disease or disorder is Pitt-Hopkins Syndrome, schizophrenia, autism, autism spectrum disorder, or 18q syndrome.

55. The use of claim 54, wherein the neurological or neurodevelopmental disease or disorder is Pitt-Hopkins Syndrome.

56. The use of any one of claims 42 to 55, wherein the subject has one or more single nucleotide polymorphisms in a TCF4 gene, or the subject has a chromosomal deletion including at least a portion of a TCF4 gene, or the subject has a complete deletion of a TCF4 gene, or the subject has a chromosomal translocation comprising at least a portion of a TCF4 gene, or the subject has a translocation, frameshift, or non-sense mutation in a TCF4 gene.

57. The use of any one of claims 42 to 56, wherein the subject is an infant or pediatric subject.

58. The use of claim 57, wherein the subject is about 16 years of age or less, or about 12 years of age or less, or about 8 years of age or less, or about 5 years of age or less, or about 2 years of age or less.

59. The use of any one of claims 42 to 56, wherein the subject is an adult subject.