CLAIMS

1. A one-vector expression system comprising a first and a second expression cassette, in which the first first expression cassette comprises a nucleotide sequence comprising a first promoter sequence operably linked to a first nucleotide sequence, the first nucleotide sequence encoding a GTP-cyclohydrolase 1 (GCH1; EC 3.5.4.16) polypeptide or a biologically active fragment or variant thereof, and in which the second expression cassette comprises a nucleotide sequence comprising a second promoter sequence operably linked to a second nucleotide sequence the second nucleotide sequence encoding a tyrosine hydroxylase (TH; EC 1.14.16.2) polypeptide or a biologically active fragment or variant thereof, and in which the vector is an adeno associated vector (AAV) and in which the vector does not comprise a nucleotide sequence encoding an aromatic amino acid decarboxylase (AADC) polypeptide, and in which the TH:GCH1 ratio expressed from the vector is between 3:1 and 10:1.

2. A vector according to Claim 1, in which the first promoter is a Synapsin 1 promoter.

3. A vector according to Claim 1 or 2, in which the second promoter is a constitutively active promoter selected from the group consisting of CAG, CMV, human UbiC, RSV, EF-1alpha, SV40 and Mt1 promoters.

4. A vector according to Claim 1 or 2, in which the second promoter is a CMV promoter.

5. A vector according to any preceding claim, in which the vector further comprises one or more enhancers or regulatory elements.

6. A vector according to Claim 6, in which the enhancer or regulatory element is an intron.

7. A vector according to Claim 1, in which the GTP-cyclohydrolase 1 (GCH1; EC 3.5.4.16) polypeptide or the biologically active fragment or variant thereof is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, and in which the tyrosine hydroxylase (TH; EC 1.14.16.2) polypeptide or a biologically active fragment or variant thereof is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13 and SEQ ID NO. 14.

8. A vector according to Claim 1, in which the vector has a packaging capacity from 1 to 40 kb, for example from 1 to 30 kb, such as from 1 to 20 kb, for example from 1 to 15 kb, such as from 1 to 10, for example from 1 to 8 kb, such as from 2 to 7 kb, for example from 3 to 6 kb, such as from 4 to 5 kb.

9. A vector according to Claim 1, in which the vector has a packaging capacity from 4.5 to 4.8 kb.

10. A vector according to Claim 1, in which the adeno associated vector (AAV) is an AAV2 vector.

11. A vector according to Claim 10, in which the capsid of the AAV2 vector is packaged in an AAV capsid other than an AAV2 capsid.

12. A vector according to Claim 11, in which the AAV2 vector is packaged in an AAV5 capsid.

13. A vector according to any preceding claim, in which the vector is functional in mammalian cells.

14. A vector according to Claim 1, in which the biologically active fragment comprises at least 50 contiguous amino acids, in which any amino acid specified in the selected sequence is altered to a different amino acid, provided that no more than 15 of the amino acid residues in the sequence are so altered.

15. A vector according to Claim 14, in which the biologically active fragment is the catalytic domain of tyrosine hydroxylase.

16. A vector according to Claim 1, in which the biologically active variant is a mutated tyrosine hydroxylase polypeptide, in which one or more of the residues S19, S31, S40 or S404 have been altered to another amino acid residue.

17. A vector according to any preceding claim, in which the GTP-cyclohydrolase 1 (GCH1) polypeptide is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 75% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 80% identical to a polypeptide selected from the

group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 85% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 90% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 95% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 96% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 97% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 98% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 99% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably 100% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6.

18. A vector according to any preceding claim, in which the tyrosine hydroxylase (TH) polypeptide is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 75% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 80% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 85% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 90% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 95% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID

NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 96% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 97% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 98% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 99% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably 100% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14.

19. A vector according to Claim 1, in which the first expression cassette or the second expression cassette further comprises a polyadenylation sequence.

20. A vector according to Claim 1, in which the first expression cassette and the second expression cassette further comprises polyadenylation sequences.

21. A vector according to Claim 19 or 20, in which the polyadenylation sequence is a SV40 polyadenylation sequence.

22. A vector according to Claim 19 or 20, in which the 5’ of the polyadenylation sequence is operably linked to the 3’ of the first and/or the second nucleotide sequence.

23. A vector according to Claim 1, in which the first nucleotide sequence encoding a GTP-cyclohydrolase 1 (GCH1) polypeptide or a biologically active fragment or variant thereof comprises the sequence of SEQ ID NO. 18.

24. A vector according to Claim 1, in which the second nucleotide sequence encoding a tyrosine hydroxylase (TH) polypeptide or a biologically active fragment or variant thereof comprises the sequence of SEQ ID NO. 21.

25. A vector according to Claim 1, in which the second nucleotide is operably liked to a Woodchuck hepatitis virus post-transcriptional regulatory element (WPRE).

26. A vector according to Claim 25, in which the Woodchuck hepatitis virus post-transcriptional regulatory element comprises a sequence that has at least 85 percent sequence identity, preferably at least 90 to 95 percent sequence identity, more preferably at least 99 percent sequence identity to SEQ ID NO: 22.

27. A vector according to Claim 1, in which the Woodchuck hepatitis virus post-transcriptional regulatory element comprises the sequence of SEQ ID NO. 22.

28. A vector according to any preceding claim, in which the expression cassettes of the vector comprises a 5' terminal repeat and a 3' terminal repeat.

29. A vector according to Claim 28, in which the 5' and 3' terminal repeats are selected from Inverted Terminal Repeats [ITR] and Long Terminal Repeats [LTR].

30. A vector according to Claim 28, in which the 5' and 3' terminal repeats are AAV Inverted Terminal Repeats [ITR].

31. A vector according to Claim 30, in which the Inverted Terminal Repeats comprises the sequences of SEQ ID NO. 15 and SEQ ID NO. 16.

32. A vector according to any preceding claim, in which the TH:GCH1 ratio is determined by measuring the activity of the expressed TH and GCH1 enzymes.

33. A vector according to any preceding claim, in which the TH:GCH1 ratio is determined by measuring the amount of Tetrahydrobiopterin (BH_4).

34. A vector according to any preceding claim, in which the TH:GCH1 ratio is determined by the amount of mRNA transcribed.

35. A vector according to any preceding claim, in which the TH:GCH1 ratio is determined by the amount of protein expressed.

36. A vector according to any preceding claim, in which the vector is the vector defined in Figure 6.

37. A vector according to any preceding claim, in which the vector is a minimally integrating vector.

38. A vector according to any preceding claim for use as a medicament.

39. An isolated host cell comprising a vector according to any preceding claim.

40. A host cell according to Claim 39, in which the cell is selected from the group consisting of eukaryotic cells, preferably mammalian cells, more preferably primate cells, more preferably human cells.

41. A host cell according to Claim 40, in which the cell is selected from the group consisting of Chinese hamster ovary cells, CHO-K1, baby hamster kidney cells, mouse fibroblast-3T3 cells, African green monkey cell lines, rat adrenal pheochromocytoma, AT3 cells, rat glial tumor cells, rat neuronal cells and rat hippocampal cells.

42. Use of a vector according to any of Claims 1 to 38, for the preparation of a medicament for the treatment of a disease associated with catecholamine dysfunction.

43. Use according to Claim 42, in which the catecholamine dysfunction is catecholamine deficiency.

44. Use according to Claim 42, in which the catecholamine dysfunction is catecholamine excess.

45. Use according to Claim 43, in which the catecholamine deficiency is dopamine deficiency.

46. Use according to Claim 44, in which the catecholamine excess is dopamine excess.

47. Use according to any of Claims 42 to 46, in which the disease associated with catecholamine dysfunction is a disease, disorder or damage of the central and/or peripheral nervous system.

48. Use according to Claim 47, in which the disease, disorder or damage of the central and/or peripheral nervous system is a neurodegenerative disorder.

49. Use according to any of Claims 42 to 48, in which the disease associated with catecholamine dysfunction is a disease of the basal ganglia.

50. Use according to any of Claims 42 to 49, in which the disease is selected from the group consisting of Parkinson's Disease (PD), DOPA responsive dystonia, ADHD, schizophrenia, depression, vascular parkinsonism, essential tremor, chronic stress, genetic dopamine receptor abnormalities, chronic opoid, cocaine, alcohol or marijuana use, adrenal insufficiency,

hypertension, noradrenaline deficiency, post-traumatic stress disorder, pathological gambling disorder, dementia, Lewy body dementia.

51. Use according to any of Claims 42 to 49, in which the neurodegenerative disorder is Parkinson's Disease (PD).

52. A vector according to any of Claims 1 to 38, for use in a method of treatment of a disease associated with catecholamine dysfunction.

53. A vector according to Claim 52, in which the catecholamine dysfunction is catecholamine deficiency.

54. A vector according to Claim 52, in which the catecholamine dysfunction is catecholamine excess.

55. A vector according to Claim 53, in which the catecholamine deficiency is dopamine deficiency.

56. A vector according to Claim 54, in which the catecholamine excess is dopamine excess.

57. A vector according to any of Claims 52 to 56, in which the disease associated with catecholamine dysfunction is a disease, disorder or damage of the central and/or peripheral nervous system.

58. A vector according to Claim 57, in which the disease, disorder or damage of the central and/or peripheral nervous system is a neurodegenerative disorder.

59. A vector according to any of Claims 52 to 58, in which the disease associated with catecholamine dysfunction is a disease of the basal ganglia.

60. A vector according to any of Claims 52 to 58, in which the disease is selected from the group consisting of Parkinson's Disease (PD), DOPA responsive dystonia, ADHD, schizophrenia, depression, vascular parkinsonism, essential tremor, chronic stress, genetic dopamine receptor abnormalities, chronic opoid, cocaine, alcohol or marijuana use, adrenal insufficiency, hypertension, noradrenaline deficiency, post-traumatic stress disorder, pathological gambling disorder, dementia, Lewy body dementia.

61. A vector according to any of Claims 52 to 49, in which the neurodegenerative disorder is Parkinson's Disease (PD).

62. A pharmaceutical composition for use in a method of treatment of Parkinson's Disease, the composition comprising a one-vector expression system and a formulation for delivering the vector to the basal ganglia, in which the one-vector expression system comprises: a first and a second expression cassette, in which the first expression cassette comprises a nucleotide sequence comprising a first promoter sequence operably linked to a first nucleotide sequence, the first nucleotide sequence encoding a GTP-cyclohydrolase 1 (GCH1; EC 3.5.4.16) polypeptide or a biologically active fragment or variant thereof, and in which the second expression cassette comprises a nucleotide sequence comprising a second promoter sequence operably linked to a second nucleotide sequence, the second nucleotide sequence encoding a tyrosine hydroxylase (TH; EC 1.14.16.2) polypeptide or a biologically active fragment or variant thereof, and in which the vector is an adeno associated vector (AAV), and in which the vector does not comprise a nucleotide sequence encoding an aromatic amino acid decarboxylase (AADC) polypeptide and in which the TH:GCH1 ratio expressed from the vector is between 3:1 and 10:1.

63. A pharmaceutical composition according to Claim 62, in which the GTP-cyclohydrolase 1 (GCH1) polypeptide or the biologically active fragment or variant thereof is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, and in which the tyrosine hydroxylase (TH) polypeptide or a biologically active fragment or variant thereof is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13 and SEQ ID NO. 14.

64. A pharmaceutical composition according to any of Claims 62 to 63, in which the formulation comprises manitol, heparin or gadolinium based MRI contrast agents.

65. A pharmaceutical composition according to any of Claims 62 to 64 further comprising trophic factors or reversible proteasome inhibitors.

66. A pharmaceutical composition according to any of Claims 62 to 65, and a pharmaceutically acceptable carrier or diluent.

67. A pharmaceutical composition according to any of Claims 62 to 66, formulated for administration by injection, sublingual tablet or spray, cutaneous administration or inhalation.

68. A pharmaceutical composition according to Claim 67, in which the injection is intracranial, intracerebral, intravenous, intravitreous, intranasal, intramuscular, intraspinal, intraperitoneal, subcutaneous, a bolus or a continuous administration.

69. A pharmaceutical composition according to any of Claims 62 to 64, in which the pH of the composition is between pH 4 and pH 10.

70. A pharmaceutical composition according to any of Claims 62 to 69, in which the dosage of the vector is between 1.5E+10 and 2.2E+12 vector genome copies per milliliter putaminal grey matter.

71. A pharmaceutical composition according to any of Claims 62 to 70, in which administration occurs at intervals of 30 minutes to 24 hours.

72. A pharmaceutical composition according to any of Claims 62 to 71, in which administration occurs at intervals of 1 to 6 hours.

73. A pharmaceutical composition according to any of Claims 62 to 71, in which the duration of the treatment is from 6 to 72 hours.

74. A pharmaceutical composition according to any of Claims 62 to 71, in which the duration of the treatment is life long.

75. A method for determining the expression ratio of GTP cyclohydroxylase1 polypeptide (SEQ ID NOs. 1, 2, 3, 4, 5 and 6) and tyrosine hydroxylase polypeptide (SEQ ID NOs. 7, 8, 9, 10, 11, 12, 13 and 14), respectively, or variants thereof, the polypeptide encoded by the vector as defined in any of claims 1 to 37, comprising measuring the enzymatic activity of the polypeptides, or amount of BH_4 produced, or amount expressed of the polypeptides, or level of transcribed mRNA corresponding to the polypeptides of GTP cyclohydroxylase1 polypeptide and tyrosine hydroxylase, respectively.

76. A method according to Claim 75, in which the ratio is determined by a combination of the activity of the polypeptides and the amount present of the polypeptides.

77. A kit in parts, the kit comprising a pharmaceutical composition according to any of Claims 62 to 74, and instructions for administration.

CLAIMS

1. A one-vector expression system comprising a first and a second expression cassette, in which:

the first expression cassette comprises a nucleotide sequence comprising a first promoter sequence operably linked to a first nucleotide sequence;

the first nucleotide sequence encoding a GTP-cyclohydrolase 1 (GCH1; EC 3.5.4.16) polypeptide or a biologically active fragment or variant thereof having at least 70% sequence identity to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6 and comprising GTP-cyclohydrolase 1 (GCH1) activity;

the second expression cassette comprises a nucleotide sequence comprising a second promoter sequence operably linked to a second nucleotide sequence;

the second nucleotide sequence encoding a tyrosine hydroxylase (TH; EC 1.14.16.2) polypeptide or a biologically active fragment or variant thereof having at least 70% sequence identity to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13 and SEQ ID NO. 14 and comprising tyrosine hydroxylase (TH) activity;

in which the vector is an adeno associated vector (AAV);

in which both the first and the second promoters are Synapsin1 promoters;

in which the second nucleotide sequence is operably linked to a Woodchuck hepatitis virus post-transcriptional regulatory element (WPRE); and

in which the TH:GCH1 ratio expressed from the vector is between 3:1 and 10:1.

2. A vector according to Claim 1, in which the GTP-cyclohydrolase 1 (GCH1; EC 3.5.4.16) polypeptide or the biologically active fragment or variant thereof is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, and in which the tyrosine hydroxylase (TH; EC 1.14.16.2) polypeptide or a biologically active fragment or variant thereof is at least 70% identical to a polypeptide selected from the group consisting of

SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13 and SEQ ID NO. 14.

3. A vector according to Claim 1, in which the vector does not comprise a nucleotide sequence encoding an aromatic amino acid decarboxylase (AADC) polypeptide.4. A vector according to Claim 1, in which the vector has a packaging capacity from 1 to 40 kb, for example from 1 to 30 kb, such as from 1 to 20 kb, for example from 1 to 15 kb, such as from 1 to 10, for example from 1 to 8 kb, such as from 2 to 7 kb, for example from 3 to 6 kb, such as from 4 to 5 kb.

5. A vector according to Claim 1, in which the vector has a packaging capacity from 4.5 to 4.8 kb.

6. A vector according to Claim 1, in which the adeno associated vector (AAV) is an AAV2 vector.

7. A vector according to Claim 6, in which the capsid of the AAV2 vector is packaged in an AAV capsid other than an AAV2 capsid.

8. A vector according to Claim 7, in which the AAV2 vector is packaged in an AAV5 capsid.

9. A vector according to any preceding claim, in which the vector is functional in mammalian cells.

10. A vector according to Claim 1, in which the biologically active fragment comprises at least 50 contiguous amino acids, in which any amino acid specified in the selected sequence is altered to a different amino acid, provided that no more than 15 of the amino acid residues in the sequence are so altered.

11. A vector according to Claim 10, in which the biologically active fragment is the catalytic domain of tyrosine hydroxylase.

12. A vector according to Claim 1, in which the biologically active variant is a mutated tyrosine hydroxylase polypeptide, in which one or more of the residues S19, S31, S40 or S404 have been altered to another amino acid residue.

13. A vector according to any preceding claim, in which the GTP-cyclohydrolase 1 (GCH1) polypeptide is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 75% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 80% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 85% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 90% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 95% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 96% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 97% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 98% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably at least 99% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, more preferably 100% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6.

14. A vector according to any preceding claim, in which the tyrosine hydroxylase (TH) polypeptide is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 75% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 80% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 85% identical to a

polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 90% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 95% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 96% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 97% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 98% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably at least 99% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14, more preferably 100% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12 SEQ ID NO. 13 and SEQ ID NO. 14.

15. A vector according to Claim 1, in which the first expression cassette or the second expression cassette further comprises a polyadenylation sequence.

16. A vector according to Claim 1, in which the first expression cassette and the second expression cassette further comprises polyadenylation sequences.

17. A vector according to Claim 15 or 16, in which the polyadenylation sequence is a SV40 polyadenylation sequence.

18. A vector according to Claim 15 or 16, in which the 5’ of the polyadenylation sequence is operably linked to the 3’ of the first and/or the second nucleotide sequence.

19. A vector according to Claim 1, in which the first nucleotide sequence encoding a GTP-cyclohydrolase 1 (GCH1) polypeptide or a biologically active fragment or variant thereof comprises the sequence of SEQ ID NO. 18.

20. A vector according to Claim 1, in which the second nucleotide sequence encoding a tyrosine hydroxylase (TH) polypeptide or a biologically active fragment or variant thereof comprises the sequence of SEQ ID NO. 21.

21. A vector according to Claim 1, in which the Woodchuck hepatitis virus post-transcriptional regulatory element comprises the sequence of SEQ ID NO. 22.

22. A vector according to any preceding claim, in which the expression cassettes of the vector comprises a 5' terminal repeat and a 3' terminal repeat.

23. A vector according to Claim 22, in which the 5' and 3' terminal repeats are selected from Inverted Terminal Repeats [ITR] and Long Terminal Repeats [LTR].

24. A vector according to Claim 22, in which the 5' and 3' terminal repeats are AAV Inverted Terminal Repeats [ITR].

25. A vector according to Claim 24, in which the Inverted Terminal Repeats comprises the sequences of SEQ ID NO. 15 and SEQ ID NO. 16.

26. A vector according to any preceding claim, in which the TH:GCH1 ratio is determined by measuring the activity of the expressed TH and GCH1 enzymes.

27. A vector according to any preceding claim, in which the TH:GCH1 ratio is determined by measuring the amount of Tetrahydrobiopterin (BH_4).

28. A vector according to any preceding claim, in which the TH:GCH1 ratio is determined by the amount of mRNA transcribed.

29. A vector according to any preceding claim, in which the TH:GCH1 ratio is determined by the amount of protein expressed.

30. A vector according to any preceding claim, in which the vector is the vector defined in Figure 6.

31. A vector according to any preceding claim, in which the vector is a minimally integrating vector.

32. A vector according to any preceding claim for use as a medicament.

33. An isolated host cell comprising a vector according to any preceding claim.

34. A host cell according to Claim 33, in which the cell is selected from the group consisting of eukaryotic cells, preferably mammalian cells, more preferably primate cells, more preferably human cells.

35. A host cell according to Claim 34, in which the cell is selected from the group consisting of Chinese hamster ovary cells, CHO-K1, baby hamster kidney cells, mouse fibroblast-3T3 cells, African green monkey cell lines, rat adrenal pheochromocytoma, AT3 cells, rat glial tumor cells, rat neuronal cells and rat hippocampal cells.

36. Use of a vector according to any of Claims 1 to 32, for the preparation of a medicament for the treatment of a disease associated with catecholamine dysfunction.

37. Use according to Claim 36, in which the catecholamine dysfunction is catecholamine deficiency.

38. Use according to Claim 37, in which the catecholamine deficiency is dopamine deficiency.

39. Use according to any of Claims 36 to 38, in which the disease associated with catecholamine dysfunction is a disease, disorder or damage of the central and/or peripheral nervous system.

40. Use according to Claim 39, in which the disease, disorder or damage of the central and/or peripheral nervous system is a neurodegenerative disorder.

41. Use according to any of Claims 36 to 40, in which the disease associated with catecholamine dysfunction is a disease of the basal ganglia.

42. Use according to any of Claims 36 to 41, in which the disease is selected from the group consisting of Parkinson's Disease (PD), DOPA responsive dystonia, ADHD, schizophrenia, depression, vascular parkinsonism, essential tremor, chronic stress, genetic dopamine receptor abnormalities, chronic opoid, cocaine, alcohol or marijuana use, adrenal insufficiency, hypertension, noradrenaline deficiency, post-traumatic stress disorder, pathological gambling disorder, dementia, Lewy body dementia.

43. Use according to any of Claims 36 to 41, in which the neurodegenerative disorder is Parkinson's Disease (PD).

44. A vector according to any of Claims 1 to 32, for use in a method of treatment of a disease associated with catecholamine dysfunction.

45. A vector according to Claim 44 for a use as specified therein, in which the catecholamine dysfunction is catecholamine deficiency.

46. A vector according to Claim 45 for a use as specified therein, in which the catecholamine deficiency is dopamine deficiency.

47. A vector according to any of Claims 44 to 46 for a use as specified therein, in which the disease associated with catecholamine dysfunction is a disease, disorder or damage of the central and/or peripheral nervous system.

48. A vector according to Claim 47 for a use as specified therein, in which the disease, disorder or damage of the central and/or peripheral nervous system is a neurodegenerative disorder.

49. A vector according to any of Claims 44 to 48 for a use as specified therein, in which the disease associated with catecholamine dysfunction is a disease of the basal ganglia.

50. A vector according to any of Claims 44 to 48 for a use as specified therein, in which the disease is selected from the group consisting of Parkinson's Disease (PD), DOPA responsive dystonia, ADHD, schizophrenia, depression, vascular parkinsonism, essential tremor, chronic stress, genetic dopamine receptor abnormalities, chronic opoid, cocaine, alcohol or marijuana use, adrenal insufficiency, hypertension, noradrenaline deficiency, post-traumatic stress disorder, pathological gambling disorder, dementia, Lewy body dementia.

51. A vector according to any of Claims 44 to 48 for a use as specified therein, in which the neurodegenerative disorder is Parkinson's Disease (PD).

52. A pharmaceutical composition for use in a method of treatment of Parkinson's Disease, the composition comprising a one-vector expression system and a formulation for delivering the vector to the basal ganglia, in which the one-vector expression system comprises:

a first and a second expression cassette, in which

the first expression cassette comprises a nucleotide sequence comprising a first promoter sequence operably linked to a first nucleotide sequence, the first nucleotide sequence encoding a GTP-cyclohydrolase 1 (GCH1; EC 3.5.4.16) polypeptide or a biologically

active fragment or variant thereof having at least 70% sequence identity to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6 and comprising GTP-cyclohydrolase 1 (GCH1) activity;

the second expression cassette comprises a nucleotide sequence comprising a second promoter sequence operably linked to a second nucleotide sequence, the second nucleotide sequence encoding a tyrosine hydroxylase (TH; EC 1.14.16.2) polypeptide or a biologically active fragment or variant thereof having at least 70% sequence identity to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13 and SEQ ID NO. 14 and comprising tyrosine hydroxylase (TH) activity;

in which the vector is an adeno associated vector (AAV);

in which the second nucleotide sequence is operably linked to a Woodchuck hepatitis virus post-transcriptional regulatory element (WPRE); and

in which the TH:GCH1 ratio expressed from the vector is between 3:1 and 10:1.

53. A pharmaceutical composition according to Claim 52, in which the GTP-cyclohydrolase 1 (GCH1) polypeptide or the biologically active fragment or variant thereof is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5 and SEQ ID NO. 6, and in which the tyrosine hydroxylase (TH) polypeptide or a biologically active fragment or variant thereof is at least 70% identical to a polypeptide selected from the group consisting of SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13 and SEQ ID NO. 14.

54. A pharmaceutical composition according to any of Claims 52 to 53, in which the formulation comprises manitol, heparin or gadolinium based MRI contrast agents.

55. A pharmaceutical composition according to any of Claims 52 to 54 further comprising trophic factors or reversible proteasome inhibitors.

56. A pharmaceutical composition according to any of Claims 52 to 55, and a pharmaceutically acceptable carrier or diluent.

57. A pharmaceutical composition according to any of Claims 52 to 56, formulated for administration by injection, sublingual tablet or spray, cutaneous administration or inhalation.

58. A pharmaceutical composition according to Claim 57 in which the injection is intracranial, intracerebral, intravenous, intravitreous, intranasal, intramuscular, intraspinal, intraperitoneal, subcutaneous, a bolus or a continuous administration.

59. A pharmaceutical composition according to any of Claims 52 to 54, in which the pH of the composition is between pH 4 and pH 10.

60. A pharmaceutical composition according to any of Claims 52 to 59, in which the dosage of the vector is between 1.5E+10 and 2.2E+12 vector genome copies per milliliter putaminal grey matter.

61. A pharmaceutical composition according to any of Claims 52 to 60, in which administration occurs at intervals of 30 minutes to 24 hours.

62. A pharmaceutical composition according to any of Claims 52 to 61, in which administration occurs at intervals of 1 to 6 hours.

63. A pharmaceutical composition according to any of Claims 52 to 61, in which the duration of the treatment is from 6 to 72 hours.

64. A pharmaceutical composition according to any of Claims 52 to 61, in which the duration of the treatment is life long.

65. A method for determining the expression ratio of GTP cyclohydroxylase1 polypeptide (SEQ ID NOs. 1, 2, 3, 4, 5 and 6) and tyrosine hydroxylase polypeptide (SEQ ID NOs. 7, 8, 9, 10, 11, 12, 13 and 14), respectively, or variants thereof, the polypeptide encoded by the vector as defined in any of claims 1 to 37, comprising measuring the enzymatic activity of the polypeptides, or amount of BH_4 produced, or amount expressed of the polypeptides, or level of transcribed mRNA corresponding to the polypeptides of GTP cyclohydroxylase1 polypeptide and tyrosine hydroxylase, respectively.

66. A method according to Claim 65, in which the ratio is determined by a combination of the activity of the polypeptides and the amount present of the polypeptides.

67. A kit in parts, the kit comprising a pharmaceutical composition according to any of Claims 52 to 64, and instructions for administration.