CLAIMS

~~What is claimed is:~~

1. ~~A method for delivering~~ Use of a ~~heterologous nucleic acid to the eye of an individual comprising administering a recombinant adeno-associated virus (~~rAAV~~)~~ particle ~~to~~ in the manufacture of a medicament for the ~~subretina~~treatment of ~~the individual~~an ocular disorder, wherein the rAAV ~~particle~~particles comprises:

a) a rAAV capsid comprising ~~rAAV~~an AAV2 capsid ~~proteins~~protein comprising one or more amino acid substitutions at one or more positions ~~that interacts with a heparan sulfate proteoglycan~~ R484, R487, K527, K532, and/or ~~at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588~~R588, numbering based on VP1 numbering of AAV2, ~~and~~

wherein the one or more amino acid substitutions is with a hydrophobic amino acid residue,

wherein the one or more amino acid substitutions reduces binding of the rAAV particle to a heparin sulfate proteoglycan, and

b) a rAAV vector comprising ~~the heterologous nucleic acid and at least one AAV inverted terminal repeat.~~

~~2. A method for improving rAAV transduction of cells following subretinal delivery of a rAAV particle to the eye of an individual compared to transduction of cells with a rAAV comprising a wild-type capsid, the method comprising incorporating one or more amino acid substitutions in an AAV capsid protein at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2; wherein the rAAV particle comprises the rAAV capsid protein and a rAAV vector comprising~~ a heterologous nucleic acid and at least one AAV terminal repeat.

~~3. A method for improving expression of a heterologous nucleic acid following subretinal delivery of a rAAV particle to the eye of an individual, the method comprising incorporating one or more amino acid substitutions in an AAV capsid protein at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2; wherein the rAAV particle comprises the rAAV capsid protein and a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat.~~

~~4. A method to treat an ocular disorder in an individual comprising delivery of a composition comprising a rAAV particle to the retina of an individual, wherein the rAAV particles comprise~~

a) a rAAV capsid comprising a rAAV capsid protein comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat.

5. The method of any one of claims 1-4, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan.

6. The method of claim 52. The use of claim 1, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.

7 The method of any one of claims 1-6, wherein the one or more amino acid substitutions comprise a substitution of a positively charged amino acid residue with an amino acid residue that is not positively charged.

8. The method of claim 7, wherein the positively charged amino acid residue is substituted with a hydrophobic amino acid residue.

9. The method of any one of claims 1-83. The use of any one of claims 1-2, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue.

10.4. The methoduse of any one of claims 1-93, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue with an alanine residue.

11. 5. The method of claim 1, wherein the rAAV particle comprises an AAV serotype 2 (AAV2) capsid.

12.The methoduse of any one of claims 1-114, wherein the one or more amino acid substitutions is at position 484, 487R484, R487, or 532K532, numbering based on VP1 numbering of AAV2.

~~13.~~ 6. The ~~method of claim 12, wherein the numbering is based on the VP1 of AAV2 comprising the amino acid sequence of SEQ ID NO:1.~~

~~14. The method~~use of any one of claims 1-~~11 and 13, wherein the one or more amino acid substitutions comprises a substitution at position R484, R487, K527, K532, R585 and/or R588, numbering based on VP1 of AAV2.~~

~~15.The method of any one of claims 1-12~~5, wherein the rAAV particle comprises one or more ~~rAAV~~AAV2 capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NOs:2, 4 and/or 6.

~~16.~~7. The ~~method~~use of any one of claims 1-~~12~~5, wherein the one or more amino acid substitutions comprises substitutions at positions R484 and R487 or at positions R585 and R588, numbering based on VP1 of AAV2.

~~17.~~8. The ~~method~~use of any one of claims 1-~~12~~5, wherein the one or more amino acid substitutions comprises R484A and R487A substitutions or R585A and R588A substitutions, numbering based on VP1 of AAV2.

~~18.~~9. The ~~method~~use of any one of claims 1-~~12~~5, wherein the ~~AAV~~AAV2 capsid protein comprises amino acid substitutions R585A and R588A, numbering based on VP1 of AAV2.

~~19.~~ 10. The ~~method~~use of any one of claims 1-~~12~~5, wherein the ~~AAV~~AAV2 capsid protein comprises amino acid substitution K532A, numbering based on VP1 of AAV2.

~~20. The method of any one of claims 1-10, wherein the rAAV particle comprises an AAV serotype rh8R (AAVrh8R) capsid.~~

~~21. The method of claim 20, wherein the one or more amino acid substitutions are at position 485, 488, 528, 533, or 589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions are at position 485, 488, 528, or 533, numbering based on VP1 numbering of AAVrh8R.~~

22. The method of claim 21, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.

23. The method of any one of claims 20-22, wherein the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, R533, or T589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, or R533, numbering based on VP1 numbering of AAVrh8R.

24. The method of any one of claims 20-23, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NO:11.

25. The method of any one of claims 20-24, wherein one amino acid substitution comprises a R533A substitution, numbering based on VP1 of AAVrh8R.

26. The method of any one of claims 1-25, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.

27. The method of any one of claim 1-26, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of an antioxidant, a neurotrophic factor, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor.

28. The method of any one of claims 1-27, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of: Prph2, RPE65, AIPL1, GUCY2D, LCA5, CRX, CEP290, MYO 7a, Clarin, ABCA4, RDH12, IMPDH1, CRB1, LRAT, NMNAT1, TULP1, MERTK, RPGR, RP2, RPGRIP, CNGA3, CNGB3, GNAT2, GDNF, CNTF, FGF2, PEDF, EPO, BCL2, BCL-X, NFκB, Endostatin, Angiostatin, sFlt, sPDGF-R, IL10, anti-IL17, sIL17R, IL1-ra, anti-TGFβ, sTNF-R I, sTNF-R II, and IL4.

29. The method of any one of claims 1-26, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.

30. The method of claim 29, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.

31. The method of any one of claims 1-30, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in the retina.

32. The method of any one of claims 1-31, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more retina cell types.

33. The method of claim 32, wherein the retina cell is a photoreceptor cell, a retinal pigmented epithelial cell, bipolar cell, horizontal cell, amacrine cell, muller cell and/or ganglion cell.

34. The method of claim 32 or 33, wherein the retina cell is a photoreceptor cell.

35. The method of any one of claims 31-34, wherein the promoter is a rhodopsin kinase (RK) promoter, an opsin promoter, a Cytomegalovirus (CMV) promoter, a chicken β-actin (CBA) promoter.

36. The method of any one of claims 1-35, wherein the individual is a human.

37. The method of claim 36, wherein the heterologous nucleic acid is used to treat an ocular disorder selected from the group consisting of: autosomal recessive severe early-onset retinal degeneration (Leber's Congenital Amaurosis), congenital achromatopsia, Stargardt's disease, Best's disease, Doyne's disease, cone dystrophy, retinitis pigmentosa, X-linked retinoschisis, Usher's

syndrome, age related macular degeneration, atrophic age related macular degeneration, neovascular AMD, diabetic maculopathy, proliferative diabetic retinopathy (PDR), cystoid macular oedema, central serous retinopathy, retinal detachment, intra-ocular inflammation, glaucoma, and posterior uveitis.

38. The method of any one of claims 1-37, wherein the rAAV vector is a self-complementary rAAV vector.

39. The method of claim 38, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

40. The method of claim 39, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

41. The method of any one of claims 1-40, wherein the rAAV particles are in a pharmaceutical composition.

42. The method of claim 41, wherein the concentration of the particles in the pharmaceutical composition is about 1×10^{6} DRP/ml to about 1×10^{14} DRP/ml.

43. The method of claim 41 or 42, wherein the pharmaceutical composition of rAAV particles is effective in treating the individual's visual function.

44. The method of claim 43, wherein visual function is assessed by microperimetry, dark-adapted perimetry, assessment of visual mobility, visual acuity, ERG, or reading assessment.

45. The method of claim 43 or 44, wherein the method results in an improvement in the individual's visual function.

46. The method of any one of claims 1-45, wherein the method results in the prevention of or a slowing of the progression of decline of the human's visual function due to progression of the ocular disorder.

47. A system for subretinal delivery of a vector to an eye of an individual, comprising

a) a composition comprising an effective amount of rAAV particles, wherein

i) a capsid protein of the rAAV particles comprises one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

ii) the vector comprises a heterologous nucleic acid encoding a therapeutic polypeptide or therapeutic RNA and at least one AAV terminal repeat; and

b) a device for subretinal delivery of the rAAV.

48. The system of claim 47, wherein the device comprises a fine-bore cannula and a syringe, wherein the fine bore cannula is 27 to 45 gauge.

49. The system of claim 48, wherein the composition of rAAV particles is contained within the syringe.

50. The system of claim 48 or 49, wherein the cannula is attached to the syringe.

51. The system of any one of claims 47-50, wherein the concentration of the particles in the composition is about 1×10^{6} DRP/ml to about 1×10^{14} DRP/ml.

52. The system of any one of claims 47-51, wherein the rAAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV6 capsid, an AAV8 capsid, an AAVrh8R capsid, an AAV9 capsid, or an AAVrh10 capsid.

53. The system of any one of claims 47-52, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan.

54. The system of claim 53, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.

55. The system of any one of claims 47-54, wherein the one or more amino acid substitutions comprise a substitution of a positively charged amino acid residue with an amino acid residue that is not positively charged.

56. The system of claim 55, wherein the positively charged amino acid residue is substituted with a hydrophobic amino acid residue.

57. The system of any one of claims 47-56, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue.

58. The system of any one of claims 47-57, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue with an alanine residue.

59. The system of any one of claims 47-58, wherein the one or more amino acid substitutions is at position 484, 487, or 532, numbering based on VP1 numbering of AAV2.

60. The system of claim 59, wherein the numbering is based on the VP1 of AAV2 comprising the amino acid sequence of SEQ ID NO:1.

61. The system of any one of claims 47-58 and 60, wherein the one or more amino acid substitutions comprises a substitution at position R484, R487, K527, K532, R585 and/or R588, numbering based on VP1 of AAV2.

62. The system of any one of claims 47-61, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NOs:2, 4 and/or 6.

63. The system of any one of claims 47-61, wherein the one or more amino acid substitutions comprises substitutions at position R484 and R487 or at positions R585 and R588, numbering based on VP1 of AAV2.

64. The system of any one of claims 47-61, wherein the one or more amino acid substitutions comprises R484A and R487A substitutions or R585A and R588A substitutions, numbering based on VP1 of AAV2.

65. The system of any one of claims 47-61, wherein the AAV capsid comprises amino acid substitutions R585A and R588A, numbering based on VP1 of AAV2.

66. The system of any one of claims 47-61, wherein the AAV capsid comprises amino acid substitutions K532A, numbering based on VP1 of AAV2.

67. The system of any one of claims 47-58, wherein the one or more amino acid substitutions are at position 485, 488, 528, 533, or 589, numbering based on VP1 numbering of AAVrh8R, or the

one or more amino acid substitutions are at position 485, 488, 528, or 533, numbering based on VP1 numbering of AAVrh8R.

68. The system of claim 67, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.

69. The system of claim 67 or 68, wherein the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, R533, or T589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, or R533, numbering based on VP1 numbering of AAVrh8R.

70. The system of any one of claims 67-69, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NO:11.

71. The system of any one of 67-70, wherein one amino acid substitution comprises a R533A substitution, numbering based on VP1 of AAVrh8R.

72. The system of any one of claims 47-71, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.

73. The system of any one of claim 47-72, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of an antioxidant, a neurotrophic factor, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor.

74. The system of any one of claims 47-73, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of: Prph2, RPE65, AIPL1, GUCY2D, LCA5, CRX,

CEP290, MYO 7a, Clarin, ABCA4, RDH12, IMPDH1, CRB1, LRAT, NMNAT1, TULP1, MERTK, RPGR, RP2, RPGRIP, CNGA3, CNGB3, GNAT2, GDNF, CNTF, FGF2, PEDF, EPO, BCL2, BCL-X, NFκB, Endostatin, Angiostatin, sFlt, sPDGF-R, IL10, anti-IL17, sIL17R, IL1-ra, anti-TGFβ, sTNF-R I, sTNF-R II, and IL4.

75. The system of any one of claims 47-72, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.

76. The system of claim 75, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.

77. The system of any one of claims 47-76, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in the retina.

78. The system of any one of claims 47-77, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more retina cell types.

79. The system of claim 78, wherein the retina cell is a photoreceptor cell, a retinal pigmented epithelial cells, bipolar cells, horizontal cells, amacrine cells, muller cells and/or ganglion cells.

80. The system of claim 79, wherein the retina cell is a photoreceptor cell.

81. The system of any one of claims 77-80, wherein the promoter is a rhodopsin kinase (RK) promoter, an opsin promoter, a Cytomegalovirus (CMV) promoter, a chicken β-actin (CBA) promoter.

82. The system of any one of claims 47-81, wherein the individual is a human.

83. The system of claim 82, wherein the heterologous nucleic acid is used to treat an ocular disorder selected from the group consisting of: autosomal recessive severe early-onset retinal degeneration (Leber's Congenital Amaurosis), congenital achromatopsia, Stargardt's disease, Best's disease, Doyne's disease, cone dystrophy, retinitis pigmentosa, X-linked retinoschisis, Usher's syndrome, age related macular degeneration, atrophic age related macular degeneration, neovascular AMD, diabetic maculopathy, proliferative diabetic retinopathy (PDR), cystoid macular oedema, central serous retinopathy, retinal detachment, intra-ocular inflammation, glaucoma, and posterior uveitis.

84. The system of any one of claims 47-83, wherein the rAAV vector is a self-complementary rAAV vector.

85. The system of claim 84, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

86. The system of claim 85, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

87. A kit for treating an ocular disorder comprising

a) a composition comprising rAAV particles, wherein the rAAV particle comprises

i) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

ii) a rAAV vector comprising the heterologous nucleic acid for treating an ocular disorder and at least one AAV inverted terminal repeat; and

b) a pharmaceutical excipient suitable for subretinal administration.

88. The kit of claim 87, wherein the rAAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV6 capsid, an AAV8 capsid, an AAVrh8R capsid, an AAV9 capsid, or an AAVrh10 capsid.

89. The kit of claim 87 or 88, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan.

90. The kit of claim 89, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.

91. The kit of any one of claims 87-90, wherein the one or more amino acid substitutions comprise a substitution of a positively charged amino acid residue with an amino acid residue that is not positively charged.

92. The kit of claim 91, wherein the positively charged amino acid residue is substituted with a hydrophobic amino acid residue.

93. The kit of any one of claims 87-92, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue.

94. The kit of any one of claims 87-93, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue with an alanine residue.

95. The kit of any one of claims 87-94, wherein the one or more amino acid substitutions is at position 484, 487, or 532, numbering based on VP1 numbering of AAV2.

96. The kit of claim 95, wherein the numbering is based on the VP1 of AAV2 comprising the amino acid sequence of SEQ ID NO:1.

97. The kit of any one of claims 87-94 and 96, wherein the one or more amino acid substitutions comprises a substitution at position R484, R487, K527, K532, R585 and/or R588, numbering based on VP1 of AAV2.

98. The kit of any one of claims 87-97, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NOs:2, 4 and/or 6.

99. The kit of any one of claims 87-97, wherein the one or more amino acid substitutions comprises substitutions at position R484 and R487 or at positions R585 and R588, numbering based on VP1 of AAV2.

100. The kit of any one of claims 87-97, wherein the one or more amino acid substitutions comprises R484A and R487A substitutions or R585A and R588A substitutions, numbering based on VP1 of AAV2.

101. The kit of any one of claims 87-97, wherein the AAV capsid comprises amino acid substitutions R585A and R588A, numbering based on VP1 of AAV-2.

102. The kit of any one of claims 87-97, wherein the AAV capsid comprises amino acid substitutions K532A, numbering based on VP1 of AAV-2

103. The kit of any one of claims 87-94, wherein the one amino acid substitutions are at position 485, 488, 528, 533, or 589, numbering based on VP1 numbering of AAVrh8R, or the one amino acid substitutions are at position 485, 488, 528, or 533, numbering based on VP1 numbering of AAVrh8R.

104. The kit of claim 103, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.

105. The kit of claim 103 or 104, wherein the one amino acid substitutions comprise a substitution at position R485, R488, K528, R533, or T589, numbering based on VP1 numbering of AAVrh8R, or the one amino acid substitutions comprise a substitution at position R485, R488, K528, or R533, numbering based on VP1 numbering of AAVrh8R.

106. The kit of any one of claims 103 to 105, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NO:11.

107. The kit of any one of 103 to 106, wherein one amino acid substitutions comprises a R533A substitution, numbering based on VP1 of AAVrh8R.

108. The kit of any one of claims 87-107, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.

109. The kit of any one of claim 87-108, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of an antioxidant, a neurotrophic factor, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor.

110. The kit of any one of claims 87-109, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of: Prph2, RPE65, AIPL1, GUCY2D, LCA5, CRX, CEP290, MYO 7a, Clarin, , ABCA4, RDH12, IMPDH1, CRB1, LRAT, NMNAT1, TULP1, MERTK, RPGR, RP2, RPGRIP, CNGA3, CNGB3, GNAT2, GDNF, CNTF, FGF2, PEDF, EPO, BCL2, BCL-X, NFκB, Endostatin, Angiostatin, sFlt, sPDGF-R, IL10, anti-IL17, sIL17R, IL1-ra, anti-TGFβ, sTNF-R I, sTNF-R II, and IL4.

111. The kit of any one of claims 87-108, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.

112. The kit of claim 111, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.

113. The kit of any one of claims 87-112, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in the retina.

114. The kit of any one of claims 87-113, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more retina cell types.

115. The kit of claim 114, wherein the retina cell is a photoreceptor cell, a retinal pigmented epithelial cells, bipolar cells, horizontal cells, amacrine cells, muller cells and/or ganglion cells.

116. The kit of claim 114, wherein the retina cell is a photoreceptor cell.

117. The kit of any one of claims 114-116, wherein the promoter is a rhodopsin kinase (RK) promoter, an opsin promoter, a Cytomegalovirus (CMV) promoter, a chicken β-actin (CBA) promoter.

118. The kit of any one of claims 87-117, wherein the individual is a human.

119. The kit of claim 118, wherein the heterologous nucleic acid is used to treat an ocular disorder selected from the group consisting of: autosomal recessive severe early-onset retinal degeneration (Leber's Congenital Amaurosis), congenital achromatopsia, Stargardt's disease, Best's

disease, Doyne's disease, cone dystrophy, retinitis pigmentosa, X-linked retinoschisis, Usher's syndrome, age related macular degeneration, atrophic age related macular degeneration, neovascular AMD, diabetic maculopathy, proliferative diabetic retinopathy (PDR), cystoid macular oedema, central serous retinopathy, retinal detachment, intra-ocular inflammation, glaucoma, and posterior uveitis.

120. The kit of claim 118, wherein the heterologous nucleic acid is used to treat an ocular disorder selected from the group consisting of: autosomal recessive severe early-onset retinal degeneration (Leber's Congenital Amaurosis), Stargardt's disease, retinitis pigmentosa, Usher's syndrome, and age related macular degeneration.

121. The kit of any one of claims 87-120, wherein the rAAV vector is a self-complementary rAAV vector.

122. The kit of claim 121, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

123. The kit of claim 122, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

124. The kit of any one of claims 87-123, further comprising a device for subretinal delivery of the composition of rAAV particles.

125. The kit of any one of claims 87-124, further comprising instructions for subretinal delivery of the composition of rAAV particles.

126. A method for delivering a heterologous nucleic acid to the central nervous system (CNS) of an individual comprising administering a recombinant adeno-associated virus (rAAV) particle to the CNS of the individual, wherein the rAAV particle comprises

a) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising the heterologous nucleic acid and at least one AAV inverted terminal repeat.

127. A method for improving rAAV transduction of cells in the central nervous system (CNS) of an individual compared to transduction of cells with a rAAV comprising a wild-type capsid, the method comprising administering a recombinant adeno-associated virus (rAAV) particle to the CNS of the individual, wherein the rAAV particle comprises

a) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV inverted terminal repeat.

128. A method for improving expression of a heterologous nucleic acid in the central nervous system (CNS) of an individual, the method comprising administering a recombinant adeno-associated virus (rAAV) particle to the CNS of the individual, wherein the rAAV particle comprises

a) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV inverted terminal repeat.

~~129. A method to treat a disorder of the central nervous system (CNS) of an individual comprising administering an effective amount of a composition comprising a rAAV particle to the CNS of the individual, wherein the rAAV particle comprises~~

~~a) a rAAV capsid comprising a rAAV capsid protein comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and~~

~~b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat.~~

~~130. The method of any one of claims 126-129, wherein the heterologous nucleic acid is expressed at an increased level of expression, as compared to the level of expression of a heterologous nucleic acid of a rAAV particle comprising a reference rAAV capsid.~~

~~131. The method of any one of claims 126-130, wherein the rAAV particle causes reduced neuroinflammation, as compared to a rAAV particle comprising a reference rAAV capsid.~~

~~132. The method of any one of claims 126-131, wherein the rAAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV6 capsid, an AAV8 capsid, an AAVrh8R capsid, an AAV9 capsid, or an AAVrh10 capsid.~~

~~133. The method of any one of claims 126-132, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan, optionally by at least about 10%, at least about 25%, at least about 50%, at least about 75%, or at least about 100%.~~

~~134. The method of any one of claims 126-133, wherein the administration comprises direct spinal cord injection, intracranial, and/or intracerebral administration.~~

~~135. The method of claim 134, wherein the intracerebral administration is at a site selected from the group consisting of the cerebrum, medulla, pons, cerebellum, intracranial cavity, meninges surrounding the brain, dura mater, arachnoid mater, pia mater, cerebrospinal fluid (CSF) of the subarachnoid space surrounding the brain, deep cerebellar nuclei of the cerebellum, ventricular system of the cerebrum, subarachnoid space, striatum, cortex, septum, thalamus, hypothalamus, and the parenchyma of the brain.~~

~~136. The method of any one of claims 126-135, wherein the administration is intracerebroventricular injection into at least one cerebral lateral ventricle.~~

~~137. The method of any one of claims 126-135, wherein the administration is intrathecal injection in the cervical, thoracic, and/or lumbar region.~~

~~138. The method of any one of claims 126-135, wherein the administration is intrastriatal injection.~~

~~139. The method of any one of claims 126-135, wherein the administration is intrathalamic injection.~~

~~140. The method of any one of claims 126-135, wherein the administration is intraparenchymal injection.~~

~~141. The method of any one of claims 126-140, wherein the rAAV particle is administered at a single site.~~

~~142. The method of claim 135, wherein the rAAV particle is delivered by stereotactic delivery.~~

~~143. The method of claim 135 or 142, wherein the rAAV particle is delivered by convection enhanced delivery.~~

~~144. The method of claim 143, wherein the rAAV particle is delivered using a CED delivery system.~~

~~145. The method of claim 144, wherein the CED delivery system comprises a cannula and/or a pump.~~

~~146. The method of claim 145, wherein the cannula is a reflux-resistant cannula or a stepped cannula.~~

~~147. The method of claim 145 or 146, wherein the pump is a manual pump.~~

~~148. The method of claim 145 or 146, wherein the pump is an osmotic pump.~~

~~149. The method of claim 145 or 146, wherein the pump is an infusion pump.~~

~~150. The method of any one of claims 126-149, wherein the heterologous nucleic acid is expressed in one or more cells of the CNS.~~

~~151. The method of claim 150, wherein the one or more cells of the CNS is an oligodendrocyte, astrocyte, neuron, brain parenchyma cell, microglial cell, ependemal cell, and/or a Purkinje cell.~~

~~152. The method of any one of claims 126-151, wherein the heterologous nucleic acid is expressed in a neuron.~~

153. The method of claim 152, wherein the heterologous nucleic acid is exclusively expressed in neurons.

154. The method of any one of claims 126-153, wherein the one or more amino acid substitutions comprise a substitution of a positively charged amino acid residue with an amino acid residue that is not positively charged.

155. The method of claim 154, wherein the positively charged amino acid residue is substituted with a hydrophobic amino acid residue.

156. The method of any one of claims 126-155, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue.

157. The method of claim 156, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue with an alanine residue.

158. The method of any one of claims 126-157, wherein the one or more amino acid substitutions are at positions 484, 487, 527, 532, 585 and/or 588, numbering based on VP1 numbering of AAV2.

159. The method of claim 158, wherein the one or more amino acid substitutions are at position 484, 487, 527, or 532, numbering based on VP1 numbering of AAV2.

160. The method of claim 158 or 159, wherein the numbering is based on the VP1 of AAV2 comprising the amino acid sequence of SEQ ID NO:1.

161. The method of any one of claims 126-158 and 160, wherein the one or more amino acid substitutions comprises a substitution at position R448, R451, R484, R487, K527, K532, R585 and/or R588, numbering based on VP1 of AAV2.

~~162. The method of any one of claims 126-161 wherein the one or more amino acid substitutions comprises a substitution at position R484, R487, K527, and/or K532, numbering based on VP1 of AAV2.~~

~~163. The method of any one of claims 126-162, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NOs:2, 4 and/or 6.~~

~~164. The method of any one of claims 126-162, wherein the one or more amino acid substitutions comprises a R484A, R487A, K527A, K532A, R585A and/or R588A substitution, numbering based on VP1 of AAV2.~~

~~165. The method of any one of claims 126-162, wherein the one or more amino acid substitutions comprises substitutions at position R484 and R487 or at positions R585 and R588, numbering based on VP1 of AAV2.~~

~~166. The method of any one of claims 126-162, wherein the one or more amino acid substitutions comprises R484A and R487A substitutions or R585A and R588A substitutions, numbering based on VP1 of AAV2.~~

~~167. The method of any one of claims 126-162, wherein the AAV capsid comprises amino acid substitutions R585A and R588A, numbering based on VP1 of AAV2.~~

~~168. The method of any one of claims 126-162, wherein the AAV capsid comprises amino acid substitutions K532A, numbering based on VP1 of AAV2.~~

169. The method of any one of claims 126-157, wherein the one or more amino acid substitutions are at position 485, 488, 528, 533, or 589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions are at position 485, 488, 528, or 533, numbering based on VP1 numbering of AAVrh8R.

170. The method of claim 169, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.

171. The method of claim 169 or 170, wherein the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, R533, or T589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, or R533, numbering based on VP1 numbering of AAVrh8R.

172. The method of any one of claims 169-171, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NO:11.

173. The method of any one of claims 169-172, wherein one amino acid substitution comprises a R533A substitution, numbering based on VP1 of AAVrh8R.

174. The method of any one of claims 126-173, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.

175. The method of any one of claims 126-174, wherein the heterologous nucleic acid encodes a CNS-associated gene.

176. The method of any one of claims 126-175, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of an enzyme, a neurotrophic factor, a polypeptide that is deficient or mutated in an individual with a CNS related disorder, an antioxidant, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor, alpha-synuclein, acid beta-glucosidase (GBA), beta-galactosidase-1 (GLB1), iduronate 2-sulfatase (IDS), galactosylceramidase (GALC), a mannosidase, alpha-D-mannosidase (MAN2B1), beta-mannosidase (MANBA), pseudoarylsulfatase A (ARSA), N-acetylglucosamine-1-phosphotransferase (GNPTAB), acid sphingomyelinase (ASM), Niemann-Pick C protein (NPC1), acid alpha-1,4-glucosidase (GAA), hexosaminidase beta subunit, HEXB, N-sulfoglucosamine sulfohydrolase (MPS3A), N-alpha-acetylglucosaminidase (NAGLU), heparin acetyl-CoA, alpha-glucosaminidase N-acetyltransferase (MPS3C), N-acetylglucosamine-6-sulfatase (GNS), alpha-N-acetylgalactosaminidase (NAGA), beta-glucuronidase (GUSB), hexosaminidase alpha subunit (HEXA), huntingtin (HTT), lysosomal acid lipase (LIPA), Aspartylglucosaminidase, Alpha-galactosidase A, Palmitoyl protein thioesterase, Tripeptidyl peptidase, Lysosomal transmembrane protein, Cysteine transporter, Acid ceramidase, Acid alpha-L-fucosidase, cathepsin A, alpha-L-iduronidase, Arylsulfatase B, Arylsulfatase A, N-acetylgalactosamine-6-sulfate, Acid beta-galactosidase, or alpha-neuramidase.

177. The method of claim 176, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of neuronal apoptosis inhibitory protein (NAIP), nerve growth factor (NGF), glial-derived growth factor (GDNF), brain-derived growth factor (BDNF), ciliary neurotrophic factor (CNTF), tyrosine hydroxylase (TH), GTP-cyclohydrolase (GTPCH), amino acid decarboxylase (AADC) , an anti-oxidant, an anti-angiogenic polypeptide, an anti-inflammatory polypeptide, and aspartoacylase (ASPA).

178. The method of any one of claims 126-175, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.

179. The method of claim 178, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.

~~180. The method of any one of claims 126-179, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in one or more cells of the CNS.~~

~~181. The method of any one of claims 126-180, wherein the heterologous nucleic acid is under the control of a promoter sequence selected from the group consisting of a cytomegalovirus (CMV) immediate early promoter, an RSV LTR, a MoMLV LTR, a phosphoglycerate kinase-1 (PGK) promoter, a simian virus 40 (SV40) promoter, a CK6 promoter, a transthyretin promoter (TTR), a TK promoter, a tetracycline responsive promoter (TRE), an HBV promoter, an hAAT promoter, a LSP promoter, a chimeric liver-specific promoter (LSP), an E2F promoter, a telomerase (hTERT) promoter; a cytomegalovirus enhancer/chicken beta-actin/Rabbit β-globin promoter (CAG) promoter, an elongation factor 1-alpha promoter (EFl-alpha) promoter, a human β-glucuronidase promoter, a chicken β-actin (CBA) promoter, a retroviral Rous sarcoma virus (RSV) LTR promoter, a dihydrofolate reductase promoter, and a 13-actin promoter.~~

~~182. The method of claim 180, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more cells of the CNS.~~

~~183. The method of claim 180, wherein the one or more cells of the CNS comprise one or more cells of the brain.~~

~~184. The method of claim 182 or 183, wherein the one or more cells of the CNS is an oligodendrocyte, astrocyte, neuron, brain parenchyma cell, microglial cell, ependemal cell, and/or a Purkinje cell.~~

~~185. The method of any one of claims 182-184, wherein the cell of the CNS is a neuron.~~

~~186. The method of any one of claims 126-185, wherein the rAAV vector is a self-complementary rAAV vector.~~

187. The method of claim 186, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

188. The method of claim 187, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

189. The method of any one of claims 126-188, wherein the individual is a human.

190. The method of any one of claims 126-189, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or a therapeutic nucleic acid used to treat a disorder of the CNS.

191. The method of claim 190, wherein the disorder of the CNS is a lysosomal storage disease (LSD), Huntington's disease, epilepsy, Parkinson's disease, Alzheimer's disease, stroke, corticobasal degeneration (CBD), corticogasal ganglionic degeneration (CBGD), frontotemporal dementia (FTD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or cancer of the brain.

192. The method of claim 191, wherein the disorder is a lysosomal storage disease selected from the group consisting of Aspartylglusoaminuria, Fabry, Infantile Batten Disease (CNL1), Classic Late Infantile Batten Disease (CNL2), Juvenile Batten Disease (CNL3), Batten form CNL4, Batten form CNL5, Batten form CNL6, Batten form CNL7, Batten form CNL8, Cystinosis, Farber, Fucosidosis, Galactosidosialidosis , Gaucher disease type 1, Gaucher disease type 2, Gaucher disease type 3, GM1 gangliosidosis, Hunter disease, Krabbe disease, α mannosidosis disease, β mannosidosis disease, Maroteaux-Lamy, metachromatic leukodystrophy disease, Morquio A, Morquio B, mucolipidosisII/III disease, Niemann-Pick A disease, Niemann-Pick B disease, Niemann-Pick C disease, Pompe disease, Sandhoff disease, Sanfillipo A disease, Sanfillipo B disease, Sanfillipo C disease, Sanfillipo D disease, Schindler disease, Schindler-Kanzaki, sialidosis, Sly disease, Tay-Sachs disease, and Wolman disease.

193. The method of claim 191, wherein the disorder of the CNS is Huntington's disease or Parkinson's disease.

194. A method to treat Huntington's Disease in an individual comprising administering an effective amount a composition comprising a recombinant adeno-associated virus (rAAV) particle to the striatum of the individual, wherein the rAAV particle comprises

a) a rAAV capsid comprising a rAAV capsid protein comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat.

195. The method of claim 194, wherein the heterologous nucleic acid encodes

a therapeutic polypeptide or therapeutic nucleic acid.

196. The method of claim 195, wherein the therapeutic polypeptide is a huntingtin polypeptide or a fragment thereof.

197. The method of claim 195, wherein the therapeutic nucleic acid comprises an RNAi directed to huntingtin.

198. The method of claim 197, wherein the RNAi is a miRNA.

199. A method to treat Parkinson's Disease in an individual comprising administering an effective amount a composition comprising a recombinant adeno-associated virus (rAAV) particle to the striatum of the individual, wherein the rAAV particle comprises

a) a rAAV capsid comprising a rAAV capsid protein comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat.

200. The method of claim 199, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.

201. The method of claim 200, wherein the therapeutic polypeptide is TH, GTPCII, GDNF, BDNF, and/or AADC; or a fragment thereof.

202. The method of claim 200 or claim 201, wherein the therapeutic polypeptide is AADC or a fragment thereof.

203. The method of any one of claims 194-202, wherein the heterologous nucleic acid is expressed at an increased level of expression, as compared to the level of expression of a heterologous nucleic acid of a rAAV particle comprising a reference rAAV capsid.

204. The method of any one of claims 194-203, wherein the rAAV particle causes reduced neuroinflammation, as compared to a rAAV particle comprising a reference rAAV capsid.

205. The method of any one of claims 194-204, wherein the rAAV particle comprises an AAV serotype 2 (AAV2) capsid.

206. The method of any one of claims 194-205, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan or increases transduction of a cell in the central nervous system.

207. The method of claim 206, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100% or increases transduction of a cell in the central nervous system by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.

208. The method of any one of claims 194-207, wherein the rAAV particle is delivered by stereotactic delivery.

209. The method of any one of claims 194-207, wherein the rAAV particle is delivered by convection enhanced delivery.

210. The method of claim 209, wherein the rAAV particle is administered using a CED delivery system.

211. The method of claim 210, wherein the CED delivery system comprises a cannula and/or a pump.

212. The method of claim 211, wherein the cannula is a reflux-resistant cannula or a stepped cannula.

213. The method of claim 211 or 212, wherein the pump is a manual pump.

214. The method of claim 211 or 212, wherein the pump is an osmotic pump.

215. The method of claim 211 or 212, wherein the pump is an infusion pump.

216. The method of any one of claims 194-215, wherein the heterologous nucleic acid is expressed in one or more cells of the CNS.

217. The method of claim 216, wherein the one or more cells of the CNS is an oligodendrocyte, astrocyte, neuron, brain parenchyma cell, microglial cell, ependemal cell, and/or a Purkinje cell.

218. The method of any one of claims 194-217, wherein the heterologous nucleic acid is expressed in a neuron.

219. The method of claim 218, wherein the heterologous nucleic acid is exclusively expressed in neurons.

220. The method of any one of claims 194-219, wherein the one or more amino acid substitutions comprise a substitution of a positively charged amino acid residue with an amino acid residue that is not positively charged.

221. The method of claim 220, wherein the positively charged amino acid residue is substituted with a hydrophobic amino acid residue.

222. The method of any one of claims 194-221, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue.

223. The method of claim 222, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue with an alanine residue.

~~224. The method of any one of claims 194-223, wherein the one or more amino acid substitutions is at 484, 487, 527, 532, 585 and/or 588, numbering based on VP1 numbering of AAV2.~~

~~225. The method of claim 224, wherein the one or more amino acid substitutions is at position 484, 487, 527, or 532, numbering based on VP1 numbering of AAV2.~~

~~226. The method of claim 224 or 225, wherein the numbering is based on the VP1 of AAV2 comprising the amino acid sequence of SEQ ID NO:1.~~

~~227. The method of any one of claims 194-224 and 226, wherein the one or more amino acid substitutions comprises a substitution at position R484, R487, K527, K532, R585 and/or R588, numbering based on VP1 of AAV2.~~

~~228. The method of any one of claims 194-227, wherein the one or more amino acid substitutions comprises a substitution at position R484, R487, and/or K532, numbering based on VP1 of AAV2.~~

~~229. The method of any one of claims 194-228, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NOs:2, 4 and/or 6.~~

~~230. The method of any one of claims 194-228, wherein the one or more amino acid substitutions comprise substitutions at position R484 and R487, numbering based on VP1 of AAV2.~~

~~231. The method of any one of claims 194-228, wherein the one or more amino acid substitutions comprise substitutions at position R585 and R588, numbering based on VP1 of AAV2.~~

~~232. The method of any one of claims 194-228, wherein the one or more amino acid substitutions comprise R484A and R487A substitutions, numbering based on VP1 of AAV2.~~

~~233. The method of any one of claims 194-228, wherein the AAV capsid comprises amino acid substitutions R585A and R588A, numbering based on VP1 of AAV2.~~

~~234. The method of any one of claims 194-228, wherein the AAV capsid comprises amino acid substitutions K532A, numbering based on VP1 of AAV2.~~

~~235. The method of any one of claims 194-223, wherein the one or more amino acid substitutions are at position 485, 488, 528, 533, or 589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions are at position 485, 488, 528, or 533, numbering based on VP1 numbering of AAVrh8R.~~

~~236. The method of claim 235, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.~~

~~237. The method of claim 235 or 236, wherein the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, R533, or T589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, or R533, numbering based on VP1 numbering of AAVrh8R.~~

~~238. The method of any one of claims 235-237, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NO:11.~~

~~239. The method of any one of claims 235-238, wherein one amino acid substitution comprises a R533A substitution, numbering based on VP1 of AAVrh8R.~~

~~240. The method of any one of claims 194-239, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in one or more cells of the CNS.~~

~~241. The method of any one of claims 194-239, wherein the heterologous nucleic acid is under the control of a promoter sequence selected from the group consisting of a cytomegalovirus (CMV) immediate early promoter, an RSV LTR, a MoMLV LTR, a phosphoglycerate kinase-1 (PGK) promoter, a simian virus 40 (SV40) promoter, a CK6 promoter, a transthyretin promoter (TTR), a TK promoter, a tetracycline responsive promoter (TRE), an HBV promoter, an hAAT promoter, a LSP promoter, a chimeric liver-specific promoter (LSP), an E2F promoter, a telomerase (hTERT) promoter; a cytomegalovirus enhancer/chicken beta-actin/Rabbit β-globin promoter (CAG) promoter, an elongation factor 1-alpha promoter (EFl-alpha) promoter, a human β-glucuronidase promoter, a chicken β-actin (CBA) promoter, a retroviral Rous sarcoma virus (RSV) LTR promoter, a dihydrofolate reductase promoter, and a 13-actin promoter.~~

~~242. The method of claim 240, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more cells of the CNS.~~

~~243. The method of claim 240, wherein the one or more cells of the CNS comprise one or more cells of the brain.~~

~~244. The method of claim 242 or claim 243, wherein the one or more cells of the CNS is an oligodendrocyte, astrocyte, neuron, brain parenchyma cell, microglial cell, ependemal cell, and/or a Purkinje cell.~~

~~245. The method of claim 243, wherein the cell of the brain is a neuron.~~

246. The method of any one of claims 194-245, wherein the rAAV vector is a self-complementary rAAV vector.

247. The method of claim 246, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

248. The method of claim 247, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

249. The method of any one of claims 37-46 and 190-248, wherein the individual is a human.

250. A kit for use in the method of any one of claims 1-46 and 126-249, comprising a recombinant adeno-associated virus (rAAV) particle, wherein the rAAV particle comprises

a) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interact with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising the heterologous nucleic acid and at least one AAV inverted terminal repeat.

251. A kit for delivering a heterologous nucleic acid to the central nervous system (CNS) of an individual comprising a composition comprising a recombinant adeno-associated virus (rAAV) particle, wherein the rAAV particle comprises

a) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interact with a heparan sulfate proteoglycan

or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV inverted terminal repeat.

252. A kit for treating a central nervous system (CNS) disorder in an individual comprising a composition comprising a recombinant adeno-associated virus (rAAV) particle, wherein the rAAV particle comprises

a) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interact with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising the heterologous nucleic acid for treating a CNS disorder and at least one AAV inverted terminal repeat.

253. The kit of claim 251 or 252, wherein the CNS disorder is Huntington's disease.

254. The kit of any one of claims 251-253, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.

255. The kit of claim 254, wherein the therapeutic polypeptide is a huntingtin polypeptide or a fragment thereof.

256. The kit of claim 254, wherein the therapeutic nucleic acid comprises an RNAi directed to huntingtin.

257. The kit of claim 256, wherein the RNAi is a miRNA.

~~258. The kit of claim 251 or 252, wherein the CNS disorder is Parkinson's disease.~~

~~259. The kit of claim 258, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.~~

~~260. The kit of claim 259, wherein the therapeutic polypeptide is TH, GTPCII, GDNF, BDNF, and/or AADC; or a fragment thereof.~~

~~261. The kit of claim 259 or claim 260, wherein the therapeutic polypeptide is AADC or a fragment thereof.~~

~~262. A recombinant adeno-associated virus (rAAV) particle for use in the method of any one of claims 1-46 and 126-249.~~

~~263. A recombinant adeno-associated virus (rAAV) particle use in the method of any one of claims 1-46.~~

~~264. A recombinant adeno-associated virus (rAAV) particle for use in the method of any one of claims 126-249.~~

~~265. A recombinant adeno-associated virus (rAAV) particle for treating Huntington's Disease or Parkinson's Disease in an individual, wherein the rAAV particle comprises~~

~~a) a rAAV capsid comprising a rAAV capsid protein comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and~~

~~b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat,~~

wherein the rAAV particle is formulated for delivery to the striatum.

266. A recombinant adeno-associated virus (rAAV) particle for treating Huntington's Disease or Parkinson's Disease in an individual, wherein the rAAV particle comprises

a) a rAAV capsid comprising a rAAV capsid protein comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat,

wherein the rAAV particle is formulated for single site delivery.

267. The kit of any one of claims 250-261 or the rAAV particle of any one of claims 262-266, wherein the heterologous nucleic acid is expressed at an increased level of expression, as compared to the level of expression of a heterologous nucleic acid of a rAAV particle comprising a reference rAAV capsid.

268. The kit of any one of claims 250-261 and 267 or the rAAV particle of any one of claims 262-267, wherein the rAAV particle causes reduced neuroinflammation, as compared to a rAAV particle comprising a reference rAAV capsid.

269. The kit of any one of claims 250-261, 267, and 268 or the rAAV particle of any one of claims 262-268, wherein the rAAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV6 capsid, an AAV8 capsid, an AAVrh8R capsid, an AAV9 capsid, or an AAVrh10 capsid.

270. The kit of any one of claims 250-261 and 267-269 or the rAAV particle of any one of claims 262-269, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan or increases transduction of a cell in the central nervous system.

271. The kit or rAAV particle of claim 270, wherein the one or more amino acid substitutions reduces binding of the rAAV particle to the heparan sulfate proteoglycan by at least about 10%, at least about 25%, at least about 50%, at least about 75%, or at least about 100% or increases transduction of the cell by at least about 10%, at least about 25%, at least about 50%, at least about 75%, or at least about 100%.

272. The kit of any one of claims 250-261 and 267-271 or the rAAV particle of any one of claims 262-271, wherein the heterologous nucleic acid is expressed in one or more cells of the CNS.

273. The kit or rAAV particle of claim 272, wherein the one or more cells of the CNS is an oligodendrocyte, astrocyte, neuron, brain parenchyma cell, microglial cell, ependemal cell, and/or a Purkinje cell.

274. The kit of any one of claims 250-261 and 267-273 or the rAAV particle of any one of claims 262-273, wherein the heterologous nucleic acid is expressed in a neuron.

275. The kit or rAAV particle of claim 274, wherein the heterologous nucleic acid is exclusively expressed in neurons.

276. The kit of any one of claims 250-261 and 267-275 or the rAAV particle of any one of claims 262-275, wherein the one or more amino acid substitutions comprise a substitution of a positively charged amino acid residue with an amino acid residue that is not positively charged.

277. The kit or rAAV particle of claim 276, wherein the positively charged amino acid residue is substituted with a hydrophobic amino acid residue.

278. The kit of any one of claims 250-261 and 267-277 or the rAAV particle of any one of claims 262-277, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue.

~~279. The kit or rAAV particle of claim 278, wherein the one or more amino acid substitutions comprises substitution of an arginine or lysine residue with an alanine residue.~~

~~280. The kit of any one of claims 250-261 and 267-279 or the rAAV particle of any one of claims 262-279, wherein the one or more amino acid substitutions is at 448, 451, 484, 487, 527, 532, 585 and/or 588, numbering based on VP1 numbering of AAV2.~~

~~281. The kit or rAAV particle of claim 280, wherein the one or more amino acid substitutions is at position 484, 487, or 532, numbering based on VP1 numbering of AAV2.~~

~~282. The kit or rAAV particle of claim 280 or 281, wherein the numbering is based on the VP1 of AAV2 comprising the amino acid sequence of SEQ ID NO:1.~~

~~283. The kit of any one of claims 250-261 and 267-280 and 282 or the rAAV particle of any one of claims 262-280 and 282, wherein the one or more amino acid substitutions comprises a substitution at position R484, R487, K527, K532, R585 and/or R588, numbering based on VP1 of AAV2.~~

~~284. The kit of any one of claims 250-261 and 267-283 or the rAAV particle of any one of claims 262-283, wherein the one or more amino acid substitutions comprises a substitution at position R484, R487, and/or K532, numbering based on VP1 of AAV2.~~

~~285. The kit of any one of claims 250-261 and 267-284 or the rAAV particle of any one of claims 262-284, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NOs:2, 4 and/or 6.~~

~~286. The kit of any one of claims 250-261 and 267-284 or the rAAV particle of any one of claims 262-284, wherein the one or more amino acid substitutions comprise substitutions at positions R484 and R487, numbering based on VP1 of AAV2.~~

~~287. The kit of any one of claims 250-261 and 267-284 or the rAAV particle of any one of claims 262-284, wherein the one or more amino acid substitutions comprises substitutions at positions R585 and R588, numbering based on VP1 of AAV2.~~

~~288. The kit of any one of claims 250-261 and 267-284 or the rAAV particle of any one of claims 262-284, wherein the one or more amino acid substitutions comprises R484A and R487A substitutions or R585A and R588A substitutions, numbering based on VP1 of AAV2.~~

~~289. The kit of any one of claims 114-261 and 267-284 or the rAAV particle of any one of claims 262-149, wherein the AAV capsid comprises amino acid substitutions R585A and R588A, numbering based on VP1 of AAV2.~~

~~290. The kit of any one of claims 250-261 and 267-284 or the rAAV particle of any one of claims 262-284, wherein the AAV capsid comprises amino acid substitutions K532A, numbering based on VP1 of AAV2.~~

~~291. The kit of any one of claims 250-261 and 267-279 or the rAAV particle of any one of claims 262-279, wherein the one or more amino acid substitutions are at position 485, 488, 528, 533, or 589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions are at position 485, 488, 528, or 533, numbering based on VP1 numbering of AAVrh8R.~~

~~292. The kit or rAAV particle of claim 291, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.~~

293. The kit or rAAV particle of claim 291 or 292, wherein the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, R533, or T589, numbering based on VP1 numbering of AAVrh8R, or the one or more amino acid substitutions comprise a substitution at position R485, R488, K528, or R533, numbering based on VP1 numbering of AAVrh8R.

294. The kit or rAAV particle of any one of claims 291-293, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NO:11.

295. The kit or rAAV particle of any one of claims 291-294, wherein one amino acid substitution comprises a R533A substitution, numbering based on VP1 of AAVrh8R.

296. The kit of any one of claims 250-261 and 267-295 or the rAAV particle of any one of claims 262-295, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in one or more cells of the CNS.

297. The kit of any one of claims 250-261 and 267-295 or the rAAV particle of any one of claims 262-295, wherein the heterologous nucleic acid is under the control of a promoter sequence selected from the group consisting of a cytomegalovirus (CMV) immediate early promoter, an RSV LTR, a MoMLV LTR, a phosphoglycerate kinase- 1 (PGK) promoter, a simian virus 40 (SV40) promoter, a CK6 promoter, a transthyretin promoter (TTR), a TK promoter, a tetracycline responsive promoter (TRE), an HBV promoter, an hAAT promoter, a LSP promoter, a chimeric liver-specific promoter (LSP), an E2F promoter, a telomerase (hTERT) promoter; a cytomegalovirus enhancer/chicken beta-actin/Rabbit β-globin promoter (CAG) promoter, an elongation factor 1-alpha promoter (EFl-alpha) promoter, a human β-glucuronidase promoter, a chicken β-actin (CBA) promoter, a retroviral Rous sarcoma virus (RSV) LTR promoter, a dihydrofolate reductase promoter, and a 13-actin promoter.

298. The kit or rAAV particle of claim 296, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more cells of the CNS.

299. The kit or rAAV particle of claim 296, wherein the one or more cells of the CNS comprise one or more cells of the brain.

300. The kit or rAAV particle of claim 298 or claim 299, wherein the one or more cells of the CNS is an oligodendrocyte, astrocyte, neuron, brain parenchyma cell, microglial cell, ependemal cell, and/or a Purkinje cell.

301. The kit or rAAV particle of claim 299, wherein the cell of the brain is a neuron.

302. The kit of any one of claims 250-127 and 267-301 or the rAAV particle of any one of claims 262-301, wherein the rAAV vector is a self-complementary rAAV vector.

303. The kit or rAAV particle of claim 302, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

304. The kit or rAAV particle of claim 303, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

305. The kit of any one of claims 250-261 and 267-304 or the rAAV particle of any one of claims 262-304, wherein the individual is a human.

306. The kit of any one of claims 250-261 and 267-305 or the rAAV particle of any one of claims 262-305, wherein the rAAV particles are in a composition.

307. The kit or rAAV particle of claim 306, wherein the composition comprises a buffer and/or a pharmaceutically acceptable excipient.

308. The kit of any one of claims 250-261 and 267-307 or the rAAV particle of any one of claims 262-307, further comprising instructions for delivery of the composition of rAAV particles to the CNS, optionally to the striatum.

309. The kit of any one of claims 250-261 and 267-308 or the rAAV particle of any one of claims 262-308, further comprising instructions for delivery of the composition of rAAV particles to a single site in the CNS.

310. A rAAV particle comprising an AAVrh8R capsid protein, wherein the AAVrh8R capsid protein comprises one or more amino acid substitutions at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2.

311. The rAAV particle of claim 310, wherein the one or more amino acid substitutions increases transduction efficiency of the rAAV particle for a cell in the eye or the central nervous system, as compared to an AAV particle comprising a wild-type AAVrh8R capsid protein, by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.

312. The rAAV particle of claim 310 or 311, wherein one amino acid substitution is at position 586, numbering based on VP1 numbering of AAVrh8R.

313. The rAAV particle of claim 312, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.

314. The rAAV particle of claim 312 or 313, wherein one amino acid substitution comprises a substitution at position A586, numbering based on VP1 numbering of AAVrh8R.

315. The rAAV particle of any one of claims 312-314, wherein one amino acid substitution comprises a A586R substitution, numbering based on VP1 numbering of AAVrh8R.

316. The rAAV particle of any one of claims 310-315, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NO:10.

317. A method of increasing the transduction efficiency of a rAAV particle comprising a AAVrh8R capsid protein, comprising introducing one or more amino acid substitutions to the capsid protein at one or more positions corresponding to amino acids 484, 487, 527, 532, 585, or 588, numbering based on VP1 numbering of AAV2, wherein the one or more amino acid substitutions increase transduction efficiency of the rAAV particle to a cell in the eye or the central nervous system as compared to an AAV particle comprising a wild type AAVrh8R capsid protein.

318. The method of claim 317, wherein the one or more amino acid substitutions increase the transduction efficiency of the rAAV particle to the cell by at least about 10%, at least about 25%, at least about 50%, at least about 75%, or at least about 100%.

319. The method of claim 317 or 318, wherein one amino acid substitution is at position 586, numbering based on VP1 numbering of AAVrh8R.

320. The method of any one of claims 317-319, wherein the VP1 of AAVrh8R comprises the amino acid sequence of SEQ ID NO:9.

321. The method of any one of claims 317-320, wherein one amino acid substitution comprises a substitution at position A586, numbering based on VP1 numbering of AAVrh8R.

322. The method of any one of claims 317-321, wherein one amino acid substitution comprises a A586R substitution, numbering based on VP1 numbering of AAVrh8R.

323. The method of any one of claims 317-322, wherein the rAAV particle comprises one or more rAAV capsid proteins having at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence identity to SEQ ID NO:10.

324. A rAAV particle comprising an AAV1 capsid protein, wherein the AAV1 capsid protein comprises one or more amino acid substitutions at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2.

325. The rAAV particle of claim 324, wherein the one or more amino acid substitutions increases transduction efficiency of the rAAV particle for a cell in the eye or the central nervous system, as compared to an AAV particle comprising a wild-type AAV1 capsid protein, by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%..

326. The rAAV particle of claim 324 or 325, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV1.

327. The rAAV particle of claim 326, wherein the numbering is based on the VP1 of AAV1 comprising the amino acid sequence of SEQ ID NO:12.

328. The rAAV particle of claim 326 or 327, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or T589, numbering based on VP1 numbering of AAV1.

329. The rAAV particle of any one of claims 326-328, wherein the one or more amino acid substitutions comprise an S586R substitution, numbering based on VP1 of AAV1.

330. The rAAV particle of any one of claims 326-329, wherein the one or more amino acid substitutions comprise a T589R substitution, numbering based on VP1 of AAV1.

331. A rAAV particle comprising an AAV6 capsid protein, wherein the AAV6 capsid protein comprises one or more amino acid substitutions at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2.

332. The rAAV particle of claim 331, wherein the one or more amino acid substitutions increases transduction efficiency of the rAAV particle for a cell in the eye or the central nervous system, as compared to an AAV particle comprising a wild-type AAV6 capsid protein, by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%

333. The rAAV particle of claim 331 or 332, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV6.

334. The rAAV particle of claim 333, wherein the numbering is based on the VP1 of AAV6 comprising the amino acid sequence of SEQ ID NO:13.

335. The rAAV particle of claim 333 or 334, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or T589, numbering based on VP1 numbering of AAV6.

336. The rAAV particle of any one of claims 333-335, wherein the one or more amino acid substitutions comprise an S586R substitution, numbering based on VP1 of AAV6.

337. The rAAV particle of any one of claims 333-336, wherein the one or more amino acid substitutions comprise a T589R substitution, numbering based on VP1 of AAV6.

338. A rAAV particle comprising an AAV8 capsid protein, wherein the AAV8 capsid protein comprises one or more amino acid substitutions at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2.

339. The rAAV particle of claim 338, wherein the one or more amino acid substitutions increases transduction efficiency of the rAAV particle for a cell in the eye or the central nervous system, as compared to an AAV particle comprising a wild-type AAV8 capsid protein, by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.

340. The rAAV particle of claim 338 or 339, wherein the one or more amino acid substitutions are at positions 588 and/or 591, numbering based on VP1 numbering of AAV8.

341. The rAAV particle of any one of claims 338-340, wherein the numbering is based on the VP1 of AAV8 comprising the amino acid sequence of SEQ ID NO:14.

342. The rAAV particle of claim 340 or 341, wherein the one or more amino acid substitutions comprise a substitution at position Q588 and/or T591, numbering based on VP1 numbering of AAV8.

343. The rAAV particle of any one of claims 340-342, wherein the one or more amino acid substitutions comprise a Q588R substitution, numbering based on VP1 of AAV8.

344. The rAAV particle of any one of claims 340-343, wherein the one or more amino acid substitutions comprise a T591R substitution, numbering based on VP1 of AAV8.

345. A rAAV particle comprising an AAV9 capsid protein, wherein the AAV9 capsid protein comprises one or more amino acid substitutions at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2.

346. The rAAV particle of claim 345, wherein the one or more amino acid substitutions increases transduction efficiency of the rAAV particle for a cell in the eye or the central nervous system, as compared to an AAV particle comprising a wild-type AAV9 capsid protein, by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.

347. The rAAV particle of claim 345 or 346, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV9.

348. The rAAV particle of claim 347, wherein the numbering is based on the VP1 of AAV9 comprising the amino acid sequence of SEQ ID NO:15.

349. The rAAV particle of claim 347 or 348, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or A589, numbering based on VP1 numbering of AAV9.

350. The rAAV particle of any one of claims 347-349, wherein the one or more amino acid substitutions comprise an S586R substitution, numbering based on VP1 of AAV9.

351. The rAAV particle of any one of claims 347-350, wherein the one or more amino acid substitutions comprise an A589R substitution, numbering based on VP1 of AAV9.

352. A rAAV particle comprising an AAVrh10 capsid protein, wherein the AAVrh10 capsid protein comprises one or more amino acid substitutions at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2.

~~353. The rAAV particle of claim 352, wherein the one or more amino acid substitutions increases transduction efficiency of the rAAV particle for a cell in the eye or the central nervous system, as compared to an AAV particle comprising a wild-type AAVrh10 capsid protein, by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.~~

~~354. The rAAV particle of claim 352 or 353, wherein the one or more amino acid substitutions are at positions 588 and/or 591, numbering based on VP1 numbering of AAVrh10.~~

~~355. The rAAV particle of claim 354, wherein the numbering is based on the VP1 of AAVrh10 comprising the amino acid sequence of SEQ ID NO:16.~~

~~356. The rAAV particle of claim 354 or 355, wherein the one or more amino acid substitutions comprise a substitution at position Q588 and/or A591, numbering based on VP1 numbering of AAVrh10.~~

~~357. The rAAV particle of any one of claims 354-356, wherein the one or more amino acid substitutions comprise a Q588R substitution, numbering based on VP1 of AAVrh10.~~

~~358. The rAAV particle of any one of claims 354-357, wherein the one or more amino acid substitutions comprise an A591R substitution, numbering based on VP1 of AAVrh10.~~

~~359. The method of any one of claims 1-46 and 126-249, wherein the rAAV particle comprises an AAV1, AAV6, or AAV9 capsid and wherein the one or more amino acid substitutions is at position 485, 488, 533, 586 and/or 589, numbering based on VP1 numbering of AAV1, AAV6, or AAV9; and/or wherein the rAAV particle comprises an AAV8 or AAVrh10 capsid and wherein the one or more amino acid substitutions is at position 487, 490, 535, 588 and/or 591, numbering based on VP1 numbering of AAV8 or AAVrh10.~~

~~360. The system of any one of claims 47-86, wherein the rAAV particle comprises an AAV1, AAV6, or AAV9 capsid and wherein the one or more amino acid substitutions is at position 485, 488, 533, 586 and/or 589, numbering based on VP1 numbering of AAV1, AAV6, or AAV9; and/or wherein the rAAV particle comprises an AAV8 or AAVrh10 capsid and wherein the one or more amino acid substitutions is at position 487, 490, 535, 588 and/or 591, numbering based on VP1 numbering of AAV8 or AAVrh10.~~

~~361. The kit of any one of claims 87-125 and 250-261, wherein the rAAV particle comprises an AAV1, AAV6, or AAV9 capsid and wherein the one or more amino acid substitutions is at position 485, 488, 533, 586 and/or 589, numbering based on VP1 numbering of AAV1, AAV6, or AAV9; and/or wherein the rAAV particle comprises an AAV8 or AAVrh10 capsid and wherein the one or more amino acid substitutions is at position 487, 490, 535, 588 and/or 591, numbering based on VP1 numbering of AAV8 or AAVrh10.~~

~~362. The rAAV particle of any one of claims 262-316, wherein the rAAV particle comprises an AAV1, AAV6, or AAV9 capsid and wherein the one or more amino acid substitutions is at position 485, 488, 533, 586 and/or 589, numbering based on VP1 numbering of AAV1, AAV6, or AAV9; and/or wherein the rAAV particle comprises an AAV8 or AAVrh10 capsid and wherein the one or more amino acid substitutions is at position 487, 490, 535, 588 and/or 591, numbering based on VP1 numbering of AAV8 or AAVrh10.~~

~~363. A rAAV particle comprising an AAV1, AAV6, or AAV9 capsid protein, wherein the capsid protein comprises one or more amino acid substitutions at position 485, 488, or 533, numbering based on VP1 numbering of AAV1, AAV6, or AAV9.~~

~~364. A rAAV particle comprising an AAV8 or AAVrh10 capsid protein, wherein the capsid protein comprises one or more amino acid substitutions at position 487, 490, or 535, numbering based on VP1 numbering of AAV8 or AAVrh10.~~

~~365. A method for delivering a heterologous nucleic acid to the retina of an individual comprising intravitreally administering a recombinant adeno-associated virus (rAAV) particle to the individual, wherein the rAAV particle comprises~~

~~a) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and~~

~~b) a rAAV vector comprising the heterologous nucleic acid and at least one AAV inverted terminal repeat.~~

~~366. A method for improving rAAV transduction of cells following intravitreal delivery of a rAAV particle to the eye of an individual compared to transduction of cells with a rAAV comprising a wild-type capsid, the method comprising incorporating one or more amino acid substitutions in an AAV capsid protein at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2; wherein the rAAV particle comprises the rAAV capsid protein and a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat.~~

~~367. A method for improving expression of a heterologous nucleic acid following intravitreal delivery of rAAV particles to the eye of an individual, the method comprising incorporating one or more amino acid substitutions in an AAV capsid protein at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2; wherein the rAAV particle comprises the rAAV capsid protein and a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat.~~

~~368. A method to treat an ocular disorder in an individual comprising intravitreal delivery of a composition comprising rAAV particles to the retina of an individual, wherein the rAAV particles comprise~~

~~a) a rAAV capsid comprising a rAAV capsid protein comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one~~

or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

b) a rAAV vector comprising a heterologous nucleic acid and at least one AAV terminal repeat.

369. The method of any one of claims 365-368, wherein the one or more amino acid substitutions alter charge on the rAAV capsid protein.

370. The method of any one of claims 365-369, wherein the one or more amino acid substitutions increase transduction efficiency of the rAAV particle to a cell in the eye by at least about 10%, at least about 25%, at least about 50%, at least about 75%, or at least about 100%.

371. The method of any one of claims 365-370, wherein the one or more amino acid substitutions comprise a substitution of an amino acid residue that is not positively charged with a positively charged amino acid residue.

372. The method of claim 371, wherein the positively charged amino acid residue replaces a hydrophobic amino acid residue.

373. The method of any one of claims 365-372, wherein the one or more amino acid substitutions comprises substitution with an arginine or lysine residue.

374. The method of any one of claims 365-373, wherein the one or more amino acid substitutions comprises substitution of an alanine, serine, glutamine, or threonine residue with an arginine or lysine residue.

375. The method of any one of claims 365-374, wherein the rAAV particle comprises an AAV serotype rh8R (AAVrh8R) capsid.

376. The method of claim 375, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAVrh8R.

377. The method of claim 376, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.

378. The method of any one of claims 375-377, wherein the one or more amino acid substitutions comprise a substitution at position A586 and/or T589, numbering based on VP1 numbering of AAVrh8R.

379. The method of any one of claims 375-378, wherein the one or more amino acid substitutions comprise an A586R or A586K substitution, numbering based on VP1 of AAVrh8R.

380. The method of any one of claims 375-379, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAVrh8R.

381. The method of any one of claims 365-374, wherein the rAAV particle comprises an AAV serotype 1 (AAV1) capsid.

382. The method of claim 381, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV1.

383. The method of claim 382, wherein the numbering is based on the VP1 of AAV1 comprising the amino acid sequence of SEQ ID NO:12.

384. The method of any one of claims 381-383, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or T589, numbering based on VP1 numbering of AAV1.

~~385. The method of any one of claims 381-384, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV1.~~

~~386. The method of any one of claims 381-385, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAV1.~~

~~387. The method of any one of claims 365-374, wherein the rAAV particle comprises an AAV serotype 6 (AAV6) capsid.~~

~~388. The method of claim 387, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV6.~~

~~389. The method of claim 388, wherein the numbering is based on the VP1 of AAV6 comprising the amino acid sequence of SEQ ID NO:13.~~

~~390. The method of any one of claims 387-389, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or T589, numbering based on VP1 numbering of AAV6.~~

~~391. The method of any one of claims 387-390, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV6.~~

~~392. The method of any one of claims 387-391, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAV6.~~

~~393. The method of any one of claims 365-374, wherein the rAAV particle comprises an AAV serotype 8 (AAV8) capsid.~~

394. The method of claim 393, wherein the one or more amino acid substitutions are at positions 588 and/or 591, numbering based on VP1 numbering of AAV8.

395. The method of claim 394, wherein the numbering is based on the VP1 of AAV8 comprising the amino acid sequence of SEQ ID NO:14.

396. The method of any one of claims 393-395, wherein the one or more amino acid substitutions comprise a substitution at position Q588 and/or T591, numbering based on VP1 numbering of AAV8.

397. The method of any one of claims 393-396, wherein the one or more amino acid substitutions comprise a Q588R or Q588K substitution, numbering based on VP1 of AAV8.

398. The method of any one of claims 393-397, wherein the one or more amino acid substitutions comprise a T591R or T591K substitution, numbering based on VP1 of AAV8.

399. The method of any one of claims 365-374, wherein the rAAV particle comprises an AAV serotype 9 (AAV9) capsid.

400. The method of claim 399, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV9.

401. The method of claim 400, wherein the numbering is based on the VP1 of AAV9 comprising the amino acid sequence of SEQ ID NO:15.

402. The method of any one of claims 399-401, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or A589, numbering based on VP1 numbering of AAV9.

403. The method of any one of claims 399-402, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV9.

404. The method of any one of claims 399-403, wherein the one or more amino acid substitutions comprise an A589R or A589K substitution, numbering based on VP1 of AAV9.

405. The method of any one of claims 365-374, wherein the rAAV particle comprises an AAV serotype rh10 (AAVrh10) capsid.

406. The method of claim 405, wherein the one or more amino acid substitutions are at positions 588 and/or 591, numbering based on VP1 numbering of AAVrh10.

407. The method of claim 406, wherein the numbering is based on the VP1 of AAVrh10 comprising the amino acid sequence of SEQ ID NO:16.

408. The method of any one of claims 405-407, wherein the one or more amino acid substitutions comprise a substitution at position Q588 and/or A591, numbering based on VP1 numbering of AAVrh10.

409. The method of any one of claims 405-408, wherein the one or more amino acid substitutions comprise a Q588R or Q588K substitution, numbering based on VP1 of AAVrh10.

410. The method of any one of claims 405-409, wherein the one or more amino acid substitutions comprise an A591R or A591K substitution, numbering based on VP1 of AAVrh10.

411. The method of any one of claims 365-410, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.

412. The method of any one of claim 365-411, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of an antioxidant, a neurotrophic factor, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor.

413. The method of any one of claims 365-412, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of: Prph2, RPE65, AIPL1, GUCY2D, LCA5, CRX, CEP290, MYO 7a, Clarin, ABCA4, RDH12, IMPDH1, CRB1, LRAT, NMNAT1, TULP1, MERTK, RPGR, RP2, RPGRIP, CNGA3, CNGB3, GNAT2, GDNF, CNTF, FGF2, PEDF, EPO, BCL2, BCL-X, NFκB, Endostatin, Angiostatin, sFlt, sPDGF-R, IL10, anti-IL17, sIL17R, IL1-ra, anti-TGFβ, sTNF-R I, sTNF-R II, and IL4.

414. The method of any one of claims 365-411, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.

415. The method of claim 414, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.

416. The method of any one of claims 365-415, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in the retina.

417. The method of any one of claims 365-416, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more retina cell types.

418. The method of claim 417, wherein the retina cell is a photoreceptor cell, a retinal pigmented epithelial cell, bipolar cell, horizontal cell, amacrine cell, muller cell and/or ganglion cell.

419. The method of claim 417 or 418, wherein the retina cell is a photoreceptor cell.

420. The method of any one of claims 416-419, wherein the promoter is a rhodopsin kinase (RK) promoter, an opsin promoter, a Cytomegalovirus (CMV) promoter, a chicken β-actin (CBA) promoter.

421. The method of any one of claims 365-420, wherein the individual is a human.

422. The method of claim 421, wherein the heterologous nucleic acid is used to treat an ocular disorder selected from the group consisting of: autosomal recessive severe early-onset retinal degeneration (Leber's Congenital Amaurosis), congenital achromatopsia, Stargardt's disease, Best's disease, Doyne's disease, cone dystrophy, retinitis pigmentosa, X-linked retinoschisis, Usher's syndrome, age related macular degeneration, atrophic age related macular degeneration, neovascular AMD, diabetic maculopathy, proliferative diabetic retinopathy (PDR), cystoid macular oedema, central serous retinopathy, retinal detachment, intra-ocular inflammation, glaucoma, and posterior uveitis.

423. The method of any one of claims 365-422, wherein the rAAV vector is a self-complementary rAAV vector.

424. The method of claim 423, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

425. The method of claim 424, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

426. The method of any one of claims 365-425, wherein the rAAV particles are in a pharmaceutical composition.

427. The method of claim 426, wherein the concentration of the particles in the pharmaceutical composition is about 1 x 10^{6} DRP/ml to about 1 x 10^{14} DRP/ml.

428. The method of claim 426 or 427, wherein the pharmaceutical composition of rAAV particles is effective in treating the individual's visual function.

429. The method of claim 428, wherein visual function is assessed by microperimetry, dark-adapted perimetry, assessment of visual mobility, visual acuity, ERG, or reading assessment.

430. The method of claim 428 or 429, wherein the method results in an improvement in the individual's visual function.

431. The method of any one of claims 365-430, wherein the method results in the prevention of or a slowing of the progression of decline of the human's visual function due to progression of the ocular disorder.

432. A system for intravitreal delivery of a vector to an eye of an individual, comprising

a) a composition comprising an effective amount of rAAV particles, wherein

i) a capsid protein of the rAAV particles comprises one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, and

ii) the vector comprises a heterologous nucleic acid encoding a therapeutic polypeptide or therapeutic RNA and at least one AAV terminal repeat; and

b) a device for intravitreal delivery of the rAAV.

433. The system of claim 432, wherein the device comprises a fine-bore cannula and a syringe, wherein the fine bore cannula is 27 to 45 gauge.

434. The system of claim 433, wherein the composition of rAAV particles is contained within the syringe.

435. The system of claim 433 or 434, wherein the cannula is attached to the syringe.

436. The system of any one of claims 432-435, wherein the concentration of the particles in the composition is about 1 x 10^{6} DRP/ml to about 1 x 10^{14} DRP/ml.

437. The system of any one of claims 432-436, wherein the rAAV particle comprises an AAV1 capsid, an AAV2 capsid, an AAV3 capsid, an AAV6 capsid, an AAV8 capsid, an AAVrh8R capsid, an AAV9 capsid, or an AAVrh10 capsid.

438. The system of any one of claims 432-437, wherein the one or more amino acid substitutions alter charge on the rAAV capsid protein.

439. The system of claim 438, wherein the one or more amino acid substitutions increase transduction efficiency of the rAAV particle to a cell in the eye by at least about 10%, at least about 25%, at least about 50%, at least about 75%, or at least about 100%.

440. The system of any one of claims 432-439, wherein the one or more amino acid substitutions comprise a substitution of an amino acid residue that is not positively charged with a positively charged amino acid residue.

441. The system of claim 440, wherein the positively charged amino acid residue replaces a hydrophobic amino acid residue.

442. The system of any one of claims 432-441, wherein the one or more amino acid substitutions comprises substitution with an arginine or lysine residue.

443. The system of any one of claims 432-442, wherein the one or more amino acid substitutions comprises substitution of an alanine, serine, glutamine, or threonine residue with an arginine or lysine residue.

444. The system of any one of claims 432-443, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAVrh8R.

445. The system of claim 444, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.

446. The system of any one of claims 432-445, wherein the one or more amino acid substitutions comprise a substitution at position A586 and/or T589, numbering based on VP1 numbering of AAVrh8R.

447. The system of any one of claims 432-446, wherein the one or more amino acid substitutions comprise an A586R or A586K substitution, numbering based on VP1 of AAVrh8R.

448. The system of any one of claims 432-447, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAVrh8R.

449. The system of any one of claims 432-448, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV1.

~~450. The system of claim 449, wherein the numbering is based on the VP1 of AAV1 comprising the amino acid sequence of SEQ ID NO:12.~~

~~451. The system of claim 449 or claim 450, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or T589, numbering based on VP1 numbering of AAV1.~~

~~452. The system of any one of claims 449-451, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV1.~~

~~453. The system of any one of claims 449-452, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAV1.~~

~~454. The system of any one of claims 432-448, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV6.~~

~~455. The system of claim 454, wherein the numbering is based on the VP1 of AAV6 comprising the amino acid sequence of SEQ ID NO:13.~~

~~456. The system of claim 454 or claim 455, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or T589, numbering based on VP1 numbering of AAV6.~~

~~457. The system of any one of claims 454-456, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV6.~~

~~458. The system of any one of claims 454-457, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAV6.~~

~~459. The system of any one of claims 432-448, wherein the one or more amino acid substitutions are at positions 588 and/or 591, numbering based on VP1 numbering of AAV8.~~

~~460. The system of claim 459, wherein the numbering is based on the VP1 of AAV8 comprising the amino acid sequence of SEQ ID NO:14.~~

~~461. The system of claim 459 or 460, wherein the one or more amino acid substitutions comprise a substitution at position Q588 and/or T591, numbering based on VP1 numbering of AAV8.~~

~~462. The system of any one of claims 459-461, wherein the one or more amino acid substitutions comprise a Q588R or Q588K substitution, numbering based on VP1 of AAV8.~~

~~463. The system of any one of claims 459-462, wherein the one or more amino acid substitutions comprise a T591R or T591K substitution, numbering based on VP1 of AAV8.~~

~~464. The system of any one of claims 432-448, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV9.~~

~~465. The system of claim 464, wherein the numbering is based on the VP1 of AAV9 comprising the amino acid sequence of SEQ ID NO:15.~~

~~466. The system of claim 464 or 465, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or A589, numbering based on VP1 numbering of AAV9.~~

~~467. The system of any one of claims 464-466, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV9.~~

~~468. The system of any one of claims 464-467, wherein the one or more amino acid substitutions comprise an A589R or A589K substitution, numbering based on VP1 of AAV9.~~

~~469. The system of any one of claims 432-448, wherein the one or more amino acid substitutions are at positions 588 and/or 591, numbering based on VP1 numbering of AAVrh10.~~

~~470. The system of claim 469, wherein the numbering is based on the VP1 of AAVrh10 comprising the amino acid sequence of SEQ ID NO:16.~~

~~471. The system of claim 469 or 470, wherein the one or more amino acid substitutions comprise a substitution at position Q588 and/or A591, numbering based on VP1 numbering of AAVrh10.~~

~~472. The system of any one of claims 469-471, wherein the one or more amino acid substitutions comprise a Q588R or Q588K substitution, numbering based on VP1 of AAVrh10.~~

~~473. The system of any one of claims 469-472, wherein the one or more amino acid substitutions comprise an A591R or A591K substitution, numbering based on VP1 of AAVrh10.~~

~~474. The system of any one of claims 432-473, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.~~

~~475. The system of any one of claims 432-474, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of an antioxidant, a neurotrophic factor, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor.~~

~~476. The system of any one of claims 432-475, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of: Prph2, RPE65, AIPL1, GUCY2D, LCA5, CRX,~~

~~CEP290, MYO 7a, Clarin, ABCA4, RDH12, IMPDH1, CRB1, LRAT, NMNAT1, TULP1, MERTK, RPGR, RP2, RPGRIP, CNGA3, CNGB3, GNAT2, GDNF, CNTF, FGF2, PEDF, EPO, BCL2, BCL-X, NFκB, Endostatin, Angiostatin, sFlt, sPDGF-R, IL10, anti-IL17, sIL17R, IL1-ra, anti-TGFβ, sTNF-R I, sTNF-R II, and IL4.~~

~~477. The system of any one of claims 432-474, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.~~

~~478. The system of claim 477, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.~~

~~479. The system of any one of claims 432-478, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in the retina.~~

~~480. The system of any one of claims 432-479, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more retina cell types.~~

~~481. The system of claim 480, wherein the retina cell is a photoreceptor cell, a retinal pigmented epithelial cells, bipolar cells, horizontal cells, amacrine cells, muller cells and/or ganglion cells.~~

~~482. The system of claim 481, wherein the retina cell is a photoreceptor cell.~~

~~483. The system of any one of claims 479-482, wherein the promoter is a rhodopsin kinase (RK) promoter, an opsin promoter, a Cytomegalovirus (CMV) promoter, a chicken β-actin (CBA) promoter.~~

~~484. The system of any one of claims 432-483, wherein the individual is a human.~~

485. The system of claim 484, wherein the heterologous nucleic acid is used to treat an ocular disorder selected from the group consisting of: autosomal recessive severe early-onset retinal degeneration (Leber's Congenital Amaurosis), congenital achromatopsia, Stargardt's disease, Best's disease, Doyne's disease, cone dystrophy, retinitis pigmentosa, X-linked retinoschisis, Usher's syndrome, age related macular degeneration, atrophic age related macular degeneration, neovascular AMD, diabetic maculopathy, proliferative diabetic retinopathy (PDR), cystoid macular oedema, central serous retinopathy, retinal detachment, intra-ocular inflammation, glaucoma, and posterior uveitis.

486. The system of any one of claims 432-485, wherein the rAAV vector is a self-complementary rAAV vector.

487. The system of claim 486, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

488. The system of claim 487, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

489. A kit for use in the method of any one of claims 365-431.

490. A kit for treating an ocular disorder comprising

a) a composition comprising rAAV particles, wherein the rAAV particle comprises

i) a rAAV capsid comprising rAAV capsid proteins comprising one or more amino acid substitutions at one or more positions that interacts with a heparan sulfate proteoglycan or at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2, and

ii) a rAAV vector comprising the heterologous nucleic acid for treating an ocular disorder and at least one AAV inverted terminal repeat; and

b) a pharmaceutical excipient suitable for intravitreal administration, optionally wherein the rAAV particle comprises an AAVrh8R, AAV1, AAV6, AAV8, AAV9, or AAVrh10 capsid.

491. The kit of claim 489 or 490, wherein the one or more amino acid substitutions alter charge on the rAAV capsid protein.

492. The kit of claim 491, wherein the one or more amino acid substitutions increase transduction efficiency of the rAAV particle to a cell in the eye by at least about 10%, at least about 25%, at least about 50%, at least about 75%, or at least about 100%.

493. The kit of any one of claims 489-492, wherein the one or more amino acid substitutions comprise a substitution of an amino acid residue that is not positively charged with a positively charged amino acid residue.

494. The kit of claim 493, wherein the positively charged amino acid residue replaces a hydrophobic amino acid residue.

495. The kit of any one of claims 489-494, wherein the one or more amino acid substitutions comprises substitution with an arginine or lysine residue.

496. The kit of any one of claims 489-495, wherein the one or more amino acid substitutions comprises substitution of an alanine, serine, glutamine, or threonine residue with an arginine or lysine residue.

497. The kit of any one of claims 489-496, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAVrh8R.

~~498. The kit of claim 497, wherein the numbering is based on the VP1 of AAVrh8R comprising the amino acid sequence of SEQ ID NO:9.~~

~~499. The kit of any one of claims 489-498, wherein the one or more amino acid substitutions comprise a substitution at position A586 and/or T589, numbering based on VP1 numbering of AAVrh8R.~~

~~500. The kit of any one of claims 489-499, wherein the one or more amino acid substitutions comprise an A586R or A586K substitution, numbering based on VP1 of AAVrh8R.~~

~~501. The kit of any one of claims 489-500, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAVrh8R.~~

~~502. The kit of any one of claims 489-496, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV1.~~

~~503. The kit of claim 502, wherein the numbering is based on the VP1 of AAV1 comprising the amino acid sequence of SEQ ID NO:12.~~

~~504. The kit of claim 502 or 503, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or T589, numbering based on VP1 numbering of AAV1.~~

~~505. The kit of any one of claims 502-504, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV1.~~

~~506. The kit of any one of claims 502-505, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAV1.~~

~~507. The kit of any one of claims 489-496, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV6.~~

~~508. The kit of claim 507, wherein the numbering is based on the VP1 of AAV6 comprising the amino acid sequence of SEQ ID NO:13.~~

~~509. The kit of claim 507 or 508, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or T589, numbering based on VP1 numbering of AAV6.~~

~~510. The kit of any one of claims 507-509, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV6.~~

~~511. The kit of any one of claims 507-510, wherein the one or more amino acid substitutions comprise a T589R or T589K substitution, numbering based on VP1 of AAV6.~~

~~512. The kit of any one of claims 489-496, wherein the one or more amino acid substitutions are at positions 588 and/or 591, numbering based on VP1 numbering of AAV8.~~

~~513. The kit of claim 512, wherein the numbering is based on the VP1 of AAV8 comprising the amino acid sequence of SEQ ID NO:14.~~

~~514. The kit of claim 512 or 513, wherein the one or more amino acid substitutions comprise a substitution at position Q588 and/or T591, numbering based on VP1 numbering of AAV8.~~

~~515. The kit of any one of claims 512-514, wherein the one or more amino acid substitutions comprise a Q588R or Q588K substitution, numbering based on VP1 of AAV8.~~

~~516. The kit of any one of claims 512-515, wherein the one or more amino acid substitutions comprise a T591R or T591K substitution, numbering based on VP1 of AAV8.~~

~~517. The kit of any one of claims 489-496, wherein the one or more amino acid substitutions are at positions 586 and/or 589, numbering based on VP1 numbering of AAV9.~~

~~518. The kit of claim 517, wherein the numbering is based on the VP1 of AAV9 comprising the amino acid sequence of SEQ ID NO:15.~~

~~519. The kit of claim 517 or 518, wherein the one or more amino acid substitutions comprise a substitution at position S586 and/or A589, numbering based on VP1 numbering of AAV9.~~

~~520. The kit of any one of claims 517-519, wherein the one or more amino acid substitutions comprise an S586R or S586K substitution, numbering based on VP1 of AAV9.~~

~~521. The kit of any one of claims 517-520, wherein the one or more amino acid substitutions comprise an A589R or A589K substitution, numbering based on VP1 of AAV9.~~

~~522. The kit of any one of claims 489-496, wherein the one or more amino acid substitutions are at positions 588 and/or 591, numbering based on VP1 numbering of AAVrh10.~~

~~523. The kit of claim 522, wherein the numbering is based on the VP1 of AAVrh10 comprising the amino acid sequence of SEQ ID NO:16.~~

~~524. The kit of claim 522 or 523, wherein the one or more amino acid substitutions comprise a substitution at position Q588 and/or A591, numbering based on VP1 numbering of AAVrh10.~~

~~525. The kit of any one of claims 522-524, wherein the one or more amino acid substitutions comprise a Q588R or Q588K substitution, numbering based on VP1 of AAVrh10.~~

~~526. The kit of any one of claims 522-525, wherein the one or more amino acid substitutions comprise an A591R or A591K substitution, numbering based on VP1 of AAVrh10.~~

~~527. The kit of any one of claims 489-526, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.~~

~~528. The kit of any one of claims 489-527, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of an antioxidant, a neurotrophic factor, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor.~~

~~529. The kit of any one of claims 489-528, wherein the heterologous nucleic acid encodes a polypeptide selected from the group consisting of: Prph2, RPE65, AIPL1, GUCY2D, LCA5, CRX, CEP290, MYO 7a, Clarin, , ABCA4, RDH12, IMPDH1, CRB1, LRAT, NMNAT1, TULP1, MERTK, RPGR, RP2, RPGRIP, CNGA3, CNGB3, GNAT2, GDNF, CNTF, FGF2, PEDF, EPO, BCL2, BCL-X, NFκB, Endostatin, Angiostatin, sFlt, sPDGF-R, IL10, anti-IL17, sIL17R, IL1-ra, anti-TGFβ, sTNF-R I, sTNF-R II, and IL4.~~

~~530. The kit of any one of claims 489-527, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.~~

~~531. The kit of claim 530, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.~~

~~532. The kit of any one of claims 489-531, wherein the heterologous nucleic acid is under the control of a promoter sequence that is expressed in the retina.~~

~~533. The kit of any one of claims 489-532, wherein the heterologous nucleic acid is operably linked to a promoter suitable for expression of the therapeutic polypeptide or therapeutic nucleic acid in one or more retina cell types.~~

~~534. The kit of claim 533, wherein the retina cell is a photoreceptor cell, a retinal pigmented epithelial cells, bipolar cells, horizontal cells, amacrine cells, muller cells and/or ganglion cells.~~

~~535. The kit of claim 534, wherein the retina cell is a photoreceptor cell.~~

~~536. The kit of any one of claims 532-535, wherein the promoter is a rhodopsin kinase (RK) promoter, an opsin promoter, a Cytomegalovirus (CMV) promoter, a chicken β-actin (CBA) promoter.~~

~~537. The kit of any one of claims 489-536, wherein the individual is a human.~~

~~538. The kit of claim 537, wherein the heterologous nucleic acid is used to treat an ocular disorder selected from the group consisting of: autosomal recessive severe early-onset retinal degeneration (Leber's Congenital Amaurosis), congenital achromatopsia, Stargardt's disease, Best's disease, Doyne's disease, cone dystrophy, retinitis pigmentosa, X-linked retinoschisis, Usher's syndrome, age related macular degeneration, atrophic age related macular degeneration, neovascular AMD, diabetic maculopathy, proliferative diabetic retinopathy (PDR), cystoid macular oedema, central serous retinopathy, retinal detachment, intra-ocular inflammation, glaucoma, and posterior uveitis.~~

~~539. The kit of claim 538, wherein the heterologous nucleic acid is used to treat an ocular disorder selected from the group consisting of: autosomal recessive severe early-onset retinal degeneration (Leber's Congenital Amaurosis), Stargardt's disease, retinitis pigmentosa, Usher's syndrome, and age related macular degeneration.~~

~~540. The kit of any one of claims 489-539, wherein the rAAV vector is a self-complementary rAAV vector.~~

~~541. The kit of claim 540, wherein the vector comprises first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.~~

~~542. The kit of claim 541, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.~~

~~543. The kit of any one of claims 489-542, further comprising a device for intravitreal delivery of the composition of rAAV particles.~~

~~544. The kit of any one of claims 489-543, further comprising instructions for intravitreal delivery of the composition of rAAV particles.~~

~~545. The method of any one of claims 422-431 or the kit of any one of claims 538-544, wherein the individual is a human.~~

~~546. A rAAV particle comprising an AAV3 capsid protein, wherein the AAV3 capsid protein comprises one or more amino acid substitutions at one or more positions corresponding to amino acids 484, 487, 527, 532, 585 or 588, numbering based on VP1 numbering of AAV2.~~

~~547. The rAAV particle of claim 546, wherein the one or more amino acid substitutions increases transduction efficiency of the rAAV particle for a cell in the eye or the central nervous system, as~~

~~compared to an AAV particle comprising a wild-type AAVrh8R capsid protein, by about at least 10%, about at least 25%, about at least 50%, about at least 75%, or about at least 100%.~~