

WHAT IS CLAIMED IS:

1. A recombinant nucleic acid, comprising:
 - a mitochondrial targeting sequence;
 - a mitochondrial protein coding sequence comprising a sequence that is at least 99% identical to SEQ ID NO: 11 or 12; and
 - a 3'UTR nucleic acid sequence.
2. The recombinant nucleic acid of claim 1, wherein said mitochondrial targeting sequence encodes a polypeptide comprising a peptide sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 129-159.
3. The recombinant nucleic acid of claim 1, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 2.
4. The recombinant nucleic acid of claim 1, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 3.
5. The recombinant nucleic acid of claim 1, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 4.
6. The recombinant nucleic acid of claim 1, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 5.
7. The recombinant nucleic acid of claim 1, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 1.
8. The recombinant nucleic acid of claim 1, wherein said mitochondrial protein coding sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 12.
9. The recombinant nucleic acid of any one of claims 1-8, wherein said 3'UTR nucleic acid sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 111-125.
10. The recombinant nucleic acid of any one of claims 1-8, wherein said 3'UTR nucleic acid sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at

least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 13 or SEQ ID NO: 14.

11. The recombinant nucleic acid of claim 1, wherein said recombinant nucleic acid comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 25-28, 39-42, 53-56, 67-70, and 81-84.

12. A recombinant nucleic acid, comprising:

a mitochondrial targeting sequence;

a mitochondrial protein coding sequence comprising a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 11 or 12; and

a 3'UTR nucleic acid sequence.

13. The recombinant nucleic acid of claim 12, wherein said mitochondrial targeting sequence comprises a sequence encodes a polypeptide selected from the group consisting of hsCOX10, hsCOX8, scRPM2, lcSirt5, tbNDUS7, ncQCR2, hsATP5G2, hsLACTB, spilv1, gmCOX2, crATP6, hsOPA1, hsSDHD, hsADCK3, osP0644B06.24-2, Neurospora crassa ATP9 (ncATP9), hsGHITM, hsNDUFAB1, hsATP5G3, crATP6_hsADCK3, ncATP9_ncATP9, zmLOC100282174, ncATP9_zmLOC100282174_spilv1_ncATP9, zmLOC100282174_hsADCK3_crATP6_hsATP5G3, zmLOC100282174_hsADCK3_hsATP5G3, ncATP9_zmLOC100282174, hsADCK3_zmLOC100282174_crATP6_hsATP5G3, crATP6_hsADCK3_zmLOC100282174_hsATP5G3, hsADCK3_zmLOC100282174, hsADCK3_zmLOC100282174_crATP6, ncATP9_zmLOC100282174_spilv1_GNFP_ncATP9, and ncATP9_zmLOC100282174_spilv1_lcSirt5_osP0644B06.24-2_hsATP5G2_ncATP9.

14. The recombinant nucleic acid of claim 12 or 13, wherein said mitochondrial targeting sequence encodes a polypeptide comprising a peptide sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 129-159.

15. The recombinant nucleic acid of any one of claims 12-14, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 2 or 3.

16. The recombinant nucleic acid of any one of claims 12-14, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 4.

17. The recombinant nucleic acid of any one of claims 12-14, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 5.
18. The recombinant nucleic acid of any one of claims 12-14, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 1.
19. The recombinant nucleic acid of any one of claims 12-18, wherein said 3'UTR nucleic acid sequence is located at 3' of said mitochondrial targeting sequence.
20. The recombinant nucleic acid of any one of claims 12-19, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hslRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L.
21. The recombinant nucleic acid of any one of claims 12-20, wherein said 3'UTR nucleic acid sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 111-125.
22. The recombinant nucleic acid of any one of claims 12-21, wherein said 3'UTR nucleic acid sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 13 or SEQ ID NO: 14.
23. The recombinant nucleic acid of any one of claims 12-22, wherein said mitochondrial targeting sequence is located at 5' of said 3'UTR nucleic acid sequence.
24. The recombinant nucleic acid of any one of claims 12-22, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.
25. The recombinant nucleic acid of any one of claims 12-24, wherein said recombinant nucleic acid comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 25-28, 39-42, 53-56, 67-70, and 81-84.
26. The recombinant nucleic acid of any one of claims 12-25, wherein said mitochondrial protein coding sequence encodes a mitochondrial protein comprising or consisting of a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 162.
27. A recombinant nucleic acid, comprising a mitochondrial protein coding sequence, wherein said mitochondrial protein coding sequence encodes a polypeptide comprising

a mitochondrial protein, wherein said mitochondrial protein coding sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 11 or 12.

28. The recombinant nucleic acid of claim 27, further comprising a mitochondrial targeting sequence.

29. The recombinant nucleic acid of claim 27 or 28, wherein said mitochondrial targeting sequence comprises a sequence encodes a polypeptide selected from the group consisting of hsCOX10, hsCOX8, scRPM2, lcSirt5, tbNDUS7, ncQCR2, hsATP5G2, hsLACTB, spilv1, gmCOX2, crATP6, hsOPA1, hsSDHD, hsADCK3, osP0644B06.24-2, Neurospora crassa ATP9 (ncATP9), hsGHITM, hsNDUFAB1, hsATP5G3, crATP6_hsADCK3, ncATP9_ncATP9, zmLOC100282174, ncATP9_zmLOC100282174_spilv1_ncATP9, zmLOC100282174_hsADCK3_crATP6_hsATP5G3, zmLOC100282174_hsADCK3_hsATP5G3, ncATP9_zmLOC100282174, hsADCK3_zmLOC100282174_crATP6_hsATP5G3, crATP6_hsADCK3_zmLOC100282174_hsATP5G3, hsADCK3_zmLOC100282174, hsADCK3_zmLOC100282174_crATP6, ncATP9_zmLOC100282174_spilv1_GNFP_ncATP9, and ncATP9_zmLOC100282174_spilv1_lcSirt5_osP0644B06.24-2_hsATP5G2_ncATP9.

30. The recombinant nucleic acid of any one of claims 27-29, wherein said mitochondrial targeting sequence encodes a polypeptide comprising a peptide sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 129-159.

31. The recombinant nucleic acid of any one of claims 27-30, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 2.

32. The recombinant nucleic acid of any one of claims 27-31, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 3.

33. The recombinant nucleic acid of any one of claims 27-32, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 4.

34. The recombinant nucleic acid of any one of claims 27-33, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 5.

35. The recombinant nucleic acid of any one of claims 27-34, wherein said mitochondrial targeting sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 1.
36. The recombinant nucleic acid of any one of claims 27-35, further comprising a 3'UTR nucleic acid sequence.
37. The recombinant nucleic acid of claim 36, wherein said 3'UTR nucleic acid sequence is located at 3' of said mitochondrial targeting sequence.
38. The recombinant nucleic acid of claim 36 or 37, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRRS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hslRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L.
39. The recombinant nucleic acid of any one of claims 36-38, wherein said 3'UTR nucleic acid sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 111-125.
40. The recombinant nucleic acid of any one of claims 36-39, wherein said 3'UTR nucleic acid sequence comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence as set forth in SEQ ID NO: 13 or SEQ ID NO: 14.
41. The recombinant nucleic acid of any one of claims 36-40, wherein said mitochondrial targeting sequence is located at 5' of said 3'UTR nucleic acid sequence.
42. The recombinant nucleic acid of any one of claims 36-41, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.
43. The recombinant nucleic acid of any one of claims 36-42, wherein said recombinant nucleic acid comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 25-28, 39-42, 53-56, 67-70, and 81-84.
44. A viral vector comprising said recombinant nucleic acid of any one of claims 1-43.
45. The viral vector of claim 44, wherein said viral vector is an adeno-associated virus (AAV) vector.
46. The viral vector of claim 45, wherein said AAV vector is selected from the group consisting of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, and AAV16 vectors.
47. The viral vector of claim 45 or 46, wherein said AAV vector is a recombinant AAV (rAAV) vector.

48. The viral vector of claim 47, wherein said rAAV vector is rAAV2 vector.
49. A pharmaceutical composition, comprising an adeno-associated virus (AAV) comprising said recombinant nucleic acid of any one of claims 1-43.
50. The pharmaceutical composition of claim 49, further comprising a pharmaceutically acceptable excipient thereof.
51. A pharmaceutical composition, comprising said viral vector of any one of claims 44-48, and a pharmaceutically acceptable excipient thereof.
52. The pharmaceutical composition of claim 50 or 51, wherein said pharmaceutically acceptable excipient comprises phosphate-buffered saline (PBS), α,α -trehalose dehydrate, L-histidine monohydrochloride monohydrate, polysorbate 20, NaCl, NaH_2PO_4 , Na_2HPO_4 , KH_2PO_4 , K_2HPO_4 , poloxamer 188, or any combination thereof.
53. The pharmaceutical composition of claim 50 or 51, wherein said pharmaceutically acceptable excipient is selected from phosphate-buffered saline (PBS), α,α -trehalose dehydrate, L-histidine monohydrochloride monohydrate, polysorbate 20, NaCl, NaH_2PO_4 , Na_2HPO_4 , KH_2PO_4 , K_2HPO_4 , poloxamer 188, and any combination thereof.
54. The pharmaceutical composition of claim 50 or 51, wherein said pharmaceutically acceptable excipient comprises poloxamer 188.
55. The pharmaceutical composition of claim 54, wherein said pharmaceutically acceptable excipient comprises 0.0001%-0.01% poloxamer 188.
56. The pharmaceutical composition of claim 55, wherein said pharmaceutically acceptable excipient comprises 0.001% poloxamer 188.
57. The pharmaceutical composition of any one of claims 50-56, wherein said pharmaceutically acceptable excipient further comprises one or more salts.
58. The pharmaceutical composition of claim 57, wherein said one or more salts comprises NaCl, NaH_2PO_4 , Na_2HPO_4 , and KH_2PO_4 .
59. The pharmaceutical composition of claim 57, wherein said one or more salts comprises 80 mM NaCl, 5 mM NaH_2PO_4 , 40 mM Na_2HPO_4 , and 5 mM KH_2PO_4 .
60. The pharmaceutical composition of any one of claims 49-59, wherein said pharmaceutical composition has a pH of 6-8.
61. The pharmaceutical composition of claim 60, wherein said pharmaceutical composition has a pH of 7.2-7.4.
62. The pharmaceutical composition of claim 61, wherein said pharmaceutical composition has a pH of 7.3.
63. The pharmaceutical composition of any one of claims 49-62, wherein said pharmaceutical composition has a viral titer of at least 1.0×10^{10} vg/mL.

64. The pharmaceutical composition of claim 63, wherein said pharmaceutical composition has a viral titer of at least 5.0×10^{10} vg/mL.
65. The pharmaceutical composition of any one of claims 49-64, when said pharmaceutical composition is subject to five freeze/thaw cycles, said pharmaceutical composition retains at least 60%, 70%, 80%, or 90% of a viral titer as compared to the viral titer prior to the five freeze/thaw cycles.
66. The pharmaceutical composition of any one of claims 49-65, wherein said pharmaceutical composition, when administered to a patient with Leber's hereditary optic neuropathy, generates a higher average recovery of vision than a comparable pharmaceutical composition without said recombinant nucleic acid.
67. The pharmaceutical composition of any one of claims 49-66, wherein said pharmaceutical composition, when administered to a patient with Leber's hereditary optic neuropathy, generates a higher average recovery of vision than a comparable pharmaceutical composition comprising a recombinant nucleic acid as set forth in SEQ ID NO: 15.
68. A method of treating an eye disorder, comprising administering said pharmaceutical composition of any one of claims 49-67 to a patient in need thereof.
69. The method of claim 68, wherein said eye disorder is Leber's hereditary optic neuropathy (LHON).
70. The method of claim 68 or 69, comprising administering said pharmaceutical composition to one or both eyes of said patient.
71. The method of any one of claims 68-70, wherein said pharmaceutical composition is administered via intraocular or intravitreal injection.
72. The method of claim 71, wherein said pharmaceutical composition is administered via intravitreal injection.
73. The method of claim 72, wherein about 0.01-0.1 mL of said pharmaceutical composition is administered via intravitreal injection.
74. The method of claim 73, wherein about 0.05 mL of said pharmaceutical composition is administered via intravitreal injection.
75. The method of any one of claims 68-74, further comprising administering methylprednisolone to said patient.
76. The method of claim 75, wherein said methylprednisolone is administered prior to said intravitreal injection of said pharmaceutical composition.
77. The method of claim 75 or 76, wherein said methylprednisolone is administered orally.

78. The method of any one of claims 75-77, wherein said methylprednisolone is administered daily for at least 1, 2, 3, 4, 5, 6, or 7 days prior to said intravitreal injection of said pharmaceutical composition.
79. The method of any one of claims 75-78, wherein said methylprednisolone is administered daily.
80. The method of any one of claims 75-79, wherein a daily dosage of about 32 mg/60 kg methylprednisolone is administered.
81. The method of any one of claims 75-80, wherein said methylprednisolone is administered after said intravitreal injection of said pharmaceutical composition.
82. The method of any one of claims 75-81, further comprising administering creatine phosphate sodium to said patient.
83. The method of claim 82, wherein said creatine phosphate sodium is administered intravenously.
84. The method of any one of claims 75-83, wherein said methylprednisolone is administered intravenously or orally.
85. The method of any one of claims 75-84, comprising administering methylprednisolone intravenously for at least one day, which is followed by administering methylprednisolone orally for at least a week.
86. The method of claim 85, comprising administering methylprednisolone intravenously for about 3 days, which is followed by administering methylprednisolone orally for at least about 6 weeks.
87. The method of any one of claims 75-86, wherein said methylprednisolone is administered intravenously at a daily dose of about 80 mg/60 kg.
88. The method of any one of claims 75-87, wherein said administering said pharmaceutical composition generates a higher average recovery of vision than a comparable pharmaceutical composition without said recombinant nucleic acid.
89. The method of any one of claims 75-88, wherein said administering said pharmaceutical composition generates a higher average recovery of vision than a comparable pharmaceutical composition comprising a recombinant nucleic acid as set forth in SEQ ID NO: 25.