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(54) Title: COMPOSITIONS AND METHODS FOR TREATING LEBER'S HEREDITARY OPTIC NEUROPATHY

(57) Abstract: Provided is a recombinant nucleic acid, comprising: a mitochondrial targeting sequence; a mitochondrial protein coding sequence, wherein said mitochondrial protein coding sequence encodes a polypeptide comprising a mitochondrial protein; and a 3'UTR nucleic acid sequence. Also provided are a pharmaceutical composition comprising the recombinant nucleic acid and a method of treating Leber's hereditary optic neuropathy (LHON) using the pharmaceutical composition.

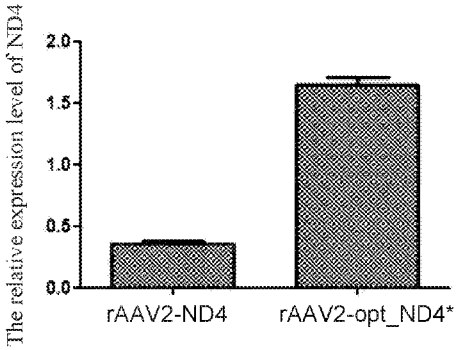


FIG. 8

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COMPOSITIONS AND METHODS FOR TREATING LEBER'S HEREDITARY OPTIC NEUROPATHY

Cross-Reference to Related Applications

[0001] This application claims the benefit of PCT Application No. PCT/CN2018/103937, filed on September 4, 2018; PCT Application No. PCT/CN2018/113799, filed on November 2, 2018; Chinese Application No. CN201811230856.2, filed on October 22, 2018; PCT Application No. PCT/CN2018/118662, filed on November 30, 2018; Chinese Application No. CN201811221305.X, filed on October 19, 2018; PCT Application No. PCT/CN2019/070461, filed on January 4, 2019; Chinese Application No. CN201810948193.1, filed on August 20, 2018; each of which are incorporated herein by reference in their entirety.

Reference to Sequence Listing

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 16, 2019, is named WNBT-005_02WO_ST25.txt and is 298 kb in size.

Background

[0003] Leber's hereditary optic neuropathy (LHON) is a mitochondrially inherited (transmitted from mother to offspring) degeneration of retinal ganglion cells (RGCs) and their axons that leads to an acute or subacute loss of central vision; this affects predominantly young adult males. LHON is only transmitted through the mother, as it is primarily due to mutations in the mitochondrial (not nuclear) genome, and only the egg contributes mitochondria to the embryo. LHON is usually due to one of three pathogenic mitochondrial DNA (mtDNA) point mutations. These mutations are at nucleotide positions 11778 G to A (G11778A), 3460 G to A (G3460A) and 14484 T to C (T14484C), respectively in the NADH dehydrogenase subunit-4 protein (ND4), NADH dehydrogenase subunit-1 protein (ND1) and NADH dehydrogenase subunit-6 protein (ND6) subunit genes of complex I of the oxidative phosphorylation chain in mitochondria. Each mutation is believed to have significant risk of permanent loss of vision. It typically progresses within several weeks to several months without pain, until the binocular vision deteriorate to below 0.1, which seriously affects the quality of life of the patient. Two LHON mutants, G3460A and T14484C, results in the reduction of the patient's platelets isolated mitochondrial NADH dehydrogenase activity by 80%. Ninety percent of the Chinese LHON patients carry the G11778A mutation. The G11778A mutation changes an arginine into histidine in

the ND4 protein, resulting the dysfunction and optic nerve damage in LHON patients. There is a need for developing compositions and methods for treating LHON with higher transfection efficiency and treatment efficacy.

SUMMARY

[0004] Disclosed here recombinant nucleic acids, pharmaceutical compositions, and methods for treating LHON. In one aspect, disclosed herein is a recombinant nucleic acid, comprising: a mitochondrial targeting sequence; a mitochondrial protein coding sequence comprising a sequence that is at least 99% identical to a sequence selected from the group consisting of SEQ ID NO: 7, 8, 10, and 12; and a 3'UTR nucleic acid sequence.

[0005] In some cases, the 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. In some cases, the 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. In some cases, the 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. In some cases, the 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. In some cases, the 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.

[0006] In some cases, the 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: 7 or 8. In some cases, the 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: 10. In some cases, the 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.

[0007] In some cases, the 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. In some cases, the 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.

[0008] In some cases, the 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: 17-20, 23-24, 27-28, 31-34, 37-38, 41-42, 45-48, 51-52, 55-56, 59-62, 65-66, 69-70, 73-76, 79-80, and 83-84.

[0009] In another aspect, disclosed herein is a recombinant nucleic acid, comprising: a mitochondrial targeting sequence comprising a sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID NO: 2, 3, 4, and 5; a mitochondrial protein coding sequence, wherein the mitochondrial protein coding sequence encodes a polypeptide comprising a mitochondrial protein; and a 3'UTR nucleic acid sequence.

[0010] In some cases, the 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. In some cases, the 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. In some cases, the 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. In some cases, the 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.

[0011] In some cases, the mitochondrial protein is selected from a group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and a variant thereof. In some cases, the mitochondrial protein comprises NADH dehydrogenase 4 (ND4), or a variant thereof. In some cases, the mitochondrial protein comprises a peptide 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: 160. In some cases, the 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: 6, 7, or 8. In some cases, the mitochondrial protein comprises NADH dehydrogenase 6 (ND6), or a variant thereof. In some cases, the mitochondrial protein 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: 161. In some cases, the 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: 9 or 10. In some cases, the mitochondrial protein comprises NADH dehydrogenase 1 (ND1), or a variant thereof. In some cases, the mitochondrial protein 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: 162. In some cases, the 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: 11 or 12.

[0012] In some cases, the 3'UTR nucleic acid sequence is located at 3' of the mitochondrial targeting sequence. In some cases, the 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L. In some cases, the 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. In some cases, the 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.

[0013] In some cases, the mitochondrial targeting sequence is located at 5' of the 3'UTR nucleic acid sequence. In some cases, the mitochondrial targeting sequence is located at 3' of the mitochondrial targeting sequence.

[0014] In some cases, the 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: 29-84.

[0015] In another aspect, disclosed herein is 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 a sequence selected from the group consisting of SEQ ID NO: 7, 8, 10, and 12; and a 3'UTR nucleic acid sequence.

[0016] In some cases, the 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. In some cases, the 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. In some cases, the 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. In some cases, the 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. In some cases, the 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.

[0017] In some cases, the 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: 7 or 8. In some cases, the 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: 10. In some cases, the 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.

[0018] In some cases, the 3'UTR nucleic acid sequence is located at 3` of the mitochondrial targeting sequence. In some cases, the 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, mSOD2, and hsOXA1L. In some cases, the 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. In some cases, the 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.

[0019] In some cases, the mitochondrial targeting sequence is located at 5' of the 3'UTR nucleic acid sequence. In some cases, the mitochondrial targeting sequence is located at 3' of the mitochondrial targeting sequence.

[0020] In some cases, the 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: 17-20, 23-24, 27-28, 31-34, 37-38, 41-42, 45-48, 51-52, 55-56, 59-62, 65-66, 69-70, 73-76, 79-80, and 83-84.

[0021] In another aspect, disclosed herein is a recombinant nucleic acid, comprising a mitochondrial targeting 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: 2, 3, and 4. In some cases, the 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. In some cases, the 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. In some cases, the 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.

[0022] In some cases, the recombinant nucleic acid further comprises a mitochondrial protein coding sequence, wherein the mitochondrial protein coding sequence encodes a polypeptide comprising a mitochondrial protein. In some cases, the mitochondrial protein is selected from a group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and a variant thereof. In some cases, the mitochondrial protein comprises NADH dehydrogenase 4 (ND4), or a variant thereof. In some cases, the mitochondrial protein comprises a peptide 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: 160. In some cases, the 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: 6, 7, or 8. In some cases, the mitochondrial protein comprises NADH dehydrogenase 6 (ND6), or a variant thereof. In some cases, the mitochondrial protein 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: 161. In some cases, the 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: 9 or 10. In some cases, the mitochondrial protein

comprises NADH dehydrogenase 1 (ND1), or a variant thereof. In some cases, the mitochondrial protein 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: 162. In some cases, the 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: 11 or 12.

[0023] In some cases, the recombinant nucleic acid further comprises a 3'UTR nucleic acid sequence. In some cases, the 3'UTR nucleic acid sequence is located at 3' of the mitochondrial targeting sequence. In some cases, the 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L. In some cases, the 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. In some cases, the 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. In some cases, the mitochondrial targeting sequence is located at 5' of the 3'UTR nucleic acid sequence. In some cases, the mitochondrial targeting sequence is located at 3' of the mitochondrial targeting sequence.

[0024] In some cases, the 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: 29-70.

[0025] In another aspect, disclosed herein is a recombinant nucleic acid, comprising a mitochondrial protein coding sequence, wherein the mitochondrial protein coding sequence encodes a polypeptide comprising a mitochondrial protein, wherein the 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 selected from the group consisting of SEQ ID NO: 7, 8, 10, and 12.

[0026] In some cases, the recombinant nucleic acid further comprises a mitochondrial targeting sequence. In some cases, the 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. In some cases, the 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. In some cases, the 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. In some cases, the 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. In some cases, the 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. In some cases, the 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.

[0027] In some cases, the 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: 7 or 8. In some cases, the 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: 10. In some cases, the 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.

[0028] In some cases, the recombinant nucleic acid further comprises a3'UTR nucleic acid sequence. In some cases, the 3'UTR nucleic acid sequence is located at 3' of the mitochondrial targeting sequence. In some cases, the 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L. In some cases, the 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. In some cases, the 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. In some cases, the mitochondrial targeting sequence is located at 5' of the 3'UTR nucleic acid sequence. In some cases, the mitochondrial targeting sequence is located at 3' of the mitochondrial targeting sequence.

[0029] In some cases, the 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: 17-20, 23-24, 27-28, 31-34, 37-38, 41-42, 45-48, 51-52, 55-56, 59-62, 65-66, 69-70, 73-76, 79-80, and 83-84.

[0030] In another aspect, disclosed herein is a viral vector comprising the recombinant nucleic acid disclosed herein. In some cases, the viral vector is an adeno-associated virus (AAV) vector. In some cases, the 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. In some cases, the AAV vector is a recombinant AAV (rAAV) vector. In some cases, the rAAV vector is rAAV2 vector.

[0031] In another aspect, disclosed herein is a pharmaceutical composition, comprising an adeno-associated virus (AAV) comprising any recombinant nucleic acid disclosed herein. In some cases, the pharmaceutical composition further comprises a pharmaceutically acceptable excipient thereof. Also disclosed is a pharmaceutical composition, comprising the viral vector disclosed herein, and a pharmaceutically acceptable excipient thereof, wherein the viral vector comprises any recombinant nucleic acid disclosed herein. Also disclosed is a pharmaceutical composition, comprising: an adeno-associated virus (AAV) comprising any recombinant nucleic acid disclosed herein, wherein the 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 as set forth in SEQ ID NO: 15; and a pharmaceutically acceptable excipient.

[0032] In some cases, the 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. In some cases, the 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. In some

cases, the pharmaceutically acceptable excipient comprises poloxamer 188. In some cases, the pharmaceutically acceptable excipient comprises 0.0001%-0.01% poloxamer 188. In some cases, the pharmaceutically acceptable excipient comprises 0.001% poloxamer 188. In some cases, the pharmaceutically acceptable excipient further comprises one or more salts. In some cases, the one or more salts comprises NaCl, NaH_2PO_4, Na_2HPO_4, and KH_2PO_4. In some cases, the one or more salts comprises 80 mM NaCl, 5 mM NaH_2PO_4, 40 mM Na_2HPO_4, and 5 mM KH_2PO_4. In some cases, the one or more salts comprises NaCl, Na_2HPO_4, and KH_2PO_4. In some cases, the one or more salts comprises 154 mM NaCl, 5.6 mM Na_2HPO_4, and 8.4 mM KH_2PO_4. In some cases, the pharmaceutical composition has a pH of 6-8. In some cases, the pharmaceutical composition has a pH of 7.2-7.4. In some cases, the pharmaceutical composition has a pH of 7.3. In some cases, the pharmaceutical composition has a viral titer of at least 1.0×10^{10} vg/mL. In some cases, the pharmaceutical composition has a viral titer of at least 5.0×10^{10} vg/mL.

[0033] In some cases, the pharmaceutical composition is subject to five freeze/thaw cycles, the 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. In some cases, the 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 the recombinant nucleic acid. In some cases, the 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.

[0034] In another aspect, disclosed herein is a method of treating an eye disorder, comprising administering any pharmaceutical composition disclosed herein to a patient in need thereof. In some cases, the eye disorder is Leber's hereditary optic neuropathy (LHON). In some cases, the method comprises administering the pharmaceutical composition to one or both eyes of the patient. In some cases, the pharmaceutical composition is administered via intraocular or intravitreal injection. In some cases, the pharmaceutical composition is administered via intravitreal injection. In some cases, about 0.01-0.1 mL of the pharmaceutical composition is administered via intravitreal injection. In some cases, about 0.05 mL of the pharmaceutical composition is administered via intravitreal injection.

[0035] In some cases, the method further comprises administering methylprednisolone to the patient. In some cases, the methylprednisolone is administered prior to the intravitreal injection of the pharmaceutical composition. In some cases, the methylprednisolone is administered orally In some

cases, the methylprednisolone is administered daily for at least 1, 2, 3, 4, 5, 6, or 7 days prior to the intravitreal injection of the pharmaceutical composition. In some cases, the methylprednisolone is administered daily. In some cases, the a daily dosage of about 32 mg/60 kg methylprednisolone is administered. In some cases, the methylprednisolone is administered after the intravitreal injection of the pharmaceutical composition. In some cases, the method further comprises administering sodium creatine phosphate to the patient. In some cases, the sodium creatine phosphate is administered intravenously. In some cases, the methylprednisolone is administered intravenously or orally. In some cases, the method comprises administering methylprednisolone intravenously for at least one day, which is followed by administering methylprednisolone orally for at least a week. In some cases, the method comprises administering methylprednisolone intravenously for about 3 days, which is followed by administering methylprednisolone orally for at least about 6 weeks. In some cases, the methylprednisolone is administered intravenously at a daily dose of about 80 mg/60 kg. In some cases, the administering the pharmaceutical composition generates a higher average recovery of vision than a comparable pharmaceutical composition without the recombinant nucleic acid. In some cases, the administering the 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: 15.

[0036] In some embodiments, the present disclosure provides a method of treating an eye disorder, comprising administering to a patient in need thereof (a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising: (i) a nucleic acid sequence encoding a mitochondrial targeting peptide; (ii) a nucleic acid sequence encoding a mitochondrial protein comprising a nucleic acid 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: 6-12; and (iii) a 3'UTR nucleic acid sequence; and (b) a second pharmaceutical composition comprising a steroid.

[0037] In some embodiments, the nucleic acid sequence encoding the mitochondrial protein encodes a polypeptide comprising an amino acid 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: 160-162. In some embodiments, the nucleic acid sequence encoding a mitochondrial targeting peptide encodes a polypeptide comprising an amino acid 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:

126-159. In some embodiments, the nucleic acid sequence encoding a mitochondrial targeting peptide comprises a nucleic acid 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: 1-5. In some embodiments, the 3'UTR nucleic acid sequence comprises a nucleic 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: 13, 14, and 111-125.

[0038] In some embodiments, the present disclosure provides a method of treating an eye disorder, comprising administering to a patient in need thereof (a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising: (i) a nucleic acid sequence encoding a mitochondrial targeting peptide comprising an amino 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: 126-159; (ii) a nucleic acid sequence encoding a mitochondrial protein; and (iii) a 3'UTR nucleic acid sequence; and (b) a second pharmaceutical composition comprising a steroid.

[0039] In some embodiments, said mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof. In some embodiments, the nucleic acid sequence encoding a mitochondrial protein comprises a nucleic acid sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO: 6-12. In some embodiments, thenucleic acid sequence encoding a mitochondrial protein encodes a polypeptide comprising an amino acid 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: 160-162. In some embodiments, the nucleic acid sequence encoding a mitochondrial targeting peptide comprises a nucleic acid 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: 1-5. In some embodiments, the 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: 13, 14, and 111-125.

[0040] In some embodiments, the present disclosure provides a method of treating an eye disorder, comprising administering to a patient in need thereof (a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising: (i)

a nucleic acid sequence encoding a mitochondrial targeting peptide comprising an amino 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: 126-159; (ii) a nucleic acid sequence encoding a mitochondrial protein comprising a nucleic acid 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: 6-12; and (iii) a 3'UTR nucleic acid 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: 13, 14, and 111-125; and (b) a second pharmaceutical composition comprising a steroid.

[0041] In some embodiments, the present disclosure provides a method of treating an eye disorder, comprising administering to a patient in need thereof (a) first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising: (i) a nucleic acid sequence encoding a mitochondrial targeting peptide; and (ii) a nucleic acid sequence encoding a mitochondrial protein; and (b) a second pharmaceutical composition comprising a steroid. In some embodiments, the mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof. In some embodiments, the 3'UTR nucleic acid sequence comprises a nucleic 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: 13, 14, and 111-125.

[0042] In some embodiments, the 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: 15-84. In some embodiments, the recombinant nucleic acid comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 15.

[0043] In some embodiments, the first pharmaceutical composition is administered via intraocular or intravitreal injection. In some embodiments, about 0.01-0.1 mL of the first pharmaceutical composition is administered via intravitreal injection. In some embodiments, about 0.05 mL of the first pharmaceutical composition is administered via intravitreal injection. In some embodiments, the first pharmaceutical composition is administered to one or both eyes of the patient.

[0044] In some embodiments, the steroid selected from the group consisting of alclometasone diproprionate, amcinonide, beclomethasone diproprionate, betamethasone, betamethasone benzoate, betamethasone diproprionate, betamethasone sodium phosphate, betamethasone sodium phosphate

and acetate, betamethasone valerate, clobetasol proprionate, clocortolone pivalate, cortisol (hydrocortisone), cortisol (hydrocortisone) acetate, cortisol (hydrocortisone) butyrate, cortisol (hydrocortisone) cypionate, cortisol (hydrocortisone) sodium phosphate, cortisol (hydrocortisone) sodium succinate, cortisol (hydrocortisone) valerate, cortisone acetate, desonide, desoximetasone, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, diflorasone diacetate, fludrocortisone acetate, flunisolide, fluocinolone acetonide, fluocinonide, fluorometholone, flurandrenolide, halcinonide, medrysone, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide or a synthetic analog thereof.

[0045] In some embodiments, the steroid is a glucocorticoid. In some embodiments, the glucocorticoid is methylprednisolone or prednisone.

[0046] In some embodiments, the methylprednisolone is formulated as a tablet or as a liquid for intravenous administration. In some embodiments, the steroid is administered orally or intravenously.

[0047] In some embodiments, the steroid is administered prior to administration of the first pharmaceutical composition. In some embodiments, the steroid is administered daily for at least 1, 2, 3, 4, 5, 6, or 7 days prior to the administration of the first pharmaceutical composition. In some embodiments, the steroid is methylprednisolone and is administered at a daily dosage of about 30 mg/60 kg to about 40 mg/60 kg or about 30 mg to about 40 mg. In some embodiments, the daily dosage of methylprednisolone is about 32 mg/60 kg or 32 mg. In some embodiments, the steroid is prednisone and is administered at a daily dosage of about 50 mg/60 kg to about 70 mg/60 kg. In some embodiments, the daily dosage of prednisone is about 60 mg/60 kg.

[0048] In some embodiments, the steroid is administered after the administration of the first pharmaceutical composition. In some embodiments, the steroid is administered daily for at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, or at least 15 weeks after the administration of the first pharmaceutical composition.

[0049] In some embodiments, the steroid is methylprednisolone and is administered at a daily dosage of between about 70 mg/60 kg and 90 mg/ 60 kg or between about 70mg and 90mg. In some embodiments, the daily dosage of methylprednisolone is about 80 mg/60 kg or 80mg. In some embodiments, the methylprednisolone is administered for at least two days after the administration of the first pharmaceutical composition. In some embodiments, subsequent doses of methylprednisolone are administered daily for at least 7 weeks after the administration of the first pharmaceutical composition and wherein the dosage of the methylprednisolone is decreased on a weekly basis.

[0050] In some embodiments, the steroid is predisone and is administered at a daily dosage of between about 50 mg/60 kg and 70 mg/ 60 kg or between about 50 mg and about 70 mg. In some embodiments, the daily dosage of predisone is about 60 mg/60 kg or about 60 mg. In some embodiments, the predisone is administered for at least seven days after the administration of the first pharmaceutical composition. In some embodiments, wherein after seven days, the predisone is administered at a daily dosage of between about 30 mg/60 kg and about 50 mg/60 kg or between about 30 mg and 50 mg. In some embodiments, the daily dosage of predisone is about 40 mg/60 kg or 40 mg. In some embodiments, subsequent doses of predisone are administered daily for at least 4 days and wherein the dosage of the predisone is decreased on a daily basis.

[0051] In some embodiments, the steroid is administered prior to and after the administration of the first pharmaceutical compound.

[0052] In some embodiments, the steroid is methylprednisolone and is administered daily for at least seven days prior to the administration of the first pharmaceutical compound and daily for at least 7 weeks after administration of the first pharmaceutical compound. In some embodiments, the methylprednisolone is administered prior to the administration of the first pharmaceutical compound at a daily dosage of about 32 mg/60 kg or 32 mg. In some embodiments, the methylprednisolone is administered at a daily dosage of about 80 mg/60 kg or 80mg for at least 2 days after the administration of the first pharmaceutical compound. In some embodiments, beginning three days after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 40 mg/60 kg or 40mg for at least 4 days. In some embodiments, beginning one week after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 32 mg/60 kg or 32mg for at least one week. In some embodiments, beginning two weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 24 mg/60 kg or 24mg for at least one week. In some

embodiments, beginning three weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 16 mg/60 kg or 16mg for at least one week. In some embodiments, beginning four weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 8 mg/60 kg or 8mg for at least one week. In some embodiments, beginning five weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 6 mg/60 kg or 6mg for at least one week. In some embodiments, beginning six weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 4 mg/60 kg or 4mg for at least one week.

[0053] In some embodiments, the steroid is prednisone and is administered daily for at least two days prior to the administration of the first pharmaceutical compound and daily for at least eleven days after administration of the first pharmaceutical compound. In some embodiments, the prednisone is administered prior to the administration of the first pharmaceutical compound at a daily dosage of about 60 mg/60 kg or 60mg. In some embodiments, the prednisone is administered at a daily dosage of about 60 mg/60 kg or 60mg for at least seven days after the administration of the first pharmaceutical compound. In some embodiments, eight days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 40 mg/60 kg or 40mg for at least one day. In some embodiments, nine days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 20 mg/60 kg or 20mg for at least one day. In some embodiments, ten days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 10 mg/60 kg or 10mg for at least one day.

[0054] In some embodiments, the methods further comprise administering sodium creatine phosphate to the patient. In some embodiments, the sodium creatine phosphate is administered intravenously prior to and/or after the administration of the first pharmaceutical composition.

[0055] In some embodiments, administration of the first and second pharmaceutical compositions generates a higher average recovery of vision than a comparable pharmaceutical composition administered without the second pharmaceutical composition. In some embodiments, administration of the first and second pharmaceutical compositions generates a lower incidence of an adverse event than a comparable pharmaceutical composition administered without the second pharmaceutical composition. In some embodiments, the adverse event is selected from anterior

chamber inflammation, vitritis, ocular hypertension, cataract removal, keratitis, vitreous hemorrhage, allergic conjunctivitis, and eye pain. In some embodiments, the higher average recovery of vision and the lower incidence of an adverse event is determined in a population of patients with the eye disorder. In some embodiments, the population of patients are ethnically matched. In some embodiments, the population of patients are Chinese or Argentinian.

[0056] In some embodiments, the eye disorder is Leber's hereditary optic neuropathy (LHON). In some embodiments, the AAV is selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AA8, AAV9, and AAV10. In some embodiments, the AAV is AAV2.

[0057] In some embodiments, the present disclosure provides a method of screening patients for treatment of an eye disorder, the method comprising: (a) obtaining a serum sample from a patient; (b) culturing a population of target cells with a composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid encoding a detectable label in the presence of the serum sample; and (c) detecting the expression level of the detectable label in the target cell population after the culturing, wherein the patient is selected for the treatment if the expression level of the detectable label in the target cell population is higher than a pre-determined threshold.

[0058] In some embodiments, the present disclosure provides a method of screening patients for treatment of an eye disorder, the method comprising: (a) culturing a population of target cells with a composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid encoding a detectable label in the presence of a serum sample from a patient; and (b) detecting the expression level of the detectable label in the target cell population after the culturing, wherein the patient is selected for the treatment if the expression level of the detectable label in the target cell population is higher than a pre-determined threshold.

[0059] In some embodiments, the present disclosure provides a method of treating an eye disorder for a patient in need thereof, comprising: (a) obtaining a serum sample from a patient; (b) culturing a population of target cells with a composition comprising a first adeno-associated virus (AAV) comprising a first recombinant nucleic acid encoding a detectable label in the presence of the serum sample; (c) detecting the expression level of the detectable label in the target cell population; and (d) administering to the patient a pharmaceutical composition comprising a second AAV comprising a second recombinant nucleic acid, wherein the expression level of the detectable label in the target cell population is higher than a pre-determined threshold.

[0060] In some embodiments, the present disclosure provides a method of treating an eye disorder for a patient in need thereof, comprising: (a) culturing a population of target cells with a composition comprising a first adeno-associated virus (AAV) comprising a first recombinant nucleic acid encoding a detectable label in the presence of a serum sample from a patient; (b) detecting the expression level of the detectable label in the target cell population; and (c) administering to the patient a pharmaceutical composition comprising a second AAV comprising a second recombinant nucleic acid, wherein the expression level of the detectable label in the target cell population is higher than a pre-determined threshold.

[0061] In some embodiments, the detectable label is a fluorescent protein. In some embodiments, the fluorescent protein is green fluorescent protein (GFP). In some embodiments, the detectable label is detected by flow cytometry or qPCR. In some embodiments, the culturing step is at least 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or longer.

[0062] In some embodiments, the pre-determined threshold is about 40% of cells expressing the detectable label when detected by flow cytometry. In some embodiments, the pre-determined threshold is a relative expression level of the detectable label of about 0.6 when detected by qPCR. In some embodiments, the target cells are HEK-293 T cells.

[0063] In some embodiments, the treatment is a recombinant AAV comprising a nucleic acid sequence encoding a mitochondrial protein. In some embodiments, the mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof. In some embodiments, the patient comprises a mutation selected from G11778A in the ND4 gene, G3460A in the ND1 gene, and T14484C in the ND6 gene.

[0064] In some embodiments, the present disclosure provides a kit, comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid encoding a detectable label, a population of target cells, and one or more reagents for detecting the detectable label. In some embodiments, the kit further comprises a transfection reagent for transfecting the population of target cells with the AAV. In some embodiments, the kit further comprises a second AAV comprising a recombinant nucleic acid encoding a mitochondrial protein. In some embodiments, the one or more reagents for detecting the detectable label are selected an antibody that binds to the detectable label and one or more primer oligonucleotides specific for the recombinant nucleic acid encoding the detectable label.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0066] **FIG. 1** shows the PCR nucleic acid electrophoresis verification of ND4 (lane A) and optimized ND4 (lane B) gene cloning results.

[0067] **FIG. 2** shows the relative expression level comparison using qPCR between the rAAV2-opt_ND4 (left black column) and rAAV2-ND4 (right black column). β-actin is the internal reference gene (white column).

[0068] **FIG. 3** shows the relative expression level comparison using immunoblotting between the rAAV2-opt_ND4 (left black column) and rAAV2-ND4 (right black column). β-actin is the internal reference gene (white column).

[0069] **FIG. 4** shows the fundus photographic results for rabbits injected with rAAV2-opt_ND4 (right) and rAAV2-ND4 (left), respectively.

[0070] **FIG. 5** shows the fundus photographic results for a patient before (left) and after (right) the injection with rAAV2-optimized ND4.

[0071] **FIG. 6** shows EGFP expression levels of rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0072] **FIG. 7** shows the ND4 expression in 293T cells: rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0073] **FIG. 8** shows the relative ND4 expression in 293T cells: rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0074] **FIG. 9** shows the ND4 expression in rabbit optic nerve cells: rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0075] **FIG. 10** shows the relative ND4 expression in rabbit optic nerve cells: rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0076] **FIG. 11** shows the fundus photographic results for rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0077] **FIG. 12** shows the microscope inspection (HE staining) results for rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0078] **FIG. 13** shows the fundus photographic results for rabbits injected with rAAV2-ND6 (A), rAAV-GFP (B) and PBS, respectively.

[0079] **FIG. 14** shows the fundus photographic results for rabbits injected with rAAV2-opt_ND6 (A), rAAV2-ND6 (B), rAAV-EGFP (C), respectively.

[0080] **FIG. 15** shows the relative ND6 expression in rabbit optic nerve cells: rAAV2-opt_ND6 (A), rAAV2-ND6 (B), and rAAV-EGFP (C).

[0081] **FIG. 16** shows the relative ND6 expression by western blot: rAAV2-opt_ND6 (A), rAAV2-ND6 (B), and rAAV-EGFP (C).

[0082] **FIG. 17** shows the relative ND1 expression in rabbit optic nerve cells: rAAV2-opt_ND1 (A), rAAV2-ND1 (B), and rAAV-EGFP (C).

[0083] **FIG. 18** shows the relative ND1 expression by western blot: rAAV2-opt_ND1 (A), rAAV2-ND1 (B), and rAAV-EGFP (C).

[0084] **FIG. 19** shows a first exemplary steroid dosing schedule.

[0085] **FIG. 20** shows a second exemplary steroid dosing schedule.

DETAILED DESCRIPTION

Definitions

[0086] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of the ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the formulations or unit doses herein, some methods and materials are now described. Unless mentioned otherwise, the techniques employed or contemplated herein are standard methodologies. The materials, methods and examples are illustrative only and not limiting.

[0087] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a plurality of such agents, and reference to "the salt" includes reference to one

or more salts (or to a plurality of salts) and equivalents thereof known to those skilled in the art, and so forth.

[0088] As used herein, unless otherwise indicated, the term "or" can be conjunctive or disjunctive. As used herein, unless otherwise indicated, any embodiment can be combined with any other embodiment.

[0089] As used herein, unless otherwise indicated, some inventive embodiments herein contemplate numerical ranges. When ranges are present, the ranges include the range endpoints. Additionally, every subrange and value within the range is present as if explicitly written out.

[0090] The term "about" and its grammatical equivalents in relation to a reference numerical value and its grammatical equivalents as used herein can include a range of values plus or minus 10% from that value, such as a range of values plus or minus 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% from that value. For example, the amount "about 10" includes amounts from 9 to 11.

[0091] The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

[0092] The term "subject" refers to a mammal that has been or will be the object of treatment, observation or experiment. The term "mammal" is intended to have its standard meaning, and encompasses humans, dogs, cats, sheep, and cows, for example. The methods described herein can be useful in both human therapy and veterinary applications. In some embodiments, the subject is a human.

[0093] The term "treating" or "treatment" encompasses administration of at least one compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a mammalian subject, particularly a human subject, in need of such an administration and includes (i) arresting the development of clinical symptoms of the disease, such as cancer, (ii) bringing about a regression in the clinical symptoms of the disease, such as cancer, and/or (iii) prophylactic treatment for preventing the onset of the disease, such as cancer.

[0094] The term "therapeutically effective amount" of a chemical entity described herein refers to an amount effective, when administered to a human or non-human subject, to provide a

therapeutic benefit such as amelioration of symptoms, slowing of disease progression, or prevention of disease.

[0095] As used herein, unless otherwise indicated, the terms "nucleic acid" and "polynucleotide" can be used interchangeably.

[0096] As used herein, unless otherwise indicated, a drug dosage of X mg/60 kg refers to X mg of the drug per 60 kg body weight of the patient. For example, a drug dosage of 100 mg/60 kg means a patient with 60 kg body weight is instructed to take 100 mg of the drug, and accordingly, another patient with 30 kg body weight is instructed to take 50 mg of the drug.

Nucleic acid and polypeptide sequences

[0097] Table 1 discloses all the nucleic acid and polypeptide sequences disclosed herein. The first column shows the SEQ ID NO of each sequence. The second column describes the nucleic acid or polypeptide construct. For example, the construct COX10-ND6-3'UTR is a nucleic acid combining the nucleic acid sequences of COX10 (**SEQ ID NO: 1**), ND6 (**SEQ ID NO: 9**), and 3'UTR (**SEQ ID NO: 13**) (from 5' to 3' without linker between the nucleic acid sequences.

Table 1 - nucleic acid and polypeptide sequences and SEQ ID NOs

SEQ	Description	Sequence
1	COX10	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACT
2	opt_COX10	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACA
3	opt_COX10 *	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACC
4	COX8	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTG
5	OPA1	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTG
6	ND4	ATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTGACATGGCTTTCCAAAAAACAC ATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGCATCATCCCTCTACTATTTTTT AACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTTTCCTCCGACCCCCTAACAACC CCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATCATGGCAAGCCAACGCCACTTA TCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCTATGCTAATCTCCCCTACAAATCTCC TTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTATATCTTCTTCGAAACCACACTT ATCCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCAGAACGCCTGAACGCAGGCACA TACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTCATCGCACTAATTTACACTCAC AACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACTGCCCAAGAACTATCAAACTCC TGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTTATGGTAAAGATGCCTCTTTAC GGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCCATCGCTGGGTCAATGGTACTT GCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGCCTCACACTCATTCTCAACCCC

SEQ	Description	Sequence
		CTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTATGGGGCATGATTATGACAAGC TCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCATACTCTTCAATCAGCCACATG GCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGCTTCACCGGCGCAGTCATTCTC ATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTAGCAAACTCAAACTACGAACGC ACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACTCTACTCCCACTAATGGCTTTT TGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCCACTATTAACCTACTGGGAGAA CTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACTCTCCTACTTACAGGACTCAAC ATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACAACACAATGGGGCTCACTCACC CACCACATTAACAACATGAAACCCTCATTCACACGAGAAAACACCCTCATGTTCATGCACCTA TCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACCGGGTTTTCCTCTTAA
7	opt_ND4	ATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTGACCTGGCTGAGCAAGAAACAC ATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGCATCATCCCTCTGCTGTTCTTC AACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTCAGCAGCGACCCTCTGACAACA CCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATCATGGCCTCTCAGAGACACCTG AGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATGCTGATCTCCCTGCAGATCTCT CTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTTTTCGAGACAACGCTG ATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCTGAGAGACTGAACGCCGGCACC TACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTGATTGCCCTGATCTACACCCAC AACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACAGCCCAAGAGCTGAGCAACAGC TGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTCATGGTCAAGATGCCCCTGTAC GGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCTATCGCCGGCTCTATGGTGCTG GCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGGCTGACCCTGATTCTGAATCCC CTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTGTGGGGCATGATTATGACCAGC AGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCCTACAGCTCCATCAGCCACATG GCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGCTTTACAGGCGCCGTGATCCTG ATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTGGCCAACAGCAACTACGAGCGG ACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACCCTCCTGCCTCTTATGGCTTTT TGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCTACCATCAATCTGCTGGGCGAG CTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACCCTGCTGCTCACCGGCCTGAAC ATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACCACACAGTGGGGAAGCCTGACA CACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAACACCCTGATGTTCATGCATCTG AGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACCGGCTTCTCCAGCTGA
8	opt_ND4*	ATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTGACCTGGCTGAGCAAGAAGCAC ATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGCATCATCCCCCTGCTGTTCTTC AACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTCAGCAGCGACCCCCTGACCACC CCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATCATGGCCAGCCAGCGCCACCTG AGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATGCTGATCAGCCTGCAGATCAGC CTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTCTTCGAGACCACCCTG ATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCCGAGCGCCTGAACGCCGGCACC TACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTGATCGCCCTGATCTACACCCAC AACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACCGCCCAGGAGCTGAGCAACAGC TGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTCATGGTGAAGATGCCCCTGTAC GGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCCCCCATCGCCGGCAGCATGGTGCTG GCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGCCTGACCCTGATCCTGAACCCC CTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTGTGGGGCATGATCATGACCAGC AGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCCTACAGCAGCATCAGCCACATG GCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGCTTCACCGGCGCCGTGATCCTG ATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTGGCCAACAGCAACTACGAGCGC ACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACCCTGCTGCCCCCTGATGGCCTTC TGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCCACCATCAACCTGCTGGGCGAG CTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACCCTGCTGCTGACCGGCCTGAAC ATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACCACCCAGTGGGGCAGCCTGACC CACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAACACCCTGATGTTCATGCACCTG AGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACCGGCTTCAGCAGCTAA

SEQ	Description	Sequence
9	ND6	ATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATGGGGTTTGTGGGGTTTTCTTCT AAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGCGGTGTGGTCGGGTGTGTTATT ATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTTTTAATTTATTTAGGGGGAATG ATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTGAGGCATGGGGGTCA GGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATGGAGGTAGGATTGGTGCTGTGG GTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAATAGTGTAGGAAGCTGGATGATT TATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATTGGTGCGGGGGCTTTGTATGAT TATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTTGTTGGTGTATATATTGTAATT GAGATTGCTCGGGGGAATTAG
10	opt_ND6	ATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATGGGCTTCGTGGGCTTCAGCAGC AAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGCGGCGTGGTGGGCTGCGTGATC ATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTCCTGATCTACCTGGGCGGCATG ATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAGTACCCCGAGGCCTGGGGCAGC GGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATGGAGGTGGGCCTGGTGCTGTGG GTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAACAGCGTGGGCAGCTGGATGATC TACGAGGGCGAGGGCAGCGGCCTGATCCGCGGAGGACCCCATCGGCGCCGGCGCCCTGTACGAC TACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTCGTGGGCGTGTACATCGTGATC GAGATCGCCCGCGGCAACTAA
11	ND1	ATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCAATGGCATTCCTAATGCTTACC GAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCCAACGTTGTAGGCCCCTACGGG CTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAAGAGCCCCTAAAACCCGCCACA TCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTCACCATCGCTCTTCTACTATGG ACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTAGGCCTCCTATTTATTCTAGCC ACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGGGCATCAAACTCAAACTACGCC CTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATATGAAGTCACCCTAGCCATCATT CTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCCACCCTTATCACAACACAAGAA CACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATGTGGTTTATCTCCACACTAGCA GAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCCGAACTAGTCTCAGGCTTCAAC ATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCCGAATACACAAACATTATTATG ATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATATGACGCACTCTCCCCTGAACTC TACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCCCTGTTCTTATGGATTCGAACA GCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTATGGAAAAACTTCCTACCACTC ACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACAATCTCCAGCATTCCCCCTCAA ACCTAA
12	opt_ND1	ATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCCATGGCCTTCCTGATGCTGACC GAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCCAACGTGGTGGGCCCCTACGGC CTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAGGAGCCCCTGAAGCCCGCCACC AGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTGACCATCGCCCTGCTGCTGTGG ACCCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTGGGCCTGCTGTTCATCCTGGCC ACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGGGCCAGCAACAGCAACTACGCC CTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTACGAGGTGACCCTGGCCATCATC CTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGCACCCTGATCACCACCCAGGAG CACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATGTGGTTCATCAGCACCCTGGCC GAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGCGAGCTGGTGAGCGGCTTCAAC ATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCCGAGTACACCAACATCATCATG ATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTACGACGCCCTGAGCCCCGAGCTG TACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGCCTGTTCCTGTGGATCCGCACC GCCTACCCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTGTGGAAGAACTTCCTGCCCCTG ACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACCATCAGCAGCATCCCCCCCCAG ACCTAA

SEQ	Description	Sequence
13	3'UTR	GAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCT GGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTG ATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCA TCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCT CTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCT TCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGG CACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTC CCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTC CCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCT GTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCC TGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTT TATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGA CTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGT GGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAG GAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAA TACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAA GAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTAC CAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCT GCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGG TCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAA AATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTC CCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCT TCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
14	3'UTR*	GAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCT GGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTG ATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCA TCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCT CTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCT TCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGG CACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTC CCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTC CCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCT GTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA
15	COX10-ND4-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTG ACATGGCTTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGC ATCATCCCTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTT TCCTCCGACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATC ATGGCAAGCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCTATG CTAATCTCCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTAT ATCTTCTTCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCA GAACGCCTGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTC ATCGCACTAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACT GCCCAAGAACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTT ATGGTAAAGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCC ATCGCTGGGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGC CTCACACTCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTA TGGGGCATGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCA TACTCTTCAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGC TTCACCGGCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTA GCAAACTCAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACT CTACTCCCACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCC ACTATTAACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACT CTCCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACA ACACAATGGGGCTCACTCACCCACCACATTAACAACATGAAACCCTCATTCACACGAGAAAAC ACCCTCATGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACC GGGTTTTCCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA

SEQ	Description	Sequence
		TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
16	COX10-ND4-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTG ACATGGCTTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGC ATCATCCCTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTT TCCTCCGACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATC ATGGCAAGCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCTATG CTAATCTCCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTAT ATCTTCTTCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCA GAACGCCTGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTC ATCGCACTAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACT GCCCAAGAACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTT ATGGTAAAGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCC ATCGCTGGGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGC CTCACACTCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTA TGGGGCATGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCA TACTCTTCAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGC TTCACCGGCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTA GCAAACTCAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACT CTACTCCCACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCC ACTATTAACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACT CTCCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACA ACACAATGGGGCTCACTCACCCACCACACATTAACAACATGAAACCCTCATTCACACGAGAAAAC ACCCTCATGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACC GGGTTTTCCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA

SEQ	Description	Sequence
17	COX10-opt_ND4-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTG ACCTGGCTGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGC ATCATCCCTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATC ATGGCCTCTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATG CTGATCTCCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTTTTCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCT GAGAGACTGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTG ATTGCCCTGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACA GCCCAAGAGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTC ATGGTCAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCT ATCGCCGGCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGG CTGACCCTGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTG TGGGGCATGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCC TACAGCTCCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGC TTTACAGGCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTG GCCAACAGCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACC CTCCTGCCCTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCT ACCATCAATCTGCTGGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACC CTGCTGCTCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACC ACACAGTGGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACC GGCTTCTCCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT

SEQ	Description	Sequence
18	COX10-opt_ND4-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTG ACCTGGCTGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGC ATCATCCCTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATC ATGGCCTCTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATG CTGATCTCCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTTTTCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCT GAGAGACTGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTG ATTGCCCTGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACA GCCCAAGAGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTC ATGGTCAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCT ATCGCCGGCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGG CTGACCCTGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTG TGGGGCATGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCC TACAGCTCCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGC TTTACAGGCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTG GCCAACAGCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACC CTCCTGCCCTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCT ACCATCAATCTGCTGGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACC CTGCTGCTCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACC ACACAGTGGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACC GGCTTCTCCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA
19	COX10-opt_ND4*-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTG ACCTGGCTGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGC ATCATCCCCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCCCTGACCACCCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATC ATGGCCAGCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATG CTGATCAGCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTCTTCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCC GAGCGCCTGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTG ATCGCCCTGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACC GCCCAGGAGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTC ATGGTGAAGATGCCCCCTGTACGGCCTGCACCTGTGGCTGCCCCAAGGCCCACGTGGAGGCCCCC ATCGCCGGCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGC CTGACCCTGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTG TGGGGCATGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCC TACAGCAGCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGC TTCACCGGCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTG GCCAACAGCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACC CTGCTGCCCCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCC ACCATCAACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACC CTGCTGCTGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACC ACCCAGTGGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACC

SEQ	Description	Sequence
		GGCTTCAGCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
20	COX10-opt_ND4*-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTG ACCTGGCTGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGC ATCATCCCCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCCCTGACCACCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATC ATGGCCAGCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATG CTGATCAGCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTCTTCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCC GAGCGCCTGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTG ATCGCCCTGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACC GCCCAGGAGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTC ATGGTGAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCCCCC ATCGCCGGCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGC CTGACCCTGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTG TGGGGCATGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCC TACAGCAGCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGC TTCACCGGCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTG GCCAACAGCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACC CTGCTGCCCCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCC ACCATCAACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACC CTGCTGCTGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACC ACCCAGTGGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACC GGCTTCAGCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA

SEQ	Description	Sequence
21	COX10-ND6-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATG GGGTTTGTGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGC GGTGTGGTCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTT TTAATTTATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAG TATCCTGAGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATG GAGGTAGGATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAAT AGTGTAGGAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATT GGTGCGGGGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTT GTTGGTGTATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATT GCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATA GACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCT CTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTAC ACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTA ACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCT CCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGG GAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCT TTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTG ACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCG GGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGG TAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTA TTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTT CACATTTGTAGAAGCTTT
22	COX10-ND6-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATG GGGTTTGTGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGC GGTGTGGTCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTT TTAATTTATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAG TATCCTGAGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATG GAGGTAGGATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAAT AGTGTAGGAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATT GGTGCGGGGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTT GTTGGTGTATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA

SEQ	Description	Sequence
23	COX10-opt_ND6-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATG GGCTTCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGC GGCGTGGTGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTC CTGATCTACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAG TACCCCGAGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATG GAGGTGGGCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAAC AGCGTGGGCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCCATC GGCGCCGGCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTC GTGGGCGTGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATT GCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATA GACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCT CTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTAC ACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTA ACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCT CCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGG GAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCT TTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTG ACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCG GGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGG TAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTA TTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTT CACATTTGTAGAAGCTTT
24	COX10-opt_ND6-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATG GGCTTCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGC GGCGTGGTGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTC CTGATCTACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAG TACCCCGAGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATG GAGGTGGGCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAAC AGCGTGGGCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCCATC GGCGCCGGCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTC GTGGGCGTGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA

SEQ	Description	Sequence
25	COX10-ND1-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCA ATGGCATTCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCC AACGTTGTAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAA GAGCCCCTAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTC ACCATCGCTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTA GGCCTCCTATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGG GCATCAAACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATAT GAAGTCACCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCC ACCCTTATCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATG TGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCC GAACTAGTCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCC GAATACACAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATAT GACGCACTCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCC CTGTTCTTATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTA TGGAAAAACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACA ATCTCCAGCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTC AGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGC AGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCA TTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTT CAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGC TCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAAT TAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTA CCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTG CTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGA TTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAA ACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAAT CACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAAC ATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGC TTT
26	COX10-ND1-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCA ATGGCATTCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCC AACGTTGTAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAA GAGCCCCTAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTC ACCATCGCTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTA GGCCTCCTATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGG GCATCAAACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATAT GAAGTCACCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCC ACCCTTATCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATG TGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCC GAACTAGTCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCC GAATACACAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATAT GACGCACTCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCC CTGTTCTTATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTA TGGAAAAACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACA ATCTCCAGCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT

SEQ	Description	Sequence
		GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCA
27	COX10-opt_ND1-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCC ATGGCCTTCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCC AACGTGGTGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAG GAGCCCCTGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTG ACCATCGCCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTG GGCCTGCTGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGG GCCAGCAACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTAC GAGGTGACCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGC ACCCTGATCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATG TGGTTCATCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGC GAGCTGGTGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCC GAGTACACCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTAC GACGCCCTGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGC CTGTTCCTGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTG TGGAAGAACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACC ATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTC AGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGC AGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCA TTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTT CAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGC TCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAAT TAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTA CCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTG CTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGA TTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAA ACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAAT CACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAAC ATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGC TTT

SEQ	Description	Sequence
28	COX10-opt_ND1-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCTCCTGACAGGTTGCGTAGGAGGCTCTGTC TGGTATCTTGAAAGAAGAACTATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCC ATGGCCTTCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCC AACGTGGTGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAG GAGCCCCTGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTG ACCATCGCCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTG GGCCTGCTGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGG GCCAGCAACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTAC GAGGTGACCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGC ACCCTGATCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATG TGGTTCATCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGC GAGCTGGTGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCC GAGTACACCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTAC GACGCCCTGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGC CTGTTCCTGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTG TGGAAGAACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACC ATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCA
29	opt_COX10-ND4-3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTG ACATGGCTTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGC ATCATCCCTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTT TCCTCCGACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATC ATGGCAAGCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCTATG CTAATCTCCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTAT ATCTTCTTCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCA GAACGCCTGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTC ATCGCACTAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACT GCCCAAGAACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTT ATGGTAAAGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCC ATCGCTGGGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGC CTCACACTCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTA TGGGGCATGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCA TACTCTTCAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGC TTCACCGGCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTA GCAAACTCAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACT CTACTCCCACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCC ACTATTAACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACT CTCCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACA ACACAATGGGGCTCACTCACCCACCACACATTAACAACATGAAACCCTCATTCACACGAGAAAAC ACCCTCATGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACC GGGTTTTCCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT

SEQ	Description	Sequence
		CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
30	opt_COX10 -ND4- 3'UTR*	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTG ACATGGCTTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGC ATCATCCCTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTT TCCTCCGACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATC ATGGCAAGCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAAACTCTACCTCTCTATG CTAATCTCCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTAT ATCTTCTTCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCA GAACGCCTGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTC ATCGCACTAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACT GCCCAAGAACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTT ATGGTAAAGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCC ATCGCTGGGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGC CTCACACTCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTA TGGGGCATGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCA TACTCTTCAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGC TTCACCGGCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTA GCAAACTCAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACT CTACTCCCACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCC ACTATTAACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACT CTCCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACA ACACAATGGGGCTCACTCACCCACCACATTAACAACATGAAACCCTCATTCACACGAGAAAAC ACCCTCATGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACC GGGTTTTCCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA

SEQ	Description	Sequence
31	opt_COX10 -opt_ND4- 3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTG ACCTGGCTGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGC ATCATCCCTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATC ATGGCCTCTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATG CTGATCTCCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTTTTCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCT GAGAGACTGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTG ATTGCCCTGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACA GCCCAAGAGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTC ATGGTCAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCT ATCGCCGGCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGG CTGACCCTGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTG TGGGGCATGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCC TACAGCTCCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGC TTTACAGGCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTG GCCAACAGCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACC CTCCTGCCCTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCT ACCATCAATCTGCTGGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACC CTGCTGCTCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACC ACACAGTGGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACC GGCTTCTCCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT

SEQ	Description	Sequence
32	opt_COX10 -opt_ND4- 3'UTR*	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTG ACCTGGCTGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGC ATCATCCCTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATC ATGGCCTCTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATG CTGATCTCCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTTTTCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCT GAGAGACTGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTG ATTGCCCTGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACA GCCCAAGAGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTC ATGGTCAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCT ATCGCCGGCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGG CTGACCCTGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTG TGGGGCATGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCC TACAGCTCCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGC TTTACAGGCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTG GCCAACAGCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACC CTCCTGCCCTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCT ACCATCAATCTGCTGGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACC CTGCTGCTCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACC ACACAGTGGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACC GGCTTCTCCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA
33	opt_COX10 -opt_ND4*- 3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTG ACCTGGCTGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGC ATCATCCCCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCCCTGACCACCCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATC ATGGCCAGCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATG CTGATCAGCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTCTTCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCC GAGCGCCTGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTG ATCGCCCTGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACC GCCCAGGAGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTC ATGGTGAAGATGCCCCCTGTACGGCCTGCACCTGTGGCTGCCCCAAGGCCCACGTGGAGGCCCCC ATCGCCGGCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGC CTGACCCTGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTG TGGGGCATGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCC TACAGCAGCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGC TTCACCGGCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTG GCCAACAGCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACC CTGCTGCCCCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCC ACCATCAACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACC CTGCTGCTGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACC ACCCAGTGGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACC

SEQ	Description	Sequence
		GGCTTCAGCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
34	opt_COX10 -opt_ND4*- 3'UTR*	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTG ACCTGGCTGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGC ATCATCCCCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCCCTGACCACCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATC ATGGCCAGCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATG CTGATCAGCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTCTTCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCC GAGCGCCTGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTG ATCGCCCTGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACC GCCCAGGAGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTC ATGGTGAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCCCCC ATCGCCGGCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGC CTGACCCTGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTG TGGGGCATGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCC TACAGCAGCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGC TTCACCGGCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTG GCCAACAGCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACC CTGCTGCCCCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCC ACCATCAACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACC CTGCTGCTGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACC ACCCAGTGGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACC GGCTTCAGCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA

SEQ	Description	Sequence
35	opt_COX10-ND6-3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATG GGGTTTGTGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGC GGTGTGGTCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTT TTAATTTATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAG TATCCTGAGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATG GAGGTAGGATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAAT AGTGTAGGAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATT GGTGCGGGGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTT GTTGGTGTATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATT GCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATA GACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCT CTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTAC ACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTA ACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCT CCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGG GAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCT TTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTG ACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCG GGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGG TAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTA TTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTT CACATTTGTAGAAGCTTT
36	opt_COX10-ND6-3'UTR*	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATG GGGTTTGTGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGC GGTGTGGTCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTT TTAATTTATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAG TATCCTGAGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATG GAGGTAGGATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAAT AGTGTAGGAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATT GGTGCGGGGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTT GTTGGTGTATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA

SEQ	Description	Sequence
37	opt_COX10-opt_ND6-3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATG GGCTTCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGC GGCGTGGTGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTC CTGATCTACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAG TACCCCGAGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATG GAGGTGGGCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAAC AGCGTGGGCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCCATC GGCGCCGGCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTC GTGGGCGTGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATT GCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATA GACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCT CTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTAC ACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTA ACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCT CCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGG GAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCT TTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTG ACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCG GGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGG TAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTA TTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTT CACATTTGTAGAAGCTTT
38	opt_COX10-opt_ND6-3'UTR*	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATG GGCTTCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGC GGCGTGGTGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTC CTGATCTACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAG TACCCCGAGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATG GAGGTGGGCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAAC AGCGTGGGCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCCATC GGCGCCGGCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTC GTGGGCGTGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA

SEQ	Description	Sequence
39	opt_COX10-ND1-3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCA ATGGCATTCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCC AACGTTGTAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAA GAGCCCCTAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTC ACCATCGCTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTA GGCCTCCTATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGG GCATCAAACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATAT GAAGTCACCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCC ACCCTTATCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATG TGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCC GAACTAGTCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCC GAATACACAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATAT GACGCACTCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCC CTGTTCTTATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTA TGGAAAAACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACA ATCTCCAGCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTC AGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGC AGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCA TTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTT CAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGC TCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAAT TAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTA CCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTG CTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGA TTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAA ACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAAT CACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAAC ATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGC TTT
40	opt_COX10-ND1-3'UTR*	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCA ATGGCATTCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCC AACGTTGTAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAA GAGCCCCTAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTC ACCATCGCTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTA GGCCTCCTATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGG GCATCAAACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATAT GAAGTCACCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCC ACCCTTATCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATG TGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCC GAACTAGTCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCC GAATACACAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATAT GACGCACTCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCC CTGTTCTTATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTA TGGAAAAACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACA ATCTCCAGCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT

SEQ	Description	Sequence
		GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCA
41	opt_COX10 -opt_ND1- 3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCC ATGGCCTTCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCC AACGTGGTGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAG GAGCCCCTGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTG ACCATCGCCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTG GGCCTGCTGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGG GCCAGCAACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTAC GAGGTGACCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGC ACCCTGATCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATG TGGTTCATCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGC GAGCTGGTGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCC GAGTACACCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTAC GACGCCCTGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGC CTGTTCCTGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTG TGGAAGAACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACC ATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTC AGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGC AGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCA TTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTT CAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGC TCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAAT TAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTA CCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTG CTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGA TTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAA ACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAAT CACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAAC ATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGC TTT

SEQ	Description	Sequence
42	opt_COX10 -opt_ND1- 3'UTR*	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGCGGCTCTGTG TGGTATCTGGAACGGCGGACAATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCC ATGGCCTTCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCC AACGTGGTGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAG GAGCCCCTGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTG ACCATCGCCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTG GGCCTGCTGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGG GCCAGCAACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTAC GAGGTGACCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGC ACCCTGATCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATG TGGTTCATCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGC GAGCTGGTGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCC GAGTACACCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTAC GACGCCCTGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGC CTGTTCCTGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTG TGGAAGAACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACC ATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCA
43	opt_COX10 *-ND4- 3'UTR	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTG ACATGGCTTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGC ATCATCCCTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTT TCCTCCGACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATC ATGGCAAGCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCTATG CTAATCTCCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTAT ATCTTCTTCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCA GAACGCCTGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTC ATCGCACTAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACT GCCCAAGAACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTT ATGGTAAAGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCC ATCGCTGGGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGC CTCACACTCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTA TGGGGCATGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCA TACTCTTCAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGC TTCACCGGCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTA GCAAACTCAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACT CTACTCCCACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCC ACTATTAACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACT CTCCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACA ACACAATGGGGCTCACTCACCCACCACACATTAACAACATGAAACCCTCATTCACACGAGAAAAC ACCCTCATGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACC GGGTTTTCCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT

SEQ	Description	Sequence
		CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
44	opt_COX10 *-ND4- 3'UTR*	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTG ACATGGCTTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGC ATCATCCCTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTT TCCTCCGACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATC ATGGCAAGCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCTATG CTAATCTCCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTAT ATCTTCTTCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCA GAACGCCTGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTC ATCGCACTAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACT GCCCAAGAACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTT ATGGTAAAGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCC ATCGCTGGGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGC CTCACACTCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTA TGGGGCATGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCA TACTCTTCAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGC TTCACCGGCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTA GCAAACTCAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACT CTACTCCCACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCC ACTATTAACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACT CTCCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACA ACACAATGGGGCTCACTCACCCACCACATTAACAACATGAAACCCTCATTCACACGAGAAAAC ACCCTCATGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACC GGGTTTTCCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA

SEQ	Description	Sequence
45	opt_COX10 *-opt_ND4-3'UTR	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTG ACCTGGCTGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGC ATCATCCCTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATC ATGGCCTCTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATG CTGATCTCCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTTTTCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCT GAGAGACTGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTG ATTGCCCTGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACA GCCCAAGAGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTC ATGGTCAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCT ATCGCCGGCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGG CTGACCCTGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTG TGGGGCATGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCC TACAGCTCCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGC TTTACAGGCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTG GCCAACAGCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACC CTCCTGCCCTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCT ACCATCAATCTGCTGGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACC CTGCTGCTCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACC ACACAGTGGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACC GGCTTCTCCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT

SEQ	Description	Sequence
46	opt_COX10 *-opt_ND4-3'UTR*	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTG ACCTGGCTGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGC ATCATCCCTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATC ATGGCCTCTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATG CTGATCTCCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTTTTCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCT GAGAGACTGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTG ATTGCCCTGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACA GCCCAAGAGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTC ATGGTCAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCT ATCGCCGGCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGG CTGACCCTGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTG TGGGGCATGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCC TACAGCTCCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGC TTTACAGGCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTG GCCAACAGCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACC CTCCTGCCCTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCT ACCATCAATCTGCTGGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACC CTGCTGCTCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACC ACACAGTGGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACC GGCTTCTCCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA
47	opt_COX10 *-opt_ND4*-3'UTR	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTG ACCTGGCTGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGC ATCATCCCCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCCCTGACCACCCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATC ATGGCCAGCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATG CTGATCAGCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTCTTCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCC GAGCGCCTGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTG ATCGCCCTGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACC GCCCAGGAGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTC ATGGTGAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCCCCC ATCGCCGGCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGC CTGACCCTGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTG TGGGGCATGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCC TACAGCAGCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGC TTCACCGGCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTG GCCAACAGCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACC CTGCTGCCCCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCC ACCATCAACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACC CTGCTGCTGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACC ACCCAGTGGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACC

SEQ	Description	Sequence
		GGCTTCAGCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGG AGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTC TGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATT GAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGT CCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACAT GTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGG TGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTC TACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTC CCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAA CAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCAC TTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAA TGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
48	opt_COX10*-opt_ND4*-3'UTR*	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTG ACCTGGCTGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGC ATCATCCCCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTC AGCAGCGACCCCCTGACCACCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATC ATGGCCAGCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATG CTGATCAGCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTAC ATCTTCTTCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCC GAGCGCCTGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTG ATCGCCCTGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACC GCCCAGGAGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTC ATGGTGAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCCCCC ATCGCCGGCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGC CTGACCCTGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTG TGGGGCATGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCC TACAGCAGCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGC TTCACCGGCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTG GCCAACAGCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACC CTGCTGCCCCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCC ACCATCAACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACC CTGCTGCTGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACC ACCCAGTGGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAAC ACCCTGATGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACC GGCTTCAGCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCA TGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGA ATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCC CAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGG GTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGG TACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACA TGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTT CTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCT GCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGC TGGACTGCCA

SEQ	Description	Sequence
49	opt_COX10 *-ND6-3'UTR	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATG GGGTTTGTGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGC GGTGTGGTCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTT TTAATTTATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAG TATCCTGAGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATG GAGGTAGGATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAAT AGTGTAGGAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATT GGTGCGGGGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTT GTTGGTGTATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATT GCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATA GACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCT CTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTAC ACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTA ACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCT CCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGG GAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCT TTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTG ACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCG GGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGG TAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTA TTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTT CACATTTGTAGAAGCTTT
50	opt_COX10 *-ND6-3'UTR*	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATG GGGTTTGTGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGC GGTGTGGTCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTT TTAATTTATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAG TATCCTGAGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATG GAGGTAGGATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAAT AGTGTAGGAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATT GGTGCGGGGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTT GTTGGTGTATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA

SEQ	Description	Sequence
51	opt_COX10 *-opt_ND6-3'UTR	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATG GGCTTCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGC GGCGTGGTGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTC CTGATCTACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAG TACCCCGAGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATG GAGGTGGGCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAAC AGCGTGGGCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCCATC GGCGCCGGCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTC GTGGGCGTGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATT GCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATA GACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCT CTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTAC ACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTA ACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCT CCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGG GAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCT TTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTG ACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCG GGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGG TAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTA TTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTT CACATTTGTAGAAGCTTT
52	opt_COX10 *-opt_ND6-3'UTR*	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATG GGCTTCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGC GGCGTGGTGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTC CTGATCTACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAG TACCCCGAGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATG GAGGTGGGCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAAC AGCGTGGGCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCCATC GGCGCCGGCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTC GTGGGCGTGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCACCGC CCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTG CTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTT TTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACA AAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTA TTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTT ACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAAC CATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTC CACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA
53	opt_COX10 *-ND1-3'UTR	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCA ATGGCATTCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCC AACGTTGTAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAA

SEQ	Description	Sequence
		GAGCCCCTAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTC ACCATCGCTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTA GGCCTCCTATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGG GCATCAAACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATAT GAAGTCACCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCC ACCCTTATCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATG TGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCC GAACTAGTCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCC GAATACACAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATAT GACGCACTCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCC CTGTTCTTATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTA TGGAAAAACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACA ATCTCCAGCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTC AGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGC AGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCA TTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTT CAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGC TCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAAT TAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTA CCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTG CTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGA TTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAA ACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAAT CACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAAC ATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGC TTT
54	opt_COX10 *-ND1-3'UTR*	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCA ATGGCATTCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCC AACGTTGTAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAA GAGCCCCTAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTC ACCATCGCTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTA GGCCTCCTATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGG GCATCAAACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATAT GAAGTCACCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCC ACCCTTATCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATG TGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCC GAACTAGTCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCC GAATACACAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATAT GACGCACTCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCC CTGTTCTTATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTA TGGAAAAACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACA ATCTCCAGCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC

SEQ	Description	Sequence
		CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCA
55	opt_COX10 *-opt_ND1- 3'UTR	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCC ATGGCCTTCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCC AACGTGGTGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAG GAGCCCCTGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTG ACCATCGCCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTG GGCCTGCTGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGG GCCAGCAACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTAC GAGGTGACCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGC ACCCTGATCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATG TGGTTCATCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGC GAGCTGGTGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCC GAGTACACCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTAC GACGCCCTGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGC CTGTTCCTGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTG TGGAAGAACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACC ATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTC AGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGC AGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCA TTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTT CAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGC TCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAAT TAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTA CCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTG CTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGA TTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAA ACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAAT CACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAAC ATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGC TTT

SEQ	Description	Sequence
56	opt_COX10 *-opt_ND1-3'UTR*	ATGGCCGCCAGCCCCCACACCCTGAGCAGCCGCCTGCTGACCGGCTGCGTGGGCGGCAGCGTG TGGTACCTGGAGCGCCGCACCATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCC ATGGCCTTCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCC AACGTGGTGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAG GAGCCCCTGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTG ACCATCGCCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTG GGCCTGCTGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGG GCCAGCAACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTAC GAGGTGACCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGC ACCCTGATCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATG TGGTTCATCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGC GAGCTGGTGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCC GAGTACACCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTAC GACGCCCTGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGC CTGTTCCTGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTG TGGAAGAACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACC ATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCT GCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAA GATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACC CAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTT TTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTC CTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACAC GCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTG CTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACT GAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAAC AATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTG GGAGTCTCAAGCTGGACTGCCA
57	COX8-ND4-3'UTR	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCA CTGACATGGCTTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATT AGCATCATCCCTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACC TTTTCCTCCGACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACA ATCATGGCAAGCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCT ATGCTAATCTCCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTT TATATCTTCTTCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAG CCAGAACGCCTGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTA CTCATCGCACTAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTC ACTGCCCAAGAACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCT TTTATGGTAAAGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCC CCCATCGCTGGGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATG CGCCTCACACTCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCC CTATGGGGCATGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATT GCATACTCTTCAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGG AGCTTCACCGGCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGC CTAGCAAACTCAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAA ACTCTACTCCCACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCC CCCACTATTAACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATC ACTCTCCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACC ACAACACAATGGGGCTCACTCACCCACCACATTAACAACATGAAACCCTCATTCACACGAGAA AACACCCTCATGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATT ACCGGGTTTTCCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGA GCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAA CGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCT CCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTG AGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGG GGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCC ACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTA

SEQ	Description	Sequence
		GTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGG CCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAAT AGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCA AGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCA AGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTC TAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTAC CTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGT ATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCC TGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCA CATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCC AGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGG GTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGT CTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTT AAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTG CACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAG GAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
58	COX8-ND4-3'UTR*	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCA CTGACATGGCTTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATT AGCATCATCCCTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACC TTTTCCTCCGACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACA ATCATGGCAAGCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCT ATGCTAATCTCCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTT TATATCTTCTTCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAG CCAGAACGCCTGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTA CTCATCGCACTAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTC ACTGCCCAAGAACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCT TTTATGGTAAAGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCC CCCATCGCTGGGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATG CGCCTCACACTCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCC CTATGGGGCATGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATT GCATACTCTTCAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGG AGCTTCACCGGCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGC CTAGCAAACTCAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAA ACTCTACTCCCACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCC CCCACTATTAACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATC ACTCTCCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACC ACAACACAATGGGGCTCACTCACCCACCACATTAACAACATGAAACCCTCATTCACACGAGAA AACACCCTCATGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATT ACCGGGTTTTCCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGA GCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAA CGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCT CCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTG AGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGG GGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCC ACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTA GTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGG CCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAAT AGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCA AGCTGGACTGCCA

SEQ	Description	Sequence
59	COX8-opt_ND4-3'UTR	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCT CTGACCTGGCTGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATC AGCATCATCCCTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACC TTCAGCAGCGACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACA ATCATGGCCTCTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGC ATGCTGATCTCCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTC TACATCTTTTTCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAG CCTGAGAGACTGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTG CTGATTGCCCTGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTG ACAGCCCAAGAGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCC TTCATGGTCAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCC CCTATCGCCGGCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATG CGGCTGACCCTGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGC CTGTGGGGCATGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATC GCCTACAGCTCCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGG AGCTTTACAGGCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGT CTGGCCAACAGCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAG ACCCTCCTGCCTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCT CCTACCATCAATCTGCTGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATC ACCCTGCTGCTCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACC ACCACACAGTGGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAG AACACCCTGATGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATC ACCGGCTTCTCCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGA GCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAA CGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCT CCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTG AGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGG GGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCC ACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTA GTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGG CCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAAT AGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCA AGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCA AGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTC TAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTAC CTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGT ATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCC TGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCA CATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCC AGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGG GTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGT CTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTT AAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTG CACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAG GAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT

SEQ	Description	Sequence
60	COX8-opt_ND4-3'UTR*	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCT CTGACCTGGCTGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATC AGCATCATCCCTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACC TTCAGCAGCGACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACA ATCATGGCCTCTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGC ATGCTGATCTCCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTC TACATCTTTTTCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAG CCTGAGAGACTGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTG CTGATTGCCCTGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTG ACAGCCCAAGAGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCC TTCATGGTCAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCC CCTATCGCCGGCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATG CGGCTGACCCTGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGC CTGTGGGGCATGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATC GCCTACAGCTCCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGG AGCTTTACAGGCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGT CTGGCCAACAGCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAG ACCCTCCTGCCTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCT CCTACCATCAATCTGCTGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATC ACCCTGCTGCTCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACC ACCACACAGTGGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAG AACACCCTGATGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATC ACCGGCTTCTCCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGA GCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAA CGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCT CCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTG AGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGG GGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCC ACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTA GTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGG CCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAAT AGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCA AGCTGGACTGCCA
61	COX8-opt_ND4*-3'UTR	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCC CTGACCTGGCTGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATC AGCATCATCCCCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACC TTCAGCAGCGACCCCCTGACCACCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACC ATCATGGCCAGCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGC ATGCTGATCAGCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTC TACATCTTCTTCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAG CCCGAGCGCCTGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTG CTGATCGCCCTGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTG ACCGCCCAGGAGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCC TTCATGGTGAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCC CCCATCGCCGGCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATG CGCCTGACCCTGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGC CTGTGGGGCATGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATC GCCTACAGCAGCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGG AGCTTCACCGGCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGC CTGGCCAACAGCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAG ACCCTGCTGCCCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCC CCCACCATCAACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATC ACCCTGCTGCTGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACC ACCACCCAGTGGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAG AACACCCTGATGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATC

SEQ	Description	Sequence
		ACCGGCTTCAGCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGA GCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAA CGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCT CCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTG AGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGG GGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCC ACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTA GTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGG CCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAAT AGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCA AGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCA AGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTC TAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTAC CTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGT ATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCC TGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCA CATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCC AGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGG GTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGT CTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTT AAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTG CACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAG GAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
62	COX8- opt_ND4*- 3'UTR*	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCC CTGACCTGGCTGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATC AGCATCATCCCCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACC TTCAGCAGCGACCCCCTGACCACCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACC ATCATGGCCAGCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGC ATGCTGATCAGCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTC TACATCTTCTTCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAG CCCGAGCGCCTGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTG CTGATCGCCCTGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTG ACCGCCCAGGAGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCC TTCATGGTGAAGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCC CCCATCGCCGGCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATG CGCCTGACCCTGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGC CTGTGGGGCATGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATC GCCTACAGCAGCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGG AGCTTCACCGGCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGC CTGGCCAACAGCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAG ACCCTGCTGCCCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCC CCCACCATCAACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATC ACCCTGCTGCTGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACC ACCACCCAGTGGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAG AACACCCTGATGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATC ACCGGCTTCAGCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGA GCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAA CGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCT CCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTG AGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGG GGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCC ACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTA GTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGG CCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAAT AGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCA AGCTGGACTGCCA

SEQ	Description	Sequence
63	COX8-ND6-3'UTR	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTA ATGGGGTTTGTGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTT AGCGGTGTGGTCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTT TTTTTAATTTATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAG GAGTATCCTGAGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCG ATGGAGGTAGGATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTT AATAGTGTAGGAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCT ATTGGTGCGGGGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTG TTTGTTGGTGTATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCAC CGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAA TTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTT TTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAAT ACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCT CTATTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATC CTTACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAG TGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGC ACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTC AACCATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGA TTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCC ATTGCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACAT ATAGACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATA CCTCTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGC TACACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGG CTAACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATA TCTCCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTC TGGGAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCA GCTTTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGC TTGACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGG TCGGGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGT AGGTAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAG GTATTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGC CTTCACATTTGTAGAAGCTTT
64	COX8-ND6-3'UTR*	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTA ATGGGGTTTGTGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTT AGCGGTGTGGTCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTT TTTTTAATTTATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAG GAGTATCCTGAGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCG ATGGAGGTAGGATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTT AATAGTGTAGGAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCT ATTGGTGCGGGGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTG TTTGTTGGTGTATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCAC CGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAA TTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTT TTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAAT ACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCT CTATTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATC CTTACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAG TGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGC ACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTC AACCATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGA TTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA

SEQ	Description	Sequence
65	COX8-opt_ND6-3'UTR	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTG ATGGGCTTCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTG AGCGGCGTGGTGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTG TTCCTGATCTACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAG GAGTACCCCGAGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCC ATGGAGGTGGGCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTC AACAGCGTGGGCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCC ATCGGCGCCGGCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTG TTCGTGGGCGTGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCAC CGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAA TTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTT TTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAAT ACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCT CTATTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATC CTTACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAG TGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGC ACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTC AACCATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGA TTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCC ATTGCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACAT ATAGACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATA CCTCTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGC TACACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGG CTAACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATA TCTCCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTC TGGGAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCA GCTTTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGC TTGACAGGATGTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGG TCGGGGTAGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGT AGGTAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAG GTATTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGC CTTCACATTTGTAGAAGCTTT
66	COX8-opt_ND6-3'UTR*	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTG ATGGGCTTCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTG AGCGGCGTGGTGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTG TTCCTGATCTACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAG GAGTACCCCGAGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCC ATGGAGGTGGGCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTC AACAGCGTGGGCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCC ATCGGCGCCGGCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTG TTCGTGGGCGTGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCAC CGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAA TTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTT TTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAAT ACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCT CTATTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATC CTTACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAG TGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGC ACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTC AACCATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGA TTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCA
67	COX8-ND1-3'UTR	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATC GCAATGGCATTCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGC CCCAACGTTGTAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACC

SEQ	Description	Sequence
		AAAGAGCCCCTAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCT CTCACCATCGCTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAAC CTAGGCCTCCTATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGG TGGGCATCAAACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCA TATGAAGTCACCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTC TCCACCCTTATCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATG ATGTGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAG TCCGAACTAGTCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATG GCCGAATACACAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACA TATGACGCACTCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACC TCCCTGTTCTTATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTC CTATGGAAAAACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATT ACAATCTCCAGCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCC GCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAA CAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATT ACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTA TTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTC CTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCA CACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGAT CTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTG ACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCT AACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCC TTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCAT TTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGA AGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACC CCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTT TTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAG AGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGA AATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAG TTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTT GTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTT CGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGT TAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCC AATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAG AACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGA AGCTTT
68	COX8-ND1-3'UTR*	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATC GCAATGGCATTCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGC CCCAACGTTGTAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACC AAAGAGCCCCTAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCT CTCACCATCGCTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAAC CTAGGCCTCCTATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGG TGGGCATCAAACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCA TATGAAGTCACCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTC TCCACCCTTATCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATG ATGTGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAG TCCGAACTAGTCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATG GCCGAATACACAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACA TATGACGCACTCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACC TCCCTGTTCTTATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTC CTATGGAAAAACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATT ACAATCTCCAGCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCC GCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAA CAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATT ACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTA TTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTC

SEQ	Description	Sequence
		CTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCA CACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGAT CTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTG ACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCT AACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCC TTGGGAGTCTCAAGCTGGACTGCCA
69	COX8-opt_ND1-3'UTR	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATC GCCATGGCCTTCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGC CCCAACGTGGTGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACC AAGGAGCCCCTGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCC CTGACCATCGCCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAAC CTGGGCCTGCTGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGC TGGGCCAGCAACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGC TACGAGGTGACCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTG AGCACCCTGATCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATG ATGTGGTTCATCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAG AGCGAGCTGGTGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATG GCCGAGTACACCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACC TACGACGCCCTGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACC AGCCTGTTCCTGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTG CTGTGGAAGAACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATC ACCATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCC GCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAA CAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATT ACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTA TTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTC CTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCA CACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGAT CTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTG ACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCT AACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCC TTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCAT TTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGA AGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACC CCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTT TTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAG AGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGA AATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAG TTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTT GTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTT CGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGT TAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCC AATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAG AACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGA AGCTTT
70	COX8-opt_ND1-3'UTR*	ATGTCCGTCCTGACGCGCCTGCTGCTGCGGGGCTTGACACGGCTCGGCTCGGCGGCTCCAGTG CGGCGCGCCAGAATCCATTCGTTGATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATC GCCATGGCCTTCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGC CCCAACGTGGTGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACC AAGGAGCCCCTGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCC CTGACCATCGCCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAAC CTGGGCCTGCTGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGC TGGGCCAGCAACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGC TACGAGGTGACCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTG AGCACCCTGATCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATG ATGTGGTTCATCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAG

SEQ	Description	Sequence
		AGCGAGCTGGTGAGCGGCTTCAACATCGAGTACGCCGCCGGGCCCCTTCGCCCTGTTCTTCATG GCCGAGTACACCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACC TACGACGCCCTGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACC AGCCTGTTCCTGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTG CTGTGGAAGAACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATC ACCATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCC GCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAA CAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATT ACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTA TTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTC CTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCA CACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGAT CTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTG ACTGAGCCAGGGCCTGCATTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCT AACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCC TTGGGAGTCTCAAGCTGGACTGCCA
71	OPA1-ND4-3'UTR	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTGACATGGC TTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGCATCATCC CTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTTTCCTCCG ACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATCATGGCAA GCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCTATGCTAATCT CCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTATATCTTCT TCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCAGAACGCC TGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTCATCGCAC TAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACTGCCCAAG AACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTTATGGTAA AGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCCATCGCTG GGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGCCTCACAC TCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTATGGGGCA TGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCATACTCTT CAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGCTTCACCG GCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTAGCAAACT CAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACTCTACTCC CACTAATGGCTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCCACTATTA ACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACTCTCCTAC TTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACAACACAAT GGGGCTCACTCACCCACCACATTAACAACATGAAACCCTCATTCACACGAGAAAACACCCTCA TGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACCGGGTTTT CCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTG GTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGT GCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAA GAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTT ATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACAT ACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAG CAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAG CTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTT TGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACC CGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTG CCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGGAGTCACA GGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTA GCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTCTGGAGTC ACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGG GAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGTCCCTTGG

SEQ	Description	Sequence
		GTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACATGTGCAAT GGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTC TCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAG TCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTCCCAGGGC ACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAACAGAGTT CTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCACTTATCTG AAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAATGTCTGG AAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
72	OPA1-ND4-3'UTR*	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGCTAAAACTAATCGTCCCAACAATTATGTTACTACCACTGACATGGC TTTCCAAAAAACACATGATTTGGATCAACACAACCACCCACAGCCTAATTATTAGCATCATCC CTCTACTATTTTTTAACCAAATCAACAACAACCTATTTAGCTGTTCCCCAACCTTTTCCTCCG ACCCCCTAACAACCCCCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACAATCATGGCAA GCCAACGCCACTTATCCAGTGAACCACTATCACGAAAAAAACTCTACCTCTCTATGCTAATCT CCCTACAAATCTCCTTAATTATGACATTCACAGCCACAGAACTAATCATGTTTTATATCTTCT TCGAAACCACACTTATCCCCACCTTGGCTATCATCACCCGATGGGGCAACCAGCCAGAACGCC TGAACGCAGGCACATACTTCCTATTCTACACCCTAGTAGGCTCCCTTCCCCTACTCATCGCAC TAATTTACACTCACAACACCCTAGGCTCACTAAACATTCTACTACTCACTCTCACTGCCCAAG AACTATCAAACTCCTGGGCCAACAACTTAATGTGGCTAGCTTACACAATGGCTTTTATGGTAA AGATGCCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGCCCCCATCGCTG GGTCAATGGTACTTGCCGCAGTACTCTTAAAACTAGGCGGCTATGGTATGATGCGCCTCACAC TCATTCTCAACCCCCTGACAAAACACATGGCCTACCCCTTCCTTGTACTATCCCTATGGGGCA TGATTATGACAAGCTCCATCTGCCTACGACAAACAGACCTAAAATCGCTCATTGCATACTCTT CAATCAGCCACATGGCCCTCGTAGTAACAGCCATTCTCATCCAAACCCCCTGGAGCTTCACCG GCGCAGTCATTCTCATGATCGCCCACGGGCTTACATCCTCATTACTATTCTGCCTAGCAAACT CAAACTACGAACGCACTCACAGTCGCATCATGATCCTCTCTCAAGGACTTCAAACTCTACTCC CACTAATGGCTTTTTTGGTGGCTTCTAGCAAGCCTCGCTAACCTCGCCTTACCCCCCACTATTA ACCTACTGGGAGAACTCTCTGTGCTAGTAACCACGTTCTCCTGGTCAAATATCACTCTCCTAC TTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTCTACATGTTTACCACAACACAAT GGGGCTCACTCACCCACCACATTAACAACATGAAACCCTCATTCACACGAGAAAACACCCTCA TGTTCATGCACCTATCCCCCATTCTCCTCCTATCCCTCAACCCCGACATCATTACCGGGTTTT CCTCTTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTG GTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGT GCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAA GAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTT ATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACAT ACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAG CAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAG CTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTT TGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACC CGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTG CCA

SEQ	Description	Sequence
73	OPA1-opt_ND4-3'UTR	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTGACCTGGC TGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGCATCATCC CTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTCAGCAGCG ACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATCATGGCCT CTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATGCTGATCT CCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTTT TCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCTGAGAGAC TGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTGATTGCCC TGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACAGCCCAAG AGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTCATGGTCA AGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCTATCGCCG GCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGGCTGACCC TGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTGTGGGGCA TGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCCTACAGCT CCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGCTTTACAG GCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTGGCCAACA GCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACCCTCCTGC CTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCTACCATCA ATCTGCTGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACCCTGCTGC TCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACCACACAGT GGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAACACCCTGA TGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACCGGCTTCT CCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTG GTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGT GCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAA GAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTT ATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACAT ACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAG CAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAG CTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTT TGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACC CGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTG CCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGGAGTCACA GGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTA GCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTCTGGAGTC ACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGG GAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGTCCCTTGG GTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACATGTGCAAT GGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTC TCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAG TCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTCCCAGGGC ACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAACAGAGTT CTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCACTTATCTG AAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAATGTCTGG AAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT

SEQ	Description	Sequence
74	OPA1-opt_ND4-3'UTR*	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCTCTGACCTGGC TGAGCAAGAAACACATGATCTGGATCAACACCACCACGCACAGCCTGATCATCAGCATCATCC CTCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTCAGCAGCG ACCCTCTGACAACACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCCTCACAATCATGGCCT CTCAGAGACACCTGAGCAGCGAGCCCCTGAGCCGGAAGAAACTGTACCTGAGCATGCTGATCT CCCTGCAGATCTCTCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTTT TCGAGACAACGCTGATCCCCACACTGGCCATCATCACCAGATGGGGCAACCAGCCTGAGAGAC TGAACGCCGGCACCTACTTTCTGTTCTACACCCTCGTGGGCAGCCTGCCACTGCTGATTGCCC TGATCTACACCCACAACACCCTGGGCTCCCTGAACATCCTGCTGCTGACACTGACAGCCCAAG AGCTGAGCAACAGCTGGGCCAACAATCTGATGTGGCTGGCCTACACAATGGCCTTCATGGTCA AGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCTAAAGCTCATGTGGAAGCCCCTATCGCCG GCTCTATGGTGCTGGCTGCAGTGCTGCTGAAACTCGGCGGCTACGGCATGATGCGGCTGACCC TGATTCTGAATCCCCTGACCAAGCACATGGCCTATCCATTTCTGGTGCTGAGCCTGTGGGGCA TGATTATGACCAGCAGCATCTGCCTGCGGCAGACCGATCTGAAGTCCCTGATCGCCTACAGCT CCATCAGCCACATGGCCCTGGTGGTCACCGCCATCCTGATTCAGACCCCTTGGAGCTTTACAG GCGCCGTGATCCTGATGATTGCCCACGGCCTGACAAGCAGCCTGCTGTTTTGTCTGGCCAACA GCAACTACGAGCGGACCCACAGCAGAATCATGATCCTGTCTCAGGGCCTGCAGACCCTCCTGC CTCTTATGGCTTTTTGGTGGCTGCTGGCCTCTCTGGCCAATCTGGCACTGCCTCCTACCATCA ATCTGCTGGGCGAGCTGAGCGTGCTGGTCACCACATTCAGCTGGTCCAATATCACCCTGCTGC TCACCGGCCTGAACATGCTGGTTACAGCCCTGTACTCCCTGTACATGTTCACCACCACACAGT GGGGAAGCCTGACACACCACATCAACAATATGAAGCCCAGCTTCACCCGCGAGAACACCCTGA TGTTCATGCATCTGAGCCCCATTCTGCTGCTGTCCCTGAATCCTGATATCATCACCGGCTTCT CCAGCTGAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTG GTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGT GCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAA GAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTT ATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACAT ACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAG CAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAG CTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTT TGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACC CGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTG CCA
75	OPA1-opt_ND4*-3'UTR	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTGACCTGGC TGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGCATCATCC CCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTCAGCAGCG ACCCCCTGACCACCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATCATGGCCA GCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATGCTGATCA GCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTCT TCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCCGAGCGCC TGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTGATCGCCC TGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACCGCCCAGG AGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTCATGGTGA AGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCCCCCATCGCCG GCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGCCTGACCC TGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTGTGGGGCA TGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCCTACAGCA GCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGCTTCACCG GCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTGGCCAACA

SEQ	Description	Sequence
		GCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACCCTGCTGC CCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCCACCATCA ACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACCCTGCTGC TGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACCACCCAGT GGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAACACCCTGA TGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACCGGCTTCA GCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTG GTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGT GCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAA GAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTTGAGGGTCTTTT ATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACAT ACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAG CAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAG CTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTT TGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACC CGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTG CCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGGAGTCACA GGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTA GCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTCTGGAGTC ACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGG GAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGTCCCTTGG GTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACATGTGCAAT GGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGGCCAGGTGTGGTC TCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTCTACAGAG TCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCAGTCTCCCAGGGC ACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACATTTAAACAGAGTT CTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCACTTATCTG AAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAATGTCTGG AAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
76	OPA1-opt_ND4*-3'UTR*	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGCTGAAGCTGATCGTGCCCACCATCATGCTGCTGCCCCTGACCTGGC TGAGCAAGAAGCACATGATCTGGATCAACACCACCACCCACAGCCTGATCATCAGCATCATCC CCCTGCTGTTCTTCAACCAGATCAACAACAACCTGTTCAGCTGCAGCCCCACCTTCAGCAGCG ACCCCCTGACCACCCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCCTGACCATCATGGCCA GCCAGCGCCACCTGAGCAGCGAGCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATGCTGATCA GCCTGCAGATCAGCCTGATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTCT TCGAGACCACCCTGATCCCCACCCTGGCCATCATCACCCGCTGGGGCAACCAGCCCGAGCGCC TGAACGCCGGCACCTACTTCCTGTTCTACACCCTGGTGGGCAGCCTGCCCCTGCTGATCGCCC TGATCTACACCCACAACACCCTGGGCAGCCTGAACATCCTGCTGCTGACCCTGACCGCCCAGG AGCTGAGCAACAGCTGGGCCAACAACCTGATGTGGCTGGCCTACACCATGGCCTTCATGGTGA AGATGCCCCTGTACGGCCTGCACCTGTGGCTGCCCAAGGCCCACGTGGAGGCCCCCATCGCCG GCAGCATGGTGCTGGCCGCCGTGCTGCTGAAGCTGGGCGGCTACGGCATGATGCGCCTGACCC TGATCCTGAACCCCCTGACCAAGCACATGGCCTACCCCTTCCTGGTGCTGAGCCTGTGGGGCA TGATCATGACCAGCAGCATCTGCCTGCGCCAGACCGACCTGAAGAGCCTGATCGCCTACAGCA GCATCAGCCACATGGCCCTGGTGGTGACCGCCATCCTGATCCAGACCCCCTGGAGCTTCACCG GCGCCGTGATCCTGATGATCGCCCACGGCCTGACCAGCAGCCTGCTGTTCTGCCTGGCCAACA GCAACTACGAGCGCACCCACAGCCGCATCATGATCCTGAGCCAGGGCCTGCAGACCCTGCTGC CCCTGATGGCCTTCTGGTGGCTGCTGGCCAGCCTGGCCAACCTGGCCCTGCCCCCCACCATCA ACCTGCTGGGCGAGCTGAGCGTGCTGGTGACCACCTTCAGCTGGAGCAACATCACCCTGCTGC TGACCGGCCTGAACATGCTGGTGACCGCCCTGTACAGCCTGTACATGTTCACCACCACCCAGT GGGGCAGCCTGACCCACCACATCAACAACATGAAGCCCAGCTTCACCCGCGAGAACACCCTGA TGTTCATGCACCTGAGCCCCATCCTGCTGCTGAGCCTGAACCCCGACATCATCACCGGCTTCA GCAGCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTG GTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGT

SEQ	Description	Sequence
		GCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAA GAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTT ATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACAT ACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAG CAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAG CTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAGGGCCTGCATTTT TGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACC CGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTG CCA
77	OPA1-ND6-3'UTR	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATGGGGTTTG TGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGCGGTGTGG TCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTTTTAATTT ATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTG AGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATGGAGGTAG GATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAATAGTGTAG GAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATTGGTGCGG GGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTTGTTGGTG TATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCACCGCCCCTTTC CCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTT TAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTAA ATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGG AATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTT TCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCA CACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTC ATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCC TTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTC CTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGT TTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATG AGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTG TTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCC CCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCAC GGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCC CACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAAT TCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTT GCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGT CCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGAT GTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGG AGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAA CATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTG TGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTT GTAGAAGCTTT
78	OPA1-ND6-3'UTR*	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGATGTATGCTTTGTTTCTGTTGAGTGTGGGTTTAGTAATGGGGTTTG TGGGGTTTTCTTCTAAGCCTTCTCCTATTTATGGGGGTTTAGTATTGATTGTTAGCGGTGTGG TCGGGTGTGTTATTATTCTGAATTTTGGGGGAGGTTATATGGGTTTAATGGTTTTTTTAATTT ATTTAGGGGGAATGATGGTTGTCTTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTG AGGCATGGGGGTCAGGGGTTGAGGTCTTGGTGAGTGTTTTAGTGGGGTTAGCGATGGAGGTAG GATTGGTGCTGTGGGTGAAAGAGTATGATGGGGTGGTGGTTGTGGTAAACTTTAATAGTGTAG GAAGCTGGATGATTTATGAAGGAGAGGGGTCAGGGTTGATTCGGGAGGATCCTATTGGTGCGG GGGCTTTGTATGATTATGGGCGTTGGTTAGTAGTAGTTACTGGTTGGACATTGTTTGTTGGTG

SEQ	Description	Sequence
		TATATATTGTAATTGAGATTGCTCGGGGGAATTAGGAGCACTGGGACGCCCACCGCCCCTTTC CCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTT TAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAA ATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGG AATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTT TCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCA CACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTC ATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCC TTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTC CTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGT TTGCCTTGGGAGTCTCAAGCTGGACTGCCA
79	OPA1-opt_ND6-3'UTR	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATGGGCTTCG TGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGCGGCGTGG TGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTCCTGATCT ACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAGTACCCCG AGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATGGAGGTGG GCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAACAGCGTGG GCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCCATCGGCGCCG GCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTCGTGGGCG TGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCACCGCCCCTTTC CCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTT TAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAA ATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGG AATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTT TCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCA CACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTC ATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCC TTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTC CTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGT TTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATG AGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTG TTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCC CCACCCCATTACTGTACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCAC GGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCC CACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAAT TCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTT GCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGT CCTTTGTGCTCCCACGGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGAT GTTTTCGATTACTCAGTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGG AGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAA CATCCAATCACTGTTTGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTG TGGAGAACATTGCATAGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTT GTAGAAGCTTT
80	OPA1-opt_ND6-3'UTR*	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGATGTACGCCCTGTTCCTGCTGAGCGTGGGCCTGGTGATGGGCTTCG TGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCTGGTGCTGATCGTGAGCGGCGTGG TGGGCTGCGTGATCATCCTGAACTTCGGCGGCGGCTACATGGGCCTGATGGTGTTCCTGATCT ACCTGGGCGGCATGATGGTGGTGTTCGGCTACACCACCGCCATGGCCATCGAGGAGTACCCCG AGGCCTGGGGCAGCGGCGTGGAGGTGCTGGTGAGCGTGCTGGTGGGCCTGGCCATGGAGGTGG GCCTGGTGCTGTGGGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACTTCAACAGCGTGG

SEQ	Description	Sequence
		GCAGCTGGATGATCTACGAGGGCGAGGGCAGCGGCCTGATCCGCGAGGACCCCATCGGCGCCG GCGCCCTGTACGACTACGGCCGCTGGCTGGTGGTGGTGACCGGCTGGACCCTGTTCGTGGGCG TGTACATCGTGATCGAGATCGCCCGCGGCAACTAAGAGCACTGGGACGCCCACCGCCCCTTTC CCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTT TAGAACAAGATTATAAACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAA ATATTACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGG AATTATTTTTCCCTTTGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTT TCTTCCTCCTCACATGGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCA CACCACACGCACACTCCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTC ATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCC TTGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTC CTTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGT TTGCCTTGGGAGTCTCAAGCTGGACTGCCA
81	OPA1-ND1-3'UTR	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCAATGGCAT TCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCCAACGTTG TAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAAGAGCCCC TAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTCACCATCG CTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTAGGCCTCC TATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGGGCATCAA ACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATATGAAGTCA CCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCCACCCTTA TCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATGTGGTTTA TCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCCGAACTAG TCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCCGAATACA CAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATATGACGCAC TCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCCCTGTTCT TATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTATGGAAAA ACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACAATCTCCA GCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGC GAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATA AACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATG CTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTT TGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACAT GGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACT CCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTG TAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAG GGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCA ATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCT CAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTC CAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCT TCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGT ACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCT GTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATT CCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTC CACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGG CCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCAC GGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCA GTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACAT TTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTT TGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCAT AGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT

SEQ	Description	Sequence
82	OPA1-ND1-3'UTR*	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGGCCAACCTCCTACTCCTCATTGTACCCATTCTAATCGCAATGGCAT TCCTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCCAACGTTG TAGGCCCCTACGGGCTACTACAACCCTTCGCTGACGCCATAAAACTCTTCACCAAAGAGCCCC TAAAACCCGCCACATCTACCATCACCCTCTACATCACCGCCCCGACCTTAGCTCTCACCATCG CTCTTCTACTATGGACCCCCCTCCCCATGCCCAACCCCCTGGTCAACCTCAACCTAGGCCTCC TATTTATTCTAGCCACCTCTAGCCTAGCCGTTTACTCAATCCTCTGGTCAGGGTGGGCATCAA ACTCAAACTACGCCCTGATCGGCGCACTGCGAGCAGTAGCCCAAACAATCTCATATGAAGTCA CCCTAGCCATCATTCTACTATCAACATTACTAATGAGTGGCTCCTTTAACCTCTCCACCCTTA TCACAACACAAGAACACCTCTGGTTACTCCTGCCATCATGGCCCTTGGCCATGATGTGGTTTA TCTCCACACTAGCAGAGACCAACCGAACCCCCTTCGACCTTGCCGAAGGGGAGTCCGAACTAG TCTCAGGCTTCAACATCGAATACGCCGCAGGCCCCTTCGCCCTATTCTTCATGGCCGAATACA CAAACATTATTATGATGAACACCCTCACCACTACAATCTTCCTAGGAACAACATATGACGCAC TCTCCCCTGAACTCTACACAACATATTTTGTCACCAAGACCCTACTTCTAACCTCCCTGTTCT TATGGATTCGAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCCTATGGAAAA ACTTCCTACCACTCACCCTAGCATTACTTATGTGGTATGTCTCCATGCCCATTACAATCTCCA GCATTCCCCCTCAAACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGC GAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATA AACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATG CTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTT TGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACAT GGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACT CCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTG TAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAG GGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCA ATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCT CAAGCTGGACTGCCA
83	OPA1-opt_ND1-3'UTR	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCCATGGCCT TCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCCAACGTGG TGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAGGAGCCCC TGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTGACCATCG CCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTGGGCCTGC TGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGGGCCAGCA ACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTACGAGGTGA CCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGCACCCTGA TCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATGTGGTTCA TCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGCGAGCTGG TGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCCGAGTACA CCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTACGACGCCC TGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGCCTGTTCC TGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTGTGGAAGA ACTTCCTGCCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACCATCAGCA GCATCCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGC GAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATA AACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATG CTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTT TGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACAT GGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACT CCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTG TAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAG

SEQ	Description	Sequence
		GGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCA ATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCT CAAGCTGGACTGCCAGCCCCTGTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTC CAAGGAGTCACAGGCATCTTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCT TCTAAAAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGT ACCTCTGGAGTCACTACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCT GTATTGAGAAGGGAAGTTAGGAAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATT CCTGTCCCTTGGGTGAAAAATACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTC CACATGTGCAATGGCTTTAAGAGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTACCTGTGG CCAGGTGTGGTCTCGGTTACCAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCAC GGGTCTACAGAGTCCCATCTGCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCGATTACTCA GTCTCCCAGGGCACTACTGGTCCGTAGGATTCGATTGGTCGGGGTAGGAGAGTTAAACAACAT TTAAACAGAGTTCTCTCAAAAATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTT TGCACTTATCTGAAATCTTCCCTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCAT AGGAATGTCTGGAAAAAGCTTCTACAACTTGTTACAGCCTTCACATTTGTAGAAGCTTT
84	OPA1-opt_ND1-3'UTR*	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTGTTTCCGTGACGGACTGAGTACGGGTGCCTGT CAGGCTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCCTCGGCCGCGGCTCTGTGCCCTTGCT GCTGAGGGCCACTTCCTGGGTCATTCCTGGACCGGGAGCCGGGCTGGGGCTCACACGGGGGCT CCCGCGTGGCCGTCTCGGCGCCTGCGTGACCTCCCCGCCGGCGGGATGTGGCGACTACGTCGG GCCGCTGTGGCCTGATGGCCAACCTGCTGCTGCTGATCGTGCCCATCCTGATCGCCATGGCCT TCCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCCAACGTGG TGGGCCCCTACGGCCTGCTGCAGCCCTTCGCCGACGCCATCAAGCTGTTCACCAAGGAGCCCC TGAAGCCCGCCACCAGCACCATCACCCTGTACATCACCGCCCCCACCCTGGCCCTGACCATCG CCCTGCTGCTGTGGACCCCCCTGCCCATGCCCAACCCCCTGGTGAACCTGAACCTGGGCCTGC TGTTCATCCTGGCCACCAGCAGCCTGGCCGTGTACAGCATCCTGTGGAGCGGCTGGGCCAGCA ACAGCAACTACGCCCTGATCGGCGCCCTGCGCGCCGTGGCCCAGACCATCAGCTACGAGGTGA CCCTGGCCATCATCCTGCTGAGCACCCTGCTGATGAGCGGCAGCTTCAACCTGAGCACCCTGA TCACCACCCAGGAGCACCTGTGGCTGCTGCTGCCCAGCTGGCCCCTGGCCATGATGTGGTTCA TCAGCACCCTGGCCGAGACCAACCGCACCCCCTTCGACCTGGCCGAGGGCGAGAGCGAGCTGG TGAGCGGCTTCAACATCGAGTACGCCGCCGGCCCCTTCGCCCTGTTCTTCATGGCCGAGTACA CCAACATCATCATGATGAACACCCTGACCACCACCATCTTCCTGGGCACCACCTACGACGCCC TGAGCCCCGAGCTGTACACCACCTACTTCGTGACCAAGACCCTGCTGCTGACCAGCCTGTTCC TGTGGATCCGCACCGCCTACCCCCGCTTCCGCTACGACCAGCTGATGCACCTGCTGTGGAAGA ACTTCCTGCCCCTGACCCTGGCCCTGCTGATGTGGTACGTGAGCATGCCCATCACCATCAGCA GCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGC GAGCATGTTGTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATA AACGAATTCGGTGCTCAGTGATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATG CTCCCCAAATAAGAAATGCATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTT TGAGGGTCTTTTATACATCTCTCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACAT GGGGGTACACATACACAGCTTCCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACT CCACATGCCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTG TAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACCCCCTTCCTTGTGACTGAGCCAG GGCCTGCATTTTTGGTTTTCCCCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCA ATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCT CAAGCTGGACTGCCA
85	β-actin-S primer	CGAGATCGTGCGGGACAT
86	β-actin-A primer	CAGGAAGGAGGGCTGGAAC
87	ND4-S primer	CTGCCTACGACAAACAGAC
88	ND4-A primer	AGTGCGTTCGTAGTTTGAG
89	ND6-F primer	ATGATGTATGCTTTGTTTCTG
90	ND6-R primer	CTAATTCCCCCGAGCAATCTC

SEQ	Description	Sequence
91	ND6-S primer	AGTGTGGGTTTAGTAATG
92	ND6-A primer	TGCCTCAGGATACTCCTC
93	β-actin-F primer	CTCCATCCTGGCCTCGCTGT
94	β-actin-R primer	GCTGTCACCTTCACCGTTCC
95	ND6-F primer	GGGTTTTCTTCTAAGCCTTCTCC
96	ND6-R primer	CCATCATACTCTTTCACCCACAG
97	opt_ND6-F primer	CGCCTGCTGACCGGCTGCGT
98	opt_ND6-R	CCAGGCCTCGGGGTACTCCT
99	ND1-F primer	ATGGCCGCATCTCCGCACACT
100	ND1-R primer	TTAGGTTTGAGGGGGAATGCT
101	ND1-F primer	AACCTCAACCTAGGCCTCCTA
102	ND1-R primer	TGGCAGGAGTAACCAGAGGTG
103	ND1-F primer	AGGAGGCTCTGTCTGGTATCTTG
104	ND1-R primer	TTTTAGGGGCTCTTTGGTGAA
105	opt-ND1-F primer	GCCGCCTGCTGACCGGCTGCGT
106	opt-ND1-R primer	TGATGTACAGGGTGATGGTGCTGG
107	ND4-S primer	GCCAACAGCAACTACGAGC
108	ND4-A primer	TGATGTTGCTCCAGCTGAAG
109	opt-ND4-S primer	GCCTGACCCTGATCCTGAAC
110	opt-ND4-A primer	GTGCGCTCGTAGTTGCTGTT
111	hsACO2	GGGCAGTGCCTCCCCGCCCCGCCGCTGGCGTCAAGTTCAGCTCCACGTGTGCCATCAGTGGAT CCGATCCGTCCAGCCATGGCTTCCTATTCCAAGATGGTGTGACCAGACATGCTTCCTGCTCCC CGCTTAGCCCACGGAGTGACTGTGGTTGTGGTGGGGGGGTTCTTAAAATAACTTTTTAGCCCC CGTCTTCCTATTTTGAGTTTGGTTCAGATCTTAAGCAGCTCCATGCAACTGTATTTATTTTTG ATGACAAGACTCCCATCTAAAGTTTTTCTCCTGCCTGATCATTTCATTGGTGGCTGAAGGATT CTAGAGAACCTTTTGTTCTTGCAAGGAAAACAAGAATCCAAAACCAGTGACTGTTCTGTGA
112	hsATP5B	GGGGTCTTTGTCCTCTGTACTGTCTCTCTCCTTGCCCCTAACCCAAAAAGCTTCATTTTTCTG TGTAGGCTGCACAAGAGCCTTGATTGAAGATATATTCTTTCTGAACAGTATTTAAGGTTTCCA ATAAAATGTACACCCCTCAG

SEQ	Description	Sequence
113	hsAK2	TGTTGGGTCCAAGAAGGAATTTCTTTCCATCCCTGTGAGGCAATGGGTGGGAATGATAGGACA GGCAAAGAGAAGCTTCCTCAGGCTAGCAAAAATATCATTTGATGTATTGATTAAAAAAGCACT TGCTTGATGTATCTTTGGCGTGTGTGCTACTCTCATCTGTGTGTATGTGTGTTGTGTGTGTGT GTGTGTGCATGCACATATGTGTTCACTCTGCTACTTTGTAAGTTTTAGGCTAGGTTGCTTTAC CAGCTGTTTACTTCTTTTTTGTTGTTGTTTTGAGACAAGGTTTCGCTCTGCCACCCTGGCTGG AGTGCAGTGGCGTGATCTTGGCTCACGGCAACCTCTGCCTCCTGGGGCTCAAGCAATTATCCC ACCTCAGCCTCCTGAGCAGCTGGGACTACAGGTGCATGCCACAACACCTGGCTGATATTTGTA TTTTTTGTAGAGACAGGATTTTGCCAAGTTGCCCAGGCTGGTCTTGAACTCCTAGGCTTAAGC AATCCACCCACCTTGGCCTCCTGAAGTGCCAGGATCACAGACGTGAGCCACTACACCCAGCCC AGCTGTTTACTTCTTTAACCATACTTTTGATTTTATTTTTTGACCAAAATGAACTAACCCAGG TAATCTTCCAGGGACCGCAATTCCAGAACCTCATAGTATTTCTTCCATTTCCAGCAGCTGATT AGAAGTCCAGGATCATGTGAAGTCAGGCAGGGTCACAGTTCCTGATGGCACATTATGGACAGA GAATTCCATTTTGTTTTCTAACCCATGATGAAAACCCACGTGAGTCAGTGTGTGAACAGGGAT CATTAATTTTTTCCCCCTAGGTGGAAGGAAAAAGGCACTTACTTTGCAGGTTACAGAAATTAC TGGGAGAGGATATCGTCATAAAAAGAGCCAGGCCAAATTGGAATATTTTTGTGATCTGCATCA TGATGCTGAAAATAGCAATTATTTGGGAATTGGGTTTGAAAACTGAATTGTTGCCAGAGAATT AAACCAGGTGAAAGGTCCTTTTGAATTCAGATTGTCTTCTGAACATCCAGGCTGATCATCTGA GAGCAGTCAAATCTACTTCCCCAAAAAGAGACCAGGGTAGGTTTATTTGCTTTTATTTTTAAT GTTTGCCTGTGTTTCCAAGTGTGAACAAAACAGTGTGTGATCTATTCTTGGATTCATTTTGAT CAGTATTTATTCAAACCCAGTCTCTCTCCAGGACATAAAACTGAAATCAGATATGTTCTTTTT AAGCCCAAACCCTCTCCTTTCTAGATCCAACCCTTCACCCCTAATTTTATGATGGCTATAGCC ATGGACTTCCCCAAGAAAAGATCACCCAGAAATAAGACCACCTGTGACAGTTACCAGCTTTTA TTCATAACCTTAGCTTCCCAACTATTGAGCATTTTCTAAGGTCCCTGCTGTCTTTTGGTCTCT GGTTTGATTTGTGGCAAACAGATGAAGTAACAGACTGCTATGAAGGACCACAAAAACGGCAGC CTCTGGAAAAACCATTAGAAAGTCAGTGGCAGATCCAGTAAATAATATCGCCAGCCTCAGCAT AATCTGCTGCTGACTCGATTCAGTGGACTCTAAAGTGCCCAGCCTCCTGACCTGAGCTCTCCT GCCATCTGTGAGACTACCAGAGGTCTTATCTGCTGTCCACATGGCAACTGGGCATGAGTACCT GGCCACCTTGCTTCCCTCTTTGCCTGGTCCAAGTGAGTGTCTGCTGCCTCTGTCCTGCCTTGT TTTCCTGGCTCTAAACCAACTCCACCCACTCTTAATGGAAACTCAGTCTGGCTTTGTGTGTTT CTGGGAAGCACATGACTTCTGGGAATGGGCAAGGAAGAGGAGTGAAACAAAAACTGTCAGCTA TGTGTGCCTGGTCTGGGATCCTTCTCTGGGTGACAGTGGCATCATGAATCTTAGAATCAGCTC CCC
114	hsALDH2	GAATCATGCAAGCTTCCTCCCTCAGCCATTGATGGAAAGTTCAGCAAGATCAGCAACAAAACC AAGAAAAATGATCCTTGCGTGCTGAATATCTGAAAAGAGAAATTTTTCCTACAAAATCTCTTG GGTCAAGAAAGTTCTAGAATTTGAATTGATAAACATGGTGGGTTGGCTGAGGGTAAGAGTATA TGAGGAACCTTTTAAACGACAACAATACTGCTAGCTTTCAGGATGATTTTTAAAAAATAGATT CAAATGTGTTATCCTCTCTCTGAAACGCTTCCTATAACTCGAGTTTATAGGGGAAGAAAAAGC TATTGTTTACAATTATATCACCATTAAGGCAACTGCTACACCCTGCTTTGTATTCTGGGCTAA GATTCATTAAAAACTAGCTGCTCTTAACTTACA
115	hsCOX10	GAGCACTGGGACGCCCACCGCCCCTTTCCCTCCGCTGCCAGGCGAGCATGTTGTGGTAATTCT CGAACACAAGAAGAGAAATTGCTGGGTTTAGAACAAGATTATAAACGAATTCGGTGCTCAGTG ATCACTTGACAGTTTTTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCA TCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTTCCCTTTGAGGGTCTTTATACATCTC TCCTCCAACCCCACCCTCTATTCTGTTTCTTCCTCCTCACATGGGGGTACACATACACAGCTT CCTCTTTTGGTTCCATCCTTACCACCACACCACACGCACACTCCACATGCCCAGCAGAGTGGC ACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTCTGTAGTTCTGTGAGCTCAGGTCC CTCAAAGGCCTCGGAGCACCCCCTTCCTGGTGACTGAGCCAGGGCCTGCATTTTTGGTTTTCC CCACCCCACACATTCTCAACCATAGTCCTTCTAACAATACCAATAGCTAGGACCCGGCTGCTG TGCACTGGGACTGGGGATTCCACATGTTTGCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCCT GTCCTCCCTTCACCCCCATTGCGTATGAGCATTTCAGAACTCCAAGGAGTCACAGGCATCTTT ATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTTCCTTCTAAAAGGGTAGCCCTGGAC TTAATACCAGCCGGATACCTCTGGCCCCCACCCCATTACTGTACCTCTGGAGTCACTACTGTG GGTCGCCACTCCTCTGCTACACAGCACGGCTTTTTCAAGGCTGTATTGAGAAGGGAAGTTAGG AAGAAGGGTGTGCTGGGCTAACCAGCCCACAGAGCTCACATTCCTGTCCCTTGGGTGAAAAAT ACATGTCCATCCTGATATCTCCTGAATTCAGAAATTAGCCTCCACATGTGCAATGGCTTTAAG AGCCAGAAGCAGGGTTCTGGGAATTTTGCAAGTTATCCTGTGGCCAGGTGTGGTCTCGGTTAC CAAATACGGTTACCTGCAGCTTTTTAGTCCTTTGTGCTCCCACGGGTCTGCAGAGTCCCATCT

SEQ	Description	Sequence
		GCCCAAAGGTCTTGAAGCTTGACAGGATGTTTTCATTACTCAGTCTCCCAGGGCACTGCTGGT CCGTAGGGATTCATTGGTCGGGGTGGGAGAGTTAAACAACATTTAAACAGAGTTCTCTCAAAA ATGTCTAAAGGGATTGTAGGTAGATAACATCCAATCACTGTTTGCACTTATCTGAAATCTTCC CTCTTGGCTGCCCCCAGGTATTTACTGTGGAGAACATTGCATAGGAATGTCTGGAAAAAGCCT CTACAACTTGTTACAGCCTTCACATTTGTACAATTCATTGATTCTCTTTTCCTTCCACAATAA AATGGTATACAAGAAC
116	hsUQCRFS 1	GAGACTTGGACTCAAGTCATAGGCTTCTTTCAGTCTTTATGTCACCTCAGGAGACTTATTTGA GAGGAAGCCTTCTGTACTTGAAGTTGATTTGAAATATGTAAGAATTGATGATGTATTTGCAAA CATTAATGTGAAATAAATTGAATTTAATGTTGAATACTTTCAGGCATTCACTTAATAAAGACA CTGTTAAGCACTGTTATGCTCAGTCATACACGCGAAAGGTACAATGTCTTTTAGCTAATTCTA ATTAAAAATTACAGACTGGTGTACAAGATACTTGTG
117	hsNDUFV1	CCCACCACCCTGGCCTGCTGTCCTGCGTCTATCCATGTGGAATGCTGGACAATAAAGCGAGTG CTGCCCACCCTCCAGCTGCC
118	hsNDUFV2	TTTATATTGAACTGTAAATATGTCACTAGAGAAATAAAATATGGACTTCCAATCTACGTAAAC TTA
119	hsSOD2	ACCACGATCGTTATGCTGAGTATGTTAAGCTCTTTATGACTGTTTTTGTAGTGGTATAGAGTA CTGCAGAATACAGTAAGCTGCTCTATTGTAGCATTTCTTGATGTTGCTTAGTCACTTATTTCA TAAACAACTTAATGTTCTGAATAATTTCTTACTAAACATTTTGTTATTGGGCAAGTGATTGAA AATAGTAAATGCTTTGTGTGATTGA
120	hsCOX6c	TCTTGGAATATAAAGAATTTCTTCAGGTTGAATTACCTAGAAGTTTGTCACTGACTTGTGTTC CTGAACTATGACACATGAATATGTGGGCTAAGAAATAGTTCCTCTTGATAAATAAACAATTAA CAAATACTTTGGACAGTAAGTCTTTCTCAGTTCTTAATGATAATGCAGGGCACTTACTAGCAT AAGAATTGGTTTGGGATTTAACTGTTTATGAAGCTAACTTGATTTCCGTGTTTTGTTAAAATT TCATTGTTCTAGCACATCTTTAACTGTGATAGTT
121	hsIRP1	GAGACGTGCACTTGGTCGTGCGCCCAGGGAGGAAGCCGCACCACCAGCCAGCGCAGGCCCTGG TGGAGAGGCCTCCCTGGCTGCCTCTGGGAGGGGTGCTGCCTTGTAGATGGAGCAAGTGAGCAC TGAGGGTCTGGTGCCAATCCTGTAGGCACAAAACCAGAAGTTTCTACATTCTCTATTTTTGTT AATCATCTTCTCTTTTTCCAGAATTTGGAAGCTAGAATGGTGGGAATGTCAGTAGTGCCAGAA AGAGAGAACCAAGCTTGTCTTTAAAGTTACTGATCACAGGACGTTGCTTTTTCACTGTTTCCT ATTAATCTTCAGCTGAACACAAGCAAACCTTCTCAGGAGGTGTCTCCTACCCTCTTATTGTTC CTCTTACGCTCTGCTCAATGAAACCTTCCTCTTGAGGGTCATTTTCCTTTCTGTATTAATTAT ACCAGTGTTAAGTGACATAGATAAGAACTTTGCACACTTCAAATCAGAGCAGTGATTCTCTCT TCTCTCCCCTTTTCCTTCAGAGTGAATCATCCAGACTCCTCATGGATAGGTCGGGTGTTAAAG TTGTTTTGATTATGTACCTTTTGATAGATCCACATAAAAAGAAATGTGAAGTTTTCTTTTACT ATCTTTTCATTTATCAAGCAGAGACCTTTGTTGGGAGGCGGTTTGGGAGAACACATTTCTAAT TTGAATGAAATGAAATCTATTTTCAGTG
122	hsMRPS12	CAGAAGAAGTGACGGCTGGGGGCACAGTGGGCTGGGCGCCCCTGCAGAACATGAACCTTCCGC TCCTGGCTGCCACAGGGTCCTCCGATGCTGGCCTTTGCGCCTCTAGAGGCAGCCACTCATGGA TTCAAGTCCTGGCTCCGCCTCTTCCATCAGGACCACT
123	hsATP5J2	AGAGGACACACTCTGCACCCCCCCCACCCCACGACCTTGGCCCGAGCCCCTCCGTGAGGAA
124	rnSOD2	AGCCCTTCCGCCAGGCTGTGTGTCAGGCCCGTGGTGGGTGTTTTGTAGTAGTGTAGAGCATTG CA
125	hsOXA1L	CTTATGTTCTGTGCGCATTCTGGCAGGAATTCTGTCTCTTCAGAGACTCATCCTCAAAACAAG ACTTGACACTGTGTCCTTGCCCCAGTCCTAGGAACTGTGGCACACAGAGATGTTCATTTTAAA AACGGATTTCATGAAACACTCTTGTACTTATGTTTATAAGAGAGCACTGGGTAGCCAAGTGAT CTTCCCATTCACAGAGTTAGTAAACCTCTGTACTACATGCTG
126	MTS-COX10	MAASPHTLSSRLLTGCVGGSVWYLEBBT
127	MTS-COX8	MSVLTRLLLRGLTRLGSAAPVRRARIHSL
128	MTS-OPA1	MWRLRRAAVA
129	hsCOX10	MAASPHTLSSRLLTGCVGGSVWYLEBBT
130	scRPM2	MAFKSFIYSKGYHRSAAQKKTATSFFDSSYQYLRQNQGLVNSDFVLHASHLHPHPVVVANVNY NNVDDILHPHDLDSSINNTNNPLTHEELLYNQNVSLRSLKQQQSTNYVNNNNNNQHRYY

SEQ	Description	Sequence
131	lcSirt5	MRKRSLRCHLWSANASLSPRKDEVTSRKESENLVKGKKNKKSHLHLLLFTASKIGTDSVFDVQ KSKECCKELGLLFTSLIHSIGSFPFDEEPKAAAVFLPGSLPQLTVLVLAPGSGSCPTGKSTPH LAASGRNAELLRPQNSMIVRQFTCRGTISSHLCAHLRKPHDSRNMARP
132	tbNDUS7	MLRRTSFNFTGRAMISRGSPEWSHRLDLKKGKKTTMMHKLGTSKPNNALQYAQMTL
133	ncQCR2	MISRSALSRGSQLALRRPAAAKTAQRGFAAAAASPAASYEPTTIAG
134	hsATP5G2	MFELILYVAITLSVAERLVGPGHACAEPSFRSSRCSAPLCLLCSGSSSPATAPHPLKMFACSK FVSTPSLVKSTSQLLSRPLSAVVLKRPEILTDESLSSLAVSCPLTSLVSSRSFQTSAISRDID TA
135	hsLACTB	MYRLMSAVTARAAAPGGLASSCGRRGVHQRAGLPPLGHGWVGGLGLGLGLALGVKLAGGLRGA APAQSPAAPDPEASPLAEPPQEQSLAPWSPQTPAPPCSRCFARAIESSRDLL
136	spilv1	MTVLAPLRRLHTRAAFSSYGREIALQKRFLNLNSCSAVRRYGTGFSNNLPIKKLKNAFGVVRA NSTKSTSTVTTASPIKYDSSFVGKTGGEIFHDMMLKHNVKHVFGYPGGAILPVFDAIYRSPHF EFILPRHEQAAGHA
137	gmCOX2	MILCPLEAFIVQHILTISVMGLLSCFRSTVLRKCSKGSSGMSRFLYTNNFQRNLISSGGNESY YGYFNRRSYTSLYMGTGTVGGITSAPIRVPNVGCEGFMCSSHLSITQRNSRLIHSTSKIVPN
138	crATP6	MALQQAAPRVFGLLGRAPVALGQSGILTGSSGFKNQGFNGSLQSVENHVYAQAFSTSSQEEQA APSIQGASGMKLPGMAGSMLLGKSRSGLRTGSMVPFAAQQAMNM
139	hsOPA1	MWRLRRAAVACEVCQSLVKHSSGIKGSLPLQKLHLVSRSIYHSHHPTLKLQRPQLRTSFQQFS SLTNLPLRKLKFSPIKYGYQPRRN
140	hsSDHD	MAVLWRLSAVCGALGGRALLLRTPVVRPAHISAFLQDRPIPEWCGVQHIHLSPSHH
141	hsADCK3	MAAILGDTIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDK HEEYFAENFGGPEGEFHFSVPHAAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYVASGPFR EAGFPGQASSPLGRANGRLFANPRDSFSAMGFQRRF
142	osP0644B06_24-2	MALLLRHSPKLPPAHAILGCERGTVVRHFSSSTCSSLVKEDTVSSSNLHPEYAKKIGGSDFSH DRQSGKELQNFKVSPQEASRASNFMRASKYGMPITANGVHSLFSCGQVVPSRCF
143	Neurospora crassa ATP9 (ncATP9)	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTRQAFQ KPA
144	hsGHITM	MLAARLVCLRTLPSRVFHPAFTKASPVVKNSITKNQWLLTPSRE
145	hsNDUFAB1	MASRVLSAYVSRLPAAFAPLPRVRMLAVARPLSTALCSAGTQTRLGTLQPALVLAQVPGRVTQ LCRQY
146	hsATP5G3	MFACAKLACTPSLIRAGSRVAYRPISASVLSRPEASRTGEGSTVFNGAQNGVSQLIQREFQTS AISR
147	crATP6_hsADCK3	MALQQAAPRVFGLLGRAPVALGQSGILTGSSGFKNQGFNGSLQSVENHVYAQAFSTSSQEEQA APSIQGASGMKLPGMAGSMLLGKSRSGLRTGSMVPFAAQQAMNMGGMAAILGDTIMVAKGLVK LTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDKHEEYFAENFGGPEGEFH FSVPHAAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYVASGPFREAGFPGQASSPLGRANG RLFANPRDSFSAMGFQRRFGG
148	ncATP9_ncATP9	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTRQAFQ KRAMASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTRQ AFQKRA
149	zmLOC100282174	MALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRCPPL PASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPY
150	ncATP9_zmLOC100282174_spilv1_ncATP9	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTRQAFQ KRAMALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRC PPLPASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMTVL APLRRLHTRAAFSSYGREIALQKRFLNLNSCSAVRRYGTGFSNNLPIKKLKNAFGVVRANSTK STSTVTTASPIKYDSSFVGKTGGEIFHDMMLKHNVKHVFGYPGGAILPVFDAIYRSPHFEFIL PPHEQAAGHAMASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSI VNATTRQAFQKRA
151	zmLOC100282174_hsADCK3_crATP6_hsATP5G3	MALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRCPPL PASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMAAILGD TIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDKHEEYFAE NFGGPEGEFHFSVPHAAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYVASGPFREAGFPGQ ASSPLGRANGRLFANPRDSFSAMGFQRRFMALQQAAPRVFGLLGRAPVALGQSGILTGSSGFK

SEQ	Description	Sequence
		NQGFNGSLQSVENHVYAQAFSTSSQEEQAAPSIQGASGMKLPGMAGSMLLGKSRSGLRTGSMV PFAAQQAMNMMFACAKLACTPSLIRAGSRVAYRPISASVLSRPEASRTGEGSTVFNGAQNGVS QLIQREFQTSAISR
152	zmLOC100 282174_hsA DCK3_hsA TP5G3	MALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRCPPL PASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMAAILGD TIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDKHEEYFAE NFGGPEGEFHFSVPHAAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYVASGPFREAGFPGQ ASSPLGRANGRLFANPRDSFSAMGFQRRFMFACAKLACTPSLIRAGSRVAYRPISASVLSRPE ASRTGEGSTVFNGAQNGVSQLIQREFQTSAISR
153	ncATP9_zm LOC100282 174	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTRQAFQ KRAMALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRC PPLPASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPY
154	hsADCK3_z mLOC1002 82174_crAT P6 _hsATP5G3	MAAILGDTIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDK HEEYFAENFGGPEGEFHFSVPHAAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYVASGPFR EAGFPGQASSPLGRANGRLFANPRDSFSAMGFQRRFMALLRAAVSELRRRGRGALTPLPALSS LLSSLSPRSPASTRPEPNNPHADRRHVIALRRCPPLPASAVLAPELLHARGLLPRHWSHASPL STSSSSSRPADKAQLTWVDKWIPEAARPYMALQQAAPRVFGLLGRAPVALGQSGILTGSSGFK NQGFNGSLQSVENHVYAQAFSTSSQEEQAAPSIQGASGMKLPGMAGSMLLGKSRSGLRTGSMV PFAAQQAMNMMFACAKLACTPSLIRAGSRVAYRPISASVLSRPEASRTGEGSTVFNGAQNGVS QLIQREFQTSAISR
155	crATP6 _hsADCK3 _zmLOC10 0282174_hs ATP5G3	MALQQAAPRVFGLLGRAPVALGQSGILTGSSGFKNQGFNGSLQSVENHVYAQAFSTSSQEEQA APSIQGASGMKLPGMAGSMLLGKSRSGLRTGSMVPFAAQQAMNMMAAILGDTIMVAKGLVKLT QAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDKHEEYFAENFGGPEGEFHFS VPHAAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYVASGPFREAGFPGQASSPLGRANGRL FANPRDSFSAMGFQRRFMALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPNN PHADRRHVIALRRCPFLPASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVD KWIPEAARPYMFACAKLACTPSLIRAGSRVAYRPISASVLSRPEASRTGEGSTVFNGAQNGVS QLIQREFQTSAISR
156	hsADCK3_z mLOC1002 82174	MAAILGDTIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDK HEEYFAENFGGPEGEFHFSVPHAAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYVASGPFR EAGFPGQASSPLGRANGRLFANPRDSFSAMGFQRRFGGMALLRAAVSELRRRGRGALTPLPAL SSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRCPPLPASAVLAPELLHARGLLPRHWSHAS PLSTSSSSSRPADKAQLTWVDKWIPEAARPYGG
157	hsADCK3_z mLOC1002 82174_crAT P6	MAAILGDTIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDK HEEYFAENFGGPEGEFHFSVPHAAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYVASGPFR EAGFPGQASSPLGRANGRLFANPRDSFSAMGFQRRFGGMALLRAAVSELRRRGRGALTPLPAL SSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRCPPLPASAVLAPELLHARGLLPRHWSHAS PLSTSSSSSRPADKAQLTWVDKWIPEAARPYGGMALQQAAPRVFGLLGRAPVALGQSGILTGS SGFKNQGFNGSLQSVENHVYAQAFSTSSQEEQAAPSIQGASGMKLPGMAGSMLLGKSRSGLRT GSMVPFAAQQAMNMGG
158	ncATP9_zm LOC100282 174_spilv1_ GNFP_ncA TP9	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTRQAFQ KRAMALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRC PPLPASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMTVL APLPRLHTRAAFSSYGREIALQKRFLNLNSCSAVRRYGTGFSNNLRIKKLKNAFGVVPANSTK STSTVTTASPIKYDSSFVGKTGGEIFHDMMLKHNVKHVFGYPGGAILPVFDAIYRSPHFEFIL PRHEQAAGHAVSGEGDATYGKLTLKFICTTGKLPVPWPTLVTTLTYGVQCFSRYPDHMKQHDF FKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYN SHNVYIMADKQKNGIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSK DPNEMASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTR QAFQKRA
159	ncATP9_zm LOC100282 174_spilv1_ lcSirt5_osP0 644B06.24-	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTRQAFQ KRAMALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPNNPHADRRHVIALRRC PPLPASAVLAPELLRARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMTVL APLRRLHTRAAFSSYGREIALQKRFLNLNSCSAVRRYGTGFSNNLRIKKLKNAFGVVRANSTK STSTVTTASPIKYDSSFVGKTGGEIFHDMMLKHNVKHVFGYPGGAILPVFDAIYRSPHFEFIL PRHEQAAGHAMRKRSLRCHLWSANASLSPRKDEVTSRKESENLVKGKRNKKSHLHLLLLFTASK

SEQ	Description	Sequence
	2_hsATP5G2_ncATP9	IGTDSVFDVQKSKECCKELGLLFTSLIHSIGSFPFDEEPKAAAVFLPGSLFQLTVLVLAPGSG SCPTGKSTPHLAASGRNAELLRPQNSMIVRQFTCRGTISSHLCAHLRKPHDSRNMARPMALLL RHSPKLRRAHAILGCERGTVVRHFSSSTCSSLVKEDTVSSSNLHPEYAKKIGGSDFSHDRQSG KELQNFKVSPQEASRASNFMRASKYGMPITANGVHSLFSCGQVVPSRCFMPELILYVAITTLSV AERLVGPGHACAEPSFRSSRCSAPLCLLCSGSSSPATAPHPLKMFACSKFVSTPSLVKSTSQL LSRPLSAVVLKPPEILTDESLSSLAVSCPLTSLVSSRSFQTSAISRDIDTAMASTRVLASRLA SQMAASAKVARPAVRVAQVSKRTIQTGSPLQTLKRTQMTSIVNATTRQAFQKRA
160	ND4	MLKLIVPTIMLLPLTWLSKKHMIWINTTTHSLIISIIPLLFFNQINNNLFSCSPTFSSDPLTT PLLMLTTWLLPLTIMASQRHLSSEPLSRKKLYLSMLISLQISLIMTFTATELIMFYIFFETTL IPTLAIITRWGNQPERLNAGTYFLFYTLVGSLPLLIALIYTHNTLGSLNILLLTLTAQELSNS WANNLMWLAYTMAFMVKMPLYGLHLWLPKAHVEAPIAGSMVLAAVLLKLGGYGMMRLTLILNP LTKHMAYPFLVLSLWGMIMTSSICLRQTDLKSLIAYSSISHMALVVTAILIQTPWSFTGAVIL MIAHGLTSSLLFCLANSNYERTHSRIMILSQGLQTLLPLMAFWWLLASLANLALPPTINLLGE LSVLVTTFSWSNITLLLTGLNMLVTALYSLYMFTTTQWGSLTHHINNMKPSFTRENTLMFMHL SPILLLSLNPDIITGFSS
161	ND6	MMYALFLLSVGLVMGFVGFSSKPSPIYGGLVLIVSGVVGCVIILNFGGGYMGLMVFLIYLGGM MVVFGYTTAMAIEEYPEAWGSGVEVLVSVLVGLAMEVGLVLWVKEYDGVVVVVNFNSVGSWMI YEGEGSGLIREDPIGAGALYDYGRWLVVVTGWTLFVGVYIVIEIARGN
162	ND1	MANLLLLIVPILIAMAFLMLTERKILGYMQLRKGPNVVGPYGLLQPFADAIKLFTKEPLKPAT STITLYITAPTLALTIALLLWTPLPMPNPLVNLNLGLLFILATSSLAVYSILWSGWASNSNYA LIGALRAVAQTISYEVTLAIILLSTLLMSGSFNLSTLITTQEHLWLLLPSWPLAMMWFISTLA ETNRTPFDLAEGESELVSGFNIEYAAGPFALFFMAEYTNIIMMNTLTTTIFLGTTYDALSPEL YTTYFVTKTLLLTSLFLWIRTAYPRFRYDQLMHLLWKNFLPLTLALLMWYVSMPITISSIPPQ T
163	GFP-F	ACAAGTTCAGCGTGTCCG
164	GFP-R	CTCGTTGGGGTCTTTGCT
165	ND4-F	ATCTCCGCACACTCTCTCCTCA
166	ND4-R	TAGGTTGTTGTTGATTTGGTT
167	B-actin-F2	CCTAGAAGCATTTGCGGT
168	B-actin-R2	GAGCTACGAGCTGCCTGA

Adeno-associated virus (AAV)

[0098] Adeno-associated virus (AAV) is a small virus that infects humans and some other primate species. The compositions disclosed herein comprises firstly an adeno-associated virus (AAV) genome or a derivative thereof.

[0099] An AAV genome is a polynucleotide sequence which encodes functions needed for production of an AAV viral particle. These functions include those operating in the replication and packaging cycle for AAV in a host cell, including encapsidation of the AAV genome into an AAV viral particle. Naturally occurring AAV viruses are replication-deficient and rely on the provision of helper functions in trans for completion of a replication and packaging cycle. Accordingly, the AAV genome of the vector of the invention is typically replication-deficient.

[0100] The AAV genome can be in single-stranded form, either positive or negative-sense, or alternatively in double-stranded form. The use of a double-stranded form allows bypass of the DNA replication step in the target cell and so can accelerate transgene expression.

[0101] The AAV genome may be from any naturally derived serotype or isolate or Glade of AAV. Thus, the AAV genome may be the full genome of a naturally occurring AAV virus. As is known to the skilled person, AAV viruses occurring in nature may be classified according to various biological systems.

[0102] Commonly, AAV viruses are referred to in terms of their serotype. A serotype corresponds to a variant subspecies of AAV which owing to its profile of expression of capsid surface antigens has a distinctive reactivity which can be used to distinguish it from other variant subspecies. Typically, a virus having a particular AAV serotype does not efficiently cross-react with neutralising antibodies specific for any other AAV serotype. AAV serotypes include AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, and AAV16, also recombinant serotypes, such as Rec2 and Rec3, recently identified from primate brain.

[0103] A preferred serotype of AAV for use in the invention is AAV2. Other serotypes of particular interest for use in the invention include AAV4, AAV5 and AAV8 which efficiently transduce tissue in the eye, such as the retinal pigmented epithelium. The serotype of AAV which is used can be an AAV serotype which is not AAV4. Reviews of AAV serotypes may be found in Choi et al (Curr Gene Ther. 2005; 5(3); 299-310) and Wu et al (Molecular Therapy. 2006; 14(3), 316-327). The sequences of AAV genomes or of elements of AAV genomes including ITR sequences, rep or cap genes for use in the invention may be derived from the following accession numbers for AAV whole genome sequences: Adeno-associated virus 1 NC_002077, AF063497; Adeno-associated virus 2 NC_001401; Adeno-associated virus 3 NC_001729; Adeno-associated virus 3B NC_001863; Adeno-associated virus 4 NC_001829; Adeno-associated virus 5 Y18065, AF085716; Adeno-associated virus 6 NC_001862; Avian AAV ATCC VR-865 AY186198, AY629583, NC_004828; Avian AAV strain DA-1 NC_006263, AY629583; Bovine AAV NC_005889, AY388617.

[0104] AAV viruses may also be referred to in terms of clades or clones. This refers to the phylogenetic relationship of naturally derived AAV viruses, and typically to a phylogenetic group of AAV viruses which can be traced back to a common ancestor, and includes all descendants thereof. Additionally, AAV viruses may be referred to in terms of a specific isolate, i.e. a genetic isolate of a specific AAV virus found in nature. The term genetic isolate describes a population of AAV viruses

which has undergone limited genetic mixing with other naturally occurring AAV viruses, thereby defining a recognizably distinct population at a genetic level.

[0105] Examples of clades and isolates of AAV that may be used in the invention include: Clade A: AAV1 NC_002077, AF063497, AAV6 NC_001862, Hu. 48 AY530611, Hu 43 AY530606, Hu 44 AY530607, Hu 46 AY530609; Clade B: Hu. 19 AY530584, Hu. 20 AY530586, Hu 23 AY530589, Hu22 AY530588, Hu24 AY530590, Hu21 AY530587, Hu27 AY530592, Hu28 AY530593, Hu 29 AY530594, Hu63 AY530624, Hu64 AY530625, Hu13 AY530578, Hu56 AY530618, Hu57 AY530619, Hu49 AY530612, Hu58 AY530620, Hu34 AY530598, Hu35 AY530599, AAV2 NC_001401, Hu45 AY530608, Hu47 AY530610, Hu51 AY530613, Hu52 AY530614, Hu T41 AY695378, Hu S17 AY695376, Hu T88 AY695375, Hu T71 AY695374, Hu T70 AY695373, Hu T40 AY695372, Hu T32 AY695371, Hu T17 AY695370, Hu LG15 AY695377; Clade C: Hu9 AY530629, Hu10 AY530576, Hu11 AY530577, Hu53 AY530615, Hu55 AY530617, Hu54 AY530616, Hu7 AY530628, Hu18 AY530583, Hu15 AY530580, Hu16 AY530581, Hu25 AY530591, Hu60 AY530622, Ch5 AY243021, Hu3 AY530595, Hu1 AY530575, Hu4 AY530602 Hu2, AY530585, Hu61 AY530623; Clade D: Rh62 AY530573, Rh48 AY530561, Rh54 AY530567, Rh55 AY530568, Cy2 AY243020, AAV7 AF513851, Rh35 AY243000, Rh37 AY242998, Rh36 AY242999, Cy6 AY243016, Cy4 AY243018, Cy3 AY243019, Cy5 AY243017, Rh13 AY243013; Clade E: Rh38 AY530558, Hu66 AY530626, Hu42 AY530605, Hu67 AY530627, Hu40 AY530603, Hu41 AY530604, Hu37 AY530600, Rh40 AY530559, Rh2 AY243007, Bb1 AY243023, Bb2 AY243022, Rh10 AY243015, Hu17 AY530582, Hu6 AY530621, Rh25 AY530557, Pi2 AY530554, Pi1 AY530553, Pi3 AY530555, Rh57 AY530569, Rh50 AY530563, Rh49 AY530562, Hu39 AY530601, Rh58 AY530570, Rh61 AY530572, Rh52 AY530565, Rh53 AY530566, Rh51 AY530564, Rh64 AY530574, Rh43 AY530560, AAV8 AF513852, Rh8 AY242997, Rh1 AY530556; Clade F: Hu14 (AAV9) AY530579, Hu31 AY530596, Hu32 AY530597, Clonal Isolate AAV5 Y18065, AF085716, AAV 3 NC_001729, AAV 3B NC_001863, AAV4 NC_001829, Rh34 AY243001, Rh33 AY243002, Rh32 AY243003.

[0106] The skilled person can select an appropriate serotype, Glade, clone or isolate of AAV for use in the present invention on the basis of their common general knowledge. For instance, the AAV5 capsid has been shown to transduce primate cone photoreceptors efficiently as evidenced by the successful correction of an inherited color vision defect (Mancuso et al., Nature 2009, 461:784-7).

[0107] It should be understood however that the invention also encompasses use of an AAV genome of other serotypes that may not yet have been identified or characterized. The AAV serotype determines the tissue specificity of infection (or tropism) of an AAV virus. Accordingly, preferred AAV serotypes for use in AAV viruses administered to patients in accordance with the invention are those which have natural tropism for or a high efficiency of infection of target cells within eye in LHON. Thus, AAV serotypes for use in AAV viruses administered to patients can be ones which infect cells of the neurosensory retina and retinal pigment epithelium.

[0108] Typically, the AAV genome of a naturally derived serotype or isolate or Glade of AAV comprises at least one inverted terminal repeat sequence (ITR). An ITR sequence acts in cis to provide a functional origin of replication, and allows for integration and excision of the vector from the genome of a cell. In preferred embodiments, one or more ITR sequences flank the polynucleotide sequence encoding ND4, ND6, or ND1 or a variant thereof. Preferred ITR sequences are those of AAV2, and variants thereof. The AAV genome typically also comprises packaging genes, such as rep and/or cap genes which encode packaging functions for an AAV viral particle. The rep gene encodes one or more of the proteins Rep78, Rep68, Rep52 and Rep40 or variants thereof. The cap gene encodes one or more capsid proteins such as VP1, VP2 and VP3 or variants thereof. These proteins make up the capsid of an AAV viral particle. Capsid variants are discussed below.

[0109] A promoter will be operably linked to each of the packaging genes. Specific examples of such promoters include the p5, p19 and p40 promoters (Laughlin et al., 1979, PNAS, 76:5567-5571). For example, the p5 and p19 promoters are generally used to express the rep gene, while the p40 promoter is generally used to express the cap gene.

[0110] As discussed above, the AAV genome used in the vector of the invention may therefore be the full genome of a naturally occurring AAV virus. For example, a vector comprising a full AAV genome may be used to prepare AAV virus in vitro. However, while such a vector may in principle be administered to patients, this will be done rarely in practice. Preferably the AAV genome will be derivatized for the purpose of administration to patients. Such derivatization is standard in the art and the present invention encompasses the use of any known derivative of an AAV genome, and derivatives which could be generated by applying techniques known in the art. Derivatization of the AAV genome and of the AAV capsid are reviewed in Coura and Nardi (Virology Journal, 2007, 4:99), and in Choi et al and Wu et al, referenced above.

[0111] Derivatives of an AAV genome include any truncated or modified forms of an AAV genome which allow for expression of a ND4, ND6, or ND1 transgene from a vector of the invention in vivo. Typically, it is possible to truncate the AAV genome significantly to include minimal viral sequence yet retain the above function. This is preferred for safety reasons to reduce the risk of recombination of the vector with wild-type virus, and also to avoid triggering a cellular immune response by the presence of viral gene proteins in the target cell.

[0112] Typically, a derivative will include at least one inverted terminal repeat sequence (ITR), preferably more than one ITR, such as two ITRs or more. One or more of the ITRs may be derived from AAV genomes having different serotypes, or may be a chimeric or mutant ITR. A preferred mutant ITR is one having a deletion of a trs (terminal resolution site). This deletion allows for continued replication of the genome to generate a single-stranded genome which contains both coding and complementary sequences i.e. a self-complementary AAV genome. This allows for bypass of DNA replication in the target cell, and so enables accelerated transgene expression.

[0113] The one or more ITRs will preferably flank the polynucleotide sequence encoding ND4, ND6, ND1, or a variant thereof at either end. The inclusion of one or more ITRs is preferred to aid concatamer formation of the vector of the invention in the nucleus of a host cell, for example following the conversion of single-stranded vector DNA into double-stranded DNA by the action of host cell DNA polymerases. The formation of such episomal concatamers protects the vector construct during the life of the host cell, thereby allowing for prolonged expression of the transgene in vivo.

[0114] In preferred embodiments, ITR elements will be the only sequences retained from the native AAV genome in the derivative. Thus, a derivative will preferably not include the rep and/or cap genes of the native genome and any other sequences of the native genome. This is preferred for the reasons described above, and also to reduce the possibility of integration of the vector into the host cell genome. Additionally, reducing the size of the AAV genome allows for increased flexibility in incorporating other sequence elements (such as regulatory elements) within the vector in addition to the transgene.

[0115] With reference to the AAV2 genome, the following portions could therefore be removed in a derivative of the invention: One inverted terminal repeat (ITR) sequence, the replication (rep) and capsid (cap) genes (NB: the rep gene in the wild type AAV genome should not to be confused with ND4, ND6, or ND1, the human gene affected in LHON). However, in some embodiments, including in vitro embodiments, derivatives may additionally include one or more rep and/or cap genes

or other viral sequences of an AAV genome. Naturally occurring AAV virus integrates with a high frequency at a specific site on human chromosome 19, and shows a negligible frequency of random integration, such that retention of an integrative capacity in the vector may be tolerated in a therapeutic setting.

[0116] Where a derivative genome comprises genes encoding capsid proteins i.e. VP1, VP2 and/or VP3, the derivative may be a chimeric, shuffled or capsid-modified derivative of one or more naturally occurring AAV viruses. In particular, the invention encompasses the provision of capsid protein sequences from different serotypes, clades, clones, or isolates of AAV within the same vector i.e. pseudotyping.

[0117] Chimeric, shuffled or capsid-modified derivatives will be typically selected to provide one or more desired functionalities for the viral vector. Thus, these derivatives may display increased efficiency of gene delivery, decreased immunogenicity (humoral or cellular), an altered tropism range and/or improved targeting of a particular cell type compared to an AAV viral vector comprising a naturally occurring AAV genome, such as that of AAV2. Increased efficiency of gene delivery may be effected by improved receptor or co-receptor binding at the cell surface, improved internalization, improved trafficking within the cell and into the nucleus, improved uncoating of the viral particle and improved conversion of a single-stranded genome to double-stranded form. Increased efficiency may also relate to an altered tropism range or targeting of a specific cell population, such that the vector dose is not diluted by administration to tissues where it is not needed.

[0118] Chimeric capsid proteins include those generated by recombination between two or more capsid coding sequences of naturally occurring AAV serotypes. This may be performed for example by a marker rescue approach in which non-infectious capsid sequences of one serotype are co-transfected with capsid sequences of a different serotype, and directed selection is used to select for capsid sequences having desired properties. The capsid sequences of the different serotypes can be altered by homologous recombination within the cell to produce novel chimeric capsid proteins.

[0119] Chimeric capsid proteins also include those generated by engineering of capsid protein sequences to transfer specific capsid protein domains, surface loops or specific amino acid residues between two or more capsid proteins, for example between two or more capsid proteins of different serotypes.

[0120] Shuffled or chimeric capsid proteins may also be generated by DNA shuffling or by error-prone PCR. Hybrid AAV capsid genes can be created by randomly fragmenting the sequences

of related AAV genes e.g. those encoding capsid proteins of multiple different serotypes and then subsequently reassembling the fragments in a self-priming polymerase reaction, which may also cause crossovers in regions of sequence homology. A library of hybrid AAV genes created in this way by shuffling the capsid genes of several serotypes can be screened to identify viral clones having a desired functionality. Similarly, error prone PCR may be used to randomly mutate AAV capsid genes to create a diverse library of variants which may then be selected for a desired property.

[0121] The sequences of the capsid genes may also be genetically modified to introduce specific deletions, substitutions or insertions with respect to the native wild-type sequence. In particular, capsid genes may be modified by the insertion of a sequence of an unrelated protein or peptide within an open reading frame of a capsid coding sequence, or at the N- and/or C-terminus of a capsid coding sequence.

[0122] The unrelated protein or peptide may advantageously be one which acts as a ligand for a particular cell type, thereby conferring improved binding to a target cell or improving the specificity of targeting of the vector to a particular cell population. An example might include the use of RGD peptide to block uptake in the retinal pigment epithelium and thereby enhance transduction of surrounding retinal tissues (Cronin et al., 2008 ARVO Abstract: D1048). The unrelated protein may also be one which assists purification of the viral particle as part of the production process i.e. an epitope or affinity tag. The site of insertion will typically be selected so as not to interfere with other functions of the viral particle e.g. internalization, trafficking of the viral particle. The skilled person can identify suitable sites for insertion based on their common general knowledge. Particular sites are disclosed in Choi et al, referenced above.

[0123] The invention additionally encompasses the provision of sequences of an AAV genome in a different order and configuration to that of a native AAV genome. The invention also encompasses the replacement of one or more AAV sequences or genes with sequences from another virus or with chimeric genes composed of sequences from more than one virus. Such chimeric genes may be composed of sequences from two or more related viral proteins of different viral species.

[0124] The vector of the invention takes the form of a polynucleotide sequence comprising an AAV genome or derivative thereof and a sequence encoding ND4, ND6, ND1 or a variant thereof.

[0125] For the avoidance of doubt, the invention also provides an AAV viral particle comprising a vector of the invention. The AAV particles of the invention include trans-capsidated forms wherein an AAV genome or derivative having an ITR of one serotype is packaged in the capsid

of a different serotype. The AAV particles of the invention also include mosaic forms wherein a mixture of unmodified capsid proteins from two or more different serotypes makes up the viral envelope. The AAV particle also includes chemically modified forms bearing ligands adsorbed to the capsid surface. For example, such ligands may include antibodies for targeting a particular cell surface receptor.

[0126] The invention additionally provides a host cell comprising a vector or AAV viral particle of the invention.

Recombinant nucleic acid sequences

[0127] Also disclosed herein are recombinant nucleic acid sequences comprising a polynucleotide sequence encoding a NADH dehydrogenase subunit-4 (ND4), NADH dehydrogenase subunit-1 (ND1) and NADH dehydrogenase subunit-6 (ND6) polypeptide or a variant thereof.

[0128] The polynucleotide sequence for ND4 is shown in **SEQ ID NO: 6** and encodes the protein shown in **SEQ ID NO: 160**. Further nucleic acid sequences for ND4 are **SEQ ID NO: 7 and 8.** The polynucleotide sequence for ND6 is shown in **SEQ ID NO: 9** and encodes the protein shown in **SEQ ID NO: 161**. A further nucleic acid sequence for ND6 is **SEQ ID NO: 10.** The polynucleotide sequence for ND1 is shown in **SEQ ID NO: 11** and encodes the protein shown in **SEQ ID NO: 162.** A further nucleic acid sequence for ND1 is **SEQ ID NO: 12.**

[0129] A variant of any one of **SEQ ID NO: 160, 161, or 162** may comprise truncations, mutants or homologues thereof, and any transcript variants thereof which encode a functional ND4, ND6, or ND1 polypeptide. Any homologues mentioned herein are typically at least 70% homologous to a relevant region of ND4, ND6, or ND1, and can functionally compensate for the polypeptide deficiency.

[0130] Homology can be measured using known methods. For example the UWGCG Package provides the BESTFIT program which can be used to calculate homology (for example used on its default settings) (Devereux et at (1984) Nucleic Acids Research 12, 387-395). The PILEUP and BLAST algorithms can be used to calculate homology or line up sequences (typically on their default settings), for example as described in Altschul S. F. (1993) J Mol Evol 36:290-300; Altschul, S, F et at (1990) J Mol Biol 215:403-10. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/).

[0131] In preferred embodiments, a recombinant nucleic acid sequence may encode a polypeptide which is at least 55%, 65%, 70%, 75%, 80%, 85%, 90% and more preferably at least 95%, 97%, 99%, 99.5%, or 100% homologous to a relevant region of ND4, ND6, or ND1 (**SEQ ID NO: 160, 161, or 162**) over at least 20, preferably at least 30, for instance at least 40, 60, 100, 200, 300, 400 or more contiguous amino acids, or even over the entire sequence of the recombinant nucleic acid. The relevant region will be one which provides for functional activity of ND4, ND6, or ND1.

[0132] Alternatively, and preferably the recombinant nucleic acid sequence may encode a polypeptide having at least 70%, 75%, 80%, 85%, 90% and more preferably at least 95%, 97%, 99%, 99.5%, or 100% homologous to full-length ND4, ND6, or ND1 (**SEQ ID NO: 160, 161, or 162**) over its entire sequence. Typically the recombinant nucleic acid sequence differs from the relevant region of ND4, ND6, or ND1 (**SEQ ID NO: 160, 161, or 162**) by at least, or less than, 2, 5, 10, 20, 40, 50 or 60 mutations (each of which can be substitutions, insertions or deletions).

[0133] A recombinant nucleic acid ND4, ND6, or ND1 polypeptide may have a percentage identity with a particular region of **SEQ ID NO: 160, 161, or 162** which is the same as any of the specific percentage homology values (i.e. it may have at least 70%, 80% or 90% and more preferably at least 95%, 97%, 99% identity) across any of the lengths of sequence mentioned above.

[0134] Variants of ND4, ND6, or ND1 (**SEQ ID NO: 160, 161, or 162**) also include truncations. Any truncation may be used so long as the variant is still functional. Truncations will typically be made to remove sequences that are non-essential for the protein activity and/or do not affect conformation of the folded protein, in particular folding of the active site. Appropriate truncations can routinely be identified by systematic truncation of sequences of varying length from the N- or C-terminus. Preferred truncations are N-terminal and may remove all other sequences except for the catalytic domain.

[0135] Variants of ND4, ND6, or ND1 (**SEQ ID NO: 160, 161, or 162**) further include mutants which have one or more, for example, 2, 3, 4, 5 to 10, 10 to 20, 20 to 40 or more, amino acid insertions, substitutions or deletions with respect to a particular region of ND4, ND6, or ND1 (**SEQ ID NO: 160, 161, or 162**). Deletions and insertions are made preferably outside of the catalytic domain as described below. Substitutions are also typically made in regions that are non-essential for protease activity and/or do not affect conformation of the folded protein.

[0136] Substitutions preferably introduce one or more conservative changes, which replace amino acids with other amino acids of similar chemical structure, similar chemical properties or

similar side-chain volume. The amino acids introduced may have similar polarity, hydrophilicity, hydrophobicity, basicity, acidity, neutrality or charge to the amino acids they replace. Alternatively, the conservative change may introduce another amino acid that is aromatic or aliphatic in the place of a pre-existing aromatic or aliphatic amino acid. Conservative amino acid changes are well known in the art and may be selected in accordance with the properties of the amino acids.

[0137] Similarly, preferred variants of the polynucleotide sequence of ND4, ND6, or ND1 (**SEQ ID NO: 6, 9, or 11**) include polynucleotides having at least 70%, 75%, 80%, 85%, 90% and more preferably at least 95%, 96%, 97%, 98%, 99%, or 99.5% homologous to a relevant region of ND4, ND6, or ND1 (**SEQ ID NO: 6, 9, or 11**). Preferably the variant displays these levels of homology to full-length ND4, ND6, or ND1 (**SEQ ID NO: 6, 9, or 11**) over its entire sequence.

[0138] Mitochondrial targeting sequences (MTSs) and three prime untranslated regions (3'UTRs) can be used to target proteins or mRNA to the mitochondria. The charge, length, and structure of the MTS can be important for protein import into the mitochondria. Particular 3'UTRs may drive mRNA localization to the mitochondrial surface and thus facilitate co-translational protein import into the mitochondria.

[0139] The polynucleotide sequence for a mitochondrial targeting sequence can encode a polypeptide selected from 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 (see Table 1 for SEQ ID NO). In one example, the polynucleotide sequences, COX10 (**SEQ ID NO: 1, 2, or 3**) can encode the mitochondrial targeting sequence, MTS-COX10 (**SEQ ID NO: 126**). In another example, the polynucleotide sequences, COX8 (**SEQ ID NO: 4**) can encode the mitochondrial targeting sequence, MTS-COX8 (**SEQ ID NO: 127**). In another example, the polynucleotide sequences, OPA1 (**SEQ ID NO: 5**) can encode the mitochondrial targeting sequence, MTS-OPA1 (**SEQ ID NO: 128**).

[0140] The 3'UTR nucleic acid sequence can be selected from hsACO2 (**SEQ ID NO: 111**), hsATP5B (**SEQ ID NO: 112**), hsAK2 (**SEQ ID NO: 113**), hsALDH2 (**SEQ ID NO: 114**), hsCOX10 (**SEQ ID NO: 115**), hsUQCRFS1 (**SEQ ID NO: 116**), hsNDUFV1 (**SEQ ID NO: 117**), hsNDUFV2 (**SEQ ID NO: 118**), hsSOD2 (**SEQ ID NO: 119**), hsCOX6c (**SEQ ID NO: 120**), hsIRP1 (**SEQ ID NO: 121**), hsMRPS12 (**SEQ ID NO: 122**), hsATP5J2 (**SEQ ID NO: 123**), rnSOD2 (**SEQ ID NO: 124**), and hsOXA1L (**SEQ ID NO: 125**). The 3'UTR nucleic acid sequence can also be a variant having at least 70%, 75%, 80%, 85%, 90% and more preferably at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 100% homologous to any 3'UTR nucleic acid sequence listed here. For example, the 3'UTR nucleic acid sequence can be **SEQ ID NO: 13 or 14.**

[0141] Also disclosed herein are recombinant nucleic acid sequences comprising a mitochondrial targeting sequence, a mitochondrial protein coding sequence, and a 3'UTR nucleic acid sequence. For example, the recombinant nucleic acid sequence can be selected from **SEQ ID NO: 15-84.** The recombinant nucleic acid sequence can also be a variant having at least 70%, 75%, 80%, 85%, 90% and more preferably at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 100% homologous to any recombinant nucleic acid sequence listed here.

Promoters and regulatory sequences

[0142] The vector of the invention also includes elements allowing for the expression of the disclosed transgene in vitro or in vivo. Thus, the vector typically comprises a promoter sequence operably linked to the polynucleotide sequence encoding the ND4, ND6, or ND1 transgene or a variant thereof.

[0143] Any suitable promoter may be used. The promoter sequence may be constitutively active i.e. operational in any host cell background, or alternatively may be active only in a specific host cell environment, thus allowing for targeted expression of the transgene in a particular cell type. The promoter may show inducible expression in response to presence of another factor, for example a factor present in a host cell. In any event, where the vector is administered for therapy, the promoter must be functional in a retinal cell background.

[0144] In some embodiments, it is preferred that the promoter shows retinal-cell specific expression in order to allow for the transgene to only be expressed in retinal cell populations. Thus, expression from the promoter may be retinal-cell specific, for example confined only to cells of the neurosensory retina and retinal pigment epithelium.

[0145] Preferred promoters for the ND4, ND6, or ND1 transgene include the chicken beta-actin (CBA) promoter, optionally in combination with a cytomegalovirus (CME) enhancer element. In some cases, the preferred promoters for the ND4, ND6, or ND1 transgene comprises the CAG promoter. A particularly preferred promoter is a hybrid CBA/CAG promoter, for example the promoter used in the rAVE expression cassette. Examples of promoters based on human sequences that would induce retina specific gene expression include rhodospin kinase for rods and cones (Allocca et al., 2007, J Viol 81:11372-80), PR2.1 for cones only (Mancuso et al. 2009, Nature) and/or RPE65 for the retinal pigment epithelium (Bainbridge et al., 2008, N Eng J Med).

[0146] The vector of the invention may also comprise one or more additional regulatory sequences with may act pre- or post-transcriptionally. The regulatory sequence may be part of the native ND4, ND6, or ND1 gene locus or may be a heterologous regulatory sequence. The vector of the invention may comprise portions of the 5′UTR or 3′UTR from the native ND4, ND6, or ND1 transcript.

[0147] Regulatory sequences are any sequences which facilitate expression of the transgene i.e. act to increase expression of a transcript, improve nuclear export of mRNA or enhance its stability. Such regulatory sequences include for example enhancer elements, postregulatory elements and polyadenylation sites. A preferred polyadenylation site is the Bovine Growth Hormone poly-A signal. In the context of the vector of the invention such regulatory sequences will be cis-acting. However, the invention also encompasses the use of trans-acting regulatory sequences located on additional genetic constructs.

[0148] A preferred postregulatory element for use in a vector of the invention is the woodchuck hepatitis postregulatory element (WPRE) or a variant thereof. Another regulatory sequence which may be used in a vector of the present invention is a scaffold-attachment region (SAR). Additional regulatory sequences may be selected by the skilled person on the basis of their common general knowledge.

Preparation of vector

[0149] The vector of the invention may be prepared by standard means known in the art for provision of vectors for gene therapy. Thus, well established public domain transfection, packaging and purification methods can be used to prepare a suitable vector preparation.

[0150] As discussed above, a vector of the invention may comprise the full genome of a naturally occurring AAV virus in addition to a polynucleotide sequence encoding ND4, ND6, or ND1 or a variant thereof. However, commonly a derivatised genome will be used, for instance a derivative which has at least one inverted terminal repeat sequence (ITR), but which may lack any AAV genes such as rep or cap.

[0151] In such embodiments, in order to provide for assembly of the derivatised genome into an AAV viral particle, additional genetic constructs providing AAV and/or helper virus functions will be provided in a host cell in combination with the derivatised genome. These additional constructs will typically contain genes encoding structural AAV capsid proteins i.e. cap, VP1, VP2, VP3, and genes encoding other functions required for the AAV life cycle, such as rep. The selection of structural capsid proteins provided on the additional construct will determine the serotype of the packaged viral vector.

[0152] A particularly preferred packaged viral vector for use in the invention comprises a derivatised genome of AAV2 in combination with AAV5 or AAV8 capsid proteins. This packaged viral vector typically comprises one or more AAV2 ITRs.

[0153] As mentioned above, AAV viruses are replication incompetent and so helper virus functions, preferably adenovirus helper functions will typically also be provided on one or more additional constructs to allow for AAV replication.

[0154] All of the above additional constructs may be provided as plasmids or other episomal elements in the host cell, or alternatively one or more constructs may be integrated into the genome of the host cell.

[0155] In these aspects, the invention provides a method for production of a vector of the invention. The method comprises providing a vector which comprises an adeno-associated virus (AAV) genome or a derivative thereof and a polynucleotide sequence encoding ND4, ND6, or ND1 or a variant thereof in a host cell, and providing means for replication and assembly of the vector into an AAV viral particle. Preferably, the method comprises providing a vector comprising a derivative of an AAV genome and a polynucleotide sequence encoding ND4, ND6, or ND1 or a variant thereof, together with one or more additional genetic constructs encoding AAV and/or helper virus functions. Typically, the derivative of an AAV genome comprises at least one ITR. Optionally, the method further comprises a step of purifying the assembled viral particles. Additionally, the method may comprise a step of formulating the viral particles for therapeutic use.

Methods of therapy and medical uses

[0156] As discussed above, the present inventors have surprisingly demonstrated that a vector of the invention may be used to address the cellular dysfunction underlying LHON. In particular, they have shown that use of the vector can correct the defect associated with LHON. This provides a means whereby the degenerative process of the disease can be treated, arrested, palliated or prevented.

[0157] The invention therefore provides a method of treating or preventing LHON in a patient in need thereof, comprising administering a therapeutically effective amount of a vector encoding a mitochondrial protein described herein to the patient by direct retinal, subretinal or intravitreal injection. In some embodiments, the methods further comprise administration of a steroid prior to, during, and/or after the administration of the vector encoding the mitochondrial protein. Accordingly, LHON is thereby treated or prevented in the patient.

[0158] Vectors suitable for use in the present methods include those described herein, comparable vectors encoding a mitochondrial protein, and biosimilars thereof. Comparable vectors encoding a mitochondrial protein suitable for use according to the present methods include those described in the art, for example, those described in Guy et al., Ophthalmology 2017; 124:1621-1634 and Vignal et al., Ophthalmology 2018; 6:945-947, each of which are incorporated by reference in their entireties. A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product ("reference product"). "Highly similar" products are products with similar purity, chemical identity, and bioactivity to a reference product. However, minor differences between the clinically inactive components of the reference product and the proposed biosimilar product in are acceptable. For example, these could include minor differences in the stabilizer or buffer compared to what is used in the reference product and slight differences (i.e., acceptable within-product variations) are expected during the manufacturing process. Any differences between the proposed biosimilar product and the reference product are carefully evaluated by FDA to ensure the biosimilar meets FDA's high approval standards. "No clinically meaningful differences" means that the biosimilar product has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness), generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.

[0159] In some embodiments, the patient in need of treatment according to the methods provided herein has one or more mitochondrial DNA (mtDNA) point mutations. In some embodiments,

the patient has a point mutation in a gene encoding a protein of complex I in the oxidative phosphorylation chain of the mitochondria. For example, patients may have one or more point mutations in the *MT-ND4* gene (also known as *ND4*, NCBI Gene ID: 4538) encoding the NADH dehydrogenase subunit-4 protein (ND4), the *MT-ND1* gene (also known as *ND1*, NCBI Gene ID: 4535) encoding the NADH dehydrogenase subunit-1 protein (ND1), or the *MT-ND6* gene (also known as *ND6*, NCBI Gene ID: 4541) encoding the NADH dehydrogenase subunit-6 protein (ND6). In some embodiments, the patient has a point mutation at nucleotide position 11778 in the *ND4* gene. In some embodiments, the point mutation is G11778A in the *ND4* gene. In some embodiments, the patient has a point mutation at nucleotide position 3460 in the *ND1* gene. In some embodiments, the point mutation is G3460A in the *ND1* gene. In some embodiments, the patient has a point mutation at nucleotide position 14484 in the *ND6* gene. In some embodiments, the point mutation is T14484C in the *ND6* gene. In some embodiments, the patient in need of treatment according to the methods provided herein has one or more of point mutations selected from G11778A in the *ND4* gene, G3460A in the *ND1* gene, and T14484C in the *ND6* gene and is of Chinese and/or Argentinean descent.

[0160] In some embodiments, the patient in need of treatment according to the methods provided herein has one or more of point mutations selected from G11778A in the *ND4* gene, G3460A in the *ND1* gene, and T14484C in the *ND6* gene and is of Argentinean descent. In some embodiments, the patient in need of treatment according to the methods provided herein has one or more of point mutations selected from G11778A in the *ND4* gene, G3460A in the *ND1* gene, and T14484C in the *ND6* gene and is of Chinese descent. In particular embodiments, the patient in need of treatment according to the methods provided herein has one or more of point mutations selected from G11778A in the *ND4* gene and is of Chinese descent.

[0161] In a related aspect, the invention provides for use of a vector of the invention in a method of treating or preventing LHON by administering said vector to a patient by direct retinal, subretinal or intravitreal injection. Additionally, the invention provides the use of a vector of the invention in the manufacture of a medicament for treating or preventing LHON by direct retinal, subretinal or intravitreal injection.

[0162] In all these embodiments, the vector of the invention may be administered in order to prevent the onset of one or more symptoms of LHON. The patient may be asymptomatic. The subject may have a predisposition to the disease. The method or use may comprise a step of identifying whether or not a subject is at risk of developing, or has, LHON. A prophylactically effective amount

of the vector is administered to such a subject. A prophylactically effective amount is an amount which prevents the onset of one or more symptoms of the disease.

[0163] Alternatively, the vector may be administered once the symptoms of the disease have appeared in a subject i.e. to cure existing symptoms of the disease. A therapeutically effective amount of the antagonist is administered to such a subject. A therapeutically effective amount is an amount which is effective to ameliorate one or more symptoms of the disease. Such an amount may also arrest, slow or reverse some loss of peripheral vision associated with LHON. Such an amount may also arrest, slow or reverse onset of LHON.

[0164] A typical single dose is between 10^{10} and 10^{12} genome particles, depending on the amount of remaining retinal tissue that requires transduction. A genome particle is defined herein as an AAV capsid that contains a single stranded DNA molecule that can be quantified with a sequence specific method (such as real-time PCR). That dose may be provided as a single dose, but may be repeated for the fellow eye or in cases where vector may not have targeted the correct region of retina for whatever reason (such as surgical complication). The treatment is preferably a single permanent treatment for each eye, but repeat injections, for example in future years and/or with different AAV serotypes may be considered.

[0165] The invention also provides a method of monitoring treatment or prevention of LHON in a patient comprising measuring activity ex vivo in retinal cells obtained from said patient following administration of the AAV vector of the invention by direct retinal, subretinal or intravitreal injection. This method can allow for determination of the efficacy of treatment.

[0166] In some embodiments, the present disclosure provides a method of treating an eye disorder (e.g., LHON) comprising administering a therapeutically effective amount of a vector described herein and a steroid. Exemplary steroids include, but are not limited to, alclometasone diproprionate, amcinonide, beclomethasone diproprionate, betamethasone, betamethasone benzoate, betamethasone diproprionate, betamethasone sodium phosphate, betamethasone sodium phosphate and acetate, betamethasone valerate, clobetasol proprionate, clocortolone pivalate, cortisol (hydrocortisone), cortisol (hydrocortisone) acetate, cortisol (hydrocortisone) butyrate, cortisol (hydrocortisone) cypionate, cortisol (hydrocortisone) sodium phosphate, cortisol (hydrocortisone) sodium succinate, cortisol (hydrocortisone) valerate, cortisone acetate, desonide, desoximetasone, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, diflorasone diacetate, fludrocortisone acetate, flunisolide, fluocinolone acetonide, fluocinonide, fluorometholone,

flurandrenolide, halcinonide, medrysone, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide or a synthetic analog thereof, or a combination thereof. In some embodiments, the steroid is a glucocorticoid. In some embodiments, the steroid is selected from prednisone, methylprednisolone, and methylprednisolone sodium succinate.

[0167] In some embodiments, the steroid is methylprednisolone. In some embodiments, the methylprednisolone is formulated as a tablet for oral administration, *e.g.*, MEDROL® tablets. For example, in some embodiments, the methylprednisolone is formulated as a tablet with one or more inactive ingredients such as calcium sterate, corn starch, erythrosine sodium, lactose, mineral oil, sorbic acid, sucrose, or FD&C Yellow No. 6. In some embodiments, the methylprednisolone is formulated is a liquid for administration by injection, *e.g.*, SOLU-MEDROL®. For example, in some embodiments, methylprednisolone sodium succinate is formulated as a liquid with one or more inactive ingredients such as monobasic sodium phosphate anhydrous, dried dibasic sodium phosphate, or lactose hydrous, optionally formulated with a preservative such as benzyl alcohol. In some embodiments, the steroid is MEDROL® or SOLU-MEDROL®, including generic versions thereof.

[0168] In some embodiments, the patient receives one or more steroid doses of between about 1 mg/60 kg to about 100 mg/60 kg, about 1 mg/60 kg to about 80 mg/60 kg, about 1 mg/60 kg to about 60 mg/60 kg, about 1 mg/60 kg to about 40 mg/60 kg, about 1 mg/60 kg to about 20 mg/60 kg, about 20 mg/60 kg to about 100 mg/60 kg, about 20 mg/60 kg to about 80 mg/60 kg, about 20 mg/60 kg to about 60 mg/60 kg, about 20 mg/60 kg to about 40 mg/60 kg, about 40 mg/60 kg to about 100 mg/60 kg, about 40 mg/60 kg to about 80 mg/60 kg, about 40 mg/60 kg to about 60 mg/60 kg, about 60 mg/60 kg to about 100 mg/60 kg, about 60 mg/60 kg to about 80 mg/60 kg, or about 80 mg/60 kg to about 100 mg/60 kg. In some embodiments, the patient receives one or more steroid doses of about 4 mg/60 kg, 6 mg/60 kg, 8 mg/60 kg, 10 mg/60 kg, 16 mg/60 kg, 20 mg/60 kg, 24 mg/60 kg, 32 mg/60 kg, 40 mg/60 kg, 48 mg/60 kg, 60 mg/60 kg, or 80 mg/60 kg. In some embodiments, the patient receives one or more steroid doses of about 1 mg to about 96 mg. In some embodiments, the patient receives one or more steroid doses of at least about 1 mg. In some embodiments, the patient receives one or more steroid doses of at most about 96 mg. In some embodiments, the patient receives one or more steroid doses of about 1 mg to about 2 mg, about 1 mg to about 4 mg, about 1 mg to about 8 mg, about 1 mg

to about 16 mg, about 1 mg to about 32 mg, about 1 mg to about 64 mg, about 1 mg to about 96 mg, about 2 mg to about 4 mg, about 2 mg to about 8 mg, about 2 mg to about 16 mg, about 2 mg to about 32 mg, about 2 mg to about 64 mg, about 2 mg to about 96 mg, about 4 mg to about 8 mg, about 4 mg to about 16 mg, about 4 mg to about 32 mg, about 4 mg to about 64 mg, about 4 mg to about 96 mg, about 8 mg to about 16 mg, about 8 mg to about 32 mg, about 8 mg to about 64 mg, about 8 mg to about 96 mg, about 16 mg to about 32 mg, about 16 mg to about 64 mg, about 16 mg to about 96 mg, about 32 mg to about 64 mg, about 32 mg to about 96 mg, or about 64 mg to about 96 mg. In some embodiments, the patient receives one or more steroid doses of about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 16 mg, about 32 mg, about 64 mg, or about 96 mg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, the steroid is prednisone.

[0169] In some embodiments, one or more doses of the steroid are administered prior to administration of the therapeutic vector (*i.e.*, one or more pre-operative steroid doses). In some embodiments, a daily dose of a steroid is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days before administration of the therapeutic vector. In some embodiments, the patient receives one or more pre-operative steroid doses of about 1 mg/60 kg to about 100 mg/60 kg, about 1 mg/60 kg to about 80 mg/60 kg, about 1 mg/60 kg to about 60 mg/60 kg, about 1 mg/60 kg to about 40 mg/60 kg, about 1 mg/60 kg to about 20 mg/60 kg, about 20 mg/60 kg to about 100 mg/60 kg, about 20 mg/60 kg to about 80 mg/60 kg, about 20 mg/60 kg to about 60 mg/60 kg, about 20 mg/60 kg to about 40 mg/60 kg, about 40 mg/60 kg to about 100 mg/60 kg, about 40 mg/60 kg to about 80 mg/60 kg, about 40 mg/60 kg to about 60 mg/60 kg, about 60 mg/60 kg to about 100 mg/60 kg, about 60 mg/60 kg to about 80 mg/60 kg, or about 80 mg/60 kg to about 100 mg/60 kg. In some embodiments, the patient receives one or more pre-operative steroid doses of about 4 mg/60 kg, 6 mg/60 kg, 8 mg/60 kg, 10 mg/60 kg, 16 mg/60 kg, 20 mg/60 kg, 24 mg/60 kg, 32 mg/60 kg, 40 mg/60 kg, 48 mg/60 kg, 60 mg/60 kg, or 80 mg/60 kg. In some embodiments, the patient receives one or more pre-operative steroid doses of about 1 mg to about 96 mg. In some embodiments, the patient receives one or more pre-operative steroid doses of at least about 1 mg. In some embodiments, the patient receives one or more pre-operative steroid doses of at most about 96 mg. In some embodiments, the patient receives one or more pre-operative steroid doses of about 1 mg to about 2 mg, about 1 mg to about 4 mg, about 1 mg to about 8 mg, about 1 mg to about 16 mg, about 1 mg to about 32 mg, about 1 mg to about 64 mg, about 1 mg to about 96 mg, about 2 mg to about 4 mg, about 2 mg to about 8 mg, about 2 mg to about 16 mg, about 2 mg to about 32 mg, about 2 mg to about 64 mg, about 2 mg to about 96 mg, about 4 mg to about 8 mg, about 4 mg to about 16 mg, about 4 mg to about 32 mg, about 4 mg to about

64 mg, about 4 mg to about 96 mg, about 8 mg to about 16 mg, about 8 mg to about 32 mg, about 8 mg to about 64 mg, about 8 mg to about 96 mg, about 16 mg to about 32 mg, about 16 mg to about 64 mg, about 16 mg to about 96 mg, about 32 mg to about 64 mg, about 32 mg to about 96 mg, or about 64 mg to about 96 mg. In some embodiments, the patient receives one or more pre-operative steroid doses of about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 16 mg, about 32 mg, about 64 mg, or about 96 mg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, the steroid is prednisone.

[0170] In some embodiments, the patient receives one or more pre-operative steroid doses of between about 20 mg/60 kg to about 45 mg/60 kg, about 25 mg/60 kg to about 45 mg/60 kg, about 30 mg/60 kg to about 45 mg/60 kg, about 35 mg/60 kg to about 45 mg/60 kg, about 40 mg/60 kg to about 45 mg/60 kg, about 20 mg/60 kg to about 40 mg/60 kg, about 25 mg/60 kg to about 40 mg/60 kg, about 30 mg/60 kg to about 40 mg/60 kg, about 35 mg/60 kg to about 40 mg/60 kg, about 20 mg/60 kg to about 35 mg/60 kg, about 25 mg/60 kg to about 35 mg/60 kg, about 30 mg/60 kg to about 35 mg/60 kg, about 20 mg/60 kg to about 30 mg/60 kg, about 25 mg/60 kg to about 30 mg/60 kg, or about 20 mg/60 kg to about 25 mg/60 kg. In some embodiments, the patient receives one or more pre-operative steroid doses of about 25 mg/60 kg, about 26 mg/60 kg, about 27 mg/60 kg, about 28 mg/60 kg, about 29 mg/60 kg, about 30 mg/60 kg, about 31 mg/60 kg, about 32 mg/60 kg, about 33 mg/60 kg, about 34 mg/60 kg, or about 35 mg/60 kg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) between about 25 mg/60 kg and about 45 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days before administration of the therapeutic vector. In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) of about 32 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days before administration of the therapeutic vector.

[0171] In some embodiments, the patient receives one or more pre-operative steroid doses of between about 50 mg/60 kg to about 70 mg/60 kg, about 55 mg/60 kg to about 70 mg/60 kg, about 60 mg/60kg to about 70 mg/60 kg, about 65 mg/60 kg to about 70 mg/60 kg, about 50 mg/60 kg to about 65 mg/60 kg, about 55 mg/60 kg to about 65 mg/60 kg, about 60 mg/60 kg to about 65 mg/60 kg, about 50 mg/60 kg to about 60 mg/60 kg, about 55 mg/60 kg to about 60 mg/60 kg, or about 50 mg/60 kg to about 55 mg/60 kg. In some embodiments, the patient receives one or more pre-operative doses of about 55 mg/60 kg, about 56 mg/60 kg, about 57 mg/60 kg, about 58 mg/60 kg, about 59 mg/60 kg,

about 60 mg/k, about 61 mg/60 kg, about 62 mg/60 kg, about 63 mg/60 kg, about 64 mg/60 kg, or about 65 mg/60 kg.. In some embodiments, the steroid is prednisone. In some embodiments, a daily dose of prednisone between about 50 mg/60 kg and about 70 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days before administration of the therapeutic vector. In some embodiments, a daily dose of prednisone of about 60 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days before administration of the therapeutic vector.

[0172] In some embodiments, one or more doses of the steroid are administered after the administration of the therapeutic vector (*i.e.*, one or more post-operative steroid doses). In some embodiments, a daily dose of a steroid is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of a steroid is delivered for at least 1 week, 2 weeks, 3 weeks, 4 weeks, 5 days, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, or at least 15 weeks after administration of the therapeutic vector. In some embodiments, the patient receives one or more post-operative steroid doses of about 1 mg/60 kg to about 100 mg/60 kg, about 1 mg/60 kg to about 80 mg/60 kg, about 1 mg/60 kg to about 60 mg/60 kg, about 1 mg/60 kg to about 40 mg/60 kg, about 1 mg/60 kg to about 20 mg/60 kg, about 20 mg/60 kg to about 100 mg/60 kg, about 20 mg/60 kg to about 80 mg/60 kg, about 20 mg/60 kg to about 60 mg/60 kg, about 20 mg/60 kg to about 40 mg/60 kg, about 40 mg/60 kg to about 100 mg/60 kg, about 40 mg/60 kg to about 80 mg/60 kg, about 40 mg/60 kg to about 60 mg/60 kg, about 60 mg to about 100 mg/60 kg, about 60 mg/60 kg to about 80 mg/60 kg and about 80 mg/60 kg to about 100 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 1 mg to about 96 mg. In some embodiments, the patient receives one or more post-operative steroid doses of at least about 1 mg. In some embodiments, the patient receives one or more post-operative steroid doses of at most about 96 mg. In some embodiments, the patient receives one or more post-operative steroid doses of about 1 mg to about 2 mg, about 1 mg to about 4 mg, about 1 mg to about 8 mg, about 1 mg to about 16 mg, about 1 mg to about 32 mg, about 1 mg to about 64 mg, about 1 mg to about 96 mg, about 2 mg to about 4 mg, about 2 mg to about 8 mg, about 2 mg to about 16 mg, about 2 mg to about 32 mg, about 2 mg to about 64 mg, about 2 mg to about 96 mg, about 4 mg to about 8 mg, about 4 mg to about 16 mg, about 4 mg to about 32 mg, about 4 mg to about 64 mg, about 4 mg to about 96 mg, about 8 mg to about 16 mg, about 8 mg to about 32 mg, about 8 mg to about 64 mg, about 8 mg to about 96 mg, about 16 mg to about 32 mg, about 16 mg to about 64 mg, about 16 mg to about 96 mg, about 32 mg

to about 64 mg, about 32 mg to about 96 mg, or about 64 mg to about 96 mg. In some embodiments, the patient receives one or more post-operative steroid doses of about 1 mg, about 2 mg, about 4 mg, about 8 mg, about 16 mg, about 32 mg, about 64 mg, or about 96 mg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, the steroid is prednisone.

[0173] In some embodiments , the patient receives one or more post-operative steroid doses of about 70 mg/60 kg to about 90 mg/60 kg, 75 mg/60 kg to about 90 mg/60 kg, about 80 mg/60 kg to about 90 mg/60 kg, about 85 mg/60 kg to about 90 mg/60 kg, about 70 mg/60 kg to about 85 mg/60 kg, about 75 mg/60 kg to about 85 mg/60 kg, about 80 mg/60 kg to about 85 mg/60 kg, about 70 mg/60 kg to about 80 mg/60 kg, about 75 mg/60 kg to about 80 mg/60 kg, or about 70 mg/60 kg to about 75 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 75 mg/60 kg, about 76 mg/60 kg, about 77 mg/60 kg, about 78 mg/60 kg, about 79 mg/60 kg, about 80 mg/60 kg, about 81 mg/60 kg, about 82 mg/60 kg, about 83 mg/60 kg, about 84 mg/60 kg, or about 85 mg/60 kg. In some embodiments, the steroid is methylprednisolone sodium succinate (e.g., SOLU-MEDROL®). In some embodiments, a daily dose of methylprednisolone sodium succinate (e.g., SOLU-MEDROL®) between about 70 mg and about 90 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of methylprednisolone sodium succinate (e.g., SOLU-MEDROL®)of about 80 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0174] In some embodiments, the patient receives one or more post-operative steroid doses of about 30 mg/60 kg to about 50 mg/60 kg, 35 mg/60 kg to about 50 mg/60 kg, about 40 mg/60 kg to about 50 mg/60 kg, about 45 mg/60 kg to about 50 mg/60 kg, about 30 mg/60 kg to about 45 mg/60 kg, about 35 mg/60 kg to about 45 mg/60 kg, about 40 mg/60 kg to about 45 mg/60 kg, about 30 mg/60 kg to about 40 mg/60 kg, about 35 mg/60 kg to about 40 mg/60 kg, or about 30 mg/60 kg to about 35 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 35 mg/60 kg, about 36 mg/60 kg, about 37 mg/60 kg, about 38 mg/60 kg, about 39 mg/60 kg, about 40 mg/60 kg, about 41 mg/60 kg, about 42 mg/60 kg, about 43 mg/60 kg, about 44 mg/60 kg, or about 45 mg/60 kg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) between about 30 mg/60 kg and about 50 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some

embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) of about 40 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0175] In some embodiments, the patient receives one or more post-operative steroid doses of about 20 mg/60 kg to about 45 mg/60 kg, 25 mg/60 kg to about 45 mg/60 kg, about 30 mg/60 kg to about 45 mg/60 kg, about 35 mg/60 kg to about 45 mg/60 kg, about 40 mg/60 kg to about 45 mg/60 kg, about 20 mg/60 kg to about 40 mg/60 kg, about 25 mg/60 kg to about 40 mg/60 kg, about 30 mg/60 kg to about 40 mg/60 kg, about 35 mg/60 kg to about 40 mg/60 kg, about 20 mg/60 kg to about 35 mg/60 kg, about 25 mg/60 kg to about 35 mg/60 kg, about 30 mg/60 kg to about 35 mg/60 kg, about 20 mg/60 kg to about 30 mg/60 kg, about 25 mg/60 kg to about 30 mg/60 kg, or about 20 mg/60 kg to about 25 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 25 mg/60 kg, about 26 mg/60 kg, about 27 mg/60 kg, about 28 mg/60 kg, about 29 mg/60 k, about 30 mg/60 kg, about 31 mg/60 kg, about 32 mg/60 kg, about 33 mg/60 kg, about 34 mg/60 kg, or about 35 mg/60 kg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) between about 20 mg/60 kg and about 45 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) of about 32 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0176] In some embodiments, the patient receives one or more post-operative steroid doses of about 15 mg/60 kg to about 35 mg/60 kg, 20 mg/60 kg to about 35 mg/60 kg, about 25 mg/60 kg to about 35 mg/60 kg, about 30 mg/60 kg to about 35 mg/60 kg, about 15 mg/60 kg to about 30 mg/60 kg, about 20 mg/60 kg to about 30 mg/60 kg, about 25 mg/60 kg to about 30 mg/60 kg, about 15 mg/60 kg to about 25 mg/60 kg, about 20 mg/60 kg to about 25 mg/60 kg, about 15 mg/60 kg to about 20 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 20 mg/60 kg, about 21 mg/60 kg, about 22 mg/60 kg, about 23 mg/60 kg, about 24 mg/60 kg, about 25 mg/60 kg, about 26 mg/60 kg, about 27 mg/60 kg, about 28 mg/60 kg, about 29 mg/60 kg, or about 30 mg/60 kg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) between about 15 mg/60 kg and about 35 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days,

7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) of about 24 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0177] In some embodiments, the patient receives one or more post-operative steroid doses of about 5 mg/60 kg to about 25 mg/60 kg, 10 mg/60 kg to about 25 mg/60 kg, about 15 mg/60 kg to about 25 mg/60 kg, about 20 mg/60 kg to about 25 mg/60 kg, about 5 mg/60 kg to about 20 mg/60 kg, about 10 mg/60 kg to about 20 mg/60 kg, about 15 mg/60 kg to about 20 mg/60 kg, about 5 mg/60 kg to about 15 mg/60 kg, about 10 mg/60 kg to about 15 mg/60 kg, or about 5 mg/60 kg to about 10 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 10 mg/60 kg, about 11 mg/60 kg, about 12 mg/60 kg, about 13 mg/60 kg, about 14 mg/60 kg, about 15 mg/60 kg, about 16 mg/60 kg, about 17 mg/60 kg, about 18 mg/60 kg, about 19 mg/60 kg, or about 20 mg/60 kg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) between about 5 mg/60 kg and about 25 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) of about 16 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0178] In some embodiments, the patient receives one or more post-operative steroid doses of about 1 mg/60 kg to about 20 mg/60 kg, 5 mg/60 kg to about 20 mg/60 kg, about 10 mg/60 kg to about 20 mg/60 kg, about 15 mg/60 kg to about 20 mg/60 kg, about 1 mg/60 kg to about 15 mg/60 kg, about 5 mg/60 kg to about 15 mg/60 kg, about 10 mg/60 kg to about 15 mg/60 kg, about 1 mg/60 kg to about 10 mg/60 kg, about 5 mg/60 kg to about 10 mg/60 kg, or about 1 mg/60 kg to about 5 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 1 mg/60 kg, about 2 mg/60 kg, about 3 mg/60 kg, about 4 mg/60 kg, about 5 mg/60 kg, about 6 mg/60 kg, about 7 mg/60 kg, about 8 mg/60 kg, about 9 mg/60 kg, about 10 mg/60 kg, about 11 mg/60 kg, about 12 mg/60 kg, about 13 mg/60 kg, about 14 mg/60 kg, or about 15 mg/60 kg. In some embodiments, the steroid is methylprednisolone (e.g., MEDROL®). In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) between about 1 mg/60 kg and about 20 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after

administration of the therapeutic vector. In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) of about 8 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) of about 6 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of methylprednisolone (e.g., MEDROL®) of about 4 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0179] In some embodiments, the patient receives one or more post-operative steroid doses of about 30 mg/60 kg to about 50 mg/60 kg, 35 mg/60 kg to about 50 mg/60 kg, about 40 mg/60 kg to about 50 mg/60 kg, about 45 mg/60 kg to about 50 mg/60 kg, about 30 mg/60 kg to about 45 mg/60 kg, about 35 mg/60 kg to about 45 mg/60 kg, about 40 mg/60 kg to about 45 mg/60 kg, about 30 mg/60 kg to about 40 mg/60 kg, about 35 mg/60 kg to about 40 mg/60 kg, or about 30 mg/60 kg to about 35 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 35 mg/60 kg, about 36 mg/60 kg, about 37 mg/60 kg, about 38 mg/60 kg, about 39 mg/60 kg, about 40 mg/60 kg, about 41 mg/60 kg, about 42 mg/60 kg, about 43 mg/60 kg, about 44 mg/60 kg, or about 45 mg/60 kg. In some embodiments, the steroid is prednisone. In some embodiments, a daily dose of prednisone between about 30 mg/60 kg and about 50 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of prednisone of about 40 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0180] In some embodiments, the patient receives one or more post-operative steroid doses of about 10 mg/60 kg to about 30 mg/60 kg, 15 mg/60 kg to about 30 mg/60 kg, about 20 mg/60 kg to about 30 mg/60 kg, about 25 mg/60 kg to about 30 mg/60 kg, about 10 mg/60 kg to about 25 mg/60 kg, about 15 mg/60 kg to about 25 mg/60 kg, about 20 mg/60 kg to about 25 mg/60 kg, about 10 mg/60 kg to about 20 mg/60 kg, about 15 mg/60 kg to about 20 mg/60 kg, or about 10 mg/60 kg to about 15 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 15 mg/60 kg, about 16 mg/60 kg, about 17 mg/60 kg, about 18 mg/60 kg, about 19 mg/60 kg, about 20 mg/60 kg, about 21 mg/60 kg, about 22 mg/60 kg, about 23 mg/60 kg, about 24 mg/60 kg,

or about 25 mg/60 kg. In some embodiments, the steroid is prednisone. In some embodiments, a daily dose of prednisone between about 10 mg/60 kg and about 30 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of prednisone of about 20 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0181] In some embodiments, the patient receives one or more post-operative steroid doses of about 1 mg/60 kg to about 20 mg/60 kg, 5 mg/60 kg to about 20 mg/60 kg, about 10 mg/60 kg to about 20 mg/60 kg, about 15 mg/60 kg to about 20 mg/60 kg, about 1 mg/60 kg to about 15 mg/60 kg, about 5 mg/60 kg to about 15 mg/60 kg, about 10 mg/60 kg to about 15 mg/60 kg, about 1 mg/60 kg to about 10 mg/60 kg, about 5 mg/60 kg to about 10 mg/60 kg, or about 1 mg/60 kg to about 5 mg/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 1 mg/60 kg, about 2 mg/60 kg, about 3 mg/60 kg, about 4 mg/60 kg, about 5 mg/60 kg, about 6 mg/60 kg, about 7 mg/60 kg, about 8 mg/60 kg, about 9 mg/60 kg, about 10 mg/60 kg, about 11 mg/60 kg, about 12 mg/60 kg, about 13 mg/60 kg, about 14 mg/60 kg, or about 15 mg/60 kg. In some embodiments, the steroid is prednisone. In some embodiments, a daily dose of prednisone between about 1 mg/60 kg and about 20 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of prednisone of about 10 mg/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0182] In some embodiments, the patient receives one or more post-operative steroid doses of about 1 g/60 kg to about 15 g/60 kg, about 5 g/60 kg to about 15 g/60 kg, about 10 g/60 kg to about 15 g/60 kg, about 1 g/60 kg to about 10 g/60 kg, about 5 g/60 kg to about 10 g/60 kg, or about 1 g/60 kg to about 5 g/60 kg. In some embodiments, the patient receives one or more post-operative steroid doses of about 1 g/60 kg, about 2 g/60 kg, about 3 g/60 kg, about 4 g/60 kg, about 5 g/60 kg, about 6 g/60 kg, about 7 g/60 kg, about 8 g/60 kg, about 9 g/60 kg, about 10 g/60 kg, about 11 g/60 kg, about 12 g/60 kg, about 13 g/60 kg, about 14 g/60 kg, or about 15 g/60 kg. In some embodiments, the steroid is sodium creatine phosphate. In some embodiments, a daily dose of sodium creatine phosphate between about 1 g/60 kg and about 15 g/60 kg is delivered for at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector. In some embodiments, a daily dose of sodium creatine phosphate of about 2 g/60 kg is delivered for

at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or at least 10 days after administration of the therapeutic vector.

[0183] In some embodiments, the patient receives an intravenous dose of sodium creatine phosphate (2 g/60 kg) and an intravenous dose of methylprednisolone sodium succinate (e.g., SOL-MEDROL®, 80 mg/60 kg) on the same day as administration of the therapeutic AAV vector and daily for 3 days following administration of the therapeutic AAV vector. On day 3 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 40 mg/60 kg for 4 days. On day 7 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 32 mg/60 kg for 7 days. On day 14 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 24 mg/60 kg for 7 days. On day 21 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 16 mg/60 kg for 7 days. On day 28 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 8 mg/60 kg for 7 days. On day 35 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 6 mg/60 kg for 7 days. On day 42 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 4 mg/60 kg for 7 days. See Figure 19 for a schematic of an exemplary treatment regimen for LHON gene therapy.

[0184] In some embodiments, the patient receives methylprednisolone (e.g., MEDROL®) tablets at a dose of 32 mg/60 kg 7 days prior to administration of the therapeutic AAV vector. On the day of administration of the therapeutic AAV vector, the patient receives an intravenous dose of methylprednisolone sodium succinate (e.g., SOL-MEDROL® (80 mg/60 kg), which is administered daily for 3 days. On day 3 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 40 mg/60 kg for 4 days. On day 7 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 32 mg/60 kg for 7 days. On day 14 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 24 mg/60 kg for 7 days. On day 21 following administration of the therapeutic AAV vector, the patient is administered

methylprednisolone (e.g., MEDROL®) tablets at a dose of 16 mg/60 kg for 7 days. On day 28 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 8 mg/60 kg for 7 days. On day 35 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 6 mg/60 kg for 7 days. On day 42 following administration of the therapeutic AAV vector, the patient is administered methylprednisolone (e.g., MEDROL®) tablets at a dose of 4 mg/60 kg for 7 days. See Figure 20 for an exemplary schematic of the treatment regimen for LHON gene therapy.

[0185] In some embodiments, the patient receives prednisone tablets at a dose of 60 mg/60 kg prior to administration of the therapeutic AAV vector and daily for 7 days following administration of the therapeutic AAV vector. On day 8 following administration of the therapeutic AAV vector, the patient is administered prednisone tablets at a dose of 40 mg/kg for one day. On day 9 following administration of the therapeutic AAV vector, the patient is administered prednisone tablets at a dose of 20 mg/kg for one day. On day 10 following administration of the therapeutic AAV vector, the patient is administered prednisone tablets at a dose of 10 mg/kg for one day. See Figure 21 for an exemplary schematic of the treatment regimen for LHON gene therapy.

[0186] Dosage amount and interval can be adjusted individually to be sufficient to maintain therapeutic effect. Skilled artisans will be able to optimize effective local dosages without undue experimentation.

[0187] In some embodiments, administration of a steroid prior to, during, and/or after administration of the therapeutic AAV vector described herein results in a higher average recovery of vision than is achieved with administration of a comparable therapeutic AAV vector without the steroid, for example, in a population of at least 10 patients. In some embodiments, administration of a steroid prior to, during, and/or after administration of the therapeutic AAV vector results in a lower incidence of an adverse event than is achieved with administration of a comparable therapeutic AAV vector without the steroid, for example, in a population of at least 10 patients. In some embodiments, the adverse event is selected from anterior chamber inflammation, vitritis, ocular hypertension, cataract removal, keratitis, vitreous hemorrhage, allergic conjunctivitis, and eye pain (*See e.g.*, Example 15).

[0188] In some embodiments, the higher average recovery of vision and the lower incidence of an adverse event achieved according to the present methods are determined by comparison to a

population of patients with the eye disorder treated with a therapeutic AAV vector without administration of a steroid prior to, during, and/or after administration of the therapeutic AAV vector. In some embodiments, the population of patients treated according to the methods of the present disclosure and the population of patients treated with a comparable therapeutic AAV vector are ethnically matched. In some embodiments, the populations of patients are Chinese or Argentinian.

Diagnostic Methods and Kits

[0189] In some embodiments, the present disclosure provides methods of screening patients for treatment of an eye disorder. In such embodiments, the methods comprise culturing a population of target cells with a composition comprising an AAV comprising a recombinant nucleic acid sequence encoding a detectable label in the presence of a serum sample obtained from a patient, and detecting the expression level of the detectable label in the target cells after the culturing, wherein the patient is selected for the treatment if the expression level of the detectable label in the target cells is higher than a pre-determined threshold. In some embodiments, the methods further comprise administering to the patient a pharmaceutical composition comprising an AAV comprising a recombinant nucleic acid sequence encoding a mitochondrial protein.

[0190] The methods of screening patients for treatment of an eye disorder described herein utilizes patient-derived serum samples to assess the immune response of particular patient against a recombinant viral vector used to deliver a therapeutic protein. Soluble factors present in patient serum, *e.g.*, antibodies, can prevent viral infection of target cells, thereby reducing the delivery of the therapeutic protein and/or reducing the efficacy of the pharmaceutical composition. Methods of the present disclosure utilize an AAV encoding a detectable label, such that the level of infectivity of target cells can be measured by detection of the label. In some embodiments, the present disclosure provides methods for identifying patients that demonstrate low immune reactivity to an AAV composition and selecting those patients for treatment with the therapeutic AAV vectors described herein. In some embodiments, the present disclosure provides methods for identifying patients that demonstrate high immune reactivity to an AAV composition and excluding those patients from future treatment with the therapeutic AAV vectors described herein.

[0191] In some embodiments, the expression level of the detectable label in the target cells correlates with the patient's immune response against the AAV vector. For example, serum from a patient demonstrating high immune reactivity to the AAV contains soluble factors preventing the AAV encoding the detectable label from infecting the target cells and preventing expression of the detectable

label in the target cells. In such instances, the expression level of the detectable label in target cells cultured in the presence of the patient serum is reduced relative to the expression level of the detectable label in target cells cultured in the absence of the patient serum. Alternatively, serum from a patient demonstrating low immune reactivity to the AAV contains fewer, or an absence of, soluble factors that prevent the AAV encoding the detectable label from infecting the target cells. In such instances, the expression level of the detectable label in target cells cultured in the presence of the patient serum is the same, or is not significantly reduced, relative to the expression level of the detectable label in target cells cultured in the absence of the patient serum.

[0192] The detectable label can be any protein or nucleic acid molecule that is not endogenously expressed by the target cell and/or the AAV vector. Examples of detectable labels include but are not limited to, FLAG tags, poly-histidine tags (*e.g.* 6xHis), SNAP tags, Halo tags, cMyc tags, glutathione-S-transferase tags, avidin, enzymes, fluorescent proteins, luminescent proteins, chemiluminescent proteins, bioluminescent proteins, and phosphorescent proteins. In some embodiments the fluorescent protein is selected from the group consisting of blue/UV proteins (such as BFP, TagBFP, mTagBFP2, Azurite, EBFP2, mKalama1, Sirius, Sapphire, and T-Sapphire); cyan proteins (such as CFP, eCFP, Cerulean, SCFP3A, mTurquoise, mTurquoise2, monomeric Midoriishi-Cyan, TagCFP, and mTFP1); green proteins (such as: GFP, eGFP, meGFP (A208K mutation), Emerald, Superfolder GFP, Monomeric Azami Green, TagGFP2, mUKG, mWasabi, Clover, and mNeonGreen); yellow proteins (such as YFP, eYFP, Citrine, Venus, SYFP2, and TagYFP); orange proteins (such as Monomeric Kusabira-Orange, mKOκ, mKO2, mOrange, and mOrange2); red proteins (such as RFP, mRaspberry, mCherry, mStrawberry, mTangerine, tdTomato, TagRFP, TagRFP-T, mApple, mRuby, and mRuby2); far-red proteins (such as mPlum, HcRed-Tandem, mKate2, mNeptune, and NirFP); near-infrared proteins (such as TagRFP657, IFP1.4, and iRFP); long stokes shift proteins (such as mKeima Red, LSS-mKate1, LSS-mKate2, and mBeRFP); photoactivatible proteins (such as PA-GFP, PAmCherry1, and PATagRFP); photoconvertible proteins (such as Kaede (green), Kaede (red), KikGR1 (green), KikGR1 (red), PS-CFP2, PS-CFP2, mEos2 (green), mEos2 (red), mEos3.2 (green), mEos3.2 (red), PSmOrange, and PSmOrange); and photoswitchable proteins (such as Dronpa). In some embodiments, the detectable tag can be selected from AmCyan, AsRed, DsRed2, DsRed Express, E2-Crimson, HcRed, ZsGreen, ZsYellow, mCherry, mStrawberry, mOrange, mBanana, mPlum, mRasberry, tdTomato, DsRed Monomer, and/or AcGFP, all of which are available from Clontech. In particular embodiments, the detectable label is GFP.

[0193] The detectable label can be detected by means commonly known in the art including, but not limited to, flow cytometry, qPCR, Western blot, ELISA, and immunohistochemistry. In particular embodiments, the detection method is a high throughput detection method such as flow cytometry or qPCR, such that multiple patient samples can be analyzed simultaneously. In some embodiments, the detection method is flow cytometry. In some embodiments, the detection method is qPCR.

[0194] In some embodiments, a pre-determined threshold for the expression level of the detectable label is set for the screening of patients for treatment of an eye disorder. In some embodiments, patients that meet or exceed this threshold are selected for treatment with a therapeutic AAV vector described herein. In some embodiments, patients that do not meet this threshold are excluded from future treatment with a therapeutic AAV vector described herein or must undergo an immunosuppression regiment prior to beginning treatment with a therapeutic AAV vector described herein.

[0195] In some embodiments, the pre-determined threshold can be expressed as an absolute expression level of the detectable label in a test sample, above which patient is characterized as suitable for gene therapy and/or below which the patient is characterized as not suitable for gene therapy. For example, in some embodiments where the detectable label is detected by qPCR, the pre-determined threshold is an absolute expression level of greater than or equal to 0.2. In such embodiments, a patient is characterized as suitable for gene therapy if the absolute expression level of the detectable label is greater than or equal to 0.2 and characterized as not suitable for gene therapy if the absolute expression level of the detectable label is less than 0.2. In some embodiments, the pre-determined threshold is an absolute expression level of greater than or equal to 0.6. In such embodiments, a patient is characterized as suitable for gene therapy if the absolute expression level of the detectable label is greater than or equal to 0.6 and characterized as not suitable for gene therapy if the absolute expression level of the detectable label is less than 0.6.

[0196] In some embodiments, where the detectable label is detected by flow cytometry, the pre-determined threshold is an absolute expression level of greater than or equal to 20% label-positive target cells in the test sample (*e.g.*, %GFP+ cells $\geq$ 20%). In such embodiments, a patient is characterized as suitable for gene therapy if the absolute expression level of the detectable label is greater than or equal to 20% label-positive target cells and characterized as not suitable for gene therapy if the absolute expression level of the detectable label is less than 20% label-positive target

cells. In some embodiments, the pre-determined threshold is an absolute expression level of greater than or equal to 40% label-positive target cells in the test sample (*e.g.*, %GFP+ cells ≥ 40%). In such embodiments, a patient is characterized as suitable for gene therapy if the absolute expression level of the detectable label is greater than or equal to 40% label-positive target cells and characterized as not suitable for gene therapy if the absolute expression level of the detectable label is less than 40% label-positive target cells.

[0197] In some embodiments, the pre-determined threshold can be expressed as a relative expression level of the detectable label in a test sample (*i.e.*, expression of the detectable label in a test sample relative to a control sample), above which patient is characterized as suitable for gene therapy and/or below which the patient is characterized as not suitable for gene therapy. In some embodiments, where the detectable label is detected by flow cytometry, the pre-determined threshold is a relative expression level of greater than or equal to 40% label-positive target cells in the test sample (*e.g.*, %GFP+ cells ≥ 40%). In such embodiments, a patient is characterized as suitable for gene therapy if the absolute expression level of the detectable label is greater than or equal to 40% label-positive target cells and characterized as not suitable for gene therapy if the absolute expression level of the detectable label is less than 40% label-positive target cells. In some embodiments, where the detectable label is detected by flow cytometry, the pre-determined threshold is a relative expression level of greater than or equal to 80% label-positive target cells in the test sample (*e.g.*, %GFP+ cells ≥ 80%). In such embodiments, a patient is characterized as suitable for gene therapy if the absolute expression level of the detectable label is greater than or equal to 80% label-positive target cells and characterized as not suitable for gene therapy if the absolute expression level of the detectable label is less than 80% label-positive target cells

[0198] In some embodiments, the patients screened for and/or selected for treatment according to the methods described herein have one or more mtDNA point mutations. In some embodiments, the patients have a point mutation in a gene encoding a protein of complex I in the oxidative phosphorylation chain of the mitochondria. For example, patients may have one or more point mutations in the *ND4* gene, the *ND1* gene, or the *ND6* gene. In some embodiments, the patients have a point mutation at nucleotide position 11778 in the *ND4* gene. In some embodiments, the point mutation is G11778A in the *ND4* gene. In some embodiments, the patients have a point mutation at nucleotide position 3460 in the *ND1* gene. In some embodiments, the point mutation is G3460A in the *ND1* gene. In some embodiments, the patients have a point mutation at nucleotide position 14484 in

the *ND6* gene. In some embodiments, the point mutation is T14484C in the *ND6* gene. In some embodiments, the patients screened for and/or selected for treatment according to the methods described herein have one or more of point mutations selected from G11778A in the *ND4* gene, G3460A in the *ND1* gene, and T14484C in the *ND6* gene and are of Chinese and/or Argentinean descent.

[0199] In some embodiments, the patients screened for and/or selected for treatment according to the methods described herein have one or more of point mutations selected from G11778A in the *ND4* gene, G3460A in the *ND1* gene, and T14484C in the *ND6* gene and are of Argentinean descent. In some embodiments, the patients screened for and/or selected for treatment according to the methods described herein have one or more of point mutations selected from G11778A in the *ND4* gene, G3460A in the *ND1* gene, and T14484C in the *ND6* gene and are of Chinese descent. In particular embodiments, the patients screened for and/or selected for treatment according to the methods described herein have one or more of point mutations selected from G11778A in the *ND4* gene and is of Chinese descent.

[0200] In some embodiments, the present disclosure provides kits for use in screening patients for treatment of an eye disorder and/or use in the election of a patient for treatment of an eye disorder. In such embodiments, the kits comprise AAV comprising a recombinant nucleic acid encoding a detectable label and one or more reagents for detecting the detectable label. In some embodiments, the one or more reagents for detecting the detectable label are selected an antibody that binds to the detectable label and one or more primer oligonucleotides specific for the recombinant nucleic acid encoding the detectable label.

[0201] In some embodiments, the kit further comprises one or more reagents for reconstituting and/or diluting the AAV vector and/or detection reagent components. In some embodiments, the kit further comprises one or more additional reagents, such as a buffer for introducing the AAV vector to a cell, a wash buffer, and/or a cell culture media. Components of a kit can be in separate containers or can be combined in a single container.

[0202] In addition to above-mentioned components, in some embodiments a kit further comprises instructions for using the components of the kit to practice the methods of the present disclosure. The instructions for practicing the methods are generally recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert or in the labeling of the container

of the kit or components thereof (*i.e.*, associated with the packaging or sub-packaging). In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, *e.g.* CD-ROM, diskette, flash drive, etc. In yet other embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, *e.g.* via the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate.

Pharmaceutical Compositions

[0203] The vector of the invention can be formulated into pharmaceutical compositions. These compositions may comprise, in addition to the vector, a pharmaceutically acceptable excipient, carrier, buffer, stabilizer or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material may be determined by the skilled person according to the route of administration, i.e. here direct retinal, subretinal or intravitreal injection.

[0204] The pharmaceutical composition is typically in liquid form. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, magnesium chloride, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. In some cases, a surfactant, such as pluronic acid (PF68) 0.001% may be used.

[0205] For injection at the site of affliction, the active ingredient will be in the form of an aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

[0206] For delayed release, the vector may be included in a pharmaceutical composition which is formulated for slow release, such as in microcapsules formed from biocompatible polymers or in liposomal carrier systems according to methods known in the art.

Samples

[0207] Samples that are suitable for use in the methods described herein can be nucleic acid samples from a subject. A "nucleic acid sample" as used herein can include RNA or DNA, or a

combination thereof. In another embodiment, a "polypeptide sample" (e.g., peptides or proteins, or fragments therefrom) can be used to ascertain information that an amino acid change has occurred, which is the result of a genetic variant. Nucleic acids and polypeptides can be extracted from one or more samples including but not limited to, blood, saliva, urine, mucosal scrapings of the lining of the mouth, expectorant, serum, tears, skin, tissue, or hair. A nucleic acid sample can be assayed for nucleic acid information. "Nucleic acid information," as used herein, includes a nucleic acid sequence itself, the presence/absence of genetic variation in the nucleic acid sequence, a physical property which varies depending on the nucleic acid sequence (e.g., Tm), and the amount of the nucleic acid (e.g., number of mRNA copies). A "nucleic acid" means any one of DNA, RNA, DNA including artificial nucleotides, or RNA including artificial nucleotides. As used herein, a "purified nucleic acid" includes cDNAs, fragments of genomic nucleic acids, nucleic acids produced using the polymerase chain reaction (PCR), nucleic acids formed by restriction enzyme treatment of genomic nucleic acids, recombinant nucleic acids, and chemically synthesized nucleic acid molecules. A "recombinant" nucleic acid molecule includes a nucleic acid molecule made by an artificial combination of two otherwise separated segments of sequence, e.g., by chemical synthesis or by the manipulation of isolated segments of nucleic acids by genetic engineering techniques. As used herein, a "polypeptide" includes proteins, fragments of proteins, and peptides, whether isolated from natural sources, produced by recombinant techniques, or chemically synthesized. A polypeptide may have one or more modifications, such as a post-translational modification (e.g., glycosylation, phosphorylation, etc.) or any other modification (e.g., pegylation, etc.). The polypeptide may contain one or more non-naturally-occurring amino acids (e.g., such as an amino acid with a side chain modification).

[0208] In some embodiments, the nucleic acid sample can comprise cells or tissue, for example, cell lines. Exemplary cell types from which nucleic acids can be obtained using the methods described herein include, but are not limited to, the following: a blood cell such as a B lymphocyte, T lymphocyte, leukocyte, erythrocyte, macrophage, or neutrophil; a muscle cell such as a skeletal cell, smooth muscle cell or cardiac muscle cell; a germ cell, such as a sperm or egg; an epithelial cell; a connective tissue cell, such as an adipocyte, chondrocyte; fibroblast or osteoblast; a neuron; an astrocyte; a stromal cell; an organ specific cell, such as a kidney cell, pancreatic cell, liver cell, or a keratinocyte; a stem cell; or any cell that develops therefrom. A cell from which nucleic acids can be obtained can be a blood cell or a particular type of blood cell including, for example, a hematopoietic stem cell or a cell that arises from a hematopoietic stem cell such as a red blood cell, B lymphocyte, T lymphocyte, natural killer cell, neutrophil, basophil, eosinophil, monocyte, macrophage, or platelet. Generally, any type of

stem cell can be used including, without limitation, an embryonic stem cell, adult stem cell, or pluripotent stem cell.

[0209] In some embodiments, a nucleic acid sample can be processed for RNA or DNA isolation, for example, RNA or DNA in a cell or tissue sample can be separated from other components of the nucleic acid sample. Cells can be harvested from a nucleic acid sample using standard techniques, for example, by centrifuging a cell sample and resuspending the pelleted cells, for example, in a buffered solution, for example, phosphate-buffered saline (PBS). In some embodiments, after centrifuging the cell suspension to obtain a cell pellet, the cells can be lysed to extract DNA. In some embodiments, the nucleic acid sample can be concentrated and/or purified to isolate DNA. All nucleic acid samples obtained from a subject, including those subjected to any sort of further processing, are considered to be obtained from the subject. In some embodiments, standard techniques and kits known in the art can be used to extract RNA or DNA from a nucleic acid sample, including, for example, phenol extraction, a QIAAMP® Tissue Kit (Qiagen, Chatsworth, Calif.), a WIZARD® Genomic DNA purification kit (Promega), or a Qiagen Autopure method using Puregene chemistry, which can enable purification of highly stable DNA well-suited for archiving.

[0210] In some embodiments, determining the identity of an allele or determining copy number can, but need not, include obtaining a nucleic acid sample comprising RNA and/or DNA from a subject, and/or assessing the identity, copy number, presence or absence of one or more genetic variations and their chromosomal locations within the genomic DNA (i.e. subject's genome) derived from the nucleic acid sample.

[0211] The individual or organization that performs the determination need not actually carry out the physical analysis of a nucleic acid sample from a subject. In some embodiments, the methods can include using information obtained by analysis of the nucleic acid sample by a third party. In some embodiments, the methods can include steps that occur at more than one site. For example, a nucleic acid sample can be obtained from a subject at a first site, such as at a health care provider or at the subject's home in the case of a self-testing kit. The nucleic acid sample can be analyzed at the same or a second site, for example, at a laboratory or other testing facility.

Nucleic Acids

[0212] The nucleic acids and polypeptides described herein can be used in methods and kits of the present disclosure. In some embodiments, aptamers that specifically bind the nucleic acids and

polypeptides described herein can be used in methods and kits of the present disclosure. As used herein, a nucleic acid can comprise a deoxyribonucleotide (DNA) or ribonucleotide (RNA), whether singular or in polymers, naturally occurring or non-naturally occurring, double-stranded or single-stranded, coding, for example a translated gene, or non-coding, for example a regulatory region, or any fragments, derivatives, mimetics or complements thereof. In some embodiments, nucleic acids can comprise oligonucleotides, nucleotides, polynucleotides, nucleic acid sequences, genomic sequences, complementary DNA (cDNA), antisense nucleic acids, DNA regions, probes, primers, genes, regulatory regions, introns, exons, open-reading frames, binding sites, target nucleic acids and allele-specific nucleic acids.

[0213] A "probe," as used herein, includes a nucleic acid fragment for examining a nucleic acid in a specimen using the hybridization reaction based on the complementarity of nucleic acid.

[0214] A "hybrid" as used herein, includes a double strand formed between any one of the abovementioned nucleic acid, within the same type, or across different types, including DNA-DNA, DNA-RNA, RNA-RNA or the like.

[0215] "Isolated" nucleic acids, as used herein, are separated from nucleic acids that normally flank the gene or nucleotide sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (e.g., as in an RNA library). For example, isolated nucleic acids of the disclosure can be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material can form part of a composition, for example, a crude extract containing other substances, buffer system or reagent mix. In some embodiments, the material can be purified to essential homogeneity using methods known in the art, for example, by polyacrylamide gel electrophoresis (PAGE) or column chromatography (e.g., HPLC). With regard to genomic DNA (gDNA), the term "isolated" also can refer to nucleic acids that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 250 kb, 200 kb, 150 kb, 100 kb, 75 kb, 50 kb, 25 kb, 10 kb, 5 kb, 4 kb, 3 kb, 2kb, 1 kb, 0.5 kb or 0.1 kb of the nucleotides that flank the nucleic acid molecule in the gDNA of the cell from which the nucleic acid molecule is derived.

[0216] Nucleic acids can be fused to other coding or regulatory sequences can be considered isolated. For example, recombinant DNA contained in a vector is included in the definition of "isolated"

as used herein. In some embodiments, isolated nucleic acids can include recombinant DNA molecules in heterologous host cells or heterologous organisms, as well as partially or substantially purified DNA molecules in solution. Isolated nucleic acids also encompass in vivo and in vitro RNA transcripts of the DNA molecules of the present disclosure. An isolated nucleic acid molecule or nucleotide sequence can be synthesized chemically or by recombinant means. Such isolated nucleotide sequences can be useful, for example, in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (e.g., from other mammalian species), for gene mapping (e.g., by in situ hybridization with chromosomes), or for detecting expression of the gene, in tissue (e.g., human tissue), such as by Northern blot analysis or other hybridization techniques disclosed herein. The disclosure also pertains to nucleic acid sequences that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleotide sequence described herein Such nucleic acid sequences can be detected and/or isolated by allele- or sequence-specific hybridization (e.g., under high stringency conditions). Stringency conditions and methods for nucleic acid hybridizations are well known to the skilled person (see, e.g., Current Protocols in Molecular Biology, Ausubel, F. et al., John Wiley & Sons, (1998), and Kraus, M. and Aaronson, S., Methods Enzymol., 200:546-556 (1991), the entire teachings of which are incorporated by reference herein.

[0217] Calculations of "identity" or "percent identity" between two or more nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first sequence). The nucleotides at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e. % identity = # of identical positions/total # of positions x 100). For example, a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[0218] In some embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%, of the length of the reference sequence. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A non-limiting example of such a mathematical algorithm is described in Karlin, S. and Altschul, S., Proc. Natl. Acad.

Sci. USA, 90- 5873-5877 (1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0), as described in Altschul, S. et al., Nucleic Acids Res., 25:3389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, any relevant parameters of the respective programs (e.g., NBLAST) can be used. For example, parameters for sequence comparison can be set at score= 100, word length= 12, or can be varied (e.g., W=5 or W=20). Other examples include the algorithm of Myers and Miller, CABIOS (1989), ADVANCE, ADAM, BLAT, and FASTA. In some embodiments, the percent identity between two amino acid sequences can be accomplished using, for example, the GAP program in the GCG software package (Accelrys, Cambridge, UK).

[0219] "Probes" or "primers" can be oligonucleotides that hybridize in a base-specific manner to a complementary strand of a nucleic acid molecule. Probes can include primers, which can be a single-stranded oligonucleotide probe that can act as a point of initiation of template-directed DNA synthesis using methods including but not limited to, polymerase chain reaction (PCR) and ligase chain reaction (LCR) for amplification of a target sequence. Oligonucleotides, as described herein, can include segments or fragments of nucleic acid sequences, or their complements. In some embodiments, DNA segments can be between 5 and 10,000 contiguous bases, and can range from 5, 10, 12, 15, 20, or 25 nucleotides to 10, 15, 20, 25, 30, 40, 50, 100, 200, 500, 1000 or 10,000 nucleotides. In addition to DNA and RNA, probes and primers can include polypeptide nucleic acids (PNA), as described in Nielsen, P. et al., Science 254: 1497-1500 (1991). A probe or primer can comprise a region of nucleotide sequence that hybridizes to at least about 15, typically about 20-25, and in certain embodiments about 40, 50, 60 or 75, consecutive nucleotides of a nucleic acid molecule.

[0220] The present disclosure also provides isolated nucleic acids, for example, probes or primers, that contain a fragment or portion that can selectively hybridize to a nucleic acid that comprises, or consists of, a nucleotide sequence, wherein the nucleotide sequence can comprise at least one polymorphism or polymorphic allele contained in the genetic variations described herein or the wild-type nucleotide that is located at the same position, or the complements thereof. In some embodiments, the probe or primer can be at least 70% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence.

[0221] In some embodiments, a nucleic acid probe can be an oligonucleotide capable of hybridizing with a complementary region of a gene associated with a condition (e.g., LHON)

containing a genetic variation described herein. The nucleic acid fragments of the disclosure can be used as probes or primers in assays such as those described herein.

[0222] The nucleic acids of the disclosure, such as those described above, can be identified and isolated using standard molecular biology techniques well known to the skilled person. In some embodiments, DNA can be amplified and/or can be labeled (e.g., radiolabeled, fluorescently labeled) and used as a probe for screening, for example, a cDNA library derived from an organism. cDNA can be derived from mRNA and can be contained in a suitable vector. For example, corresponding clones can be isolated, DNA obtained fallowing in vivo excision, and the cloned insert can be sequenced in either or both orientations by art-recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. Using these or similar methods, the polypeptide and the DNA encoding the polypeptide can be isolated, sequenced and further characterized.

[0223] In some embodiments, nucleic acid can comprise one or more polymorphisms, variations, or mutations, for example, single nucleotide polymorphisms (SNPs), single nucleotide variations (SNVs), copy number variations (CNVs), for example, insertions, deletions, inversions, and translocations. In some embodiments, nucleic acids can comprise analogs, for example, phosphorothioates, phosphoramidates, methyl phosphonate, chiralmethyl phosphonates, 2-0-methyl ribonucleotides, or modified nucleic acids, for example, modified backbone residues or linkages, or nucleic acids combined with carbohydrates, lipids, polypeptide or other materials, or peptide nucleic acids (PNAs), for example, chromatin, ribosomes, and transcriptosomes. In some embodiments nucleic acids can comprise nucleic acids in various structures, for example, A DNA, B DNA, Z-form DNA, siRNA, tRNA, and ribozymes. In some embodiments, the nucleic acid may be naturally or non-naturally polymorphic, for example, having one or more sequence differences, for example, additions, deletions and/or substitutions, as compared to a reference sequence. In some embodiments, a reference sequence can be based on publicly available information, for example, the U.C. Santa Cruz Human Genome Browser Gateway (genome.ucsc.edu/cgi-bin/hgGateway) or the NCBI website (www.ncbi.nlm.nih.gov). In some embodiments, a reference sequence can be determined by a practitioner of the present disclosure using methods well known in the art, for example, by sequencing a reference nucleic acid.

[0224] In some embodiments, a probe can hybridize to an allele, SNP, SNV, or CNV as described herein. In some embodiments, the probe can bind to another marker sequence associated with LHON as described herein.

[0225] One of skill in the art would know how to design a probe so that sequence specific hybridization can occur only if a particular allele is present in a genomic sequence from a test nucleic acid sample. The disclosure can also be reduced to practice using any convenient genotyping method, including commercially available technologies and methods for genotyping particular genetic variations

[0226] Control probes can also be used, for example, a probe that binds a less variable sequence, for example, a repetitive DNA associated with a centromere of a chromosome, can be used as a control. In some embodiments, probes can be obtained from commercial sources. In some embodiments, probes can be synthesized, for example, chemically or in vitro, or made from chromosomal or genomic DNA through standard techniques. In some embodiments sources of DNA that can be used include genomic DNA, cloned DNA sequences, somatic cell hybrids that contain one, or a part of one, human chromosome along with the normal chromosome complement of the host, and chromosomes purified by flow cytometry or microdissection. The region of interest can be isolated through cloning, or by site-specific amplification using PCR.

[0227] One or more nucleic acids for example, a probe or primer, can also be labeled, for example, by direct labeling, to comprise a detectable label. A detectable label can comprise any label capable of detection by a physical, chemical, or a biological process for example, a radioactive label, such as 32P or 3H, a fluorescent label, such as FITC, a chromophore label, an affinity-ligand label, an enzyme label, such as alkaline phosphatase, horseradish peroxidase, or I2 galactosidase, an enzyme cofactor label, a hapten conjugate label, such as digoxigenin or dinitrophenyl, a Raman signal generating label, a magnetic label, a spin label, an epitope label, such as the FLAG or HA epitope, a luminescent label, a heavy atom label, a nanoparticle label, an electrochemical label, a light scattering label, a spherical shell label, semiconductor nanocrystal label, such as quantum dots (described in U.S. Pat. No. 6,207,392), and probes labeled with any other signal generating label known to those of skill in the art, wherein a label can allow the probe to be visualized with or without a secondary detection molecule. A nucleotide can be directly incorporated into a probe with standard techniques, for example, nick translation, random priming, and PCR labeling. A "signal," as used herein, include a signal suitably detectable and measurable by appropriate means, including fluorescence, radioactivity, chemiluminescence, and the like.

[0228] Non-limiting examples of label moieties useful for detection include, without limitation, suitable enzymes such as horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or

acetylcholinesterase; members of a binding pair that are capable of forming complexes such as streptavidin/biotin, avidin/biotin or an antigen/antibody complex including, for example, rabbit IgG and anti-rabbit IgG; fluorophores such as umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, tetramethyl rhodamine, eosin, green fluorescent protein, erythrosin, coumarin, methyl coumarin, pyrene, malachite green, stilbene, lucifer yellow, Cascade Blue, Texas Red, dichlorotriazinylamine fluorescein, dansyl chloride, phycoerythrin, fluorescent lanthanide complexes such as those including Europium and Terbium, cyanine dye family members, such as Cy3 and Cy5, molecular beacons and fluorescent derivatives thereof, as well as others known in the art as described, for example, in Principles of Fluorescence Spectroscopy, Joseph R. Lakowicz (Editor), Plenum Pub Corp, 2nd edition (July 1999) and the 6th Edition of the Molecular Probes Handbook by Richard P. Hoagland; a luminescent material such as luminol; light scattering or plasmon resonant materials such as gold or silver particles or quantum dots; or radioactive material include 14C, 123I, 124I, 125I, Tc99m, 32P, 33P, 35S or 3H.

[0229] Other labels can also be used in the methods of the present disclosure, for example, backbone labels. Backbone labels comprise nucleic acid stains that bind nucleic acids in a sequence independent manner. Non-limiting examples include intercalating dyes such as phenanthridines and acridines (e.g., ethidium bromide, propidium iodide, hexidium iodide, dihydroethidium, ethidium homodimer-1 and -2, ethidium monoazide, and ACMA); some minor grove binders such as indoles and imidazoles (e.g., Hoechst 33258, Hoechst 33342, Hoechst 34580 and DAPI); and miscellaneous nucleic acid stains such as acridine orange (also capable of intercalating), 7-AAD, actinomycin D, LDS751, and hydroxystilbamidine. All of the aforementioned nucleic acid stains are commercially available from suppliers such as Molecular Probes, Inc. Still other examples of nucleic acid stains include the following dyes from Molecular Probes: cyanine dyes such as SYTOX Blue, SYTOX Green, SYTOX Orange, POPO-1, POPO-3, YOYO-1, YOYO-3, TOTO-1, TOTO-3, JOJO-1, LOLO-1, BOBO-1, BOBO-3, PO-PRO-1, PO-PRO-3, BO-PRO-1, BO-PRO-3, TO-PRO-1, TO-PRO-3, TO-PRO-5, JO-PRO-1, LO-PRO-1, YO-PRO-1, YO-PRO-3, PicoGreen, OliGreen, RiboGreen, SYBR Gold, SYBR Green I, SYBR Green II, SYBR DX, SYTO-40, -41, -42, -43, -44, -45 (blue), SYTO-13, -16, -24, -21, -23, -12, -11, -20, -22, -15, -14, -25 (green), SYTO-81, -80, -82, -83, -84, -85 (orange), SYTO-64, -17, -59, -61, -62, -60, -63 (red).

[0230] In some embodiments, fluorophores of different colors can be chosen, for example, 7-amino-4-methylcoumarin-3-acetic acid (AMCA), 5-(and-6)-carboxy-X-rhodamine, lissamine

rhodamine B, 5-(and-6)-carboxyfluorescein, fluorescein-5-isothiocyanate (FITC), 7-diethylaminocoumarin-3-carboxylic acid, tetramethylrhodamine-5-(and-6)-isothiocyanate, 5-(and-6)-carboxytetramethylrhodamine, 7-hydroxycoumarin-3-carboxylic acid, 6-[fluorescein 5-(and-6)-carboxamido]hexanoic acid, N-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a diaza-3-indacenepropionic acid, eosin-5-isothiocyanate, erythrosin-5- isothiocyanate, TRITC, rhodamine, tetramethylrhodamine, R-phycoerythrin, Cy-3, Cy-5, Cy-7, Texas Red, Phar-Red, allophycocyanin (APC),and CASCADETM blue acetylazide, such that each probe in or not in a set can be distinctly visualized. In some embodiments, fluorescently labeled probes can be viewed with a fluorescence microscope and an appropriate filter for each fluorophore, or by using dual or triple band-pass filter sets to observe multiple fluorophores. In some embodiments, techniques such as flow cytometry can be used to examine the hybridization pattern of the probes.

[0231] In other embodiments, the probes can be indirectly labeled, for example, with biotin or digoxygenin, or labeled with radioactive isotopes such as 32P and/or 3H. As a non-limiting example, a probe indirectly labeled with biotin can be detected by avidin conjugated to a detectable marker. For example, avidin can be conjugated to an enzymatic marker such as alkaline phosphatase or horseradish peroxidase. In some embodiments, enzymatic markers can be detected using colorimetric reactions using a substrate and/or a catalyst for the enzyme. In some embodiments, catalysts for alkaline phosphatase can be used, for example, 5-bromo-4-chloro-3-indolylphosphate and nitro blue tetrazolium. In some embodiments, a catalyst can be used for horseradish peroxidase, for example, diaminobenzoate.

Formulations, routes of administration, and effective doses

[0232] Yet another aspect of the present disclosure relates to formulations, routes of administration and effective doses for pharmaceutical compositions comprising an agent or combination of agents of the instant disclosure. Such pharmaceutical compositions can be used to treat a condition (e.g., LHON) as described above.

[0233] Compounds of the disclosure can be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, transdermal patch, pulmonary, vaginal, suppository, or parenteral (including intraocular, intravitreal, intramuscular, intraarterial, intrathecal, intradermal, intraperitoneal, subcutaneous and intravenous) administration or in a form suitable for administration by aerosolization, inhalation or insufflation. General information

on drug delivery systems can be found in Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems (Lippencott Williams & Wilkins, Baltimore Md. (1999).

[0234] In various embodiments, the pharmaceutical composition includes carriers and excipients (including but not limited to buffers, carbohydrates, mannitol, polypeptides, amino acids, antioxidants, bacteriostats, chelating agents, suspending agents, thickening agents and/or preservatives), water, oils including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like, saline solutions, aqueous dextrose and glycerol solutions, flavoring agents, coloring agents, detackifiers and other acceptable additives, adjuvants, or binders, other pharmaceutically acceptable auxiliary substances to approximate physiological conditions, such as pH buffering agents, tonicity adjusting agents, emulsifying agents, wetting agents and the like. Examples of excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. In some embodiments, the pharmaceutical preparation is substantially free of preservatives. In other embodiments, the pharmaceutical preparation can contain at least one preservative. General methodology on pharmaceutical dosage forms is found in Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems (Lippencott, Williams, & Wilkins, Baltimore Md. (1999)). It can be recognized that, while any suitable carrier known to those of ordinary skill in the art can be employed to administer the compositions of this disclosure, the type of carrier can vary depending on the mode of administration.

[0235] Compounds can also be encapsulated within liposomes using well-known technology. Biodegradable microspheres can also be employed as carriers for the pharmaceutical compositions of this disclosure. Suitable biodegradable microspheres are disclosed, for example, in U.S. Pat. Nos. 4,897,268, 5,075,109, 5,928,647, 5,811,128, 5,820,883, 5,853,763, 5,814,344 and 5,942,252.

[0236] The compound can be administered in liposomes or microspheres (or microparticles). Methods for preparing liposomes and microspheres for administration to a subject are well known to those of skill in the art. U.S. Pat. No. 4,789,734, the contents of which are hereby incorporated by reference, describes methods for encapsulating biological materials in liposomes. Essentially, the material is dissolved in an aqueous solution, the appropriate phospholipids and lipids added, and along with surfactants if required, and the material dialyzed or sonicated, as necessary. A review of known methods is provided by G. Gregoriadis, Chapter 14, "Liposomes," Drug Carriers in Biology and Medicine, pp. 2.sup.87-341 (Academic Press, 1979).

[0237] Microspheres formed of polymers or polypeptides are well known to those skilled in the art, and can be tailored for passage through the gastrointestinal tract directly into the blood stream. Alternatively, the compound can be incorporated and the microspheres, or composite of microspheres, implanted for slow release over a period of time ranging from days to months. See, for example, U.S. Pat. Nos. 4,906,474, 4,925,673 and 3,625,214, and Jein, TIPS 19:155-157 (1998), the contents of which are hereby incorporated by reference.

[0238] The concentration of drug can be adjusted, the pH of the solution buffered and the isotonicity adjusted to be compatible with intraocular or intravitreal injection.

[0239] The compounds of the disclosure can be formulated as a sterile solution or suspension, in suitable vehicles. The pharmaceutical compositions can be sterilized by conventional, well-known sterilization techniques, or can be sterile filtered. The resulting aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration. Suitable formulations and additional carriers are described in Remington "The Science and Practice of Pharmacy" (20th Ed., Lippincott Williams & Wilkins, Baltimore MD), the teachings of which are incorporated by reference in their entirety herein.

[0240] The agents or their pharmaceutically acceptable salts can be provided alone or in combination with one or more other agents or with one or more other forms. For example, a formulation can comprise one or more agents in particular proportions, depending on the relative potencies of each agent and the intended indication. For example, in compositions for targeting two different host targets, and where potencies are similar, about a 1:1 ratio of agents can be used. The two forms can be formulated together, in the same dosage unit e.g., in one cream, suppository, tablet, capsule, aerosol spray, or packet of powder to be dissolved in a beverage; or each form can be formulated in a separate unit, e.g., two creams, two suppositories, two tablets, two capsules, a tablet and a liquid for dissolving the tablet, two aerosol sprays, or a packet of powder and a liquid for dissolving the powder, etc.

[0241] The term "pharmaceutically acceptable salt" means those salts which retain the biological effectiveness and properties of the agents used in the present disclosure, and which are not biologically or otherwise undesirable.

[0242] Typical salts are those of the inorganic ions, such as, for example, sodium, potassium, calcium, magnesium ions, and the like. Such salts include salts with inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, methanesulfonic

acid, p toluenesulfonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, mandelic acid, malic acid, citric acid, tartaric acid or maleic acid. In addition, if the agent(s) contain a carboxyl group or other acidic group, it can be converted into a pharmaceutically acceptable addition salt with inorganic or organic bases. Examples of suitable bases include sodium hydroxide, potassium hydroxide, ammonia, cyclohexylamine, dicyclohexyl-amine, ethanolamine, diethanolamine, triethanolamine, and the like.

[0243] A pharmaceutically acceptable ester or amide refers to those which retain biological effectiveness and properties of the agents used in the present disclosure, and which are not biologically or otherwise undesirable. Typical esters include ethyl, methyl, isobutyl, ethylene glycol, and the like. Typical amides include unsubstituted amides, alkyl amides, dialkyl amides, and the like.

[0244] In some embodiments, an agent can be administered in combination with one or more other compounds, forms, and/or agents, e.g., as described above. Pharmaceutical compositions with one or more other active agents can be formulated to comprise certain molar ratios. For example, molar ratios of about 99:1 to about 1:99 of a first active agent to the other active agent can be used. In some subset of the embodiments, the range of molar ratios of a first active agent: other active agents are selected from about 80:20 to about 20:80; about 75:25 to about 25:75, about 70:30 to about 30:70, about 66:33 to about 33:66, about 60:40 to about 40:60; about 50:50; and about 90:10 to about 10:90. The molar ratio of a first active: other active agents can be about 1:9, and in some embodiments can be about 1:1. The two agents, forms and/or compounds can be formulated together, in the same dosage unit e.g., in one cream, suppository, tablet, capsule, or packet of powder to be dissolved in a beverage; or each agent, form, and/or compound can be formulated in separate units, e.g., two creams, suppositories, tablets, two capsules, a tablet and a liquid for dissolving the tablet, an aerosol spray a packet of powder and a liquid for dissolving the powder, etc.

[0245] If necessary or desirable, the agents and/or combinations of agents can be administered with still other agents. The choice of agents that can be co-administered with the agents and/or combinations of agents of the instant disclosure can depend, at least in part, on the condition being treated.

[0246] The agent(s) (or pharmaceutically acceptable salts, esters or amides thereof) can be administered per se or in the form of a pharmaceutical composition wherein the active agent(s) is in an admixture or mixture with one or more pharmaceutically acceptable carriers. A pharmaceutical composition, as used herein, can be any composition prepared for administration to a subject.

Pharmaceutical compositions for use in accordance with the present disclosure can be formulated in conventional manner using one or more physiologically acceptable carriers, comprising excipients, diluents, and/or auxiliaries, e.g., which facilitate processing of the active agents into preparations that can be administered. Proper formulation can depend at least in part upon the route of administration chosen. The agent(s) useful in the present disclosure, or pharmaceutically acceptable salts, esters, or amides thereof, can be delivered to a subject using a number of routes or modes of administration, including oral, buccal, topical, rectal, transdermal, transmucosal, subcutaneous, intravenous, intraocular, intravitreal, and intramuscular applications, as well as by inhalation.

[0247] In some embodiments, oils or non-aqueous solvents can be used to bring the agents into solution, due to, for example, the presence of large lipophilic moieties. Alternatively, emulsions, suspensions, or other preparations, for example, liposomal preparations, can be used. With respect to liposomal preparations, any known methods for preparing liposomes for treatment of a condition can be used. See, for example, Bangham et al., J. Mol. Biol. 23: 238-252 (1965) and Szoka et al., Proc. Natl Acad. Sci. USA 75: 4194-4198 (1978), incorporated herein by reference. Ligands can also be attached to the liposomes to direct these compositions to particular sites of action. Agents of this disclosure can also be integrated into foodstuffs, e.g., cream cheese, butter, salad dressing, or ice cream to facilitate solubilization, administration, and/or compliance in certain subject populations.

[0248] The compounds of the disclosure can be formulated for parenteral administration (e.g., by injection, for example, intraocular or intravitreal injection) and can be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example, solutions in aqueous polyethylene glycol.

[0249] For injectable formulations, the vehicle can be chosen from those known in art to be suitable, including aqueous solutions or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. The formulation can also comprise polymer compositions which are biocompatible, biodegradable, such as poly(lactic-co-glycolic)acid. These materials can be made into micro or nanospheres, loaded with drug and further coated or derivatized to provide superior sustained release performance. Vehicles suitable for periocular or intraocular injection include, for example, suspensions of therapeutic agent in injection grade water, liposomes and vehicles suitable for lipophilic substances. Other vehicles for periocular or intraocular injection are well known in the art.

[0250] In some embodiments, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition can also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[0251] When administration is by injection, the active compound can be formulated in aqueous solutions, specifically in physiologically compatible buffers such as Hanks solution, Ringer's solution, or physiological saline buffer. The solution can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active compound can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. In some embodiments, the pharmaceutical composition does not comprise an adjuvant or any other substance added to enhance the immune response stimulated by the peptide. In some embodiments, the pharmaceutical composition comprises a substance that inhibits an immune response to the peptide. Methods of formulation are known in the art, for example, as disclosed in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Co., Easton P.

[0252] In some embodiments, eye disorders can be effectively treated with ophthalmic solutions, suspensions, ointments or inserts comprising an agent or combination of agents of the present disclosure. Eye drops can be prepared by dissolving the active ingredient in a sterile aqueous solution such as physiological saline, buffering solution, etc., or by combining powder compositions to be dissolved before use. Other vehicles can be chosen, as is known in the art, including but not limited to: balance salt solution, saline solution, water soluble polyethers such as polyethyene glycol, polyvinyls, such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, polymers of acrylic acid such as carboxypolymethylene gel, vegetable fats such as peanut oil and polysaccharides such as dextrans, and glycosaminoglycans such as sodium

hyaluronate. If desired, additives ordinarily used in the eye drops can be added. Such additives include isotonizing agents (e.g., sodium chloride, etc.), buffer agent (e.g., boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol, etc.), thickeners (e.g., saccharide such as lactose, mannitol, maltose, etc.; e.g., hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate, etc.; e.g., mucopolysaccharide such as chondroitin sulfate, etc.; e.g., sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art).

[0253] The solubility of the components of the present compositions can be enhanced by a surfactant or other appropriate co-solvent in the composition. Such cosolvents include polysorbate 20, 60, and 80, Pluronic F68, F-84 and P-103, cyclodextrin, or other agents known to those skilled in the art. Such co-solvents can be employed at a level of from about 0.01% to 2% by weight.

[0254] The compositions of the disclosure can be packaged in multidose form. Preservatives can be preferred to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. In the prior art ophthalmic products, such preservatives can be employed at a level of from 0.004% to 0.02%. In the compositions of the present application the preservative, preferably benzalkonium chloride, can be employed at a level of from 0.001% to less than 0.01%, e.g., from 0.001% to 0.008%, preferably about 0.005% by weight. It has been found that a concentration of benzalkonium chloride of 0.005% can be sufficient to preserve the compositions of the present disclosure from microbial attack.

[0255] In some embodiments, the agents of the present disclosure are delivered in soluble rather than suspension form, which allows for more rapid and quantitative absorption to the sites of action. In general, formulations such as jellies, creams, lotions, suppositories and ointments can provide an area with more extended exposure to the agents of the present disclosure, while formulations in solution, e.g., sprays, provide more immediate, short-term exposure.

[0256] It is envisioned additionally, that the compounds of the disclosure can be attached releasably to biocompatible polymers for use in sustained release formulations on, in or attached to inserts for topical, intraocular, periocular, or systemic administration. The controlled release from a

biocompatible polymer can be utilized with a water soluble polymer to form an instillable formulation, as well. The controlled release from a biocompatible polymer, such as for example, PLGA microspheres or nanospheres, can be utilized in a formulation suitable for intra ocular implantation or injection for sustained release administration, as well any suitable biodegradable and biocompatible polymer can be used.

EXAMPLES

[0257] The following exemplary embodiments further describe the present invention. It should be understood that these examples are only intended to illustrate the invention, but not to limit the scope of the present invention. Unless otherwise indicated, the methods and conditions disclosed in e.g., sambrook et al, molecular cloning: a laboratory manual (New York: cold spring harbor laboratory press, 1989) or the conditions recommended by the manufacturer can be used in the examples below.

Example 1 – ND4 plasmid and virus preparation

1.1 plasmid preparation

[0258] The nucleotide sequence for human ND4 (**SEQ ID NO: 6**) was obtained based on US National Center for Biotechnology Information reference sequence yp_003024035.1. The sequences for the non-optimized mitochondrial targeting sequence COX10 is **SEQ ID NO: 1**. The optimized sequences for the mitochondrial targeting sequence COX10 (opt_COX10, **SEQ ID NO: 2**) and the coding sequence of human ND4 (opt_ND4, **SEQ ID NO: 7**) were designed to improve the transcription efficiency and the translation efficiency. The optimized COX10-ND4 sequence, which is about 75.89% homology to the non-optimized COX10-ND4, was followed by a three prime untranslated region (i.e., 3'UTR, **SEQ ID NO: 13**) to a recombinant nucleic acid, opt_COX10-opt_ND4-3'UTR (as shown in **SEQ ID NO: 31**).

[0259] The synthesized recombinant nucleic acid, opt_COX10-opt_ND4-3'UTR, was incorporated into an adeno-associated virus (AAV) vector by PCR amplification (**FIG. 1**). The opt_COX10-opt_ND4-3'UTR was cut by the EcoRI/SalI restriction enzymes to form cohesive ends, and then embedded into an AAV vector with EcoRI/SalI restriction sites, such as the pSNaV vector, to generate the pSNaV/rAAV2/2-ND4 plasmid (i.e., the pAAV2-optimized ND4 plasmid). The pAAV2-opt_ND4 plasmid was compared to the non-optimized pAAV2-ND4 plasmid.

[0260] The recon screening and identifying steps were similar to the CN102634527B: the plasmid was cultured at 37 °C in a LB plate. Blue colonies and white colonies were appeared, where white colonies were recombinant clones. The white colonies were picked, added to 100 mg/L ampicillin-containing LB culture medium, cultured at 37 °C, 200 rpm for 8 hours and then the plasmid were extracted from the cultured bacterial medium based on the Biomiga plasmid extraction protocol. The identification of the plasmid was confirmed using the EcoRI/SalI restriction enzymes.

1.2 cell transfection

[0261] One day before transfection, HEK293 cells were inoculated to 225 cm^2 cell culture bottle: at the inoculation density of 3.0×10^7 cells/ml, the culture medium was the Dulbecco's Modified Eagle Medium (DMEM) with 10% bovine serum, at 37 °C in a 5% CO_2 incubator overnight. The culture medium were replaced with fresh DMEM with 10% bovine serum on the day of transfection.

[0262] After the cells grow to 80-90%, discard the culture medium and transfect the cells with the pAAV2-ND4 and pAAV2-opt_ND4 plasmid, using the PlasmidTrans (VGTC) transfection kit. The detailed transfection protocol was described in CN102634527B example 1. The cells were collected 48 h after the transfection.

1.3 Collection, concentration and purification of the recombinant adeno-associated virus

[0263] Virus collection: 1) dry ice ethanol bath (or liquid nitrogen) and a 37 °C water bath were prepared; 2) the transfected cells along with media were collected in a 15 ml centrifuge tube; 3) the cells were centrifuged for 3 minutes at 1000 rpm/min; the cells and supernatant were separated; the supernatant were stored separately; and the cells were re-suspended in 1 ml of PBS; 4) the cell suspension were transferred between the dry ice-ethanol bath and 37 °C water bath repeatedly, freeze thawing for four times for 10 minutes each, slightly shaking after each thawing.

[0264] Virus concentration: 1) cell debris were removed with 10,000 g centrifugation; the centrifugal supernatant was transferred to a new centrifuge tube; 2) impurities were removed by filtering with a 0.45 μm filter; 3) each 1/2 volume of 1M NaCl and 10% PEG 8000 solution were added in the sample, uniformly mixed, and stored at 4 °C overnight; 4) supernatant was discarded after 12,000 rpm centrifugation for 2 h; after the virus precipitate was completely dissolving in an appropriate amount of PBS solution, sterilizing the sample with a 0.22 μm filter; 5) adding benzonase nuclease was added to remove residual plasmid DNA (final concentration at 50 U/ml). The tube was

inverted several times to mix thoroughly and then incubated at 37 °C for 30 minutes; 6) the sample was filtered with a 0.45 μm filtration head; the filtrate is the concentrated rAAV2 virus.

[0265] Virus purification: 1) CsCl was added to the concentrated virus solution until a density of 1.41 g/ml (refraction index at 1.372); 2) the sample was added to in the ultracentrifuge tube and filled the tube with pre-prepared 1.41 g/ml CsCl solution; 3) centrifuged at 175,000 g for 24 hours to form a density gradient. Sequential collection of different densities of the sample was performed. The enriched rAAV2 particles were collected; 4) repeating the process one more time. The virus was loaded to a 100 kDa dialysis bag and dialyzed/desalted at 4 °C overnight. The concentrated and purified recombinant adeno-associated virus were rAAV2-ND4 and rAAV2-optimized ND4.

[0266] Similarly, other mitochondrial targeting sequences (MTS), such as OPA1 (**SEQ ID NO: 5**) can be used to replace COX10 in the above example and create AAV with recombinant plasmids.

Example 2 – Intravitreal injection of rAAV2 in rabbit eyes

[0267] Twelve rabbits were divided into 2 group: rAAV2-ND4 and rAAV2-optimized ND4. Virus solution (1×10^{10} vg/0.05 mL) was punctured into the vitreous cavity from 3 mm outside the corneal limbus at the pars plana. After the intravitreal injection, the eyes were examined using slit lamp exam and fundus photography inspection. Injection for 30 days. RT-PCR detection and immunoblotting were carried out in each group respectively.

Example 3 – Real-time PCR for the expression of ND4

[0268] The RNAs from the transfected rAAV2-ND4 and rAAV2-optimized ND4 rabbit optic nerve cells were extracted using the TRIZOL total RNA extraction kit. cDNA templates were synthesized by reverse transcription of the extracted RNA.

[0269] The NCBI conserved structural domain analysis software were used to analyze the conservative structure of ND4, ensuring that the designed primers amplified fragments were located at non-conserved region; then primers were designed according to the fluorescent quantitative PCR primer design principle:

(a) β-actin-S : CGAGATCGTGCGGGACAT (**SEQ ID NO: 85**) ;

(b) β-actin-A : CAGGAAGGAGGGCTGGAAC (**SEQ ID NO: 86**);

(c) ND4-S : CTGCCTACGACAAACAGAC (**SEQ ID NO: 87**);

(d) ND4-A : AGTGCGTTCGTAGTTTGAG (**SEQ ID NO: 88**);

[0270] The fluorescent quantitative PCR reaction and protocol: fluorescence quantitative PCR were measured in a real-time PCR detection system. In a 0.2 ml PCR reaction tube, SYBR green mix 12.5 μl, ddH_2O 8 μl, 1 μl of each primer, and the cDNA sample 2.5 μl, were added to an overall volume of 25 μl. Each sample was used for amplification of the target gene and amplifying the reference gene β-actin, and each amplification were repeated three times. The common reagents were added together and then divided separately to minimize handling variation. The fluorescent quantitative PCR were carried out: pre-denaturation at 95 °C for 1 s, denaturation at 94 °C for 15 s, annealing at 55 °C for 15 sec, extension at 72 °C for 45 s. A total of 40 cycles of amplification reaction were performed and fluorescence signal acquisition was done at the extension phase of each cycle. After the reaction, a 94 °C to 55 °C melting curve analysis was done. By adopting a relative quantitative method research of gene expression level difference to beta-actin was used as an internal reference gene.

[0271] As shown in **FIG. 2**, the relative expression level (mRNA level) of the rAAV2-ND4 and rAAV2-optimized ND4 were 0.42 ± 0.23 and 0.57 ± 0.62, respectively ($p < 0.05$, **FIG. 2**). The results unexpectedly show that the optimized ND4 (opt_ND4, **SEQ ID NO: 7**) coding nucleic acid sequence and the corresponding recombinant nucleic acid (opt_COX10-opt_ND4-3'UTR, **SEQ ID NO: 31**) surprisingly increased the transcription efficiency, increasing the expression of the rAAV2-optimized ND4 by about 36%. The results showed that the transcription efficiency of the rAAV2-optimized ND4 is significantly higher.

Example 4 - Immunoblotting detection of ND4 expression

[0272] The ND4 protein was purified from the rabbit nerve cells transfected by rAAV2-optimized ND4 and rAAV2-ND4, respectively. After a 10% polyacrylamide gel electrophoresis, and transferred to a polyvinylidene difluoride membrane (Bio-Rad, HER-hercules, CA, USA) for immune detection. β-actin was used as an internal reference gene. The film strip was observed on an automatic image analysis instrument (Li-Cor; Lincoln, NE, USA) and analyzed using the integrated optical density of the protein band with integral normalization method, so as to obtain the same sample corresponding optical density value. The statistical analysis software SPSS 19.0 was used for the data analysis.

[0273] The results was shown in **FIG. 3**. The average relative protein expression level of ND4 for rAAV2-optimized ND4 (left black column) and rAAV2-ND4 was 0.32 ± 0.11 and 0.68 ± 0.20, respectively ($p < 0.01$, **FIG. 3**). The results unexpectedly show that the optimized ND4 coding nucleic acid sequence (opt_ND4, **SEQ ID NO: 7**) and the corresponding recombinant nucleic acid

(opt_COX10-opt_ND4-3'UTR, **SEQ ID NO: 31**) surprisingly increased the translation efficiency, increasing the expression of the rAAV2-optimized ND4 by about 112%. The results showed that the translation efficiency of the rAAV2-optimized ND4 is also significantly higher.

Example 5 - Rabbits intraocular pressure and eye-ground photography

[0274] Slit lamp examination and intraocular pressure measurement was performed on both groups of rabbits at 1, 3, 7, and 30 days after the surgery. No obviously abnormality, conjunctival congestion, secretions, or endophthalmitis were observed and the intraocular pressure were not elevated in all the rabbits.

[0275] The fundus photographic results were shown in **FIG. 4**. No obvious damage or complication to the optic nerve and retinal vascular of the rabbits, indicating the standard intravitreal injection is safe without noticeable inflammation reaction or other complications.

Example 6 – Human clinical trial

[0276] Two groups of patients were tested: 1) between 2011 and 2012, 9 patients received intravitreal injection of 1×10^{10} vg/0.05 mL rAAV2-ND4 in a single eye, as a control group; and 2) between 2017 and January 2018, 20 patients received intravitreal injection of 1×10^{10} vg/0.05 mL rAAV2-optimized ND4 in a single eye, as an experimental group. The results of the clinical trial were analyzed using the statistical analysis SPSS 19.0.

[0277] The comparison of the two groups is shown in Table 2. The fastest eyesight improving time was 1 month in the experimental group, which was significantly faster than the control group at 3 months ($p < 0.01$); the optimal recovery of vision for the experimental group was 1.0, which was obviously higher than the control group at 0.8 ($p < 0.01$); the average recovery of vision in the experimental group was 0.582 ± 0.086, which was obviously higher than the control group at 0.344 ± 0.062 ($p < 0.01$). The fundus photographic results were shown in **FIG. 5**. No obvious damage or complication to the optic nerve and retinal vascular of the patients in the experimental and control groups, indicating the safety of the intravitreal injection of rAAV2-optimized ND4 and rAAV2-ND4.

Table 2: The comparison of rAAV2-optimized ND4 and rAAV2-ND4 in LHON gene therapy

group	Patient number	Fastest eyesight improving time (month)	Number of patients with improved vision	optimal recovery of vision	average recovery of vision
control	9	3	6 (67%)	0.8	0.344±0.062
experimental	20	1	15 (75%)	1.0	0.582±0.086
P value		<0.01	<0.01	<0.01	<0.01

Example 7 – OPA1 as the mitochondrial targeting sequences

[0278] The COX10 and 3'UTR sequences in the recombinant nucleic acid (opt_COX10-opt_ND4-3'UTR, **SEQ ID NO: 31**) in examples 1-6 were replaced with another mitochondrial targeted sequence, OPA1 (**SEQ ID NO: 5**) and another 3'UTR sequence, 3'UTR* (**SEQ ID NO: 14**) respectively, to generate a new recombinant nucleic acid, OPA1-opt_ND4-3'UTR* (**SEQ ID NO: 74**).

[0279] Experimental methods were the same as examples 1-6, where the recombinant nucleic acid opt_COX10-opt_ND4-3'UTR (**SEQ ID NO: 31**) was replaced by OPA1-opt_ND4-3'UTR* (**SEQ ID NO: 74**). It was found that, the optimized ND4 sequence has significantly improved transcription and translation efficiencies, expression levels, as well as higher efficacy and safety in treating LHON when compared to non-optimized ND4 (COX10-ND4-3'UTR, **SEQ ID NO: 15**).

Example 8 – Optimized ND4 sequence opt_ND4*

[0280] Similar experimental methods in examples 1-6 were followed using the nucleic acid, opt_COX10*-opt_ND4*-3'UTR (**SEQ ID NO: 47**). Follow the similar procedures as in example 1, virus tagged with a fluorescent protein, EGFP, was prepared as rAAV2-ND4-EGFP and rAAV2-opt_ND4*-EGFP.

[0281] The frozen 293T cell was resuscitated and allowed to grow in a T75 flask to about 90%. The cells were precipitated and resuspended in DMEM complete medium to a cell density of 5×10^4 cells/mL. The cells were resuspended. About 100 μl of the cell suspension (about 5000 cells) were added in each well of a 96 well plate. The cells were cultured and grown to 50% under 37 °C and 5% CO_2. About 0.02 μl PBS was mixed with 2×10^{10} vg/0.02 μl of the virus rAAV2-ND4-EGFP and rAAV2-opt_ND4*-EGFP, respectively. After 48 hours, fluorescence microscopy and RT-PCR detection and immunoblotting experiments were performed. As shown in **FIG. 6**, EGFP was

successfully expressed, indicating that rAAV carrying the EGFP gene was successfully transfected in the 293T cells and rAAV2-ND4-EGFP and rAAV2-opt_ND4*-EGFP were successfully expressed.

[0282] Real-time PCR tests similar to example 3 was following using the following primers:

(a) β-actin-S: CGAGATCGTGCGGGACAT (**SEQ ID NO: 85**) ;

(b) β-actin-A: CAGGAAGGAGGGCTGGAAC (**SEQ ID NO: 86**);

(c) ND4-S: GCCAACAGCAACTACGAGC (**SEQ ID NO: 107**);

(d) ND4-A: TGATGTTGCTCCAGCTGAAG (**SEQ ID NO: 108**);

[0283] The results unexpectedly show that the optimized ND4* (opt_ND4, **SEQ ID NO: 8**) coding nucleic acid sequence and the corresponding recombinant nucleic acid (opt_COX10*-opt_ND4*-3'UTR, **SEQ ID NO: 47**) surprisingly increased the transcription efficiency, increasing the expression of the rAAV2-opt_ND4 by about 20%. The results showed that the transcription efficiency of the rAAV2-opt_ND4 is significantly higher.

[0284] **FIG. 7** shows the ND4 expression in 293T cells. The average expression of ND4 protein for rAAV2-ND4 is 0.36, while the average expression of ND4 protein for rAAV2-opt_ND4* is 1.65, which is about 4.6 times higher than the rAAV2-ND4 group ($p < 0.01$) (see **FIG. 8**).

[0285] **FIG. 9** shows the ND4 expression in rabbit optic nerve cells. The average expression of ND4 protein for rAAV2-ND4 is 0.16, while the average expression of ND4 protein for rAAV2-opt_ND4* is 0.48, which is about 3 times higher than the rAAV2-ND4 group ($p < 0.01$) (see **FIG. 10**).

[0286] Similar to example 5, slit lamp examination and intraocular pressure measurement was performed on both groups of rabbits at 1, 3, 7, and 30 days after the surgery. No obviously abnormality, conjunctival congestion, secretions, or endophthalmitis were observed and the intraocular pressure were not elevated in all the rabbits.

[0287] The fundus photographic results for rAAV2-ND4 and rAAV2-opt_ND4* were shown in **FIG. 11**. No obvious damage or complication to the optic nerve and retinal vascular of the rabbits, indicating the standard intravitreal injection is safe without noticeable inflammation reaction or other complications.

[0288] Eye balls from both rabbit groups were removed after the slit lamp examination and intraocular pressure measurement. Eye balls were fixed, and dehydrated using paraffin. Tissues were pathologically sectioned along the direction of optic nerves. After further dehydration, the tissue sample was dyed using hematoxylin and eosin. The microscope inspection result is referred to **FIG.**

12. As shown in the HE staining results, the rabbit retinal ganglion fiber layer was not damaged and the number of ganglion cells was not reduced, indicating the intravitreal injection did not produce retinal toxicity or nerve damage, and can be used safely.

[0289] Experimental methods were the same as example 8, where the recombinant nucleic acid opt_COX10*-opt_ND4*-3'UTR (**SEQ ID NO: 47**) was replaced by OPA1-opt_ND4*-3'UTR* (**SEQ ID NO: 76**). It was found that, the optimized ND4 sequence has significantly improved transcription and translation efficiencies, expression levels, as well as higher efficacy and safety in treating LHON when compared to non-optimized ND4 (COX10-ND4-3'UTR, **SEQ ID NO: 15**).

Example 9 – ND6 sequence

[0290] Similar experimental methods in examples 1-6 were followed using the nucleic acid, COX10-ND6-3'UTR (**SEQ ID NO: 21**), which is the combination (5' to 3') of COX10 (**SEQ ID NO: 1**), ND6 (**SEQ ID NO: 9**), and 3'UTR (**SEQ ID NO: 13**).

[0291] The plasmid screening for COX10-ND6-3'UTR (**SEQ ID NO: 21**) used the following primers:

(a) ND6-F: ATGATGTATGCTTTGTTTCTG (**SEQ ID NO: 89**);

(b) ND6-R: CTAATTCCCCCGAGCAATCTC (**SEQ ID NO: 90**).

[0292] The transfected and screened virus rAAV2-ND6 had a viral titer of 2.0×10^{13} vg/mL. Similar to example 5, slit lamp examination and intraocular pressure measurement was performed on three groups of rabbits (A: rAAV2-ND6; B: rAAV-GFP; C: PBS) at 1, 7, and 30 days after the surgery (**FIG. 13**). No obviously abnormality, conjunctival congestion, secretions, or endophthalmitis were observed and the intraocular pressure were not elevated in all the rabbits.

[0293] Real-time PCR tests similar to example 3 was following using the following primers:

(a) β-actin-S: CGAGATCGTGCGGGACAT (**SEQ ID NO: 85**);

(b) β-actin-A: CAGGAAGGAGGGCTGGAAC (**SEQ ID NO: 86**);

(c) ND6-S: AGTGTGGGTTTAGTAATG (**SEQ ID NO: 91**);

(d) ND4-A: TGCCTCAGGATACTCCTC (**SEQ ID NO: 92**).

[0294] The results show that the expression of ND6 for rAAV2-ND6 and control (PBS) was 0.59 ± 0.06 and 0.41 ± 0.03, respectively. The results showed that the transcription efficiency of the rAAV2-ND6 is higher than the control group ($p<0.01$).

Example 10 – Optimized opt_ND6 sequence

[0295] Similar experimental methods in examples 1-6 were followed using the nucleic acid, opt_COX10*-opt_ND6-3'UTR (**SEQ ID NO: 51**), which is the combination (5' to 3') of opt_COX10* (**SEQ ID NO: 3**), opt_ND6 (**SEQ ID NO: 10**), and 3'UTR (**SEQ ID NO: 13**).

[0296] Three groups of rabbits were injected: A: 10^{10} vg/50 µl of rAAV2-opt_ND6, B: 10^{10} vg/50 µl of rAAV2-ND6 (example 9), and C: 10^{10} vg/50 µl of rAAV2-EGFP. **FIG. 14** shows the fundus photographic results for rabbits injected with rAAV2-opt_ND6 (A), rAAV2-ND6 (B), rAAV-EGFP (C), respectively. No obviously abnormality, conjunctival congestion, secretions, or endophthalmitis were observed and the intraocular pressure were not elevated in all the rabbits.

[0297] Real-time PCR tests similar to example 3 was following using the following primers:

(a) β-actin-F: CTCCATCCTGGCCTCGCTGT (**SEQ ID NO: 93**);

(b) β-actin-R: GCTGTCACCTTCACCGTTCC (**SEQ ID NO: 94**);

(c) ND6-F: GGGTTTTCTTCTAAGCCTTCTCC (**SEQ ID NO: 95**);

(d) ND6-R: CCATCATACTCTTTCACCCACAG (**SEQ ID NO: 96**);

(e) opt_ND6-F: CGCCTGCTGACCGGCTGCGT (**SEQ ID NO: 97**);

(f) opt_ND6-R: CCAGGCCTCGGGGTACTCCT (**SEQ ID NO: 98**).

[0298] As shown in **FIG. 15**, rAAV2-opt_ND6 (A) and rAAV2-ND6 (B) both had higher ($p<0.05$) relative ND6 expression levels than the control group (C). rAAV2-opt_ND6 (A) had a little higher relative ND6 expression levels than rAAV2-ND6 (B). As shown in the western blot in **FIG. 16**, rAAV2-opt_ND6 (A) had more than 3 times higher relative ND6 expression levels than rAAV2-ND6 (B).

[0299] Experimental methods were the same as example 8, where the recombinant nucleic acids, COX10-ND6-3'UTR (**SEQ ID NO: 21**) and opt_COX10*-opt_ND6-3'UTR (**SEQ ID NO: 51**), were replaced by OPA1-ND6-3'UTR (**SEQ ID NO: 77**) and OPA1-opt_ND6-3'UTR (**SEQ ID NO: 79**). It was found that, the optimized ND6 sequence has significantly improved transcription and translation efficiencies, expression levels, as well as higher efficacy and safety in treating LHON.

Example 11 – ND1 and opt_ND1 sequences

[0300] Similar experimental methods in examples 1-6 were followed using rAAV2-ND1, COX10-ND1-3'UTR (**SEQ ID NO: 25**), which is the combination (5' to 3') of COX10 (**SEQ ID NO: 1**), ND1 (**SEQ ID NO: 11**), and 3'UTR (**SEQ ID NO: 13**); and rAAV2-opt_ND1, opt_COX10*-

opt_ND1-3'UTR (**SEQ ID NO: 55**), which is the combination (5' to 3') of opt_COX10* (**SEQ ID NO: 3**), opt_ND1 (**SEQ ID NO: 12**), and 3'UTR (**SEQ ID NO: 13**).

[0301] The plasmid screening for COX10-ND1-3'UTR (**SEQ ID NO: 25**) used the following primers:

(a) ND1-F: ATGGCCGCATCTCCGCACACT (**SEQ ID NO: 99**),

(b) ND1-R: TTAGGTTTGAGGGGGAATGCT (**SEQ ID NO: 100**),

[0302] The plasmid screening for opt_COX10*-opt_ND1-3'UTR (**SEQ ID NO: 55**) used the following primers:

(a) ND1-F: AACCTCAACCTAGGCCTCCTA (**SEQ ID NO: 101**),

(b) ND1-R: TGGCAGGAGTAACCAGAGGTG (**SEQ ID NO: 102**),

[0303] Three groups of rabbits were injected: A: 10^{10} vg/50 µl of rAAV2-opt_ND1, B: 10^{10} vg/50 µl of rAAV2-ND1 (example 9), and C: 10^{10} vg/50 µl of rAAV2-EGFP. No obviously abnormality, conjunctival congestion, secretions, or endophthalmitis were observed and the intraocular pressure were not elevated in all the rabbits.

[0304] Real-time PCR tests similar to example 3 was following using the following primers:

(a) ND1-F: AGGAGGCTCTGTCTGGTATCTTG (**SEQ ID NO: 103**);

(b) ND1-R: TTTTAGGGGCTCTTTGGTGAA (**SEQ ID NO: 104**);

(c) opt_ND1-F: GCCGCCTGCTGACCGGCTGCGT (**SEQ ID NO: 105**);

(d) opt_ND1-R: TGATGTACAGGGTGATGGTGCTGG (**SEQ ID NO: 106**);

[0305] As shown in **FIG. 17**, rAAV2-opt_ND1 (A) and rAAV2-ND1 (B) both had higher ($p<0.05$) relative ND1 expression levels than the control group (C). As shown in the western blot in **FIG. 18**, rAAV2-opt_ND1 (A) had more than 2 times higher relative ND6 expression levels than rAAV2-ND1 (B).

[0306] Experimental methods were the same as example 8, where the recombinant nucleic acids, COX10-ND1-3'UTR (**SEQ ID NO: 25**) and opt_COX10*-opt_ND1-3'UTR (**SEQ ID NO: 55**), were replaced by OPA1-ND1-3'UTR (**SEQ ID NO: 81**) and OPA1-opt_ND1-3'UTR (**SEQ ID NO: 83**). It was found that, the optimized ND1 sequence has significantly improved transcription and translation efficiencies, expression levels, as well as higher efficacy and safety in treating LHON.

Example 12 – Other fusion proteins

[0307] Similar experimental methods in examples 1-6 can be followed using other fusion proteins as set forth in SEQ ID NO: 15-84. And similar results are expected to be achieved.

Example 13 – Formulation development

[0308] AAV2 virus samples were used to screen different AAV formulations. The stability of the different AAV formulations were evaluated using the StepOnePlus real-time PCR system. The viral titer of each formulation under a freeze/thaw cycle condition was measured.

[0309] First, three different formulations were tested under 1, 2, 3, 4, and 5 freeze/thaw cycles and the viral titers were measured and summarized in Table 3. The three formulations tested were: A: phosphate-buffered saline (PBS); B: 1% α,α-trehalose dehydrate, 1% L-histidine monohydrochloride monohydrate, and 1% polysorbate 20; and C: 180 mM NaCl, 10 mM NaH_2PO_4/Na_2HPO_4, and 0.001% poloxamer 188, pH 7.3. As shown in Table 3, formulation C has the lowest relative standard deviation (RSD) after 5 freeze/thaw cycles, indicating superior stability as an AAV formulation.

Table 3 –Viral titers of formulations A, B, and C

	0 cycle	1 cycle	2 cycles	3 cycles	4 cycles	5 cycles	RSD
Formulation A	1.15E+11	9.48E+10	6.16E+10	2.90E+10	1.56E+10	5.26E+09	83.18
Formulation B	4.25E+11	5.12E+11	6.66E+11	4.30E+11	4.77E+11	4.20E+11	19.30
Formulation C	4.96E+11	6.91E+11	7.69E+11	6.82E+11	6.83E+11	7.27E+11	13.90

[0310] As shown in Table 3, formulation C has the lowest relative standard deviation (RSD) after 5 freeze/thaw cycles, indicating superior stability as an AAV formulation.

[0311] Second, another group of three different formulations were tested under 1, 2, 3, 4, and 5 freeze/thaw cycles and the viral titers were measured and summarized in Table 4. The three formulations tested were: D: phosphate-buffered saline (PBS), pH 7.2-7.4; E: PBS and 0.001% poloxamer 188, pH 7.2-7.4; and F: 80 mM NaCl, 5 mM NaH_2PO_4, 40 mM Na_2HPO_4, 5 mM KH_2PO_4 and 0.001% poloxamer 188, 7.2-7.4.

Table 4 – Viral titers of Formulations of D, E, and F

	0 cycle	1 cycle	2 cycles	3 cycles	4 cycles	5 cycles	RSD
Formulation D	1.13E+10	4.62E+09	2.25E+09	1.25E+09	1.01E+09	9.48E+08	113.25
Formulation E	4.72E+10	5.48E+10	5.33E+10	5.33E+10	4.94E+10	4.08E+10	10.53
Formulation F	6.61E+10	6.08E+10	6.47E+10	6.84E+10	6.52E+10	6.05E+10	4.81

[0312] As shown in Table 4, formulation F has the lowest relative standard deviation (RSD) after 5 freeze/thaw cycles, indicating superior stability as an AAV formulation. Overall, formulation F also has the lowest RSD among all tested formulations and can be used as the AAV formulation for future development.

[0313] A third group of formulations were tested under 1, 2, 3, and 4 freeze/thaw cycles and the viral titers were determined using qRT-PCR. In addition to formulation F, the two other formulations tested were: G: 8.4 mM KH_2PO_4, 5.6 mM Na_2HPO_4 and 154 mM NaCl; H: 8.4 mM KH_2PO_4, 5.6 mM Na_2HPO_4, 0.15 M NaCl and 0.001% poloxamer 188, pH 7.2-7.4.

[0314] *HEK293 cell culture and rAAV2 transduction*: A cryotube containing HEK293 cells was thawed and dispensed into a cell culture flask containing high-glucose DMEM media supplemented with 10% fetal bovine serum. HEK293 cells were incubated for 24 hours at 37°C in 5% CO_2. HEK293 cells were seeded into 24 well plates and transduced with the AAV2 formulation F, G, or H at a MOI of 20000. The control group was incubated with PBS alone.

RNA extraction:

[0315] Total RNA was isolated from transduced HEK293 cells using TRIZOL and cDNA was synthesized by reverse transcription. Primers for RT-PCR analysis were as follows:

(a) β-actin-F: CTCCATCCTGGCCTCGCTGT (SEQ ID NO: 93)

(b) β-actin-R: GCTGTCACCTTCACCGTTCC (SEQ ID NO: 94)

(c) ND4-F: ATCTCCGCACACTCTCTCCTCA (SEQ ID NO: 165)

(d) ND4-R: TAGGTTGTTGTTGATTTGGTT (SEQ ID NO: 166)

[0316] qRT-PCR: A reaction mix was prepared containing 10 μL of TB Green, 0.3 μL of forward and reverse primers, 0.4 μL ROX Reference Dye, 4.3 μL EASY Dilution and 5 μL of cDNA. Quantitative RT-PCR was performed by pre-denaturation at 95°C for 10 minutes followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. The fluorescence signals were collected during

the extension phase of each cycle. The ND4 expression level (relative quantification) can be calculated as $2^{-(Ct(ND4,sample)-Ct(\beta-actin,sample)-Ct(ND4,control)-Ct(\beta-actin,control))}$.

Table 17: ND4 Expression normalized to PBS control

	original	1 cycle	2 cycles	3 cycles	4 cycles	average	RSD
Formulation G	13.21	11.27	12.77	14.95	13.37	13.05	10.11%
Formulation H	105.39	104.60	71.80	102.28	107.29	96.0175	15.53%
Formulation F	122.45	35.19	89.60	78.85	30.93	81.5225	47.28%

[0317] As shown in Table 17, formulations F and H showed higher relative expression of ND4 after 4 freeze/thaw cycles, especially formulation H, which indicated superior stability and transduction efficiency as an AAV formulation.

Example 14 - Preparation of recombinant adeno-associated virus

[0318] A recombinant adeno-associated virus rAAV2/2-ND4 was prepared according to the methods described in Example 1.

[0319] Plasmid preparation: The fusion nucleic acid according to SEQ ID NO: 6 was synthesized by Chengdu Qingke Yuxi Biotechnology Co., Ltd. The full-length gene was amplified by PCR, and the sticky terminus was formed on the fusion gene by EcoRI/SalI digestion. The fusion gene was inserted into the adeno-associated virus carrier pSNaV with the EcoRI/SalI restriction site, that is, pSNaV/rAAV2/2-ND4 (hereinafter referred to as pAAV2-ND4). Briefly, after incubation at 37°C, the LB plate showed blue colonies and white colonies, wherein the white colonies were recombinant clones. White colonies were picked and added to LB liquid medium containing ampicillin (100 mg/L), and cultured at 37°C at 200 rpm for 8 hours. After culturing, the bacterial solution was obtained and the plasmid was extracted. In the plasmid extraction step, EcoRI/SalI enzyme digestion was used with reference to Biomega instructions.

[0320] Cell transfection: HEK293 cells were seeded in 225 cm^2 cell culture flasks at a density of 3.0×10^7 cells/mL in DMEM containing 10% bovine serum and incubated overnight at 37°C and 5% CO_2. When the cells reached 80-90% confluency, the medium was discarded and the cells were transfected with pAAV2-ND4 (for specific transfection steps, see Example 1) using the PlasmidTrans II (VGTC) transfection kit. The cells were harvested 48 hours following transfection.

[0321] Collection and concentration of virus: The transduced cells were collected with medium into a 15 mL centrifuge tube and centrifuged at 1000 rpm for 3 minutes. The cells and

supernatant were separated, the supernatant was additionally stored, and the cells were resuspended in 1 mL of PBS. The cell suspension was repeatedly frozen in a dry ice ethanol bath or liquid nitrogen bath and thawed in a 37°C water bath four times for 10 minutes each, and slightly vortexed after each melting. The supernatants were centrifuged at 10,000 × g to remove cell debris, transferred to a new centrifuge tube and filtered using a 0.45 μm filter to remove impurities. A half volume of 1M NaCl 10% PEG8000 solution was added to the supernatant, thoroughly mixed, and kept overnight at 4° C. The following day, the virus was centrifuged at 12,000 rpm for 2 h, the supernatant was discarded, and the precipitated virus was resuspended in an appropriate amount of PBS solution and filtered using a 0.22 μm filter for sterilization. The remaining plasmid DNA was removed by digestion with Benzonase Nuclease (50 U/mL) at 37° C for 30 minutes and refiltered with a 0.45 μm filter head to obtain concentrated rAAV2 virus.

[0322] Purification of virus: Solid CsCl was added to the concentrated virus to a density of 1.41 g/mL (refractive index was 1.372). The sample was placed in an ultracentrifuge tube and the remaining space of the centrifuge tube was filled with pre-formulated 1.41 g/mL CsCl solution. The sample was centrifuged at 175,000 × g for 24 hours to form a density gradient to collect samples of different densities. The viral titer of the samples was determined and components enriched with rAAV2 particles were collected. This process was repeated, loading the virus into a 100 kDa dialysis bag and stored overnight at 4°C for dialysis.

Example 15 – Gene therapy for treatment of Leber's Hereditary Optic Neuropathy

[0323] A multicenter prospective clinical trial was performed to assess the efficacy of rAAV-ND4 in patients meeting the diagnostic criteria for LHON.

Study Design

[0324] *Research site*: This study was a clinical trial, and the genetic diagnosis was performed at the Genetic Diagnosis Center at Tongji Hospital. Ophthalmic examination was completed in the ophthalmology examination room of Tongji Hospital. The whole body examination (partial) was performed by designated personnel and standard equipment in the laboratory.

[0325] *Patient recruitment guidelines:* Patients were required to be diagnosed as LHON by genetic testing for the 11778 site mutation. The subjects were age 10-65 years old, male or female. Patients were observed at least three months for an improvement in vision. Patients were excluded from the study if they had a terminal disease, previous ocular disease history, allergies to essential drugs used during the treatment, or demonstrated positive results in an AAV2 humoral response test.

Patients were required to sign the Informed Consent Form for Leber's Gene Therapy and Informed Consent for Vitreous Injection.

[0326] *Pre-operative guidelines*: Medical staff were advised to disinfect the operating room and medical supplies before surgery, and prepare for consumables during the operation and to strictly abide by the surgical grading system and aseptic operation principles.

[0327] *Pre-operative examination:* Patients underwent a whole body examination prior to surgery including blood analysis, urine analysis, liver and kidney function, blood coagulation function, infectious disease screening, immune analysis (cell immunity: CD3, CD4, CD8; humoral immunity: IgA, IgM, IgG); electrocardiogram and chest fluoroscopy. Patients additionally underwent pre-operative ophthalmologic examinations including visual acuity, intraocular pressure, slit lamp examination, fundus examination, fundus photography, anterior segment photography, optic nerve OCT, visual field examination, and VEP. These series of examinations were performed not less than three times within 6 months. Patients were screened for the mtDNA base pair mutation G11778A in Leber's disease. That is, the arginine of the NADH dehydrogenase subunit 4 protein was converted into histidine, resulting in a loss-of-function disorder, an optic nerve injury, and Leber hereditary optic nerve lesion, which has a high incidence and a poor prognosis (see Chinese Patent CN 102634527 B). An AAV2 humoral immunological assay (described below in Examples 16) was also performed prior to treatment.

[0328] *Pre-operative treatment:* Patients receiving LHON gene therapy were administered a daily 32 mg/60 kg dose of the oral steroid, MEDROL® , once a day starting 7 days before surgery. An AAV2 humoral immunological examination using patient serum was performed to determine if the pre-treatment rAAV2 immunity of the patient was low before beginning rAAV2 treatment. Antibiotic eye drops and eye ointment were applied on the day before surgery to wash the lacrimal conjunctival sac.

Intravitreal injection:

[0329] The clinical grade rAAV2-ND4 dosage form (State Key Laboratory of Biotherapy of Sichuan University) was used as an injection. The recombinant adeno-associated virus rAAV2-ND4 (SEQ ID NO: 6) was prepared as described in Example 14. The dose was 1×10^{10} vg/0.05 mL. The amount of drug for intravitreal injection under local anesthesia was 0.05 mL. A single dose of the drug was administered by intraluminal injection under local anesthesia. Disinfection measures and surgical

consumables were prepared in a laminar flow operation room. Routine disinfection of the towel, face, and eye was performed before surgery, and the eye was marked for injection.

[0330] Gene drugs were managed by designated personnel. Before the drug was administered, the information of the patient was checked to make sure that the drug packaging was complete and non-polluted, and the drug packaging was strictly sterilized. When the drug was extracted from the vial, the operation was slow and smooth, and the drug was pumped once, and the bottle wall was not repeatedly sucked and touched to avoid drug contamination. After the drug was extracted from the vial, the injection was completed within half an hour. After the injection was completed, the drug package and the remaining drug were retained and stored at -20° C for reference. Absolute aseptic operation was required during the drug extraction process. If the drug fell to the ground, or the suction needle touched the contaminated area, the drug was discarded. Any drug with a risk of contamination was not injected into the patient's vitreous cavity.

[0331] Specific operating guidelines for vitreous cavity injection: preparation of instruments and drugs before injection, and assistants to perform routine vitreous cavity injection operations such as disinfection and drape. The drug was removed from dry ice and held tightly by hand for 2-3 minutes until the drug thawed into liquid. The bottle cap and bottle were wiped with gauze containing iodophor twice for sterilization, then dry gauze was used to wipe the bottle and the bottle cap. It should be noted that the wiping was clockwise to prevent the bottle mouth from opening and iodophor infiltration. After completing the disinfection, the bottle cap was opened, and the operator took the drug with an insulin needle, and the volume was adjusted to 0.05 mL. At the same time, the assistant prepared for anesthesia injection, disinfection, reclamation, etc., and washed the conjunctival sac with 0.5% povidone iodine 3 times, and injected the vitreous cavity according to the vitreous cavity injection guidelines. Immediately after withdrawal of the needle, the injection site was pressed with a cotton swab and massaged for 10 seconds to prevent drug leakage.

[0332] After injecting the drug, an antibiotic eye ointment was applied to the injected eye and the eye was covered with a cotton swab. The patient laid flat for 20 min and then returned to the ward. The patient was told not to rub their eyes. After completing the injection, attention was paid to the recovery of the patient following gene therapy.

Post-operative medication:

[0333] Systemic medication:

(a) MEDROL® tablet, 32 mg/60 kg, for 7 days prior to the surgery;

(b) Sodium creatine phosphate iv drip, 2 g/60 kg, for 3 days after the surgery (including the day of surgery);

(c) SOLU-MEDROL® iv drip, 80 mg/60 kg, for 3 days after the surgery (including the day of surgery);

(d) On the third day after surgery, SOLU-MEDROL® was changed to MEDROL®, po, 40 mg/60 kg; once a day for 4 days;

(e) In the second week after surgery, MEDROL® was reduced, po, 32 mg/60 kg; once a day for 7 days;

(f) In the third week after surgery, MEDROL® was reduced, po, 24 mg/60 kg; once a day for 7 days;

(g) In the fourth week after surgery, MEDROL® was reduced, po, 16 mg/60 kg; once a day for 7 days;

(h) In the fifth week after surgery, MEDROL® was reduced, po, 8 mg/60 kg; once a day for 7 days;

(i) In the sixth week after surgery, MEDROL® was reduced, po, 6 mg/60 kg; once a day for 7 days;

(j) In the seventh week after surgery, MEDROL® was reduced, po, 4 mg/60 kg; once a day for 7 days.

[0334] Topical medications:

(a) tobramycin dexamethasone: eye drops, once a day for 7 days;

(b) tobramycin dexamethasone eye ointment: eye drops, once a day for 7 days.

[0335] A schematic showing the medication dosing schedule is provided in Fig. 19.

Post-operative Examination and Review

[0336] The first day after surgery, patients underwent post-operative ophthalmic examination including visual acuity, intraocular pressure, slit lamp examination, fundus examination anterior segment photography and fundus photography. The second day after surgery, patients underwent testing for visual acuity, intraocular pressure, and slit lamp and fundus examination. The third day after surgery, patients underwent testing for visual acuity, intraocular pressure, and slit lamp and fundus examination.

[0337] Patients receiving LHON eye gene therapy were informed to go to the hospital for consultation at a time reserved with the physician or if they felt any discomfort. Post-operative

examinations were performed by professionals. All inspection reports were reviewed and signed by medical personnel. It was forbidden for non-professionals or medical personnel who were not familiar with the field to check the patient or answer the patient's condition without authorization.

[0338] Before all inspections, alcohol was used to wipe the contact area between the instrument and the patient. After the examination was completed, antibiotic eye drops were given. It was forbidden to drop contaminated eye drops and eye drops into the conjunctival sac.

Results

Efficacy evaluation:

[0339] The International Standard Guide for Improving Vision provides that a visual acuity improvement by 0.3 logMAR (15 letters) is considered a significant improvement and an improvement of 0.2 logMAR (10 letters) is considered an improvement. An improvement below 0.1 logMAR (5 letters) signifies no improvement. A treatment resulting in a vision improvement of 0.2 logMAR is considered effective.

[0340] In a first phase of the study, a total of 145 patients were treated. Within one day of treatment, 24 cases (16.55%) showed a significant improvement of 0.3 logMAR and 6 cases (4.14%) showed an improvement of 0.2 logMAR. The total efficacy one day after treatment was 20.69%, with vision loss occurring in 2 cases (1.38%). Within 2 days of treatment, 35 cases (24.14%) showed a significant improvement of 0.3 logMAR, 12 cases (8.22%) showed an improvement of 0.2 logMAR, and the total efficacy was 32.41%. Within 3 days of treatment, 42 cases (28.96%) showed a significant improvement of 0.3 logMAR, 11 cases (7.59%) showed an improvement of 0.2 logMAR, and the total efficacy was 36.55%. These results are summarized below in Table 5.

Table 5. Treatment efficacy 3 days post-surgery

	Increase 0.3 logMAR	**Increase 0.2 logMAR**	**Vision loss**	**Total efficiency (%)**
First day	24 cases (16.55%)	6 cases (4.14%)	2 cases (1.38%)	20.69
Second day	35 cases (24.14%)	12 cases (8.22%)	None	32.41
Third day	42 cases (28.96%)	13 cases (7.59%)	None	42.63

[0341] 129 patients completed the review one month after surgery. Of these patients, 55 patients (42.66%) had a significant improvement of 0.3 logMAR in vision, and 16 (12.40%) had an improvement of 0.2 logMAR in vision. The one month review indicated that the total effective rate of

improved vision was 55.04%. The vision of 9 patients (6.98%) decreased. 67 patients completed the review after three months after surgery. Of these patients, 37 patients (55.22%) had a significant improvement of 0.3 logMAR in vision and 8 patients (11.94%) had an improvement of 0.2 logMAR in vision. The three month review indicated that the total effective rate of improved vision was 67.16%. The vision of 4 patients (5.97%) decreased. More recently, a total of 159 were treated: 64.66% of the patients had a significant improvement of 0.3 logMAR in vision, and 6.89% of the patients had an improvement of 0.2 logMAR in vision. Efficacy of treatment is shown below in Table 6.

Table 6. Treatment efficacy 1 and 3 months post-surgery

	Increase 0.3 logMAR	**Increase 0.2 logMAR**	**Vision loss**	**Total efficiency (%)**
One month review (n=129)	55 cases (42.66%)	13 cases (11.02%)	9 cases (6.98%)	55.04
Three month review (n=67)	37 cases (55.22%)	8 cases (11.94%)	4 cases (5.97%)	67.16
Six month review	64.66%	6.89%	n.a.	71.55%

[0342] Safety results: A total of 143 patients were treated in an early phase of the study, including 7 Argentine international patients. The onset time was divided into two years and two years or more, and safety tests were performed regularly. We examined ocular adverse reactions three days, one month and three months after surgery. There were 21 patients with mild ocular hypertension three days after surgery, which was a mild complication and recovered spontaneously without other serious complications. There were 17 patients with ocular hypertension one month after surgery, and only 5 patients with ocular hypertension three months after surgery. There were no other adverse reactions. Adverse reactions are summarized in Table 7.

Table 7. Complications of gene therapy for LHON

	3 days post-surgery (n=141)	**1 month post-surgery (n=102)**	**3 months post-surgery (n=41)**
Anterior chamber inflammation	0	0	0
Vitritis	0	0	0
Ocular hypertension	21	17	5
Cataract removal	0	0	0
Keratitis	0	0	0
Vitreous hemorrhage	0	0	0
Allergic conjunctivitis	0	0	0

	3 days post-surgery (n=141)	1 month post-surgery (n=102)	3 months post-surgery (n=41)
Eye pain	0	0	0

[0343] A total of 10 Argentine patients were treated. A safety examination conducted on day 3 after the surgery showed that there was no safety issue. Another safety examination conduct on day 10 showed that one subject had mild ocular hypertension, which returned to normal following drug treatment within one month. An efficacy examination was also conducted on day 3 after the surgery. The improvement of 0.3 logMAR and 0.2 logMAR in vision among these Argentine patients were 50% and 10%, respectively. The improvement of 0.3 logMAR in vision at one-month, three-month, and six-month were 60%, 90%, and 100%, respectively.

[0344] A similar study was conducted by GenSight Biologics: 15 subjects with the ND4-G11778A mutation received a single intravitreal injection of rAAV2/2-ND4 in the worse-seeing eye. The study design included an initial follow-up period of 48 weeks, followed by a long-term period of an additional 4 years. Patients were divided into two groups: 6 months and 6 to 12 months at the time of onset. In general, patients with shorter onset time had less optic nerve cell damage and the best prognosis for gene therapy. As onset time increased, the prognosis was worse. In the 15 patients treated, there were 10 cases of ocular hypertension, 2 patients with selective cataract removal, 2 patients with severe anterior chamber inflammation and vitritis events, and many other adverse reactions such as keratitis, vitreous hemorrhage, allergic conjunctivitis and eye pain (see Table 7). See Vignal et al., Ophthalmology 2018; 6:945-947.

[0345] In a separate study by Guy et al., 14 patients with LHON received a single intravitreal injection of AAV2(Y444,500,730F)-P1ND4v2 with 18 months of follow-up. The patients were separated into two groups, one for onset time of more than 12 months and the other for onset time of less than 12 months. Similar to GenSight Biologics, patients with an onset of less than 12 months had a better prognosis for gene therapy. Two cases of uveitis, 1 case of keratitis, 1 case of eye pain and 1 case of ocular hypertension was observed. See Guy et al., Ophthalmology 2017; 124:1621-1634. As shown in Table 8 below, the methods of the present disclosure resulted in fewer post-surgical complication than the methods of either GenSight Biologics or Guy et al.

Table 8. Comparison of complications of Leber's disease gene therapy

	3 days after surgery (n=141)	1 mth after surgery (n=102)	3 mths after surgery (n=41)	GenSight Biologics (n=15)	Guy et al. (n=14)
Cataract removal	0	0	0	2	No statistics
Uveitis	0	0	0	0	2
Vitritis	0	0	0	13	No statistics
Keratitis	0	0	0	7	1
Anterior chamber inflammation	0	0	0	14	No statistics
Vitreous hemorrhage	0	0	0	2	No statistics
Eye pain*	0	0	0	2	1
Allergic conjunctivitis*	0	0	0	3	No statistics
Ocular hypertension*	21	17	5	10	1

*Mild complications (could be self-recovered)

[0346] Notably, the methods of the present disclosure did not result in any post-surgical cases of uvetis. Uvetis is considered a serious complication and many types of uveitis require treatment with hormones and immunosuppressive agents. In the West, about a quarter of uveitis patients require treatment of hormones and immunosuppressive agents, and even then, 35% of patients have vision disability. Ocular hypertension is considered a mild complication and is the most common complication in ophthalmic surgery. Under normal circumstances, patients self-recover and the intraocular pressure returns to normal levels.

[0347] In summary, the methods of the present disclosure provided a safe and effective treatment for LHON, and no severe complications were observed.

[0348] Similar experiments are performed to assess the efficacy of rAAV2 comprising the nucleic acid sequence of SEQ ID NO: 7. These results are expected to show that administration of rAAV2-SEQ5 is a safe and effective treatment for ocular diseases.

Example 16 – Diagnostic assay for LHON gene therapy

[0349] In the present example, green fluorescent protein was used as a reporter gene in the rAAV2 vector (rAAV2-GFP). HEK293T cells were cultured with serum from different patients and were transduced with rAAV2-GFP. Transduction efficiency of rAAV2 was determined using RT-PCR

or flow cytometry in order to determine the ability of the rAAV2 vector to infect cells in the presence of patient serum. The method of the present disclosure can be used to screen patients prior to treatment with the rAAV2 vector to identify those patients with low immune responses to the rAAV2 vector (i.e., high rAAV2 vector transduction) and high immune responses to the rAAV2 vector (i.e., low rAAV2 vector transduction). In this example, patients with low immune responses to the rAAV2 vector were categorized as patients suitable for treatment with the rAAV2 vector.

Preparation of rAAV2-GFP virus

[0350] HEK293T cells were seeded at a density of 3.0×10^7 cells/mL in 225 cm^2 cell culture flasks in DMEM containing 10% bovine serum and cultured overnight in a 37°C incubator containing 5% CO_2. When the HEK293T cells reached 80-90% confluency, the culture medium was discarded and cells were transfected with rAAV2-GFP using the Plasmid Trans II (VGTC) transfection kit. Two days following transfection, HEK293T cells were harvested, and the collected cells were re-suspended in PBS, frozen and thawed 3 times, then separated, concentrated and purified to obtain recombinant adeno-associated virus rAAV2-GFP. The titer was measured and the product was customized by Guangzhou Paizhen Biotechnology Co., Ltd.

Isolation of patient serum

[0351] 2 mL of whole blood was collected from patients and centrifuged to isolate serum. The serum was separately added into two tubes and stored at -20°C or -80 °C for later use. The remaining whole blood was placed in a test tube. Patient information was recorded.

HEK293T cell culture

[0352] *Sterilization*: High temperature sterilization and UV disinfection of tips (1 mL, 5 mL, 0 mL) and EP tubes was carried out for a minimum of 30 minutes before usage. After sterilization, the tips and EP tubes were stored up to 12 hours, which did not result in cell contamination.

[0353] *Cell culture media preparation*: 1:9 media preparation or 1:4 media preparation, kept at 4°C, wherein 1:9 media preparation: 5 mL fetal calf serum, 45 mL DMEM high glucose cell culture medium, and 0.5 mL or 1 mL penicillin (10000 U/mL) and streptomycin (10000 /mL)were added to 50 mL centrifuge tube and mixed; 1:4 dosing: 10 mL fetal calf serum, 40 mL DMEM high glucose cell culture medium and 0.5 mL or 1 mL penicillin (10000 U/mL) and streptomycin (10000 /mL) were added to a 50 mL centrifuge tube and mixed.

Passage and seeding of HEK293T cells

[0354] A cryotube containing HEK293T cells was removed from liquid nitrogen and rapidly transferred to a 37°C water bath for 1-2 min. After thawing, the outer part of the cryotube was wiped with alcohol and placed in an ice bath at 4°C. The cryotube was occasionally shaken in the water bath to ensure even heat distribution.

[0355] After disinfection, the HEK293T cells were transferred to a centrifuge tube and 10 times the volume of high glucose DMEM was added to the cells. The suspension was then centrifuged at 1000 rpm for 5 min, the supernatant was discarded, and the HEK293T cells were resuspended in culture medium. The cell suspension was then transferred to a 4 mL culture medium vial and the vial was transferred to the incubator to allow the HEK293T cells to adhere to the wall of the vial. After the cells adhered, the medium was carefully removed and 5 mL of fresh medium was added to continue the culture. After HEK293T cells were incubated for 24 h, the culture medium was replaced and the cells were grown until a monolayer formed, which was then used for cell passage. The tissue culture media was replaced every 2 to 3 days by removing old media, rinsing the cells with PBS 3 times, and adding newly-prepared medium to the cells.

[0356] *Cell passage in flasks:* Once the cells reached confluency and had a round shape, the media was removed from the flask using a 10 mL pipette and the HEK293T cells were washed three times with 5 mL of PBS. After washing, 5 mL of EDTA was added to the cells, incubated for 3 min, and then 20 mL of media was rapidly added to the flask. Air was repeatedly blown into the culture using a 10 mL pipette until the cells were evenly resuspended. Half of the cell suspension was transferred to another flask and culture medium was added to a volume of 20 mL for both flasks.

[0357] *Cell passage in 24-well plate*: Once the cells reached confluency and had a round shape, the media was removed from the flask using a 10 mL pipette and the HEK293T cells were washed three times with 5 mL of PBS. After washing, 5 mL of EDTA was added to the cells, incubated for 3 min, and then 50 mL of media was rapidly added to the flask. Air was repeatedly blown into the culture using a 10 mL pipette until the cells were evenly resuspended. Two mLs of the cell suspension was distributed into each well of the 24-well plate, the flask was fixed to a total volume of 20 mL, and both the flask and 24-well plate were placed in the incubator to continue the culture. Once the HEK293T cells in the 24-well plate reached confluency (2-3 days later), the cells received 1.7 mL of fresh media and were transduced with rAAV2-GFP virus as described below.

Transduction of rAAV2-GFP in HEK293T cells in the presence of patient serum

[0358] Viral dilution: 1 μL of rAAV2-GFP was diluted to 40 μL of PBS and was added to 1960 μL of high glucose DMEM in a 4 mL EP tube. After the rAAV2-GFP dilution was prepared, the EP tube seal was kept at 4°C.

[0359] Patient serum and diluted rAAV2-GFP was prepared as follows:

(a) 1:20 group: 300 μL patient serum + 300 μL culture medium + 300 μL of the virus dilution (1:3 working dilution);

(b) 1:60 group: 100 μL patient serum + 500 μL culture medium + 300 μL of the virus dilution (1:9 working dilution);

(c) Control group: 600 μL culture medium (or 300 μL PBS + 300 μL culture medium) + 300 μL of the virus dilution.

[0360] rAAV2-GFP transduction: 300 μL of patient serum/rAAV2-GFP from the 1:20 group, 1:60 group, and the control groups was added to each well of HEK293T cells and incubated for 48 hours following transduction. The experiment was performed in triplicate for each group.

Example 17 - RT-PCR analysis of rAAV2-GFP expression

[0361] Total RNA was isolated from transduced HEK293T cells using TRIZOL, and cDNA was synthesized by reverse transcription. Primers for RT-PCR analysis were designed using Primer Premier 5 and are as follows:

(a) β-actin-F: CCTAGAAGCATTTGCGGT (SEQ ID NO: 167)

(b) β-actin-R: GAGCTACGAGCTGCCTGA (SEQ ID NO: 168)

(c) GFP-F: ACAAGTTCAGCGTGTCCG (SEQ ID NO: 163)

(d) GFP-R: CTCGTTGGGGTCTTTGCT (SEQ ID NO: 164)

[0362] For qRT-PCR analysis, a reaction mix was prepared containing 5 μL of SYBR Green, 8 μL of ddH_2O, 1 μL each of forward and reverse primers, and 2.5 μL of cDNA. The reaction mix was added to a 0.2 mL PCR reaction tube at a total volume of 25 μL. Each sample was analyzed in triplicate. In order to reduce error, the reagents were mixed in each PCR reaction tube and then dispensed. After the sample was added, quantitative RT-PCR was performed by pre-denaturation at 95°C for 1 s, denaturation at 94°C for 15 s, annealing at 55°C for 15 s, and extension at 72°C for 45 s for a total of 40 cycles on a RT-PCR detection system. The fluorescence signals were collected during the extension phase of each cycle. After each cycle, the melting curve analysis of 94°C - 55°C was performed.

[0363] The relative expression value = GFP expression level / β-actin, and the expression level of GFP and the expression level of the internal reference gene was 1. The screening criteria of GFP expression level was as follows:

(a) Low expression = relative expression value < 0.2

(b) Moderate expression = 0.2 ≤ relative expression value < 0.6

(c) High expression = 0.6 ≤ relative expression value;

[0364] High and moderate expression of GFP indicated that the serum of the patient did not contain anti-rAAV2 antibodies that prevented infection of HEK293T cells and that the probability of an immune response against the virus was low. These patients were identified as those suitable for gene therapy. Low GFP expression indicated that the serum of the patient contained anti-rAAV2 antibodies that prevented infection of HEK293T cells and that rAAV gene therapy may cause an immune response, requiring the patient to undergo immunotherapy before gene therapy treatment. Results are shown in Table 9 below.

Table 9. GFP expression by qPCR in HEK293T cells + Patient serum

	GFP/β-actin relative expression value		
	1:20	1:60	Control group
Patient A	0.33	0.55	0.78
Patient B	0.35	0.52	0.79
Patient C	0.29	0.56	0.78
Patient D	0.61	0.68	0.77
Patient E	0.12	0.18	0.79

Example 18 – GFP expression in HEK293T cells by flow cytometry

[0365] HEK293T cells transduced with rAAV2-GFP were resuspended in the well and transferred to a flow cytometry tube. GFP expression in HEK293T cells was determined using the Beckman Coulter Cyto FLEX S.

[0366] Untransduced cells (no drug) were used as a negative control for GFP expression (data not shown). Cells transduced with the rAAV2-GFP vector in the absence of patient serum were used as positive controls for GFP expression (control group described in Example 16). The infection efficiency of the control group was set to 50%. GFP expression in HEK293T cells after incubation with serum dilutions from Patient A is shown in Table 10, GFP expression in HEK293T cells after incubation with serum dilutions from Patient B is shown in Table 11, GFP expression in HEK293T cells after incubation with serum dilutions from Patient C is shown in Table 12, GFP expression in

HEK293T cells after incubation with serum dilutions from Patient D is shown in Table 13, GFP expression in HEK293T cells after incubation with serum dilutions from Patient E is shown in Table 14.

Table 10. %GFP expression in HEK293T cells + Patient A serum

Replicate	1:20	1:60	Control group
1	25.80	37.63	48.56
2	25.03	36.21	52.09
3	25.51	40.32	50.07
Mean %GFP+ cells	25.45	38.05	50.24

Table 11. %GFP expression in HEK293T cells + Patient B serum

Replicate	1:20	1:60	Control group
1	33.90	36.59	48.26
2	29.05	33.84	53.88
3	31.35	33.86	51.37
Mean %GFP+ cells	31.43	34.76	51.17

Table 12. %GFP expression in HEK293T cells + Patient C serum

Replicate	1:20	1:60	Control group
1	31.45	38.16	51.56
2	28.92	33.60	50.09
3	30.41	36.58	50.33
Mean %GFP+ cells	30.26	36.11	50.66

Table 13. %GFP expression in HEK293T cells + Patient D serum

Replicate	1:20	1:60	Control group
1	41.11	45.15	51.56
2	40.33	43.12	52.17
3	43.93	46.04	50.28
Mean %GFP+ cells	41.79	44.77	51.34

Table 14. % GFP expression in HEK293T cells + Patient E serum

Replicate	1:20	1:60	Control group
1	12.07	15.85	49.00
2	16.27	16.94	53.88
3	13.70	14.07	50.37
Mean %GFP+ cells	14.01	15.62	51.08

[0367] GFP expression (i.e., the percentage of cells that are GFP+ by flow cytometry) can be expressed as absolute fluorescence (percentage of GFP+ cells in a test sample; as shown in Tables 10-14) or as relative fluorescence ([percentage of GFP+ cells in a test sample / percentage of GFP+ cells in a control sample] * 100; as shown in the "Relative GFP fluorescence" column in Table 15). The criteria for screening patients by relative GFP expression is as follows:

(a) Low expression = % GFP+ cells < 20%

(b) Moderate expression = 20% ≤ % GFP+ cells < 40%

(c) High expression = 40% ≤ % GFP+ cells

[0368] High and moderate GFP expression indicated that the serum of the patient did not contain anti-rAAV2 antibodies that prevented infection of target cells and gene therapy could be performed. Low GFP expression indicated that the serum of the patient contained anti-rAAV2 antibodies that prevented infection of target cells and that gene therapy with rAAV may cause an immune response, and immunotherapy should be performed before proceeding with gene therapy.

[0369] GFP expression of patients A, B, C, and D were all higher than 20% (as shown in Tables 10-14, indicating that patient serum did not contain anti-rAAV2 antibodies that prevented infection of target cells and that the gene therapy could be directly performed. In particular, the GFP expression level of patient D was higher than 40%, indicating that the patient was in ideal condition for gene therapy (Table 13). The GFP expression level tested for patient E was less than 20% (Table 14), indicating that gene therapy with rAAV2 may cause an immune response and that immunotherapy was needed before starting treatment.

Example 19– Efficiency of gene therapy in patients with low immunity to rAAV2

[0370] The relationship between GFP expression and gene therapy was first discovered by the inventors. There were no relevant reports in the prior art, and no standard for the relationship between specific expression level and the effect of gene therapy had been established in the art.

[0371] In the clinic, the inventors unexpectedly found that subjects with GFP expression levels below 20% experienced an immune response to rAAV2 gene therapy, and for safety reasons, were not further included in the study. Subjects with an expression level higher than 50% were rare, so the purpose of this example was to verify subjects with expression levels between 20% and 50%.

[0372] Candidates for gene therapy were screened for an immune response to recombinant adeno-associated virus as described above (Examples 16-18). The patient recruiting guidelines and

pre- and post-operative examination procedures are described in Example 15. The dose for intravitreal injection under local anesthesia was 1×10^{10} vg/0.05 mL. A single administration was performed. Clinical observation lasted for 3 months and vision acuity was observed over time.

[0373] Subjects were grouped according to %GFP+ cells: Group A = high GFP expression (40% ≤ %GFP+ cells ≤ 50%) and Group B = moderate GFP expression (20% ≤ %GFP+ cells <40%). Target cells were transduced with rAAV2-GFP such that approximately 50% of the cells in the control group were transduced with the vector. In the 20-50% GFP+ range, the inventors found a relationship between expression level and the effect of gene therapy. In subjects with %GFP+ cells below 40% gene therapy was slightly less effective than in subjects with %GFP+ cells greater than or equal to 40%. Therefore, the above criteria for low expression, moderate expression, and high expression was established.

[0374] The results are shown in Table 15. The gene therapy was significantly more efficacious in group A (high expression) than in group B (moderate expression) ($P<0.05$). Guidelines for evaluation of efficiency and visual acuity are described in Example 15.

Table 15. Comparison of efficacy between group A and group B

Group	Number of cases	Efficiency	
Group A	66	47 (71.21%)	P<0.05
Group B	39	20 (51.28%)	

Example 20 – Screening patients for LHON gene therapy

[0375] The effectiveness of the diagnostic assays described above were further verified in additional patients. Serum from 37 patient was diluted as described above in Example 16 and evaluated in the qPCR and flow cytometry assays described above in Example 17 and 18. Testing of each sample was repeated 3 times (n=3) and an average value was obtained (i.e., mean %GFP+ cells). Relative %GFP+ cells for the 1:20 and 1:60 dilutions was calculated relative to the mean %GFP+ cells of the control sample, and subjects were classified as suitable or not suitable for therapy with the rAAV2 vector based on the relative %GFP+ cells (suitable for therapy = relative %GFP+ cells ≥ 40%; not suitable for therapy = relative %GFP+ cells < 40%). Using the methods described herein, 28 patients were classified as suitable and 9 patients were classified as unsuitable for therapy. The results for 37 subjects are shown in Table 16.

Table 16. %GFP+ HEK293T cells + Patient serum

	Mean %GFP+ cells			%GFP+ Test / %GFP+ Control		
Case No.	**1:20**	**1:60**	**Control**	**1:20**	**1:60**	**Classification**
A1	52.25	83.66	55.13	94.8%	151.7%	Suitable for therapy
A2	41.32	80.20	55.13	74.9%	145.5%	Suitable for therapy
A3	32.43	78.86	55.13	58.8%	143.0%	Suitable for therapy
A4	52.79	53.8	49.58	106.5%	108.5%	Suitable for therapy
A5	55.7	61.79	49.58	112.3%	124.6%	Suitable for therapy
A6	53.69	64.51	49.58	108.3%	130.1%	Suitable for therapy
A7	54.31	58.85	49.58	109.5%	118.7%	Suitable for therapy
A8	50.43	57.24	49.58	101.7%	115.4%	Suitable for therapy
A9	47.87	57.21	49.58	96.6%	115.4%	Suitable for therapy
A10	49.27	55.43	54.19	90.9%	102.3%	Suitable for therapy
A11	30.26	36.11	51.37	58.9%	70.3%	Suitable for therapy
A12	31.43	34.76	51.37	61.2%	67.7%	Suitable for therapy
A13	25.86	32.03	51.37	50.3%	62.4%	Suitable for therapy
A14	25.45	38.05	51.37	49.5%	74.1%	Suitable for therapy
A15	33.82	37.84	51.37	65.8%	73.7%	Suitable for therapy
A16	39.34	39.08	51.37	76.6%	76.1%	Suitable for therapy
A17	35.39	43.65	51.37	68.9%	85.0%	Suitable for therapy
A18	41.08	43.74	51.37	80.0%	85.1%	Suitable for therapy
A19	34.55	50.39	51.37	67.3%	98.1%	Suitable for therapy
A20	58.96	52.91	57.84	101.9%	91.5%	Suitable for therapy
A21	49.09	64.89	57.84	84.9%	112.2%	Suitable for therapy
A22	55.13	71.83	57.84	95.3%	124.2%	Suitable for therapy
A23	50.39	59.43	57.84	87.1%	102.7%	Suitable for therapy
A24	68.34	78.68	57.84	118.2%	136.0%	Suitable for therapy
A25	54.38	84.02	57.84	94.0%	145.3%	Suitable for therapy
A26	60.39	64.2	57.84	104.4%	111.0%	Suitable for therapy
A27	49.62	47.91	57.84	85.8%	82.8%	Suitable for therapy
A28	58.59	62.54	57.84	101.3%	108.1%	Suitable for therapy
B1	15.26	17.32	63.19	24.1%	27.4%	Not suitable for therapy
B2	3.59	2.15	12.32	29.1%	17.5%	Not suitable for therapy
B3	12	9.81	35.4	33.9%	27.7%	Not suitable for therapy
B4	0.72	1.35	12.32	5.8%	11.0%	Not suitable for therapy
B5	2.96	2.43	12.32	24.0%	19.7%	Not suitable for therapy
B6	4.38	24.4	63.03	6.9%	38.7%	Not suitable for therapy
B7	1.58	2.85	63.19	2.5%	4.5%	Not suitable for therapy
B8	13.92	7.92	51.34	27.1%	15.4%	Not suitable for therapy
B9	4.78	9.06	51.08	9.4%	17.7%	Not suitable for therapy

[0376] The 28 patients classified as suitable for therapy received the rAAV2 gene therapy vector. Of the 28 patients that received therapy, the therapy was effective in 20 patients (efficacy rate of 71.43% (20/28)). Of the 9 patients classified as not suitable for therapy, 6 patients still wanted to receive gene therapy. However, the therapy was only effective in one patient classified as not suitable for therapy (efficacy rate of 16.67% (1/6)).

Example 21 – Prednisone treatment regimen for LHON gene therapy

[0377] This study will be conducted following the patient recruitment guidelines, surgery and examination procedures as described in Example 15.

[0378] Patients undergoing gene therapy for LHON will receive the following treatment regimen:

(a) 2 days before surgery: prednisone tablets, 60 mg/60 kg, once per day for 10 days;

(b) 8 days after surgery: prednisone tablets, 40 mg/60 kg, once per day for 1 day;

(c) 9 days after surgery: prednisone tablets, 20 mg/60 kg, once per day for 1 day;

(d) 10 days after surgery: prednisone tablets, 10 mg/60 kg, once per day for 1 day;

(e) 11 days after surgery: stop steroid treatment.

[0379] A schematic showing the medication dosing schedule is provided in Fig. 20. Patients will be monitored for 3 months following surgery and will be advised to consult a physician if they felt any discomfort or pain throughout the study.

[0380] Results are expected to show an improvement in visual acuity with minimal side effects in LHON patients following intravitreal administration of AAV2-ND4 and the treatment regimen described above.

[0381] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

FURTHER NUMBERED EMBODIMENTS

[0382] Further embodiments of the instant invention are provided in the numbered embodiments below:

[0383] Embodiment 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 a sequence selected from the group consisting of SEQ ID NO: 7, 8, 10, and 12; and a 3'UTR nucleic acid sequence.

[0384] Embodiment 2. The recombinant nucleic acid of Embodiment 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.

[0385] Embodiment 3. The recombinant nucleic acid of Embodiment 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.

[0386] Embodiment 4. The recombinant nucleic acid of Embodiment 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.

[0387] Embodiment 5. The recombinant nucleic acid of Embodiment 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.

[0388] Embodiment 6. The recombinant nucleic acid of Embodiment 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.

[0389] Embodiment 7. The recombinant nucleic acid of Embodiment 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: 7 or 8.

[0390] Embodiment 8. The recombinant nucleic acid of Embodiment 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: 10.

[0391] Embodiment 9. The recombinant nucleic acid of cl Embodiment aim 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.

[0392] Embodiment 10. The recombinant nucleic acid of Embodiment 1, 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.

[0393] Embodiment 11. The recombinant nucleic acid of Embodiment 1, 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.

[0394] Embodiment 12. The recombinant nucleic acid of Embodiment 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: 17-20, 23-24, 27-28, 31-34, 37-38, 41-42, 45-48, 51-52, 55-56, 59-62, 65-66, 69-70, 73-76, 79-80, and 83-84.

[0395] Embodiment 13. A recombinant nucleic acid, comprising: a mitochondrial targeting sequence comprising a sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID NO: 2, 3, 4, and 5; a mitochondrial protein coding sequence, wherein said mitochondrial protein coding sequence encodes a polypeptide comprising a mitochondrial protein; and a 3'UTR nucleic acid sequence.

[0396] Embodiment 14. The recombinant nucleic acid of Embodiment 13, 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.

[0397] Embodiment 15. The recombinant nucleic acid of any one of Embodiments 13-14, 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: 3.

[0398] Embodiment 16. The recombinant nucleic acid of any one of Embodiments 13-15, 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.

[0399] Embodiment 17. The recombinant nucleic acid of any one of Embodiments 13-16, 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.

[0400] Embodiment 18. The recombinant nucleic acid of any one of Embodiments 13-17, wherein said mitochondrial protein is selected from a group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and a variant thereof.

[0401] Embodiment 19. The recombinant nucleic acid of Embodiment 18, wherein said mitochondrial protein comprises NADH dehydrogenase 4 (ND4), or a variant thereof.

[0402] Embodiment 20. The recombinant nucleic acid of any one of Embodiments 13-19, wherein said mitochondrial protein comprises a peptide 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: 160.

[0403] Embodiment 21. The recombinant nucleic acid of any one of Embodiments 13-20, 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: 6, 7, or 8.

[0404] Embodiment 22. The recombinant nucleic acid of Embodiment 18, wherein said mitochondrial protein comprises NADH dehydrogenase 6 (ND6), or a variant thereof.

[0405] Embodiment 23. The recombinant nucleic acid of any one of Embodiments 13-22, wherein said mitochondrial protein 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: 161.

[0406] Embodiment 24. The recombinant nucleic acid of any one of Embodiments 13-23, 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: 9 or 10.

[0407] Embodiment 25. The recombinant nucleic acid of any one of Embodiments 13-24, wherein said mitochondrial protein comprises NADH dehydrogenase 1 (ND1), or a variant thereof.

[0408] Embodiment 26. The recombinant nucleic acid of any one of Embodiments 13-25, wherein said mitochondrial protein 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: 162.

[0409] Embodiment 27. The recombinant nucleic acid of any one of Embodiments 13-26, 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: 11 or 12.

[0410] Embodiment 28. The recombinant nucleic acid of any one of Embodiments 13-27, wherein said 3'UTR nucleic acid sequence is located at 3' of said mitochondrial targeting sequence.

[0411] Embodiment 29. The recombinant nucleic acid of any one of Embodiments 13-28, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L.

[0412] Embodiment 30. The recombinant nucleic acid of any one of Embodiments 13-29, 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.

[0413] Embodiment 31. The recombinant nucleic acid of any one of Embodiments 13-29, 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.

[0414] Embodiment 32. The recombinant nucleic acid of any one of Embodiments 13-31, wherein said mitochondrial targeting sequence is located at 5' of said 3'UTR nucleic acid sequence.

[0415] Embodiment 33. The recombinant nucleic acid of any one of Embodiments 13-32, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.

[0416] Embodiment 34. The recombinant nucleic acid of any one of Embodiments 13-33, 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: 29-84.

[0417] Embodiment 35. 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 a sequence selected from the group consisting of SEQ ID NO: 7, 8, 10, and 12; and a 3'UTR nucleic acid sequence.

[0418] Embodiment 36. The recombinant nucleic acid of Embodiment 35, 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.

[0419] Embodiment 37. The recombinant nucleic acid of any one of Embodiments 35-36, 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.

[0420] Embodiment 38. The recombinant nucleic acid of any one of Embodiments 35-37, 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.

[0421] Embodiment 39. The recombinant nucleic acid of any one of Embodiments 35-38, 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.

[0422] Embodiment 40. The recombinant nucleic acid of any one of Embodiments 35-39, 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.

[0423] Embodiment 41. The recombinant nucleic acid of any one of Embodiments 35-40, 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: 7 or 8.

[0424] Embodiment 42. The recombinant nucleic acid of any one of Embodiments 35-41, 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: 10.

[0425] Embodiment 43. The recombinant nucleic acid of any one of Embodiments 35-42, 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.

[0426] Embodiment 44. The recombinant nucleic acid of any one of Embodiments 35-43, wherein said 3'UTR nucleic acid sequence is located at 3' of said mitochondrial targeting sequence.

[0427] Embodiment 45. The recombinant nucleic acid of any one of Embodiments 35-44, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L.

[0428] Embodiment 46. The recombinant nucleic acid of any one of Embodiments 35-45, 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.

[0429] Embodiment 47. The recombinant nucleic acid of any one of Embodiments 35-46, 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.

[0430] Embodiment 48. The recombinant nucleic acid of any one of Embodiments 35-47, wherein said mitochondrial targeting sequence is located at 5' of said 3'UTR nucleic acid sequence.

[0431] Embodiment 49. The recombinant nucleic acid of any one of Embodiments 35-48, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.

[0432] Embodiment 50. The recombinant nucleic acid of any one of Embodiments 35-49, 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: 17-20, 23-24, 27-28, 31-34, 37-38, 41-42, 45-48, 51-52, 55-56, 59-62, 65-66, 69-70, 73-76, 79-80, and 83-84.

[0433] Embodiment 51. A recombinant nucleic acid, comprising a mitochondrial targeting 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: 2, 3, and 4.

[0434] Embodiment 52. The recombinant nucleic acid of Embodiment 51, 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.

[0435] Embodiment 53. The recombinant nucleic acid of any one of Embodiments 51-52, 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.

[0436] Embodiment 54. The recombinant nucleic acid of any one of Embodiments 51-53, 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.

[0437] Embodiment 55. The recombinant nucleic acid of any one of Embodiments 51-54, further comprising a mitochondrial protein coding sequence, wherein said mitochondrial protein coding sequence encodes a polypeptide comprising a mitochondrial protein.

[0438] Embodiment 56. The recombinant nucleic acid of any one of Embodiments 51-55, wherein said mitochondrial protein is selected from a group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and a variant thereof.

[0439] Embodiment 57. The recombinant nucleic acid of any one of Embodiments 51-56, wherein said mitochondrial protein comprises NADH dehydrogenase 4 (ND4), or a variant thereof.

[0440] Embodiment 58. The recombinant nucleic acid of any one of Embodiments 51-57, wherein said mitochondrial protein comprises a peptide 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: 160.

[0441] Embodiment 59. The recombinant nucleic acid of any one of Embodiments 51-58, 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: 6, 7, or 8.

[0442] Embodiment 60. The recombinant nucleic acid of any one of Embodiments 51-59, wherein said mitochondrial protein comprises NADH dehydrogenase 6 (ND6), or a variant thereof.

[0443] Embodiment 61. The recombinant nucleic acid of any one of Embodiments 51-60, wherein said mitochondrial protein 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: 161.

[0444] Embodiment 62. The recombinant nucleic acid of any one of Embodiments 51-61, 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: 9 or 10.

[0445] Embodiment 63. The recombinant nucleic acid of any one of Embodiments 51-62, wherein said mitochondrial protein comprises NADH dehydrogenase 1 (ND1), or a variant thereof.

[0446] Embodiment 64. The recombinant nucleic acid of any one of Embodiments 51-63, wherein said mitochondrial protein 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: 162.

[0447] Embodiment 65. The recombinant nucleic acid of any one of Embodiments 51-64, 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: 11 or 12.

[0448] Embodiment 66. The recombinant nucleic acid of any one of Embodiments 51-65, further comprising a 3'UTR nucleic acid sequence.

[0449] Embodiment 67. The recombinant nucleic acid of any one of Embodiments 51-66, wherein said 3'UTR nucleic acid sequence is located at 3' of said mitochondrial targeting sequence.

[0450] Embodiment 68. The recombinant nucleic acid of any one of Embodiments 51-67, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, mSOD2, and hsOXA1L.

[0451] Embodiment 69. The recombinant nucleic acid of any one of Embodiments 51-68, 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.

[0452] Embodiment 70. The recombinant nucleic acid of any one of Embodiments 51-69, 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.

[0453] Embodiment 71. The recombinant nucleic acid of any one of Embodiments 51-70, wherein said mitochondrial targeting sequence is located at 5' of said 3'UTR nucleic acid sequence.

[0454] Embodiment 72. The recombinant nucleic acid of any one of Embodiments 51-71, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.

[0455] Embodiment 73. The recombinant nucleic acid of any one of Embodiments 51-72, 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: 29-70.

[0456] Embodiment 74. 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 a sequence selected from the group consisting of SEQ ID NO: 7, 8, 10, and 12.

[0457] Embodiment 75. The recombinant nucleic acid of Embodiment 74, further comprising a mitochondrial targeting sequence.

[0458] Embodiment 76. The recombinant nucleic acid of any one of Embodiments 74-75, wherein said mitochondrial targeting sequence comprises a sequence encodes a polypeptide selected from the group consisting of hsCOX10, hsCOX8, scRPM2, leSirt5, 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.

[0459] Embodiment 77. The recombinant nucleic acid of any one of Embodiments 74-76, 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.

[0460] Embodiment 78. The recombinant nucleic acid of any one of Embodiments 74-77, 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.

[0461] Embodiment 79. The recombinant nucleic acid of any one of Embodiments 74-78, 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.

[0462] Embodiment 80. The recombinant nucleic acid of any one of Embodiments 74-79, 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.

[0463] Embodiment 81. The recombinant nucleic acid of any one of Embodiments 74-80, 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.

[0464] Embodiment 82. The recombinant nucleic acid of any one of Embodiments 74-81, 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: 7 or 8.

[0465] Embodiment 83. The recombinant nucleic acid of any one of Embodiments 74-80, 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: 10.

[0466] Embodiment 84. The recombinant nucleic acid of any one of Embodiments 74-83, 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.

[0467] Embodiment 85. The recombinant nucleic acid of any one of Embodiments 74-84, further comprising a3'UTR nucleic acid sequence.

[0468] Embodiment 86. The recombinant nucleic acid of any one of Embodiments 74-85, wherein said 3'UTR nucleic acid sequence is located at 3' of said mitochondrial targeting sequence.

[0469] Embodiment 87. The recombinant nucleic acid of any one of Embodiments 74-86, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, mSOD2, and hsOXA1L.

[0470] Embodiment 88. The recombinant nucleic acid of any one of Embodiments 74-87, 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. |

[0471] Embodiment 89. The recombinant nucleic acid of any one of Embodiments 74-88, 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.

[0472] Embodiment 90. The recombinant nucleic acid of any one of Embodiments 74-89, wherein said mitochondrial targeting sequence is located at 5' of said 3'UTR nucleic acid sequence.

[0473] Embodiment 91. The recombinant nucleic acid of any one of Embodiments 74-90, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.

[0474] Embodiment 92. The recombinant nucleic acid of any one of Embodiments 74-91, 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: 17-20, 23-24, 27-28, 31-34, 37-38, 41-42, 45-48, 51-52, 55-56, 59-62, 65-66, 69-70, 73-76, 79-80, and 83-84.

[0475] Embodiment 93. A viral vector comprising said recombinant nucleic acid of any one of Embodiments 1-92. |

[0476] Embodiment 94. The viral vector of Embodiment 93, wherein said viral vector is an adeno-associated virus (AAV) vector.

[0477] Embodiment 95. The viral vector of Embodiment 94, 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.

[0478] Embodiment 96. The viral vector of any one of Embodiments 93-95, wherein said AAV vector is a recombinant AAV (rAAV) vector.

[0479] Embodiment 97. The viral vector of Embodiment 96, wherein said rAAV vector is rAAV2 vector.

[0480] Embodiment 98. A pharmaceutical composition, comprising an adeno-associated virus (AAV) comprising said recombinant nucleic acid of any one of Embodiments 1-92.

[0481] Embodiment 99. The pharmaceutical composition of Embodiment 98, further comprising a pharmaceutically acceptable excipient thereof.

[0482] Embodiment 100. A pharmaceutical composition, comprising said viral vector of any one of Embodiments 93-97, and a pharmaceutically acceptable excipient thereof, wherein said viral vector comprises said recombinant nucleic acid of any one of Embodiments 1-92.

[0483] Embodiment 101. A pharmaceutical composition, comprising: an adeno-associated virus (AAV) comprising a recombinant nucleic acid of any one of Embodiments 1-92, 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 as set forth in SEQ ID NO: 15; and a pharmaceutically acceptable excipient.

[0484] Embodiment 102. The pharmaceutical composition of any one of Embodiments 98-101, 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.

[0485] Embodiment 103. The pharmaceutical composition of any one of Embodiments 98-102, 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.

[0486] Embodiment 104. The pharmaceutical composition of Embodiment 102, wherein said pharmaceutically acceptable excipient comprises poloxamer 188.

[0487] Embodiment 105. The pharmaceutical composition of Embodiment 104, wherein said pharmaceutically acceptable excipient comprises 0.0001%-0.01% poloxamer 188.

[0488] Embodiment 106. The pharmaceutical composition of Embodiment 105, wherein said pharmaceutically acceptable excipient comprises 0.001% poloxamer 188.

[0489] Embodiment 107. The pharmaceutical composition of any one of Embodiments 98-106, wherein said pharmaceutically acceptable excipient further comprises one or more salts.

[0490] Embodiment 108. The pharmaceutical composition of Embodiment 107, wherein said one or more salts comprises NaCl, NaH_2PO_4, Na_2HPO_4, and KH_2PO_4.

[0491] Embodiment 109. The pharmaceutical composition of Embodiment 107, 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.

[0492] Embodiment 109.1. The pharmaceutical composition of Embodiment 107, wherein said one or more salts comprises NaCl, Na_2HPO_4, and KH_2PO_4.

[0493] Embodiment 109.2. The pharmaceutical composition of Embodiment 107, wherein said one or more salts comprises 154 mM NaCl, 5.6 mM Na_2HPO_4, and 8.4 mM KH_2PO_4.

[0494] Embodiment 110. The pharmaceutical composition of any one of Embodiments 98-109, wherein said pharmaceutical composition has a pH of 6-8.

[0495] Embodiment 111. The pharmaceutical composition of Embodiment 110, wherein said pharmaceutical composition has a pH of 7.2-7.4.

[0496] Embodiment 112. The pharmaceutical composition of Embodiment 111, wherein said pharmaceutical composition has a pH of 7.3.

[0497] Embodiment 113. The pharmaceutical composition of any one of Embodiments 98-112, wherein said pharmaceutical composition has a viral titer of at least 1.0×10^{10} vg/mL.

[0498] Embodiment 114. The pharmaceutical composition of Embodiment 113, wherein said pharmaceutical composition has a viral titer of at least 5.0×10^{10} vg/mL.

[0499] Embodiment 115. The pharmaceutical composition of any one of Embodiment 98-114, 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.

[0500] Embodiment 116. The pharmaceutical composition of any one of Embodiment 98-115, 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.

[0501] Embodiment 117. The pharmaceutical composition of any one of Embodiment 98-116, 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.

[0502] Embodiment 118. A method of treating an eye disorder, comprising administering said pharmaceutical composition of any one of Embodiments 98-117 to a patient in need thereof.

[0503] Embodiment 119. The method of Embodiment 118, wherein said eye disorder is Leber's hereditary optic neuropathy (LHON).

[0504] Embodiment 120. The method of Embodiment 118 or 119, comprising administering said pharmaceutical composition to one or both eyes of said patient.

[0505] Embodiment 121. The method of any one of Embodiments 118-120, wherein said pharmaceutical composition is administered via intraocular or intravitreal injection.

[0506] Embodiment 122. The method of Embodiment 121, wherein said pharmaceutical composition is administered via intravitreal injection.

[0507] Embodiment 123. The method of Embodiment 122, wherein about 0.01-0.1 mL of said pharmaceutical composition is administered via intravitreal injection.

[0508] Embodiment 124. The method of Embodiment 123, wherein about 0.05 mL of said pharmaceutical composition is administered via intravitreal injection.

[0509] Embodiment 125. The method of any one of Embodiments 118-124, further comprising administering methylprednisolone to said patient.

[0510] Embodiment 126. The method of Embodiment 125, wherein said methylprednisolone is administered prior to said intravitreal injection of said pharmaceutical composition.

[0511] Embodiment 127. The method of any one of Embodiments 125-126, wherein said methylprednisolone is administered orally.

[0512] Embodiment 128. The method of any one of Embodiments 125-127, 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.

[0513] Embodiment 129. The method of any one of Embodiments 125-128, wherein said methylprednisolone is administered daily.

[0514] Embodiment 130. The method of any one of Embodiments 125-129, wherein a daily dosage of about 32 mg/60 kg methylprednisolone is administered.

[0515] Embodiment 131. The method of any one of Embodiments 125-130, wherein said methylprednisolone is administered after said intravitreal injection of said pharmaceutical composition.

[0516] Embodiment 132. The method of any one of Embodiments 125-131, further comprising administering sodium creatine phosphate to said patient.

[0517] Embodiment 133. The method of Embodiment 132, wherein said sodium creatine phosphate is administered intravenously.

[0518] Embodiment 134. The method of any one of Embodiments 125-133, wherein said methylprednisolone is administered intravenously or orally.

[0519] Embodiment 135. The method of any one of Embodiments 125-134, comprising administering methylprednisolone intravenously for at least one day, which is followed by administering methylprednisolone orally for at least a week.

[0520] Embodiment 136. The method of Embodiment 135, comprising administering methylprednisolone intravenously for about 3 days, which is followed by administering methylprednisolone orally for at least about 6 weeks.

[0521] Embodiment 137. The method of any one of Embodiments 125-136, wherein said methylprednisolone is administered intravenously at a daily dose of about 80 mg/60 kg.

[0522] Embodiment 138. The method of any one of Embodiments 125-137, wherein said administering said pharmaceutical composition generates a higher average recovery of vision than a comparable pharmaceutical composition without said recombinant nucleic acid.

[0523] Embodiment 139. The method of any one of Embodiments 125-138, 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: 15.

[0524] Embodiment 140. A method of treating an eye disorder, comprising administering to a patient in need thereof (a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising: (i) a nucleic acid sequence encoding a mitochondrial targeting peptide; (ii) a nucleic acid sequence encoding a mitochondrial protein comprising a nucleic acid 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: 6-12; and (iii) a 3'UTR nucleic acid sequence; and (b) a second pharmaceutical composition comprising a steroid.

[0525] Embodiment 141. The method of Embodiment 140, wherein the nucleic acid sequence encoding the mitochondrial protein encodes a polypeptide comprising an amino acid 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: 160-162.

[0526] Embodiment 142. The method of Embodiment 140 or Embodiment 141, wherein the nucleic acid sequence encoding a mitochondrial targeting peptide encodes a polypeptide comprising an amino acid 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: 126-159.

[0527] Embodiment 143. The method of any one of Embodiments 140-142, wherein the nucleic acid sequence encoding a mitochondrial targeting peptide comprises a nucleic acid 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: 1-5.

[0528] Embodiment 144. The method of any one of Embodiments 140-143, wherein the 3'UTR nucleic acid sequence comprises a nucleic 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: 13, 14, and 111-125.

[0529] Embodiment 145. A method of treating an eye disorder, comprising administering to a patient in need thereof (a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising: (i) a nucleic acid sequence encoding

a mitochondrial targeting peptide comprising an amino 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: 126-159; (ii) a nucleic acid sequence encoding a mitochondrial protein; and (iii) a 3'UTR nucleic acid sequence; and (b) a second pharmaceutical composition comprising a steroid.

[0530] Embodiment 146. The method of Embodiment 145, wherein said mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof.

[0531] Embodiment 147. The method of Embodiment 146, wherein the nucleic acid sequence encoding a mitochondrial protein comprises a nucleic acid sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO: 6-12.

[0532] Embodiment 148. The method of Embodiment 146 or 147, wherein nucleic acid sequence encoding a mitochondrial protein encodes a polypeptide comprising an amino acid 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: 160-162.

[0533] Embodiment 149. The method of any one of Embodiments 146-148, wherein the nucleic acid sequence encoding a mitochondrial targeting peptide comprises a nucleic acid 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: 1-5.

[0534] Embodiment 150. The method of any one of Embodiments 146-149, wherein the 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: 13, 14, and 111-125.

[0535] Embodiment 151. A method of treating an eye disorder, comprising administering to a patient in need thereof (a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising: (i) a nucleic acid sequence encoding a mitochondrial targeting peptide comprising an amino 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: 126-159; (ii) a nucleic acid sequence encoding a mitochondrial protein comprising a nucleic acid 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: 6-12; and (iii) a 3'UTR nucleic acid 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: 13, 14, and 111-125; and (b) a second pharmaceutical composition comprising a steroid.

[0536] Embodiment 152. A method of treating an eye disorder, comprising administering to a patient in need thereof (a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising: (i) a nucleic acid sequence encoding a mitochondrial targeting peptide; and (ii) a nucleic acid sequence encoding a mitochondrial protein; and (iii) a second pharmaceutical composition comprising a steroid.

[0537] Embodiment 153. The method of Embodiment 152, wherein the mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof.

[0538] Embodiment 154. The method of Embodiment 152 or 153, wherein the 3'UTR nucleic acid sequence comprises a nucleic 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: 13, 14, and 111-125.

[0539] Embodiment 155. The method of any one of Embodiments 140-154, wherein the 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: 15-84.

[0540] Embodiment 156. The method of any one of Embodiments 140-155, wherein the recombinant nucleic acid comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 15.

[0541] Embodiment 157. The method of any one of Embodiments 140-156, wherein the first pharmaceutical composition is administered via intraocular or intravitreal injection.

[0542] Embodiment 158. The method of any one of Embodiments 140-157, wherein about 0.01-0.1 mL of the first pharmaceutical composition is administered via intravitreal injection.

[0543] Embodiment 159. The method of any one of Embodiments 140-158, wherein about 0.05 mL of the first pharmaceutical composition is administered via intravitreal injection.

[0544] Embodiment 160. The method of any one of Embodiments 140-159, wherein the first pharmaceutical composition is administered to one or both eyes of the patient.

[0545] Embodiment 161. The method of any one of Embodiments 140-160, wherein the steroid is selected from the group consisting of alclometasone diproprionate, amcinonide, beclomethasone diproprionate, betamethasone, betamethasone benzoate, betamethasone diproprionate, betamethasone sodium phosphate, betamethasone sodium phosphate and acetate, betamethasone valerate, clobetasol proprionate, clocortolone pivalate, cortisol (hydrocortisone), cortisol (hydrocortisone) acetate, cortisol (hydrocortisone) butyrate, cortisol (hydrocortisone) cypionate, cortisol (hydrocortisone) sodium phosphate, cortisol (hydrocortisone) sodium succinate, cortisol (hydrocortisone) valerate, cortisone acetate, desonide, desoximetasone, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, diflorasone diacetate, fludrocortisone acetate, flunisolide, fluocinolone acetonide, fluocinonide, fluorometholone, flurandrenolide, halcinonide, medrysone, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide or a synthetic analog thereof.

[0546] Embodiment 162. The method of Embodiments 140-161, wherein the steroid is a glucocorticoid.

[0547] Embodiment 163. The method of Embodiment 162, wherein the glucocorticoid is methylprednisolone or prednisone.

[0548] Embodiment 164. The method of Embodiment 163, wherein the methylprednisolone is formulated as a tablet or as a liquid for intravenous administration.

[0549] Embodiment 165. The method of any one of Embodiments 140-164, wherein the steroid is administered orally or intravenously.

[0550] Embodiment 166. The method of any one of Embodiments 140-165, wherein the steroid is administered prior to administration of the first pharmaceutical composition.

[0551] Embodiment 167. The method of Embodiment 166, wherein the steroid is administered daily for at least 1, 2, 3, 4, 5, 6, or 7 days prior to the administration of the first pharmaceutical composition.

[0552] Embodiment 168. The method of Embodiment 167, wherein the steroid is methylprednisolone and is administered at a daily dosage of about 30 mg/60 kg to about 40 mg/60 kg or about 30 mg to about 40 mg.

[0553] Embodiment 169. The method of Embodiment 168, wherein the daily dosage of methylprednisolone is about 32 mg/60 kg or 32 mg.

[0554] Embodiment 170. The method of Embodiment 168, wherein the steroid is prednisone and is administered at a daily dosage of about 50 mg/60 kg to about 70 mg/60 kg.

[0555] Embodiment 171. The method of Embodiment 170, wherein the daily dosage of prednisone is about 60 mg/60 kg.

[0556] Embodiment 172. The method of any one of Embodiments 140-171, wherein the steroid is administered after the administration of the first pharmaceutical composition.

[0557] Embodiment 173. The method of Embodiment 172, wherein the steroid is administered daily for at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, or at least 15 weeks after the administration of the first pharmaceutical composition.

[0558] Embodiment 174. The method of Embodiment 173, wherein the steroid is methylprednisolone and is administered at a daily dosage of between about 70 mg/60 kg and 90 mg/60 kg or between about 70mg and 90mg.

[0559] Embodiment 175. The method of Embodiment 174, wherein the daily dosage of methylprednisolone is about 80 mg/60 kg or 80mg.

[0560] Embodiment 176. The method of Embodiment 174 or 175, wherein the methylprednisolone is administered for at least two days after the administration of the first pharmaceutical composition.

[0561] Embodiment 177. The method of Embodiment 176, wherein subsequent doses of methylprednisolone are administered daily for at least 7 weeks after the administration of the first pharmaceutical composition and wherein the dosage of the methylprednisolone is decreased on a weekly basis.

[0562] Embodiment 178. The method of Embodiment 173, the steroid is predisone and is administered at a daily dosage of between about 50 mg/60 kg and 70 mg/ 60 kg or between about 50 mg and about 70 mg.

[0563] Embodiment 179. The method of Embodiment 178, wherein the daily dosage of predisone is about 60 mg/60 kg or about 60 mg.

[0564] Embodiment 180. The method of Embodiment 178 or 179, wherein the predisone is administered for at least seven days after the administration of the first pharmaceutical composition.

[0565] Embodiment 181. The method of Embodiment 180, wherein after seven days, the predisone is administered at a daily dosage of between about 30 mg/60 kg and about 50 mg/60 kg or between about 30 mg and 50 mg.

[0566] Embodiment 182. The method of Embodiment 181, wherein the daily dosage of predisone is about 40 mg/60 kg or 40 mg.

[0567] Embodiment 183. The method of Embodiment 182, wherein subsequent doses of predisone are administered daily for at least 4 days and wherein the dosage of the predisone is decreased on a daily basis.

[0568] Embodiment 184. The method of any one of Embodiments 140-183, wherein the steroid is administered prior to and after the administration of the first pharmaceutical compound.

[0569] Embodiment 185. The method of Embodiment 184, wherein the steroid is methylprednisolone and is administered daily for at least seven days prior to the administration of the first pharmaceutical compound and daily for at least 7 weeks after administration of the first pharmaceutical compound.

[0570] Embodiment 186. The method of Embodiment 185, wherein the methylprednisolone is administered prior to the administration of the first pharmaceutical compound at a daily dosage of about 32 mg/60 kg or 32 mg.

[0571] Embodiment 187. The method of Embodiment 185 or 186, wherein the methylprednisolone is administered at a daily dosage of about 80 mg/60 kg or 80mg for at least 2 days after the administration of the first pharmaceutical compound.

[0572] Embodiment 188. The method of Embodiment 187, wherein beginning three days after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 40 mg/60 kg or 40mg for at least 4 days.

[0573] Embodiment 189. The method of Embodiment 188, wherein beginning one week after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 32 mg/60 kg or 32mg for at least one week.

[0574] Embodiment 190. The method of Embodiment 189, wherein beginning two weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 24 mg/60 kg or 24mg for at least one week.

[0575] Embodiment 191. The method of Embodiment 190, wherein beginning three weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 16 mg/60 kg or 16mg for at least one week.

[0576] Embodiment 192. The method of Embodiment 191, wherein beginning four weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 8 mg/60 kg or 8mg for at least one week.

[0577] Embodiment 193. The method of Embodiment 192, wherein beginning five weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 6 mg/60 kg or 6mg for at least one week.

[0578] Embodiment 194. The method of Embodiment 193, wherein beginning six weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 4 mg/60 kg or 4mg for at least one week.

[0579] Embodiment 195. The method of Embodiment 194, wherein the steroid is prednisone and is administered daily for at least two days prior to the administration of the first pharmaceutical compound and daily for at least eleven days after administration of the first pharmaceutical compound.

[0580] Embodiment 196. The method of Embodiment 195, wherein the prednisone is administered prior to the administration of the first pharmaceutical compound at a daily dosage of about 60 mg/60 kg or 60mg.

[0581] Embodiment 197. The method of Embodiment 195 or 196, wherein the prednisone is administered at a daily dosage of about 60 mg/60 kg or 60mg for at least seven days after the administration of the first pharmaceutical compound.

[0582] Embodiment 198. The method of Embodiment 197, wherein eight days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 40 mg/60 kg or 40mg for at least one day.

[0583] Embodiment 199. The method of Embodiment 198, wherein nine days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 20 mg/60 kg or 20mg for at least one day.

[0584] Embodiment 200. The method of Embodiment 199, wherein ten days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 10 mg/60 kg or 10mg for at least one day.

[0585] Embodiment 201. The method of any one of Embodiments 140-200, further comprising administering sodium creatine phosphate to the patient.

[0586] Embodiment 202. The method of Embodiment 201, wherein said sodium creatine phosphate is administered intravenously prior to and/or after the administration of the first pharmaceutical composition.

[0587] Embodiment 203. The method of any one of Embodiments 140-202, wherein administration of the first and second pharmaceutical compositions generates a higher average recovery of vision than a comparable pharmaceutical composition administered without the second pharmaceutical composition.

[0588] Embodiment 204. The method of any one of Embodiments 140-203, wherein administration of the first and second pharmaceutical compositions generates a lower incidence of an adverse event than a comparable pharmaceutical composition administered without the second pharmaceutical composition.

[0589] Embodiment 205. The method of Embodiment 204, wherein the adverse event is selected from anterior chamber inflammation, vitritis, ocular hypertension, cataract removal, keratitis, vitreous hemorrhage, allergic conjunctivitis, and eye pain.

[0590] Embodiment 206. The method of any one of Embodiments 203-205, wherein the higher average recovery of vision and the lower incidence of an adverse event is determined in a population of patients with the eye disorder.

[0591] Embodiment 207. The method of Embodiment 206, wherein the population of patients are ethnically matched.

[0592] Embodiment 208. The method of Embodiment 207, wherein the population of patients are Chinese or Argentinian.

[0593] Embodiment 209. The method of any one of Embodiments 140-208, wherein the eye disorder is Leber's hereditary optic neuropathy (LHON).

[0594] Embodiment 210. The method of any one of Embodiments 140-209, wherein the AAV is selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AA8, AAV9, and AAV10.

[0595] Embodiment 211. The method of any one of Embodiments 140-210, wherein the AAV is AAV2.

[0596] Embodiment 212. A method of screening patients for treatment of an eye disorder, the method comprising: (a) obtaining a serum sample from a patient; (b) culturing a population of target cells with a composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid encoding a detectable label in the presence of the serum sample; and (c) detecting the expression level of the detectable label in the target cell population after the culturing, wherein the patient is selected for the treatment if the expression level of the detectable label in the target cell population is higher than a pre-determined threshold.

[0597] Embodiment 213. A method of treating an eye disorder for a patient in need thereof, comprising: (a) obtaining a serum sample from a patient; (b) culturing a population of target cells with a composition comprising a first adeno-associated virus (AAV) comprising a first recombinant nucleic acid encoding a detectable label in the presence of the serum sample; (c) detecting the expression level of the detectable label in the target cell population; and (d) administering to the patient a pharmaceutical composition comprising a second AAV comprising a second recombinant nucleic acid, wherein the expression level of the detectable label in the target cell population is higher than a pre-determined threshold.

[0598] Embodiment 214. The method of Embodiment 212 or 213, wherein the detectable label is a fluorescent protein.

[0599] Embodiment 215. The method of Embodiment 214, wherein the fluorescent protein is green fluorescent protein (GFP).

[0600] Embodiment 216. The method of any one of Embodiments 212-215, wherein the detectable label is detected by flow cytometry or qPCR.

[0601] Embodiment 217. The method of any one of Embodiments 212-216, wherein the pre-determined threshold is about 40% of cells expressing the detectable label when detected by flow cytometry.

[0602] Embodiment 218. The method of any one of Embodiments 212-216, wherein the pre-determined threshold is a relative expression level of the detectable label of about 0.6 when detected by qPCR.

[0603] Embodiment 219. The method of any one of Embodiments 212-218, wherein the target cells are HEK-293 T cells.

[0604] Embodiment 220. The method of any one of Embodiments 212-219, wherein the treatment is a recombinant AAV comprising a nucleic acid sequence encoding a mitochondrial protein.

[0605] Embodiment 221. The method of Embodiment 220, wherein the mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof.

[0606] Embodiment 222. The method of any one of Embodiments 212-221, wherein the patient comprises a mutation selected from G11778A in the *ND4* gene, G3460A in the *ND1* gene, and T14484C in the *ND6* gene.

[0607] Embodiment 223. The method of any one of Embodiments 212-222, wherein the culturing step is at least 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or longer.

[0608] Embodiment 224. A kit, comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid encoding a detectable label, a population of target cells, and one or more reagents for detecting the detectable label.

[0609] Embodiment 225. The kit of Embodiment 224, further comprising a transfection reagent for transfecting the population of target cells with the AAV.

[0610] Embodiment 225. The kit of Embodiment 224 or 225, further comprising a second AAV comprising a recombinant nucleic acid encoding a mitochondrial protein.

[0611] Embodiment 225. The kit of Embodiment 224, wherein the one or more reagents for detecting the detectable label are selected an antibody that binds to the detectable label and one or more primer oligonucleotides specific for the recombinant nucleic acid encoding the detectable label.

INCORPORATION BY REFERENCE

[0612] All references, articles, publications, patents, patent publications, and patent applications cited herein are incorporated by reference in their entireties for all purposes. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as, an acknowledgment or any form of suggestion that they constitute valid prior art or form part of the common general knowledge in any country in the world.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating an eye disorder, comprising administering to a patient in need thereof

a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising:

i) a nucleic acid sequence encoding a mitochondrial targeting peptide;

ii) a nucleic acid sequence encoding a mitochondrial protein comprising a nucleic acid 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: 6-12; and

iii) a 3'UTR nucleic acid sequence; and

b) a second pharmaceutical composition comprising a steroid.

2. The method of claim 1, wherein the nucleic acid sequence encoding the mitochondrial protein encodes a polypeptide comprising an amino acid 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: 160-162.

3. The method of claim 1 or claim 2, wherein the nucleic acid sequence encoding a mitochondrial targeting peptide encodes a polypeptide comprising an amino acid 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: 126-159.

4. The method of any one of claims 1-3, wherein the nucleic acid sequence encoding a mitochondrial targeting peptide comprises a nucleic acid 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: 1-5.

5. The method of any one of claims 1-4, wherein the 3'UTR nucleic acid sequence comprises a nucleic 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: 13, 14, and 111-125.

6. A method of treating an eye disorder, comprising administering to a patient in need thereof

a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising:

i) a nucleic acid sequence encoding a mitochondrial targeting peptide comprising an amino 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: 126-159;

ii) a nucleic acid sequence encoding a mitochondrial protein; and

iii) a 3'UTR nucleic acid sequence; and

b) a second pharmaceutical composition comprising a steroid.

7. The method of claim 6, wherein said mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof.

8. The method of claim 6 or 7, wherein the nucleic acid sequence encoding a mitochondrial protein comprises a nucleic acid sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO: 6-12.

9. The method of claim 7 or 8, wherein nucleic acid sequence encoding a mitochondrial protein encodes a polypeptide comprising an amino acid 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: 160-162.

10. The method of any one of claims 7-9, wherein the nucleic acid sequence encoding a mitochondrial targeting peptide comprises a nucleic acid 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: 1-5.

11. The method of any one of claims 7-10, wherein the 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: 13, 14, and 111-125.

12. A method of treating an eye disorder, comprising administering to a patient in need thereof

a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising:

i) a nucleic acid sequence encoding a mitochondrial targeting peptide comprising an amino 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: 126-159;

ii) a nucleic acid sequence encoding a mitochondrial protein comprising a nucleic acid 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: 6-12; and

iii) a 3'UTR nucleic acid 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: 13, 14, and 111-125; and

(b) a second pharmaceutical composition comprising a steroid.

13. A method of treating an eye disorder, comprising administering to a patient in need thereof

(a) a first pharmaceutical composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid comprising:

(i) a nucleic acid sequence encoding a mitochondrial targeting peptide; and

(ii) a nucleic acid sequence encoding a mitochondrial protein; and

(b) a second pharmaceutical composition comprising a steroid.

14. The method of claim 13, wherein the mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof.

15. The method of claim 13 or 14, wherein the 3'UTR nucleic acid sequence comprises a nucleic 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: 13, 14, and 111-125.

16. The method of any one of claims 1-15, wherein the 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: 15-84.

17. The method of any one of claims 1-16, wherein the recombinant nucleic acid comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to SEQ ID NO: 15.

18. The method of any one of claims 1-17, wherein the first pharmaceutical composition is administered via intraocular or intravitreal injection.

19. The method of any one of claims 1-18, wherein about 0.01-0.1 mL of the first pharmaceutical composition is administered via intravitreal injection.

20. The method of any one of claims 1-19, wherein about 0.05 mL of the first pharmaceutical composition is administered via intravitreal injection.

21. The method of any one of claims 1-20, wherein the first pharmaceutical composition is administered to one or both eyes of the patient.

22. The method of any one of claims 1-21, wherein the steroid selected from the group consisting of alclometasone diproprionate, amcinonide, beclomethasone diproprionate, betamethasone, betamethasone benzoate, betamethasone diproprionate, betamethasone sodium phosphate, betamethasone sodium phosphate and acetate, betamethasone valerate, clobetasol proprionate, clocortolone pivalate, cortisol (hydrocortisone), cortisol (hydrocortisone) acetate, cortisol (hydrocortisone) butyrate, cortisol (hydrocortisone) cypionate, cortisol (hydrocortisone) sodium phosphate, cortisol (hydrocortisone) sodium succinate, cortisol (hydrocortisone) valerate, cortisone acetate, desonide, desoximetasone, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, diflorasone diacetate, fludrocortisone acetate, flunisolide, fluocinolone acetonide, fluocinonide, fluorometholone, flurandrenolide, halcinonide, medrysone, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide or a synthetic analog thereof.

23. The method of any one of claims 1-22, wherein steroid is a glucocorticoid.

24. The method of claim 23, wherein the glucocorticoid is methylprednisolone or prednisone.

25. The method of claim 24, wherein the methylprednisolone is formulated as a tablet or as a liquid for intravenous administration.

26. The method of any one of claims 1-25, wherein the steroid is administered orally or intravenously.

27. The method of any one of claims 1-26, wherein the steroid is administered prior to administration of the first pharmaceutical composition.

28. The method of claim 27, wherein the steroid is administered daily for at least 1, 2, 3, 4, 5, 6, or 7 days prior to the administration of the first pharmaceutical composition.

29. The method of claim 28, wherein the steroid is methylprednisolone and is administered at a daily dosage of about 30 mg/60 kg to about 40 mg/60 kg or about 30 mg to about 40 mg.

30. The method of claim 29, wherein the daily dosage of methylprednisolone is about 32 mg/60 kg or 32 mg.

31. The method of claim 28, wherein the steroid is prednisone and is administered at a daily dosage of about 50 mg/60 kg to about 70 mg/60 kg.

32. The method of claim 31, wherein the daily dosage of prednisone is about 60 mg/60 kg.

33. The method of any one of claims 1-26, wherein the steroid is administered after the administration of the first pharmaceutical composition.

34. The method of claim 33, wherein the steroid is administered daily for at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, or at least 15 weeks after the administration of the first pharmaceutical composition.

35. The method of claim 34, wherein the steroid is methylprednisolone and is administered at a daily dosage of between about 70 mg/60 kg and 90 mg/60 kg or between about 70 mg and 90 mg.

36. The method of claim 35, wherein the daily dosage of methylprednisolone is about 80 mg/60 kg or 80 mg.

37. The method of claim 35 or 36, wherein the methylprednisolone is administered for at least two days after the administration of the first pharmaceutical composition.

38. The method of claim 37, wherein subsequent doses of methylprednisolone are administered daily for at least 7 weeks after the administration of the first pharmaceutical composition and wherein the dosage of the methylprednisolone is decreased on a weekly basis.

39. The method of claim 34, the steroid is predisone and is administered at a daily dosage of between about 50 mg/60 kg and 70 mg/ 60 kg or between about 50 mg and about 70 mg.

40. The method of claim 39, wherein the daily dosage of predisone is about 60 mg/60 kg or about 60 mg.

41. The method of claim 39 or 40, wherein the predisone is administered for at least seven days after the administration of the first pharmaceutical composition.

42. The method of claim 41, wherein after seven days, the predisone is administered at a daily dosage of between about 30 mg/60 kg and about 50 mg/60 kg or between about 30 mg and 50 mg.

43. The method of claim 42, wherein the daily dosage of predisone is about 40 mg/60 kg or 40 mg.

44. The method of claim 43, wherein subsequent doses of predisone are administered daily for at least 4 days and wherein the dosage of the predisone is decreased on a daily basis.

45. The method of any one of claims 1-44, wherein the steroid is administered prior to and after the administration of the first pharmaceutical compound.

46. The method of claim 45, wherein the steroid is methylprednisolone and is administered daily for at least seven days prior to the administration of the first pharmaceutical compound and daily for at least 7 weeks after administration of the first pharmaceutical compound.

47. The method of claim 46, wherein the methylprednisolone is administered prior to the administration of the first pharmaceutical compound at a daily dosage of about 32 mg/60 kg or 32 mg.

48. The method of claim 46 or 47, wherein the methylprednisolone is administered at a daily dosage of about 80 mg/60 kg or 80 mg for at least 2 days after the administration of the first pharmaceutical compound.

49. The method of claim 48, wherein beginning three days after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 40 mg/60 kg or 40 mg for at least 4 days.

50. The method of claim 49, wherein beginning one week after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 32 mg/60 kg or 32 mg for at least one week.

51. The method of claim 50, wherein beginning two weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 24 mg/60 kg or 24 mg for at least one week.

52. The method of claim 51, wherein beginning three weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 16 mg/60 kg or 16 mg for at least one week.

53. The method of claim 52, wherein beginning four weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 8 mg/60 kg or 8 mg for at least one week.

54. The method of claim 53, wherein beginning five weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 6 mg/60 kg or 6 mg for at least one week.

55. The method of claim 54, wherein beginning six weeks after administration of the first pharmaceutical compound, the methylprednisolone is administered at a daily dosage of about 4 mg/60 kg or 4 mg for at least one week.

56. The method of claim 45, wherein the steroid is prednisone and is administered daily for at least two days prior to the administration of the first pharmaceutical compound and daily for at least eleven days after administration of the first pharmaceutical compound.

57. The method of claim 56, wherein the prednisone is administered prior to the administration of the first pharmaceutical compound at a daily dosage of about 60 mg/60 kg or 60 mg.

58. The method of claim 56 or 57, wherein the prednisone is administered at a daily dosage of about 60 mg/60 kg or 60mg for at least seven days after the administration of the first pharmaceutical compound.

59. The method of claim 58, wherein eight days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 40 mg/60 kg or 40 mg for at least one day.

60. The method of claim 59, wherein nine days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 20 mg/60 kg or 20 mg for at least one day.

61. The method of claim 60, wherein ten days after administration of the first pharmaceutical compound, the prednisone is administered at a daily dosage of about 10 mg/60 kg or 10 mg for at least one day.

62. The method of any one of claims 1-61, further comprising administering sodium creatine phosphate to the patient.

63. The method of claim 62, wherein said sodium creatine phosphate is administered intravenously prior to or after the administration of the first pharmaceutical composition.

64. The method of any one of claims 1-63, wherein administration of the first and second pharmaceutical compositions generates a higher average recovery of vision than a comparable pharmaceutical composition administered without the second pharmaceutical composition.

65. The method of any one of claims 1-64, wherein administration of the first and second pharmaceutical compositions generates a lower incidence of an adverse event than a comparable pharmaceutical composition administered without the second pharmaceutical composition.

66. The method of claim 65, wherein the adverse event is selected from anterior chamber inflammation, vitritis, ocular hypertension, cataract removal, keratitis, vitreous hemorrhage, allergic conjunctivitis, and eye pain.

67. The method of any one of claims 64-66, wherein the higher average recovery of vision and the lower incidence of an adverse event is determined in a population of patients with the eye disorder.

68. The method of claim 67, wherein the population of patients are ethnically matched.

69. The method of claim 68, wherein the population of patients are Chinese or Argentinian.

70. The method of any one of claims 1-69, wherein the eye disorder is Leber's hereditary optic neuropathy (LHON).

71. The method of any one of claims 1-70, wherein the AAV is selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AA8, AAV9, and AAV10.

72. The method of any one of claims 1-71, wherein the AAV is AAV2.

73. A method of screening patients for treatment of an eye disorder, the method comprising:

(a) obtaining a serum sample from a patient;

(b) culturing a population of target cells with a composition comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid encoding a detectable label in the presence of the serum sample; and

(c) detecting the expression level of the detectable label in the target cell population after the culturing, wherein the patient is selected for the treatment if the expression level of the detectable label in the target cell population is higher than a pre-determined threshold.

74. A method of treating an eye disorder for a patient in need thereof, comprising:

(a) obtaining a serum sample from a patient;

(b) culturing a population of target cells with a composition comprising a first adeno-associated virus (AAV) comprising a first recombinant nucleic acid encoding a detectable label in the presence of the serum sample;

(c) detecting the expression level of the detectable label in the target cell population; and

(d) administering to the patient a pharmaceutical composition comprising a second AAV comprising a second recombinant nucleic acid, wherein the expression level of the detectable label in the target cell population is higher than a pre-determined threshold.

75. The method of claim 73 or 74, wherein the detectable label is a fluorescent protein.

76. The method of claim 75, wherein the fluorescent protein is green fluorescent protein (GFP).

77. The method of any one of claims 73-76, wherein the detectable label is detected by flow cytometry or qPCR.

78. The method of any one of claims 73-77, wherein the pre-determined threshold is about 40% of cells expressing the detectable label when detected by flow cytometry.

79. The method of any one of claims 73-77, wherein the pre-determined threshold is a relative expression level of the detectable label of about 0.6 when detected by qPCR.

80. The method of any one of claims 73-79, wherein the target cells are HEK-293 T cells.

81. The method of any one of claims 73-80, wherein the treatment is a recombinant AAV comprising a nucleic acid sequence encoding a mitochondrial protein.

82. The method of claim 81, wherein the mitochondrial protein is selected from the group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), NADH dehydrogenase 1 (ND1), and variants thereof.

83. The method of any one of claims 73-82, wherein the patient comprises a mutation selected from G11778A in the *ND4* gene, G3460A in the *ND1* gene, and T14484C in the *ND6* gene.

84. The method of any one of claims 73-83, wherein the culturing step is at least 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or longer.

85. A kit, comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid encoding a detectable label, a population of target cells, and one or more reagents for detecting the detectable label.

86. The kit of claim 85, further comprising a transfection reagent for transfecting the population of target cells with the AAV.

87. The kit of claim 85 or 86, further comprising a second AAV comprising a recombinant nucleic acid encoding a mitochondrial protein.

88. The kit of any one of claims 85-87, wherein the one or more reagents for detecting the detectable label are selected an antibody that binds to the detectable label and one or more primer oligonucleotides specific for the recombinant nucleic acid encoding the detectable label.

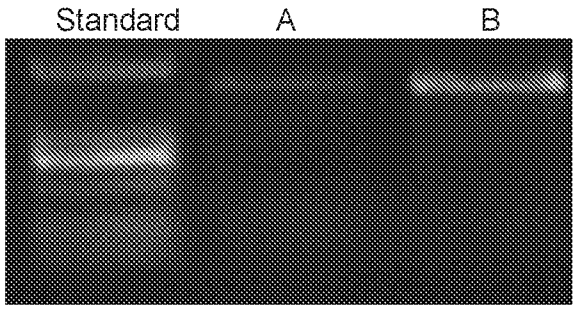


FIG. 1

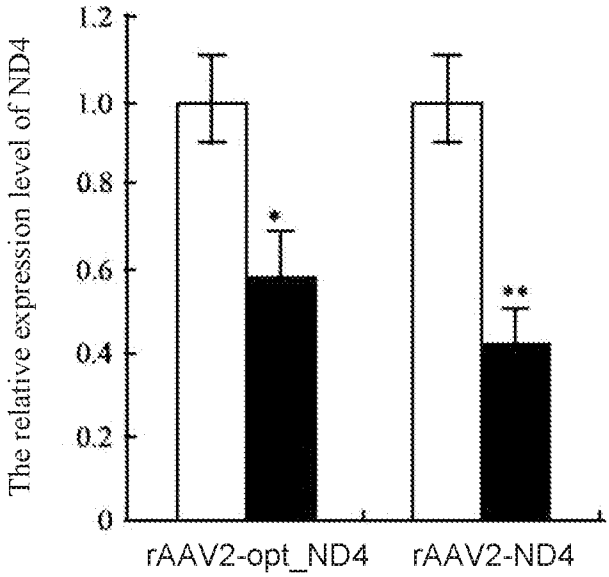

The relative expression level of ND4
1.2
1.0
0.8
0.6
0.4
0.2
0
*
**
rAAV2-opt_ND4
rAAV2-ND4

FIG. 2

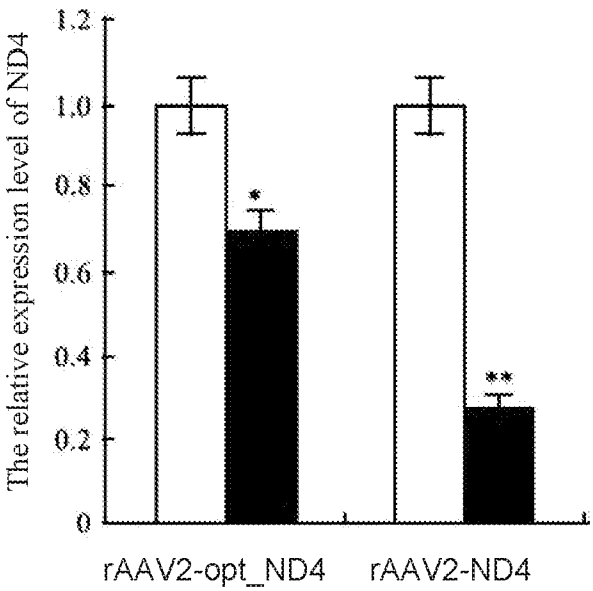

The relative expression level of ND4
1.2
1.0
0.8
0.6
0.4
0.2
0
*
**
rAAV2-opt_ND4
rAAV2-ND4

FIG. 3

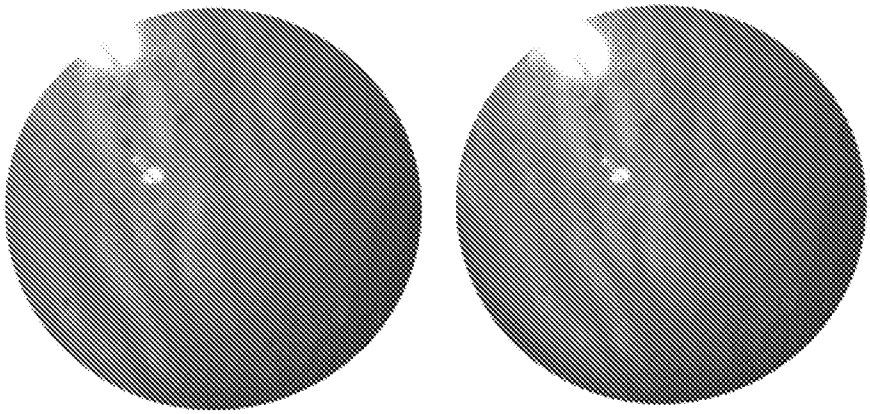


FIG. 4

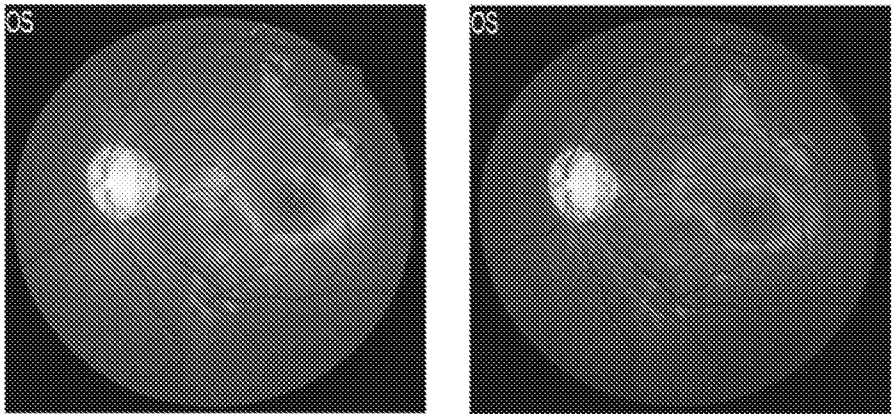


FIG. 5

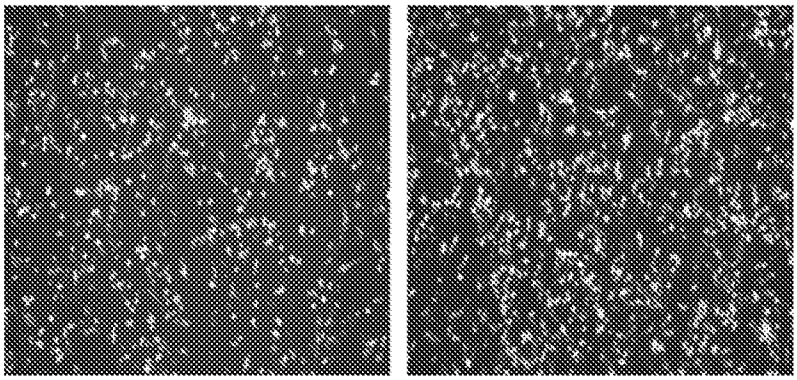


FIG. 6

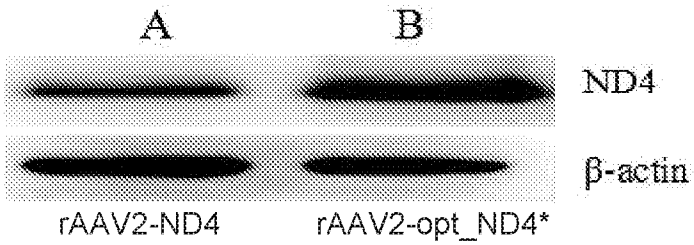


FIG. 7

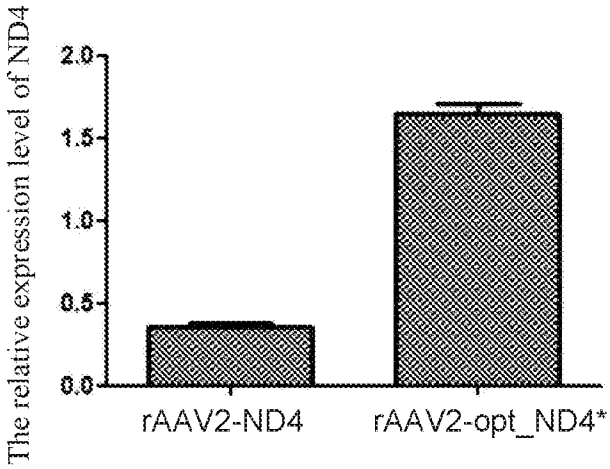

The relative expression level of ND4
2.0
1.5
1.0
0.5
0.0
rAAV2-ND4
rAAV2-opt_ND4*

FIG. 8

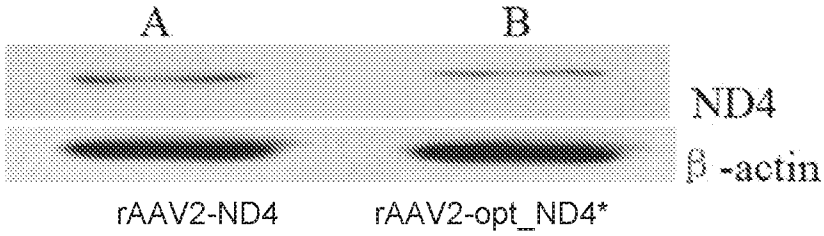


FIG. 9

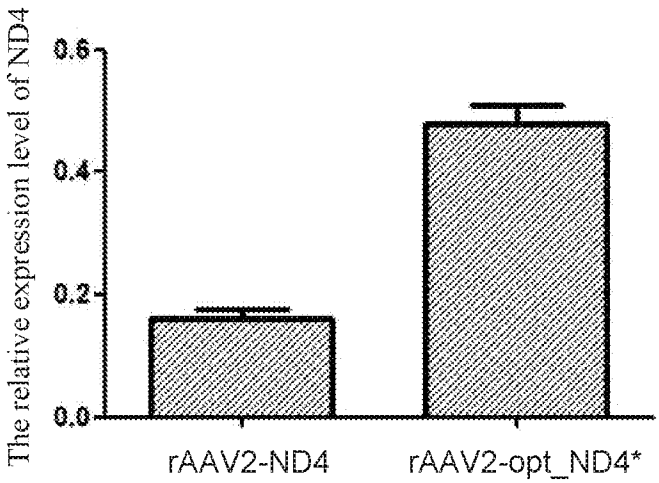

The relative expression level of ND4
0.6
0.4
0.2
0.0
rAAV2-ND4
rAAV2-opt_ND4*

FIG. 10

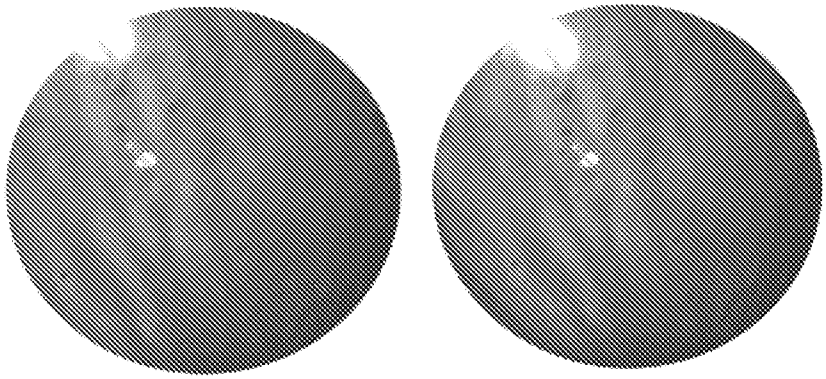


FIG. 11

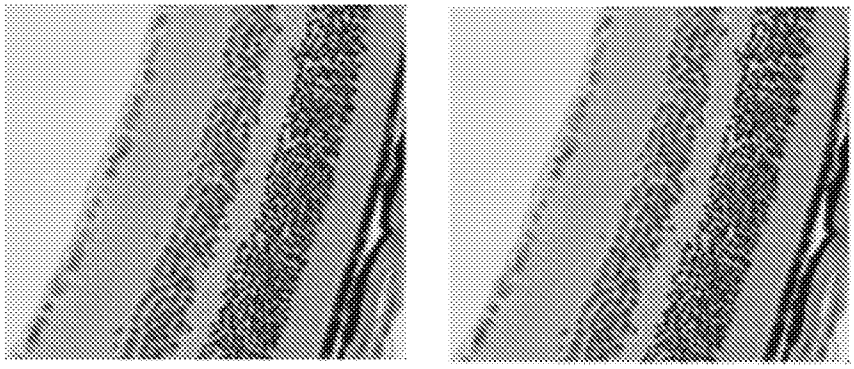


FIG. 12

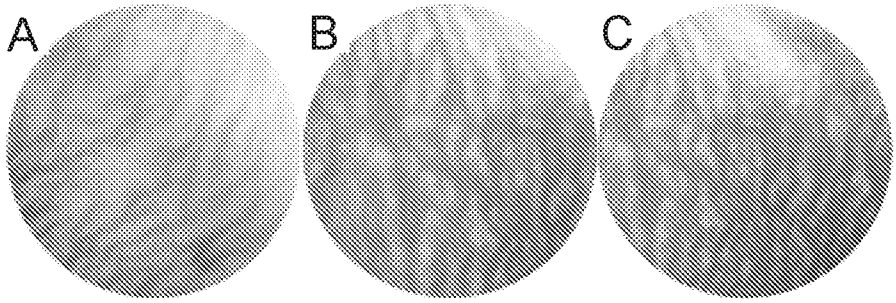
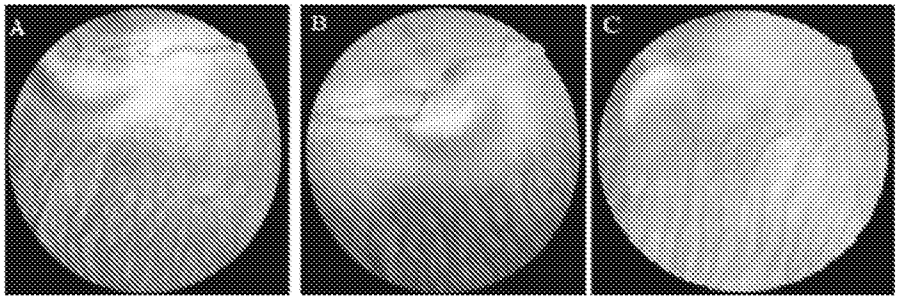


FIG. 13



A B C

FIG. 14

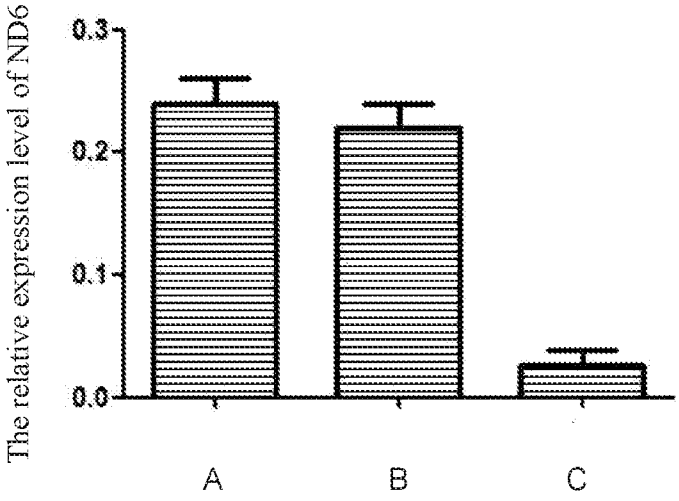


FIG. 15

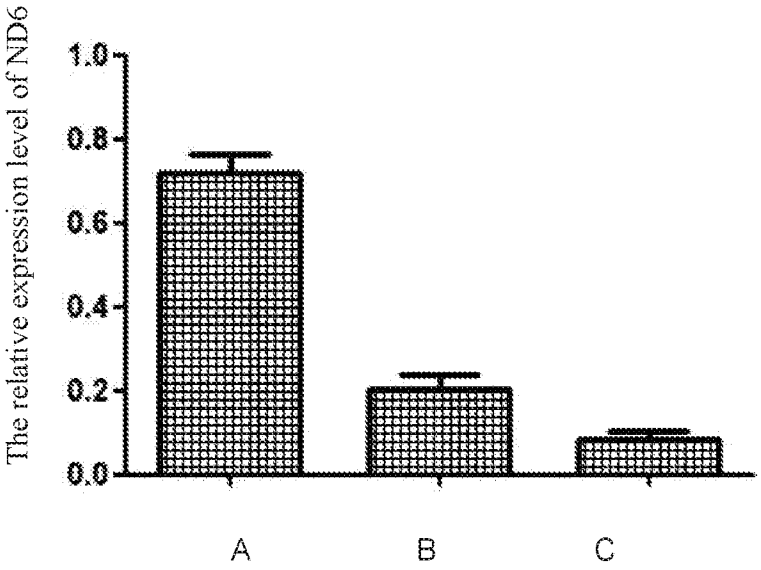


FIG. 16

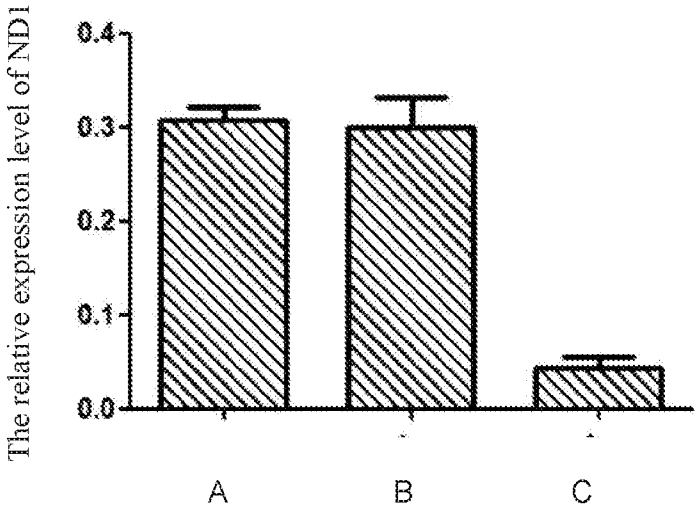


FIG. 17

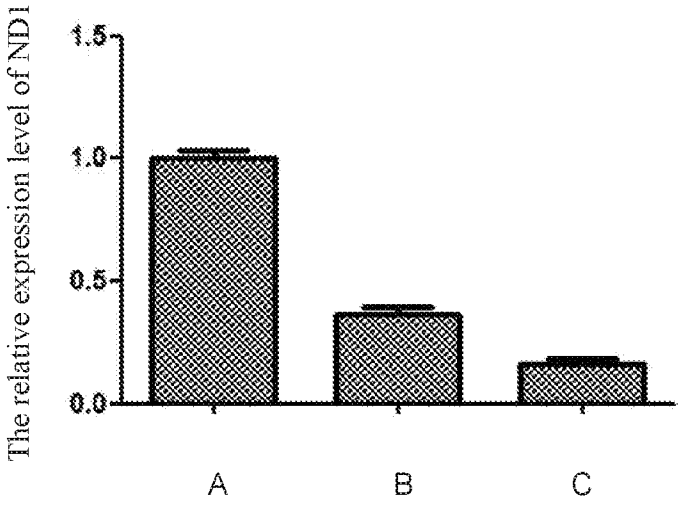


FIG. 18

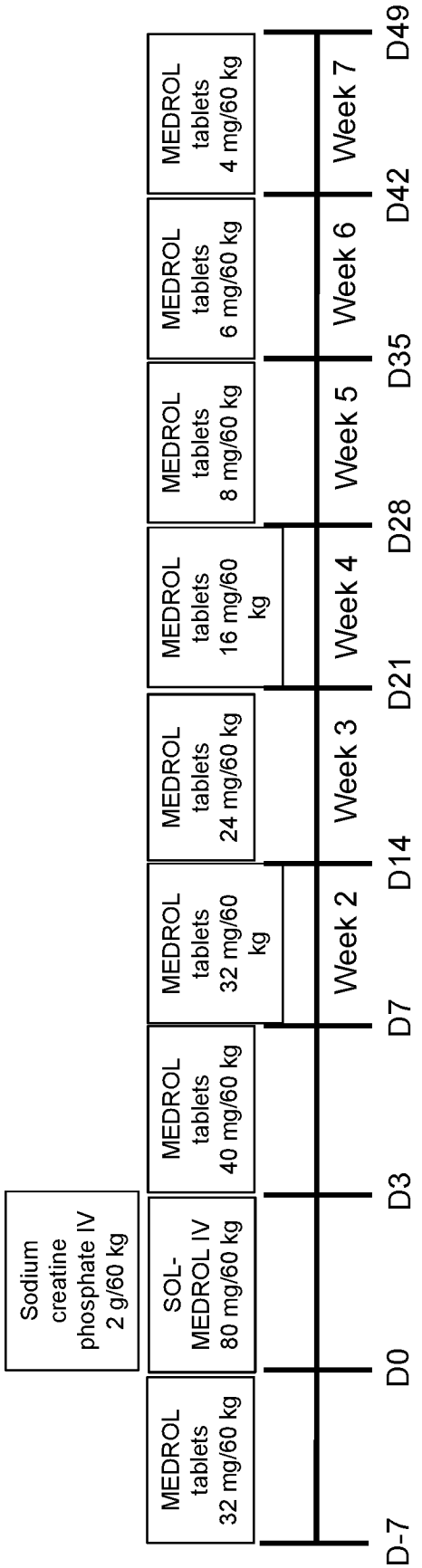

MEDROL tablets 32 mg/60 kg
Sodium creatine phosphate IV 2 g/60 kg
SOL-MEDROL IV 80 mg/60 kg
MEDROL tablets 40 mg/60 kg
MEDROL tablets 32 mg/60 kg
MEDROL tablets 24 mg/60 kg
MEDROL tablets 16 mg/60 kg
MEDROL tablets 8 mg/60 kg
MEDROL tablets 6 mg/60 kg
MEDROL tablets 4 mg/60 kg
D-7
D0
D3
D7
D14
D21
D28
D35
D42
D49
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Intravitreal injection of rAAV2-ND4

FIG. 19

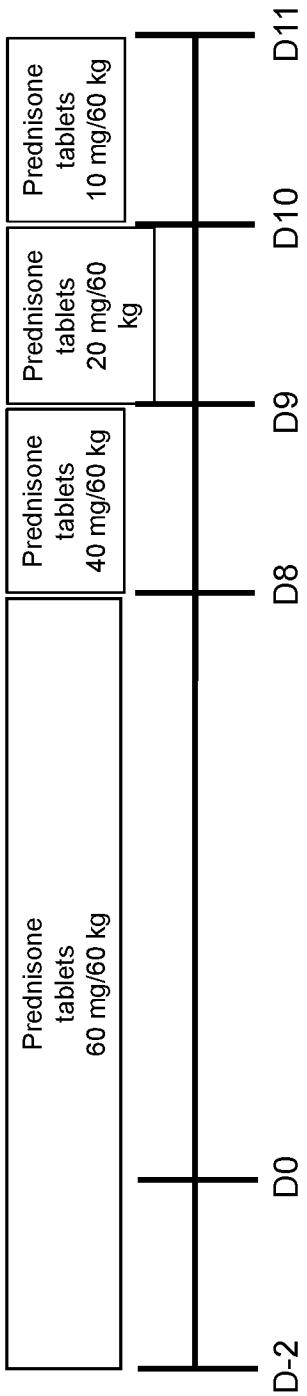

Prednisone tablets 60 mg/60 kg
Prednisone tablets 40 mg/60 kg
Prednisone tablets 20 mg/60 kg
Prednisone tablets 10 mg/60 kg
D-2
D0
D8
D9
D10
D11
Intravitreal injection of rAAV2-ND4

FIG. 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/101538

A. CLASSIFICATION OF SUBJECT MATTER

A61K 48/00(2006.01)i; C12N 15/66(2006.01)i; C12N 15/864(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K;C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

VEN, CNABS, PubMed, ISI Web of Knowledge, NCBI Genbank, EMBL-EBI, CNKI:WUHAN NEUROPHTH,Gensight,AVV, ND4,steroid,prednisolone,ILON,leber,SEQ ID NO: 6-12,126-159,160-162

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WAN, X. et al. "Efficacy and Safety of rAAV2-ND4 Treatment for Leber's Hereditary Optic Neuropathy" *SCIENTIFIC REPORTS,* Vol. 6, 19 February 2016 (2016-02-19), Article 21587	1-72
X	YANG, S. et al. "Long-term outcomes of gene therapy for the treatment of Leber's hereditary optic neuropathy" *EBIOMEDICINE,* Vol. 10, 06 July 2016 (2016-07-06), pages 258-268	1-72
X	YANG, S. et al. "Study on transfection of adeno associated virus 2-ND4 gene into mitochondri" *CHINESE JOURNAL OF EXPERIMENTAL OPHTHALMOLOGY,* Vol. 32, No. 8, 31 August 2014 (2014-08-31), pages 693-695	85-88
A	WO 2008063802 A2 (UNIV. FLORIDA RES. FOUNDATION, INC.) 29 May 2008 (2008-05-29) the whole document	1-88
A	WO 2016044023 A1 (UNIV. IOWA RES. FOUNDATION) 24 March 2016 (2016-03-24) the whole document	1-88

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2019	**20 November 2019**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **XI,Jing** Telephone No. **86-(10)-53961974**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017011519 A1 (SANGAMO BIOSCIENCES, INC.) 19 January 2017 (2017-01-19) the whole document	1-88
A	CN 102634527 A (UNIV. HUAZHONG TONGJI MEDICAL COLLEGE) 15 August 2012 (2012-08-15) the whole document	1-88

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/101538

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☑ forming part of the international application as filed:
      ☑ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.
   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/101538

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **1-72, 74-84**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 1-72 and 74-84 direct to a method of treating diseases or condition in a subject and therefore do not warrant an international search according to the criteria set out in PCT Rule 39.1(iv). The search has been carried out and based on the use of the pharmaceutical composition for manufacturing of a medicament for the treatment of diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/101538

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2008063802 A2	29 May 2008	WO 2008063802 A3	23 October 2008
		US 2010041741 A1	18 February 2010
		AU 2007324073 A1	29 May 2008
		EP 2089412 A4	27 January 2010
		WO 2008063802 A9	24 July 2008
		EP 2089412 A2	19 August 2009
		CA 2667705 A1	29 May 2008
WO 2016044023 A1	24 March 2016	EP 3194595 A4	20 June 2018
		CN 107002079 A	01 August 2017
		CA 2961568 A1	24 March 2016
		BR 112017005524 A2	06 March 2018
		SG 11201702116V A	27 April 2017
		US 2018000925 A1	04 January 2018
		KR 20170066433 A	14 June 2017
		EP 3194595 A1	26 July 2017
		JP 2017530968 A	19 October 2017
		AU 2015318283 A1	06 April 2017
WO 2017011519 A1	19 January 2017	AU 2016291778 A1	25 January 2018
		CN 108024544 A	11 May 2018
		EP 3322297 A1	23 May 2018
		JP 2018525979 A	13 September 2018
		EP 3322297 A4	17 April 2019
		US 2017016027 A1	19 January 2017
		CA 2991301 A1	19 January 2017
CN 102634527 A	15 August 2012	CN 102634527 B	06 November 2013