

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
02 January 2020 (02.01.2020)

(10) International Publication Number
WO 2020/001657 A1

(51) International Patent Classification:

CI2N 15/09 (2006.01) *A61K 48/00* (2006.01)
CI2N 15/63 (2006.01) *A61P 27/02* (2006.01)
CI2N 15/86 (2006.01)

C270-271 B1, No. 666 Ave Gaoxin, Wuhan, Hubei 430060 (CN).

(21) International Application Number:

PCT/CN2019/094136

(72) Inventor: **LI, Bin**; C270-271 B1, No. 666 Ave Gaoxin, Wuhan, Hubei 430060 (CN).

(22) International Filing Date:

01 July 2019 (01.07.2019)

(74) Agent: **METIS IP (CHENGDU) LLC**; Room 808, 8th Floor, Building B7, Block D, Tianfu Jingrong Center, No. 99 West Section of Hupan Road, Tianfu New District, Chengdu, Sichuan 610213 (CN).

(25) Filing Language:

English

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(26) Publication Language:

English

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(30) Priority Data:

201810703168.7	29 June 2018 (29.06.2018)	CN
201810702492.7	29 June 2018 (29.06.2018)	CN
PCT/CN2018/095023		
	09 July 2018 (09.07.2018)	CN
201810948193.1	20 August 2018 (20.08.2018)	CN
PCT/CN2018/103937		
	04 September 2018 (04.09.2018)	CN
201811221305.X	19 October 2018 (19.10.2018)	CN
201811230856.2	22 October 2018 (22.10.2018)	CN
PCT/CN2018/113799		
	02 November 2018 (02.11.2018)	CN
PCT/CN2018/118662		
	30 November 2018 (30.11.2018)	CN
PCT/CN2019/070461		
	04 January 2019 (04.01.2019)	CN

(71) Applicant: **WUHAN NEUROPHTH BIOLOGICAL TECHNOLOGY LIMITED COMPANY [CN/CN]**

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

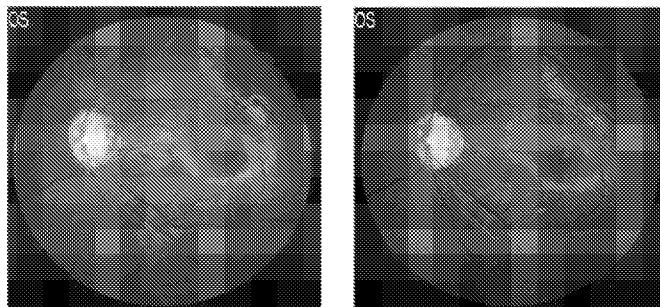


FIG. 5

(57) Abstract: Disclosed herein 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 disclosed is a pharmaceutical composition comprising the recombinant nucleic acid and a method of treating Leber's hereditary optic neuropathy (LHON) using the pharmaceutical composition.

Published:

- *with international search report (Art. 21(3))*
- *with sequence listing part of description (Rule 5.2(a))*

COMPOSITIONS AND METHODS FOR TREATING LEBER'S HEREDITARY OPTIC NEUROPATHY

CROSS-REFERENCE

[0001] This application claims the benefit of PCT Application No. PCT/CN2018/095023, filed on July 9, 2018; PCT Application No. PCT/CN2018/103937, filed on September 4, 2018; Chinese Application Nos. CN201810703168.7 and CN201810702492.7, both filed on June 29, 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; all of which are incorporated herein by reference in their entirety.

REFERENCE TO A 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 June 30, 2019, is named 207298476_1.txt and is 304,914 bytes in size.

BACKGROUND OF THE INVENTION

[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 OF THE INVENTION

[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, hsUQCRRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRPI, 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, hsUQCRCFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXAIL. 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 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, hsUQCRCFS1, 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, NaH₂PO₄, Na₂HPO₄, KH₂PO₄, K₂HPO₄, 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, NaH₂PO₄, Na₂HPO₄, KH₂PO₄, K₂HPO₄, 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, NaH₂PO₄, Na₂HPO₄, and KH₂PO₄. In some cases, the one or more salts comprises 80 mM NaCl, 5 mM NaH₂PO₄, 40 mM Na₂HPO₄, and 5 mM KH₂PO₄. 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 creatine phosphate sodium to the patient. In some cases, the creatine phosphate sodium 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.

INCORPORATION BY REFERENCE

[0036] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] 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:

[0038] FIG. 1 shows the PCR nucleic acid electrophoresis verification of ND4 (lane A) and optimized ND4 (lane B) gene cloning results.

[0039] 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).

[0040] 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).

[0041] FIG. 4 shows the fundus photographic results for rabbits injected with rAAV2-opt_ND4 (right) and rAAV2-ND4 (left), respectively.

[0042] FIG. 5 shows the fundus photographic results for a patient before (left) and after (right) the injection with rAAV2-optimized ND4.

[0043] FIG. 6 shows EGFP expression levels of rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0044] FIG. 7 shows the ND4 expression in 293T cells: rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0045] FIG. 8 shows the relative ND4 expression in 293T cells: rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0046] FIG. 9 shows the ND4 expression in rabbit optic nerve cells: rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0047] FIG. 10 shows the relative ND4 expression in rabbit optic nerve cells: rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0048] FIG. 11 shows the fundus photographic results for rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0049] FIG. 12 shows the microscope inspection (HE staining) results for rAAV2-ND4 (left) and rAAV2-opt_ND4* (right).

[0050] FIG. 13 shows the fundus photographic results for rabbits injected with rAAV2-ND6 (A), rAAV-GFP (B) and PBS, respectively.

[0051] FIG. 14 shows the fundus photographic results for rabbits injected with rAAV2-opt_ND6 (A), rAAV2-ND6 (B), rAAV-EGFP (C), respectively.

[0052] FIG. 15 shows the relative ND6 expression in rabbit optic nerve cells: rAAV2-opt_ND6 (A), rAAV2-ND6 (B), and rAAV-EGFP (C).

[0053] FIG. 16 shows the relative ND6 expression by western blot: rAAV2-opt_ND6 (A), rAAV2-ND6 (B), and rAAV-EGFP (C).

[0054] FIG. 17 shows the relative ND1 expression in rabbit optic nerve cells: rAAV2-opt_ND1 (A), rAAV2-ND1 (B), and rAAV-EGFP (C).

[0055] FIG. 18 shows the relative ND1 expression by western blot: rAAV2-opt_ND1 (A), rAAV2-ND1 (B), and rAAV-EGFP (C).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] As used herein, unless otherwise indicated, the terms “nucleic acid” and “polynucleotide” can be used interchangeably.

Nucleic acid and polypeptide sequences

[0066] 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

8	opt_ND4*	ATGCTGAAGCTGATCGTGCCACCATCATGCTGCTGCCCTGACCTGGCTGAGCAAGAACATGA TCTGGATCAACACCACCCACAGCCTGATCATCAGCATCATCCCCCTGCTGTTCTCAACCAAGATC AAACAACAACCTGTCAGCTGCAGCCCCACCTTCAGCAGCGACCCCTGACCAACCCCCCTGCTGATGC TGACCAACCTGGCTGTCGCCCTGACCATCATGGCCAGCGCAGCCACCTGAGCAGCGAGCCCCCTGA GCCGCAAGAAGCTGACCTGAGCATGCTGATCAGCCTGAGCATGACCCCTGACCATCATGACCCCTG CACCAGAGCTGATCATGTTACATCTCTCGAGACCAACCCCTGATCCCCACCCCTGGCCATCATCACCC GCTGGGCAACCAAGCCGAGCGCCTGACGCCGACCTACTTCTGTTCTACACCCGGTGGCA GCCTGCCCTGCTGATGCCCTGATCTACACCCACAACACCCCTGGCAGCCTGAAACATCCTGCTGCT GACCTGACCGCCCAGGAGCTGAGCAACAGCTGGCCAACAACCTGATGTTGCTGGCTGCCATACCCAT GCCCTCATGGTGAAGATGCCCTGACGGCTGACCTGTGGCTGCCAAGGCCACGTGGAGGC CCCCATGCCGGCAGCATGGTCTGCCGCCGCTGCTGAGCTGGGCCCTACGGCATGATGCC CTGACCCCTGATCTGAAACCCCTGACCAAGCACATGGCTACCCCTGCTGGTGTGAGCTGCTG GGCATGATCATGACCGCAGCATCTGCCCTGCCAGACCGACCTGAGAGCTGATGCCCTACAGCA GCATCAGCCACATGCCCTGGTGGTGGCAGGCCATCTGATCCAGACCCCTGGAGCTTACCGGGCG CCGTGATCCTGATGATGCCACGGCCTGACCGAGCAGCCTGCTGTTCTGCCCTGGCAACAGCAACTA CGAGCGCACCCACAGCCGATCATGATCCTGAGCCAGGGCTGAGACCCCTGCTGCCCTGATGCC CTCTGGTGGCTGCTGGCCAGCCTGGCCACCTGGCCCTGCCACCATCAACCTGCTGGGCA GCTGAGCGCTGCTGTGACCCCTGAGCAGCACATCACCCCTGCTGCTGACCCGGCTGAAACATG CTGGTACCGCCCTGATCACGCTGATGTTACCCACCAACCCCTGATGTTCATGACCTGAGCCCCATCCTG CTGCTGAGCCTGAAACCCGACATCATCACCGGCTCAGCAGCTA
9	ND6	ATGATGTATGCTTTGTTCTGTTGAGTGTGGGTTAGTAATGGGTTGTGGGTTCTCTAAGCCT TCTCCTATTATGGGGTTAGTTGATTGTTAGCGGTGTTGCTGGGTGTTTATTCTGAATTGG GGGGAGGTTATATGGGTTAATGGGTTTAAATTTATTAGGGGAAATGATGGTTGCTTGGATATAAC TACAGCGATGGCTATTGAGGAGTATCCTGAGGGCATGGGGCTCAGGGGTTGAGGTCTGGTGTGAGTT TTAGGGGTTAGCGATGGGGTAGGATTGGTGTGTTGGTGAAGAGTATGATGGGGTGGTGGTT TGGTAAACTTAATAGTGTAGGAAGCTGGATGATTATGAAGGGAGGGGTCAGGGTTGATTGGGAG GATCCTATTGGTGCAGGGGGCTTGTATGATTATGGGCTTGGTTAGTAGTACTGGTGGACATT GTTTGGTGGTGTATATATTGTAATTGAGATTGCTCGGGGAAATTAG
10	opt_ND6	ATGATGTACGCCCTGCTCTGCTGAGCGCTGGGCCCTGGTGTGGGCTTCAAGCAGCAAGC CCAGCCCCATCACGGCGGCCCTGGTGTGATCGTGAAGCGGCCGCTGGTGGGCTGCGTGTGATCATCCTGA ACTCTGGCGGCCGCTACATGGGCCCTGATGGTCTCTGATCATACCTGGGCCATGATGGTGGTGT CGGCTACACCACCGCCATGGCATCGAGGAGTACCCCGAGGCCCTGGGGCAGCGCGCTGGAGGTGC TGGTGAACGTGCTGGTGGGCTGGCCATGGAGGTGGGCCCTGGTGTGGGTGAAGGAGTACGACG GCGTGGTGGTGGTGAACTTCAACAGCGTGGCAGCTGGATGATCATCGAGGGCGAGGGCAGCG GCGTGTGGTGGTGGTGAACTTCAACAGCGTGGCAGCTGGATGATCATCGAGGGCGAGGGCAGCG GTGACCGGCTGGACCCCTGGTGTGACATCGTGTGATCGAGATCGCCGGCGGCCAACTAA
11	ND1	ATGGCCAACCTCTACTCCTCATGGTACCCATTCTAAATCGCAATGGCATCCTAAATGCTTACCGAACGA AAAATTCTAGGCTATATGCAACTACGCAAAGGCCCAACGTTGAGGCCCTACGGGCTACTACAAAC CTCGCTACGCCATAAAACTCTCACCAAAGGCCCTAAACCCGCCACATCTACCATCACCCCT ACATCACCGCCCCGACCTAGCTCTCACCATCGCTCTACTATGGACCCCCCTCCCATGCCAAC CCCTGGTCAACCTCAACCTAGGCCCTCCATTATTCTAGCCACCTCTAGCCTAGCCGTTACTCAATC CTCTGGTCAAGGGGGCATCAAACACTCAAACACTACGCCCTGATGGCGCACTGCCAGCAGCTAGGCCAA CAATCTCATATGAACTCACCTAGCCATCATTCTACTATCAAACACTTAATGAGTGGCTCTTTAACCT CTCCACCCCTATCACACAAAGAACACCTCTGGTTACTCCTGCATCATGGGCTTGGCATGATG GGTTTATCTCCACACTAGCAGAGGACCAACCGAACCCCTTCGACCTTGGCGAAGGGGAGTCCGAAC AGTCTCAGGCTTCAACATCGAATACGCCGAGGGCCCTTCGCCCTATTCTCATGGCGAACACAA ACATTATTATGATGAACACCCCTACCAACTACAATCTTCTAGGAACAACATATGACGCACTCTCCCTG AACTCTACACAACATATTTGTCACCAAGACCCCTACTTCTAACCTCCCTGTTCTATGGATTCGAACAGC ATACCCCCGATTCCCTACGACCAACTCATGCAACCTCTATGGAAAAACTTCTCAGGACCTACCCCTAG CATTACTATGTTGATGTTGCTCATGCCATTACAAATCTCCAGGATCCCCCTCAAACCTAA
12	opt_ND1	ATGGCCAACCTGCTGCTGCTGATCGTGCCTACATGCGAGCTGCCAAGGGCCCCAACGTTGGTGGGCCCTACGGCCTGCTGC GCAAGATCTGGCTACATGCGAGCTGCCAAGGGCCCCAACGTTGGTGGGCCCTACGGCCTGCTGC AGCCCTCGCCGACGCCATCAAGCTGTTACCAAGGGAGGCCCTGAAGCCCCCCCCACAGCACCATCAC CTGTACATCACCGCCCCACCCCTGGCCTGACCATGCCCTGCTGCTGTGGACCCCCCTGCCCATG CCCAACCCCTGGTGAACCTGACCTGGGCCAGCAACAGCAACTACGCCCTGATCGGCCCTGGCCGTG ACAGCATCTGTGGAGCGGCCAGCAACAGCAACTACGCCCTGATCGGCCCTGGCCGTG TGGGCCAGACCATCAGTACAGGGTGAACCTGGGCCATCATCTGGCTGAGCAGCCCTGCTGAGCG CAGCTAACCTGAGCACCCCTGATCACCAACCCAGGAGCACCTGTTGCTGCTGCCAGCTGGCC CTGGCCATGATGTGGTTCATAGCACCCCTGGCCAGACCAACCCGACCCCCCTTCGACCTGGCCGAGG GCGAGAGCGAGCTGGTGAAGGGCTTCAACATCGAGTACGCCGGCCCCCTTCGCCCTGTTCTCAT GGCCGAGTACACCAACATCATGATGAACACCCCTGACCAACCCATCTCTGGGCCACCACTACG ACGCCCTGAGCCCCGAGCTGACCCACTACTTCGTCGACCAAGACCCCTGCTGCTGACCAAGCCCTG CTGTGGATCCGACCCCTACCCCCGGCTTCCGCTACGACCAAGCTGATGTCACCTGCTGTTGGAAAGAAC TTCTGGCCCTGACCCCTGGCCCTGCTGATGTTGAGCTGACCATGCCCATCACCATCAGCAGCATCC CCCCCCAGACCTAA

13	3'UTR	GAGCACTGGGACGCCACCGCCCTTCCCGTGCAGGCAGCATGTTGGTAATTCTGGAA ACAAGAAGAGAAATTGCTGGGTTAGAACAGATTATAAACGAATTCGGTCTCAGTGATCACTTGAC AGTTTTTTTTAAATATTACCAAATGCTCCCAATAAGAAATGCATCAGCTCAGTCAGTGAAT ACAAAAAAGGAATTATTTCCCTTGAGGGTCTTATACATCTCTCCAACCCCACCTCTATTCT GTTTCTTCTCCTCACATGGGGTACACATACAGCTTCTCTTTGGTCCATCCTTACCCACAC CACACGCACACTCCACATGCCAGCAGAGTGGCAGTGGTGGCCAGAAAGTGTGAGCCTCATGATCT GCTGTCTGAGTCTGTGAGCTCAGGCTCCTAACGGCTGGAGCACCCCCCTCCTGTGAGTGA CCAGGGCTGCATTTGGTTCCACCCACACATTCTAACCATAGTCCTCTAACATACCAAT AGCTAGGACCCGGCTGTGCACTGGACTGGGACTTCCACATGTTGCCTGGGAGTCTCAAGCT GGACTGCCAGCCCCCTGCCTCCCTCACCCCCATTGCGTATGAGCATTTCAGAACCTCAAGGAGTCAC AGGCATCTTATAGTCACGTTAACATATAGACACTGTTGGAAGCAGTCTCTCTAAAAGGGTAGCCCT GGACTTAATACCAGCCGGATACCTCTGGCCCCACCCCTACTGTACCTCTGGAGTCACTACTGTGG GTCGCCACTCTCTGTCACACAGCACGGCTTCAAGGCTGATTGAGAAGGGTAGGAGAAG GGTGTCTGGCTAACCAGCCCAGAGCTCACATTCTGTCCTGGTGAAGGTTAACATGTCATC CTGATATCTCTGAATTCAAGAAATTAGCCTCACATGTGCAATGGCTTAAGAGCAGAACGGTT CTGGGAATTTGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAATACGGTTACCTGCAGCTT TTAGTCCTTGTGCTCCACGGGACTACTCCACGGGACTACTGGCCGTAGGATTGAGCAGGA TGTTTCGATTACTCAGTCCTCCACGGGACTACTGGCCGTAGGATTGAGCAGGA TTAAACACATTAAACAGAGTCTCTCAAAATGTCAGGATTGAGTAAACATCCAATCAC TGTGCACTTATCTGAAATTCTCCCTCTGGCTGCCCAAGGTTACCTGTGAGAACATTGCA GAATGTCTGGAAAAGCTTACAACTTGTACAGCCTCACATTGTAGAACGGTT
14	3'UTR*	GAGCACTGGGACGCCACCGCCCTTCCCGTGCAGGCAGCATGTTGGTAATTCTGGAA ACAAGAAGAGAAATTGCTGGGTTAGAACAGATTATAAACGAATTCGGTCTCAGTGATCACTTGAC AGTTTTTTTTAAATATTACCAAATGCTCCCAATAAGAAATGCATCAGCTCAGTCAGTGAAT ACAAAAAAGGAATTATTTCCCTTGAGGGTCTTATACATCTCTCCAACCCCACCTCTATTCT GTTTCTTCTCCTCACATGGGGTACACATACAGCTTCTCTTTGGTCCATCCTTACCCACAC CACACGCACACTCCACATGCCAGCAGAGTGGCAGTGGTGGCCAGAAAGTGTGAGCCTCATGATCT GCTGTCTGAGTCTGTGAGCTCAGGCTCCTAACGGCTGGAGCACCCCCCTCCTGTGAGTGA CCAGGGCTGCATTTGGTTCCACCCACACATTCTAACCATAGTCCTCTAACATACCAAT AGCTAGGACCCGGCTGTGCACTGGACTGGGACTTCCACATGTTGCCTGGGAGTCTCAAGCT GGACTGCCA
15	COX10-ND4-3'UTR	ATGGCCGATCTCCGCACACTCTCTCCCTCACGCCCTCTGACAGGTTGCGTAGGAGGCTCTGCTGGT ATCTGAAAGAAGAAACTATGCTAAACAACTATCGTCCCAACAAATTATGTTACTACCAACTGACATGGCTTC CAAAACACATGATTGGTACACAAACACACAGCTTAATTATAGCATCATCCCTACTATT TTAACCAAATCAACACAACACTATTAGCTGTCCTCACCCCTCACAATCATGGCAAGCCAAGGCCACTTATCAGTGA ACCACATACGAAAAAAACTCTACCTCTCTATGCTAATCTCCCTACAAATCTCTTAATTATGACATT ACAGCCACAGAAACTATGTTTATCTCTCTGAAACCACACTTATCCCACCTGGCTATCATCA CCCGATGGGCAACAGCCAGAACGCCCTGACAGCACACTCTCTACCCCTAGTAG CTCCCTCCCTACTCATGCTACTATTACACTCACAAACACCTAGGCTACTAAACATTCTACT ACTCTCAGCCAAAGAACTATCAACTCTCTGCGGCAACAACTTAATGTCAGCTACACATGG CTTATGGTAAAGATGCTCTTACGGACTCCACTTATGGCTCCCTAAAGCCATGCGAACCCCCA TCGCTGGGCAATGGTACTTGCCTGAGTACTCTTAAACTAGGGGGTATGGTATGCGCTCACA CTCATTCTAACCCCTGACAAAACACATGGCTACCCCTCTGTAATCTCTATGGGCGATGATT ATGACAAGCTCATGCTCTGCTACGACAAACAGACCTAAATGCTCATGCTACTCTCAATAGCCAC ATGGCCCTGCTAGTACAGCCATTCTCATCCAAACCCCTGGGACTTCACCGGGCGAGTCATTCTCAT GATGCCAACGGGCTACATCTCTTACTATTCTGCTCTGCAACACTAACAGAACGCACTCACA GTCGCATCATGATCTCTCAAGGACTCTAACACTCTCCACTAATGGCTTTGGTGGCTCTAG CAAGGCTCGCTAACCTCGCTTACCCCCCACTATTAACCTACTGGGAGAACTCTGTGCTAGTAACC ACGTTCTCTGGTCAAATATCACTCTCTACTACAGGACTCAACATGCTAGTCACAGCCCTATACTCC CTCTACATGTTACCAACACAATGGGCTACTCAGCCACCATAACACATGAAACCCCTATT ACACGAGAAAACACCTCATGTCATGCACCTATCCCCATTCTCCCTATCCCTAACCCCGACATC ATTACGGGGTTCTCTTAAGGACTGGGACCCACGCCCTGGGCTACCCGCGAGCGAG CATGTTGGTAAATTCTGGACACAAAGAGAAGGATTGCTGGGTTAGAACAGATTAAACGAATT GGTGTCTAGTACACTGACAGTTTTTTAAATATTACCAAATGCTCCCAATAAGAAA TGCATCAGCTCAGTGAATACAAAAAAGGAATTATTCTCTTGGGACTTACCTGTGAGGAGTCT CTCCAAACCCACCTCTATTCTGTTCTCTCTCACATGGGGTACACATACAGCTCTCTTT GGTCCATCTTACCAACACAGCAGACTCCACATGCCAGAGTGGCAGTGGCACTGGTGGCCA GAAAGTGTGAGGCTCATGATCTGCTGTGAGTCTGTGAGCTCAGGCTCCCTCAAAGGCGCTGGAGC ACCCCCCTCTGTGACTGAGCCAGGGCTGCAATTGGTTTCCCCACACATTCTCAACCC AGTCCTCTAACAAACATGAGTAGGACGGGCTGCTGCACTGGGACTGGGAGTCCACATGTT TGCTTGGGAGTCTCAAGCTGGACTGCCAGGGCTGCTCTCCCTCACCCCATGGCTATGAGCATT TCAGAACCTCAAGGAGTCACAGGCATCTTATAGTCAGCTAACATATAGACACTGTTGAGCAGTT CCTCTAAAGGGTAGCCCTGGACTTAATACAGCCGGACACTCTGCTCACAGCACGGCTTT CTCTGGAGTCACTACTGTGGGCTGCCACTCTGCTCACAGCACGGCTTTCAAGGCTGTATTGA GAAGGGAAGTTAGGAAGAAGGGTAGGCTGGCTACCCAGAACAGAGCTCACATTCTGCTCC GGTGAAGGAAACTATGTCATGCTGATATCTCTGCAATTGAGAACAGGCTCATGCTGGTACCA TAAGAGCCAGAAGCAGGGTTCTGGAAATTGCAAGTACCTGTGGCCAGGTGTGGCTCGGTTACCA AATACGGTACCTGCACTTTAGTCCTTGTGCTCCACGGGCTACAGAGTCCCATCTGCCAAA GGTCTTGAAGCTTGACAGGATGTTGCACTTATCTGAAATCTCCCTCTGGCTGCCCAAGGAT GATTGGTGGGGTAGGAGAGTAAACACATTAAACAGAGGTTCTCAAAATGCTAAAGGGATTGT AGGTAGATAACATCCAATCACTGTTGCACTTATCTGAAATCTCCCTCTGGCTGCCCAAGGAT ACTGTGGAGAACATTGCACTAGGAATGTCAGGAAAGCTTCAACACTTGTACAGCCTCACATTG AGAAGCTT

16	COX10-ND4-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCTCACGCCCTCTGACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAGAAGAAGAACTATGCTAAACACTATCGTCCAAACAATTATGTTACTACCACTGACATGGCTTC CAAAAAACACATGATTGGATCAACACAACCACCCCACAGCCTAATTATTAGCATCATCCCTACTATT TTAACCAAATCAACACAACCTATTTAGCTGTTCCCAACCTTTCCGACCCCTAACACCCCC CTCCTAATGCTAACTACCTGGCTCCCTACCCCTCACAAATCATGGCAAGCCAACGCCACTTATCAGTGA ACCACTATCACGAAAAAAACTCTACCTCTATGCTAATCTCCCTAACAAATCTCCTTAATTATGACATT ACAGGCCACAGAACTAATCATGTTTATCTCTCGAAACACACTTACCCACCTTGGCTATCATCA CCCGATGGGGCAACCCAGCCAGAACGCCGAACGCAGGGACATACTTCTATTCTACACCCTAGTAGG CTCCCTCCCTACTCATCGCACTAATTACACTCACAAACACCCTAGGCTACTAAACATTACTACT CACTCTCACTGCCAAGAAGAACTATCAAACCTCTGGGCAACAAACTTAATGTTAGCTTACACAATGG CTTTATGGTAAAGATGCCCTTTACGGACTCCACTTATGGCTCCAAAGGCCATGTCGAAGGCC TCGCTGGGCAATGGTACTTGGCGAGTACTCTTAAACAGGCCATGGTATGATGCGCTCATCA CTCATTCTCAACCCCCGACAAAACATGGCTACCCCTCTGTACTATCCCTATGGGGCATGATT ATGACAAGCTCATGCTCACGCAAAACAGACCTAAATCGCTATGCAACTCTCAATCAGCCAC ATGGCCCTCGTAGTAACAGCCTATCTCATCCAAACCCCCCTGGAGCTCACCGGCCACTTCT GATCGCCCACGGGCTTACATCCTCTTACTATTCTGCTCTAGCAAACACTCAAACACTACGAACGCAC GTCGCATCATGATCCTCTCAAGGACTTCAAACACTCTACTCCCCTAATGGCTTTGGCTCTAG CAAGCCTCGCAACCTCGCCTACCCCCACTATTAAACACTACTGGGAGAAGCTCTGTGCTAGTAACC ACGTTCTCTGGTCAAATCACTCTCACTTACAGGACTCAACATGCTACTGACAGGCCCTACTCC CTCTACATGTTTACCAACAACTGGGCTACTCACCACCACTTAAACACATGAAACACCTCATTC ACACGAGAAAACACCCCTATGTCATGCACTTACCCCTATCTCTCTATCCCTCAACCCCCGACATC ATTACCGGGTTTCTCTTAAGAGCACTGGGACGCCACGCCCTTCCCTCCGCTGCCAGGGGAG CATGTTGGTAATTCTGGAACACAAGAAGAATTGCTGGGTTAGAACAGATTATAAACGAATT GGTGCAGTGATCACTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCAAATAAGAAA TGCACTAGCTCACTGAGTAATACAAAAAGAATTATTCTCTCTTACAGGGGATCTTTATACATCTC CTCCAACCCCCCTTACTCTCTTACCCACACAGCACACTCCATGCCAGAGTGGCACTTGGGCC GGTCCATCTTACCCACACAGCACACTCCATGCCAGAGTGGCACTTGGGCC GAAAGTGTGAGCCTCATGATCTGCTGTAGTTCTGAGCTCAGGTCCCTCAAAGGCCCTGGAGC ACCCCTCTTGTGACTGAGCCAGGGCCTGCACTTTGGGTTCCACACATTCTAACCAT AGTCTTCTAACAAATACCAATAGCTAGGACCCGGCTGCTGCACTGGGACTGGGATCCACATGTT TGCTTGGGAGTCTCAAGCTGGACTGCC
17	COX10-opt_ND4-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCTCACGCCCTCTGACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAGAAGAAGAACTATGCTGAAGCTGATGTCCTGCCCCACCATCATGCTGCTGCTGACCTGGCTG AGCAAGAAACACATGATCTGGATCACACCAACGCCACGCCCTGATCATCAGCATCATCCCTCTGACAA CACCTCTGCTGATGCTGACCCCTGGCTGCTGCCCTCACAAATCATGGCTCTCAGAGACACCTGAG CAGCGAGCCCTGAGCCGGAAAGAAACTGTACCTGAGCATGCTGATCTCCCTGCAAGATCTCTGATC ATGACCTCACCGCCACCGAGCTGATCATGTTCTACATCTTTGAGACAACCGTGTACCCACACT GGCCATCATCACCAGATGGGCAACCCAGCCTGAGAGAGACTGAACGCCGGCACCTACTCTGTTCTAC ACCCCTGTTGGGCAACCTGCTGATGTTGCTGATCACACCCACAAACCCCTGGCTCTGAC ACATCTGCTGCTGACTGACAGCCCAAGAGCTGAGCAACAGCTGGCCAACAAATCTGATGTTGCT GGCCTACACAATGGCTCTGATGGCAAGATGCCCTGTACGGCTGCACTGTGGCTGCCCTAAAGCT CATGTGGAAGCCCTATGCCGGCTCTATGGTCTGGCTGAGTGTGCTGAAACTCGGGGGCTACG GCATGATGCCGCTGACCTGATTCTGAATCCCTGACCAAGCACATGGCTATCCATTCTGGTCTG AGCCTGTGGGAGTATTGACAGCAGCAGCATGCTGCTGCGGAGACCCGATCTGAGTCCCTGATCG CCTACAGCTCCATGCCACATGCCCTGGGTCACCCGCACTCTGATTGAGACCCCTTGGAGCTT ACAGGCCGTGATCTGATGTTGCCACGGCTGACAGGACGCTGCTGTTGCTGGGCTGAA GCAACTACGGAGCCGACCCACAGCAGAAATCATGATCTGCTCAGGGCTGCAAGACCCCTGGCT TATGGCTTTGGTGGCTGCTGCCCTCTGGCCAATCTGGCACTGCCCTCTACCATCAATCTGCTGG GCGAGCTAGCGTGTGGCTGCCACATTGAGCTGGCTGACAGGACGCTGCTGCTGCTGCT CATGCTGGTACAGCCCTGACTCCCTGATCATGTTGACCCACACAGTGGGAGGCCCTGACACACC ACATCAACAAATATGAGCCGAGCTTACCCCGAGAACACCCCTGATGTTGATGCTGAGCCCT CTGCTGCTGCTGATCTGATCATCACCCTGCTCTGGCTGAGAGCAGCTGGGAGCC GCCCTTCCCTCCGCTGCCAGGGAGCATGTTGTTGTAATTCTGAAACAAAGAAGAGAAATTGCTG GGTTAGAACAGATTATAACGAATTGGTGTGCTAGTGTACTTGACAGTTTTTTTTAAATAT TACCCAAATGCTCCCAAATAAGAAATGCACTGAGCTGAGTGTGAAATACAAAAAGGAATTATTTT CCCTTGAGGGCTTTTATACATCTCTCCAAACCCACCCCTATTTCTGTTCTCTACATGG GGGTACACATCACAGCTCTCTTGGTCCATCTTACACACACAGCACACTCCACATG CCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGGCTCTGATCTGCTGCTGTTG GCTCAGGCTCTCAAGGCCCTGGAGCACCCCTCTGTTGACTGAGCCAGGGCTGCACTTTGG TTTCCCCACCCACACATTCTCAACCATAGCTCTCTAACAAATACCAATAGCTAGGACCCGGCTG TGCACTGGGACTGGGATTCCACATGTTGCTCTGGAGTCTCAAGCTGGACTGCCAGCCCTG TCCCTCACCCTCTGCTGATGAGCATTTGAGCAACTCCAAGGGAGTCACAGGCATCTTATAGTT TTAACATATAGACACTGTTGGAAGCAGTTCTCTAACAGGGTAGGCTGACTTAAACAG ACCTCTGGCCCCACCCATTACTGTACCTCTGGAGTCACTACTGTTGGGTGCGCACTCTGCT CACAGCAGGCTTCAAGGCTGTTGAGAAGGGAGTAGGAAGAAGGGTAGGAGGTTAAACAA CCCCAGAGCTCACATTCTGCTCCCTGGTAAAGAGCCAGAACAGCAGGGCTGGG AAATTAGCTCCACATGTGCAATGGCTTAAAGAGCCAGAACAGCAGGGCTGG CTGTTGCGCAGGTGTGGCTCGCTTACCAATACGGTTACCTGAGCTTTAGTCTCTTGTG GGGGTCTACAGAGTCCCATCTGCCAAAGGTCTTGAAGCTGACAGGATGTTTCGATTACTCAGT CCCAGGGCACTACTGGTCCGTTAGGAGTCAGTTGGTAGGAGAGTTAAACAA CTACAACCTGTTACAGCCTCACATTGTTAGAACAGCTT

18	COX10-opt_Nd4-3'UTR*	<p>ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCCTCGTACAGGTTGCGTAGGAGGCTCTGTCTGGT</p> <p>ATCTTGAAGAAGAACATGCTGAAGCTGATCGTGCCTCACCATGCTGCTGCCTGACCTGGCTG</p> <p>AGCAAGAACACATGATCTGGATCACACCACCGCACAGCCTGATCATCAGCATCATCCCCCTGCT</p> <p>GTTCTTCAACCAGATCAACAACACCTGTCAGCTGCAGCCCCACCTCAGCAGCGACCCCTGACAA</p> <p>CACCTCTGCTGATGCTGACCACCTGGCTGCTGCCCTCACAAATCATGGCTCTCAGAGACACCTGAG</p> <p>CAGCGAGCCCCCTGAGCCCCAGAAAACCTGTAACCTGAGCATGCTGATCTCCCTGCAAGATCTCTGATC</p> <p>ATGACCTTCACCGCCACCGAGCTGATCATGTTTACATCTTTGAGAGACATGAAACCGCTGATCCCCACACT</p> <p>GGCCATCATCACCGCTGGGCAACCCAGCGCCTGTAACGGCCTGACCTACTTCTGTTTAC</p> <p>ACCCCTGGGGCAGCCCTGCTGATCATCACCCAGAGCTGAGCAACAGCTGGGCAACACCCCTGAGCTGA</p> <p>ACATCCTGCTGCTGCCCTGACCCCTGACCCAGGGAGCTGAGCAACAGCTGGGCAACACCTGATGTGGCT</p> <p>GGCCTACACCATGGCCTCATGGTGAAGATGCCCTGTAACGGCCTGCACCTGTTGGCTGCCAACGGCC</p> <p>CACGTGGAGGCCCCCATGCCGGCAGCATGGTGTGGCCCGTGTGCTGAAGCTGGGGCTAC</p> <p>GCGATGATGCGCTGACCCCTGATCTGTAACCCCTGACCAAGCAGCACATGGCTACCCCTTCTGGTGC</p> <p>TGAGCCTGTPGGGCTGATCATGACCAAGCAGCATGCTGCGCCAGACCTGAAGAGCCTGAT</p> <p>CGCCTACAGCAGCATGCCACATGGCCCTGGTGGTACCCAGGCACTCTGATCCAGACCCCCCTGGAGC</p> <p>TTACCGGGCCGTGATCTGATGTCGCCACGGCTGACGGCTGTACAGCTGACCTGAGGAGCTGCTGCTGCTGGG</p> <p>ACAGCAACTACGAGCGCACCCACAGCGCATCATGATCTGAGCCAGGGCTGCAGACCCCTGCTGCC</p> <p>CCTGATGCCCTCTGGTGGCTGTCGCCAGGGCTGGCCAACCTGGCCCTGCCACCATCACCTG</p> <p>CTGGGCGAGCTGAGCGTGTGGTACCCAGGCTGACGGCTGTACAGCTGACCTGAGGAGCTGAGCC</p> <p>CTGAACATGCTGGTACCCAGGCTGTACAGCTGACATGTTACCCAGGCTGAGGAGCTGAGCC</p> <p>CCCACCCACATCAACAACATGAAGGCCAGCTTACCCGGAGAACACCCCTGATGTTCATGACCTGAGC</p> <p>CCCACCTCTGCTGTCAGCTGACCCAGACATCATCACCCGGCTTACGGAGCTGAAGAGCACTGGAGC</p> <p>CCCACCGGCCCCCTTCCCTCGCTGCCAGGGAGCATGTTGTGTAATTCTGAAACACAAGAGAGAA</p> <p>ATTGCTGGGTTAGAACAAGATTATAACGAATTGGTGTGACTGATCACTTGACAGTTTTTTT</p> <p>TTAAATATTACCCAAATGCTCCCAAATAAGAAATGCATCAGCTGAGTGAATACAAAAAAAGGAA</p> <p>TTATTTTCCCTTGAGGGTCTTTATACATCTCTCCAAACCCACCCCTTATCTGTTCTCCCT</p> <p>CACATGGGGTACACATACAGCTTCTCTTGGTTCATCTTACCCACACACCGCACACT</p> <p>CCACATGCCCAAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGGCTCATGATCTGCTGTGAGT</p> <p>TCTGAGGCTCAGGCTCTCAAGGGCTCGGAGCACCCCTTCTGTGACTGAGCCAGGGCTGCA</p> <p>TTTTGGTTTCCCCACACCATCTCAACCATAGCTCTTCAACAAACCAATAGCTAGGACCCG</p> <p>GCTGCTGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGACTGCCAGCC</p> <p>CCTGTCCTCCCTCACCCCCCATTGCGTATGAGCATTCTGAGCAACTCCAAAGGAGTCACAGGCATCTTATA</p> <p>GTTCACGTTAACATATAGACACTGTTGGAAGCAGTCTTCTAAAGGGTAGCCCTGGACTTAATACCA</p> <p>GCCGGATACTCTGGCCCCACCCATTACTGTAACCTCTGGAGTCACACTGTTGGCTGCACTCT</p> <p>CTGCTACACAGCAGGGCTTCAAGGGCTGATTGAGAAGGGAGTTAGGAAGAAGGGTGTGCTGG</p> <p>CTAACAGCCCACAGAGCTCACATTCTGTCCTTGGGTAAGGAAACATGTCATCTGATATCTCT</p> <p>GAATTGAGAAATTAGCTCCACATGTCATGGTTAAAGGGTAGGTTAGATAACATCCAATCACTGTTGACTT</p> <p>CAAGTTACCTGTCAGGGCTACAGAGTCACATCTGCCAACAGGCTTGAAGGCTGACAGGAGTTAGCTTGTGATTAC</p> <p>TCAGTCTCCAGGGCACTACTGGTCCGTAGGATTGAGCTGGTGGAGAGTTAAACACACATT</p> <p>AAACAGAGTTCTCAAAATGTCATAAGGGATTGAGGAGTTAGATAACATCCAATCACTGTTGACTT</p> <p>CTGAAATCTCCCTGGCTGCCAACAGGTTACTGTTGAGAAGACATTGCAAGGAATGTCAGGAA</p> <p>AAAGCTTCAACACTGTTACAGCCTCACATTGAGCTTT</p>
19	COX10-opt_Nd4*-3'UTR	<p>ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCCTCGTACAGGTTGCGTAGGAGGCTCTGTCTGGT</p> <p>ATCTTGAAGAAGAACATGCTGAAGCTGATGTCCTGCCACCATGCTGCTGCCCTGACCTGGCTG</p> <p>AGCAAGAACACATGATCTGGATCACACCACGCCCTGACCATGCTGATCATCAGCATCATCCCCCTGCT</p> <p>GTTCTTCAACCAGATCAACAACACCTGTCAGCTGCAGCCCCACCTCAGCAGCGACCCCTGACCA</p> <p>CCCCCTGCTGATGCTGACCACCTGGCTGCTGCCCTGACCATCATGGCAGGCCAGCGCCACCTGAG</p> <p>CAGCGAGCCCCCTGAGGCCAGAAAGCTGTAACCTGAGCATGCTGATGCCCTGCAGATGCCCTGATC</p> <p>ATGACCTTCACCGCCACCGAGCTGATCATGTTTACATCTTCTGAGACCACCCCTGATCCCCACCT</p> <p>GGCCATCATCACCGCTGGGCAACCCAGCGCCTGTAACGGCCTGACCTGAGCCTGACCTGCTGATC</p> <p>ACCCCTGGGGCAGCCCTGCTGATGCCCTGATCATCACCCACACCTGAGGAGCTGAGACCTGAT</p> <p>ACATCCTGCTGCTGCCCTGACCCCTGACCCAGGGAGCTGAGCAACAGCTGGGCAACACCTGATGTGGCT</p> <p>GGCCTACACCATGGCCTCATGGTGAAGATGCCCTGTAACGGCCTGCACCTGTTGGCTGCCAACGGCC</p> <p>CACGTGGAGGCCCCCATGCCGGCAGCATGGTGTGGCCCGTGTGCTGAAGCTGGGGCTAC</p> <p>GCGATGATGCGCTGACCCCTGATCTGTAACCCCTGACCAAGCAGCACATGGCTACCCCTTCTGGTGC</p> <p>TGAGCCTGTPGGGCTGATCATGACCAAGCAGCATGCTGCGCCAGACCTGAAGAGCCTGAT</p> <p>CGCCTACAGCAGCATGCCACATGGCCCTGGTGGTACCCAGGCACTCTGATCCAGACCCCCCTGGAGC</p> <p>TTACCGGGCCGTGATCTGATGTCGCCACGGCTGACGGCTGTGGCCAGGAGCAGGGCTGCTGCTGGG</p> <p>ACAGCAACTACGAGCGCACCCACAGCGCATCATGATCTGAGCCAGGGCTGCAGACCCCTGCTGCC</p> <p>CCTGATGCCCTCTGGTGGCTGTCGCCAGGGCTGGCCAACCTGGCCCTGCCACCATCACCTG</p> <p>CTGGGCGAGCTGAGCGTGTGGTACCCAGGCTGACGGCTGTACGGAGCAACATCACCTGCTGCTGACCC</p> <p>CTGAACATGCTGGTACCCAGGCTGTACAGCTGACATGTTACCCAGGCTGAGGAGCTGAGCC</p> <p>CCCACCCACATCAACAACATGAAGGCCAGCTTACCCGGAGAACACCCCTGATGTTCATGACCTGAGC</p> <p>CCCACCTCTGCTGTCAGCTGACCCAGACATCATCACCCGGCTTACGGAGCTGAAGAGCACTGGAGC</p> <p>CCCACCGGCCCCCTTCCCTCGCTGCCAGGGAGCATGTTGTGTAATTCTGAAACACAAGAGAGAA</p> <p>ATTGCTGGGTTAGAACAAGATTATAACGAATTGGTGTGACTGATCACTTGACAGTTTTTTT</p> <p>TTAAATATTACCCAAATGCTCCCAAATAAGAAATGCATCAGCTGAGTGAATACAAAAAAAGGAA</p> <p>TTATTTTCCCTTGAGGGTCTTTATACATCTCTCCAAACCCACCCCTTATCTGTTCTCCCT</p> <p>CACATGGGGTACACATACAGCTTCTCTTGGTTCATCTTACCCACACACCGCACACT</p> <p>CCACATGCCCAAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGGCTCATGATCTGCTGTGAGT</p> <p>TCTGAGGCTCAGGCTCTCAAGGGCTCGGAGCACCCCTTCTGTGACTGAGCCAGGGCTGCA</p> <p>TTTTGGTTTCCCCACACCATCTCAACCATAGCTCTTCAACAAACCAATAGCTAGGACCCG</p> <p>GCTGCTGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGACTGCCAGCC</p> <p>CCTGTCCTCCCTCACCCCCCATTGCGTATGAGCATTCTGAGCAACTCCAAAGGAGTCACAGGCATCTTATA</p> <p>GTTCACGTTAACATATAGACACTGTTGGAAGCAGTCTTCTAAAGGGTAGCCCTGGACTTAATACCA</p> <p>GCCGGATACTCTGGCCCCACCCATTACTGTAACCTCTGGAGTCACACTGTTGGCTGCACTCT</p> <p>CTGCTACACAGCAGGGCTTCAAGGGCTGATTGAGAAGGGAGTTAGGAAGAAGGGTGTGCTGG</p> <p>CTAACAGCCCACAGAGCTCACATTCTGTCCTTGGGTAAGGAAACATGTCATCTGATATCTCT</p> <p>GAATTGAGAAATTAGCTCCACATGTCATGGTTAAAGGGTAGGTTAGATAACATCCAATCACTGTTGACTT</p> <p>CAAGTTACCTGTCAGGGCTACAGAGTCACATCTGCCAACAGGCTTGAAGGCTGACAGGAGTTAGCTTGTGATTAC</p> <p>TCAGTCTCCAGGGCACTACTGGTCCGTAGGATTGAGCTGGTGGAGAGTTAAACACACATT</p> <p>AAACAGAGTTCTCAAAATGTCATAAGGGATTGAGGAGTTAGATAACATCCAATCACTGTTGACTT</p> <p>CTGAAATCTCCCTGGCTGCCAACAGGTTACTGTTGAGAAGACATTGCAAGGAATGTCAGGAA</p> <p>AAAGCTTCAACACTGTTACAGCCTCACATTGAGCTTT</p>

20	COX10-opt_ND4*-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCCTCGACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAGAAGAACATGCTGAAGCTGATCGTGCCTCACATGCTGCTGCCCTGACCTGGCTG AGCAAGAACATGATCTGGATCAACACCACCCACAGCCTGATCATCAGCATCATCCCCCTGCT GTTCTTCAACCAGATCAACAACACTGTTCACTGCAGCTGCAGCCCACCTTCAGCAGCGACCCCTGACCA CCCCCCTGCTGATGCTGACCCACCTGGCTGCTGCCCTGACCATCATGGCCAGCAGCGCCACCTGAG CAGCGAGCCCCCTGAGCCGCAAGAACGCTGACCTGAGCATGCTGATGCCCTGAGCATGAGCTGATC ATGACCTTCACCGCCACCGAGCTGATCATGTTACATCTTCTCGAGACCACCCCTGATCCCCACCCCT GGCCATCATCACCGCTGGGGCAACCAAGCCGAGCGCCTGAACGCCGGCACCTACTTCTGTTCTAC ACCCTGGTGGGAGCCTGCCCCCTGCTGATGCCCTGATCTACACCCACAACACCCCTGGGAGCCTGA ACATCCTGCTGCTGACCCCTGACCCAGGAGCTGAGCAACAGCTGGCCAACAACACTGATGTGGCT GGCCTACACCATGGCCTCATGGTAAGATGCCCTGACCGCCTGACCCCTGAGCTGGCTGCCCAAGGCC CACGTGGAGGCCCCCATGCCGGCAGCATGGCTGCCGGCGCTGCTGAGCTGGGGCTAC GGCAAGCATGTCGCGCTGACCCCTGATCTGAAACCCCTGACCAAGCACATGCCCTACCCCTTCTGGTGC TGAGCCTGTTGGGATGATCATGAGCAGCAGCATCTGCTGCCAGACCGACTGAAGAGCCTGAT CGCCTACAGCAGCATGCCACATGGCCCTGGTGGTACCGCCATCTGATCCAGACCCCTGGAGC TTCACCGGGCGCCGTGATCCTGATGATCGCCACGGCCCTGACCAAGCAGCAGCTGCTGTTCTGCCCTGAGCA ACAGCAACTACGAGCGCACCCACAGCCGATCATGATCCTGAGCCAGGGCCTGAGACCCCTGCTGCC CCTGATGCCCTGCTGCTGTTGCTGCCAGCCCTGACCTGGCCAACCTGGCCCTGCCACCCATCAACCTG CTGGAGCTGAGCTGAGCCCTGCTGCCAGGCGAGCATGGTGGCAGACCTGGTGTGAGCTGAGCCAGGGCTGA CTGAACATGCTGGTACCGCCCTGACAGCCTGATCATGTTACATCTGACCCACCCAGTGGGAGCAGGGCTGA CCCACACCATCAACAAACATGAAGCCCAGCTTCAACCCCGAGAACACCCCTGATGTTACATGACCTGAGC CCCATCCTGCTGCTGAGCCTGAGACCCCGACATCATCACCGGCTTCAAGCAGTAAGAGCACTGGAGC CCCACCGCCCCCTTCCCTCCGCTGCCAGGCGAGCATGTTGTTAATTCTGAAACACAAGAAGAGAA ATTGCTGGTTAGAACAGATTAAACGAATTGGTGTCACTGATCACTTGACAGTTTTTTTTTT TTAAATATTACCCAAAATGCTCCCAAATAAGAACATGCTAGCTCAGTCAGTCAGTGAATACAAAAAAGGAA TTATTTTCCCTTGAGGGTCTTTATACATCTCCCTCAAACCCACCCCTTCTGTTCTCCCTCC CATGGGGGTACACATACAGCTTCCCTGGTCACTGAGCAGCACATTGAGCAGTGGTGTGAGCAGACACT CCACATGCCAGCAGGTGGCACTGGTGGCAGAAAGTGTGAGCCTCATGATCTGCTGCTGAGT TCTGTGAGCTCAGGTCCCTAAAGGGCTCGAGCACCCCTTCTGTGACTGAGCCAGGGCTGCA TTTTGGTTTCCCCACCCACACATTCTCAACCATAGTCTCTTAACAATACCAATAGCTAGGACCCG GCTGCTGTGACTGGGACTGGGATTCCACATGTTGCTTGGAGCTCAAGCTGGACTGCCA 21 COX10-ND6-3'UTR ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCCTCGACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAGAAGAACATGATGATGTTCTGTTGAGTGTGGTTAGTAATGGGTTGTGATGTTAGCGGTGTTGGTGG TTATTTCTCTTAAGCCTCTCTCTTATGGGGTTAGTATGGGTTAATGGTTTTTAATTATTAGGGGAATGAT GGTGCTTGGATATACTACAGCGATGGCTATTGAGGAGTATCTGAGGCATGGGGCTAGGGGTT GAGGTCTGGTAGTGTAGTGGGGTTAGCGATGGAGGTAGGATTGGTGTGTTGGTGAAGAGT ATGATGGGGTGGTGGTAACCTTAATAGTGTAGGAAGCTGGATGATTATGAAGGAGGGG TCAGGGTTGATTGGAGGATCATTGGTGCCTGGGGCTTTGTATGATTATGGCTGGTTAGTAGT AGTTACTGGTGGACATTGGTGGTGTATATTGTAATTGAGATTGCTGGGGGAATTAGGAGCA CTGGGACCCCACCCCTTCCCTCGCTGCCAGGCGAGCATGGTGTGTTAATTCTGAAACACAA GAAGAGAAATTGCTGGGTTAGAACAGATTAAACGAATTGGTGTCACTGATCACTTGACAGTT TTTTTTTAAATATTACCCAAAATGCTCCCAAATAAGAAATGATCAGCTCAGTCAGTGAATACAA AAAAGGAATTATTTCCCTTGAGGGTCTTTATACATCTCTCCCAAACCCACCCCTTACCTGTT CTCCCTCCATGAGGGTACACATACACAGCTCTCTTGGTCCATCTTACCAACACCCACA CGCACACTCCACATGCCAGCAGGTGGCACTGGTGGCAGAAAGTGTGAGCCTCATGATCTGCTG TCTGAGTTCTGTGAGCTGGTCCCTCAAGGGCTGGAGCACCCCTTCTGTGACTGAGCCG GGCCTGCATTGGTCCCTCCACACATTCTCAACCATAGTCTCTTAACAATACCAATAGCT AGGACCCGGCTGTGCACTGGACTGGGATTCCACATGTTGCTTGGAGTCTCAAGCTGGAC TGCCAGCCCCCTGTGCTCCCTTACCCCAATTGGTATGACCATTCAGAAACTCCAAGGAGTCACAGGC ATCTTATAGTCAGTTAACATATAGACACTGTTGGAAGCAGTCCTCTGGAGTCAGTGGGTOG CCACCTCTGTCACACAGCAGCGCTTCAAGGGCTGATTGAGAAGGGAGTTAGGAAGAAGGGTG TGCTGGGTAACAGCCCCACAGAGCTCACATTCTGTCCCTGGGTTAGAAATACATGTCATCTGA TATCTCTGAATTCAAAGATTAGCTCCACATGTGCAATTGGCTTAAGAGCCAGAACAGGGTCTGG GAATTGGCAAGTTACCTGTGGCAGGTGTGGTCTGGTACCAAATACGGTTACCTGCAGCTTTAG TCTTTGTCTCCACGGGCTACAGAGTCCATCTGCCAAAGGTTGAGCTGACAGGATGTT TCAGTACTCAGTCTCCAGGGCACTACTGGTCCGTAGGATTGAGTTGGTGGGGTAGGAGAGTTAA CAACATTAAACAGAGTTCTCAAAATGTCTAAAGGGATTGAGTAGATAACATCCAATCACTGTT GCACATTACTGAAATCTCCCTGGCTGCCACGGTATTACTGTGGAGACATTGCACTGGATAGGAAATGCTGG AAAAGGAAAGCTCTACAACTGTTACAGCTTCACTTGTAGAAGCTT
22	COX10-ND6-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCCTCGACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAGAAGAACATGATGATGTTCTGTTGAGTGTGGTTAGTAATGGGTTGTGG TTATTTCTCTTAAGCCTCTCTCTTATGGGGTTAGTATGGGTTAATGGTTTTTAATTATTAGGGGAATGAT GGTGCTTGGATATACTACAGCGATGGCTATTGAGGAGTATCTGAGGCATGGGGCTAGGGGTT GAGGTCTGGTGGTGGTAACCTTAATAGTGTAGGAAGCTGGATGATTATGAAGGAGGGG TCAGGGTTGATTGGAGGATCATTGGTGCCTGGGGCTTTGTATGATTATGGCTGGTTAGTAGT AGTTACTGGTGGACATTGGTGGTGTATATTGTAATTGAGATTGCTGGTGTGTTAATTCTGAAACACAA GAAGAGAAATTGCTGGGTTAGAACAGATTAAACGAATTGGTGTCACTGATCAGCTCAGTCAGTGAATACAA AAAAGGAATTATTTCCCTTGAGGGTCTTTATACATCTCTCCCAAACCCACCCCTTACCTGTT

		CTTCCTCCACATGGGGTACACATACACAGCTTCCCTTTGGTCCATCCTTACCAACACACACA CGCACACTCCACATGCCAGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTG TCTGTAGTTCTGTGAGCCTAGGTCCCTAAAGGCCCGAGCACCCCTTCTTGACTGAGCCAG GCCTGCATTTGGTTCCCCACACATTCTAACCATAGTCCCTCTAACAAATACCAATAGCT AGGACCCGGCTGCTGTGCACTGGGACTGGGATTCCACATGTTGCCCTGGAGTCTAACAGCTGGAC TGCCA
23	COX10-opt_ND6-3'UTR	ATGGCCGCATCTCCGCACACTCTCTCCACGCCCTCCTGACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAAGAAGAAACTATGATGTACGCCCTGTTCCCTGCTGAGCGTGGGCTGGTGTGGATGGGCTTCGTG GGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCCTGGTGTGATCGTGAACGGCGTGGTGGGC TGCGTGATCATCCTGAACCTCGGCGGCCCTGACATGGGCTGATGGTGTGGCTGATCTACCTGGCG GCATGATGGTGGTGTGGCTGGCTACACCACGCCATGGCATCGAGGAGTACCCCGAGGCCCTGGGCA GCGCGCTGGAGGGTGTGGCTGGTGAACCTAACAGCGCTGGGAGTGGATGATCTAC GTGAAGGAGTACGACGGCGTGGCTGGTGTGGCTGGTGAACCTAACAGCGCTGGGAGTGGATGATCTAC GAGGGCGAGGGCAGGGCCTGATCCGCGAGGACCCATCGGCGCCGGCCCTGTACGACTACCG CCGCTGGCTGGTGGTGTGACCCGCTGGACCCCTGTTGGCTGGCGTGTACATGTAACGAGATCGC CCGCGGCCACTAAGAGCACTGGGACGCCACCGGCCCTTCCCTCCGCTGCCAGGGCAGGCATGTTG TGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTAGAACAGATTATAACGAATTGGTGTGTC AGTGATCACTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCAAATAAGAAATGCACTCAG CTCACTGCACTGAATACAAAAGGAATTTTTCCCTGGGACTTTATACATCTCTCCAAACC CCACCCCTATTCTGTTCTCCCTCACATGGGGTACACATACAGCTCCCTCTGGTCCAT CCTTACCAACACACACGCACACTCCACATGCCAGAGTGGCACTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTGAGCTGAGCTCAGGTCCCTCAAAGGCCCTGGGAGCACCCCTT CCTTGTGACTGAGCCAGGGCCTGCACTTTGGTTCCACCCACACATTCTAACCATAGTCCCTC TAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGACTGGGATTCACATGTTGCCCTGG GAGTCTCAAGCTGGACTGCCAGCCCTGTCCTCCCTCACCCCATGGTGTGAGCATTCAACT CCTTACCAACACACACGCACACTCCACATGCCAGAGTGGCACTGGTGGCCAGAAAGTGT GAGCAGGAGTCACGGCATTTATAGTTCACGTTAACATATAGACACTGTTGGAAAGCAGTCCCTCTAA AAGGGTAGCCCTGGACTTAATACCGGGGATAACCTCTGGGGGGGACCCCATTTACTGTAACCTCTGGA GTCACTACTGTGGTGCCTCTGCTACACAGCACGGCTTTTCAAGGCTGATTGAGAAGGGGA AGTTAGGAAGAAGGGTGTGCTGGCTAACCAGCCCACAGAGCTCACATTCTGTCCTGGTCAAAGGCTTAA GATACATGTCCATCCTGATATCTCTGAATTAGAAATTAGCCTCCACATGTGCAATGGCTTAAGAGC CAGAAGCAGGGTCTGGGAAATTGCAAGTACCTGTGGCCAGGTGTGGTCTGGTACCAAATACGG TTACCTGCAGCTTTAGTCTCTGGCTCCACGGGTCTACAGAGTCCCCTGCCCCAAAGGCTTGA AGCTTGACAGGATGTTTCGATTACTCAGTCTCCAGGGCACTACTGGTGGCTAGGATTGATTTGGTC GGGGTAGGAGAGTTAACACATTAAACAGAGTTCTCTAAAATGTCATAAGGGATTGAGTAGAT AACATCCAATCACTGTTGCACTTATCTGAAATTCTCCCTTGGCTGCCAACAGGTATTACTGTGGA GAACATTGCAAGGAATTGCTGGAAAAAGCTCTACAACTTGTACAGCCTCACATTGTAGAAGCTT
24	COX10-opt_ND6-3'UTR*	ATGGCCGCATCTCCGCACACTCTCTCCACGCCCTCCTGACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAAGAAGAAACTATGATGTACGCCCTGTTCCCTGCTGAGCGTGGGCTGGTGTGGATGGGCTTCGTG GGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCCTGGTGTGATCGTGAACGGCGTGGTGGGC TGCGTGATCATCCTGAACCTGGGGCGGCCCTGACATGGGCTGATGGTGTGGCTGATCTACCTGGCG GCATGATGGTGGTGTGGCTGGCTACACCACGCCATGGCATCGAGGAGTACCCCGAGGCCCTGGGCA GCGCGCTGGAGGGTGTGGCTGGTGAACCTAACAGCGTGGGAGCTGGATGATCTAC GTGAAGGAGTACGACGGCGTGGTGGTGGTGAACCTAACAGCGTGGGAGCTGGATGATCTAC GAGGGCGAGGGCAGGGCCTGATCCGCGAGGACCCATCGGCGCCGGCCCTGTACGACTACGG CCTGCTGGCTGGTGGTGAACCCGCTGGACCCCTGTTGGCTGGCGTACATCGTGAACGAGATCGC CCTGCGGCCACTAAGAGCACTGGGACGCCACCGGCCCTTCCCTCCGCTGCCAGGGCAGGCATGTTG TGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTAGAACAGATTAAACGAATTGGTGTGTC AGTGATCACTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCAAATAAGAAATGCACTCAG CTCACTGCACTGAATACAAAAAGGAATTATTTCACATGGGGTACACATACAGCTCCCTTTGGTCCAT CCTTACCAACACACACGCACACTCCACATGCCAGAGTGGCACTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGTGAGCTGAGCTCAGGTCCCTCAAGGCCCTGGAGCACCCCTT CCTTGTGACTGAGCCAGGGCCTGCACTTTGGTTCCACCCACACATTCTAACCATAGTCCCTC TAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGATTCACATGTTGCCCTGG GAGTCTCAAGCTGGACTGCCA

25	COX10-ND1-3'UTR	<p>ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCCTCGTACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAGAAGAAGAAGAACTATGGCCAACCTCTACTCCCTATTGTAACCCATTCTAACATCGCAATGGCATTC TAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCAACGTTGAGGCC TACGGGCTACTACAAACCTTCGCTGACGCCATAAAACTCTCACCAAAAGAGGCCCTAAAACCAGGCCAC ATCTACCATCACCCCTACATCACGCCCGACCTAGCTCTCACCATCGCTCTACTATGGACCCC CCTCCCCATGCCAACCCCCCTGGTCAACCTCAACCTAGGCCCTCTATTATTCTAGCCACCTCTAGCC TAGCGTTACTCACTCTGGTCAGGGTGGCATCAAACCTCAAACACTACGCCCTGATGCCGC CGAGCAGTAGGCCAACAACTCTCATATGAAGTCACCCCTAGCCATCTACTATCAACATTACTATG AGTGGCTCTTAAACCTCTCCACCCCTTACACAACACAAGAACCCCTCTGGTTACTCTG CCCTGGGATGATGTGGTTATCTCACACTAGCAGAGACCAACCGAACCCCCCTTGCACCTTGCG AAGGGAGTCCGAACTAGTCTCAGGCTAACATCGAATACGCCGCAGGCCCTTGCC TGGCGAACATACAAACATTATTATGATGAACACCCCTACCAACTACATCT ACCTCCAGCATTACCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCT ACCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCT TGGCGAACATACACCCCGATTCCGCTACGCCACTATGCCATTACAACTCT ACCTCCAGCATTACCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCT TATGGATTGAAACAGCATAACCCCGATTCCGCTACGCCACTATGCCATTACAACTCT ACCTCCAGCATTACCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCT CTACCACTCACCCCTAGCATTACTTATGTGGTATGTCCTCATGCCATTACAACTCT ACCTCCAGCATTACCTCTGTTCTCTGTTCTCTGTTCTCTGTTCTCTGTTCT CAAACCTAAGAGCACTGGGACGCCACGCCCTTCCCTCCGCTGCCAGGGCAG ATTCTGGAACACAAGAGAGAAATTGCTGGGTTAGAACAGATTATAACGAATT CGTCTGGTGGCATAGCTG TCACTTGACAGTTTTTTTTAAATATTACCCAAAATGCTCCCCAATAAGAA ATGCATCAGCTAG TCAGTGAATACAAAAAAGGAATTATTCTCCCTTGAGGGCTTTTACAT CTCTCTCCCTAACATGGGGTACACATACAGCTTCTCTTGGT GGGCCCCCACCACATTCTAACCCATAGTCCTCTAAC TACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGATT CCACATGTTGCCTTGGAGTC TCAAGCTGGACTGCCA</p>
26	COX10-ND1-3'UTR*	<p>ATGGCCGCATCTCCGCACACTCTCTCCTCACGCCCTCGTACAGGTTGCGTAGGAGGCTCTGTCTGGT ATCTTGAAGAAGAAGAAGAACTATGGCCAACCTCTACTCCCTATTGTAACCCATTCTAACATCGCAATGGCATTC TAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCAACGTTGAGGCC TACGGGCTACTACAAACCTCTGGCTGACGCCATAAAACTCTCACCAAGGCC ATCTACCATCACCCCTACATCACGCCCGACCTAGCTCTCACCATCGCTCTACTATGGACCCC CCTCCCCATGCCAACCCCCCTGGTCAACCTCAACCTAGGCCCTCTATTATTCTAGCCACCTCTAGCC TAGCGTTACTCACTCTGGTCAGGGTGGCATCAAACCTCAAACACTACGCCCTGATGCCGC CGAGCAGTAGGCCAACAACTCTCATATGAAGTCACCCCTAGCCATCTACTATCAACATTACTATG AGTGGCTCTTAAACCTCTCCACCCCTTACACAACACAAGAACCCCTCTGGTTACTCTG CCCTGGGATGATGTGGTTATCTCACACTAGCAGAGACCAACCGAACCCCCCTTGCACCTTGCG AAGGGAGTCCGAACTAGTCTCAGGCTAACATCGAATACGCCGCAGGCCCTTGCC TGGCGAACATACAAACATTATTATGATGAACACCCCTACCAACTACATCT ACCTCCAGCATTACCTCTGTTCTCTGTTCTCTGTTCTCTGTTCT TATGGATTGAAACAGCATAACCCCGATTCCGCTACGCCACTATGCCATTACAACTCT ACCTCCAGCATTACCTCTGTTCTCTGTTCTCTGTTCTCTGTTCT CTACCACTCACCCCTAGCATTACTTATGTGGTATGTCCTCATGCCATTACAACTCT ACCTCCAGCATTACCTCTGTTCTCTGTTCTCTGTTCTCTGTTCT CAAACCTAAGAGCACTGGGACGCCACGCCCTTCCCTCCGCTGCCAGGGCAG ATTCTGGAACACAAGAGAGAAATTGCTGGGTTAGAACAGATTATAACGAATT CGTCTGGTGGCATAGCTG TCACTTGACAGTTTTTTTTAAATATTACCCAAAATGCTCCCCAATAAGAA ATGCATCAGCTAG TCAGTGAATACAAAAAAGGAATTATTCTCCCTTGAGGGCTTTTACAT CTCTCTCCCTAACATGGGGTACACATACAGCTTCTCTTGGT GGGCCCCCACCACATTCTAACCCATAGTCCTCTAAC TACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGATT CCACATGTTGCCTTGGAGTC TCAAGCTGGACTGCCA</p>

29	opt_COX10-ND4-3'UTR	<p>ATGGCCGCCCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGCTAAAACAATCTGTCCTAACAAATTATGTTACTACCAACTGACATGGCTT CAAAAAAACACATGATTGGATCAACACAACCACCCACAGCCAATTATTAGCATCATCCCTACTATT TTTAACCAAATCAACAACACCTATTAGCTGTTCCCCAACCTTCTCCGACCCCTAACAAACCCC CCTCTTAATGCTAACTACCTGGCTCTCACCTCACAACTATGGCAAGCCAACGCCACTTATCCAGTG AACCAACTATCACGAAAAAAACTCTACCTCTCTATGCTAATCTCCCTAACAAATCTCTTAATTATGACATT CACAGGCCACAGAACTAATCATGTTTATATCTCTCGAACACACTTACCCACCTTGGCTATCATC ACCCGATGGGGCAACCAGCCAGAACGCCTGAACGCAGGCACATACTTCTTACACCCCTAGTAG GCTCCCTCCCTACTCATCGCACTAATTACACTCACAAACACCCCTAGGCTACTAAACATTCTACTAC TCACTCTCAACCCCCCTGACAAAACATGGCTTACCCCTCTGTACTATCCCTATGGGGCATGATT ATGACAAGCTCATCGCTACGACAAACAGACCTAAATCGCTATTGCTACTCTCAATCAGCCAC ATGGCCCTCGTAGTAACAGCCTATCTCATCCAAACCCCCCTGGAGCTTACCCGGCAGCTTCT GATCGCCCACGGGCTTACATCTCTTACTTCTGCTACTGCTAACACTCAAACACTGACAGCAGCAGC GTCGCATCATGATCCTCTCAAGGACTTCAACACTCTACTCCCACTAATGGCTTTGGGCTTCT CAAGGCTCGCTAACCTGCCCTACCCCCCACTATTAAACCTACTGGGAGAACTCTGTGCTAGTAACC ACGTTCTCTGGTCAAATACTCTCTACTTACAGGACTCAACATGCTAGTCAGCAGCCCTATACTCC CTCTACATGTTACCCACACAATGGGCTACTCTACCCACACATTAACACATGAAACACTCT ACACGAGAAAACACCCCTATGTTCTTAAGAGCACTGGGACGCCACGGGCCCTTCCCTCCGCTGCCAGGGAG CATGTTGTGGTAATTCTGGAACACAAGAGAAATTGCTGGGTTAGAACAGATTATAAACGAATT TGCACTCAGCTCAGTGTAAACAAAAAGGAATTATTCTCTTGTGAGCTAACATACAGCTTCTCTT CTCCAAACCCCCACCCCTTATTCTGTTCTCTCACATGGGGGTACACATACACAGCTTCTCTT GGTCCTCATCTTACCCACACACAGCAGCAGACTCCACATGCCAGAGTGGCACTGGGACTGGGATTCCACATGTT TGCCCTGGGAGTCTCAAGCTGGACTGCC</p>
30	opt_COX10-ND4-3'UTR*	<p>ATGGCCGCCCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGCTAAAACAATCTGTCCTAACAAATTATGTTACTACCAACTGACATGGCTT CAAAAAAACACATGATTGGATCAACACAACCACCCACAGCCAATTATTAGCATCATCCCTACTATT TTTAACCAAATCAACAACACCTATTAGCTGTTCCCCAACCTTCTCCGACCCCTAACAAACCCC CCTCTTAATGCTAACTACCTGGCTCTCACCTCACAACTATGGCAAGCCAACGCCACTTATCCAGTG AACCAACTATCACGAAAAAAACTCTACCTCTCTATGCTAATCTCCCTAACAAATCTCTTAATTATGACATT CACAGGCCACAGAACTAATCATGTTTATATCTCTCGAACACACTTACCCACCTTGGCTATCATC ACCCGATGGGGCAACCAGCCAGAACGCCTGAACGCAGGCACATACTTCTTACACCCCTAGTAG GCTCCCTCCCTACTCATCGCACTAATTACACTCACAAACACCCCTAGGCTACTAAACATTCTACTAC TCACTCTCACTGCCAAGAACAATCTGGGCAACACTAAACACTTATGGCTACTACACATGAAACACTGG CTTTATGGTAAAGATGGCTTACGGACTCCACTTATGGCTTACCTAAAGGGCATGTCGAAGCCCCCA TCGCTGGGTCAATGGTACTTGGCCAGACTCTTAAACACTAGGGGGCTATGGTATGATGCGCTCATC CTCTACATGTTACCCACACATGGCTTACCCCTCTGTACTATCCCTATGGGGCATGATT ATGACAAGCTCATCGCTACGACAAACAGACCTAAATCGCTATTGCTACTCTCAATCAGCCAC ATGGCCCTCGTAGTAACAGCCTATCTCATCCAAACCCCCCTGGAGCTTACCCGGCAGCTTCT GATCGCCCACGGGCTTACATCTCTTACTTCTGCTACTGCTAACACTCAAACACTGACAGCAGC GTCGCATCATGATCCTCTCAAGGACTTCAACACTCTACTCCCACTAATGGCTTTGGGCTTCT CAAGGCTCGCTAACCTGCCCTACCCCCCACTATTAAACCTACTGGGAGAACTCTGTGCTAGTAACC ACGTTCTCTGGTCAAATACTCTCTACTTACAGGACTCAACATGCTAGTCAGCAGCCCTATACTCC CTCTACATGTTACCCACACAATGGGCTACTCTACCCACACATTAACACATGAAACACTCT ACACGAGAAAACACCCCTATGTTCTTAAGAGCACTGGGACGCCACGGGCCCTTCCCTCCGCTGCCAGGGAG CATGTTGTGGTAATTCTGGAACACAAGAGAAATTGCTGGGTTAGAACAGATTATAAACGAATT TGCACTCAGCTCAGTGTAAACAAAAAGGAATTATTCTCTTGTGAGCTAACATACAGCTTCTCT CTCCAAACCCCCACCCCTTATTCTGTTCTCTCACATGGGGGTACACATACACAGCTTCTCTT GGTCCTCATCTTACCCACACACAGCAGCAGACTCCACATGCCAGAGTGGCACTGGGACTGGGATTCCACATGTT TGCCCTGGGAGTCTCAAGCTGGACTGCC</p>

31	opt_COX10-opt_Nd4-3'UTR	<p>ATGGCCGCCCTCACCACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGCTGAAGCTGATCGTGCCCCACCATCATGCTGCTGCCCTGACCTGGCT GAGCAAGAAAACACATGATCTGGATCAACACCACCGCACAGCCTGATCATCAGCATCATCCCTCTGC TGGTCTTCACCAGATCAACAACACTGTTAGCTGAGCTGAGCCCCACCTCAGCAGCGACCCCTGACA ACACCTCTGCTGATGCTGACCAACTGGCTGCTGCCCCCTACAATCATGGCCTCTCAGAGACACCTGA GCAGCGAGGCCCTGAGCGGAAAGAAAAGTGTACCTGAGCATGCTGATCTCCCTGAGATCTCTGTGAT CATGACCTTCACGCCACCGAGCTGATCATGTTCTACATTTTGAGAGACATGAAACGCCGACCT GCCCATCATACCAGATGGGGCAACCAGCTGAGAGACTGAAACGCCGACCTACTTCTGTTCTAC ACCCTCGTGGCAGCTGCCACTGCTGATTGCCCTGATCTACACCCACAAACCCCTGGGCTCCCTGA ACATCCTCTGCTGACACTGAGCAGCCAAAGAGCTGAGCAACAGCTGGGCAACAATCTGATGTGGCT GGCTCACACAATGGCTTCATGGTCAAGATGCCCTGATGGCCTGACCTGTGGCTGCTGAA CATGTGGAAAGCCCCATCGCCGCTATGGTGTGGCTGAGCTGCTGCTGAAACTCGGCGCTACG GCATGATGCCGCTGACCCCTGATTCTGAATCCCTGACCAAGCACATGCCCTACATTCTGGTGTG AGCCTGTGGGAGCTGATTGACAGCAGCATCTGCTGGGGAGCGACCTGCTGAGCTGCTGCTG CCTACAGCTCCATGCCACATGCCCTGGTGGTACCGCCATCTGCTGAGCTGCTGAGCTT ACAGGGCCGTGATCTGATGATTGCCACGGCCATGACAAGCAGCTGCTGCTGAGCTGCTG GCAACTACGAGCGGACCCACAGCAGAAATCATGATCTGCTGAGGGCTGAGCCACTCCTGG TATGGCTTTGGTGGCTGCCCTCTGGCCAATCTGGCACTGCCCTACCATCAATCTGCTGG GCGAGCTGAGCGTGTGGTACCCACATTGAGCTGGTCAATATCACCCCTGCTGCTGAGCC CATGCTGGTACAGCCCTGACTCCCTGATCATGCCGAGAACACCCCTGATGTTGATGCTG ACATCAACAAATGAGCCAGCTTACCCGCGAGAACACCCCTGATGTTGATGCTGAGCT CTGCTGCTGCCCTGAATCTGATCATGCCGCTTCCAGCTGAGAGCACTGGGACCC GCCCCCTTCCCTGCCGAGGGAGGAGCTGTTGGTAATTCTGGAAACACAAGAAGAGAAATTGCTG GGTTAGAAGAACAGATTATAACGAATTGGTGTGAGCTGATCACTGAGCTGAGCTG TTTTCCCCACACATCTCAACCATAGTCTGCTTCAACAAATACCAATAGCTAGGACCC CCCAGCAGAGTGGCACTGGTGGCAGAAAGTGTGAGGCTCATGATCTGCTGCTGAGTCTG GCTCAGGTCCCTCAAGGCCCTGGAGCACCCCTTCTGTGACTGAGCCAGGGCTG TTTTCCCCACACATCTCAACCATAGTCTGCTTCAACAAATACCAATAGCTAGGACCC TGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGACTGCA</p>
32	opt_COX10-opt_Nd4-3'UTR*	<p>ATGGCCGCCCTCACCACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGCTGAAGCTGATCGTGCCCCACCATCATGCTGCTGCCCTGACCTGGCT GAGCAAGAAAACACATGATCTGGATCAACACCACCGCACAGCCTGATCATCAGCATCATCCCTCTGC TGGTCTTCACCAGATCAACAACACTGTTAGCTGAGCTGAGCCCCACCTCAGCAGCGACCCCTGACA ACACCTCTGCTGATGCTGACCAACTGGCTGCTGCCCCCTACAATCATGGCCTCTCAGAGACACCTGA GCAGCGAGCCCCCTGAGCGGAAAGAAAAGTGTACCTGAGCATGCTGATCTCCCTGAGATCTCTGTGAT CATGACCTTCACGCCACCGAGCTGATCATGTTCTACATTTTGAGAGACATGAAACGCCGACCT GCCCATCATACCAGATGGGGCAACCAGCTGAGAGACTGAAACGCCGACCTACTTCTGTTCTAC ACCCTCGTGGCAGCTGCCACTGCTGATTGCCCTGATCTACACCCACAAACCCCTGGGCTCCCTGA ACATCCTCTGCTGACACTGAGCAGCCAAAGAGCTGAGCAACAGCTGGGCAACAATCTGATGTGGCT GGCTCACACAATGGCTTCATGGTCAAGATGCCCTGATGGCCTGACCTGTGGCTGCTGAA CATGTGGAAAGCCCCATCGCCGCTATGGTGTGGCTGAGCTGCTGCTGAAACTCGGCGCTACG GCATGATGCCGCTGACCCCTGATTCTGAATCCCTGACCAAGCACATGCCCTACATTCTGGTGTG AGCCTGTGGGAGCTGATTGACAGCAGCATCTGCTGGGGAGCGACCTGCTGAGCTGCTG CCTACAGCTCCATGCCACATGCCCTGGTGGTACCGCCATCTGCTGAGCTGCTGAGCTT ACAGGGCCGTGATCTGATGATTGCCACGGCCATGACAAGCAGCTGCTGCTGAGCTGCTG GCAACTACGAGCGGACCCACAGCAGAAATCATGATCTGCTGAGGGCTGAGCCACTCCTGG TATGGCTTTGGTGGCTGCCCTCTGGCCAATCTGGCACTGCCCTACCATCAATCTGCTGG GCGAGCTGAGCGTGTGGTACCCACATTGAGCTGGTCAATATCACCCCTGCTGCTGAGCC CATGCTGGTACAGCCCTGACTCCCTGATCATGCCGAGAACACCCCTGATGTTGATGCTG ACATCAACAAATGAGCCAGCTTACCCGCGAGAACACCCCTGATGTTGATGCTGAGCT CTGCTGCTGCCCTGAATCTGATCATGCCGCTTCCAGCTGAGAGCACTGGGACCC GCCCCCTTCCCTGCCGAGGGAGGAGCTGTTGGTAATTCTGGAAACACAAGAAGAGAAATTGCTG GGTTAGAAGAACAGATTATAACGAATTGGTGTGAGCTGATCACTGAGCTGAGCTG TTTTCCCCACACATCTCAACCATAGTCTGCTTCAACAAATACCAATAGCTAGGACCC CCCAGCAGAGTGGCACTGGTGGCAGAAAGTGTGAGGCTCATGATCTGCTGCTGAGTCTG GCTCAGGTCCCTCAAGGCCCTGGAGCACCCCTTCTGTGACTGAGCCAGGGCTG TTTTCCCCACACATCTCAACCATAGTCTGCTTCAACAAATACCAATAGCTAGGACCC TGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGACTGCA</p>

33	opt_COX10-opt_Nd4*-3'UTR	ATGGCCGCCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGCTGAAGCTGATCGTGCCCCACCATCATGCTGCTGCCCCCTGACCTGGCT GAGCAAGAAGCACATGATCTGGATCAACACCACCCACAGCCTGATCATCAGCATCATCCCCCTGC TGGTCTTCACCAGATCAACAACACCTGTTCACTGAGCTGAGCTGAGCCACCTGACAGCGACCCCTGAC ACCCCCCTGCTGATGCTGACCAACTGGCTGCTGCCCCCTGACCATCATGGCCAGCGGCCACCTGA GCAGCGAGCCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATGCTGATCAGCTGAGCCAGCGACCCCTGAC CATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTCAGAGACCACCCCTGATCCCCACCC TGGCCATCATCACCCGCTGGGGCAACCAGCCGAGCGCCTGAACGCCGGACCTACTTCCTGTTCA CACCCCTGGTGGGCAGGCTGCCCTGCTGATGCCCTGACGGCCACCTGAGCTGGGCAACAACCTGATGTGGC AACATCTCTGCTGACCCCTGACGGCCAGGAGCTGAGCAACAGCTGGGCAACAACCTGATGTGGC TGGCCTACACAGCATGGCTTCTATGGTGAAGATGCCCTGATGGGCTGACCTGTCCTGCCCCAAGGC CCACGTGGAGGGCCCCCATGCCGGCAGCATGGTGTCTGCCGGCGTGTCTGAAGCTGGGGCT CGGCATGATGCCCTGACCCCTGATCCTGAACCCCTGACCAAGCAGCATGGCTACCCCTTCTGGT CTGAGCCTGTGGGCATGATGAGCAGCAGCATCTGCCCTGCGCCAGACCGACCTGAAGAGGCTGA TCGCCTACAGCAGCATCAGCACATGCCCTGGTGTGGTACCCCTGATCAGCTGCTGAGCCAGCCCTGGAG CTTCACCGGCCGGTGTCTGATGAGTGGCTGACCCCTGACGGAGCAGCCCTGCTGCTGCTGCTG AACAGCAACTACGAGCGCACCCACAGGCCATCATGATCTGAGCCAGGGCTGAGACCCCTGCTG CCCTGATGGCTTCTGGTGTCTGCCAGCCCTGGCAACCTGGGCTGCCCTGGGACCATCAACCT GCTGGGGAGCTGAGCGTGTGGTACCCCTGACAGCTGATGTTACCTGAGCAACATCACCCCTGCTGACCGG CCTGAACATGCTGGTACCCCTGACAGCTGATGTTACCTGAGCAACATCACCCCTGCTGACCG ACCCACACATCAACACATGAAGCCAGCTTACCCCGAGAACACCCCTGATGTTCATGCACTGAG CCCCATCTGCTGAGCCGACATCATCACCGGCTCAGCAGCTAAAGAGCACTGGGAC GCCAACCCGGGCTTCCCTCCGCTGCCAGGGAGCATTTGGTAAATTCTGGAACACAAGAAGAGA AATTGCTGGGTTAGAACAGATTAAACGAATTGGTGTCACTGATCACTTGACAGTTTTTTTT TTTAAATATTACCCAAAATGCTCCCAAATAAGAAATGCACTGAGCTCACTGAGTAATAACAAAAAGGA ATTATTTTCCCTTGAGGGCTTTATACTATCTCCTCCAAACCCACCCCTTATCTGTTCTCCTCC TCACATGGGGTACACATACAGCTTCCCTCTTGTACATGTTCTGCCTCATCCTTACCCACACCACGCACACT CCACATGCCAGCAGTGGCACTGGTGGCAGAAAGTGTGAGCCTCATGATCTGCTGCTGAGT TCTGTGAGCTCAGGTCCCTGAGGAGCTGGCTGACCCCTTCTTGTGACTGAGCCAGGGCTGCA TTTTGGTTTCCCCACACCATCTCAACCATGCTTCTTAACAAATACCAATAGCTAGGACCCG GCTGCTGCACTGGACTGGGAGTGGGATTGACATGTTGCTGGAGTCTCAAGCTGGACTGCA
34	opt_COX10-opt_Nd4*-3'UTR*	ATGGCCGCCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGCTGAAGCTGATCGTGCCCCACCATCATGCTGCTGCCCCCTGACCTGGCT GAGCAAGAAGCACATGATCTGGATCAACACCACCCACAGCCTGATCATCAGCATCATCCCCCTGC TGGTCTTCACCAGATCAACAACACCTGTTCACTGAGCTGAGCCACCTGACAGCGACCCCTGAC ACCCCCCTGCTGATGCTGACCAACTGGCTGCTGCCCCCTGACCATCATGGCCAGCCAGCGACCCCTGAC GCAGCGAGCCCCCTGAGCCGCAAGAAGCTGTACCTGAGCATGCTGATCAGCTGAGCCAGCGACCCCTGAC CATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTCAGAGACCACCCCTGATCCCCACCC TGGCCATCATCACCCGCTGGGGCAACCAGCCGAGCGCCTGAACGCCGGACCTACTTCCTGTTCA CACCCCTGGTGGGCAGGCTGCCCTGCTGATGCCCTGACCTACACCCACACCCCTGGCAGCCCTG AACATCTCTGCTGACCCCTGACGGCCAGGAGCTGAGCAACAGCTGGGCAACAACCTGATGTGGC TGGCCTACACAGCATGGCTTCTATGGTGAAGATGCCCTGATGGGCTGACCTGTCCTGCCCCAAGGC CCACGTGGAGGGCCCCCATGCCGGCAGCATGGTGTCTGCCGGCGTGTCTGAAGCTGGGGCT CGGCATGATGCCCTGACCCCTGATCCTGAACCCCTGACCAAGCAGCATGGCTACCCCTTCTGGT CTGAGCCTGTGGGCATGATGAGCAGCAGCATCTGCCCTGCGCCAGACCGACCTGAAGAGGCTGA TCGCCTACAGCAGCATCAGCACATGCCCTGGTGTGGTACCCCTGATCAGCTGCTGAGCCAGCCCTGGAG CTTCACCGGCCGGTGTCTGATGAGTGGCTGACCCCTGACGGAGCAGCCCTGCTGTTCTGCTG AACAGCAACTACGAGCGCACCCACAGGCCATCATGATCTGAGCCAGGGCTGAGACCCCTGCTG CCCTGATGGCTTCTGGTGTCTGCCAGCCCTGGCAACCTGGGCTGCCCTGGGACCATCAACCT GCTGGGGAGCTGAGCGTGTGGTACCCCTGACAGCTGATGTTACCTGAGCAACATCACCCCTGCTGACCGG CCTGAACATGCTGGTACCCCTGACAGCTGATGTTACCTGAGCAACATCACCCCTGCTGACCG ACCCACACATCAACACATGAAGCCAGCTTACCCCGAGAACACCCCTGATGTTCATGCACTGAG CCCCATCTGCTGAGCCGACATCATCACCGGCTCAGCAGCTAAAGAGCACTGGGAC GCCAACCCGGGCTTCCCTCCGCTGCCAGGGAGCATTTGGTAAATTCTGGAACACAAGAAGAGA AATTGCTGGGTTAGAACAGATTAAACGAATTGGTGTCACTGATCACTTGACAGTTTTTTTT TTTAAATATTACCCAAAATGCTCCCAAATAAGAAATGCACTGAGCTCACTGAGTAATAACAAAAAGGA ATTATTTTCCCTTGAGGGCTTTATACTATCTCCTCCAAACCCACCCCTTATCTGTTCTCCTCC TCACATGGGGTACACATACAGCTTCCCTCTTGTACATGTTCTGCCTCATCCTTACCCACACCACGCACACT CCACATGCCAGCAGTGGCACTGGTGGCAGAAAGTGTGAGCCTCATGATCTGCTGCTGAGT TCTGTGAGCTCAGGTCCCTGAGGAGCTGGCTGACCCCTTCTTGTGACTGAGCCAGGGCTGCA TTTTGGTTTCCCCACACCATCTCAACCATGCTTCTTAACAAATACCAATAGCTAGGACCCG GCTGCTGCACTGGACTGGGAGTGGGATTGACATGTTGCTGGAGTCTCAAGCTGGACTGCA

35	opt_COX10-ND6-3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGATGATGCTTGTGAGTGTGGGTTACTAATGGGGTTGTG GGGTTTCTCTAAGCCTCTCCTATTATGGGGTTAGTATTGATTGTTAGCGGTGTTAGGGTCAAGGGGTT GTTATTATTCTGAATTGGGGAGGTTATGGGTTAATGGTTTTAATTTATTAGGGGAATGA TGGTTGTCTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTGAGGCATGGGGTCAGGGGTT GAGGTCTTGGTGAGTGTAGTGGGTTAGCGATGGAGGTAGGATTGGTCTGTGGGTGAAGAGT ATGATGGGGTGGTGGTTGTGTTAACTTAATAGTGTAGGAAGCTGGATGATTATGAAGGAGGGG TCAGGGTTGATCGGGAGGATCCTATTGGTGCCTGGGGCTTGTATGATTATGGCGTTGGTTAGTGT AGTTACTGGTTGGACATTGTTGTGGTATATATTGTAATTGAGATGCTCGGGGAAATTAGGAGCA CTGGGACCCCACCCCTCCCTCGCTGCCAGGGAGCATGTTGTGGTAATTCTGGAACACAA GAAGAGAAATTGCTGGGTTAGAACAGATTAAACGAATTGGCTCAGTCAGTCAGTCAGTGAATACAA AAAAGGAATTATTTCCCTTGAGGGTCTTTATACATCTCCTCCAACCCACCCCTTATTCTGTT CTTCCCTCACATGGGGTACACATACAGCTTCTCTTGGTCCATCCTTACCCACACCA CGCACACTCCACATGCCAGCAGACTGGCAGTGGCTTGGCAGAAAGTGTGAGCCTCATGATCTGCTG TCTGTAGTTCTGTGAGGCTCAGGTCCTCAAAGGCTCGGAGCACCCCTTCTGTGACTGAGCCAG GGCTGCATTTGGTTCCCCACACATTCTCAACCAGTCTTCTTAACAATACCAATAGCT AGGACCCCCGCTGTGCACTGGGACTGGGATTCACATGTTGCTTGGGAGTCTCAAGCTGGAC TGCA
36	opt_COX10-ND6-3'UTR*	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGATGATGCTTGTGAGTGTGGGTTACTAATGGGGTTGTG GGGTTTCTCTAAGCCTCTCCTATTATGGGGTTAGTATTGATTGTTAGCGGTGTTGGTGGGTGT GTTATTATTCTGAATTGGGGAGGTTATGGGTTAATGGTTTTAATTTATTAGGGGAATGA TGGTTGTCTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTGAGGCATGGGGTCAGGGGTT GAGGTCTTGGTGAGTGTAGTGGGTTAGCGATGGAGGTAGGATTGGTCTGTGGGTGAAGAGT ATGATGGGGTGGTGGTTGTGTTAACTTAATAGTGTAGGAAGCTGGATGATTATGAAGGAGGGG TCAGGGTTGATCGGGAGGATCCTATTGGTGCCTGGGGCTTGTATGATTATGGCGTTGGTTAGTGT AGTTACTGGTTGGACATTGTTGTGGTATATATTGTAATTGAGATGCTCGGGGAAATTAGGAGCA CTGGGACCCCACCCCTCCCTCGCTGCCAGGGAGCATGTTGTGGTAATTCTGGAACACAA GAAGAGAAATTGCTGGGTTAGAACAGATTAAACGAATTGGCTCAGTCAGTCAGTCAGTGAATACAA AAAAGGAATTATTTCCCTTGAGGGTCTTTATACATCTCCTCCAACCCACCCCTTATTCTGTT CTTCCCTCACATGGGGTACACATACAGCTTCTCTTGGTCCATCCTTACCCACACCA CGCACACTCCACATGCCAGCAGACTGGCAGTGGCTTGGCAGAAAGTGTGAGCCTCATGATCTGCTG TCTGTAGTTCTGTGAGGCTCAGGTCCTCAAAGGCTCGGAGCACCCCTTCTGTGACTGAGCCAG GGCTGCATTTGGTTCCCCACACATTCTCAACCAGTCTTCTTAACAATACCAATAGCT AGGACCCCCGCTGTGCACTGGGACTGGGATTCACATGTTGCTTGGGAGTCTCAAGCTGGAC TGCA
37	opt_COX10-opt_Nd6-3'UTR	ATGGCCGCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGATGATGCTGACGCCCTGTTCTGCTGAGCGTGGGCTGTGATGGGCTTCGT GGGCTTCAGCAGCAAGGCCAGCCCCATCTAGGGCGGGCTGGTCTGTGAGCGGGCTGGTGGG CTGCGTGTATCCTCGAACCTCGCGGGCGCTACATGGGCCTGATGGTGTCTCTGATCTACCTGGGC GGCGATGATGGTGTGGTCTCGGCTACACCCACCCGCGATGGCCATGAGGAGTACCCCGAGGCCTGGGGC AGCGCGTGGAGGTGCTGGTGAAGCGTGTGGTGGGCTGGCCATGGAGGTGGGCTGGTCTGTG GGTGAAGGAGTACGACGGCGTGGTGGTGGTGGTGAACCTCAACAGCGTGGGAGCAGCTGGATGATCTA CGAGGGCGAGGGCAGCGGCCCTGATCCCGAGGGACCCCATCGGCCGCCGCCCTGTACGACTACG GCGCCTGCTGGTGGTGGTGAACCGGCTGGACCCCTGTTCTGTGGGCTGTACATCGTGTACGAGATCG CCCGCGGCAACTAACAGAGCACTGGGACGCCACCCGCCCTTCCCTCCCGCTGCCAGGGAGCATGTT GTGGTAATTCTGGAAACACAAGAAGAGAAATTGCTGGGTTAGAACACAAGATTAAACGAATTGGTGTGCT CAGTGTACATCTGAGCTTTTTTTAAATTACCAAAATGCTCCCAAATAAGAAATGCTACAC CCCACCCCTTATTCTGTTCTCCCTCACATGGGGGTACACATACAGCTTCTCTTTGGTCCA CCTTACCAACACACAGCACGCAACTCCACATGCCAGCAGACTGGCAGTGGCACTGGTGGCCAGAAAGTG TGAGCCTCATGATCTGCTGTAGTTCTGTGAGGCTCAGGTCCTCAAAGGCTCGGAGCACCCCT TCCCTGTGACTGAGCCAGGGCCTGCACTTTGGTTTCCCCACCCCATCTCAACCCATAGCTTCTT CTAACAAATACCAATAGCTAGGACCGGGCTGCTGTGCACTGGGACTGGGATTCACATGTTGCTTGGG GGAGTCTCAAGCTGGACTGCCAGCCCCCTGCTCCCTCACCCTTGGCTATGAGCATTTCAGAAC TCCAAGGAGTCAGGGCATCTTATAGTTCAGTTAACATATAGACACTGTTGGAGAGCAGTTCTCTA AAAGGGTAGCCCTGGACTTAATACCAGCCGGATAACCTCTGGCCCCCACCCATTACTGTACCTCTGGA GTCACTACTGTGGGTGCCACTCTCTGCTACACAGCACGGCTTTCAAGGCTGTATTGAGAAGGGG AGTTAGGAAGAAGGGTGTGCTGGGCTAACAGGCCACAGAGCTCACATTCCCTGCCCCCTGGTAAA AATACATGTCATCTGATATCTCTGAAATTCAAGAAATTAGCCTCCACATGTCATGGCTTAAAGAGC CAGAAGCAGGGTTCTGGGAATTGGCAAGTTACCTGTGGCCAGGTGTGGTCTCGGTTACCAAACACGG

		TTACCTGCAGCTTTAGTCCCTTGTGCTCCCACGGGTACAGAGTCCCCTGCCCCAAGGTCTTGA AGCTTGACAGGATGTTTCGATTACTCAGTCCTCAGGGCACTACTGGTCCGTAGGATTGATGGTC GGGGTAGGAGAGTTAACACATTAAACAGAGTTCTCAAAAATGTCTAAAGGGATTGTAGGTAGAT AACATCCAATCACTGTTGCACTTATCTGAAATCTTCCCTTGGCTGCCCTCAGGTATTACTGTGGA GAACATTGCATAGGAATGTCTGGAAAAAGCTTACAACCTGTTACAGCCTCACATTGTAGAAGCTT T
38	opt_COX10- opt_ND6- 3'UTR*	ATGGCCGCCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGATGTCAGCCCTGTTCTGCTGAGCGTGGGCTGGTGTGATGGGCTTCGT GGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGCGGCCCTGGTGTGATCGTGAACGGCGTGGTGGG CTGCGTGTGATCATCCTGAACTTCGGCGGCCCTACATGGGCTGATGTTCTGATCACCTGGGC GGCATGATGGTGGTGGCGCTACACCACGCCATGGCCATCGAGGAGTACCCGAGGCCTGGG AGCGCGTGGAGGTGCTGGTGGCGTGGTGGGGCTGGCCATGGAGGTGGGCTGGTGTG GGTGAAGGAGTACGACCGCGTGGTGGTGGGGTAACCTCAACAGCGTGGGAGCTGGATGATCTA CGAGGGCGAGGGCGAGCCGCGCTGATCGCGAGGACCCCTGACCGCCGGCGCCCTGTACCGACTACG GCCGCTGGCTGGTGGTGGACCGCCCTGGGCTGGGACCTGTTCTGGGCGTGTACATCGTGAATCGAGATCG CCCGCGGCAACTAAGAGCACTGGGACGCCACCGCCCTTCCCTCGCTGCCAGCGAGCATGTT GTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTAGAACAAAGATTATAAACGAATTGGTGTG CACTGATCACTTGACAGTTTTTTTTAAATATTACCCAAAATGCTCCCCAATAAGAAATGCATCA GCTCACTGAGTAACAAAAAAGGAATTATTTCCCTTGAGGGTCTTTATACATCTCTCCAAAC CCCAACCCCTCTATTCTGTTCTCCCTACATGGGGGTACACATACAGCTTCTTGTGTTCCA TCCTTACCAACACACAGCACACTCCACATGCCAGCAGGTGGCAGCTGGTGGCAGAAAGTG TGAGCCTCATGATCTGCTGTGAGTTCTGTGAGCTCAGGTCCTCAAAGGCCCTGGAGCACCCCT TCCTTGTGACTGAGCCAGGGCTGCATTTGGTTTCCCACACATCTCAACCATAGTCCT CTAACAAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGATTCCACATGTTGCTTG GGAGTCTCAAGCTGGACTGCCA
39	opt_COX10- ND1-3'UTR	ATGGCCGCCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGGCAACCTCTACTCCTCATTGTAACCATTCATCGCAATGGCATTC CTAATGCTTACCGAACGAAAAATTCTAGGCTATGCAACTACGCAAAGGCCCAACGTTGAGGGCC CTACGGGCTACTACAACCCCTCGCTGACGCCATAAAACCTTCACCAAAAGAGCCCTAAACCGGCCA CATCTACCATCACCCCTACATCACCGCCCGACCTTAGGCTCTACCATCGCTCTACTATGGACCC CCCTCCCATGCCAACCCCTGGTCAACCTAACCTAACCTAGGCTCTATTTATTCTAGCCACCTCTAGC CTAGCCGTTACTCAATCCTCTGGTCAAGGGTGGGATCAAACACTCAAACACTACGCCCTGATCGCGCACT GCCAGCAGTAGCCAAACATCTCATATGAAGTCACCCCTAGCCATCATTCTACTATCAACATTACTAAT GAGTGGCTCTTTAACCTCTCCACCCCTTACACAACACAAGAACACCTCTGGTTACTCCTGCCATCATG GCCCTGGCCATGATGTGGTTATCTCCACACTAGCAGAGAACCCCTTCGACCTTGCG AAGGGAGTCCGAACTAGTCTCAGGCTTACATCGAATACGCCAGGCCCTCGCCCTATTCTC ATGGCCGAATACACAAACATTATTATGATGAACACCCCTACCACTACAATCTCTCTAGGAACACATAT GACGCACTCTCCCTGAACTCTACACAACATATTGTCAACAGACCCCTACTCTTAACCTCCCTGTT TTATGGATTGAAACAGCATACCCCGATTCCGCTACGACCAACTCATGCACCTCTATGGAAAAACTTC CTACCACTACCCCTAGCATTACTTATGTGGTATGTCCTGACCTGCCCCATTACAATCTCCAGCATTCC CAAACCTAACGACTGGGACCCGCCCCCTTCCCTCGCTGCCAGGCAGCATGTTGTTGA ATTCTGGAACACAAGAAGAGAAATTGCTGGGTTAGAACAAAGATTAAACGAATTGGTGTGCTAGTGA TCAGTGAATACAAAAAAGGAATTATTTCCCTTGAGGGTCTTTATACATCTCTCTCCAAACCCACC CTCTATTCTGTTCTCTCCACATGGGGTACACATACAGCTTCTCTTGGTCCATCCTTAC CACCAACACACAGCACACTCCACATGCCAGCAGGTGGCACTTGGTGGCCAGAAAGTGAGCCT CATGATCTGCTGCTGTAGTTCTGAGCTCAGGTCCTCAAAGGCCCTGGAGCACCCCTCTCTG GACTGAGCCAGGGCTGCATTGGGTTCCCGCCACACATTCACATTCTCAACCATAGTCCTCTAACA TACCAATAGCTAGGACCCGGCTGTCAGTGGACTGGGGATTCCACATGTTGCTTGGAGTC TCAAGCTGGACTGCCAGCCCTGTCCTCCCTCACCCCATTCGCTATGAGCATTCAAGACTCCAAG GAGTCACAGGCATTTAATAGTACGTTACGTTACATATAGACACTGTTGGAAGCAGTTCTCTAAAGGG TAGCCCTGGACTTAATACCAAGCCGGATACCTCTGGCCCCACCCATTACTGTACCTCTGGAGTC ACTGTGGGTCGCCACTCCTCTGCTACACAGCACGGCTTTCAAGGCTGATTGAGAAGGGAAAGTTAG GAAGAAGGGGTGTCTGGGCTAACAGGCCACAGAGCTACATTCGCAATGGCTTAAGAGCCAGAAGC AGGGTTCTGGAAATTGCAAGTTACCTGTGGCCAGGTGGTCTGGTACCAAAATCGTACCTG CAGCTTTAGTCTCTTGCTCCACGGGCTACAGAGTCCCAGGGCACTACTGGTCCGTAGGATTG ACAGGATGTTTCGATTACTCAGTCCTCCAGGGCACTACTGGTCCGTAGGATTGATTGGTGGGGTA GGAGAGTTAACACATTAAACAGAGTTCTCTAAAGGGATTGTAGGTAGATAACATC CAATCACTGTTGCACCTATCTGAAATCTTCCCTTGGCTGCCCTCAGGTATTACTGTGGAGAACAT TGCATAGGAATGTCTGGAAAAAGCTTACAACACTGTTACAGCCTCACATTGTAGAAGCTT

40	opt_COX10-ND1-3'UTR*	ATGGCCGCCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGGCCAACCTCTACTCCTCATTTGTAACCTCTAATCGCAATGGCATT CTAATGCTTACCGAACGAAAAATTCTAGGCTATGCAACTACGCAAAGGCCCCAACGTTGAGGCC CTACGGGCTACTACAACCCTCGCTACGCCATAAAACTCTCACCAAGAGGCCCTAAAACCGCCA CATCTACCATCACCCCTACATCACCGCCCCGACCTTAGCTCTCACCATCGCTCTACTATGGACCC CCCTCCCCATGCCAACCCCTGGTCAACCTCACCTAGGCCCTCTATTCTAGCCACCTCTAGC CTAGCCGTTACTCAATCCTCTGGTCAGGGGGCATCAAACACTACGCCCTGATCGGGCACT GCGAGCAGTAGCCAAACAATCTCATATGAAGTCACCCCTAGCCATCATTCTACTATCAACATTAAAT GAGTGGCTCCTTAACCTCTCCACCCCTATCACAAACACAAGAACACCTCTGGTTACTCTGCCATCATG GCCCTGGCCATGATGTGGTTATCTCCACACTAGCAGAGACCAACCGAACCCCCTCGACCTTGCG AAGGGGAGTCCGAACTAGTCTCAGGCTTCAACATCGAAATACGCCGAGGCCCTCGCCCTATTCTC ATGGCCGAATACACAAACATTATATTGATGAACACCCCTACCAACTACAACTCTCCCTAGGAACACATAT GACGCACTCTCCCTGAACTCTACACAACATATTGTCACCAAGACCTACTCTTAACCTCCCTGTT TTATGGATTGCAACAGCATACCCCCGATTCCGCTACGACCAACTCATGCACCTCTATGGAAAACCTC CTACCACTCACCCCTAGCATTACTTATGTGGTATGTCATGCCATTACAATCTCAGCATTCCCC CAAACCTAAGAGCACTGGGACGCCACGCCCTTCCCTCGCTGCCAGGCAGCATGTTGTTGTA ATTCTGGACACACAAGAAGAGAAATTGCTGGGTTAGAACAGATTATAACGAATTGGTGTCACTG TCAGTTGACAGTTTTTTTTAAATTATACCCAAAATGCTCCCCAAATAAGAAATGCATCAGCTCAG TCAGTGAATACAAAAAAGGAATTTTTCCCTTGAGGGCTTTTACATCTCTCCCTCAACCC CTCTATTCTGTTCTCCTCCTACATGGGGTACACATACAGCTCTCTTTGGTTCCATCCTAC CACCAACACACAGCACACTCCACATGCCACAGCAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCT CATGATCTGCTGTCTGAGTTCTGTGAGCTCAGGTCCCTCAAGGCCCTGGAGCACCCCTTCTGT GACTGAGCCAGGGCCTGCATTTGGTTTCCCCACACATTCTAACCATAGTCCTCTAACAA TACCAATAGCTAGGACCCGGCTGTGCACTGGACTGGGATTCCACATGTTGCCTGGAGTC TCAAGCTGGACTGCCA
41	opt_COX10-opt_ND1-3'UTR	ATGGCCGCCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGTTGGGGCTCTGTGTGGT ATCTGGAACGGCGGACAATGGCCAACCTCTGCTGCTGATCGTCCCACCTGATGCCATGGCCTT CCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATCGAGCTGCCAAGGGCCCCAACGTTGTTG CCCGCTACGGCCTGCTGAGGCCCTCGGCCAGGCCATCAAGCTGTTACCCAAGGGAGGCCCTGAGGCC GCCACCAAGCACCACATCACCCCTGTACATCACCGCCCCCACCTGGCCCTGACCATCGCCCTGCTG GGACCCCCCTGCCATGCCAACCCCTGGTGAACCTGAAACCTGGGCTGCTGTTCATCTGGCCAC CAGCAGCCTGGCGTGTACAGCATCCTGTGAGCGGGCTGGGCCAGCAACAGCAACTACGCCCTGAT CGGCGCCCTGGCGCCGGCTGGCCAGACCATCAGCTACGGGTGACCCCTGCCCCATCATCTGGCTG CACCCCTGCTGATGAGGGCAGCTTCAACCTGAGCACCCCTGATCACCCCTGGCCAGGAGCACCTGTTG CTGCTGCCAGCTGGCCCTGGCCATGATGTGGTTCATAGCACCCCTGGCCAGGAGAACACCC CCTTCGACCTGGCCAGGGCGAGAGCGAGCTGGTGGAGGGCTTCAACATCGAGTACGCCGGGG CCTTCGCCCTGTTCTCATGGCCAGTACACAAACATCATCATGATGAAACACCCCTGACCACCA TTCCCTGGGACCCACCTACGACGCCCTGAGCCCCGAGCTGACACCACCTACTCGTGTACCAAGACCC TGCTGCTGACCGCCCTGTTCTGTGGATCCGACCCGCCCTACCCCGCTTCCCGTACGACCCAGCTGAT GCACCCCTGCTGTGGAGAACACTCTCTGCCCTGACCCCTGGCCCTGCTGATGTGGTACGTGAGCATGCC ATCACCATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCACCCGGGGCTTCCCTCG CTGCCAGGGCAGCATGGTGGTAATTCTGGAAACACAAGAAGAGAAATTGCTGGGTTAGAACAAAGAT TATAAACGAATTGGTGTCACTGATCACTTGACAGTTTTTTTTAAATTACCCAAAATGCTCC CCAAATAAGAAATGCATCAGCTCAGTCACTGAAATACAAAAAAGGAATTTTTCCCTTGAGGGCTTT TATACATCTCTCCCTCAACCCACCCCTCTATTCTGTTCTCCTCCTACATGGGGTACACATACACA GCTTCCCTTTGGTCCATCTTACCCACACCCAGACACTTACGACACTGGGACGCCACCCGGGGCTTCC CTGCCAGGGCAGCATGGTGGTAATTCTGGAAACACAAGAAGAGAAATTGCTGGGTTAGAACAAAGAT CTTGGTGGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG GGCCTGGAGCAGCCCTCTGACTGAGCCAGGGCTGCTTGGTGGTGGAGGAGGAGGAGGAGGAGGAG CATTCTCAACCATAGTCTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGG GATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGACTGCCAGCCCCCTGTCCTCCCTCACCC GCCTGGTGGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG CTGGTGGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG CCCATTAAGCTGGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG CCCATTAAGCTGGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG AAGGCTGATTGAGAAGGGAGGAGTGGAGAAGAAGGGTGTGCTGGGCTAACAGGCCACAGAGCTACA TTCCCTGTCCTGGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG TGTGCAATGGCTTAAGAGCCAGAAGCAGGGTCTGGGAATTGCAAGTTACCTGTGGCCAGGTG GTCTCGGTTACCAATACGGTTACCTGCACTGAGCTTTAGTCCTTGTGCTCCCACGGGTACAGAGTC CCATCTGCCAACAGGCTTGAAGCTGACAGGATGTTTCGATTACTCAGTCTCCACAGGGCACTACTG GTCCCGTAGGATTGAGTACATCCACATGGTGGAGGAGGAGTAAACACATTAAACAGAGTTCTCA CTAAAGGGATTGAGGAGTACATCCACATGGTGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG CCCCAGGGATTACTGTGGAGAACATTGCACTGAGGAGTACATGGTGGAGAACAGCTTCA CCTTCACATTTGAGAAGCTT

42	opt_COX10- opt_ND1- 3'UTR*	ATGGCCGCCCTCTCCACACACACTGAGTAGCAGACTGCTGACCGGCTGTGGGGGCTCTGTGTGGT ATCTGGAAACGGCGGACAATGGCCAACCTGCTGCTGATCGGCCATCCTGATGCCATGGCCTT CCTGATGCTGACCGAGCGCAAGATCCTGGGCTACATGCAGCTGCGCAAGGGCCCAACGTGGTGGG CCCCTACGGCCTGTCAGGCCCTCGCGACGCCATCAAGCTGTTACCAAGGAGCCCTGAAGCCC GCCACCGACCATCACCCCTGTACATCACCGCCCCCACCCCTGGGCCATGCCATCGCCCTGCTGCTGT GGACCCCCCTGCCCCATGCCAACCCCCCTGGTGAAACCTGCGGCCATGCCATCGCCCTGCTGCTGT GCGAGCTGGCCGTGTACAGCATCCTGTCAGCGGCCAGACCATCAGCTACGGGTGACCCCTGGCATCATCCTGCTGAG CACCCCTGCTGATGAGGGCAGCTCACCTGAGCACCCCTGATCACACACCAGGAGCACCTGTGGCTG CTGCTGCCAGCTGGCCCTGGCCATGATGTGGTTCATCAGCACCCCTGGCGAGACCAACCCGACCC CCTTCGACCTGGCCGAGGGCGAGAGCGAGCTGGTGAGCGGCCATCACATCGAGTACGCCGCCGGCC CCTTCGCCCCGTGTCTCATGGCCAGTGACCCACATCATGATGTAACACCCCTGACCCACCCATC TTCTGGGACCCACTACGAGCCCTGAGGCCGAGCTGACCCACTTCTGACCCACCCATC TGCTGCTGACCGAGCTGTTCTGTCAGTGATGACTGGACAGTTTTTTTTAAATTAACCCAAATGCTCC CGACCTGCTGTGGAAAGAACTTCTGCCCCCTGACCCCTGGCCCTGCTGATGTGGTAGCTGAGCATGCC ATCACCATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCACCCGCCCCCTTCCCTCCG ATCACCATGTTCTCCTCATGGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGGCC CATCGCTGGGCACTGGGACTTGGCAGTACTCTAAACTAGGGGGCTATGGTATGATGCCCTCA CACTCATTCTCAACCCCTGACAAACACATGGCCTACCCCTTCTGTACTATCCTATGGGCATGA TTATGACAAGCTCATCTGCCTACGACAAACAGACCTAAATCGCTCATTCATCAGCCACATCTCAATCAGCC ACATGGCCCTCGTAGAACGCCATTCTCATCCAAACCCCCCTGGAGCTCACCAGGCGAGTCAGTCTCCTCATCAGCC ATGATCGCCACGGGCTTACATCTCATTAACGACTTCTGCTAGCAAACACTAACAGCAGCTCAC AGTGCATCATGATCTCTCTCAAGGACTTCAAACACTCTACTCCCACATAAGCTTTGGGCTTCTA GCAAGCCTCGCTAACCTCGCTTACCCCCCACTATTAACACTGGGAGAACTCTGTGCTAGTAAC CACGTTCTCTGGTCAAATATCCTACTCTACTACAGGACTCAACATGCTAGTCAAGCCCTATACTC CCTCTACATGTTACCCACACACATGGGGCTCACTCACCCACCACATAACACATGAAACCCCTCATT CACACGAGAAAACACCCCTCATGTTCATGCACCTATCCCCATTCTCTCATGCCAACCCGACAT CATTACGGGGTTTCTCTTAAGGACTGGGACCCACGGGCTTCTCCCTCGCATGCCAGGCGA GCATGTTGGTAATTCTGGAACACAAGAAGGAAATTGCTGGTTAGAACAGATTAAACGAATT CGGTGCTAGTGTACTTGACAGTTTTTTTTAAATATTACCAAAATGCTCCCCAAATAAGAA ATGCATCAGCTCAGTGATGAAATACAAAAAAGGAATTATTTCTCTTGTAGGGTCTTTATACATCTCT CCTCCAACCCACCCCTCTATTCTGTTCTCTCACATGGGGTACACATACAGCTCCCTCTT TGGTCTCATCTTACCCACACCGCACAGCAGCAGCTCCACATGCCAGCAGAGTGGCACTTGGTGGCC AGAAAGTGTGAGCCTCATGATCTGCTGTCAGTCTGAGCTCAGGTCCTCAAGGGCTTCTCAAGGGCTCGAG CACCCCTCTGTGACTGAGCCAGGGCTGCATTGGTTCTCCACACATTCTCAACCCATGCTCCTCCTT CACACGAGAAAACACCCCTCATGTTCATGCACCTATCCCCATTCTCTCATGCCAACCCGACAT ATAGCTCTCTAACAAATACCAATAGCTAGGACCCGGCTGCTGCACTGGACTGGGACTGGGATTCCACATG TTTGCCCTGGGAGTCTCAAGCTGGACTGCCAGCCCTGCTCTCCCTCACCCCATGCTGATGAGCA TTCAGAACTCCAAGGAGTCACAGGCATCTTATAGTTCACGTTAACATATAGACACTGTTGGAGCAG TTCTCTCTAAAAGGGTAGGGCTGGACTTAATACCAAGCCGATACCTCTGGCCCCCACCCATTACTGT ACCTCTGGAGTCACTACTGTTGGCTGCACTCTCTGCTACACAGCACGCCACTTCAAGGCTGTATT TGGTGAAGGAAAGTGGAGAGAAGGAGGGTGTGCTGGGCTAACAGGCCACAGAGCTCACATTCTGTGATT GAGAAGGAGTGGAGAGTGGAGAGTAAACACATTTAACAGAGTCTCTCTAACAGAGTCCCATCTGCCCA AAGGTCTGAAGCTTGACAGGATTTGCAAGTTACCTGTTGCTGCCAGGGCTACAGAGTCCCATCTGCCCA TCGATTGGTCGGGGTAGGGAGACTTAAACACATTTAACAGAGTCTCTCTAACAGAGTCCCATCTGCCCA TTAGGTTAGAACATCCAATCACTGTTGCACTTATCTGAAATCTCCCTCTTGCTGCCCCCAGGTAT TTACTGTTGAGAACATGCACTGCAAGGAAATCTCCCTCTTGCTGCCCCCAGGTAT GTAGAAGCTT
43	opt_COX10*- ND4-3'UTR	ATGGCCGCCAGCCCCACACCCCTGAGCAGCGCCCTGCTGACCGGCTGTGGGGCGAGCGTGTG GTACCTGGAGCGCCGCCACCATGCTAAACAACTATGCTCCAAACAAATTATGTTACTACCACTGACATGCC TTCCAAAAAAACACATGATTGGATCACACACACCCAGCCTAATTATTAGCATCATCCTCTACT ATTTTTAACAAATCAACAAACACCTATTAGCTGTTCCCAACCTTTCTCCGACCCCTAAACACC CCCTCCTAATGCTAACTACCTGGCTCCTACCCCTCACATCATGGCAAGCCAACGCCACTTATCCAG TGAACCAACTATCACGACAAAAAAACTCTACCTCTCTATGCTAACTCTCCCTACAAATCTCTTAAATTATGACA TTCACAGGCCACAGAAACTAATCATGTTTATATCTCTCTGCAAACACACACTTATCCCACCTTGTGCTATCA TCACCCGATGGGCAACCCAGGCAACGCCCTGAACGCCAGGCACTATCTCTTCTACACCCCTAGTA GGCTCCCTCCCTACTCATGCCTACTAACACTAACCTGGGCAACAAACTTAATGTTGCTAGCTAACATGCTA CTCACCTCTCACTGCCCAAGAAACTATCAAACCTCTGGGCAACAAACTTAATGTTGCTAGCTAACATGCTA GCTTTTATGGTAAAGATGCTCTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGGCC CATCGCTGGGCACTGGTACTTGGCAGTACTCTAAACTAGGGGGCTATGGTATGATGCCCTCA CACTCATTCTCAACCCCTGACAAACACATGGCCTACCCCTTCTGTACTATCCTATGGGCATGA TTATGACAAGCTCATCTGCCTACGACAAACAGACCTAAATCGCTCATTCATCAGCCACATCTCAATCAGCC ACATGGCCCTCGTAGAACGCCATTCTCATCCAAACCCCCCTGGAGCTCACCAGGCGAGTCAGTCTCCTCATCAGCC ATGATCGCCACGGGCTTACATCTCATTAACGACTTCTGCTAGCAAACACTAACAGCAGCTCAC AGTGCATCATGATCTCTCTCAAGGACTTCAAACACTCTACTCCCACATAAGCTTTGGGCTTCTA GCAAGCCTCGCTAACCTCGCTTACCCCCCACTATTAACACTGGGAGAACTCTGTGCTAGTAAC CACGTTCTCTGGTCAAATATCCTACTCTACTACAGGACTCAACATGCTAGTCAAGCCCTATACTC CCTCTACATGTTACCCACACACATGGGGCTCACTCACCCACCACATAACACATGAAACCCCTCATT CACACGAGAAAACACCCCTCATGTTCATGCACCTATCCCCATTCTCTCATGCCAACCCGACAT CATTACGGGGTTTCTCTTAAGGACTGGGACCCACGGGCTTCTCCCTCGCATGCCAGGCGA GCATGTTGGTAATTCTGGAACACAAGAAGGAAATTGCTGGTTAGAACAGATTAAACGAATT CGGTGCTAGTGTACTTGACAGTTTTTTTTAAATATTACCAAAATGCTCCCCAAATAAGAA ATGCATCAGCTCAGTGATGAAATACAAAAAAGGAATTATTTCTCTTGTAGGGTCTTTATACATCTCT CCTCCAACCCACCCCTCTATTCTGTTCTCTCACATGGGGTACACATACAGCTCCCTCTT TGGTCTCATCTTACCCACACCGCACAGCAGCAGCTCCACATGCCAGCAGAGTGGCACTTGGTGGCC AGAAAGTGTGAGCCTCATGATCTGCTGTCAGTCTGAGCTCAGGTCCTCAAGGGCTTCTCAAGGGCTCGAG CACCCCTCTGTGACTGAGCCAGGGCTGCATTGGTTCTCCACACATTCTCAACCCATGCTCCTCCTT CACACGAGAAAACACCCCTCATGTTCATGCACCTATCCCCATTCTCTCATGCCAACCCGACAT ATAGCTCTCTAACAAATACCAATAGCTAGGACCCGGCTGCTGCACTGGACTGGGACTGGGATTCCACATG TTTGCCCTGGGAGTCTCAAGCTGGACTGCCAGCCCTGCTCTCCCTCACCCCATGCTGATGAGCA TTCAGAACTCCAAGGAGTCACAGGCATCTTATAGTTCACGTTAACATATAGACACTGTTGGAGCAG TTCTCTCTAAAAGGGTAGGGCTGGACTTAATACCAAGCCGATACCTCTGGCCCCCACCCATTACTGT ACCTCTGGAGTCACTACTGTTGGCTGCACTCTCTGCTACACAGCACGCCACTTCAAGGCTGTATT TGGTGAAGGAAAGTGGAGAGAAGGAGGGTGTGCTGGGCTAACAGGCCACAGAGCTCACATTCTGTGATT GAGAAGGAGTGGAGAGTGGAGAGTAAACACATTTAACAGAGTCTCTCTAACAGAGTCCCATCTGCCCA AAGGTCTGAAGCTTGACAGGATTTGCAAGTTACCTGTTGCTGCCAGGGCTACAGAGTCCCATCTGCCCA TCGATTGGTCGGGGTAGGGAGACTTAAACACATTTAACAGAGTCTCTCTAACAGAGTCCCATCTGCCCA TTAGGTTAGAACATCCAATCACTGTTGCACTTATCTGAAATCTCCCTCTTGCTGCCCCCAGGTAT TTACTGTTGAGAACATGCACTGCAAGGAAATCTCCCTCTTGCTGAAAAAGCTTCTACAAACTGTTACAGCCTTACATTT GTAGAAGCTT

44	opt_COX10*-ND4-3'UTR*	ATGGCCGCCAGCCCCACACCCGTAGCAGCCGCTGCTGACCGGCTGCGTGGCGGCAGCGTGTG GTACCTGGAGGCCGACCATGCTAAAACATACTGGATCAACACAACCACGCCAATTCTCCGACCCCTACT TTTCCAAAAAACACATGATTTGGATCAACACAACCACGCCAATTCTCCGACCCCTACT ATTTTTAACCAAATCAACAACAACTATTAAGCTGTTCCCAACCTTTCTCCGACCCCTACT CAACACAACCCGACAAACATGGCTTACCCCTTCTTGTACTATCCCCTAAACACC CCCCTCCTAATGCTAATCACCTGGCTCCACCCCTCACAAATCATGGCAAGCCAACGCCACTTATCCAG TGAACCAACTATCACGAAAAAAACTCTACCTCTCTATGCTAATCTCCCTACAAATCTCCCTAAATTATGACA TTCAAGCCAGACAATACTATGTTATCTCTTGAAACCAACTATCCCCACCTTGCTATCA TCACCCGATGGGGCAACCAGCCAGAACGCCAAGCCTGAAACGCCAGGACATACTTCTCTTACACCCCTAGTA GGCTCCCTCCCTACTCATCGACTAATTACACTCACAAACACCCTAGGCTACTAAACATTCTACTA CTCACTCTACTGCCAACAGAAACTATCAAACCTGGGCAACAACTTAATGTGGTAGCTTACACAATG GCTTTATGGTAAAGATGCCCTTACGGACTCCACTTATGGCTCCCTAAAGCCATGTCGAAGCCCC CATCGCTGGTCAATGGTACTTGGCCAGTCTCTAAACTAGGCCGCTATGGTATGATGCCCTCA CACTCATTCTCAACCCCCGACAAACATGGCTTACCCCTTCTTGTACTATCCCCTATGGGCATGA TTATGACAAGCTCATCTGCCAACGACAAACAGACCTAAATCGCTCATCTTCAATCAGCC ACATGGCCCTCGTAGTAAACAGCATTCTCATCAAACCCCCCTGGAGCTCACGGCGCAGTCATTCTC ATGATGCCAACGGGTTACATCCTCATTACTATTCTGCTCTAGCAAACCTAAACACTACGAACGCACTCAC AGTCGCATCATGATCCTCTCAAGGACTCTAAACTCTACTCCACTAATGGCTTTGGTGGCTCTA GCAAGCCCTGCTAACCTGCCAACCCCCACTATTAACACTACTGGAGAACTCTCTGTGCTAGTAAC CACGTTCTCTGGTAAATCACTCTCTACTACAGGACTCAACATGCTAGTCAGCAGGCCCTACT CCTCTACATGTTTACCAACACATGGGCTCACTACCCACCATTCACAAACATGAAACCCCTATT CACAGAGAAAACACCCCTCATGTTCATGCACCTATCCCCATTCTCTCTATCCCCTAACCCCCGACAT CATTACGGGTTTCTCTTAAGAGCACTGGGACGCCAACGGCCCTTCCCTCCGCTGCCAGGG GCATGTTGGTAAATTCTGGAACACAAGAGAAAATTGCTGGGTTAGAACAGATTATAACGAATT CGGTGCTAGTGTACTTGACAGTTTTTTAAATATTACCAAAATGCTCCCCAAATAAGAA ATGCATCAGCTCAGTCAAGTAAACAAAAAGGAATTATTTCTGAGGGTCTTTATACATCT CCTCCAAACCCACCCCTTATCTGTTCTCCATACGGGGTACACACAGCTTCTCT TGGTCCATCTTACCCACACCCAGCACACTGGCAGAGTGGCAGTGGGAG AGAAAGTGTGAGCCTCATGATCTGCTGTAGTTCTGAGCTCAGGTCCTCAAAGGCCCGAG CACCCCTCCTGTACTGAGGCCAGGGCCTGATTGGGTTTCCCCACACATTCTCAACC ATAGCTCTTAACAATACCAATAGCTAGGACCCGGCTGCTGTGACTGGACTGGGACTGGGATTCCACATG TTGCTGGGAGTCTCAAGCTGACTGCCA
45	opt_COX10*-opt_ND4-3'UTR	ATGGCCGCCAGCCCCACACCCGTAGCAGCCGCTGCTGACCGGCTGCGTGGCGGCAGCGTGTG GTACCTGGAGGCCGACCATGCTGAAGCTGATCTGCTGCCACCATGCTGCTGCCCTCTGACCTGG CTGAGCAAGAAAACACATGATCTGATCAACACACCACGCCACAGCTGATCATCAGCATCTCCCT GCTGTTCTCAACCAGATCAACACAAACCTGTTCTGCTGAGCCCCCACCTCTGAGCAGCAGCAGCCCTCTGA CAACACCTCTGCTGATGCTGACCCACCTGGCTGCTGCCCTCACAAATCATGGCTCTGAGAGACACCTG AGCAGCGAGCCCTGAGCCGGAAAGAAACTGTACCTGAGCATGCTGATCTCCCTGAGATCTCT TCATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTTTGAGACAACGCTGATCCCCACAC TGGCCATCATCACCAAGATGGGCAACCCAGCCTGAGAGACTGAACGCCGGCACCTACTTCTGTTCTA CACCCCTGCTGGGAGGGCTGCCACTGCTGATTGCTGATCATACCCACACCCCTGGCTCCCTG AACATCCTGCTGCTGACACTGACAGCCCAAGAGACTGAGCAACAGCTGGGCAACAAATCTGATGTTGGC TGGCCTACACAATGGGCTTACGGTCAAGATGCCCCTGTAACGGGCTGACCTGTTGCTGCTGCTGCTGCTAAAGC TCATGTTGGAAAGCCCTATGCCGGCTCATGGTGTGGCTGAGTGTGCTGAAACTCGGGGGCTAC GGCATGATGCGGCTGACCCCTGATTGTAATCCCCTGACCAAGCACATGGCCTATCCATTCTGGTCT GAGCCTGTGGGGCATGATTATGACCAAGCAGCAGCATCTGCTGCGGCCAGACCGATCTGAAAGTCCCTGATC GCCTACAGCTCCATCAGCCACATGGGCTGGTGGTACCCGCACTCTGATTGCTGACCCCTGGAGCT TTACAGGGGGTGTGCTCTGATGTTGGGCTGCTGGCTCTCTGGCCAATCTGGCACTGCTCTTACCATCAATCTGCT GGCGAGCTGAGCGTGTGGTACCCGCACTTACAGCTGGTCAACATACCCCTGCTGCTCACCCGCTG AACATGCTGGTACAGCCCTGACTCCCTGATGTTGACCAACACAGTGGGAGCCGTGACACA CCACATCAACAAATATGAAAGCCGACTCTACCCGGAGAACCCCTGATGTTCTGACATCTGAGCCCC TTCTGCTGTGCTGCCATCTGATATCATACCCGCTTCCAGCTGAGAGCCTGACATCTGAGGCC CGCCCACTTCTCCCGCTGCCAGGGAGCATGTTGTTGTAATTCTGAAACACAAGAGAAAATTGCT GGGTTAGAACAGATTATAACGAATTGGTGTGCTGAGTGTACTTGACAGTTTTTTAAAT ATTACCCAAATGCTCCCCAAATAAGAAATGATCAGCTCAGTCAGTCAGTGAATACAAAAAGGAATTATTT TCCCTTGGGGCTTTATACATCTCTCTCAACCCACCCCTTATTCTGTTCTCTCCATCATG GGGGTACACATACACAGCTTCTCTTGGTCCATCTTACCAACACAGCAGCAGCTCCACAT GCCCAAGCAGACTGGCACTTGGTGGCCAGAAAGTGTGAGGCCCTCATGATCTGCTGTGAGTCTG AGCTCAGGTOCCCTCAAGGGCTCCGGAGCACCCCTTCTCTGACTGAGGCCAGGGCTGCTG GTTTCTCCACCCACACATTCTCAACCATAGTCCTCTAACAATACCAATAGCTAGGACCCGGCTGCT GTGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGACTGCCAGCCCTGTC CTCCCTCACCCCTTCTGCTGATGAGCATTCTGAGACTCAAGGAGTCACAGGACATCTTATAGTCAC GTTAACATATAGACACTGTTGGAAGCAGTCTTCTAAAGGGTAGCCCTGGACTTAATACCAAGCCGG ATACCTCTGGCCCCACCCCTTACACTGTACCTCTGGAGTCACACTGTGGGTGCCACTCTCTGCTA CACAGCACGGCTTCAAGGGCTGATTGAGAAGGGAGTAGGAAGAAGGGGTGTGCTGGGCTAACCC AGCCCAAGAGACTCACATTCTGCTCCCTGGGAGAAAAATACATGTCATCTGATATCTCTGAAATT AGAAATTAGCCTCCACATGTCATGGCTTAAAGGCCAGAGCAGGGTTCTGGGAAATTGCAAGTT ACCTGTTGCCAGGTGTGGCTGGGAGTACGGTACCTGAGCTTGTGCTGAGCTTTAGTCTTGTGCTCC CACGGGCTACAGAGTCCCATCTGCCAACAGGTCTTGAAGCTGACAGGATGTTTCGATTACTCAGT CTCCCAAGGGCACTACTGGTCCGTAGGATCCATTGGTGGGGTAGGAGAGTTAACACATTAAACA GAGTTCTCTCAAAATGTCATAAGGGGATTGAGGTAGATAACATCCAACTACTGTTGCACTTATCTGA AATCTTCCCTCTGGTGGCCCCAGGTATTACTGTTGAGAACATTGCACTAGGAATGTCAGGAAAAG CTTCTACAACATTGTTACAGCCTCAGCTTCAACATTGAGAGCTT

46	opt_COX10*- opt_Nd4*- 3'UTR*	ATGGCCGCCAGCCCCACACCCGTAGCAGCCGCTGCTGACCGGCTGCGTGGCGGGCAGCGTGTG GTACCTGGAGGCCGACCATGTAAGCTGATCGTGCACCATCATGCTGCTGCCCTGACCTGG CTGAGCAAGAAACACATGATCTGGATCAACACCACGCCACAGCTGATCATCAGCATCATCCCT GCTGTTCTCAACCAGATCAACAACACCTGTTAGCTGAGCTGAGCCCCCACCTCAGCAGCAGC CAACACCTCTGCTGATGCTGACCCACTGGCTGCTGCCCTCACAACTATGGCCTCTCAGAGACAC AGCAGCGAGCCCCCTGAGCCGAGAAGAAACTGTACCTGAGCATGCTGATCTCCCTGAGATCTCT TCATGACCTTCACCGCCACCGAGCTGATCATGTTCACATTTTCAGAGACAACGCTGATCCCAC TGGCCATCATCACCAAGATGGGGCAACCAGCTGAGAGACTGAACGCCGGCACCTACTTCTGTT CACCCCTGCGGGCAGCCTGCCACTGCTGATTGCCCTGATCTACACCCACAACACCCCTGGGCT AACATCCTGCTGACACTGACAGCCAAGAGCTGAGCAACAGCTGGGCAACAATCTGATGTTG TGGCCTACAGCTCCATCAGCCACATGCCCTGGTGGTCAAATATCACCGCTGCTGCTCACCGGCT AACATGCTGGTACAGCCCTGACTCCCTGATCTGTTACATGTTCACCCACACAGGGGAGGCTGAC CCACATCAACAATATGAAGGCCAGCTTACCCCGAGAACACCCCTGATGTTCATGCACTGAG TTCTGCTGCTGTCCTGAATCTGATATCATCACCGGCTCTCCAGCTGAGAGCACTGGGACGCC CGCCCCCTTCCCTCCGCTGCCAGCGAGCATGTTGTGGAATTCTGGAACACAAGAGAAATTG GGGTTAGAACAGATTATAACGAATTGGTGCTCAGTGATCACTTGACAGTTTTTTAAAT ATTACCCAAAATGCTCCCAAATAAGAAATGATCAGCTGAGCTGTAATACAAAAAGGAATTATTT TCCCTTGAGGGCTTTTACATCTCTCCAAACCCACCCCTTACCTGTTCTCCACATG GGGGTACACATACACGCTTCTTTGGTTCATCTTACCCACACGCAACTCCACATG GCCCAAGCAGAGTGGCACTTGGTGGCCAGAACAGTGTGAGCCTCATGATCTGCTGAGTCTG AGCTCAGGCTCCCTAAAGGCCCTGGAGCACCCCTTCTGTACTGAGCCAGGGCTGCTGATTTG GTTTCCCCACACCACTCAACCATACTGCTCTAACAATACCAATAGCTAGGACCCGGCTGCT GTGCACTGGGACTGGGATTCCACATGTTGCCCTGGAGTCTCAAGCTGGACTGCA
47	opt_COX10*- opt_Nd4*- 3'UTR	ATGGCCGCCAGCCCCACACCCGTAGCAGCCGCTGCTGACCGGCTGCGTGGCGGGCAGCGTGTG GTACCTGGAGGCCGACCATGTAAGCTGATCGTGCACCATCATGCTGCTGCCCTGACCTGG CTGAGCAAGAAAGCACATGATCTGGATCAACACCACACCCACAGCTGATCATCAGCATCATCCCT GCTGTTCTCAACCAGATCAACAACACCTGTTAGCTGAGCTGAGCCCCCACCTCAGCAGCAGC CAACCCCTGCTGATGCTGACCCACTGGCTGCTGCCCTGACCATCATGGCAGCCAGCAGC GAGCAGCGAGCCCCCTGAGCCGCAAGAAGCTGACCTGAGCATGCTGATCAGCCTGAGATCAGC ATCATGACCTTCACCGCCACCGAGCTGATCATGTTACATCTCTCGAGACCACCCCTGATCC CCTGGCCATCATACCCCGCTGGGCAACCCAGCCGAGCCCTGAGACGCCGACCCACTTCTGTT TACACCCCTGGGGCAGCCTGCCCTGCTGATCGCCCTGATCTACACCCACAACACCCCTGGGAGCC TGAACATCTGCTGCTGACCCCTGACCGCCAGGGAGCTGAGCAACAGCTGGGCAACACG GCTGGCCTACACCATGGCTTACGGTGAAGATGCCCTGATCGGCCCTGACCTGTTGGCTGCC GCCCACGTGGAGGGCCCCCATGCCGGCAGCATGGTCTGGCCGCGGTGCTGCTGAGCTGGCG CTACGGCATGATGCCCTGACCCCTGATCTGTAACCCCTGACCAAGACATGGCTTACCCCT GTGCTGAGCCTGTTGGGAGCTGATCATGACCGAGCATCTGCCCTGCCAGACCGACCTGAAGAGC CTGATGCCCTACAGCAGCATGCCGACATGCCCTGGGGTGTGACCCCATCTGATCTGAGAC GGAGCTTACCCGGCGGTGATCCTGATGATGCCCTGGGGTGTGACCCCATCTGATCTGAGAC GGCCAAACGCAACTACGAGCGACCCACAGCGCATCATGATCTGAGCCAGGGCTGAGAC GCTGCCCTGATGGCTTCTGGTGGCTGCTGGCCAGCCTGACCTGGAGCAACATCAC CTGCTGAGACCCCCCTGGCCACCCATCTGATGATGCCCTGGGGTGTGACCCCAT CAACCTGCTGGGAGCTGAGCGTGTACAGCCCTGACAGCTGCTACATGTTACCCAC ACCGGCTGAACTGCTGGTGTACAGCTGACCCACACAGGGCTGCTGAGAC GCCTGACCCACACATCAACAACATGAAGGCCAGCTCACCCCGAGAACACCCCTGATGTT CTGAC CTGAGGCCCTGCTGCTGACCCACACAGGGCTGCTGAGAC GGGACGCCACCGCCCTTCCCTGCCAGGGAGCATGTTGGTGAATTCTGGAAACACAAGA AGAGAAATTGCTGGGTTAGAACAGATTATAACGAATTGGTGTACTGATCACTTGACAG TTTTTTTTAAATATTACCCAAAATGCTCCCAAATAAGAAATGATCAGCTGAGCTGAGTGA AAACAAAGAGAAATTATTTCCCTTGAGGGTCTTTTACATCTCTCCAAACCCACCC TCCCTCTCACATGGGGTACACATACAGCTTCTCTTGGTCCATCTTACCCACAC CACACCTCCACATGCCAGAGCTGGCAGGGCTGACTGGTGGCCAGAGAACAG GTTAGTTCTGAGCTCAGGCTCCCTCAAGGGCTCGGAGCACCCCTTCTGTGACTGAG CCTGCATTTTGGTTCTCCACACCATCTCAACCATACTGCTTCTAACAATACCA GACCCGGCTGCTGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCT CCAGCCCCGTGCTGCCCTCCTTACCCCAATTGCGTATGAGCATTT CTTTATAGTTACGTTACAGACTGTTGGAGCAGTCTCTTAAAGGGTAG AATACCAGCCGGATAACCTCTGGCCCCACCCATTACTGACCTCTGGAGTCA ACTCTCTGCTACACAGCAGGGCTTGGGCTGATTTCAAGGGCTGAT CTGGGCTAACCCAGCCACAGAGCTCACATTCTGTTCCCTGGGAGTCT TCTCCTGAATTGAGAACATTAGCCTCACATGTCATGGCTTAAAGAG GAGAGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG GTTTGTGCTCCACGGGTCTACAGAGTCCCATCTGCCAAAGGTCT GATTACTCAGTCTCCAGGGCACTACTGGTCCGTAGGATTGAGCTGG ACATTAAACAGAGTCTCTCAAATAAGGGATTGAGTAGATAAC ACTTATCTGAAATCTTCCCTTGGCTGCCCTGGAGGTTACTG TGGAAAAAGCTTCTACAACCTGTTACAGCCTCACATTGAGCTT

48	opt_COX10*-ND4*-3'UTR*	ATGGCCGCCAGCCCCACACCCGTAGCAGCCGCTGCTGACCGGCTGCGTGGCGGGCAGCGTGTG GTACCTGGAGCGCCGCACCATGATGAGCTGATCGTGCCTGACCATCATGCTGCTGCCCTGACCTGG CTGAGCAAGAAGCACATGATCTGGATCAACACCACCCACAGCCTGATCATCAGCATCATCCCCCT GCTGTTCTCAACCAGATCAACAAACCTGTTAGCTGAGCTGAGCCACCTTCAGCAGCGACCCCCCTGA CCACCCCCCTGCTGATGCTGACCAACCTGGCTGCTGCCCTGACCATCATGGCCAGCCAGGCCACCT GAGCAGCGAGCCCCCTGAGCCGCAAGAACGCTGACCTGAGCATGCTGATCACGCCAGCATAGCCTG ATCATGACCTTCACCGCCACCGAGCTGATCATGTTCTACATCTTCTGAGAACCCCTGATCCCCAC CCTGGCCATCATCACCCGCTGGGCAACCAGCCCAGCGCCTGAAACGCCGGCACCTACTTCTGTT TACACCCCTGGTGGGAGCCGCTGCCCTGCTGATGCCCTGATCTACACCCACAACACCCCTGGCAGCC TGAACATCCTGCTGACCCGTACCGGCCAGGAGCTGAGCAACAGCTGGCCAACAACCTGATGTTG GCTGGCTACACCATGGCCTCATGGTGAAGATGCCCTGACGCCCTGACCTGTTGGCTGCCAAG GCCCAACAGCAACTACGAGCGCACCCACAGCGCAGCATGATCTGAGCCAGGGCCTGAGCACCC GCTGCCCTGATGGCCTCTGGGGCTGCTGGCCAGCCTGGCAACCTGGCCCTGCCACCCACCAT CAACCTGCTGGGGAGCTGAGCGTGGCTGACCCCTGACCTGAGGACACATCACCCCTGCTGCTG ACCGGCTGACATGCTGGTGAACGCCCTGATGCCCTGACCCCTGATCTGACCTGACCCAGTGGGCA GCCCTGACCCACCATCAACACATGAAGGCCAGCTCACCCGCGAGAACACCTGATGTTCATGCA CTGAGCCCCATCTGCTGAGCCTGAAACCCGACATCATCACCCGCTTCAGCAGCTAAGAGCACT GGGAGCACCACCGCCCTTCCCTCCGCTGCCAGGGAGCATGTTGTGTAATTCTGGAACACAAGA AGAGAAATTGCTGGTTTAGAACAGATTATAAACGAATTGGTGCTAGTGTACACTGACAGTTTT TTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCTACAGCTAGTGTAACTACAAAA AAGGAATTATTTTCCCTTGAGGGTTTTATACATCTCTCCAAACCCACCCCTATTCTGTTCT TCCCTCTCATGGGGTACACATACAGCTCTCTTTGGTCCATCTTACACACACACAG CACACTCCACATGCCAGCAGGGTCACTGGTGGCCAGAAAGTGTGAGCCTCATGATGCTGTC TGTAGTTCTGTGAGCCTAGGCCCCCAAAGGCTCGGAGCACCCCTTCTGTGACTGAGCCAGGG CCTGCATTGGTTTCCCCACACATTCTCAACCATAGTCTCTAACAATACCAATAGCTAG GACCCGGCTGCTGCACTGGACTGGGATTCCACATGTTGCTGGAGTCTAAGGCT CCA
49	opt_COX10*-ND6-3'UTR	ATGGCCGCCAGCCCCACACCCGTAGCAGCCGCTGCTGACCGGCTGCGTGGCGGGCAGCGTGTG GTACCTGGAGCGCCGCACCATGATGATGCTTGTCTGTTGAGTGTGGTTAGTAATGGGTTG TGGGGTTTCTCTAACGCTCTCTCTATTATGGGGTTAGTATTGATGTTAGCGGTGTGGCTGGGT GTGTTATTATTCTGAATTGGGGAGGTTATATGGGTTAATGGTTTTTAATTATTAGGGGGAAAT GATGGTTGCTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTGAGGCAATGGGTTG GTTGAGGTCTGGTGAAGTGTGTTAGCGATGGAGGATTGGTGTGGTGGGAAAG AGTATGATGGGGTGGGGTGGGTTAGTAACTTAAATAGTGTAGGAAGCTGGATGTTATGAAGGAGAG GGGTGAGGTCTGGTGAAGTGTGTTAGGGTTAGCGATGGAGGATTGGTGTGGTGGGAAAG TAGTAGTTACTGGTGGACATGGTGTGTTAGGTTATGGTGTGTTAGGTTAGGTTAGGTTAG AGCACTGGGAGCACCACCGCCCTTCCCTCCGCTGCCAGGGAGCATGTTGTGTTAATTCTGGAAC ACAAGAAGAGAAATTGCTGGTTAGAACAGATTATAAACGAATTGGTGCTAGTGTACACTGACA GTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCTACAGCTAGTGTAA CAAAAAGGAATTATTTTCCCTTGAGGGTTTTATACATCTCTCCAAACCCACCCCTATTCTG TTTCTCTCATGGGGTACACATACAGCTCTCTTTGGTCCATCTTACACACACACC ACACGACACACTCCACATGCCAGCAGGGTGGCACTGGGACTGGGATTCCACATGTTGCTTGGGAGTCT CTGTCTGTAGTTCTGTGAGCTAGGTCTCTCAAAGGCCCTGGAGCACCCCTCTCTGACTGAGCC AGGGCCTGCATTGGTTTCCACCCACACATTCTCAACCATAGTCTCTCTAACAATACCAATAG CTAGGACCCGGCTGCTGCACTGGGACTGGGATTCCACATGTTGCTTGGGAGTCTAAGGCT ACTGCCAGCCCTGCTCTCCCTCACCCACATTGCGTATGAGCATTCTAGCAACTCAAGGAGCACAG GCATCTTATAGTCACGTTAACATAGACACTGTTGGAGCAGTCTCTCTAAAGGGTAGCCCTGG ACTTAATACAGCGGAGTACCTCTGGCCCCACCCATTACTGTACCTCTGGAGTCACTACTGTGGG GCCACCTCTCTGCTCACACAGCACGGCTTTCTAAGGCTGTTAGGATGATTGAGAAGGGAGTTAG GTGTGCTGGGCTAACAGCCCACAGAGCTCACATTCTGCTCCCTGGGTGAAAATACATGTCATCC TGATATCTCTGAATTAGAACATTAGCTCCACATGTGCAATGGCTTAAGAGCCAGAACAGGGTTCT GGGAATTGGCAAGTACCTGTGCCAGGTGTGGTCTGGTTACCAAATACGGTTACCTGCAGCTTT TAGTCTCTTGCTCCACGGGCTACAGAGTCCCATCTGCCCAAAGGTCTGAGCTTGAACAGGGATG TTTCGATTACTGAGTCTCCCAGGGCACTACTGGTCCGTTAGGATTGATTGGTCCGGGGTAGGGAGTT AAACAACTTAAACAGAGTTCTCTAAAGGTTCTAACAGGAGTTGAGGAGATAACATCCAATCACT GTTGCACCTATCTGAATTCTGAAATTCTCCCTTGGCTGCCCTGGAGTATTACTGTGGAGAACATTGCA ATTGTCGGAAAAGCTTCTACAAACTGTTACAGCTTCACTTGTAGAAGCTTT
50	opt_COX10*-ND6-3'UTR*	ATGGCCGCCAGCCCCACACCCGTAGCAGCCGCTGCTGACCGGCTGCGTGGCGGGCAGCGTGTG GTACCTGGAGCGCCGCACCATGATGATGCTTGTCTGTTGAGTGTGGTTAGTAATGGGTTG TGGGGTTTCTCTAACGCTCTCTCTATTATGGGGTTAGTATTGATGTTAGCGGTGTGGCTGGGT GTGTTATTATTCTGAATTGGGGAGGTTATATGGGTTAATGGTTTTTAATTATTAGGGGGAAAT GATGGGGTCTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTGAGGCAATGGGGTCA GTTGAGGTCTGGTGAAGTGTGTTAGGGTTAGCGATGGAGGATTGGTGTGGTGGGAAAG AGTATGATGGGGTGGGGTGGGTTAGTAACTTAAATAGTGTAGGAAGCTGGATGTTATGAAGGAGAG GGGTGAGGTCTGGTGAAGTGTGTTAGGGTTAGCGATGGAGGATTGGTGTGGTGGGAAAG TAGTAGTTACTGGTGGACATTGTTGGTGTATATATTGTAATTGAGATTGCTGGGGAGTTAGG AGCACTGGGAGCACCACGCCCTTCCCTCCGCTGCCAGGGAGCATGTTGTGGTGGTAATTCTGGAAC ACAAGAAGAGAAATTGCTGGTTAGAACAGATTATAAACGAATTGGTGCTAGTGTACACTGACA GTTTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGCTACAGCTAGTGTAA

53	opt_COX10*-ND1-3'UTR	ATGGCCGCCAGCCCCCACACCTGAGCAGCCGCCGTGACCGGCTGCCTGGCGGAGCGTGTG GTACCTGGAGCGCCGACCATGCCAACCTCTACTCCCTCATTTGACCCATTCTAATCGCAATGGC ATTCATAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCCAAAGGCCAACGTTGAG GCCCTACGGCTACTACAACCCCTCGCTACGCCATAAAACTCTCACCAAAAGAGGCCCTAAACCCGC CACATCTACCATCACCCCTACATCACCGCCCCGACCTAGGCTCTCACCATCGCTTCTACTATGGAC CCCCCTCCCCATGCCAACCCCCCTGGCTAACCTCAACCTAGGCTCTATTCTAGGCCACCTCTA GCCTAGCCGTTACTCAATCTCTGGTAGGGCTCAACACTCAAACACTACGCCCTGATCGCGCA CTGCGAGCAGTAGCCAAACAATCTCATATGAAGTCACCCCTAGCCATCATTCTACTATCAACATTACTA ATGAGTGGCTCTTAACTCTCCACCCCTATCACAAACACAAGAACACCTCTGGTTACTCTGCCATCA TGGCCCTGGCCATGATGTGGTTATCTCCACACTAGCAGAGGCCAACCGAACCCCTTCGCCCTATT CGAAGGGGAGTCCGAACTAGTCTCAGGCTCAACATCGAAATGCCGAGGCCAACCGAACCCCTTCGCCCTATT TTCATGGCGAAACACAACTATTATGATGAACACCCCTACCAACTACAATCTCTAGGAACAACA TATGACGCACTCTCCCTGAACTCTACACAAACATATTGTCACCAAGACCCCTACTCTAACCCTCCCTG TTCTTATGGATTGAAACAGCATAACCCCCGATTCCGCTACGCCATTACAATCTCAGCATTCCC CCTCAAAACCTAAAGAGCACTGGGACGCCACCGCCCCCTTCCCTCCGCTGCCAGGCGAGCATGGTG GTAATTCTGGAACACAAGAGAAAATTGCTGGGTTAGAACAGATTAAACGAATTGGTGCTCAG TGATCACTTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCAAAATAAGAAATGCATCAGCT CAGTCAGTGAATACAAAAAAAGGAATTTTTCCCTTGAGGGTCTTTTATACATCTCTCCAAACCC ACCCCTCTATTCTGTTCTCCCTCACATGGGGTACACATACAGCTTCTCTGGTCCATCC TTACCAACACCCACAGCACACTCCACATGCCAGCAGAGTGGCAGTGGCTGGCCAGAAAGTGTGA GCCTCATGATCTGCTGTGAGGCTCTGAGGCTCACAGGCCCTGGTGCCAGAACCCCTCC TTGTGACTGAGCCAGGGCCTGCACTTTGGTTTCCCCACACATTCTCAACCCATAGCTCTCTA ACAATACCAATAGCTAGGACCCGGCTGCTGCACTGGGACTGGGAGTCCACATGTTGCTTGGG AGTCTCAAGCTGGACTGCA
54	opt_COX10*-ND1-3'UTR*	ATGGCCGCCAGCCCCCACACCTGAGCAGCCGCCGTGACCGGCTGCCTGGCGGAGCGTGTG GTACCTGGAGCGCCGACCATGCCAACCTCTACTCCCTCATTTGACCCATTCTAATCGCAATGGC ATTCATAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCCAAAGGCCAACGTTGAG GCCCTACGGCTACTACAACCCCTCGCTACGCCATAAAACTCTCACCAAAAGAGGCCCTAAACCCGC CACATCTACCATCACCCCTACATCACCGCCCCGACCTAGGCTCTCACCATCGCTTCTACTATGGAC CCCCCTCCCCATGCCAACCCCCCTGGCTAACCTCAACCTAGGCTCTATTCTAGGCCACCTCTA GCCTAGCCGTTACTCAATCTCTGGTAGGGCTCAACACTCAAACACTACGCCCTGATCGCGCA CTGCGAGCAGTAGCCAAACAATCTCATATGAAGTCACCCCTAGCCATCATTCTACTATCAACATTACTA ATGAGTGGCTCTTAACTCTCCACCCCTATCACAAACACAAGAACACCTCTGGTTACTCTGCCATCA TGGCCCTGGCCATGATGTGGTTATCTCCACACTAGCAGAGGCCAACCGAACCCCTTCGCCCTATT CGAAGGGGAGTCCGAACTAGTCTCAGGCTCAACATCGAAATGCCGAGGCCAACCGAACCCCTTCGCCCTATT TTCATGGCGAAACACAACTATTATGATGAACACCCCTACCAACTACAATCTCTAGGAACAACA TATGACGCACTCTCCCTGAACTCTACACAAACATATTGTCACCAAGACCCCTACTCTAACCCTCCCTG TTCTTATGGATTGAAACAGCATAACCCCCGATTCCGCTACGCCATTACAATCTCAGCATTCCC CCTCAAAACCTAAAGAGCACTGGGACGCCACCGCCCCCTTCCCTCCGCTGCCAGGCGAGCATGGTG GTAATTCTGGAACACAAGAGAAAATTGCTGGGTTAGAACAGATTAAACGAATTGGTGCTCAG TGATCACTTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCAAAATAAGAAATGCATCAGCT CAGTCAGTGAATACAAAAAAAGGAATTTTTCCCTTGAGGGTCTTTTATACATCTCTCCAAACCC ACCCCTCTATTCTGTTCTCCCTCACATGGGGTACACATACAGCTTCTCTGGTCCATCC TTACCAACACCCACAGCACACTCCACATGCCAGCAGAGTGGCAGTGGCTGGCCAGAAAGTGTGA GCCTCATGATCTGCTGTGAGGCTCACAGGCCCTGGTGCCAGAACCCCTCC TTGTGACTGAGCCAGGGCCTGCACTTTGGTTTCCCCACACATTCTCAACCCATAGCTCTCTA ACAATACCAATAGCTAGGACCCGGCTGCTGCACTGGGACTGGGAGTCCACATGTTGCTTGGG AGTCTCAAGCTGGACTGCA

55	opt_COX10*- opt_ND1- 3'UTR	<p>ATGGCCGCCAGCCCCACACCCCTGAGCAGCGCCTGCTGACC GGCTGCGTGGCGGGCAGCGTGTG GTACCTGGAGCGCCGCACCATGGCCAACCTGCTGCTGATCGTGCCTGATCGCCATGGCC TTCTGATGCTGACCGAGCGCAAGATCCTGGCTACATGCAGCTGCCAAGGGCCCAACGTTG GGCCCTACGGCCTGCTGCAGCCTCGCCGACGCCATCAAGCTGTTACCAAGGAGGCCCTGAAG CCGCCACCGACCATCACCCCTGACATCACCGCCCCACCCCTGGCCCTGACCATGCCCTGCTGC TGTGGACCCCCCTGCCCATGCCAACCCCCCTGGTGAACCTGAACCTGGGCTGCTGTTCATCTGGC CACAGCAGCCTGGCGTGTACAGCATCTGTGGAGCGGCTGGCCAGCAACAGCAACTACGCCCT GATCGGCGCCCTGCGCCGCTGGCCAGACCATCAGCTACGAGGTGACCCCTGCCATCATCTGCT GAGCACCCCTGCTGATGAGCGGAGCTGGTGAACCTGAGCCCTGATACCACCCAGGAGCACCTGTT CTGCTGCTGCCAGCTGGCCAGGGCGAGAGCGAGCTGGTGAACCTGGGCTTCAACATCGAGTACGCCCG GCCCTTCTGCCCTGTTCTCATGGCCAGTACACCAACATCATGATGAACACCCCTGACCCAC ATCTTCTGGGACCCACTACGACGCCCTGAGCCCCAGCTGATACACCACCTACTCTGTGACCAAGA CCCTGCTGCTGACCGCTGTTCTGTGGATCCGACCCCTAACCCCGCTTCCGCTACGAC GATGCACCTGCTGAGAAGAACTTCTGCCCTGACCCCTGGCCCTGCTGATGTGGTACGTGAGCATG CCCACATCACCATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCACCGCCCTTCC CGCTGCAGCGAGCATGTTGGTAATTCTGAACACAAGAAGAGAAATTGCTGGGTTAGAACAA GATTATAAACGAATTGGTGCTAGTGTACCTGACGTTTTTTAAATATTACCCAAAATGC TCCCCAAATAAGAAATGCACTCAGCTCAGTCAGTGAATACAAAAAGGAATTATTTTCCCTTGAGGGT CTTTTATACATCTCTCCAAACCCACCCCTTATTCTGTTCTCTCTCATGATGGGGTACACATAC ACAGCTCTCTCTTGGTCCATCTTACCCACACACGCACACTCCACATGCCAGCAGAGTG GCACTTGGTGGCAGAAAGTGTGAGCCTCATGATCTGCTGTGAGCTCAGGTCC AAAGGCCTCGGAGCACCCCTTCTGTGACTGAGCCAGGGGCTGCA TTTGGTTTCCCCACCCCC CACATTCTAACCATAGTCTTCTAACATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGACTG GGGATTCCACATGTTGCCCTTGGGAGTCTCAAGCTGGACTGCCAGCCCTGCTGCCCTCCACCCCC</p>
56	opt_COX10*- opt_ND1- 3'UTR*	<p>ATGGCCGCCAGCCCCACACCCCTGAGCAGCGCCTGCTGACC GGCTGCGTGGCGGGCAGCGTGTG GTACCTGGAGCGCCGCACCATGGCCAACCTGCTGCTGATCGTGCCTGATCGCCATGGCC TTCTGATGCTGACCGAGCGCAAGATCCTGGCTACATGCAGCTGCCAAGGGCCCAACGTTG GGCCCTACGGCCTGCTGCAGCCTCGCCGACGCCATCAAGCTGTTACCAAGGAGGCCCTGAAG CCGCCACCGACCATCACCCCTGACATCACCGCCCCACCCCTGGCCCTGACCATGCCCTGCTGC TGTGGACCCCCCTGCCCATGCCAACCCCCCTGGTGAACCTGAACCTGGGCTGCTGTTCATCTGGC CACAGCAGCCTGGCGTGTACAGCATCTGTGGAGCGGCTGGCCAGCAACAGCAACTACGCCCT GATCGGCGCCCTGCGCCGCTGGCCAGACCATCAGCTACGAGGTGACCCCTGCCATCATCTGCT GAGCACCCCTGCTGATGAGCGGAGCTGGTGAACCTGAGCCCTGATACCACCCAGGAGCACCTGTT CTGCTGCTGCCAGCTGGCCAGGGCGAGAGCGAGCTGGTGAACCTGGGCTTCAACATCGAGTACGCCCG GCCCTTCTGCCCTGTTCTCATGGCCAGTACACCAACATCATGATGAACACCCCTGACCCAC ATCTTCTGGGACCCACTACGACGCCCTGAGCCCCAGCTGATACACCACCTACTCTGTGACCAAGA CCCTGCTGCTGACCGCTGTTCTGTGGATCCGACCCCTAACCCCGCTTCCGCTACGAC GATGCACCTGCTGAGAAGAACTTCTGCCCTGACCCCTGGCCCTGCTGATGTGGTACGTGAGCATG CCCACATCACCATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCACCGCCCTTCC CGCTGCAGCGAGCATGTTGGTAATTCTGAACACAAGAAGAGAAATTGCTGGGTTAGAACAA GATTATAAACGAATTGGTGCTAGTGTACCTGACGTTTTTTAAATATTACCCAAAATGC TCCCCAAATAAGAAATGCACTCAGCTCAGTCAGTGAATACAAAAAGGAATTATTTTCCCTTGAGGGT CTTTTATACATCTCTCCAAACCCACCCCTTATTCTGTTCTCTCTCATGATGGGGTACACATAC ACAGCTCTCTCTTGGTCCATCTTACCCACACACGCACACTCCACATGCCAGCAGAGTG GCACTTGGTGGCAGAAAGTGTGAGCCTCATGATCTGCTGTGAGCTCAGGTCC AAAGGCCTCGGAGCACCCCTTCTGTGACTGAGCCAGGGGCTGCA TTTGGTTTCCCCACCCCC CACATTCTAACCATAGTCTTCTAACATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGACTG GGGATTCCACATGTTGCCCTTGGGAGTCTCAAGCTGGACTGCCA</p>

57	COX8-ND4-3'UTR	<p>ATGTCGGTCTGACGCGCCTGCTGCGGGGTTGACACGGCTCGGCTGGCGCTCCAGTGC GG CGGCCAGAACATTGCTGATGCTAAAACATACTGCTCCAACAATTATGTTACTACC ACTGACATGG CTTTCAAAAAACACATGATTGGATCAACACAACCACCCACAGCCTAAATTATTAGCATCATC CCTCTA CTATTTTAACCAAATCAACAACACCTATTAGCTGTTCCCACCTTCCGACCCCCCTAACAA CCCCCCTCCTAAATGCTAACTACCTGGCTCACCACTATGCTAATCTCCTACAAATCTCCTTAATTATGA CATTACAGCCACAGAACTAATCATGTTTATATCTTCTCGAAACCCACACTTACCCACCTTACCTGCT CATCACCCGATGGGCAACCAGCCAGAACGCGTGAACGCAGGCACATACTTCTTACACCCCTA GTAGGCTCCCTCCCTACTCATCGACTAACTTACACTCACAAACACCCCTAGGCTACTAAACATTCTA CTACTCACTCTCACTGCCAAGAACTATCAAACACTCTGGGCAACGACTCTTACGCTACTAAACATTCTA ATGGCTTTATGGTAAGATGCCCTTACGGACTCCACTTATGGCTCCCTAACAGCCATGTGCGAGCC CCCATCGCTGGGCAATGGTACTTGCAGACTCTTAAACACTAGGCGGCTATGGTATGTGCGCT CACACTCATCTCAACCCCCCTGACAAAACACATGGCTTACCCCTTCCCTGACTATCCCTATGGGCAT GATTATGACAAGCTCATCTGCTACGACAAACAGACCTAAATGCTCATTGCTACTCTCAATCAG CCACATGGCCCTCGTAGTAACAGCATTCTCATCAAACCCCCCTGGAGCTCACCGCGCAGTCATT TCATGATGCCAACGGCTTACATCCTCTTACGACTTACGCTACTGCTAGCAAACACTCAAACACTCGAACGCACTC ACAGTCGATCATGATCCTCTCAAGGACTTCAAACACTCTACTCCCCTAAATGGCTTTGGTGGCTC TAGCAAGGCTCGCTACCTCGCTTACCCCCCTACTTAAACACTACTGGGAGAACCTCTGTGCTAGTA ACCACGTTCTCTGGCTAAATACTCTCTTACGACTCAACATGCTAGTCAGTCACAGCCCTATAC TCCCTCATGTTACCTACACAAATGGGCTCACTCCTCACCCACCACTTAAACACATGAAACCCCTCA TTCACACGAGAAAACACCCCTCATGTTCATGCACTTACCTCTTCCCTTATCCCTCAACCCGAC ATCATTACCGGTTTCTCTTAAAGAGCACTGGGACGCCACCGGCCACCGGCCCTTCCCTCCGCTGCCAGGC GAGCATGTTGGTAATTCTGGAACACAAGAGAGAAATTGCTGGGTTAGAACAAAGATTATAAACGAA TTGGGTGCTCAGTGCACTTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCCAAATAAG AAATGCACTAGCTCAGTGAATACAAAAAAAGGAATTATTCTCTTGAGGGTCTTATACATCT CTCCCTCAACCCCCACCCCTTATTCTGTTCTCTCCTCACATGGGGTACACATACAGCTCCCTCT TTGGGTTCCATCTTACCCACACACCACAGCAGACTCCACATGCCAGCAGTGGCACTTGGTGGC CAGAAAGTGTGAGCTCATGATCTGCTGTAGTCTGTGAGCTCAGGCTCCCTCAAAGGCTCGGA GCACCCCCCTCTTGTGACTGAGCCAGGGCTGCATTGGTTTCCCCACCCACACATTCTCAAC CATAGTCCTTCAACAAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGACTGGGACTGGGATTCACAT GTTGCCCTGGGAGTCTCAAGCTGGACTGCCA</p>
58	COX8-ND4-3'UTR*	<p>ATGTCGGTCTGACGCGCCTGCTGCGGGGTTGACACGGCTCGGCTGGCGCTCCAGTGC GG CGGCCAGAACATTGCTGATGCTAAAACATACTGCTCCAACAATTATGTTACTACC ACTGACATGG CTTTCAAAAAACACATGATTGGATCAACACAACCACCCACAGCCTAAATTATTAGCATCATC CCTCTA CTATTTTAACCAAATCAACAACACCTATTAGCTGTTCCCACCTTCCGACCCCCCTAACAA CCCCCCTCCTAAATGCTAACTACCTGGCTCACCACTATGCTAATCTCCTACAAATCTCCTTAATTATGA CATTACAGCCACAGAACTAATCATGTTTATATCTTCTCGAAACCCACACTTACCCACCTTACCTGCTAT CATCACCCGATGGGCAACCAGCCAGAACGCGTGAACGCAGGCACATACTTCTTACACCCCTA GTAGGCTCCCTCCCTACTCATCGACTAACTTACACTCACAAACACCCCTAGGCTACTAAACATTCTA CTACTCACTCTCACTGCCAAGAACTATCAAACACTCTGGGCAACGACTTACGCTACTAAACATTCTA ATGGCTTTATGGTAAGATGCCCTTACGGACTCCACTTATGGCTCCCTAACAGCCATGTGCGAGCC CCCATCGCTGGGCAATGGTACTTGCAGACTCTTAAACACTAGGCGGCTATGGTATGTGCGCT CACACTCATCTCAACCCCCCTGACAAAACACATGGCTTACCCCTTCCCTGACTATCCCTATGGGCAT GATTATGACAAGCTCATCTGCTACGACAAACAGACCTAAATGCTCATTGCTACTCTCAATCAG CCACATGGCCCTCGTAGTAACAGCATTCTCATCAAACCCCCCTGGAGCTCACCGCGCAGTCATT TCATGATGCCAACGGCTTACATCCTCTTACGACTTACGCTACTGCTAGCAAACACTCAAACACTCGAACGCACTC ACAGTCGATCATGATCCTCTCAAGGACTTCAAACACTCTACTCCCCTAAATGGCTTTGGTGGCTC TAGCAAGGCTCGCTACCTCGCTTACCCCCCTACTTAAACACTACTGGGAGAACCTCTGTGCTAGTA ACCACGTTCTCTGGCTAAATACTCTCTTACGACTCAACATGCTAGTCAGTCACAGCCCTATAC TCCCTCATGTTACCTACACAAATGGGCTCACTCCTCACCCACCACTTAAACACATGAAACCCCTCA TTCACACGAGAAAACACCCCTCATGTTCATGCACTTACCTCTTCCCTTATCCCTCAACCCGAC ATCATTACCGGTTTCTCTTAAAGAGCACTGGGACGCCACCGGCCACCGGCCCTTCCCTCCGCTGCCAGGC GAGCATGTTGGTAATTCTGGAACACAAGAGAGAAATTGCTGGGTTAGAACAAAGATTATAAACGAA TTGGGTGCTCAGTGCACTTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCCAAATAAG AAATGCACTAGCTCAGTGAATACAAAAAAAGGAATTATTCTCTTGAGGGTCTTATACATCT CTCCCTCAACCCCCACCCCTTATTCTGTTCTCTCCTCACATGGGGTACACATACAGCTCCCTCT TTGGGTTCCATCTTACCCACACACCACAGCAGACTCCACATGCCAGCAGTGGCACTTGGTGGC CAGAAAGTGTGAGCTCATGATCTGCTGTAGTCTGTGAGCTCAGGCTCCCTCAAAGGCTCGGA GCACCCCCCTCTTGTGACTGAGCCAGGGCTGCATTGGTTTCCCCACCCACACATTCTCAAC CATAGTCCTTCAACAAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGACTGGGACTGGGATTCACAT GTTGCCCTGGGAGTCTCAAGCTGGACTGCCA</p>

59	COX8-opt_ND4-3'UTR	<p>ATGTCGGTCTGACGCGCCTGCTGCGGGGCTTGACACGGCTCGGCTCGGGGCTCCAGTGC GG CGGCCAGAACATTGCTGAGCTGATCGTGCCTCTGACCTG GCTGAGCAAGAACACATGATCTGGATCACACCACCGCACAGCCTGATCATCAGCATCATCCCCTC TGCTGTTCTCAACCAGATCAACAAACACTGTTCAGCTGCAGCCCCACCTCAGCAGCAGCCTCTG ACAACACCTCTGCTGATGCTGACCCCTGGCTGCTGCCCTCACAAATCATGGCCTCTCAGAGAACACCT GAGCAGCGAGCCCCCTGAGCCGGAAGAACACTGTACCTGAGCATGCTGATCTCCCTGAGCATCTCTG ATCATGACCTTCACCGCACCAGCTGATCATGTTACATCTTTGAGAGACACTGAACGCCGGCACCTACTTTCTGTTCT CTGGCCATCATCACCAAGATGGGCAACCAGCCTGAGAGACACTGAACGCCGGCACCTACTTTCTGTTCT ACACCCCTGTTGGCAGCCTGCCACTGCTGATTGCCCTGATCTAACCCACAACACCCCTGGGCTCCCT GAACATCTGCTGACTGACACTGACGCCAGAGCTGAGCAACAGCTGGGCAACATCTGATGTGG CTGGCCTACACATGGCCTCATGGTCAAGATGCCCTGTAACGGCTGCTGCCAGCTGCTGCTGAAACACTGGGGCTA CTGGCATGATGCCCTGACCCCTGATTCTGAATCCCTGACCAAGCAGCATGGCTATCCATTTCTGGTGC TGAGCCTGTTGGGAGCATGATTATGACCAGCAGCATCTGCTGCCAGGGCATCTGAGTCTGAGTCTG CGCCTACAGCTCATGCCACATGGGCCCTGGTGGTACCCGCATCTGATTCAAGACAGCCCTTGGAGC TTACAGGGCGCTGATCTGATGATTGCCACGGGCTGACAAGCAGCCTGCTGAGGAGTGTGCTTAC CTATGTTGAAGCCCCATCGCCGGCTATGGTCTGAGCTGCTGAGAGACTGGGAGGAGTTAACACATTAA GAGTTCTCTAAAGGATTGTAAGTAGATAACATCCAACTACTGTTGCACTTATCTGA AATCTTCCCTTGGCTGCCCTCAGGTATTACTGTGGAGAACATTGCAAGGAATGTC CTTCTACAACCTGTTACAGCCCTCACATTGAGAACGTT</p>
60	COX8-opt_ND4-3'UTR*	<p>ATGTCGGTCTGACGCGCCTGCTGCGGGGCTTGACACGGCTCGGCTCGGGGCTCCAGTGC GG CGGCCAGAACATTGCTGAGCTGATCGTGCCTCTGACCTG GCTGAGCAAGAACACATGATCTGGATCACACCACCGCACAGCCTGATCATCAGCATCATCCCCTC TGCTGTTCTCAACCAGATCAACAAACACTGTTCAGCTGCAGCCCCACCTCAGCAGCAGCCTCTG ACAACACCTCTGCTGATGCTGACCCCTGGCTGCTGCCCTCACAAATCATGGCCTCTCAGAGAACACCT GAGCAGCGAGCCCCCTGAGCCGGAAGAACACTGTACCTGAGCATGCTGATCTCCCTGAGCATCTCTG ATCATGACCTTCACCGCACCAGCTGATCATGTTACATCTTTGAGAGACACTGAACGCCGGCACCTACTTTCTGTTCT CTGGCCATCATCACCAAGATGGGCAACCAGCCTGAGAGACACTGAACGCCGGCACCTACTTTCTGTTCT ACACCCCTGTTGGCAGCCTGCCACTGCTGATTGCCCTGATCTAACCCACAACACCCCTGGGCTCCCT GAACATCTGCTGACTGACACTGACGCCAGAGCTGAGCAACAGCTGGGCAACATCTGATGTGG CTGGCCTACACATGGCCTCATGGTCAAGATGCCCTGTAACGGCTGCTGCCAGCTGCTGCTGAAACACTGGGGCTA CTGGCATGATGCCCTGACCCCTGATTCTGAATCCCTGACCAAGCAGCATGGCTATCCATTTCTGGTGC TGAGCCTGTTGGGAGCATGATTATGACCAGCAGCATCTGCTGCCAGGGCATCTGAGTCTGAGTCTG CGCCTACAGCTCATGCCACATGGGCCCTGGTGGTACCCGCATCTGATTCAAGACAGCCCTGCTGTTGCT TTACAGGGCGCTGATCTGATGATTGCCACGGGCTGACAAGCAGCCTGCTGAGGAGTGTGCTTAC CTATGTTGAAGCCCCATCGCCGGCTATGGTCTGAGCTGCTGAGAGACTGGGAGGAGTTAACACATTAA GAGTTCTCTAAAGGATTGTAAGTAGATAACATCCAACTACTGTTGCACTTATCTGA AATCTTCCCTTGGCTGCCCTCAGGTATTACTGTGGAGAACATTGCAAGGAATGTC CTTCTACAACCTGTTACAGCCCTCACATTGAGAACGTT</p>

		GACCCGGCTGCTGTGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGACTG CCA
63	COX8-ND6- 3'UTR	ATGTCGGCCTGACGCCCTGCTGCCGGGCTTGACACGGCTGGCTGGCGGCCAGTGC CGCCGCCAGAATCATTGGTGTGATGATGCTTGTGTTCTGTTGAGTGTGGGTTAGTAATGGGTT GTGGGGTTTCTCTAAGCCTCTCCTATTATGGGGTTAGTATTGATTGTTAGCGGTG TGTGTTATTATTCTGAATTGGGGAGGTTATGGGTTAATGGTTTAAATTAGGGGAA TGATGGTTGTCTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTGAGGC GTGAGGTCTTGGTGTGAGTGTGTTAGTGGGGTAGCGATGGAGGTAGGATTGGTGT AGTATGGGGTGGTGGTTGGTAAACTTAATAGTGTAGGAAGCTGGATGATT GGGTAGGGTTGATTGGGAGGATCCTATTGGTGGGGGCTTGTATGATT TAGTAGTTACTGGTGGACATTGTTGGTGTATATATTGTAATTGAGATTGCT AGCACTGGGACGCCAACGCCCTTCCCGTGCAGGGCAGCATGGTGGTAATTCTGAA ACAAGAAGAGAAATTGCTGGTTAGAACAGATTATAACGAATTGGTGT GTTTTTTTTTTAAATTACCAAAAATGCTCCCCAAATAAGAACATGGTCA AAAAAAAGGAATTATTTCCCCTTGAGGGTCTTATACATCTCCTC TTCTCCTCCTCAGATGGGGTACACATACAGCTCCTCTGGTGG ACACGGCACACTCCACATGCCAGCAGGGTGGCACTGGGAG CTGTCGTAGTTCTGTGAGCTCAGGTCCCTCAAGGGCTCGGAG AGGGCCTGCATTGGTTTCCCCACACATTCTCAACC CTAGGACCCGGCTGCTGTGCACTGGGACTGGGATTC ACTGGCAGCCCCCTGCTCCCTCACCCTGCGTATGAGC GCATCTTATAGTTCACGTTACATAGACACTGTTGGAGC ACTTAATACCGCCGGACCTCTGGCCCCACCC CGCCACTCCTGCTACACAGCACGGCTTTCAAGGCTG GTGTGCTGGCTAACCAAGGCCACAGAGCTCACATT TGATATCTCCTGAAATTAGCCTCACATGT GGGAATTGGCAAGTTACCTGTGGCCAGGTGT TAGTCCTTGCTCCACGGGTACAGAGT TTTCGATTACTCAGTCTCCAGGGCACT AAACACATTAAACAGAGTTCTCA GTTTGCACCTATCTGAAATCT AAAGCTTCTGAGGATTTACT AATGTCTGGAAAAAGCTCTACA GGGACTGGTACAGCCTCACATTG 64 COX8-ND6- 3'UTR* ATGTCGGCCTGACGCCCTGCTGCCGGGCTTGACACGGCTGGCTGGCGGCCAGTGC CGCCGCCAGAATCATTGGTGTGATGATGCTTGTGTTCTGTTGAGTGTGGGTTAGTAATGGGTT GTGGGGTTTCTCTAAGCCTCTCCTATTATGGGGTTAGTATTGATTGTTAGCGGTG TGTGTTATTATTCTGAATTGGGGAGGTTATGGGTTAATGGTTTAAATT TGATGGTTGTCTTGGATATACTACAGCGATGGCTATTGAGGAGTATCCTGAGGC GTGAGGTCTTGGTGTGAGTGTGTTAGTGGGGTAGCGATGGAGGTAGGATTGGTGT AGTATGGGGTGGTGGTTGTGAAACTTAATAGTGTAGGAAGCTGGATGATT GGGTAGGGTTGATTGGGAGGATCCTATTGGTGGGGCTTGT TAGTAGTTACTGGTGGACATTGTTGGTGTATATTGTAATTGAGATTGCT AGCACTGGGACGCCAACGCCCTTCCCGTGCAGGGCAG ACAAGAAGAGAAATTGCTGGTTAGAACAGATTAAACGA GTTTTTTTTTTAAATTACCAAAAATGCT AAAGGAATTATTTCCCCTTGAGGGTCTTATACATCTCCT TTCTCCTCCTCACATGGGGTACACATACAGCT ACACGGCACACTCCACATGCCAGCAGGGTGGCA CTGTCGTAGTTCTGTGAGCTCAGGT AGGGCCTGCATTGGTTTCCCCACACATTCTCA CTAGGACCCGGCTGCTGTGCACTGGGACTGGG ACTGGGATTCCACATGTTGCC ACTGGGAGTCTCAAGCTGG

65	COX8-opt_ND6-3'UTR	ATGTCGGTCTGACGCGCCTGCTGCTGCCGGGCTTGACACGGCTCGGCTCGGGGCTCCAGTGC GG CGCGCCAGAATCCATTGTTGATGATGTACGCCCTGTTCTGCTAGCGTGGGCTGGTATGGGCT TCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGGGCGCTGGTCTGATGGTCTGTATCTACCT GGGCGGCATGATGGTGTGTTGGCTACACACCACCGCCATGGCATCGAGGAGTACCCGAGGGCTG GGGCAGCGCGCTGGAGGTGCTGGTGAACGGCTGCTGGTGGTGAACCTAACAGCGTGGCAGCTGGATGA TGTGGGTAAGGAGTACGACGGCTGGTGTGGTGAACCTAACAGCGTGGCAGGACCCATGGCGCCGGCCCTGTACGAC TCTACGAGGGCAGGGCAGGGCTGATCCCGAGGGACCCATGGCGCCGGCCCTGTACGAC TACGGGGCTGGTGTGGTGGACCCCTGTTCTGTTGACATCGTGATCGAG ATCGCCCGGGCAACTAAGAGCACTGGGACCCCACCGCCCTTCCCTCGCTGCCAGGGAGCA TGGTGTGTAATTCTGAAACACAAGAAGAGAAATTGCTGGTTAGAACAGATTATAAACGAATTCGG TGCTCAGTGTACACTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCTAACATAAGGATTTACATCTCCTC CAACCCCAACCCCTATTCTGTTCTCCTCCTACATGGGGTACACATACACAGCTTCTCTTGGT TCCATCCTTACCAACACACAGCACACTCCACATGCCAGCAGAGTGGCAGTGGGACTGGGAGCTGGGCCAGAA AGTGTGAGCCTCATGATCTGCTGCTGTAGTTCTGTGAGCTCAGGTCCTCAAAGGCTCGGAGCACC CCTTCTCTGTGACTGAGCCAGGGCTGCATTTGGTTTCCCACACATTCTCAACCATAGT CTTCTAACAATACCAATAGCTAGGACCCGGCTGTGACTGGGACTGGGACTGGGACATGGGACTGGGACATGGTGTG CTTGGGAGCTCAAGCTGGACTGCCA
66	COX8-opt_ND6-3'UTR*	ATGTCGGTCTGACGCGCCTGCTGCTGCCGGGCTTGACACGGCTCGGCTCGGGGCTCCAGTGC GG CGCGCCAGAATCCATTGTTGATGATGTACGCCCTGTTCTGCTAGCGTGGGCTGGTATGGGCT TCGTGGGCTTCAGCAGCAAGCCCAGCCCCATCTACGGGGCGCTGGTCTGATGGTCTGTATCTACCT GGGCGGCATGATGGTGTGTTGGCTACACACCACCGCCATGGCATCGAGGAGTACCCGAGGGCTG GGGCAGCGCGCTGGAGGTGCTGGTGAACGGCTGCTGGTGGGCTGGCATGGAGGTGGGCTGGTGC TGTGGGTAAGGAGTACGACGGCTGGTGTGGTGAACCTAACAGCGTGGCAGCTGGATGA TCTACGAGGGCAGGGCAGGGCTGATCCCGAGGGACCCATGGCGCCGGCCCTGTACGAC TACGGGGCTGGTGTGGTGGACCCCTGTTCTGTTGACATCGTGATCGAG ATCGCCCGGGCAACTAAGAGCACTGGGACCCCACCGCCCTTCCCTCGCTGCCAGGGAGCA TGGTGTGTAATTCTGAAACACAAGAAGAGAAATTGCTGGTTAGAACAGATTATAAACGAATTCGG TGCTCAGTGTACACTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCTAACATAAGGATTTACATCTCCTC CAACCCCAACCCCTATTCTGTTCTCCTCCTACATGGGGTACACATACACAGCTTCTCTTGGT TCCATCCTTACCAACACACAGCACACTCCACATGCCAGCAGAGTGGCAGTGGGACTGGGAGCTGGGCCAGAA AGTGTGAGCCTCATGATCTGCTGCTGTAGTTCTGTGAGCTCAGGTCCTCAAAGGCTCGGAGCACC CCTTCTCTGTGACTGAGCCAGGGCTGCATTTGGTTTCCCACACATTCTCAACCATAGT CTTCTAACAATACCAATAGCTAGGACCCGGCTGTGACTGGGACTGGGACTGGGACATGGTGTG CTTGGGAGCTCAAGCTGGACTGCCA
67	COX8-ND1-3'UTR	ATGTCGGTCTGACGCGCCTGCTGCTGCCGGGCTTGACACGGCTCGGCTCGGGGCTCCAGTGC GG CGCGCCAGAATCCATTGTTGATGGCCAACCTCTACTCCCTCATGGTACCCATTCTAACATCGCAATGGC ATTCTAATGCTTACCGAAGAAAATTCTAGCTATGCAACTACCGCAAAGGCCAACCGTGTAGG CCTCTACGGGCTACTACAAACCTCTCGCTGACGCCATAAAACTCTCCACAAAGAGCCCTAAACCGC CCACATCTACCATCACCTCTACATCACCGCCCCGACCTAGCTCTACCATCGCTTCTACTATGGA CCCCCCTCCCCATGCCAACCCCTGGTCAACCTAACCTAGGCCTCTATTATCTAGCCACCTCT AGCCTAGCCGTTACTCAATCTCTGGTCAGGGTGGGCATCAAACCTAACACTACGCCCTGATGGCGC ACTGCGAGCAGTAGGCCAACAACTCTCATGAGTCACCCTAGGCCATCTACTATCAACATTACT ATATGAGTGCTCTTAACTCCACCTTACACAAACACAAGAACACCTCTGGTTACTCTGCCATC ATGGGCTTGGCATGATGGTTATCTCCACACTAGCAGAGGACCAACCGAACCCCCCTCGACCTTG CGAACGGGAGTCCGAACTAGCTCAGGCTTACACATCGAACATCGAACACGCCAGGCCCTTCGCCATT CTTCATGGCGAACACAAACATTATTATGTAACACCCCTACCAACTACAATCTCTCTAGGAAACAC ATATGACGCACTCTCCCTGAACTCTACACAAACATATTGTCACCAAGACCCCTACTCTAACCTCCCT GTTCTTATGGATTGCAACAGCATACCCCGATTCCGCTACGACCAACTCATGCACCTCTATGGAAA ACTTCCTACCAACTCACCTAGCATTACTTATGTTGATGCTCCATGCCATTACAATCTCCAGCATTC CCCCTCAAACCTAACAGAGCACTGGGACGCCACCGCCCCCTTCCCTCGCTGCCAGGGAGCATGGT TGGTAATTCTGGAACACAAAGAAGAGAAATTGCTGGGTTAGAACAGATTAAACGAATTCTGGTGC AGTGATCACTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCTAACAGAAATGCTCCTC CTCAGTCAGTGAATACAAAAAGGAATTATTTCCCTTGGGGTCTTTATACATCTCCTCCAAAC CCACCCCTATTCTGTTCTCCTCCTACATGGGGTACACATACAGCTTCTCTTTGGTCCAT CCTTACCAACACACCGCACACTCCACATGCCAGCAGAGTGGCAGTGGCAGGGACTGGGACTGGGACATGGTGTG GAGCCTCATGATCTGCTGCTGTAGTTCTGTGAGCTCAGGTCCTCAAAGGCCCTCGGAGCACCCCCCT CCTTGTGACTGAGCCAGGGCTGCATTTGGTTTCCCACACATTCTCAACCATAGTCCTC TAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGACTGGGACTGGGACATGGTGTG

		GAGTCTCAAGCTGGACTGCCAGCCCCGTCTCCCTTCACCCCATCGTATGAGCATTAGAACT CCAAGGAGTCACAGGCATCTTATAGTTCACGTTAACATATAGACACTGTTGGAAGCAGTCCCTCTAA AAGGGTAGCCCTGGACTTAATACCAGCCGGATACCTCTGGCCCCACCCCATCTGTACCTCTGGA GTCACTACTGTGGGTGCCACTCTCTGCTACACAGCACGGCTTTCAAGGCTGTATTGAGAAGGGGA AGTTAGGAAGAAGGGTGTGCTGGCTAACAGCCCACAGAGCTCACATTCTGTCCTGGGTGAAA AATACATGTCCATCTGATATCTCTGAATTCAAGAAATTAGCCTCCACATGTGCAATGGCTTAAGAGC CAGAAGCAGGGTCTGGGAATTTCAGTTCAAGTACCTGTGCCAGGTGTTCTGGTACCAAATACGG TTACCTGCAGCTTTAGTCCTTGCTCCACGGGACTACTGGTCCGTAGGATTGATTGGTC AGCTTGACAGGATTTGATTACTCACGTCCTCCAGGGACTACTGGTCCGTAGGATTGATTGGTC GGGGTAGGAGAGTTAACACATTAAACAGAGTTCTCAAAATGTCTAAAGGGATTGAGGTAGAT AACATCCAATCACTGTGACTTATCTGAAATCTCCCTTGGCTGCCCTCAGGTATTACTGTGGA GAACATTGCATAGGAATGTCTGGAAAAGCTCTACAACCTGTTACAGCCTCACATTGAGAAGCTT T
68	COXB-ND1- 3'UTR*	ATGTCGGCTCTGACGCCCTGCTGCGGGGTTGACACGGCTGGCTGGGGCTCCAGTGC GG CGGCCAGAACATCATTGTTGATGGCAACCTCTACTCCTCATTTGTAACCAATTCAATCGCAATGGC ATTCTTAATGCTTACCGAACGAAAAATTCTAGGCTATATGCAACTACGCCAACGGCCAAACGGTGTAGG CCCTACTGGGCTACTACAACCCCTCGCTGACGCCATAAAACTCTCACCAAAGAGGCCCTAAACCCG CCACATCTACCATCACCTCTACATCACGCCGGACCTAGCTCTCACCTCGCTCTACTATGGA CCCCCTCCCCATGCCAACCCCTGGTCAACCTAACCTAGGGCTCTATTATTCTAGCCACCTCT AGCCTAGGGCTTACTCAATCTGGTCAAGGGTGGCATCAAACACTACGCCCTGATGGCGC ACTGCGAGCAGTAGGCCAACAACTCATATGAAGTCACCCTAGGCCATATTACTATCAACATTACT AATGAGTGGCTCTTAACTCTCCACCCATTACAAACACAAGAACACCTCTGGTACTCCTGCCATC ATGGCCCTGGCATGATGTGGTTATCTCACACTAGCAGAGAACCGAACCCCTTCGACCTTG CGAAGGGAGTCCGAACTAGTCAGGCTTCAACATCGAACGCGCAGGCCCTCGCCCTATT CTTCATGGCCGAAATACACAAACATTATTATGATGAAGCACCCCTACCAACTACCCCTAGGAAACAC ATATGACGCCACTCTCCCTGAACTCTACACACATATTGTCAACAGACCTACTTCTAACCTCCCT GTTCTTATGGATTGCAACAGCATAACCCGATTCCGCTACGCCAACATGCAACCTCTATGGAAA ACTTCTACCAACTCACCTAGCATTACTTATGTGGTATGTCCTCATGCCATTACAATCTCACGATT CCCCCTCAAACCTAACAGACTGGGACGCCACCGCCCTTCCCTCCGCTGCCAGGCAGCATGTT TGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGTTAGAACAGATTAAACGAATTGGTGTC AGTGTACACTGACAGTTTTTTTTAAATATTACCCAAAATGCTCCCAAATAGAACATGCA CTCAGTCAGTGAATACACAAAGGAATTTTTCCCTTGAGGGCTTTTACATCTCTCCAAAC CCACCCCTATTCTGTTCTCTCTCACATGGGGTACACATCACGCTCCCTTTGGTCCAT CCTTACCAACACACACGCCACTCCACATGCCAGAGGTGGCACTGGTGGCCAGAAAGTGT GAGCCTCATGATCTGCTGCTGAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCCTGGAGCACCCCTT CCTTGTGACTGAGCCAGGGCTGCATTGGTGGTTCCCCACACATTCTAACCATAGCTCTTC TAACAATACCAATAGCTAGGACCCGGCTGCTGCACTGGGACTGGGATTCACATGTTGCCCTGG GAGTCTCAAGCTGGACTGCCA
69	COX8- opt_ND1- 3'UTR	ATGTCGGCTCTGACGCCCTGCTGCGGGGTTGACACGGCTGGCTGGGGCTCCAGTGC GG CGGCCAGAACATCATTGTTGATGGCAACCTCTACTGCTGCTGATCGTCCCACCTGTATGCCATGG CTTCTCTGATGCTGACCGAGCGAACATCCTGGCTACATGCCAGCTGCCAGGCCAACGTGGT GGGCCCTACGGCCTGCTGCAGGCCCTCGCCGACGCCATCAAGTGTTCACCAAGGAGGCCCTGAA GCCCGCACCAGCACCATCACCCCTGTACATCACGCCACCCCTGGCCCTGACCATGCCCTGCTG CTGTGGACCCCCCTGCCCATGCCAACCCCTGGTGAACCTGAACTGGCCCTGCTGTTCATCTGG CCACCCAGCGCTGGCGTCAAGCATCTGTGGAGGGCTGGCCAGCAACAGCAACTACGCC TGATCGGCCCTGCGCTGAGCGCAGCTTCAACCTGAGCACCCCTGATGTGGTTCATGCCACCC TGAGCACCCCTGCTGAGCGCAGCTTCAACCTGAGCACCCCTGATCACGCCACCC GCTGCTGCTGCCAGCTGGCCCTGGCATGATGTGGTTCATGCCACCC CACCCCCCTCGACCTGGCGAGGGCGAGAGCGAGCTGGTGAAGGCCCTCAACATGAGTACGCC CGGCCCTCGCCCTGTTCTCATGGCGAGTACACCAACATCATGATGAACACCC GCCATCTCTGGCACCCACTACGACGCCCTGAGGCCAGCTGTACACCC GACCCCTGCTGACCGAGCTGGCTTCTGTGGATCCGCAACGCCCTACCCCGCTCCGCTACGAC CTGATGCACCCCTGCTGAGAACACTTCTGCCCTGACCCCTGGCCCTGCTGATGTGGTACG TGCCCATCACCATGAGCATCCCCCCCCAACCTAACAGAGCACTGGGAGGCCACCGCCCC CTCGCTGCCAGGGAGCATGTTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGTTAGAAC AAGATTATAACGAATTGGTGCTCACTGATCACTTGACAGTTTTTTTTAAATATTACCCAAAAT GCTCCCAAATAAGAAATGCACTGAGCTCACTGAGCTGAATACAAAAAGGAATTATTCTGCT ACACAGCTCTCTTGGTCCATGCCCTACCCACACACGCCACACTCCACATGCCAGAG TGGCACTGGTGGGCCAGAAAGTGTGAGGCTCATGATCTGCTGTGAGCTCAGGCTCC TCAAAGGCCCTGGAGCACCCCTCTCTGTGACTGAGGCCAGGGCTGCTGCACTGGGAC CACACATTCTCAACCATAGCTCTCTAACAAATACCAATAGCTAGGACCCGGCTGCTGCACTGGGAC TGGGAGTCCACATGTTGCCCTGGAGTCTAAGCTGGACTGCCAGGCCCTGCTCTCCCTCACCCCC CATTGCGTATGAGCATTCAAGAACCTCAAGGAGTCACAGGCATCTTATAGTTACGTTACG CACTGTTGAGCAGTCCCTCTAAAGGGTAGGACTAACACGCCGATACCTCTGGGCC CCACCCCCATTACTGTAACCTCTGGAGTCACTACTGTGGGCGCCACTCTCTGCTACACAGCACGGCTT TTTCAAGGGTGTATTGAGAAGGGAGTGAAGAAGGGTGTGCTGGGCTAACAGGCCACAGAGCT CACATTCTGTCCTGGTGAAGAACATGTCATCTCTGATATCTCTGAAATTGAGCCTC

		CACATGTGCAATGGCTTAAGAGCCAGAAGCAGGGTTGGGAATTTCAGTACCTGTGGCCAGGTGGTCTCGGTACCAAATACGGTTACCTGCAGCTTTAGTCCTTGTGCTCCACGGGTCTACAGAGTCCCAC TGCCAAAGGTCTTGAAGCTTGACAGGATGTTGATTACTCAGTCTCCAGGGCACTA CTGGTCCGTAAGGATTGATTGGCTGGGTAAGGAGAGTTAACACATTAAACAGAGTTCTCAAAAATGTCTAAAGGGATTGAGTAGATAACATCCAATCACTGTTGCACCTATCTGAAATCTCCCTCTTG GCTGCCAGGTTACTGTGAGAACATTGATAGGAATGTCAGGAAAGCTTACAACCTGTTACAGCCTCACATTGAGCTTT
70	COXB-opt_ND1-3'UTR*	ATGTCGGTCTGACGCGCCTGCTGCGGGGTTGACACGGCTCGGCTGGCGCTCCAGTGC GGCGCCAGAATCCATTGTTGATGGCAACCTGCTGCTGATCGGCCATCCTGATGCCATGG CTTCTGATGCTGACCGAGCGCAAGATCCTGGCTACATGCAGCTGCAGAAGGGCCCAACGTGGT GGGCCCCCTACGGCCTGCTGCAGGCCCTCGCCGACGCCATCAAGCTTCACCAAGGAGGCCCTGAA GGCCGCCACCAGCACCATACCCCTGACATCACCGCCCCCACCCCTGGCCCTGACCATGCCCTGCTG CTGTTGGACCCCTGCCCCTGCCCCATGCCCAACCTGGTGAACCTGGGCTGCTGTTGATCCCTGG CCACCAAGCAGCCTGGCGTGTACAGCATCCTGTTGGAGGCCCTGGCCAGAACAGCAACTAGGCC TGATCGGCCCTGCGCCCTGCGCCGCTGGCCAGACCATCAGCTACGGGTGACCCCTGGCCATCATCCTGC TGAGCACCCCTGCTGATGAGCGGAGCTTCAACCTGAGCACCCCTGATCACCAACCCAGGAGCACCTG TGCTGCTGCCCAGCTGGCCCTGGCATGATGTGGTTCATCAGCACCCCTGGCGAGAACCAACG CACCCCTTCGACCTGGCGAGGGCGAGAGCGAGCTGGTGAAGCGCTTCACATCGAGTACGCC CGGGCCCCCTCGCCCTGTTCTCATGGCGAGTACACCAACATCATGATGAACACCCCTGACCAACCA CCATTTCTGGCACACCATCAGCACGCCCTGGCCAGCTGAGCACCCCTGACCCCTGGCTACGACCA AGCACCTGCTGCTGACCGAGCCCTGTTCTGTGATCCGCACCGCCTACCCCGCTTCCGCTACGACCA CGTGTGACACTGCTGTGAGAACACTTCCCTGCCCTGACCCCTGGCCCTGCTGATGTGGTACGTGAGCA TGCCCATACCATCAGCAGCATCCCCCCCCAGACCTAAGAGCACTGGGACGCCACCGGCCCTTCC CTCCGCTGCCAGGCAGCATGTTGTGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTAGAAC AAGATTATAAACGAATTGGTGTCACTGATGACTACTGACAGTTTTTTTTAAATATTACCAAAAT GCTCCCCAAATAAGGAATGATCAGCTCAGTGAATACAAAAAGGAATTATTTCCTTGTGAGG GTCTTTTATACATCTCTCTCAACCCCACCCCTTCTATTCTGTTCTCTCATGATGGGGTACACAT ACACAGCTCCCTTTGGTTCATCCTTACACCAACACGCCACACTCCACATGCCAGCAGAG TGGCACTTGGTGGCAGAAAGTGTGAGCCTCATGATCTGCTGTGAGCTCAGGTCCC TCAAAGGCCTCGGAGCACCCCTCTTGTGACTGAGCAGGGCCTGCATTTGGTTTCCCCACCC CACACATTCTAACCATAGCTCTTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGGAC TGGGGATTCCACATGTTGCTTGGGAGTCTAACAGCTGCA
71	OPA1-ND4-3'UTR	GTGCTGGCCGAGCTAGAAAGGGTGAAGTGGTGTCTTCCGTGACGGACTGAGTACGGGTGCCTGTCAGG CTCTTGCGGAAGTCCATGCGCCTTGGGAGGGCTCGGGCGGGCTGTGCCCCCTGCTGAGG GCCACTTCTGGGTCTTCCCTGGGACGGGGAGCGGGCTGGGCTCACACGGGGCTCCCGCGTG CGCGTCTGGCGCCTGCGTGAACCTCCCCGCCGGGGATGTGGCGACTACGTGGGCCGTGTGG CTGATGCTAAACTAATCGTCCAAACAATTATGTTACTACCACTGACATGGCTTCAAAAAACACATG ATTGGATCAACACAACCCACAGCTAAATTAGCATCATCCCTACTATTTTAAACAAATCA ACAACAAACCTATTAGCTGTTCCCAACCTTCTCCGACCCCTTAACAACCCCCCTCTAATGCTAA CTACCTGGCTCTACCCCTCACAAATCATGGCAAGGCCAACGCCACTTACAGTGAACCCACTATCACGA AAAAAACTCTACCTCTATGCTATCTCTCATCAAATCTCTTAAATTATGACATTACGCCACAGAAC TAATCATGTTTATATCTCTGAAACCACACTTATCCCACCTGGCTATCATCACCGATGGGCA ACCAGCCAGAACGCCGTAACGCAGGCACATACTTCTTACACCCTAGTAGGCTCCCTCCCTA CTCATCGACTAATTACACTCACAAACACCCCTAGGCTACTAACATTCTACTACTCACTGCC CAAGAACTATCAAACCTCTGGGCAACAACCTTAATGTTGCTAGCTACACAATGGCTTTATGGTAAAG ATGCTCTTTACGGACTCCACTTATGGCTCCCTAAAGCCCATGTCGAAGGCCCATGCTGGCTCAAT GGTACTTGGCGCAGTACTCTAAACCTAGGGGGTATGGTATGCGCCTCACACTCATCTCAACC CCTGACAAAACACATGGCTACCCCTTCTGACTATCCCCTATGGGGCATGATTATGACAAGCTCC ATCTGCTACGACAAACAGACCTAAATGCTCATTGCTACTCTCAATCAGCCACATGGCCCTCGTA GTAACAGCCATTCTCATCAAACCCCTGGAGCTTCACCGCGCAGTCATTCTCATGTCGCCACGG GCTTACATCTCATTACTATTCTGCTTAGCAAACCTACAACACTGCAACGCCACTCACAGTCGATCATGAT CCTCTCTCAAGGACTCCTAACACTACTCCCACTAATGGCTTTGGGCTTAGCAAGCCTCGCTAA CCTCGCCTTACCCCAACTTAAACCTACTGGGAGAACCTCTCTGTGCTAGTAACCAACGTTCTCTGGT CAAATATCCTCTACTTACAGGACTCAACATGCTAGTCACAGCCCTATACTCCCTACATGTTTAC CACAAACACAATGGGCTCACTCACCCACCACTTAAACACATGAAACCCCTCATCACAGAGAAAAC ACCCTCATGTTCATGCAACCTATCCCCATTCTCTCTCATCCCTCAACCCCGACATCATTACCGGGTT TCCCTTAAGAGCACTGGGACGCCACGCCCTTCCCTCGCTGCCAGGGAGCATGTTGGTAA ATTCTGGACACAAAGAAGAGAAATTGCTGGGTTAGAACAGATTATAACGAATTGGTGCTCAGTGA TCAGTGAATACAAAAAGGAATTATTACCCAAAATGCTCCCCAAATAAGAACATGCACTAGCTCAG CTCTATTCTGTTCTCTCATGAGGTTACACATCACAGCTCTCTTGGTTCCATCCTTAC CACACACCCACACGCCACACTCCACATGCCAGCAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCT

		CATGATCTGCTGTCTGAGTCTGAGCTCAGGTCCCTAAAGGCCTGGAGCACCCCTTCTGT GACTGAGCCAGGGCTGCATTGGTTTCCCCACACATTCTCAACCATACTGCTTCTGGAGTC TCAAGCTGACTGCCAGCCCTGCTCCTACCCCATTCAGCTATGAGCATTCAAGAACCTCAAG GAGTCACAGGCATTTAGTCAGCTAACATAGACACTGGGACTTGTGAAGCAGTCTTCTAAAGGG TAGCCCTGGACTTAATACCAAGCCGGATACCTCTGGCCCCACCCCATACTGTACCTCTGGAGTC ACTGTGGGTGCACTCTCTGCTACACAGCACGGCTTTCAAGGCTGATTGAGAAGGGATTTAG GAAGAAGGGTGTGCTGGCTAACCAAGCCACAGAGCTCACATTCTGCTCCCTGGGTAAAAATACAT GTCCATCTGATATCTCTGAATTCAAGAAATTAGCCTCACATGTGCAATGGCTTAAGAGCCAGAAGC AGGGTTCTGGGAATTTCAGTTACCTGTGCCAGGTGTTCTGGTACCAAATACGGTTACCTG CAGCTTTAGTCCTTGTGCTCCACGGGTCTACAGAGTCCCCTGCCCCAAAGGTCTGAAGCTTG ACAGGATTTGCTGATTACTCAGTCCTCCAGGGACTACTGGTCCGTAGGATTGCTGGTCCCCGTA GGAGAGTTAAACACATTAAACAGAGTTCTCTCAAAGGATTGAGATAACATC CAATCACTGTTGCACCTATCTGAATCTCCCTTGGCTGCCAGGTATTACTGTGGAGAACAT TGATAGGAATGCTGGAAAAGCTCTACAACCTGTTACAGCCTCACATTGTAGAAGCTT
72	OPA1-ND4- 3'UTR*	GTGCTGCCGCCTAGAAAGGGTGAAGTGGTTTCCGTGACGGACTGAGTACGGGTGCCTGTCAGG CTCTGCGGAAGTCCATGCCATTGGAGGGCTCGGCCGGCTGTGCCCTTGTCTGAGG GCCACTTCTGGGTCTTGGACCCGGGGAGCCGGGCTGGGCTCACACGGGGCTCCCGCTGG CCGCTCTGGCGCTGCGTACCTCCCGCCGGGGATGTGGCAGACTCGTCTGGCGCTGTGGC CTGATGCTAAACTAACTGCTCCAAACATTAGTTACTACACTGACATGGCTTCCAAAAAACACATG ATTGGATCAACACAACCCACAGCTAAATTAGCATCTCCCTACTATTTTAAACCAAATCA ACAACAAACCTATTAGCTGTTCCCAACCTTCTCGACCCCCCTAACACCCCCCTCTAACATGCTAA CTACCTGGCTCTACCCCTACAATCATGGCAAGCCAACGCCACTTATCCAGTGAACCAACTATCACGA AAAAAAACTCTACCTCTATGCTAATCTCCCTACAAATCTCTTAATTATGACATTACAGCCACAGAAC TAATCATGTTTATCTTCGAAACCACACTTATCCCACCTTGGCTATCATCACCGATGGGCA ACCAGCCAGAACGCCCTGAAACGCCAGGCACACTTCTACACCCCTAGTAGGCTCCCTCCCTA CTCATCGCACTAATTACACTCACACACCCCTAGGCTCATAAACATTCTACTACTCACTCGCC CAAGAACTATCAAACACTCTGGCCAACAAACTTATGTGGTAGGCTTACACAATGGCTTTATGGTAAAG ATGCCCTTACGGACTCACTTGGCTCTAACGCCATGTCGAACCCCCATGCTGGGCA GGTACTTGGCGCAGTACTCTTAAACTAGGCGCTATGGTATGATGCCCTCACACTCATTCTCAACC CCCTGACAAAACACATGGCCTACCCCTTCTGTACTATCCCTATGGGCGATGATTGACAAGCTCC ATCTGCCTACGACAACACAGACCTAAATCGCTCATTGCACTCTTCAATCAGCACATGGCCTCGTA GTAACAGCCATTCTCATCCAAACCCCTGGAGCTCACCCGCCAGTCATTCTCATGATGCCACCG GCTTACATCTCAAGGACTCAAACACTCCTTCCACTAATGGCTTTGGCTCTAGCAAGCGCTCGCTAA CTCGCCTTACCCCAACTATTAAACCTACTGGGAGAACTCTGTGCTAGTAACACAGTCTCCCTGGT CAAATATCACTCTCTACTTACAGGACTCAACATGCTAGTCACGCCCTACTCCCTCTACATGTTA CCACAAACACAATGGGCTCACTCACCCACCCACATTAACAAACATGAAACCCCTATTACACAGAGAAAAC ACCCTCATGTTCATGCACCTATCCCCATTCTCTCTATCCCTCAACCCGACATCATTACGGGTT TCCTCTTAAGAGCACTGGGACGCCACCCGCCCTTCCCTCGCTGCCAGGCGAGCATGTTGGTA ATTCTGGAACACAAAGAGAAATTGCTGGGTTAGAACAGATTAAACGAATTGCTGGCTCAGTGA TCACTTGACAGTTTTTTTTAAATATTACCCAAATGCTCCCAATAAGAAATGCACTCAGCTCAG TCAGTGAATACAAAAAAGGAATTATTCTCCCTTGAGGGCTTTTACATCTCTCCACCCCC CTCTATTCTGTTCTCCCTCACATGGGGTACACATACAGCTTCTCTTGGTCCATCCTAC CACCAACACCACAGCACACTCCACATGCCAGCAGAGTGGCAGTGGCTGGGCCAGAAAGTGTGAGCCT CATGATCTGCTGTGAGTCTGAGCTCAGGTCCCTAAAGGCCTGGAGCACCCCTTCTGT GACTGAGCCAGGGCTGCATTGGTTTCCCCACACATTCTCAACCATACTGCTTCTAAACAA TACCAATAGCTAGGACCCGGCTGCTGCACTGGGACTGGGACTTCCACATGTTGCCCTGGAGTC TCAAGCTGGACTGCCA

		TATACATCTCTCCCAACCCCACCCCTATTCTGTTCTCCTCACATGGGGTACACATACACA GCTTCCTCTTTGGTCCATCCTTACCAACCACACCACAGCACACTCCACATGCCAGCAGAGTGGCA CTTGGTGGCCAGAAAGTGTGAGCCTCATGATCTGCTGTAGTTCTGTGAGCTCAGGTCCCTCAA GGCCTCGAGCACCCCTCCTTGACTGAGCCAGGGCTGCATTGGTTCCCCACCCACA CATTCTCAACCATACTGCTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACGGACTGG GATTCCACATGTTGCCTGGGAGTCTAACAGCTGGACTGCCA
75	OPA1- opt_ND4*- 3'UTR	GTGCTGCCGCCCTAGAAAGGGTGAAGTGGTTCCGTGACGGACTGAGTACGGGTGCCTGTCAGG CTCTTGCGGAAGTCCATGCGCATTGGGAGGGCTCGGCCGCGCTGTGCCCCCTGCTGAGG GCCACTTCTGGGTCAATTCTGGACCCGGAGCCGGGCTGGGGCTCACACGGGGCTCCCGCGTGG CCGTCTCGCGCCTGCGTACCTCCGCCGGGGATGTGGCAGACTACGTGGGCCGCTGTGGC CTGATGCTGAAGCTGATCGCCACCATCATGCTGTCGCCCCCTGACCTGGCTGAGCAAGAACACA TGATCTGGATCAACACCACCCACAGCTGATCATCAGCATCATCCCCCTGCTGTTCTAACCA ATCAACAACAACCTGTTAGCTGAGCCCCACCTTCAGCAGCGACCCCTGACCACCCCCCTGCTGA TGCTGACCAACCTGGCTGCTGCCCTGACCATATGGCAGCCAGCGCCACCTGAGCGAGGCC TGAGCCGAAGAAGCTGTACCTGAGCATGCTGATCAGCGCTGAGCATCGCTGATCATGACCTTCACC GCCACCGAGCTGATCTGTTACATCTTCTGAGACCACCCCTGATCCCCACCCCTGGCCATCATCAC CCGCTGGGGCAACCAGCCCGAGCGCCTGAAACGCCGGCACCTACTTCTGTTACACCCCTGGTGG CAGCCTGCCCTGCTGATGCCCCGATCTACACCCACAACACCCCTGGGAGCCTGAAACATCTGCTG CTGACCCCTGACCGCCCAAGGAGCTGAGCAACAGCTGGGCAACAAACCTGATGTGGCTGGCTACACCA TGGCCTCATGGTGAAGATGCCCTGTACGCCCTGACCTGTGGCTGCCCAAGGCCACGTGGAGG CCCCCATCGCCGGCAGCATGGTGTGGCCGGCTGCTGAGCTGGGGCTACGGCATGATG GCCCTGACCCCTGATCCTGAAACCCCCCTGACCAAGCACATGCCCTACCCCTTCTGGTGTGAGCCTGTG GGCATGATCATGACCAAGCAGCATCTGCCCTGCCAGACCCAGCTGAAAGAGCCTGATGCCCTACAGC AGCATCAGCCACATGCCCTGGTGGTACGCCCATCTGATCCAGACCCCCCTGGAGGCTTCAACGGCG CCGTGATCCTGATGATGCCCAACGGCGCATCATGATCCTGAGCCAGGGCTGAGCACCCCTGCTG CGAGCGACCCACAGCCGATCATGATCCTGAGCCACCATCACCTGCTGAGCACCCCTGCTG CTTCTGGGGCTGCTGGCCAGCCTGGCAACCTGGCCCTGCCCTGCCCCCACCATCACCTGCTGGCG GCTGAGCGTGTGGTACGGACCCCTCAGCTGAGCAACATCACCCCTGCTGACCCGGCTGAAACATG CTGGTACCCGCCCCCTGACGCTGACCATGTTACGGACCCACCCAGTGGGGCAGCCTGACCCACCA TCAACAAACATGAAGGCCAGCTTACCCCGAGAACACCCCTGATGTTCATGCACTGAGGCCCTG CTGCTGAGCCTGAAACCCGACATCATCACCCGCTCAGCAGCTAAGAGCACTGGAGCAGGCCACCGCC CTTTCCCTCCGCTGCCAGGGAGCATGTTGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGT TTAGAACAGATTATAAACGAATTGGTGTCACTGATCACTTGACAGTTTTTTTTAAATATTAC CCAAATGCTCCCCAAATAAGAAATGCACTAGCTCAGTCAGTGAATAACAAAAAGGAATTTTTCCC TTTGAGGGCTTTTACATCTCCTCTCCAAACCCACCCCTTACCTGTTCTCCCTCACATGGGG GTACACATACACGCTTCTCTTGGTCCATCCTTACCCACACACGCAACACTCCACATGGGG AGCAGAGTGGCACTTGGTGGCCAGAAAGTGTGAGCCTGATGTCGTTAGTGTGAGCT AGGTCCCTCAAGGCCTGGAGCACCCCTTCTGTGACTGAGCCAGGGCTGCATTGGTTTC CCCCACACATCTCAACCCTAGTCCTCTAACAATACCAATAGCTAGGACCCGGCTGCTGTGCA CTGGGACTGGGATTCACATGTTGCCCTGGAGTCTAAGCTGGACTGCCAGCCCTGCTCTCCC TTCACCCCATTCGCTGAGCATTCAGAAGCTTCAAGGGAGTCACAGGCACTTTATAGTTCACTG CATATAGACACTGTTGGAGGAGCATTCCTCTAAAGGGTAGCCCTGGACTTAAACAGGGGATACC TCTGGCCCCCAGCCATTACTGTAACCTCTGGAGTCAACTGTGGGTGCCACTCTCTGCT CACGGCTTTCAAGGCTGATTGAGAAGGGAGTTAGGAAGAAGGGGTGTGCTGGCTAACAGCCC ACAGAGCTCACATTCTGTCCTGGTGAAAAATACATGTCATCTGATATCTCTGAATTCA TTAGCCTCCACATGTGCAATGGCTTAAGAGCCAGAAGCAGGGTTCTGGGAATTGCAAGTTACCTG TGGCCAGGTGTGGTCTCGGTTACCAATACGGTACCTGCACTGTTAGTCTTGTGCTCCACGG GTCTACAGAGTCCCACATGCCCCAAAGGTCTTGAAGCTTGACAGGATGTTTCGATTACTCAGTCCTCCA GGGCACTACTGGTCCGAGGATTGAGGAGCTTAAACACATTAAACAGAGTTC TCTCAAAATGTCTAACGGGATTGAGGAGATAACATCCAATCACTGTTGCACCTATCTGAATCTC CCTCTGGCTGCCCTCAGGTATTACTGTTGAGGAGACATTGCAAGGAATGTCTGGAAAAGCTTAC AACTGTTACAGCCTTCACATTGAGCTTAAAGAGCCAGAAGCAGGGTTCTGGGAATTGCAAGTTACCTG

		TAGGACCCGGCTGCTGTGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGA CTGCCA
81	OPA1-ND1- 3'UTR	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTTCCGTGACGGACTGAGTACGGGTGCCTGTCAGG CTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCTCGGCCGCGGCTGTGCCCTGCTGTCAGG GCCACTTCTGGGTCAATTCTGGACCGGGAGCCGGCTGGGCTCACACGGGGCTCCCGCGTGG CCGTCTGGCGCCTGCGTACCTCCCCGCCGGGGATGTGGCAGACTACGTGGGCCGCTGTGG CTGATGGCCAACCTCTACTCCTATTGTAACCATTCTAACATGCAATGGCATTCATACTGCTACCGAA CGAAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCCAACGTTGAGGCCCCACGGGCTACTACA ACCCCTCGCTGACGCCATAAAACTCTTACCCAAAGAGCCCCAACGGGCTACCGGACATCTACCC TCTACATCACCGCCCCGACCTTAGCTCACCACATGCCCTTACTATGGAGCCCCCTCCCCATGCC AACCCCTGGTCAACCTAACCTGGCCCTCTTATTCTAGGACACCTCTAGGCTAGCGTTACTCA ATCCTCTGGTCAGGGGGCATCAAACACTCAAACACTACGCCCTGATGGCAGACTGCGAGCAGTAGGCC AAACAATCTCATATGAAGTCACCCATGCCATATTCTACTATCAACATTACTAATGAGTGGCTCTTAA CCTCTCCACCCCTATCACAAACACAAGAACACCTCTGGTACTCCTGCCATCATGGCCCTGGCATGA TGTGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCTCGACCTTGCCGAAGGGAGTCCGA ACTAGTCTCAGGGCTTCAACATCGAATACGCCGCAGGGCCCTTGCCCTTACTCTCATGGCCGAATACA CAAACATTATTATGATGAACACCCCTCAGGACTAACATCTCTAGGAAACAACATATGACGCACTCTCC CTGAACCTCACAAACATATTTCGACCAAGGCCCCACTTCTAACCTCCCTGTTTATGGATTGCAAC AGCATAACCCCGATCCGCTACGACCAACTCATGCCCTCATGGAAAACCTCTACCAACTCACCC TAGCATTACTATGTGGTATGTCATGCCATTACAATCTCAGCATTCCCCCTCAAACCTAACAGAGC ACTGGGACGCCACCGCCCCCTTCCCTCCGCTGCCAGGGCAGCATTTGTGGTAACTCTGGGAAACACA AGAAGAGAAATTGCTGGGTTAGAACAGATTATAACGAATTGGCTGCTCAGTGATCACTTGACAGTT TTTTTTTTAAATTTACCCAAATGCTCCCAAAATAAGAAATGCTACGCTCAGTGAGTGAATACA AAAAAGGAATTATTTCCCTTGAGGGCTTTATACATCTCTCCAAACCCCACCCCTATCTGTT TCTTCTCTCACATGGGGTACACATCACAGCTTCTTGGTCCATCCTTACCAACACCAC ACGCACACTCCACATGCCAGCAGTGGCACTTGGTGGCCAGAAAGTGTGAGGCTCATGACTGCT GTCTGTAGTTCTGTGAGCTCAGGCCCTCAAAGGCCCTGGAGCACCCCTTCTGTGACTGAGCCA GGGCCTGCATTTGGTTTCCCACCCACACATTCTCAACCATAGCTCTTAACAATACCAATAGC TAGGACCCGGCTGCTGTGCACTGGGACTGGGATTCCACATGTTGCCCTGGGAGTCTCAAGCTGGA CTGCCAGCCCCCTGCTCCCTCACCCATGCGTATGAGCATTTCTCAGAACTCCAAGGGAGTCACAGG CATCTTATAGTTCACTTAACATAGACACTGTTGAAAGCAGTCTCTTAAAGGGTAGCCCTGGA CTTAATACCAGCCGGATAACCTCTGGCCCCCACCCATTACTGACCTCTGGAGTCACTACTGTGGGTC GCCACTCCTCTGCTACACAGCACGGCTTTCAAGGCTGATTGAGAAGGGAAAGTAGGAAGAACGGG GTGCTGGCTAACAGCCCACAGAGCTCACATTCTGTCCTGGGTGAAAAATACATGTCATCTG ATATCTCTGAATTGAGAAATTAGCCTCCACATGTCATGGCTTAAGAGCCAGAGCAGGTTCTG GGAATTGGTCAAGTTACCTGTGGCAGGTGGTCTCGGTTACCAAAACAGGTTACCTGCACTGGTT GTCTTGTGCTCCACGGGTCTACAGGTTCCATGCCCCAAAGGCTTGAAGGTTACAGGATGTT TCGATTACTCAGTCTCCACGGGACTACTGTCCTGAGGATTGAGTTGGCTGGGGTAGAGGAGTTAA ACAACATTAAACAGAGTTCTCAAAATGCTAAAGGGATTGAGGATAGATAACATCCAATCACTGTT TGCACTTATCTGAATCTCCCTCTGGTGCACCCACGGTATTTACTGTGGAGAACATGCACTAGGAAT GTCTGGAAAAAGCTCTACAACATTGTTACAGCCTCACATTGTTAGAAGCTT
82	OPA1-ND1- 3'UTR*	GTGCTGCCCGCCTAGAAAGGGTGAAGTGGTTTCCGTGACGGACTGAGTACGGGTGCCTGTCAGG CTCTTGCGGAAGTCCATGCGCCATTGGGAGGGCTCGGCCGCGGCTGTGCCCTGCTGTCAGG GCCACTTCTGGTCAATTCTGGACCCGGGGAGCCGGCTGGGCTCACACGGGGCTCCCGCGTGG CCGTCTGGCGCCTGCGTACCTCCCCGCCGGGGATGTGGCAGACTACGTGGGCCGCTGTGG CTGATGGCCAACCTCTACTCCTATTGTAACCATTCTAACATGCAATGGCATTCATACTGCTACCGAA CGAAAAAATTCTAGGCTATATGCAACTACGCAAAGGCCCCAACGTTGAGGCCCCACGGGCTACTACA ACCCCTCGCTGACGCCATAAAACTCTCACCCAAAGAGCCCCAACGGGCCACATCTACCC TCTACATCACCGCCCCGACCTTAGCTCACCACATGCCCTTACTATGGACCCCCCTCCCCATGCC AACCCCTGGTCAACCTAACCTAGGCTCTTATTCTAGGACACCTCTAGGCTAGCGTACT ATCCTCTGGTCAGGGGGCATCAAACACTAACAGCCTGATGGCAGACTGCGAGCAGTAGGCC AAACAATCTCATATGAAGTCACCCATGCCATATTCTACTATCAACATTACTAATGAGTGGCTCTTAA CCTCTCCACCCCTATCACAAACACAAGAACACCTCTGGTACTCCTGCCATCATGGCCCTGGCATGA TGTGGTTTATCTCCACACTAGCAGAGACCAACCGAACCCCTCGACCTTGCCGAAGGGGAGTCCGA ACTAGTCTCAGGGCTAACATGCAATACGCCGCAGGCCCTTGCCCTTATTCTCATGGCCGAATACA CAAACATTATTATGATGAACACCCCTCACCACATCTCTAGGAAACACATATGACGCACTCTCC CTGAACCTACACAACATATTGTCACCAAGGACCCACTTCTAACCTCCCTGTTCTTATGGATTGCAAC AGCATACCCCGATCCGCTACGACCAACTCATGCACTCCCTATGGAAAAACTTCTACCAACTCACCC TAGCATTACTATGTGGTATGTCCTCATGCCATTACAATCTCAGCATTCCCCCTCAAACCTAACAGAGC ACTGGGACGCCACCGCCCCCTTCCCTCCGCTGCCAGGGCAGCATTTGTGGTAACTCTGGGAAACACA AGAAGAGAAATTGCTGGGTTAGAACAGATTATAACGAATTGGTCTGCTCAGTGATCACTTGACAGTT TTTTTTTTAAATATTACCCAAATGCTCCCAAAATAAGAAATGCACTCAGTGAGTGAATACA AAAAAGGAATTATTTCCCTTGAGGGTCTTTATACATCTCTCTCAACCCCACCCCTTATCTGTT TCTTCTCTCACATGGGGTACACATACAGCTTCTCTTGGTCCATCCTTACCAACACCAC ACGCACACTCCACATGCCAGCAGTGGCACTTGGTGGCCAGAAAGTGTGAGGCTCATGACTGCT

		GTCTGTAGTTCTGTGAGCTCAGGCCCTAAAGGCCGCGAGCACCCCTTCTGTGACTGAGCCA GGGCCCTGCATTTTGGTTCCCCACACATTCTCAACCATACTGGGACTGGGACATGTTGCCTGGAGTCAGCTGGA CTGCCA
83	OPA1-opt_ND1-3'UTR	GTGCTGCCCGCCTAGAAAGGGTAAGTGGTTTCCGTGACGGACTGAGTACGGGTGCCGTCAAGG CTCTTGCGGAAGTCCATGCCCATGGGAGGGCCTGGCCCGGGCTCTGCCCCCTGCTGAGG GCCACTTCCTGGTCATTCTGGACCCGGAGCCGGCTGGGGCTCACACGGGGCTCCCGCGTGG CCGTCGGCGCTGCGTGAACCTCCCCGGGGATGTGGCGACTACGTCGGCCCTGTGGC CTGATGGCAACCTGCTGCTGATCGTCCCACATCTGATGCCATGGCCCTCTGATGCTGACCC AGCGCAAGATCTGGGCTACATGCAGCTCGCAAGGGCCCCAACGTGGTGGGGCCCTGACCGCTG TGCAGCCCTCGCCGACGCCATCAAGTGTTCACCAAGGAGCCCTGAAGGCCGCCACAGCACCA CACCTGTACATCACGCCCCACCCCTGGCCCTGACCATGCCCTGCTGCTGTTGACCCCTGCCC ATGCCCAACCCCTGGTGAACCTGAACCTGGGCTGCTGTTCATCCTGGCCACAGCACCTGGCG TGTACAGCATCCTGAGCCGCTGGGGCAGCAACAGCAACTACGCCCTGATCGGCCCTGCG CCGTCGGGAGGACCATCAGCTACGAGGTGACCCCTGCCATCATCTGCTGAGCACCCTGCTGATGAG CGGCAGCTTCACCTGAGCACCCTGATGCCACCCAGGAGCACCTGTCGCTGCTGCCAGCTGG CCCTGGCCATGATGTGGTTCATCAGCACCCCTGGCCGAGACCAACCGCACCCCTTGCACCTGGCG AGGGCGAGAGCGAGCTGGTGAAGGGCTCAACATCGAGTACGCCGCCGGGCCCCCTTGCACCTGGT TCATGGCGAGTACACCAACATCATCATGATGAACACCCCTGACCACCACTTCTGGGACCCACC TACGACGCCCTGAGCCCGAGGCTGTACACCACCTACTTCGTGACCAAGACCCCTGCTGACCGCC TGTTCCTGTGGATCCGACCCGCTACCCCGCTTCCGCTACGACCGAGCTGATGCACTGCTGTTG GAACCTCTGCCCTGACCTGGGCTGGTGTGGTACGTGAGCATGCCATCACCATCGACGAGC ATCCCCCCCAGACCTAACAGGACTGGGACGCCAACCGGCCCTTCCCTCGCTGCCAGGAGCAT GTTGGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTAGAACAAAGATTATAACGAATTGGT GCTCAGTGTACTTGACAGTTTTTTAAATATTACCCAAAATGCTCCCAAATAAGAAATGC ATCAGCTAGTCAGTGAATACAAAAAGGAATTATTTCCCTTGGGACTTACATCTCTCCTC CAACCCACCCCTTACCTGTTCTCCCTCACATGGGGTACACATACACAGCTTCTCTTTGGT TCCATCCTTACCCACACCCAGCACACTCCACATGCCAGAGCTGGGACTTGGTGGCAGAA AGTGTGAGCCTCATGATCTGCTGTTGACTGCTGACGCTCAGGCTCCCTGCCAAAGGCTGGAGGCC CCCTCCCTGTGACTGAGCAGGGCTGCACTTTGGTTTCCCACCCACATTCTCAACCATAGT CCTCTAACAAATACCAATAGCTAGGACCCGGCTGCTGCACTGGGACTGGGATTCCACATGTTGC CTGGGAGTCTCAAGCTGGACTGCCAGCCCTGTCCTCCCTCACCCCATGCTATGAGCATTTCA GAACCTCAAGGAGTCACAGGCATCTTATAGTTCACGTTAACATATAGACACTGTTGAGCAGTCC TCTAAAGGGTAGCCCTGGACTTAACACAGCCGGATACCTCTGGCCCCACCCATTACTGTACCTC TGGAGTCACTACTGTGGGTGCCACTCCCTGCTACACGACCCGGCTTTCAAGGCTGTATTGAGAA GGGAAGTTAGGAAGAAGGGTAGCTGGCTGGGCTAACAGGCCACAGAGCTCACATCTGTCCTTGGG AAAAATACATGTCATCTGATATCTCTGAAATTGCTCCACATGTCATGGCTTAA GAGCCAGAAGCAGGGTCTGGAAATTGCAAGTTACCTGTGGCAGGTGTTGCTCGTTACCAAA ACGGTTACCTGCACTTTAGTCTTGTGCTCCACGGGTACAGAGTCCATCTGCCAAAGGT CTTGAAGCTGACAGGATGTTTCAACACATTAAACAGAGTCTCTCAAAATGCTAAAGGATTGAG TGGTGGGGTAGGAGAGTTAACACATTCTGAAATCTCCCCTTGGCTGCCAACGGTATTTC GTAGATAACATCCAACTACTGTTGCACTTACGTTGACTATCTGAATCTCCCCTTGGCTGCCAACGGTATTTC TGTGGAGAACATTGCAAGGAATGTCCTGAAAAAGCTTCAACACTGTTACAGCCTTCACATTGAG AAGCTT
84	OPA1-opt_ND1-3'UTR*	GTGCTGCCCGCCTAGAAAGGGTAAGTGGTTTCCGTGACGGACTGAGTACGGGTGCCGTCAAGG CTCTTGCGGAAGTCCATGCCCATGGGAGGGCCTGGCCCGGGCTCTGCCCCCTGCTGAGG GCCACTTCCTGGTCATTCTGGACCCGGAGCCGGCTGGGGCTCACACGGGGCTCCCGCGTGG CCGTCGGCGCTGCGTGAACCTCCCCGGGGATGTGGCGACTACGTCGGCCCTGTGGC CTGATGGCAACCTGCTGCTGATCGTCCCACATCTGATGCCATGGCCCTCTGATGCTGACCC AGCGCAAGATCTGGGCTACATGCAGCTCGCAAGGGCCCCAACGTGGTGGGCCCTGACCGCTG TGCAGCCCTCGCCGACGCCATCAAGCTGTTACCAAGGAGCCCTGAAGGCCGCCACAGCACCA CACCTGTACATCACGCCCCACCCCTGGCCCTGACCATGCCCTGCTGCTGGACCCCTGCCC ATGCCCAACCCCTGGTGAACCTGAACCTGGGCTGCTGTTACCTCTGCCCCACAGCACCTGGCG TGTACAGCATCTGTTGGAGCCGGCTGGGAGCACAGCAACTACGCCCTGATGCCGCCCTGCG CCGTCGGGCCAGACCATCAGTACGAGGTGACCCCTGCCATCATCTGCTGAGCACCCTGCTGATGAG CGGCAGCTTCACCTGAGCACCCTGATGCCACCCAGGAGCACCTGTCCTGCTGCCAGCTGG CCCTGGCCATGATGTGGTTCATCAGCACCCCTGGCCGAGACCAACCGCACCCCTTGCACCTGGCG AGGGCGAGAGCGAGCTGGTGAAGGGCTCAACATCGAGTACGCCGCCGGGCCCCCTTGCACCTGGT TCATGGCCGAGTACACCAACATCATGATGAACACCCCTGACCACCACTTCTCTGGGACCCACC TACGACGCCCTGAGCCCGAGCTGACACCACCTACTTCGTGACCAAGACCCCTGCTGCTGACCGCC TGTTCCTGTGGATCCGACCCGCTACCCCGCTTCCGCTACGGGAGCACCTGATGCACTGCTGTTG GAACCTCTGCCCTGACCCCTGGCCCTGCTGAGTGGTAGCTGAGCATGCCACCATCACCATCAGC ATCCCCCCCCAGACCTAACAGGACTGGGACGCCAACCGGCCCTTCCCTCCGCTGCCAGGGAGCAT GTTGGGTAATTCTGGAACACAAGAAGAGAAATTGCTGGGTTAGAACAAAGATTATAACGAATTGGT

		GCTCAGTGATCACTGACAGTTTTTTTTAAATATTACCCAAAATGCTCCCCAAATAAGAAATGC ATCAGCTCAGTCAGTGAATACAAAAAAGGAATTATTTTCCCTTGAGGGTCTTTATACATCTCCTC CAACCCCACCCCTTCTATTCTGTTCTCCTCACATGGGGGTACACATACACAGCTCCCTTTGGT TCCATCCTTACCAACCACACCACCGCACACTCCACATGCCAGCAGAGTGGCACTTGGTGGCAGAA AGTGTGAGGCCATGATCTGCTGTAGTTCTGTGAGCTCAGGTCCCTCAAAGGCCTCGGAGCACC CCCTTCCCTGTGACTGAGCCAGGGCCTGCATTGGTCCCCACACATTCTAACCATAGT CCTTCAACAATACCAATAGCTAGGACCCGGCTGCTGTGCACTGGACTGGGACTGGGACATGTTGC CTTGGAGCTCAAGCTGGACTCCA
85	β-actin-S primer	CGAGATCGTGCGGGACAT
86	β-actin-A primer	CAGGAAGGAGGGCTGGAAC
87	ND4-S primer	CTGCCTACGACAAACAGAC
88	ND4-A primer	AGTGCCTTCGTTAGTTGAG
89	ND6-F primer	ATGATGTATGCTTGTCTG
90	ND6-R primer	CTAATCCCCCGAGCAATCTC
91	ND6-S primer	AGTGTGGGTTAGTAATG
92	ND6-A primer	TGCCTCAGGATACTCCTC
93	β-actin-F primer	CTCCATCCTGGCCTCGCTGT
94	β-actin-R primer	GCTGTCACCTTCACCGTTCC
95	ND6-F primer	GGGTTTCTCTAACGCCTCTCC
96	ND6-R primer	CCATCATACTTTCACCCACAG
97	opt_ND6-F primer	CGCCTGCTGACCGGCTGCGT
98	opt_ND6-R	CCAGGCCTCGGGGTACTCCT
99	ND1-F primer	ATGGCCGCATCTCCGCACACT
100	ND1-R primer	TTAGGTTTGGGGGGAAATGCT
101	ND1-F primer	AACCTCAACCTAGGCCTCTA
102	ND1-R primer	TGGCAGGAGTAACCAAGAGGTG
103	ND1-F primer	AGGAGGCTCTGTCTGGTATCTG
104	ND1-R primer	TTTTAGGGGCTTTGGTGAA
105	opt-ND1-F primer	GCCGCCTGCTGACCGGCTGCGT
106	opt-ND1-R primer	TGATGTACAGGGTGTGGTGTGG
107	ND4-S primer	GCCAACAGCAACTACGAGC
108	ND4-A primer	TGATGTTGCTCCAGCTGAAG
109	opt-ND4-S primer	GCCTGACCCCTGATCCTGAAC
110	opt-ND4-A primer	GTGCGCTCGTAGTTGCTGTT
111	hsACO2	GGGCAGTGCCTCCCCGCCCCGCCGCTGGCGTCAAGTTCAGCTCCACGTGTGCCATCAGTGGATCCG ATCCGTCCAGCCATGGCTTCTATTCCAAGATGGTGTGACAGACATGCTTCTGCTCCCCGCTTAGC CCACGGAGGTGACTGTGGTTGTGGGGGGGGTCTTAAATAACTTTTAGCCCCCGTCTTCTATT GAGTTGGTTCAGATCTAACGAGCTCCATGCAACTGTATTGATGACAAGACTCCCATCTAA GTTTTCTCCTGCCTGATCATTGTTGCTGAAGGATTCTAGAGAACCTTTGTTCTTGAAGGA AAACAAGAATCCAAAACCAGTGAAGTGTGAGCTGTTCTGTGA
112	hsATP5B	GGGGTCTTGTCTCTGTACTGCTCTCCCTGCCCCTAACCCAAAAAGCTTCATTCTGTGTA CTGCACAAAGAGCCTGATTGAAGATATTCTTCTGAACAGTATTAAAGGTTCCAATAAAATGTACAC CCCTCAG

113	hsAK2	TGTTGGGTCCAAGAAGGAATTCTTCATCCCTGTGAGGCCAATGGGGAAATGATAGGACAGGCAA AGAGAACGCTTCCCTCAGGCTAGCAAAATATCATTTGATGTATTGATTAAGGAAACTTGCTTGATGTAT CTTGGCGTGTGTGCTACTCTCATCTGTGTATGTGTGTGTGTGCATGCACATAT GTGTTCACTCTGCTACCTGTAAAGTTAGGCTAGGTTGCTTACCAAGCTGTAACTCTTTTGTGTT GTTTGAGACAAGGTTCTGCTGCCACCTGGCTGGAGGTGAGCTGGCAGTCTGGCTACGGCA ACCTCTGCTCTGGCTCAAGCAATTATCCCACCTCAGCCTCCTGAGCAGCTGGGACTACAGGTG CATGCCACAACACCTGGCTGATATTGTATTTGTAGAGACAGGATTGCCAAGTGTGCCAGGATCACAGCTG GTCTGAACTCTAGGCTAACGCAATCCACCCACCTGGCCTCTGAAGTGCAGGATCACAGCTG AGCCACTACACCCAGCCCCAGCTGTTACTCTTTAACCATACTTTGATTTATTTTGACCAAAATGA ACTAACCCAGGAATCTTCAGGGACCGCAATTCCAGAACCTCATAGTATTCTTCATTTCCAGCAGC TGATTAGAAGTCCAGGATCATGTAAGTCAGGCAGGGTCACAGTCTGTGATGGCACATTATGGACAGA GAATTCCATTTCTAACCCATGATGAAACAAACCCACGTGAGTCAGTGTGACAGGGATCATTAA TTTTTCCCCCTAGGGAAAGGAAAAGGACACTACTTGCAGGGTACAGAAATTACTGGGAGGAGGAT ATCGTCATAAAAAGAGCCAGGCCAATTGGAAATTATTTGTATCTGATCATGATGCTGAAATAGCA ATTATTGGGATTGGGTTGAAACTGAATTGTCAGGAAATTAAACCAGGTGAAAGGTCTTTG AATTTCAGATTGTCTCTGAACATCCAGGCTGATCATCTGAGAGCAGTCAAATCTACTTCCCCAAAAAGA GACCAGGGTAGGTTTATTGCTTTATTTAATGTTGCTGTGTTCAAGTGTGAAACAAACAGTGT GTGATCTATTCTGGATTCTTGATCAGTATTCAACCCAGTCTCTCCAGGACATAAAACTG AAATCAGAATGTTCTTTAACGCCAACCCCTCTCTTCTAGATCCTAACCCCTAACCCCTAATTTAT GATGGCTATAGCCATGGACTTCCCAGAAAAGATCACCAGAAATAAGACACCTGTGACAGTTCAC AGCTTTATTCTAACCTTAGCTTCCCACATTGAGCATTTCTAACGGTCCCTGCTCTGGTCTC TGGTTGATTGTGGCAAACAGATGAAAGTAACAGACTGCTATGAGGACCAAAAAACGGCAGCCTCT GGAAAAACCCATTAGAAAGTCAGTGGCAGATCCAGTAATAATATGCCAGCCTCAGCATAATCTGCTG CTGACTCGATTCACTGGACTCTAAAGTGCCTCAGCTGGCAGCTGGCAGACTGGCAGTGGCTGAGCTCTCTGCCATCTGTGAGAC TACCAAGGGTCTTATCTGCTGTCACATGGCAACTGGGAGTGGCTGAGTACCTGGCCACCTTGTCTTCCCTCT TTGCCCTGGCCAAGTGTGCTGCTGCCCTGTGTTCTGGCTCTGGCTCTGGCTCTAAACCAACTCCA CCACTCTTAATGGAAACTCAGTGGCTTGTGTTCTGGGACATGACTCTGGGAAACATGACTCTGGGAAATGGG CAAGGAAGAGGAGTGAACAAACACTGTCAGCTATGTCAGGATCTGGGCTGGTCTGGGATCTTCTGGGTGAC AGTGGCAGTCATGAACTTCTAGAATCAGCTCCCC
114	hsALDH2	GAATCATGCAAGCTTCCCTCCCTCAGCCATTGATGGAAAGTTCAGCAAGATCAGCAACAAACCAAGAA AAATGATCTTGCCTGCTGAATATCTGAAAAGAGAAATTCTTCTACAAAAATCTTGGGTCAGAAAG TTCTAGAATTGAAATTGATAAACATGGTGGGTTGAGGGTAAGAGTATGAGGAAACCTTTAAC GACAACAATACTGCTAGCTTCTAGGATGATTTTAAAGGAAATTAGATCAATGTTATCCTCTCTGAA ACGCTTCTCTAACATCAGTGGTTATAGGGAAAGAAAAGCTATTGTTCAATTATACCAATTAGCA ACTGCTACACCCCTGCTTGTATTCTGGGCTAAGGATTCTTAAACACTAGCTGCTTAACTTACA
115	hsCOX10	GAGCACTGGGACGCCACCGCCCTTCCCTCCGCTGCCAGGCGAGCATGTTGGTAATTCTGGAA ACAAGAAGAGAAATTGCTGGGTTAGAACAGATTATAAACGAATTGGTCTCAGTGTACTGAC AGTTTTTTTTTTAAATATTACCAAATGCTCCCAATAAGAAATGCTCAGTCAGTCAGTGAAT ACAACAAAGGAATTCTTCTGAGGGCTTTATACATCTCTCCCTCCACCCCTCTATTCTG TTCTTCTCTCACATGGGGTACACATACAGCTTCTCTTGGTCCATCTTACCAACACC ACACGCACACTCACATGCCAGAGTGGCAGTGGCTGAGGAGCTGAGCCTCATGATCTG CTGCTGTAGTTCTGAGCTAGGCTCCCTCAAAGGCTCGGAGCACCCCCCTCTGGTACTGAGC AGGGCCTGCATTGGTTTCTCCACCCCCACACATTCTCAACCATAGTCTCTCTAACAAATCCAATA GCTAGGACCCGGCTGCTGCACTGGACTGGGAGTCCACATGTTGCTTGGAGTCTCAAGCTG GACTGCCAGCCCTGCTCTCCCTCACCCCCATTGCGTATGAGCATTCTAGAACCTCAAGGAGTCACA GGCATCTTATAGTCACGTTAACATAGAACACTGTTGGAGCAGTCTCTCTAACAAAGGGTAGCCCTG GACTTAATACCGCCGGATACCTCTGGGCCCCACCCATTACTGTAACCTCTGGAGTCACTACTGTGG TCGCCACTCTCTGCTACACAGCACGGCTTTCAAGGCTGATTGAGAAGGGAGTTAGGAAGG GTGTGCTGGCTAACAGCCCACAGAGCTCACATTCTGCTCCCTGGGTGAAAATACATGTCACATCC TGATATCTCTGAAATTGAGAACATTAGCCTCCACATGTGCAATGGCTTAAGAGCCAGAAGCAGGGTCT GGGAATTGGCAAGTTATCTGTGGCCAGGTGTGGCTCGGTTACCAAATACGGTACCTGCACTGCTT TTAGTCCTTGCTCCCACGGGCTGAGAGTCCCATGCCCCAAAGGTCTGAGGCTGACAGGAT GTTTCATTACTCAGTCTCCAGGGACTGCTGGCTGGTAGGGATTCTGGTGGGGAGAGGTT AAACACATTTAACAGAGTCTCTCTAACAAATGCTAACAGGGATTGTAGGATATAACATCCAATCACT GTTGCACCTATCTGAAATCTTCTCTTGGCTGCCCTGGTACAGCTTACATTTGACAATTGATTCTTCTT AAATGTCGGAAAAGCCTCTACAACTGTTACAGCTTACATTTGACAATTGATTCTCTTCT TTCCACAATAAAATGGTATACAAGAAC
116	hsUQCRFS1	GAGACTGGACTCAAGTCATAGGCTTCTTCAGTCTTATGTCACCTCAGGAGACTTATTGAGAGGAA GCCTCTGCTACTGAAATTGATTTGAAATATGTAAGAATTGATGATGTTGCAAAACATTAATGTTGAA AAATTGAAATTAAATGTTGAAATCTTCAGGCATTACTTAATAAAGACACTGTTAGCACTGTTATGCT CAGTCATACACGCCAGGAAAGGTACAATGTCCTTAGCTAATTCTAACAAATTACAGACTGGTGTACAA GATACTTGTG
117	hsNDUFV1	CCCACCAACCTGGCTGCTGCCCTGCTATCCATGTGGAATGCTGGACAATAAGCGAGTGCTGC CCACCCCTCCAGCTG
118	hsNDUFV2	TTTATATTGAACTGTAATATGTCAGTAGAGAAATAAAATATGGACTTCAATCTACGTAAACTTAA
119	hsSOD2	ACCACGATCGTTATGCTGAGTATGTTAGGCTTTGACTGTTGTTGAGTGGTATAGAGTACTGCAG AATACAGTAAGCTGCTCTATTGTAAGCATTCTGATGTTGCTTAGTCACCTATTCTAACAAACTTAAT GTTCTGAAATAATTCTTACTAAACATTGTTATTGGGCAAGTGATTGAAAATAGTAAATGCTTGTG ATTGA
120	hsCOX6c	TCTTGGAAATAAGAATTCTCAGGTTGAATTACCTAGAAGTTGCACTGACTGTGTTCTGAACT ATGACACATGAAATATGTTGGGCTAAGAAATAGTTCTCTTGTATAACAAATAACAAACTTGGAC AGTAAGTCTTCTCAGTTCTAACATGATAATGCAAGGGCACTTACTAGCATAAGAATTGGTTGGGATTAA

		CTGTTTATGAAGCTAACCTGATTCCGTGTTTGTAAAATTCTATTGTTAGCACATCTTAACGTGATAGTT
121	hsIRP1	GAGACGTGCACCTGGTCGTGCCCGAGGGAGGAAGCCGCACCACCAGCCAGCGCAGGGCCCTGGTGAGAGGCCCTGGCTGGGAGGGTGCTGCCTGTAGATGGAGCAAGTGAGCACTGAGGTCTGGTCCAATCTGTAGGCACAAACAGAAGCTTCTACATTCTCTATAATTGGTAAATCATCTCTCTTTTCCAGAATTGGAAAGCTAGAAATGGTGGGAATGTCAGTAGTGCAGAAAGAGAGAAACCAAGCTGCTCTTAAAGTACTGATCACAGGAGCTGGCTTCACTGTTCTCTTAAATCTCAGCTGCTCAATGAAACCTCCTCTGAGGGTCATTTCTCTGTATTAATTACCAAGTGTAAAGTGCACATAGATAAGAACATTGACACAAACCTCTCAGGAGGGTGTCTCCTACCCCTTATTGTCCTTACGCTGCTCAATGAAACCTCCTCTGAGGGTCATTTCTCTGTATTAATTACCAAGTGTAAAGTGCACATAGATAAGAACATTGACACAAACCTCTCAGGAGGGTGTCTCCTACCCCTTTCAGAGTGAATCATCCAGACTCCTCATGGATAGTGGGGTGTAAAGTGTGTTGATTATGACCTTGTATGAGATCCACATAAAAGAAATGTGAGTTTCTTACTATCTTTCAAGCAGAGACCTTGTGGGAGGGCGTTGGGAGAACACA
122	hsMRPS12	CAGAAGAAGTGACGGCTGGGGCACAGTGGGCTGGGCCCCCTGCAGAACATGAACCTCCGCTCCGGCTCCACAGGGTCTCCGATGCTGGCTTGCCTCTAGAGGCAGCCACTCATGGATTCAAGTCCTGGCTCCGCCTTCCCATCAGGACCACT
123	hsATP5J2	AGAGGACACACTCTGCACCCCCCACGACCTGGCCCGAGCCCCCTCCGTGAGGAA
124	mrSOD2	AGCCCTCCGCCAGGCTGTGTGTCAGGCCGTGGTGGGTGTTGTTAGTAGTGAGCATTGCA
125	hsOXA1L	CTTATGTTCTGTGCGCATTCTGGCAGGAATTCTGTCTCTCAGAGACTCATCCTCAAACAGACTTGA CACTGTGTCCTTGCCCCAGTCTAGGAACTGTGCCACACAGAGATGTTACTTAAAAACGGATTCTCATGAAACACTTGTACTTATGTTATAAGAGAGCACTGGTAGCCAAGTGATCTCCATTACAGAGATTAGTAAACCTCTGTACTACATGCTG
126	MTS-COX10	MAASPHTLSSRLLTGVGGSVWYLERRT
127	MTS-COX8	MSVLTRLLRGLTRLGSAAPVRRARIHSL
128	MTS-OPA1	MWRLRRAAVA
129	hsCOX10	MAASPHTLSSRLLTGVGGSVWYLERRT
130	scRPM2	MAFKSFYISKYHRSAQKKTATSSFDSSYQYLQRQNQGLVNSDPVLHASHLHPHPVVVANVNYYNNVDDILH PHDLDSSINNTNNPLTHEELLYNQNVSLSLKCQQSTNYVNNNNNNQHRYY
131	IcSirt5	MRKRSLRCHLWSANASL.SPRKDEVTSRKESENIVKGKKKKSHLHLLLFTASKIGTDSDVFDVQKSKECCKE LGLLFTSLIHSIGSPFPDEEPKAAAVFLPGSLPQLTVLVLAPGSGSCPTGKSTPHLAASGRNAELLRPQNSMIVRQFTCRGTTISHLCALRKPHDSPRNMARP
132	IbNDUS7	MLRRTSFNFTGRAMISRGSPEWSHRLDKKKTTMMHKLGTSKPNNALQYAQMTL
133	ncQCR2	MISRSALSRGSQALRRPAAAKTAQRGFAAAASPAASYEPTTIAG
134	hsATP5G2	MPELILYVAILTSLVAERLVPGPHACAEPSSRCSAPLCLCSGSSPATAPHPLKMFACSKFVSTPSLVK STSQLLSRPLSAVVLKRPEILTDESSSLAVSCPITSVSSRSFQTSAISRDIDTA
135	hsLACTB	MYRLMSAVTARAAAPQGLASSCGRGVCQHQRALPPLGHQWVGGLGLGLALGVKLAGGLRGAAPAGS PAAPDPEASPLAEPPEQSLAPWSPOTAPPSCRCFARAIESRDL
136	spilv1	MTVLAPLRLHLTRAFFSSYGREIALQKRFNLNNSCSAVRYYGTGFNSNLLRKKLKNAFGVVRANSTKSTSTV TTASPIKYDSSFVGKTGGEIFHDMMLKHNVKHVFYPGGAILPVFDAIYRSPHFEFILPRHEQAAGHA
137	gmCOX2	MILCPLEAFIVQHILTISVMGLLSCFRSTVLRKCKGSSGMRSFLYTNNFQRNLISSGGNESYYGYFNRRSY TSLYMGTVGGITSARIRVPNVGCEGFMCSSHLSITQRNSRLIHSTSCKIPN
138	crATP6	MALQQAAPRVFGLLGRAPVALGQSGILTGSSEGFKNQGFNGSLQSVENHVYAQAFSTSSSQEEQAAPSIQGA SGMKLPGMAGSMILLGKSRSGLRTGSMVPFAAQAMNMGGMAILGDTIMVAKGLVHLTQAAVETHLQHL
139	hsOPA1	MWRLRRAAVACEVCQSLVKHSSGIKGSPLQLKHLVSRSIYHSHHPTLKLQRPQLRTSFQQFSNLPLRKLFSPIKYGYQPRRN
140	hsSDHD	MAVLWRLSAVCQGALGGRALLRTPVVRPAHISAFLQDRPIPEWCQVQHILSPSHH
141	hsADCK3	MAAILGDTIMVAKGLVQLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGKVQGQDKHEEYFAENFG GEGEWFHFSVPHAAAGASTDFSSASAPDQSAPPGLAHSEGPPAAYVASGPFRAGFPQASSPLGRA NGRLFANPRDSFSAMGFQRRRF
142	osP0644B06. 24-2	MALLLRHSPKLRRRAHILGCTGERTVVRHFSSSTCSSLVKEDTVSSSNLHPEYAKKIGGDFSHDRQSGKEL QNFKVSPQEASRASNFMRASKYGMPIТАNGVHSLFSCGQVWPSRCF
143	Neurospora crassa ATP9 (ncATP9)	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPQLTKRTQMTSIVNATTRQAFQKRA
144	hsGHITM	MLAARLVCRLTLPSRVFHFAFTKASPVVKNSITKNQWLTPSRE
145	hsNDUFAB1	MASRVLSAYVSRLPAAFPLPRVRMLAVARPLSTALCSAGTQTRLGTLQPALVLAQVPGRVTLQLCRQY
146	hsATP5G3	MFACAKLACTPSLIRAGSRVAYRPISAVSLRPEASRTGEGSTVFNGAGNGVSQLIOREFQTSAIR
147	crATP6 _hsADCK3	MALQQAAPRVFGLLGRAPVALGQSGILTGSSEGFKNQGFNGSLQSVENHVYAQAFSTSSSQEEQAAPSIQGA SGMKLPGMAGSMILLGKSRSGLRTGSMVPFAAQAMNMGGMAILGDTIMVAKGLVHLTQAAVETHLQHL GIGGELIMAARALQSTAVEQIGMFLGKVQGQDKHEEYFAENFGGPEGEFHFSVPHAAAGASTDFSSASAPD QSAPPGLAHSEGPPAAYVASGPFRAGFPQASSPLGRANGRLFANPRDSFSAMGFQRRFGG
148	ncATP9_ncAT P9	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPQLTKRTQMTSIVNATTRQAFQKRAMAST RVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSPQLTKRTQMTSIVNATTRQAFQKRA

149	zmLOC10028_2174	MALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPHADRRHVIALRRCPLPASAVLAPE LLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPY
150	ncATP9_zmL_OC100282174_spilv1_ncATP9	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRITQGTGPLQLKRTQMTSIVNATTRQAQFKRAMALLR AAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPHADRRHVIALRRCPLPASAVLAPELLHAR GLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMTV LAPLRRLHTRAAFSSYGREIALQKRF LNLNNSCSAVRRYGTGFNSNNLRIKKLNNAFGVVRANSTKSTVTTASPIKYDSSFVGKTGGEIFHDMLKH NVKHFVGGPGAILPVFDAYRSRHFEPILPRHEQAAGHAMASTRVLASRLASQMAASAKVARPAVRVAQV SKRTIQTGPLQLKRTQMTSIVNATTRQAQFKRA
151	zmLOC10028_2174_hsADC_K3_crATP6_hsATP5G3	MALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPHADRRHVIALRRCPLPASAVLAPE LLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMAAILGDTIMVAKGLVKLTQAAVE THLQHLGIGGELIMAARALQSTAVEQIGMFLGVQGQDKHEEYFAENFGGPEGEFHFSVPHAGASTDFS SASAPDQSAPPSLGHAHSEGPAPAYASGPFRAGFPQASSPLGRANGLRFANPRDSFSAMGFORRF MALQQAAQPRVFGLLGRAPVALGQSGILTGSQFKNQGFNGQLQSVENHVYQAQFSTSSSQEEQAQPSIQGA SGMKLPGMAGSMILLGKSRSGLRTGSMVPFAAQQMNMFAACAKLACTPSLIRAGSRVAYRPISASVLSR PEASRTGEGSTVFNGAQNGVSQLIQRFTSAIR
152	zmLOC10028_2174_hsADC_K3_hsATP5G3	MALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPHADRRHVIALRRCPLPASAVLAPE LLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMAAILGDTIMVAKGLVKLTQAAVE THLQHLGIGGELIMAARALQSTAVEQIGMFLGVQGQDKHEEYFAENFGGPEGEFHFSVPHAGASTDFS SASAPDQSAPPSLGHAHSEGPAPAYASGPFRAGFPQASSPLGRANGLRFANPRDSFSAMGFORRF MFACAKLACTPSLIRAGSRVAYRPISASVLSRPEASRTGEGSTVFNGAQNGVSQLIQRFTSAIR
153	ncATP9_zmL_OC100282174	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRITQGTGPLQLKRTQMTSIVNATTRQAQFKRAMALLR AAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPHADRRHVIALRRCPLPASAVLAPELLHAR GLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPY
154	hsADCK3_zm_LOC100282174_crATP6_hsATP5G3	MAAILGDTIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGVQGQDKHEEYFAENF GGPEGEFHFSVPHAGASTDFSSASAPDQSAPPSLGHAHSEGPAPAYASGPFRAGFPQASSPLGRA NGRLFANPRDSFSAMGFQRRFMALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPH DRRHVIALRRCPLPASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPY MALQQAAQPRVFGLLGRAPVALGQSGILTGSQFKNQGFNGQLQSVENHVYQAQFSTSSSQEEQAQPSIQGA SGMKLPGMAGSMILLGKSRSGLRTGSMVPFAAQQMNMFAACAKLACTPSLIRAGSRVAYRPISASVLSR PEASRTGEGSTVFNGAQNGVSQLIQRFTSAIR
155	crATP6_hsADCK3_zmLOC100282174_hsATP5G3	MALQQAAQPRVFGLLGRAPVALGQSGILTGSQFKNQGFNGQLQSVENHVYQAQFSTSSSQEEQAQPSIQGA SGMKLPGMAGSMILLGKSRSGLRTGSMVPFAAQQMNMMAAILGDTIMVAKGLVKLTQAAVETHLQHLGIG GELIMAARALQSTAVEQIGMFLGVQGQDKHEEYFAENFGGPEGEFHFSVPHAGASTDFSSASAPDQSA PPSLGHAHSEGPAPAYASGPFRAGFPQASSPLGRANGLRFANPRDSFSAMGFQRRFMALLRAAVSE LRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPHADRRHVIALRRCPLPASAVLAPELLHARGLLPR HWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMFACAKLACTPSLIRAGSRVAYRPISASVLSRPE ASRTGEGSTVFNGAQNGVSQLIQRFTSAIR
156	hsADCK3_zm_LOC100282174	MAAILGDTIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGVQGQDKHEEYFAENF GGPEGEFHFSVPHAGASTDFSSASAPDQSAPP SLGHAHSEGPAPAYASGPFRAGFPQASSPLGRA NGRLFANPRDSFSAMGFQRRFGGMALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNP HADRRHVIALRRCPLPASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARP YGG
157	hsADCK3_zm_LOC100282174_crATP6	MAAILGDTIMVAKGLVKLTQAAVETHLQHLGIGGELIMAARALQSTAVEQIGMFLGVQGQDKHEEYFAENF GGPEGEFHFSVPHAGASTDFSSASAPDQSAPP SLGHAHSEGPAPAYASGPFRAGFPQASSPLGRA NGRLFANPRDSFSAMGFQRRFGGMALLRAAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNP HADRRHVIALRRCPLPASAVLAPELLHARGLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARP YGGMALQQAAQPRVFGLLGRAPVALGQSGILTGSQFKNQGFNGQLQSVENHVYQAQFSTSSSQEEQAQPSI QGASGMKLPGMAGSMILLGKSRSGLRTGSMVPFAAQQMNM
158	ncATP9_zmL_OC100282174_spilv1_GNFP_ncATP9	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRITQGTGPLQLKRTQMTSIVNATTRQAQFKRAMALLR AAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPHADRRHVIALRRCPLPASAVLAPELLHAR GLLPRHWSHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMTV LAPLRRLHTRAAFSSYGREIALQKRF LNLNNSCSAVRRYGTGFNSNNLRIKKLNNAFGVVRANSTKSTVTTASPIKYDSSFVGKTGGEIFHDMLKH NVKHFVGGPGAILPVFDAYRSRHFEPILPRHEQAAGHAMRKRSLRCHLWSANASLSPRKDEVTSRKESE NLVKGKKNNKKSHLHLLL TASKIGTDSVFDVQKSKECCCKELGLLFTSLIHISIGSFPDEEPKAAAVFLPGSLP QLTVLVAPGSGSCPTGKSTPHLAASGRNAELLRPQNMSMVRQFTCRGTTSHLCAHLRKPHDSRNMRP MALLLRHSPKLRRRAHALGCERGTVRHFSSSTCSSLVKEDTVSSSNLHPEYAKKIGGSDFSHDRQSGKEL QNFKVSPQEASRASRASNFMRASKYGMPIANGVHSLFCGQVVPSCRCMPPELILYVAITLSVAERLVGP AEPSPFRSSRCSCAPLCCLCGSSSPATAPHPLKMFACSKFVSTPSLVKSTSQQLSRPLSAVVLKRPEILTD LSSLA VSCPLTSVSSRSFQTS AISRDIDTAMA STRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSP LQTLKRTQMTSIVNATTRQAQFKRA
159	ncATP9_zmL_OC100282174_spilv1_IcSirt5_24_2_hsATP5G2_ncATP9	MASTRVLASRLASQMAASAKVARPAVRVAQVSKRITQGTGPLQLKRTQMTSIVNATTRQAQFKRAMALLR AAVSELRRRGRGALTPLPALSSLLSSLSPRSPASTRPEPPNNPHADRRHVIALRRCPLPASAVLAPELLHAR GLLPRHW SHASPLSTSSSSSRPADKAQLTWVDKWIPEAARPYMTV LAPLRRLHTRAAFSSYGREIALQKRF LNLNNSCSAVRRYGTGFNSNNLRIKKLNNAFGVVRANSTKSTVTTASPIKYDSSFVGKTGGEIFHDMLKH NVKHFVGGPGAILPVFDAYRSRHFEPILPRHEQAAGHAMRKRSLRCHLWSANASLSPRKDEVTSRKESE NLVKGKKNNKKSHLHLLL TASKIGTDSVFDVQKSKECCCKELGLLFTSLIHISIGSFPDEEPKAAAVFLPGSLP QLTVLVAPGSGSCPTGKSTPHLAASGRNAELLRPQNMSMVRQFTCRGTTSHLCAHLRKPHDSRNMRP MALLLRHSPKLRRRAHALGCERGTVRHFSSSTCSSLVKEDTVSSSNLHPEYAKKIGGSDFSHDRQSGKEL QNFKVSPQEASRASRASNFMRASKYGMPIANGVHSLFCGQVVPSCRCMPPELILYVAITLSVAERLVGP AEPSPFRSSRCSCAPLCCLCGSSSPATAPHPLKMFACSKFVSTPSLVKSTSQQLSRPLSAVVLKRPEILTD LSSLA VSCPLTSVSSRSFQTS AISRDIDTAMA STRVLASRLASQMAASAKVARPAVRVAQVSKRTIQTGSP LQTLKRTQMTSIVNATTRQAQFKRA
160	ND4	MLKLIVPTIMLPLTLWLSKKHMIWINTTHSLIIISIPLFFNQINNNLFSCSPTFSSDPLTTPLLMLTTWLLPLTI MASQRHLSSEPLSLRKKLYLSMLISLGQISLIMTFATELIMFYIFFETTLIPTLAIITRWGNQPERLNAGTYFLFY LVGSLPLPLLIAIYTHNTLGLSNLNNLTLT A QELSNSWANNLMWLAYTMAMFVKMPLYGLHLWLPKAHVEAPIA GSMVLA VLLKLGGYGMMLRRTLILNPLTKHMAYPFLVLSLWGMIMTSSICLRQDLKSLIAYSSISHMALVVT

		AIIQTPWSFTGAVILMIAHGLTSSLFCCLANSNYERTHSRIMILSQGLQTLPLMAFWLLASLANLALPPTINLLGELSVLVTTFSWSNITLLTGLENMLVTALYSLYMFTTQWGSLSHHINNMKPSFTRENTLMFMHLSPILLSLNPDIITGFSS
161	ND6	MMYALFLLSVGLVMGPGFVGFSKPSPPIYGGLVLIVSGVVGCVIILNFGGGYMGLMVFLYLGGMMVFGYTTA MAIEEYPEAWGSGVEVLVSVLVGLAMEVGLVWWKEYDGVVVVNFNSVGSWMIYEGEGLIREDPIGA GALYDYGRWLVVVTGWTLFVGVYIVIEIARGN
162	ND1	MANLLLLIVPILIAMAFMLTERKILGYMQLRKGPNVGPYGLLQPFADAIKLFTKEPLKPATSTITLYITAPTLA LTIALLLWTPLPMPNPLVNLNLGLLFILATSSLAVYSLWSGWASNSNYALIGALRAVAQTISYEVTLAIILLSTL LMSGSFNLSTLTTQEHWLWLLPSWPLAMMWFISTLAETNRTPFDLAEGESELVSGFNIEYAAGPFAFFMA EYTNIIMMNTLTTTIFLGTTYDALSPELYTTYFVTKLTLTSFLWIRTAYPRFRYDQLMHLLWKNFLPLTLALL MWYVSMPIISSIPPQT

Adeno-associated virus (AAV)

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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 recognisably distinct population at a genetic level.

[0074] 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, Hu_22 AY530588, Hu_24 AY530590, Hu_21 AY530587, Hu_27 AY530592, Hu_28 AY530593, Hu_29 AY530594, Hu_63 AY530624, Hu_64 AY530625, Hu_13 AY530578, Hu_56 AY530618, Hu_57 AY530619, Hu_49 AY530612, Hu_58 AY530620, Hu_34 AY530598, Hu_35 AY530599, AAV2 NC_001401, Hu_45 AY530608, Hu_47 AY530610, Hu_51 AY530613, Hu_52 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: Hu_9 AY530629, Hu_10 AY530576, Hu_11 AY530577, Hu_53 AY530615, Hu_55 AY530617, Hu_54 AY530616, Hu_7 AY530628, Hu_18 AY530583, Hu_15 AY530580, Hu_16 AY530581, Hu_25 AY530591, Hu_60 AY530622, Ch_5 AY243021, Hu_3 AY530595, Hu_1 AY530575, Hu_4 AY530602 Hu_2, AY530585, Hu_61 AY530623; Clade D: Rh_62 AY530573, Rh_48 AY530561, Rh_54 AY530567, Rh_55 AY530568, Cy_2 AY243020, AAV7 AF513851, Rh_35 AY243000, Rh_37 AY242998, Rh_36 AY242999, Cy_6 AY243016, Cy_4 AY243018, Cy_3 AY243019, Cy_5 AY243017, Rh_13 AY243013; Clade E: Rh_38 AY530558, Hu_66 AY530626, Hu_42 AY530605, Hu_67 AY530627, Hu_40 AY530603, Hu_41 AY530604, Hu_37 AY530600, Rh_40 AY530559, Rh_2 AY243007, Bb_1 AY243023, Bb_2

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.

[0075] 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).

[0076] 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 characterised. 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.

[0077] 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.

[0078] 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.

[0079] 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 derivatised for the purpose of administration to patients. Such derivatisation 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. Derivatisation 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.

[0080] 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.

[0081] 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.

[0082] 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*.

[0083] 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.

[0084] 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 wildtype 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.

[0085] 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.

[0086] 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 internalisation, 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.

[0087] 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 cotransfected 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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. internalisation, 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.

[0092] 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.

[0093] 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.

[0094] 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 transcapsidated 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.

[0095] The invention additionally provides a host cell comprising a vector or AAV viral particle of the invention.

Recombinant nucleic acid sequences

[0096] 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.

[0097] 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**.

[0098] 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.

[0099] 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 al (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 al (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/>).

[00100] 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.

[00101] 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).

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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 cotranslational protein import into the mitochondria.

[00108] 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), hsGHTM, 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**).

[00109] 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**), hsUQCRRFS1 (**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**), mSOD2 (**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**.

[00110] 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

[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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 rhodopsin kinase for rods and cones (Allocca et al., 2007, J Virol 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).

[00115] The vector of the invention may also comprise one or more additional regulatory sequences which 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.

[00116] 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.

[00117] 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

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] 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.

[00123] 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.

[00124] 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

[00125] 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.

[00126] 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 of the invention to the patient by direct retinal, subretinal or intravitreal injection. Accordingly, LHON is thereby treated or prevented in the patient.

[00127] 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.

[00128] 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.

[00129] 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.

[00130] 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.

[00131] 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.

Pharmaceutical Compositions

[00132] 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, stabiliser 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.

[00133] 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.

[00134] 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.

[00135] 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

[00136] 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).

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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

[00141] 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.

[00142] 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.

[00143] 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.

[00144] “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.

[00145] 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.

[00146] 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.

[00147] 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).

[00148] “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.

[00149] 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.

[00150] 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.

[00151] 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 following *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.

[00152] 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, chiral/methyl phosphonates, 2-O-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.

[00153] 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.

[00154] 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

[00155] 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.

[00156] 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.

[00157] 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.

[00158] 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 groove 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).

[00159] 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-indacene)propionic 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.

[00160] In other embodiments, the probes can be indirectly labeled, for example, with biotin or digoxigenin, 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

[00161] 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.

[00162] 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)).

[00163] 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.

[00164] 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.

[00165] 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).

[00166] 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.

[00167] 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.

[00168] 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.

[00169] 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.

[00170] 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.

[00171] 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.

[00172] 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.

[00173] 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.

[00174] 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.

[00175] 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.

[00176] 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.

[00177] 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.

[00178] 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.

[00179] 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.

[00180] 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.

[00181] 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 polyethylene 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).

[00182] 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.

[00183] 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.

[00184] 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.

[00185] 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

[00186] 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

[00187] *1.1 plasmid preparation*

[00188] 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**).

[00189] 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/Sall restriction enzymes to form cohesive ends, and then embedded into an AAV vector with EcoRI/Sall 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.

[00190] 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.

[00191] *1.2 cell transfection*

[00192] One day before transfection, HEK293 cells were inoculated to 225 cm² 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% CO₂ incubator overnight. The culture medium were replaced with fresh DMEM with 10% bovine serum on the day of transfection.

[00193] 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.

[00194] *1.3 Collection, concentration and purification of the recombinant adeno-associated virus*

[00195] 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.

[00196] 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.

[00197] 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.

[00198] 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

[00199] 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

[00200] 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.

[00201] 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:

β-actin-S: CGAGATCGTGCAGGACAT (SEQ ID NO: 85);

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

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

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

[00202] 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 μ l, ddH₂O 8 μ l, 1 μ l of each primer, and the cDNA sample 2.5 μ l, were added to an overall volume of 25 μ l. 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.

[00203] 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

[00204] 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.

[00205] 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

[00206] 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.

[00207] 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

[00208] 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.

[00209] 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

[00210] 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**).

[00211] 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*

[00212] 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.

[00213] 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 μ l 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% CO₂. About 0.02 μ l PBS was mixed with 2×10^{10} vg/0.02 μ l 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.

[00214] Real-time PCR tests similar to example 3 was following using the following primers:
 β-actin-S: CGAGATCGTGCAGGACAT (**SEQ ID NO: 85**);
 β-actin-A: CAGGAAGGAGGGCTGGAAC (**SEQ ID NO: 86**);
 ND4-S: GCCAACAGCAACTACGAGC (**SEQ ID NO: 107**);

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

[00215] 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.

[00216] **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**).

[00217] **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**).

[00218] 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.

[00219] 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.

[00220] 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.

[00221] 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

[00222] 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**).

[00223] The plasmid screening for COX10-ND6-3'UTR (**SEQ ID NO: 21**) used the following primers:

ND6-F: ATGATGTATGCTTGTTCTG (**SEQ ID NO: 89**),

ND6-R: CTAATTCCCCGAGCAATCTC (**SEQ ID NO: 90**),

[00224] The transfected and screened virus rAAV2-ND6 had a viral titer of 2.0×10^{11} 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.

[00225] Real-time PCR tests similar to example 3 was following using the following primers:

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

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

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

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

[00226] 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

[00227] 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**).

[00228] Three groups of rabbits were injected: A: 10^{10} vg/50 μ l of rAAV2-opt_ND6, B: 10^{10} vg/50 μ l of rAAV2-ND6 (example 9), and C: 10^{10} vg/50 μ l 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.

[00229] Real-time PCR tests similar to example 3 was following using the following primers:

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

β -actin-R: GCTGTCACCTCACCGTIC (SEQ ID NO: 94);
 ND6-F: GGGTTTCTTCTAACGCCTCTCC (SEQ ID NO: 95);
 ND6-R: CCATCATACTCTTCACCCACAG (SEQ ID NO: 96);
 opt_ND6-F: CGCCTGCTGACCGGCTGCGT (SEQ ID NO: 97);
 opt_ND6-R: CCAGGCCTCGGGTACTCCT (SEQ ID NO: 98);

[00230] 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).

[00231] 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

[00232] 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).

[00233] The plasmid screening for COX10-ND1-3'UTR (SEQ ID NO: 25) used the following primers:

ND1-F: ATGGCCGCATCTCCGACACT (SEQ ID NO: 99),

ND1-R: TTAGGTTGAGGGGAATGCT (SEQ ID NO: 100),

[00234] The plasmid screening for opt_COX10*-opt_ND1-3'UTR (SEQ ID NO: 55) used the following primers:

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

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

[00235] Three groups of rabbits were injected: A: 10^{10} vg/50 μ l of rAAV2-opt_ND1, B: 10^{10} vg/50 μ l of rAAV2-ND1 (example 9), and C: 10^{10} vg/50 μ l of rAAV2-EGFP. No obviously

abnormality, conjunctival congestion, secretions, or endophthalmitis were observed and the intraocular pressure were not elevated in all the rabbits.

[00236] Real-time PCR tests similar to example 3 was following using the following primers:
ND1-F: AGGAGGCTCTGTCTGGTATCTTG (SEQ ID NO: 103);
ND1-R: TTTTAGGGCTTTGGTGAA (SEQ ID NO: 104);
opt_ND1-F: GCCGCCTGCTGACCGGCTGCGT (SEQ ID NO: 105);
opt_ND1-R: TGATGTACAGGGTGATGGTGCCTGG (SEQ ID NO: 106);

[00237] 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).

[00238] 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

[00239] 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

[00240] 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.

[00241] 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 NaH₂PO₄/Na₂HPO₄, 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 – the viral titers of formulations A, B, and C

viral titers	0 cycle	1 cycle	2 cycles	3 cycles	4 cycles	5 cycles	RSD
--------------	---------	---------	----------	----------	----------	----------	-----

A	1.15E+11	9.48E+10	6.16E+10	2.90E+10	1.56E+10	5.26E+09	83.18
B	4.25E+11	5.12E+11	6.66E+11	4.30E+11	4.77E+11	4.20E+11	19.30
C	4.96E+11	6.91E+11	7.69E+11	6.82E+11	6.83E+11	7.27E+11	13.90

[00242] 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.

[00243] 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 NaH₂PO₄, 40 mM Na₂HPO₄, 5 mM KH₂PO₄ and 0.001% poloxamer 188, 7.2-7.4.

Table 4 – the viral titers of formulations D, E, and F

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

[00244] 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.

[00245] 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.

CLAIMS

WHAT IS CLAIMED IS:

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

10. The recombinant nucleic acid of claim 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.

11. The recombinant nucleic acid of claim 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.

12. The recombinant nucleic acid of claim 1, wherein said recombinant nucleic acid comprises a sequence that is at least 90%, at least 95%, at least 97%, at least 99%, or 100% identical to a sequence selected from the group consisting of SEQ ID NO: 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.

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.

14. The recombinant nucleic acid of claim 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.

15. The recombinant nucleic acid of any one of claims 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.

16. The recombinant nucleic acid of any one of claims 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.

17. The recombinant nucleic acid of any one of claims 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.

18. The recombinant nucleic acid of any one of claims 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.

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

20. The recombinant nucleic acid of any one of claims 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.

21. The recombinant nucleic acid of any one of claims 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.

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

23. The recombinant nucleic acid of any one of claims 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.

24. The recombinant nucleic acid of any one of claims 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.

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

26. The recombinant nucleic acid of any one of claims 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.

27. The recombinant nucleic acid of any one of claims 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.

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

29. The recombinant nucleic acid of any one of claims 13-28, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRCFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L.

30. The recombinant nucleic acid of any one of claims 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.

31. The recombinant nucleic acid of any one of claims 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.

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

33. The recombinant nucleic acid of any one of claims 13-32, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.

34. The recombinant nucleic acid of any one of claims 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.

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.

36. The recombinant nucleic acid of claim 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.

37. The recombinant nucleic acid of any one of claims 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.

38. The recombinant nucleic acid of any one of claims 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.

39. The recombinant nucleic acid of any one of claims 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.

40. The recombinant nucleic acid of any one of claims 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.

41. The recombinant nucleic acid of any one of claims 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.

42. The recombinant nucleic acid of any one of claims 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.

43. The recombinant nucleic acid of any one of claims 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.

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

45. The recombinant nucleic acid of any one of claims 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.

46. The recombinant nucleic acid of any one of claims 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.

47. The recombinant nucleic acid of any one of claims 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.

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

49. The recombinant nucleic acid of any one of claims 35-48, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.

50. The recombinant nucleic acid of any one of claims 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.

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.

52. The recombinant nucleic acid of claim 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.

53. The recombinant nucleic acid of any one of claims 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.

54. The recombinant nucleic acid of any one of claims 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.

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

56. The recombinant nucleic acid of any one of claims 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.

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

58. The recombinant nucleic acid of any one of claims 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.

59. The recombinant nucleic acid of any one of claims 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.

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

61. The recombinant nucleic acid of any one of claims 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.

62. The recombinant nucleic acid of any one of claims 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.

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

64. The recombinant nucleic acid of any one of claims 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.

65. The recombinant nucleic acid of any one of claims 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.

66. The recombinant nucleic acid of any one of claims 51-65, further comprising a 3'UTR nucleic acid sequence.

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

68. The recombinant nucleic acid of any one of claims 51-67, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRRFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L.

69. The recombinant nucleic acid of any one of claims 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.

70. The recombinant nucleic acid of any one of claims 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.

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

72. The recombinant nucleic acid of any one of claims 51-71, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.

73. The recombinant nucleic acid of any one of claims 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.

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.

75. The recombinant nucleic acid of claim 74, further comprising a mitochondrial targeting sequence.

76. The recombinant nucleic acid of any one of claims 74-75, 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_lsADCK3_crATP6_lsATP5G3, ncATP9_zmLOC100282174, hsADCK3_zmLOC100282174_crATP6_hsATP5G3, crATP6_hsADCK3_zmLOC100282174_hsATP5G3, hsADCK3_zmLOC100282174_crATP6, ncATP9_zmLOC100282174_spilv1_GNFP_ncATP9, and ncATP9_zmLOC100282174_spilv1_lcSirt5_osP0644B06.24-2_hsATP5G2_ncATP9.

77. The recombinant nucleic acid of any one of claims 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.

78. The recombinant nucleic acid of any one of claims 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.

79. The recombinant nucleic acid of any one of claims 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.

80. The recombinant nucleic acid of any one of claims 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.

81. The recombinant nucleic acid of any one of claims 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.

82. The recombinant nucleic acid of any one of claims 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.

83. The recombinant nucleic acid of any one of claims 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.

84. The recombinant nucleic acid of any one of claims 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.

85. The recombinant nucleic acid of any one of claims 74-84, further comprising a 3'UTR nucleic acid sequence.

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

87. The recombinant nucleic acid of any one of claims 74-86, wherein said 3'UTR nucleic acid sequence comprises a sequence selected from the group consisting of hsACO2, hsATP5B, hsAK2, hsALDH2, hsCOX10, hsUQCRCFS1, hsNDUFV1, hsNDUFV2, hsSOD2, hsCOX6c, hsIRP1, hsMRPS12, hsATP5J2, rnSOD2, and hsOXA1L.

88. The recombinant nucleic acid of any one of claims 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.

89. The recombinant nucleic acid of any one of claims 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.

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

91. The recombinant nucleic acid of any one of claims 74-90, wherein said mitochondrial targeting sequence is located at 3' of said mitochondrial targeting sequence.

92. The recombinant nucleic acid of any one of claims 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.

93. A viral vector comprising said recombinant nucleic acid of any one of claims 1-92.

94. The viral vector of claim 93, wherein said viral vector is an adeno-associated virus (AAV) vector.

95. The viral vector of claim 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.

96. The viral vector of any one of claims 93-95, wherein said AAV vector is a recombinant AAV (rAAV) vector.

97. The viral vector of claim 96, wherein said rAAV vector is rAAV2 vector.

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

99. The pharmaceutical composition of claim 98, further comprising a pharmaceutically acceptable excipient thereof.

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

101. A pharmaceutical composition, comprising:

an adeno-associated virus (AAV) comprising a recombinant nucleic acid of any one of claims 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.

102. The pharmaceutical composition of any one of claims 98-101, wherein said pharmaceutically acceptable excipient comprises phosphate-buffered saline (PBS), α,α -trehalose dehydrate, L-histidine monohydrochloride monohydrate, polysorbate 20, NaCl, NaH₂PO₄, Na₂HPO₄, KH₂PO₄, K₂HPO₄, poloxamer 188, or any combination thereof.

103. The pharmaceutical composition of any one of claims 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, NaH₂PO₄, Na₂HPO₄, KH₂PO₄, K₂HPO₄, poloxamer 188, and any combination thereof.

104. The pharmaceutical composition of claim 102, wherein said pharmaceutically acceptable excipient comprises poloxamer 188.

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

106. The pharmaceutical composition of claim 105, wherein said pharmaceutically acceptable excipient comprises 0.001% poloxamer 188.

107. The pharmaceutical composition of any one of claims 98-106, wherein said pharmaceutically acceptable excipient further comprises one or more salts.

108. The pharmaceutical composition of claim 107, wherein said one or more salts comprises NaCl, NaH₂PO₄, Na₂HPO₄, and KH₂PO₄.

109. The pharmaceutical composition of claim 107, wherein said one or more salts comprises 80 mM NaCl, 5 mM NaH₂PO₄, 40 mM Na₂HPO₄, and 5 mM KH₂PO₄.

110. The pharmaceutical composition of any one of claims 98-109, wherein said pharmaceutical composition has a pH of 6-8.

111. The pharmaceutical composition of claim 110, wherein said pharmaceutical composition has a pH of 7.2-7.4.

112. The pharmaceutical composition of claim 111, wherein said pharmaceutical composition has a pH of 7.3.

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

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

115. The pharmaceutical composition of any one of claims 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.

116. The pharmaceutical composition of any one of claims 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.

117. The pharmaceutical composition of any one of claims 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.

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

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

120. The method of claim 118 or 119, comprising administering said pharmaceutical composition to one or both eyes of said patient.

121. The method of any one of claims 118-120, wherein said pharmaceutical composition is administered via intraocular or intravitreal injection.

122. The method of claim 121, wherein said pharmaceutical composition is administered via intravitreal injection.

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

124. The method of claim 123, wherein about 0.05 mL of said pharmaceutical composition is administered via intravitreal injection.

125. The method of any one of claims 118-124, further comprising administering methylprednisolone to said patient.

126. The method of claim 125, wherein said methylprednisolone is administered prior to said intravitreal injection of said pharmaceutical composition.

127. The method of any one of claims 125-126, wherein said methylprednisolone is administered orally.

128. The method of any one of claims 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.

129. The method of any one of claims 125-128, wherein said methylprednisolone is administered daily.

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

131. The method of any one of claims 125-130, wherein said methylprednisolone is administered after said intravitreal injection of said pharmaceutical composition.

132. The method of any one of claims 125-131, further comprising administering creatine phosphate sodium to said patient.

133. The method of claim 132, wherein said creatine phosphate sodium is administered intravenously.

134. The method of any one of claims 125-133, wherein said methylprednisolone is administered intravenously or orally.

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

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

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

138. The method of any one of claims 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.

139. The method of any one of claims 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.

1/18

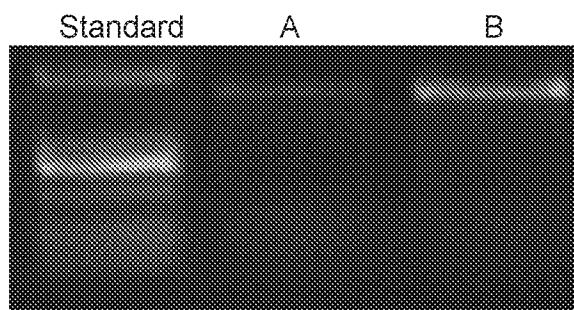


FIG. 1

2/18

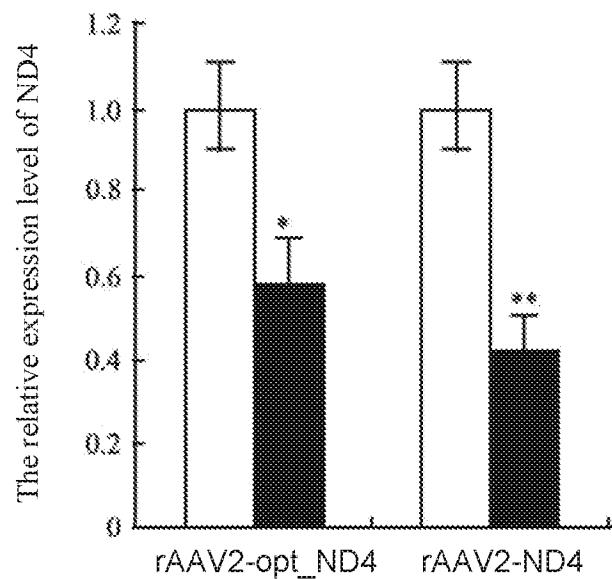


FIG. 2

3/18

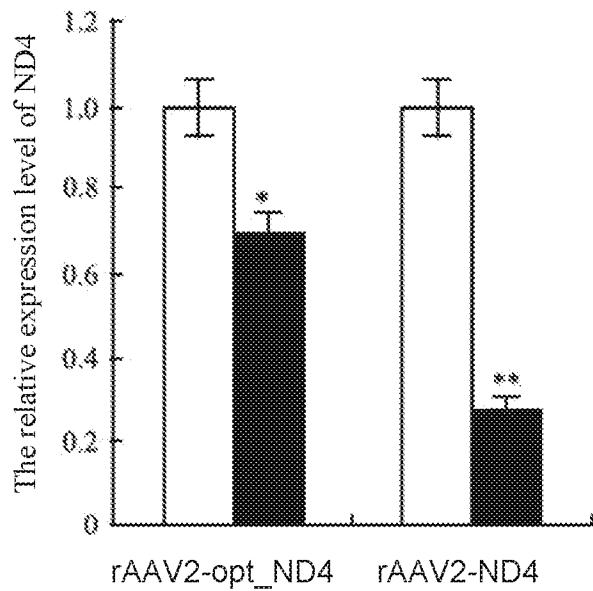


FIG. 3

4/18

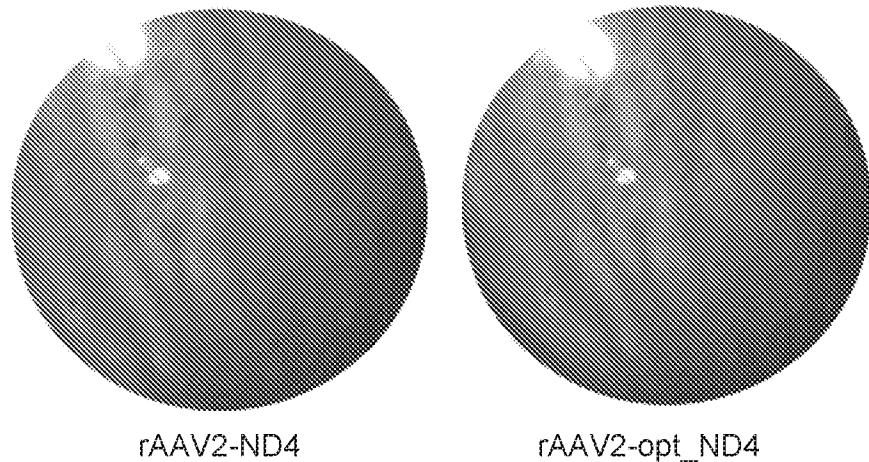


FIG. 4

5/18

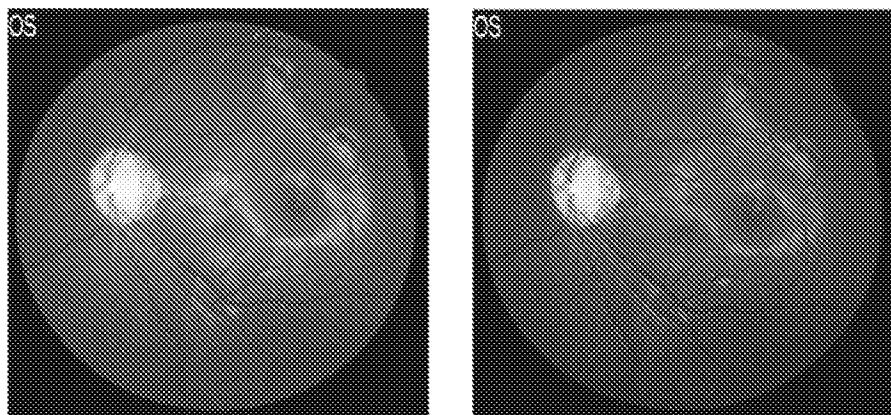


FIG. 5

6/18

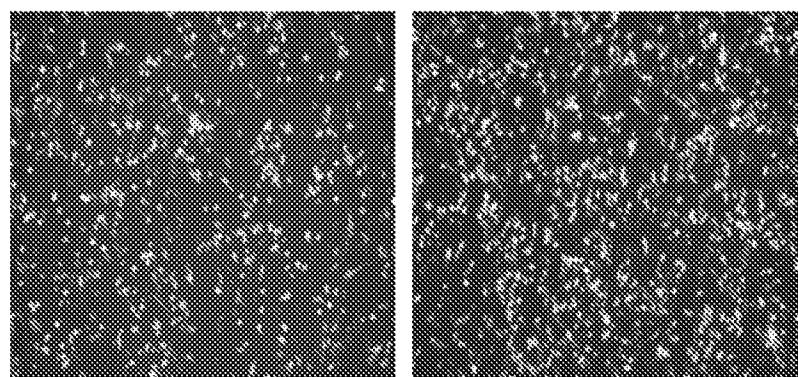


FIG. 6

7/18

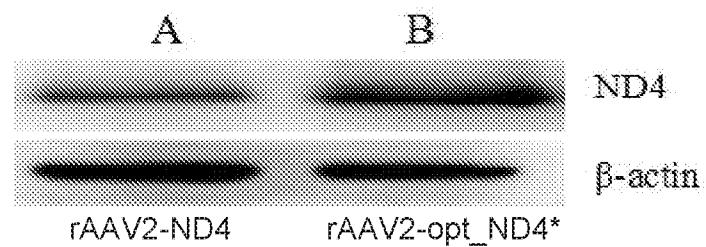


FIG. 7

8/18

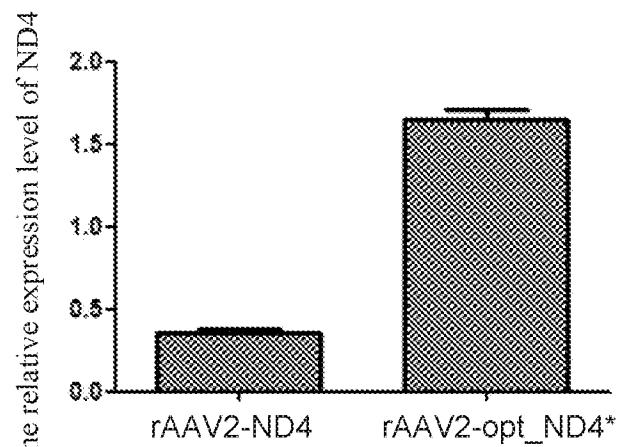


FIG. 8

9/18



FIG. 9

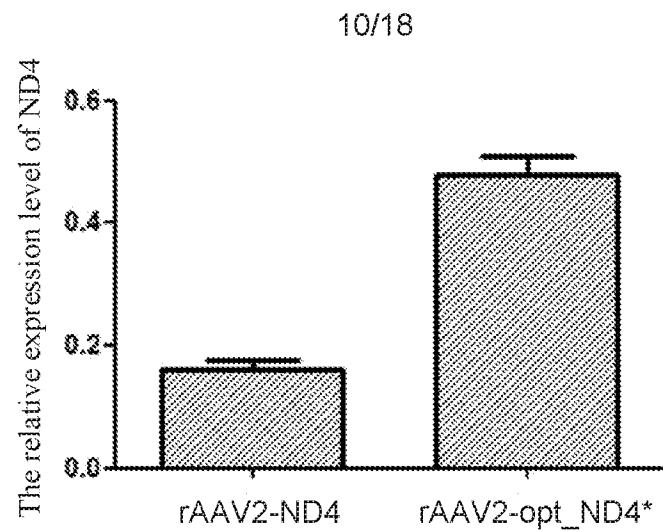


FIG. 10

11/18

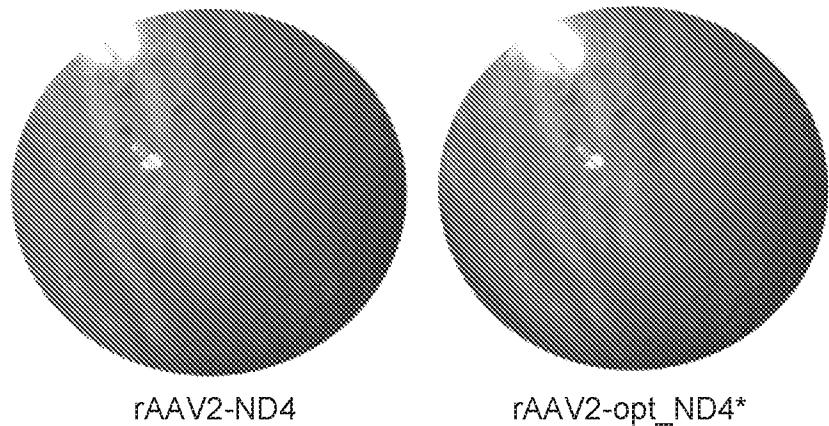


FIG. 11

12/18

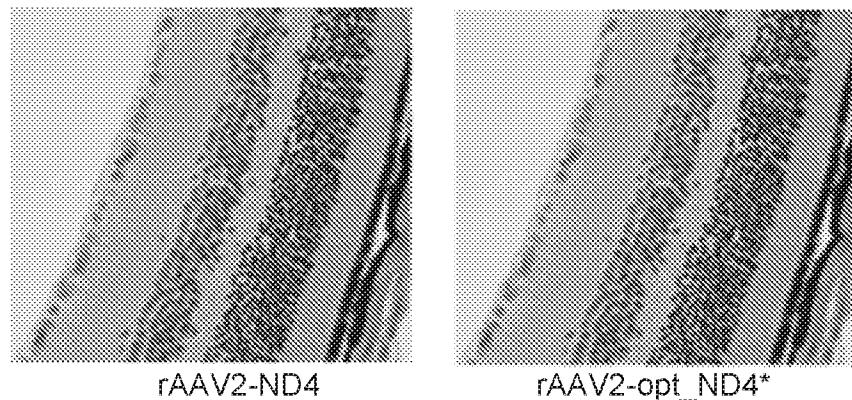


FIG. 12

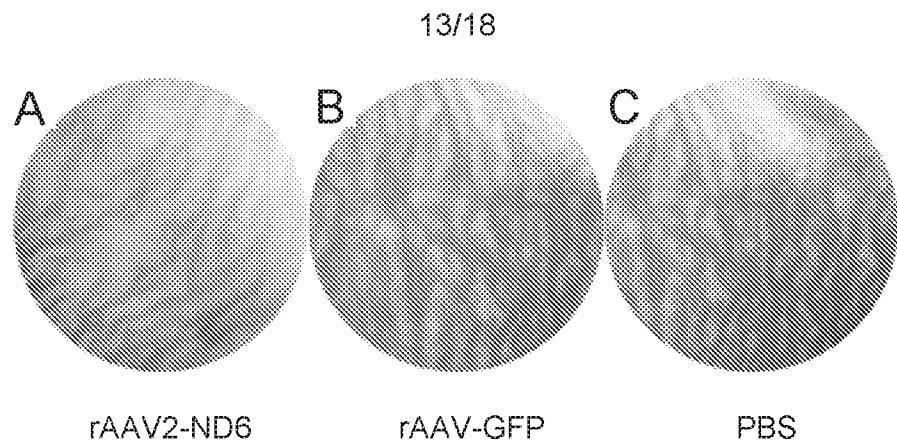
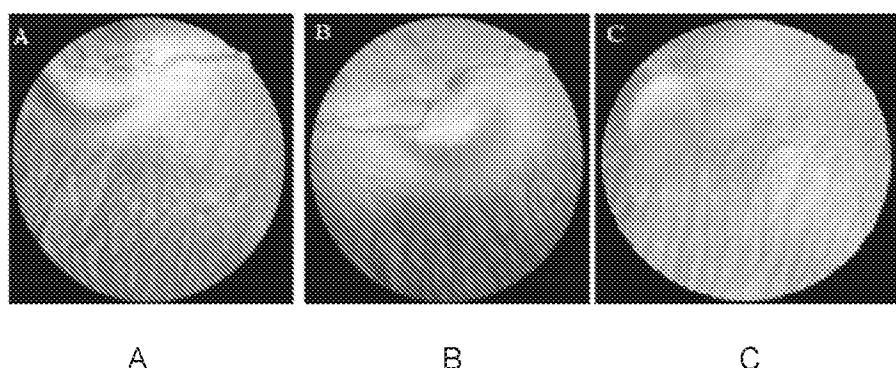


FIG. 13

14/18



A

B

C

FIG. 14

15/18

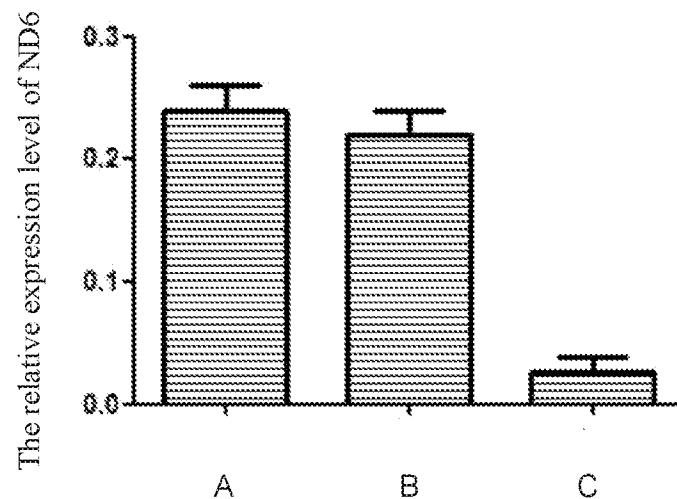


FIG. 15

16/18

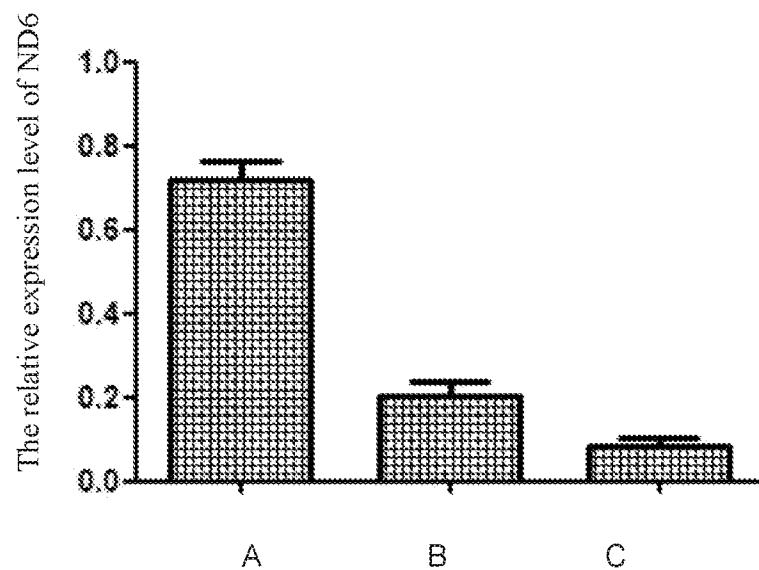


FIG. 16

17/18

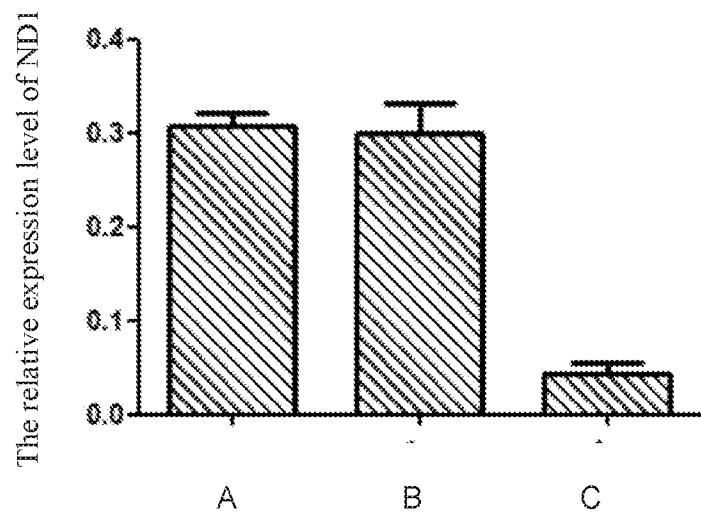


FIG. 17

18/18

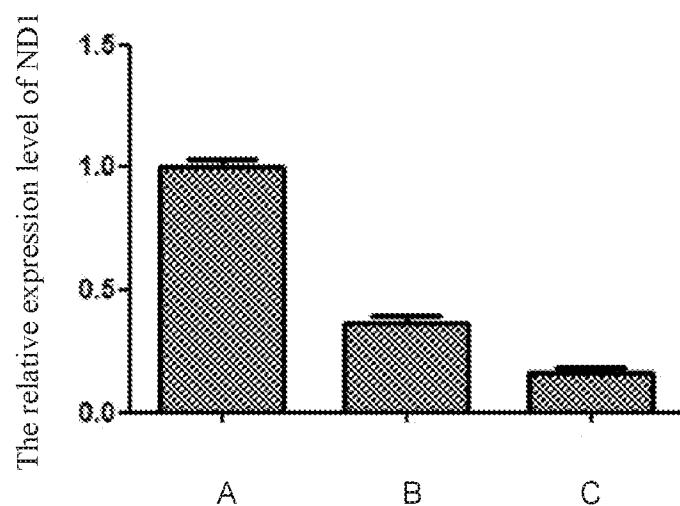


FIG. 18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2019/094136

A. CLASSIFICATION OF SUBJECT MATTER

C12N 15/09(2006.01)i; C12N 15/63(2006.01)i; C12N 15/86(2006.01)i; A61K 48/00(2006.01)i; A61P 27/02(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)

C12N; A61K; A61P

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)

TWTXT;GBTXT;CATXT;SGTXT;ATTXT;EPTXT;DWPI;LEXTXT;USTXT;CHTXT;WOTXT;CNTXT;CNABS;CNKI;
 NCBI;ISI-WEB OF SCIENCE;ELSEVIER;GOOGLE SCHOLAR;BLAST:laber, LHON, ND1, ND4, ND6, COX10,COX8,
 OPA1,optimized, AAV, sequence search of SEQ ID NO: 2, 3, 4, 5, 7, 8, 10, 12

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006117250 A2 (INST NAT SANTE RECH MEDET AL.) 09 November 2006 (2006-11-09) see the whole document, especially claims 13 and 24	1-117
A	CN 102634527 A (UNIV HUAZHONG TONGJI MEDICAL COLLEGE) 15 August 2012 (2012-08-15) see the whole document, especially the abstract, claims 1-4	1-117
A	BONNET, Crystel et al. "The optimized allotopic expression of ND1 or ND4 genes restores respiratory chain complex I activity in fibroblasts harboring mutations in these genes" <i>Biochimica et Biophysica Acta</i> , Vol. 1783, No. 10, 31 October 2008 (2008-10-31), pages 1707-1717 see the whole document, especially page 1708	1-117

 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
28 September 2019Date of mailing of the international search report
10 October 2019Name and mailing address of the ISA/CN
**National Intellectual Property Administration, PRC
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088
China**Authorized officer
TIAN, Yuan

Facsimile No. (86-10)62019451

Telephone No. 62411047

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2019/094136**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 13ter.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 13ter.1(a)).
 - on paper or in the form of an image file (Rule 13ter.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/CN2019/094136**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.: **118-139**
because they relate to subject matter not required to be searched by this Authority, namely:
 - [1] The subject matter of claims 118-139 relates to a treatment method of the human or animal body, and therefore, according to the criteria set out in Rule 39.1(iv), relates to subject matter for which an international search is not required.
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/CN2019/094136

Patent document cited in search report		Publication date (day/month/year)		Patent family member(s)			Publication date (day/month/year)	
WO	2006117250	A2	09 November 2006	US	2015087054	A1	26 March 2015	
				EP	1880008	B1	08 April 2015	
				DK	1880008	T3	13 July 2015	
				EP	2913403	A1	02 September 2015	
				US	2009306188	A1	10 December 2009	
				US	2014377869	A1	25 December 2014	
				WO	2006117250	A3	03 May 2007	
				ES	2541771	T3	24 July 2015	
				US	2015225740	A1	13 August 2015	
				EP	1880008	A2	23 January 2008	
				PT	1880008	E	27 August 2015	
				US	2018355372	A1	13 December 2018	
				US	9017999	B2	28 April 2015	
CN	102634527	A	15 August 2012	CN	102634527	B	06 November 2013	