CLAIMS

1. A recombinant nucleic acid, comprising:

a mitochondrial targeting sequence;

a NADH dehydrogenase 4 (ND4)~~mitochondrial protein~~ coding sequence comprising a sequence that is at least ~~95%~~99% identical to ~~a sequence selected from the group consisting of~~ SEQ ID NO: 7~~, 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 95% 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 95% identical to a sequence selected from the group consisting of SEQ ID NO: 2-5.

4. The recombinant nucleic acid of claim 1, wherein said mitochondrial targeting sequence comprises a sequence that 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_zmLOC 100282174, 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.

~~5. The recombinant nucleic acid of claim 1, wherein said mitochondrial protein is selected from a group consisting of NADH dehydrogenase 4 (ND4), NADH dehydrogenase 6 (ND6), and NADH dehydrogenase 1 (ND1).~~

~~6. The recombinant nucleic acid of claim 5, wherein said mitochondrial protein comprises NADH dehydrogenase 4 (ND4).~~

~~7~~5. The recombinant nucleic acid of claim ~~6~~1, wherein said ND4~~mitochondrial protein~~ coding sequence comprises a sequence that is ~~at least 99%~~100% identical to ~~a sequence as set forth in~~ SEQ ID NO: 7.

~~8. The recombinant nucleic acid of claim 5, wherein said mitochondrial protein comprises NADH dehydrogenase 6 (ND6).~~

~~9. The recombinant nucleic acid of claim 8, wherein said mitochondrial protein coding sequence comprises a sequence that is at least 95% identical to a sequence as set forth in SEQ ID NO: 10.~~

~~10. The recombinant nucleic acid of claim 5, wherein said mitochondrial protein comprises NADH dehydrogenase 1 (ND1).~~

~~11. The recombinant nucleic acid of claim 10, wherein said mitochondrial protein coding sequence comprises a sequence that is at least 95% identical to a sequence as set forth in SEQ ID NO: 12.~~

~~12~~6. The recombinant nucleic acid of claim 1, 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.

~~13~~7. The recombinant nucleic acid of claim 1, wherein said 3'UTR nucleic acid sequence comprises a sequence that is at least 95% identical to a sequence selected from the group consisting of SEQ ID NO: 111-125.

~~14~~8. An adeno-associated viral (AAV) vector comprising a recombinant nucleic acid, comprising: a mitochondrial targeting sequence; a NADH dehydrogenase 4 (ND4)~~mitochondrial protein~~ coding sequence comprising a sequence that is at least ~~95%~~99% identical to ~~a sequence selected from the group consisting of~~ SEQ ID NO: 7~~, 10, and 12~~; and a 3'UTR nucleic acid sequence.

~~15~~9. The AAV vector of claim ~~14~~8, wherein said AAV vector is a recombinant AAV (rAAV) vector.

~~16~~10. The AAV vector of claim ~~15~~9, wherein said rAAV vector is rAAV2 vector.

11. The AAV vector of any one of claims 8-10, wherein said ND4 coding sequence comprises a sequence that is 100% identical to SEQ ID NO: 7.

~~17~~12. A pharmaceutical composition, comprising an adeno-associated virus (AAV) comprising a recombinant nucleic acid and a pharmaceutically acceptable excipient thereof, wherein said recombinant nucleic acid comprises: a mitochondrial targeting sequence; a NADH dehydrogenase 4 (ND4)~~mitochondrial protein~~ coding sequence comprising a sequence that is at least ~~95%~~99% identical to ~~a sequence selected from the group consisting of~~ SEQ ID NO: 7~~, 10, and 12~~; and a 3'UTR nucleic acid sequence.

~~18~~13. The pharmaceutical composition of claim ~~17~~12, wherein said pharmaceutically acceptable excipient comprises phosphate-buffered saline (PBS), α,α-trehalose dehydrate, L-histidine monohydrochloride monohydrate, polysorbate 20, NaCl, NaH_2PO_4, Na_2HPO_4, KH_2PO_4, K_2HPO_4, poloxamer 188, or any combination thereof.

~~19~~14. The pharmaceutical composition of claim ~~18~~13, wherein said pharmaceutically acceptable excipient comprises poloxamer 188.

~~20~~15. The pharmaceutical composition of claim ~~19~~14, wherein said pharmaceutically acceptable excipient comprises 0.0001%-0.01% poloxamer 188.

~~21~~16. The pharmaceutical composition of claim ~~17~~12, wherein said pharmaceutical composition has a viral titer of at least 5.0×10^{10} vg/mL.

~~22~~17. The pharmaceutical composition of claim ~~17~~12, 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.

18. The pharmaceutical composition of any one of claims 12-17, wherein said ND4 coding sequence comprises a sequence that is 100% identical to SEQ ID NO: 7.