CLAIMS

~~What is claimed is:~~

1. A recombinant adeno-associated virus (rAAV) vector comprising a polynucleotide that comprises a sequence that is at least 90%, at least 95%, or at least 99.5% identical to any one of the nucleotide sequences of SEQ ID NOs: 6-8, 16, and 21.

2. The rAAV vector of claim 1, wherein the polynucleotide comprises any one of the sequences set forth as SEQ ID NOs: 6-8, 16, and 21.

3. An rAAV vector for delivering two or more transgenes into the heart of a subject, wherein said vector comprises a polynucleotide that comprises two or more transgenes, wherein a first transgene encodes an S100 family protein and a second transgene encodes a cardiac Apoptosis Repressor with Caspase Recruitment Domain (cARC),

and wherein the first transgene comprises a nucleotide sequence that is at least 90%, at least 95%, or at least 99.5% identical to any one of the sequences set forth as SEQ ID NOs: 5, 8, and 19-21, and the second transgene comprises a nucleotide sequence that is at least 90%, at least 95%, or at least 99.5% identical to any one of the sequences set forth as SEQ ID NOs: 6, 7, and 15-18.

4. The rAAV vector of claim 3, wherein the second transgene comprises any one of the sequences set forth as SEQ ID NOs: 6 and 7.

5. The rAAV vector of claim 3 or 4, wherein the S100 family protein is cardiac S100 calcium-binding protein A1 (cS100A1) or a variant thereof.

6. The rAAV vector of any one of claims 3-5, wherein the first transgene comprises the nucleotide sequence set forth as SEQ ID NO: 5.

7. The rAAV vector of any one of claims 3-5, wherein the first transgene comprises the nucleotide sequence set forth as SEQ ID NO: 8.

8. The rAAV vector of any one of claims 3-7, wherein an Internal Ribosome Entry Site (IRES) is present between the cS100A1 transgene and cARC transgene.

9. The rAAV vector of any one of claims 1-8, wherein the transgene is operably linked to a promoter.

10. The rAAV vector of claim 9; optionally, wherein the promoter is a cardiac-restricted promoter selected from cardiac troponin C, cardiac troponin I, and cardiac troponin T (cTnT).

110. The rAAV vector of claim 9, wherein the promoter is a cardiac-restricted promoter derived from a gene selected from the group consisting of: α-myosin heavy chain gene, 6-myosin heavy chain gene, myosin light chain 2v gene, myosin light chain 2a gene, CARP gene, cardiac α-actin gene, cardiac m2 muscarinic acetylcholine gene, ANF, cardiac sarcoplasmic reticulum Ca-ATPase gene, and skeletal α-actin; or is an artificial cardiac promoter derived from MLC-2v gene.

12. The rAAV vector of claim 9, ; optionally wherein the promoter is cTnT.

131. The rAAV vector of any one of claims 1-120, wherein the rAAV vector is self-complementary.

142. The rAAV vector of any one of claims 1-131, wherein the vector comprises a nucleotide sequence that is at least 80%, at least 90%, at least 95% or at least 99.5% identical to any one of the sequences set forth in SEQ ID NOs: 9-12.

15. The rAAV vector of claim 14,; optionally wherein the vector comprises the nucleotide sequence set forth as SEQ ID NO: 12.

163. An rAAV particle comprising the rAAV vector of any one of claims 1-152 encapsidated in an AAV capsid.

174. The rAAV particle of claim 163, wherein the AAV capsid comprises a capsid protein derived from the AAV1, AAV2, AAV3, AAV6, AAV8, AAVrh.74, AAVrh.10, AAV2/6 or AAV9 serotypes.

~~18. The rAAV particle of claim 16 or 17,;~~ optionally wherein the AAV capsid comprises a capsid protein ~~derived~~ from the AAVrh.10 serotype.

1~~9~~5. A composition comprising the rAAV particle of ~~any one of~~ claim~~s~~ 1~~6~~3~~-~~ or 1~~8~~4.

~~20~~16. Use of the rAAV particle of any one of claims 13 or 14 or the composition of claim 15 for the preparation of a medicament for treating~~A method of treatment of~~ a human subject suffering from a heart disease. ~~comprising administering to the subject the composition of claim 19 or the rAAV particle of any one of claims 16-18.~~

~~2~~17. The ~~method~~ use of claim ~~20~~16, wherein the heart disease causes heart failure in the subject.

~~22~~18. The ~~method~~ use of claim ~~20~~16 or ~~2~~17, wherein the heart disease is cardiomyopathy~~.~~

~~23. The method use of any one of claims 20-22,;~~ optionally wherein the heart disease is hypertrophic cardiomyopathy or dilated cardiomyopathy.

~~24~~19. The ~~method~~ use of claim ~~20~~16 or ~~2~~17, wherein the heart disease is acute ischemia.

2~~5~~0. The ~~method~~ use of any one of claims ~~20~~16-~~24~~19, wherein the ~~composition~~medicament is to be administered via injection into the heart of the subject or intravascular injection into the coronary arteries of the subject.

2~~6~~1. The ~~method~~ use of any one of claims ~~20~~16-2~~5~~0, wherein the ~~step of administering~~medicament results in expression of the two or more transgenes in the subject's heart.

2~~7~~2. The rAAV vector of any one of claims 3-1~~2~~0, wherein the transgene comprising an S100 family protein is positioned 5′ to the transgene comprising the cARC.

2~~8~~3. The rAAV vector of any one of claims 3-1~~5~~2, wherein the transgene comprising the cARC is positioned 5′ to the transgene comprising an S100 family protein.

294. The rAAV vector of any one of claims 1-195 or and 272-283, wherein the vector comprises a nucleotide sequence that is at least 80%, at least 90%, at least 95% or at least 99.5% identical to any of the sequences set forth as SEQ ID NOs: 9-12.

30. The rAAV vector of claim 29, ; optionally wherein the vector comprises the nucleotide sequence set forth as SEQ ID NO: 11.

3125. The rAAV vector of claim 294, wherein the vector comprises any one of the nucleotide sequences set forth as SEQ ID NOs: 9, 10, and 12.

326. The method use of any one of claims 2016-261, wherein the step of administeringmedicament results in improved cardiac function in the subject.

3327. The method use of any one of claims 16-21 and claim 3026, wherein the step of administeringmedicament results in improved cardiac function in the subject for more than 10 months.

3428. The rAAV vector of any one of claims 1-195 or and 272-3125, wherein the rAAV vector encodes a protein comprising an amino acid sequence at least 90%, at least 95%, or at least 99.5% identical to SEQ ID NO: 13 or 14.

35. The rAAV vector of any one of claims 1-19 or 27-31, ; optionally wherein the rAAV vector encodes a protein comprising the amino acid sequence of SEQ ID NO: 13 or 14.