CLAIMS

1. A recombinant adeno-associated virus (rAAV) nucleic acid vector for delivering two or more transgenes into the heart of a subject, wherein said vector comprises, from 5' to 3', in order, a first adeno-associated virus (AAV) inverted terminal repeat (ITR) sequence, two or more transgenes and a promoter operably linked to the two or more transgenes, a polyadenylation (polyA) signal, and a second AAV ITR sequence,

wherein the two or more transgenes encode an S100 family protein and an apoptotic inhibitor, respectively, and

wherein the transgene encoding an S100 family protein comprises a sequence that is at least 95%, at least 98%, or at least 99.5% identical to either of the nucleotide sequences of SEQ ID NOs: 25 and 26, optionally wherein the transgene encoding an S100 family protein comprises either of the nucleotide sequences of SEQ ID NOs: 25 and 26,

optionally wherein the transgene encoding an S100 family protein comprises a sequence having a reduced guanosine (G) and cytosine (C) (G/C) content, relative to any one of the nucleotide sequences of SEQ ID NOs: 5, 8, 19, and 20, optionally wherein the G/C content is reduced by 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15%, relative to any one of the nucleotide sequences of SEQ ID NOs: 5, 8, 19, and 20,

optionally wherein the apoptotic inhibitor is cardiac Apoptosis Repressor with Caspase Recruitment Domain (ARC) or a variant thereof, and

optionally wherein an Internal Ribosome Entry Site (IRES) is present between the transgene encoding an S100 family protein and the transgene encoding an apoptotic inhibitor.

2. The rAAV nucleic acid vector of claim 1, wherein the polyA signal comprises a nucleotide sequence that has at least 90%, 92.5%, 95%, 98%, or 99% identity to the nucleotide sequence of SEQ ID NO: 28, optionally wherein the polyA signal comprises the nucleotide sequence of SEQ ID NO: 28.

3. The rAAV nucleic acid vector of claim 1 or claim 2, wherein the transgene encoding an apoptotic inhibitor 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: 3, 6, 7, and 15-18, optionally wherein the transgene encoding an apoptotic inhibitor comprises any one of the nucleotide sequences of SEQ ID NOs: 3, 6, 7, and 15-18.

4. The rAAV nucleic acid vector of any one of claims 1-3, wherein the promoter is a cardiac-restricted promoter, optionally wherein the promoter is a cardiac-restricted promoter selected from the group consisting of: cardiac troponin C, cardiac troponin I, and cardiac troponin T (cTnT), and optionally wherein the promoter is cTnT, optionally 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.

5. The rAAV nucleic acid vector of any one of claims 1-4, wherein the rAAV nucleic acid vector comprises a nucleotide sequence that is at least 90%, at least 95% or at least 99.5% identical to either of the nucleotide sequences of SEQ ID NOs: 22 and 23, optionally wherein the rAAV nucleic acid vector comprises the nucleotide sequence of SEQ ID NO: 22, optionally wherein the rAAV nucleic acid vector comprises the nucleotide sequence of SEQ ID NO: 23.

6. An rAAV particle comprising the rAAV nucleic acid vector of any one of claims 1-5 encapsidated in an AAV capsid, optionally wherein the AAV capsid comprises a capsid protein derived from an AAV1, AAV2, AAV3, AAV6, AAV8, AAVrh.74, AAVrh.10, AAV2/6, or AAV9 serotype, and optionally wherein the AAV capsid comprises a capsid protein derived from an AAVrh.10 serotype.

7. A composition comprising the rAAV particle of claim 6.

8. Use of the rAAV particle of claim 6 in the preparation of a medicament for treating a heart disease in a subject, wherein the medicament is to be administered to the subject, optionally wherein the heart disease causes heart failure in the subject, optionally wherein the heart disease is cardiomyopathy, optionally wherein the heart disease is hypertrophic cardiomyopathy or dilated cardiomyopathy, optionally wherein the heart disease is acute ischemia.

9. The use of claim 8, wherein the composition is to be administered via injection into the heart of the subject or intravascular injection into the coronary arteries of the subject, optionally

wherein the administration results in expression of the two or more transgenes in the subject's heart.

10. The use of claim 8 or claim 9, wherein the subject is a mammal, optionally wherein the mammal is a human or a companion animal, optionally wherein the companion animal is a dog or a cat.

11. The use of any one of claims 8-10, wherein the administration results in improved cardiac function in the subject, optionally wherein the administration results in improved cardiac function in the subject for more than 10 months.

12. The rAAV nucleic acid vector of any one of claims 1-5, wherein the transgene encoding an S100 family protein is positioned 5′ to the transgene encoding an apoptotic inhibitor.

13. The rAAV nucleic acid vector of any one of claims 1-5, wherein the transgene encoding an apoptotic inhibitor is positioned 5′ to the transgene encoding an S100 family protein.

14. The rAAV nucleic acid vector of any one of claims 1-5, 12, and 13, wherein the rAAV nucleic acid vector encodes a protein comprising an amino acid sequence at least 90%, at least 95%, or at least 99.5% identical to the amino acid sequence of SEQ ID NO: 13 or 14, optionally wherein the rAAV nucleic acid vector encodes a protein comprising the amino acid sequence of SEQ ID NO: 13 or 14.

15. The rAAV nucleic acid vector of any one of claims 1-5 and 12-14, wherein the rAAV nucleic acid vector encodes a protein comprising an amino acid sequence at least 90%, at least 95%, or at least 99.5% identical to the amino acid sequence of SEQ ID NO: 24 or 29, optionally wherein the rAAV nucleic acid vector encodes a protein comprising the amino acid sequence of SEQ ID NO: 24 or 29.