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(54) **PLAKOPHILIN-2 (PKP2) GENE THERAPY USING AAV VECTOR**

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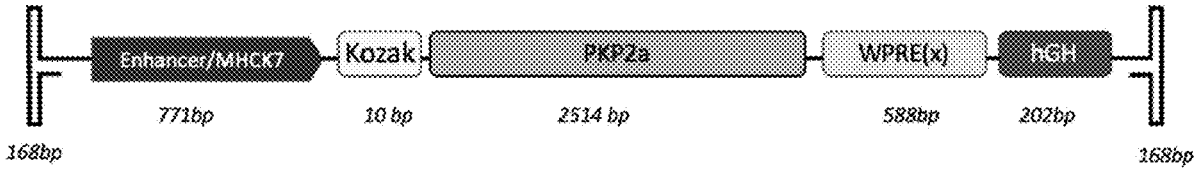
CPC .. ***A61K 48/005*** (2013.01); *C12N 2750/14143* (2013.01); ***C12N 15/86*** (2013.01); ***C12N 15/113*** (2013.01)

(57) **ABSTRACT**

Provided herein is a gene therapy for PKP2 (Plakophilin-2), e.g. using an adeno-associated virus (AAV) vector. The promoter of the vector may be a MHCK7 promoter or a cardiac troponin T (HTNNT2) promoter. The capsid may be an AAV9 or AAVrh74 capsid or a functional variant thereof. Other promoters or capsids may be used. Further provided are methods of treatment, such as by intravenous, intracoronary, intracarotid or intracardiac administration of the rAAV vector, and other compositions and methods.

Specification includes a Sequence Listing.



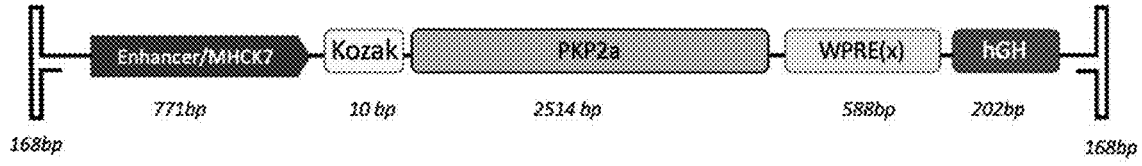


FIG. 1

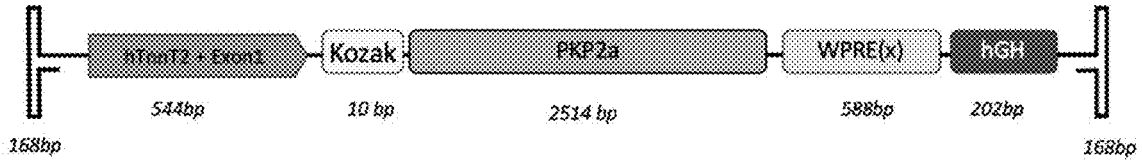


FIG. 2

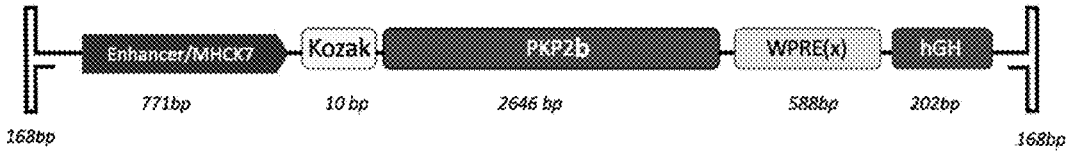


FIG. 3

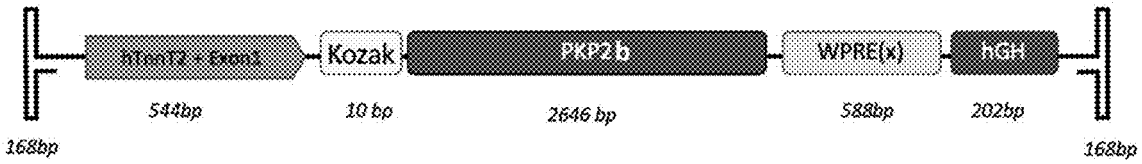


FIG. 4

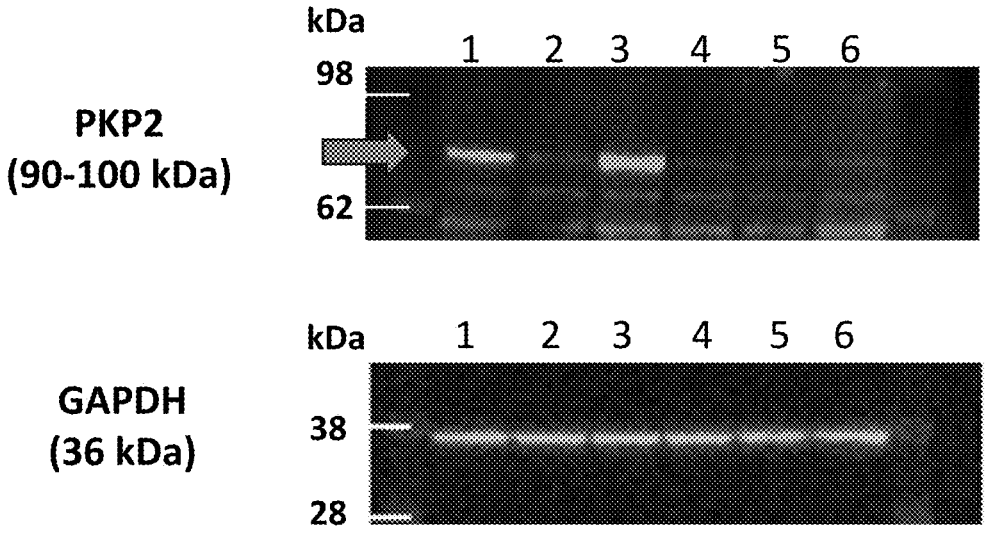

kDa
1 2 3 4 5 6
98
62
PKP2
(90-100 kDa)
kDa
1 2 3 4 5 6
38
28
GAPDH
(36 kDa)

FIG. 5A

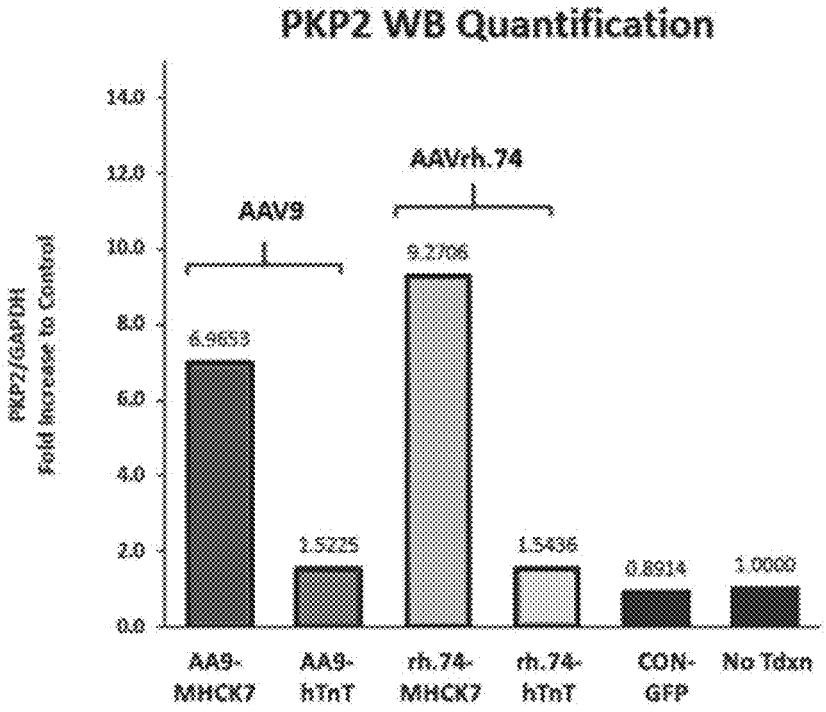
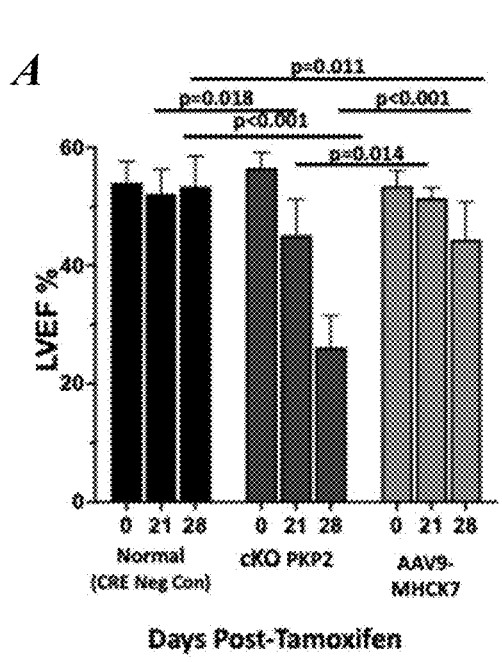
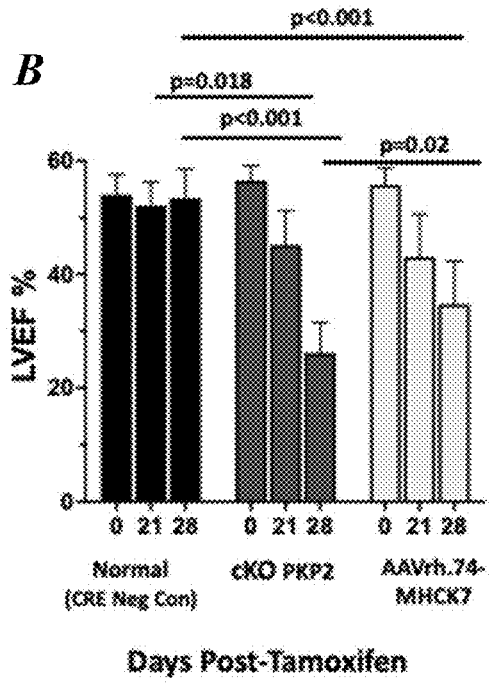
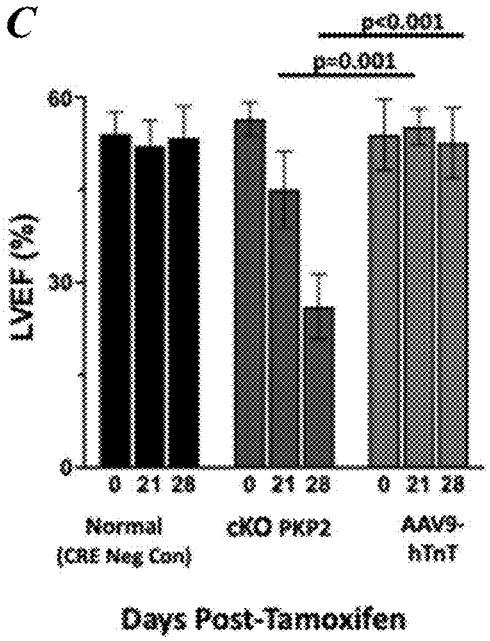
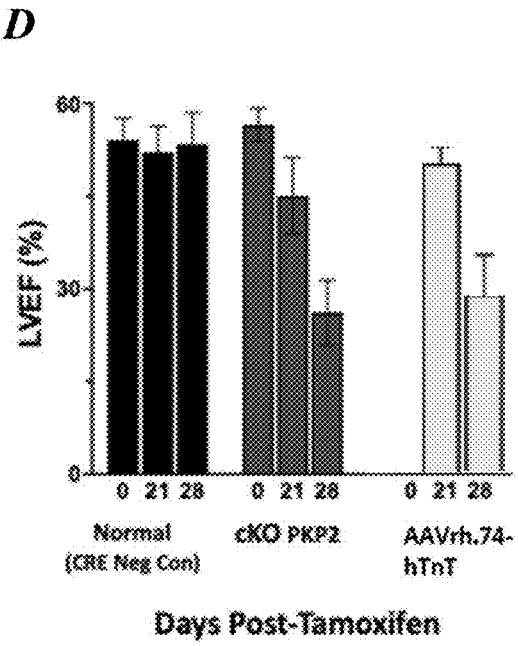

PKP2 WB Quantification
PKP2/GAPDH
fold increase to Control
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
AAV9
AAVrh.74
6.9653
1.5225
9.2706
1.5436
0.8914
1.0000
AA9-
MHCK7
AA9-
hTnT
rh.74-
MHCK7
rh.74-
hTnT
CON-
GFP
No Tdxn

FIG. 5B

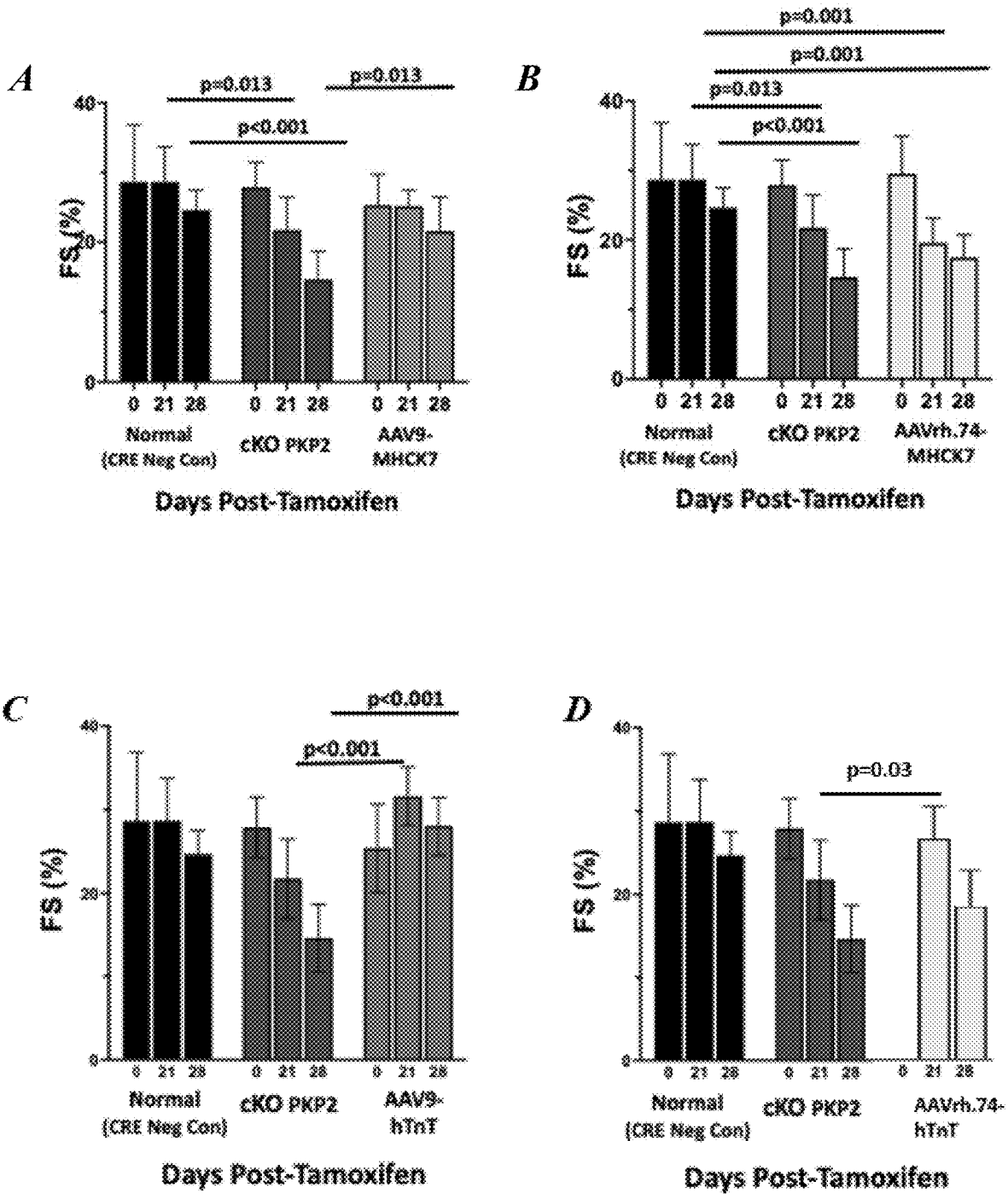

A
p=0.011
p=0.018
p<0.001
p<0.001
p=0.014
LVEF %
60
40
20
0
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAV9-MHCK7
Days Post-Tamoxifen


B
p<0.001
p=0.018
p<0.001
p=0.02
LVEF %
60
40
20
0
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAVrh.74-MHCK7
Days Post-Tamoxifen

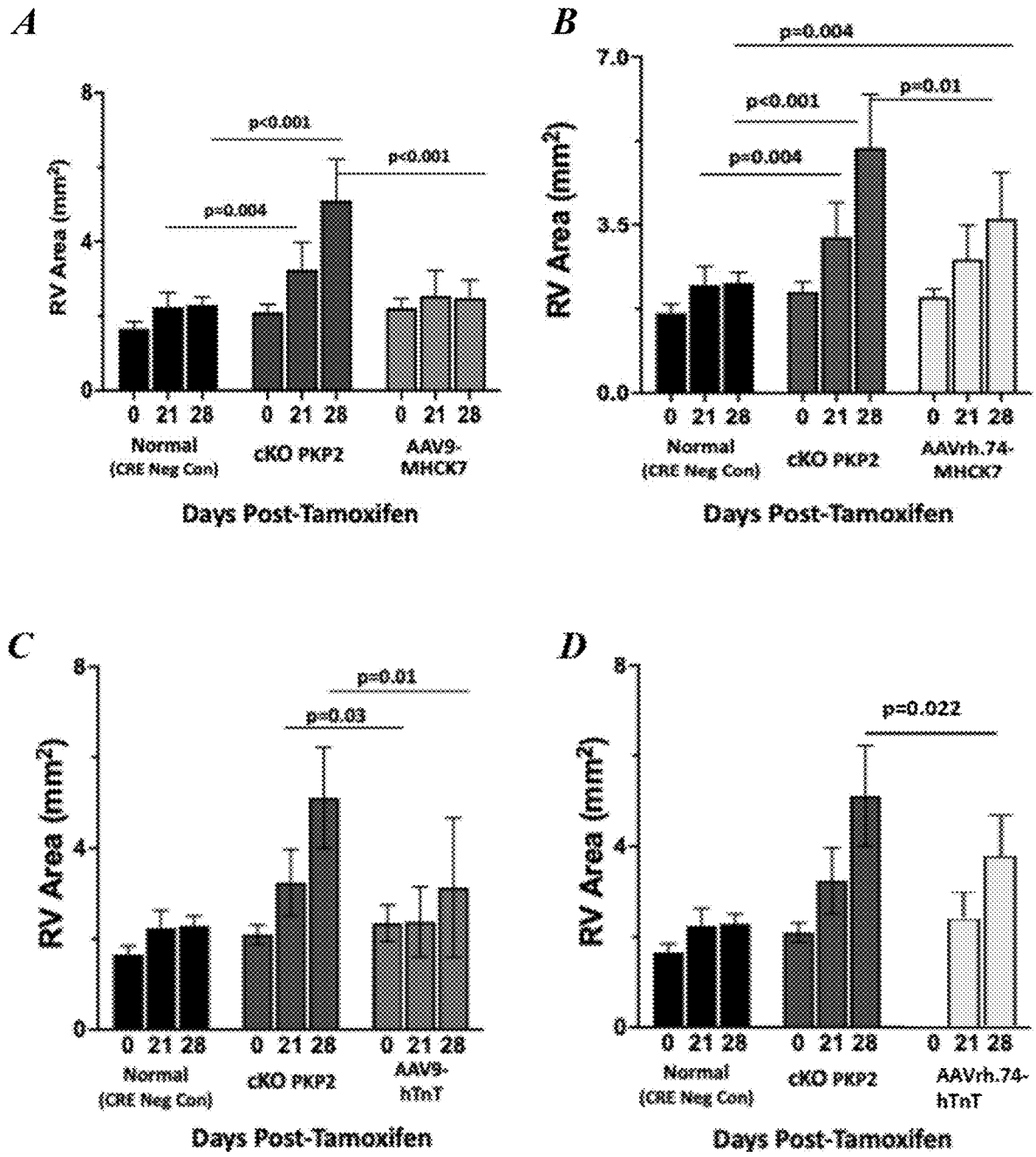

C
p<0.001
p=0.001
LVEF (%)
60
30
0
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAV9-hTnT
Days Post-Tamoxifen


D
LVEF (%)
60
30
0
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAVrh.74-hTnT
Days Post-Tamoxifen

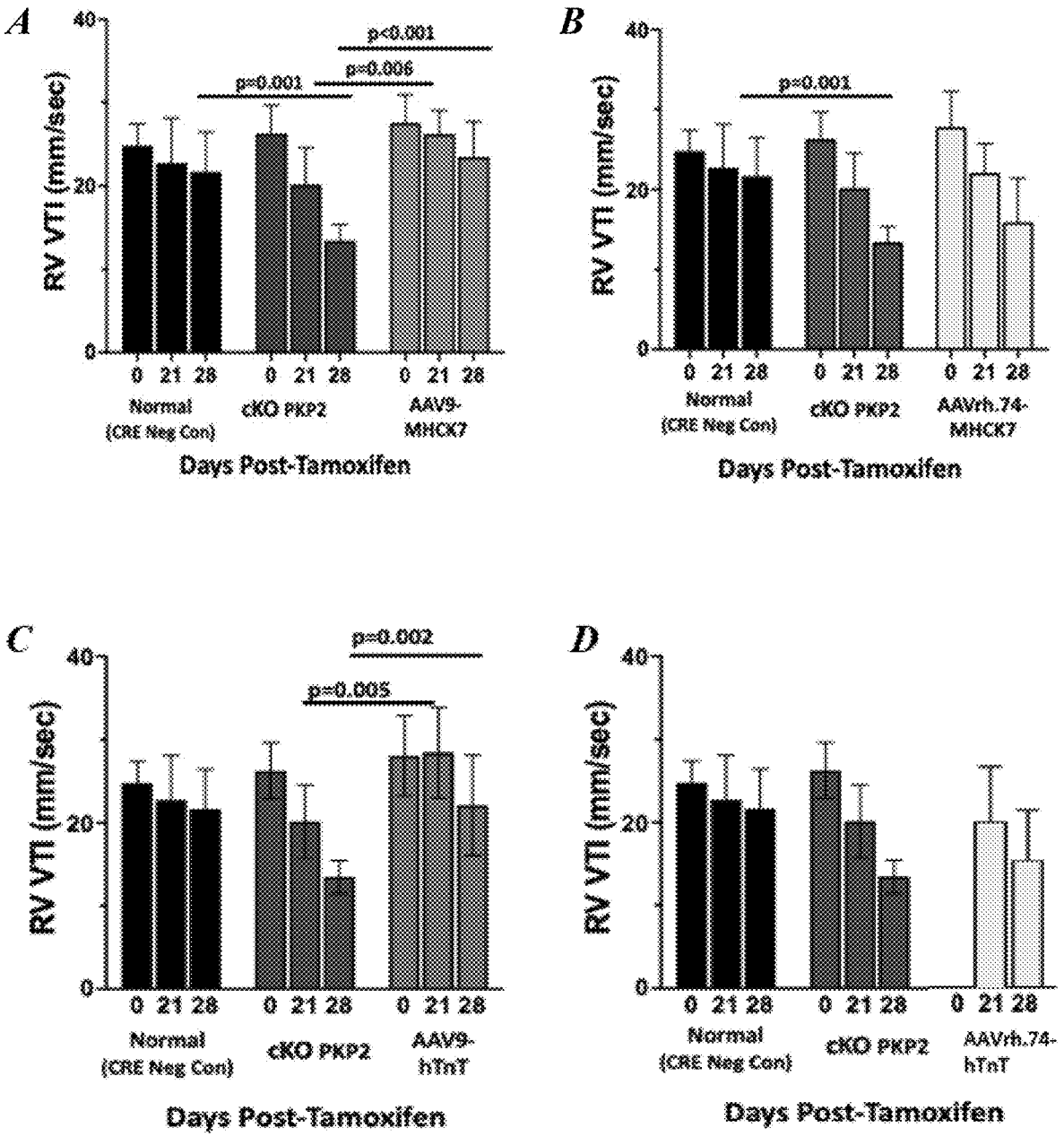
FIGs. 6A-6D


A
p=0.013
p=0.013
p<0.001
FS (%)
40
20
0
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAV9-MHCK7
Days Post-Tamoxifen
B
p=0.001
p=0.001
p=0.013
p<0.001
FS (%)
40
20
0
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAVrh.74-MHCK7
Days Post-Tamoxifen
C
p<0.001
p<0.001
FS (%)
40
20
0
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAV9-hTnT
Days Post-Tamoxifen
D
p=0.03
FS (%)
40
20
0
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAVrh.74-hTnT
Days Post-Tamoxifen

FIGs. 7A-7D


A
RV Area (mm²)
p<0.001
p<0.001
p=0.004
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAV9-MHCK7
Days Post-Tamoxifen
B
RV Area (mm²)
p=0.004
p<0.001
p=0.01
p=0.004
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAVrh.74-MHCK7
Days Post-Tamoxifen
C
RV Area (mm²)
p=0.01
p=0.03
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAV9-hTnT
Days Post-Tamoxifen
D
RV Area (mm²)
p=0.022
0 21 28 0 21 28 0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAVrh.74-hTnT
Days Post-Tamoxifen

FIGs. 8A-8D


A
RV VTI (mm/sec)
40
20
0
p<0.001
p=0.006
p=0.001
0 21 28
Normal (CRE Neg Con)
cKO PKP2
AAV9-MHCK7
Days Post-Tamoxifen
B
RV VTI (mm/sec)
p=0.001
AAVrh.74-MHCK7
C
p=0.002
p=0.005
AAV9-hTnT
D
AAVrh.74-hTnT

FIGs. 9A-9D

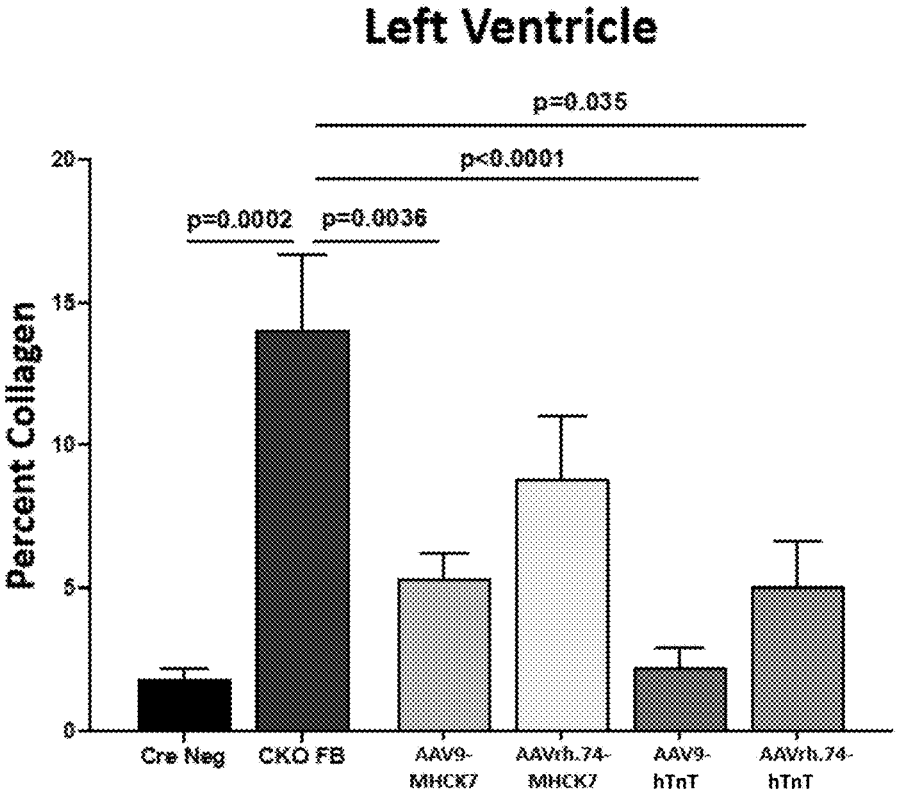


FIG. 10A

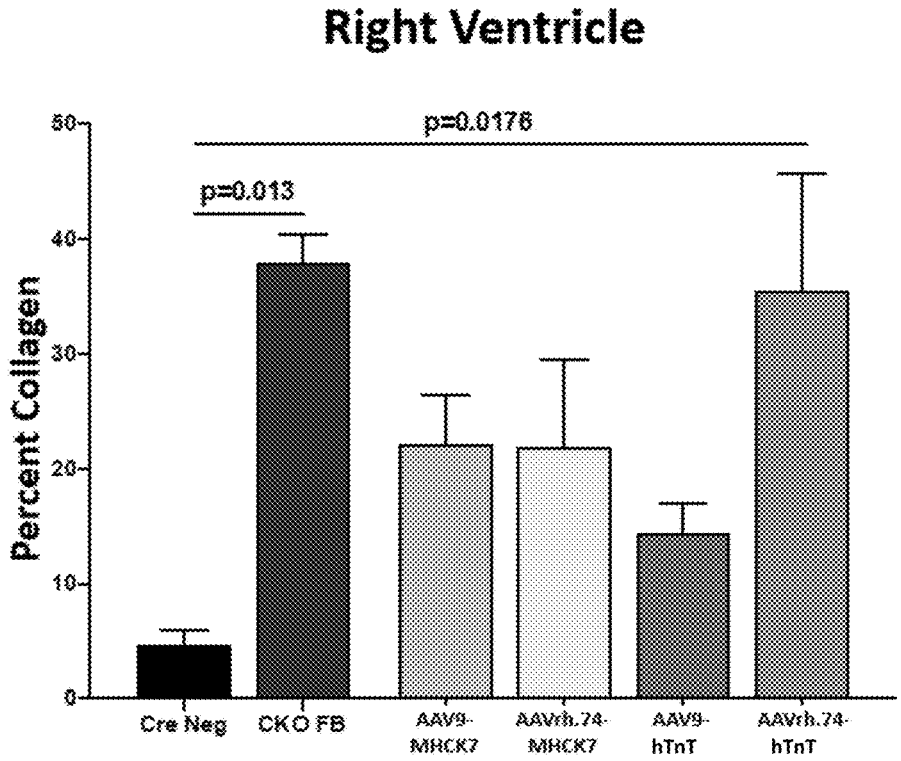


FIG. 10B

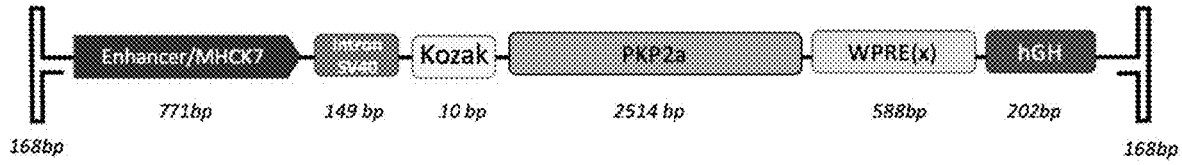


FIG. 11

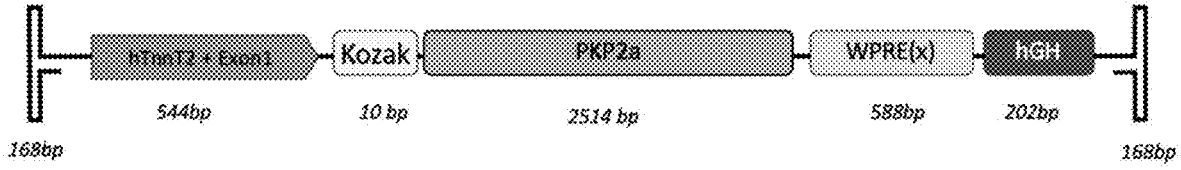


FIG. 12

FIG. 13

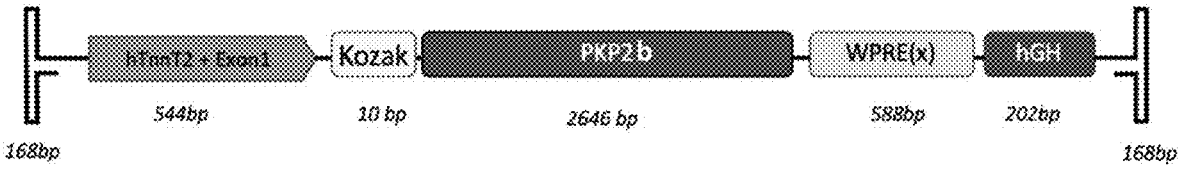


FIG. 14

PLAKOPHILIN-2 (PKP2) GENE THERAPY USING AAV VECTOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of International Application No. PCT/US2021/045220, filed Aug. 9, 2021, which claims the benefit of U.S. Provisional Application No. 63/063,032, filed Aug. 7, 2020, which is incorporated by reference herein in its entirety.

STATEMENT REGARDING THE SEQUENCE LISTING

[0002] The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is ROPA_021_01WO_ST25.txt. The text file is about 212 KB, created on Aug. 8, 2021, and is being submitted electronically via EFS-Web.

BACKGROUND

[0003] Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a form of adult-onset heart disease, which impacts an estimated 1 in 1,000 to 1 in 1,250 people. It manifests as breakdown of the muscular wall of the heart (the myocardium) over time, which leads to increased risk of abnormal heartbeat (arrhythmia) and an increased risk of sudden death when an affected individual exercises strenuously. Individuals may also experience a sensation of fluttering or pounding in the chest (palpitations), light-headedness, fainting (syncope), shortness of breath, and abnormal swelling in the legs or abdomen. Over time, ARVC can lead to heart failure.

[0004] At least 13 genes are implicated in ARVC, many of which are involved in the biogenesis of desmosomes, which are intracellular junctions that provide strong adhesion between cells. When desmosomes fail to form properly, myocardial cells may detach from one another and die. The right ventricle in particular may develop weakness, while fatty deposits and scar tissue may replace the damaged myocardium, leading to distension of the right ventricle. These alterations ultimately prevent effective heart pumping and disrupt the electrical signals that control the heartbeat, leading to arrhythmia. Autosomal dominant plakophilin-2 (PKP2) cardiomyopathy is an inherited ARVC in which mutations affecting PKP2 are detected.

[0005] There remains, therefore, an unmet need in the art for treatments for PKP2-related diseases and disorders, including ARVC. The compositions and methods disclosed herein address this need.

SUMMARY

[0006] The present invention relates generally to gene therapy for a disease or disorder, e.g., a cardiac disease or disorder, using a vector expressing PKP2 or a functional variant thereof.

[0007] In one aspect, the disclosure provides polynucleotide, comprising an expression cassette and optionally flanking adeno-associated virus (AAV) inverted terminal repeats (ITRs), wherein the polynucleotide comprises a polynucleotide sequence encoding a Plakophilin-2 (PKP2) or a functional variant thereof, operatively linked to a promoter.

[0008] In some embodiments, the promoter is a cardiac-specific promoter.

[0009] In some embodiments, the promoter is a muscle-specific promoter.

[0010] In some embodiments, the promoter is a cardiomyocyte-specific promoter.

[0011] In some embodiments, the promoter is a Myosin Heavy-chain Creatine Kinase 7 (MHCK7) promoter.

[0012] In some embodiments, the MHCK7 promoter shares at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 31.

[0013] In some embodiments, the promoter is a cardiac troponin T (hTNNT2) promoter.

[0014] In some embodiments, the hTNNT2 promoter shares at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 32.

[0015] In some embodiments, the expression cassette comprises exon 1 of the cardiac troponin T (hTNNT2) gene, wherein optionally the hTNNT2 promoter and exon 1 together share at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 32.

[0016] In some embodiments, the promoter is a ubiquitous promoter, optionally a CMV promoter or a CAG promoter.

[0017] In some embodiments, the expression cassette comprises a polyA signal.

[0018] In some embodiments, the polyA signal is a human growth hormone (hGH) polyA.

[0019] In some embodiments, the expression cassette comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE), optionally a WPRE(x).

[0020] In some embodiments, the Plakophilin-2 (PKP2) or functional variant thereof is a PKP2.

[0021] In some embodiments, the PKP2 is a functional PKP2.

[0022] In some embodiments, the PKP2 is a human PKP2.

[0023] In some embodiments, the PKP2 is PKP2 isoform A.

[0024] In some embodiments, the PKP2 isoform A shares at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 1.

[0025] In some embodiments, the PKP2 is PKP2 isoform B.

[0026] In some embodiments, the PKP2 shares at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 2.

[0027] In some embodiments, the polynucleotide sequence encoding PKP2 is a human PKP2 polynucleotide.

[0028] In some embodiments, the polynucleotide sequence encoding PKP2 shares at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 3.

[0029] In some embodiments, the polynucleotide sequence encoding PKP2 shares at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 4.

[0030] In some embodiments, the polynucleotide comprises at least about 4.0 kb, at least about 4.1 kb, at least about 4.2 kb, at least about 4.3 kb, at least about 4.4 kb, or at least about 4.5 kb.

[0031] In some embodiments, the polynucleotide comprises at most about 4.1 kb, at most about 4.2 kb, at most about 4.3 kb, at most about 4.4 kb, at most about 4.5 kb, or at most about 4.6 kb.

[0032] In some embodiments, the polynucleotide comprises 4.0 kb to 4.6 kb, 4.0 kb to 4.5 kb, or 4.0 kb to 4.4 kb or wherein the polynucleotide comprises 4.0 kb to 4.3 kb, 4.0 kb to 4.2 kb, or 4.0 kb to 4.1 kb.

[0033] In some embodiments, the PKP2 or functional variant thereof comprises at least 800 or at least 830 amino acids.

[0034] In some embodiments, the polynucleotide shares at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with any one of SEQ ID NOs: 8-15.

[0035] In some embodiments, the expression cassette is flanked by 5' and 3' inverted terminal repeats (ITRs)

[0036] In some embodiments, the ITRs are AAV2 ITRs and/or the ITRs share at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with any one of SEQ ID NO: 20-26.

[0037] In another aspect, the disclosure provides a gene therapy vector, comprising the polynucleotide of any one of the preceding embodiments.

[0038] In some embodiments, the gene therapy vector is a recombinant adeno-associated virus (rAAV) vector.

[0039] In some embodiments, the rAAV vector is an AAV9 or a functional variant thereof.

[0040] In some embodiments, the rAAV vector comprises a capsid protein that shares 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NO: 77.

[0041] In some embodiments, the rAAV vector is an AAVrh10 or a functional variant thereof.

[0042] In some embodiments, the rAAV vector comprises a capsid protein that shares 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NO: 79.

[0043] In some embodiments, the rAAV vector is an AAV6 or a functional variant thereof.

[0044] In some embodiments, the rAAV vector comprises a capsid protein that shares 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NO: 78.

[0045] In some embodiments, the rAAV vector is an AAVrh74 or a functional variant thereof.

[0046] In some embodiments, the rAAV vector comprises a capsid protein that shares 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NO: 80.

[0047] In another aspect, the disclosure provides a method of treating and/or preventing a disease or disorder in a subject in need thereof, comprising administering the vector of any one of the preceding embodiments to the subject.

[0048] In some embodiments, the disease or disorder is a cardiac disorder.

[0049] In some embodiments, the disease or disorder is cardiomyopathy.

[0050] In some embodiments, the cardiomyopathy is arrhythmogenic right ventricular cardiomyopathy (ARVC).

[0051] In some embodiments, the cardiomyopathy is hypertrophic cardiomyopathy or dilated cardiomyopathy.

[0052] In some embodiments, the disease or disorder is characterized by fibrofatty infiltration of myocardium.

[0053] In some embodiments, the disease or disorder is heart failure.

[0054] In some embodiments, the subject is a mammal.

[0055] In some embodiments, the subject is a primate.

[0056] In some embodiments, the subject is a human.

[0057] In some embodiments, the subject has a mutation in a PKP2 gene.

[0058] In some embodiments, the vector is administered by intravenous injection, intracardiac injection, intracardiac infusion, and/or cardiac catheterization.

[0059] In some embodiments, the administration increases PKP2 expression by at least about 5%.

[0060] In some embodiments, the administration increases PKP2 expression by at least about 30%.

[0061] In some embodiments, the administration increases PKP2 expression by at least about 70%.

[0062] In some embodiments, the administration increases PKP2 expression by about 5% to about 10%.

[0063] In some embodiments, the administration increases PKP2 expression by about 30% to about 50%.

[0064] In some embodiments, the administration increases PKP2 expression by about 50% to about 70%.

[0065] In some embodiments, the administration increases PKP2 expression by about 70% to about 100%.

[0066] In some embodiments, the method treats and/or prevents the disease or disorder.

[0067] In some embodiments, the method comprises administering an effective amount of the vector.

[0068] In some embodiments, the disease or disorder is related to or caused by loss of function in PKP2 in the subject.

[0069] In some embodiments, the disease or disorder is related to or caused by gain of function in PKP2 in the subject.

[0070] In some embodiments, the subject has a mutation that causes an amino acid substitution selected from p.Arg490Trp, Asp26Asn, Thr50 Va151SerfsX60, Arg79X, Tyr86X, Gln133X, Va1406SerfsX3, Tyr616X, Trp676X, Cys796Arg, Cys796E, Tyr807X, Glu62Lys, S688P, Trp848X, Y86X, V406X, Y616X, W848X, and Y807X, relative to a human PKP2 gene encoding a human PKP2 having the sequence of SEQ ID NO: 2.

[0071] In some embodiments, the method comprises administering a pharmaceutical composition comprising an effective amount of the vector.

[0072] In some embodiments, the method comprises administering between about 1×10^{11} vector genomes and about 1×10^{13} vector genomes of the vector to the subject, administering between about 1×10^{12} vector genomes and about 1×10^{14} vector genomes of the vector to the subject, or administering between about 1×10^{13} vector genomes and about 1×10^{15} vector genomes of the vector to the subject.

[0073] In another aspect, the disclosure provides a pharmaceutical composition comprising the vector of any one of the preceding embodiments.

[0074] In another aspect, the disclosure provides a kit comprising the vector of any one of the preceding embodiments or the pharmaceutical composition of the preceding embodiment and optionally instructions for use.

[0075] In another aspect, the disclosure provides a use of the vector of any one of the preceding embodiments in treating a disease or disorder, optionally according to the method of any one of the preceding embodiments.

[0076] In another aspect, the disclosure provides a vector according to any one of the preceding embodiments for use in treating a disease or disorder, optionally according to the method of any one of the preceding embodiments.

[0077] In another aspect, the disclosure provides a polynucleotide, comprising a polynucleotide sequences that shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any one of SEQ ID NOs: 12-15 and 89-92 or to any one of SEQ ID NOs: 8-11 and 93-96.

[0078] In some embodiments, the promoter is a MHCK7 promoter.

[0079] In some embodiments, the MHCK7 promoter shares at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identity with SEQ ID NO: 31.

[0080] In some embodiments, the PKP2 is a human PKP2.

[0081] In some embodiments, the PKP2 is PKP2 isoform A.

[0082] In some embodiments, the PKP2 isoform A shares at least 80%, 90%, 95%, 99% or 100% identity with SEQ ID NO: 1.

[0083] In another aspect, the disclosure provides a gene therapy vector, comprising the polynucleotide of any one of the preceding embodiments.

[0084] In some embodiments, the gene therapy vector is a recombinant adeno-associated virus (rAAV) vector.

[0085] In some embodiments, the rAAV vector is an AAV9 vector.

[0086] In some embodiments, the rAAV vector is an AAVrh74 vector.

[0087] In another aspect, the disclosure provides a method of treating and/or preventing a cardiac disorder in a subject identified as having a mutation in the PRP2 gene, comprising administering the vector of any one of the preceding embodiments to the subject.

[0088] In some embodiments, the cardiac disorder is cardiomyopathy, optionally arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy, or dilated cardiomyopathy.

[0089] In some embodiments, the cardiac disorder is heart failure.

[0090] In some embodiments, the subject is a mammal.

[0091] In some embodiments, the vector is administered by intravenous injection, intracardiac injection, intracardiac infusion, and/or cardiac catheterization.

[0092] In some embodiments, the method prevents or reduces a decrease in left ventricle ejection fraction percentage (LVEF %), optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the decrease observed in an untreated subject identified as having a mutation in the PRP2 gene.

[0093] In some embodiments, the method prevents or reduces a decrease in left ventricle fractional shortening percentage (FS %), optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the decrease observed in an untreated subject identified as having a mutation in the PRP2 gene.

[0094] In some embodiments, the method prevents or reduces an increase in right ventricle area in millimeters squared (RV Area (mm2), optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the increase observed in an untreated subject identified as having a mutation in the PRP2 gene.

[0095] In some embodiments, the method prevents or reduces a decrease in right ventricle velocity time integral in millimeters per second (RV VTI (mm/sec), optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the decrease observed in an untreated subject identified as having a mutation in the PRP2 gene.

[0096] In some embodiments, the method prevents or reduces an increase in left ventricle or right ventricle fibrosis, optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the increase observed in an untreated subject identified as having a mutation in the PKP2 gene.

[0097] Various other aspects and embodiments are disclosed in the detailed description that follows. The invention is limited solely by the appended claims.

BRIEF DESCRIPTION OF FIGURES

[0098] FIG. **1** shows a diagram illustrating a non-limiting example of a vector genome. The full polynucleotide sequence of the vector genome is SEQ ID NO: 12. The expression cassette is SEQ ID NO: 8. The MHCK7 promoter as described herein is labelled "Enhancer/MHCK7" in the diagram.

[0099] FIG. **2** shows a diagram illustrating a non-limiting example of a vector genome. The full polynucleotide sequence of the vector genome is SEQ ID NO: 13. The expression cassette is SEQ ID NO: 9.

[0100] FIG. **3** shows a diagram illustrating a non-limiting example of a vector genome. The full polynucleotide sequence of the vector genome is SEQ ID NO: 14. The expression cassette is SEQ ID NO: 10. The MHCK7 promoter as described herein is labelled "Enhancer/MHCK7" in the diagram.

[0101] FIG. **4** shows a diagram illustrating a non-limiting example of a vector genome. The full polynucleotide sequence of the vector genome is SEQ ID NO: 15. The expression cassette is SEQ ID NO: 11.

[0102] FIGS. **5**A-**5**B show PKP2 protein expression in transduced differentiated AC16 cells. FIG. **5**A shows Western Blots (WB) of PKP2 (top panel) or loading control, GAPDH (bottom panel). FIG. **5**B show a bar graph of the Western Blot. The AAV vector serotype (AAV9 or rh74) and the promoter (MHCK7 or hTnT) are noted. Controls included a GFP vector (CON-GFP) and no transduction (No Tdxn).

[0103] FIGS. **6**A-**6**D show left ventricle ejection fraction percentage (LVEF %) for normal mice (left bars), untreated PKP2 knockout mice (middle bars, cKO PKP2), or treated mice (right bars). FIG. **6**A shows results with the AAV9 vector and MHCK7 promoter (AAV9-MHCK7). FIG. **6**B shows results with the AAVrh.74 vector and MHCK7 promoter (AAVrh.74-MHCK7). FIG. **6**C shows results with the AAV9 vector and hTnT promoter (AAV9-hTnT). FIG. **6**D shows results with the AAVrh.74 vector and hTnT promoter (AAVrh.74-hTnT).

[0104] FIGS. **7**A-**7**D show left ventricle fractional shortening percentage (FS %) for normal mice (left bars), untreated PKP2 knockout mice (middle bars, cKO PKP2), or treated mice (right bars). FIG. **7**A shows results with the AAV9 vector and MHCK7 promoter (AAV9-MHCK7). FIG. **7**B shows results with the AAVrh.74 vector and MHCK7 promoter (AAVrh.74-MHCK7). FIG. **7**C shows results with

the AAV9 vector and hTnT promoter (AAV9-hTnT). FIG. **7**D shows results with the AAVrh.74 vector and the hTnT promoter (AAVrh.74-hTnT).

[0105] FIGS. **8**A-**8**D show right ventricle area in millimeters squared (RV Area (mm^2)) for normal mice (left bars), untreated PKP2 knockout mice (middle bars, cKO PKP2), or treated mice (right bars). FIG. **8**A shows results with the AAV9 vector and MHCK7 promoter (AAV9-MHCK7). FIG. **8**B shows results with the AAVrh.74 vector and MHCK7 promoter (AAVrh.74-MHCK7). FIG. **8**C shows results with the AAV9 vector and hTnT promoter (AAV9-hTnT). FIG. **8**D shows results with the AAVrh.74 vector and hTnT promoter (AAVrh.74-hTnT).

[0106] FIGS. **9**A-**9**D show right ventricle velocity time integral in millimeters per second (RV VTI (mm/sec)) for normal mice (left bars), untreated PKP2 knockout mice (middle bars, cKO PKP2), or treated mice (right bars). FIG. **9**A shows results with the AAV9 vector and MHCK7 promoter (AAV9-MHCK7). FIG. **9**B shows results with the AAVrh.74 vector and MHCK7 promoter (AAVrh.74-MHCK7). FIG. **9**C shows results with the AAV9 vector and hTnT promoter (AAV9-hTnT). FIG. **9**D shows results with the AAVrh.74 vector and hTnT promoter (AAVrh.74-hTnT).

[0107] FIGS. **10**A-**10**B illustrate the degree of fibrosis in left and right ventricles based on quantitation of the Percent Collagen following trichrome histological staining of the heart. Control animals without the conditional PKP2 gene knock-out (Cre Neg group) were found to have very little collagen, while control PKP2 knock-out animals receiving Formulation Buffer (CKO FB group) were found to have substantially greater proportion of collagen in both left and right ventricles. AAV-mediated overexpression of PKP2 resulted in robust attenuation of collagen, to varying degrees, in all AAV-injected groups [n=4 for all groups; p-values reflect results from One-way ANOVA with Bonferroni post-hoc analyses]. FIG. **10**A is a bar graph of percent collagen in the left ventricle. FIG. **10**B is a bar graph of percent collagen in the right ventricle.

[0108] FIG. **11** shows a diagram illustrating a non-limiting example of a vector genome. The full polynucleotide sequence of the vector genome is SEQ ID NO: 89. The expression cassette is SEQ ID NO: 93. The MHCK7 promoter as described herein is labelled "Enhancer/MHCK7" in the diagram.

[0109] FIG. **12** shows a diagram illustrating a non-limiting example of a vector genome. The full polynucleotide sequence of the vector genome is SEQ ID NO: 90. The expression cassette is SEQ ID NO: 94.

[0110] FIG. **13** shows a diagram illustrating a non-limiting example of a vector genome. The full polynucleotide sequence of the vector genome is SEQ ID NO: 91. The expression cassette is SEQ ID NO: 95. The MHCK7 promoter as described herein is labelled "Enhancer/MHCK7" in the diagram.

[0111] FIG. **14** shows a diagram illustrating a non-limiting example of a vector genome. The full polynucleotide sequence of the vector genome is SEQ ID NO: 92. The expression cassette is SEQ ID NO: 96.

DETAILED DESCRIPTION OF THE INVENTION

[0112] The present disclosure provided gene therapy vectors for PKP2 that deliver a polynucleotide encoding a PKP2 polypeptide or a functional variant thereof, along with methods of use, and other compositions and methods. In particular embodiments, the disclosure relates to a gene therapy vector comprising a promoter sequence operatively linked to a polynucleotide encoding a PKP2 polypeptide or a functional variant thereof. In some embodiments, the promoter is a Myosin Heavy-chain Creatine Kinase 7 (MHCK7) promoter. In some embodiment, the AAV vector is an AAV9 vector. In some embodiments, the promoter is an MHCK7 promoter and the AAV vector is an AAV9 vector. In some embodiments, the promoter is a hTNNT2 promoter. In some embodiment, the promoter is an hTNNT2 promoter and the AAV vector is an AAV9 vector. In some embodiments, the PKP2 is human PKP2a. In some embodiments, the PKP2 is human PKP2b. In some embodiment, the AAV vector is an rh74 vector. In some embodiments, the promoter is an MHCK7 promoter and the AAV vector is an rh74 vector. In some embodiments, the promoter is a hTNNT2 promoter. In some embodiment, the promoter is an hTNNT2 promoter and the AAV vector is an rh74 vector. In some embodiments, the PKP2 is human PKP2a. In some embodiments, the PKP2 is human PKP2b.

[0113] This disclosure further provides methods of treating a disorder or disorder in a subject by administering a gene therapy vector of the disclosure to the subject. In a certain embodiment, the disorder or disorder is arrhythmogenic right ventricular cardiomyopathy (ARVC).

[0114] In certain embodiments, the subject being treated is an ARVC patient having one or more mutation in a PKP2 gene. More than half of ARVC patients carry mutations in the desmosomal gene PKP2 encoding the protein Plakophilin-2 (PKP2). PKP2 is also associated with Brugada syndrome (BrS) and idiopathic ventricular fibrillation. It is a member of the armadillo repeat and plakophilin protein family. The protein contains nine central, conserved armadillo repeat domains flanked by N-terminal and C-terminal domains. It functions to link cadherins to intermediate filaments in the cytoskeleton

[0115] Plakophilin 2 localizes to cell desmosomes and nuclei and binds plakoglobin, desmoplakin, and the desmosomal cadherins via an N-terminal head domain. PKP2 provides a lateral stabilizing force with the desmosomal-intermediate filament assembly facilitating cell-to-cell contact. It may also serve roles in intracellular signaling regulation, electrophysiologic and trafficking regulation, and control of transcription processes.

[0116] Intravenous injection of an AAV9 vector encoding a C-terminal deletion mutant of PKP2a (R735X) in the heart of wild-type mice accelerates the appearance of ARVC when treated mice are subjected to exercise training. Cruz et al. *J Am Coll Cardiol.* 65(14):1438-50 (2015). Mutant PKP2a causes a disease phenotype; and control AAV9 vector expressing the non-mutant PKP2a causes no phenotypic change in wild type mice. Heterologous expression of wild-type human PKP2a does not induce disease or altered function. These studies demonstrate that mutant PKP2a can cause a disease phenotype. They fail to demonstrate a curative role for PKP2, because heterologous expression of non-mutant PKP2 resulted in no phenotypic change in the wild-type mouse.

[0117] In accordance with the present invention, a polynucleotide encoding a PKP2 or functional variant thereof, wherein the PKP2 or functional variant thereof comprises at least 800 or at least 830 amino acids (e.g., no C terminal truncation at Arg-735), may be employed in generating a

gene therapy vector. The resulting vector may be employed in treating diseases or disorders, e.g. a PKP2-related disease or disorder, e.g. ARVC, Brugada syndrome (BrS), idiopathic ventricular fibrillation, dilated cardiomyopathy (DCM), and others.

[0118] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety. In cases of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples described herein are illustrative only and are not intended to be limiting.

[0119] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment, or any form of suggestion, that they constitute valid prior art or form part of the common general knowledge in any country in the world.

[0120] In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. The term "about", when immediately preceding a number or numeral, means that the number or numeral ranges plus or minus 10%. It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components unless otherwise indicated. The use of the alternative (e.g., "or") should be understood to mean either one, both, or any combination thereof of the alternatives. The term "and/or" should be understood to mean either one, or both of the alternatives. As used herein, the terms "include" and "comprise" are used synonymously.

[0121] As used herein, the terms "identity" and "identical" refer, with respect to a polypeptide or polynucleotide sequence, to the percentage of exact matching residues in an alignment of that "query" sequence to a "subject" sequence, such as an alignment generated by the BLAST algorithm. Identity is calculated, unless specified otherwise, across the full length of the subject sequence. Thus a query sequence "shares at least x % identity to" a subject sequence if, when the query sequence is aligned to the subject sequence, at least x % (rounded down) of the residues in the subject sequence are aligned as an exact match to a corresponding residue in the query sequence. Where the subject sequence has variable positions (e.g., residues denoted X), an alignment to any residue in the query sequence is counted as a match. Sequence alignments may be performed using the NCBI Blast service (BLAST+ version 2.12.0).

[0122] As used herein, the term "operatively linked" refers to a functional relationship between two or more nucleic acid (e.g., DNA) segments. Typically, it refers to the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter sequence is operatively linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system. Generally, promoter transcriptional regulatory sequences that are operatively linked to a transcribed sequence are physically contiguous to the transcribed sequence, i.e., they are cis-acting. However, some transcriptional regulatory sequences, such as enhancers, need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

[0123] As used herein, an "AAV vector" or "rAAV vector" refers to a recombinant vector comprising one or more polynucleotides of interest (or transgenes) that are flanked by AAV inverted terminal repeat sequences (ITRs). Such AAV vectors can be replicated and packaged into infectious viral particles when present in a host cell that has been transfected with a plasmid encoding and expressing rep and cap gene products. Alternatively, AAV vectors can be packaged into infectious particles using a host cell that has been stably engineered to express rep and cap genes.

[0124] As used herein, an "AAV virion" or "AAV viral particle" or "AAV vector particle" refers to a viral particle composed of at least one AAV capsid protein and an encapsidated polynucleotide AAV vector. As used herein, if the particle comprises a heterologous polynucleotide (i.e., a polynucleotide other than a wild-type AAV genome such as a transgene to be delivered to a mammalian cell), it is typically referred to as an "AAV vector particle" or simply an "AAV vector." Thus, production of AAV vector particle necessarily includes production of AAV vector, as such a vector is contained within an AAV vector particle.

[0125] As used herein, "promoter" refers to a polynucleotide sequence capable of promoting initiation of RNA transcription from a polynucleotide in a eukaryotic cell.

[0126] As used herein, "vector genome" refers to the polynucleotide sequence packaged by the vector (e.g., an rAAV virion), including flanking sequences (in AAV, inverted terminal repeats). The terms "expression cassette" and "polynucleotide cassette" refer to the portion of the vector genome between the flanking ITR sequences. "Expression cassette" implies that the vector genome comprises at least one gene encoding a gene product operatively linked to an element that drives expression (e.g., a promoter).

[0127] As used herein, the term "patient in need" or "subject in need" refers to a patient or subject at risk of, or suffering from, a disease, disorder or condition that is amenable to treatment or amelioration with a recombinant gene therapy vector or gene editing system disclosed herein. A patient or subject in need may, for instance, be a patient or subject diagnosed with a disorder associated with heart. A subject may have a mutation in an PKP2 gene or deletion of all or a part of PKP2 gene, or of gene regulatory sequences, that causes aberrant expression of the PKP2 protein. "Subject" and "patient" are used interchangeably herein. The subject treated by the methods described herein may be an adult or a child. Subjects may range in age.

[0128] As used herein, the term "variant" refers to a protein that has one or more amino-acid substitution, insertion, or deletion as compared to a parental protein. As used herein, the term "functional variant" refers to a protein that has one or more amino-acid substitution, insertion, or dele-

tion as compared to a parental protein, and which retains one or more desired activities of the parental protein.

[0129] As used herein, "treating" refers to ameliorating one or more symptoms of a disease or disorder. The term "preventing" refers to delaying or interrupting the onset of one or more symptoms of a disease or disorder or slowing the progression of PKP2-related disease or disorder, e.g., arrhythmogenic right ventricular cardiomyopathy (ARVC).

[0130] Adeno-associated virus (AAV) is a replication-deficient parvovirus, the single-stranded DNA genome of which is about 4.7 kb in length including two ~145-nucleotide inverted terminal repeat (ITRs). There are multiple known variants of AAV, also sometimes called serotypes when classified by antigenic epitopes. The nucleotide sequences of the genomes of the AAV serotypes are known. For example, the complete genome of AAV-1 is provided in GenBank Accession No. NC_002077; the complete genome of AAV-2 is provided in GenBank Accession No. NC_001401 and Srivastava et al., J. Virol., 45: 555-564 (1983); the complete genome of AAV-3 is provided in GenBank Accession No. NC_1829; the complete genome of AAV-4 is provided in GenBank Accession No. NC_001829; the AAV-5 genome is provided in GenBank Accession No. AF085716; the complete genome of AAV-6 is provided in GenBank Accession No. NC_00 1862; at least portions of AAV-7 and AAV-8 genomes are provided in GenBank Accession Nos. AX753246 and AX753249, respectively; the AAV-9 genome is provided in Gao et al., J. Virol., 78: 6381-6388 (2004); the AAV-10 genome is provided in Mol. Ther., 13(1): 67-76 (2006); and the AAV-11 genome is provided in Virology, 330(2): 375-383 (2004). The sequence of the AAVrh.74 genome is provided in U.S. Pat. No. 9,434,928, incorporated herein by reference. Cis-acting sequences directing viral DNA replication (rep), encapsidation/packaging and host cell chromosome integration are contained within the AAV ITRs. Three AAV promoters (named p5, p19, and p40 for their relative map locations) drive the expression of the two AAV internal open reading frames encoding rep and cap genes. The two rep promoters (p5 and p19), coupled with the differential splicing of the single AAV intron (at nucleotides 2107 and 2227), result in the production of four rep proteins (rep78, rep68, rep52, and rep40) from the rep gene. Rep proteins possess multiple enzymatic properties that are ultimately responsible for replicating the viral genome. The cap gene is expressed from the p40 promoter and it encodes the three capsid proteins VP1, VP2, and VP3. Alternative splicing and non-consensus translational start sites are responsible for the production of the three related capsid proteins. A single consensus polyadenylation site is located at map position 95 of the AAV genome. The life cycle and genetics of AAV are reviewed in Muzyczka, Current Topics in Microbiology and Immunology, 158: 97-129 (1992).

[0131] AAV possesses unique features that make it attractive as a vector for delivering foreign DNA to cells, for example, in gene therapy. AAV infection of cells in culture is noncytopathic, and natural infection of humans and other animals is silent and asymptomatic. Moreover, AAV infects many mammalian cells allowing the possibility of targeting many different tissues in vivo. Moreover, AAV transduces slowly dividing and non-dividing cells, and can persist essentially for the lifetime of those cells as a transcriptionally active nuclear episome (extrachromosomal element). The AAV proviral genome is inserted as cloned DNA in plasmids, which makes construction of recombinant genomes feasible. Furthermore, because the signals directing AAV replication and genome encapsidation are contained within the ITRs of the AAV genome, some or all of the internal approximately 4.3 kb of the genome (encoding replication and structural capsid proteins, rep-cap) may be replaced with foreign DNA. To generate AAV vectors, the rep and cap proteins may be provided in trans. Another significant feature of AAV is that it is an extremely stable and hearty virus. It easily withstands the conditions used to inactivate adenovirus (56° to 65° C. for several hours), making cold preservation of AAV less critical. AAV may even be lyophilized. Finally, AAV-infected cells are not resistant to superinfection.

[0132] Gene delivery viral vectors useful in the practice of the present invention can be constructed utilizing methodologies well known in the art of molecular biology. Typically, viral vectors carrying transgenes are assembled from polynucleotides encoding the transgene, suitable regulatory elements and elements necessary for production of viral proteins, which mediate cell transduction. Such recombinant viruses may be produced by techniques known in the art, e.g., by transfecting packaging cells or by transient transfection with helper plasmids or viruses. Typical examples of virus packaging cells include but are not limited to HeLa cells, SF9 cells (optionally with a baculovirus helper vector), 293 cells, etc. A Herpesvirus-based system can be used to produce AAV vectors, as described in US20170218395A1. Detailed protocols for producing such replication-defective recombinant viruses may be found for instance in WO95/14785, WO96/22378, U.S. Pat. Nos. 5,882,877, 6,013,516, 4,861,719, 5,278,056 and WO94/19478, the complete contents of each of which is hereby incorporated by reference.

[0133] The present disclosure contemplates compositions and methods of use related to Plakophilin-2 (PKP2) proteins or polypeptides. Various mutations in PKP2 are known to be associated with cardiomyopathy and heart failure, including diseases like those described in van Tintelen et al. *Circulation* 113:1650-58 (2006); *Novelli Front. Cardiovasc. Med.* (2008); and in other sources. Viral vector-mediated delivery of the PKP2 gene may therefore serve as a viable therapeutic for PKP2-related human diseases such as cardiomyopathy and heart failure.

[0134] More than 230 mutations in the PKP2 gene have been identified in people with arrhythmogenic right ventricular cardiomyopathy (ARVC). (See "PKP2 gene," MedlinePlus). This condition most commonly affects the myocardium surrounding the right ventricle, one of the two lower chambers of the heart. ARVC increases the risk of an abnormal heartbeat (arrhythmia) and sudden death. Some PKP2 gene mutations lead to the production of an abnormally short version of plakophilin 2. Other mutations alter the structure of plakophilin 2 by adding, deleting, or changing one or more of its protein building blocks (amino acids). Studies suggest that the altered protein impairs the formation and function of desmosomes.

[0135] Without normal desmosomes, cells of the myocardium detach from one another and die, particularly when the heart muscle is placed under stress (such as during vigorous exercise). The damaged myocardium is gradually replaced by fat and scar tissue. As this abnormal tissue builds up, the walls of the right ventricle become stretched out, preventing the heart from pumping blood effectively. These changes also disrupt the electrical signals that control the heartbeat,

which can lead to arrhythmia. Description of PKP2-related disease may be found in the following references: Bonne et al. Genomics 51:452-454 (1998) [PubMed: 9721216]; Bonne et al. *Cytogenet. Cell Genet.* 88:286-287 (2000) [PubMed: 10828611]; Dalal et al., *Circulation* 113:1641-1649 (2006) [PubMed: 16549640]; Gerull et al. *Nature Genet.* 36:1162-1164 (2004 [PubMed: 15489853]; Grossmann et al. *J. Cell Biol.* 167:149-160 (2004) [PubMed: 15479741]; Marcus et al. *Circulation* 65:384-398 (1982) [PubMed: 7053899]; and Mertens et al. *J. Cell Biol.* 135: 1009-1025 (1996) [PubMed: 8922383]. See also OMIM.org entry 602861 ("PLAKOPHILIN 2; PKP2").

[0136] The native sequences of human PKP2a and its isoform PKP2b are shown below, with Arg-735 underlined:

PKP2a-837 amino acids

(SEQ ID NO: 1)

```
  1 MAAPGAPAEY GYIRTVLGQQ ILGQLDSSSL ALPSEAKLKL
 41 AGSSGRGGQT VKSLRIQEQV QQTLARKGRS SVGNGNLHRT
 81 SSVPEYVYNL HLVENDFVGG RSPVPKTYDM LKAGTTATYE
121 GRWGRGTAQY SSQKSVEERS LRHPLRRLEI SPDSSPERAH
161 YTHSDYQYSQ RSQAGHTLHH QESRRAALLV PPRYARSEIV
201 GVSRAGTTSR QRHFDTYHRQ YQHGSVSDTV FDSIPANPAL
241 LTYPRPGTSR SMGNLLEKEN YLTAGLTVGQ VRPLVPLQPV
281 TQNRASRSSW HQSSFHSTRT LREAGPSVAV DSSGRRAHLT
321 VGQAAAGGSG NLLTERSTFT DSQLGNADME MTLERAVSML
361 EADHMLPSRI SAAATFIQHE CFQKSEARKR VNQLRGILKL
401 LQLLKVQNED VQRAVCGALR NLVFEDNDNK LEVAELNGVP
441 RLLQVLKQTR DLETKKQITG LLWNLSSNDK LKNLMITEAL
481 LTLTENIIIP FSGWPEGDYP KANGLLDFDI FYNVTGCLRN
521 MSSAGADGRK AMRRCDGLID SLVHYVRGTI ADYQPDDKAT
561 ENCVCILHNL SYQLEAELPE KYSQNIYIQN RNIQTDNNKS
601 IGCFGSRSRK VKEQYQDVPM PEEKSNPKGV EWLWHSIVIR
641 MYLSLIAKSV RNYTQEASLG ALQNLTAGSG PMPTSVAQTV
681 VQKESGLQHT RKMLHVGDPS VKKTAISLLR NLSRNLSLQN
721 EIAKETLPDL 7SIIPDTVPS TDLLIETTAS ACYTLNNIIQ
761 NSYQNARDLL NTGGIQKIMA ISAGDAYASN KASKAASVLL
801 YSLWAHTELH HAYKKAQFKK TDFVNSRTAK AYHSLKD
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PKP2b-881 amino acids

(SEQ ID NO: 2)

```
  1 MAAPGAPAEY GYIRTVLGQQ ILGQLDSSSL ALPSEAKLKL
 41 AGSSGRGGQT VKSLRIQEQV QQTLARKGRS SVGNGNLHRT
 81 SSVPEYVYNL HLVENDFVGG RSPVPKTYDM LKAGTTATYE
121 GRWGRGTAQY SSQKSVEERS LRHPLRRLEI SPDSSPERAH
161 YTHSDYQYSQ RSQAGHTLHH QESRRAALLV PPRYARSEIV
201 GVSRAGTTSR QRHFDTYHRQ YQHGSVSDTV FDSIPANPAL
241 LTYPRPGTSR SMGNLLEKEN YLTAGLTVGQ VRPLVPLQPV
281 TQNRASRSSW HQSSFHSTRT LREAGPSVAV DSSGRRAHLT
321 VGQAAAGGSG NLLTERSTFT DSQLGNADME MTLERAVSML
361 EADHMLPSRI SAAATFIQHE CFQKSEARKR VNQLRGILKL
401 LQLLKVQNED VQRAVCGALR NLVFEDNDNK LEVAELNGVP
441 RLLQVLKQTR DLETKKQITD HTVNLRSRNG WPGAVAHACN
481 PSTLGGQGGR ITRSGVRDQP DQHGLLWNLS SNDKLKNLMI
521 TEALLTLTEN IIIPFSGWPE GDYPKANGLL DFDIFYNVTG
561 CLRNMSSAGA DGRKAMRRCD GLIDSLVHYV RGTIADYQPD
601 DKATENCVCI LHNLSYQLEA ELPEKYSQNI YIQNRNIQTD
641 NNKSIGCFGS RSRKVKEQYQ DVPMPEEKSN PKGVEWLWHS
681 IVIRMYLSLI AKSVRNYTQE ASLGALQNLT AGSGPMPTSV
721 AQTVVQKESG LQHTRKMLHV GDPSVKKTAI SLLRNLSRNL
761 SLQNEIAKET LPDLVSIIPD TVPSTDLLIE TTASACYTLN
801 NIIQNSYQNA RDLLNTGGIQ KIMAISAGDA YASNKASKAA
841 SVLLYSLWAH TELHHAYKKA QFKKTDFVNS RTAKAYHSLK
881 D
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[0137] One experimental model of PKP2-related disease is the R735X model, as described in Cruz et al. *J Am Coll Cardiol* 65:1438-50 (2015). R735X is numbered according to the PKP2b isoform. The R735X mutant of PKP2a is 690 amino acids in length, due to C-terminal truncation at Arg-690, (Arg-735 relative to PKP2b, SEQ ID NO: 2).

[0138] In some embodiments, the PKP2 protein comprises a polypeptide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NO: 1 or SEQ ID NO: 2. In some embodiments, the PKP2 protein is a wild-type or native PKP2 protein, e.g. human PKP2a or human PKP2b.

[0139] In some embodiments, the disclosure provides a recombinant adeno-associated virus (rAAV) virion, comprising a capsid and a vector genome, wherein the vector genome comprises a polynucleotide sequence encoding an PKP2 or a functional variant thereof, operatively linked to a promoter. In some embodiments, the disclosure provides a recombinant adeno-associated virus (rAAV) virion, comprising a capsid and a vector genome, wherein the vector genome comprises a polynucleotide sequence encoding an PKP2, operatively linked to a promoter. The polynucleotide encoding the PKP2a may comprise a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 3.

[0140] The polynucleotide encoding the PKP2b may comprise a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 4.

[0141] Optionally, the polynucleotide sequence encoding the vector genome may comprise a Kozak sequence, including but not limited to GCCACCATGG (SEQ ID NO: 5). Kozak sequence may overlap the polynucleotide sequence encoding an PKP2a protein or a functional variant thereof. For example, the vector genome may comprise a polynucleotide sequence (with first ten nucleotides constituting the

Kozak sequence) at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 6.

[0142] Kozak sequence may overlap the polynucleotide sequence encoding an PKP2b protein or a functional variant thereof. For example, the vector genome may comprise a polynucleotide sequence (with first ten nucleotides constituting the Kozak sequence) at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

[0143] In some embodiments, the Kozak sequence is an alternative Kozak sequence comprising or consisting of any one of:

(SEQ ID NO: 16)
(gcc)gccRccAUGG;

AGNNAUGN;

ANNAUGG;

ANNAUGC;

ACCAUGG;
and

(SEQ ID NO: 18)
GACACCAUGG.

[0144] In some embodiments, the vector genome comprises no Kozak sequence.

[0145] The polynucleotide sequence may be codon-optimized. For example, the vector genome may comprise a polynucleotide sequence encoding a PKP2a that shares at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 87.

[0146] The vector genome may comprise a polynucleotide sequence encoding a PKP2b that shares at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 88.

[0147] The AAV virions of the disclosure comprise a vector genome. The vector genome may comprise an expression cassette (or a polynucleotide cassette for gene-editing applications not requiring expression of the polynucleotide sequence). Any suitable inverted terminal repeats (ITRs) may be used. The ITRs may be AAV ITRs from the same serotype as the capsid present in the AAV virion, or a different serotype from the capsid (e.g., AAV2 ITRs may be used with an AAV virion having an AAV9 capsid or an AAVrh74 capsid). In each case, the serotype of the capsid determines the name applied to the virion. The ITR are generally the most 5' and most 3' elements of the vector genome. The vector genome will also generally contain, in 5' to 3' order, a promoter, a transgene, 3' untranslated region (UTR) sequences (e.g., a WPRE element), and a polyadenylation sequence. In variations, the vector genome includes an enhancer element (generally 5' to the promoter) and/or an exon (generally 3' to the promoter). In variations, the vector genomes of the disclosure encode a partial or complete transgene sequence used as a repair template in a gene editing system. In such variations, the vector genome may comprise an exogenous promoter, or the gene editing system may insert the transgene into a locus in the genome having an endogenous promoter, such as a cardiac- or myocyte-specific promoter.

[0148] In some embodiments, the 5' ITR comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 20.

[0149] In some embodiments, the 5' ITR comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 21.

[0150] In some embodiments, the 5' ITR comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 22)

[0151] In some embodiments, the 5' ITR comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 23.

[0152] In some embodiments, the 3' ITR comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 24.

[0153] In some embodiments, the 3' ITR comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25.

[0154] In some embodiments, the 3' ITR comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 26.

[0155] In some embodiments the vector genome comprises one or more filler sequences, e.g., at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 27; SEQ ID NO: 28; or SEQ ID NO: 29.

[0156] In some embodiments, the polynucleotide sequence encoding an PKP2 protein or functional variant thereof is operatively linked to a promoter. In certain embodiments, the promoter is an MHCK7 promoter. In certain embodiments, the promoter is an TNNT2 promoter.

[0157] The present disclosure contemplates use of various promoters. Promoters useful in embodiments of the present disclosure include, without limitation, a cytomegalovirus (CMV) promoter, phosphoglycerate kinase (PGK) promoter, or a promoter sequence comprised of the CMV enhancer and portions of the chicken beta-actin promoter and the rabbit beta-globin gene (CAG). In some cases, the promoter may be a synthetic promoter. Exemplary synthetic promoters are provided by Schlabach et al. *PNAS USA*. 107(6):2538-43 (2010). In some embodiments, the promoter comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 30.

[0158] In some embodiments, a polynucleotide sequence encoding an PKP2 protein or functional variant thereof is operatively linked to an inducible promoter. An inducible promoter may be configured to cause the polynucleotide sequence to be transcriptionally expressed or not transcriptionally expressed in response to addition or accumulation of an agent or in response to removal, degradation, or dilution of an agent. The agent may be a drug. The agent may be tetracycline or one of its derivatives, including, without limitation, doxycycline. In some cases, the inducible promoter is a tet-on promoter, a tet-off promoter, a chemically-regulated promoter, a physically-regulated promoter (i.e., a promoter that responds to presence or absence of light or to

low or high temperature). Inducible promoters include heavy metal ion inducible promoters (such as the mouse mammary tumor virus (mMTV) promoter or various growth hormone promoters), and the promoters from T7 phage which are active in the presence of T7 RNA polymerase. This list of inducible promoters is non-limiting.

[0159] In some cases, the promoter is a tissue-specific promoter, such as a promoter capable of driving expression in a cardiac cell to a greater extent than in a non-cardiac cell. In some embodiments, tissue-specific promoter is a selected from any various cardiac cell-specific promoters including but not limited to, desmin (Des), alpha-myosin heavy chain (α-MHC), myosin light chain 2 (MLC-2), cardiac troponin C (cTnC), cardiac troponin T (hTNNT2), muscle creatine kinase (CK) and combinations of promoter/enhancer regions thereof, such as MHCK7. In some cases, the promoter is a ubiquitous promoter. A "ubiquitous promoter" refers to a promoter that is not tissue-specific under experimental or clinical conditions. In some cases, the ubiquitous promoter is any one of Cytomegalovirus (CMV), Cytomegalovirus early enhancer element chicken beta-Actin gene intron with the splice acceptor of the rabbit beta-Globin gene (CAG), ubiquitin C (UBC), Phosphoglycerate Kinase (PGK), Eukaryotic translation elongation factor 1 alpha 1 (EF1-alpha), Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), simian virus 40 (SV40), Hepatitis B virus (HBV), chicken beta-actin, and human beta-actin promoters.

[0160] In some embodiments, the promoter sequence is selected from Table 3. In some embodiments, the promoter comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS: 31-51. In some embodiments, the promoter comprises a fragment of a polynucleotide sequence of any one of SEQ ID NOs: 31-51, e.g., a fragment comprising at least 25%, at least 50%, at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of any one of SEQ ID NOs: 31-51.

TABLE 3

PROMOTER	SEQUENCE	SEQ ID NO:
MHCK7	ACCCTTCAGATTAAAAATAACTGAGGTAAGGGCCTGGGTAGG GGAGGTGGTGTGAGACGCTCCTGTCTCTCCTCTATCTGCCCA TCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACTAAAAAA AGGCCATGGAGCCAGAGGGGCGAGGGCAACAGACCTTTCATG GGCAAACCTTGGGGCCCTGCTGTCTAGCATGCCCCACTACGG GTCTAGGCTGCCCATGTAAGGAGGCAAGGCCTGGGGACACCC GAGATGCCTGGTTATAATTAACCCAGACATGTGGCTGCCCCC CCCCCCCCAACACCTGCTGCCTCTAAAAATAACCCTGTCCCT GGTGGATCCCCTGCATGCGAAGATCTTCGAACAAGGCTGTGG GGGACTGAGGGCAGGCTGTAACAGGCTTGGGGGCCAGGGCTT ATACGTGCCTGGGACTCCCAAAGTATTACTGTTCCATGTTCC CGGCGAAGGGCCAGCTGTCCCCCGCCAGCTAGACTCAGCACT TAGTTTAGGAACCAGTGAGCAAGTCAGCCCTTGGGGCAGCCC ATACAAGGCCATGGGGCTGGGCAAGCTGCACGCCTGGGTCCG GGGTGGGCACGGTGCCCGGGCAACGAGCTGAAAGCTCATCTG CTCTCAGGGGCCCCTCCCTGGGGACAGCCCCTCCTGGCTAGT CACACCCTGTAGGCTCCTCTATATAACCCAGGGGCACAGGGG CTGCCCTCATTCTACCACCACCTCCACAGCACAGACAGACAC TCAGGAGCCAGCCAG	31
Human cardiac troponin T promoter (without exon 1) hTnnT2/ HTNNT2	CTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTACC CCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCT CTGCCTTCCAAGATTCTGGTGCTGAGACTTATGGAGTGTCTT GGAGGTTGCCTTCTGCCCCCCAACCCTGCTCCCAGCTGGCCC TCCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGATTCTC AAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCAT ATCTGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGA CCACATGGGCTTATATGGCGTGGGGTACATGTTCCTGTAGCC TTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCCAC CCCCACCGCCATCCCCCTGCCCCACCCGTCCCCTGTCGCACA TTCCTCCCTCCGCAGGGCTGGCTCACCAGGCCCCAGCCCACA TGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCACCCAGT	33
Human cardiac troponin T promoter (with exon 1, underlined) hTnnT2/ HTNNT2	CTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTACC CCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCT CTGCCTTCCAAGATTCTGGTGCTGAGACTTATGGAGTGTCTT GGAGGTTGCCTTCTGCCCCCCAACCCTGCTCCCAGCTGGCCC TCCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGATTCTC AAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCAT ATCTGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGA CCACATGGGCTTATATGGCGTGGGGTACATGTTCCTGTAGCC TTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCCAC CCCCACCGCCATCCCCCTGCCCCACCCGTCCCCTGTCGCACA TTCCTCCCTCCGCAGGGCTGGCTCACCAGGCCCCAGCCCACA TGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCACCCAGTCC CCGCTGAGACTGAGCAGACGCCTCCAGGATCTGTCGGCAG	32

TABLE 3-continued

PROMOTER	SEQUENCE	SEQ ID NO:
Mouse α-cardiac myosin heavy chain promoter (αMHC)	GGTACCGGATCCTGCAAGGTCACACAAGGGTCTCCACCCACC AGGTGCCCTAGTCTCAATTTCAGTTTCCATGCCTTGTTCTCA CAATGCTGGCCTCCCCAGAGCTAATTTGGACTTTGTTTTTAT TTCAAAAGGGCCTGAATGAGGAGTAGATCTTGTGCTACCCAG CTCTAAGGGTGCCCGTGAAGCCCTCAGACCTGGAGCCTTTGC AACAGCCCTTTAGGTGGAAGCAGAATAAAGCAATTTTCCTTA AAGCCAAAATCCTGCCTCTAGACTCTTCTTCTCTGACCTCGG TCCCTGGGCTCTAGGGTGGGGAGGTGGGGCTTGGAAGAAGAA GGTGGGGAAGTGGCAAAAGCCGATCCCTAGGGCCCTGTGAAG TTCGGAGCCTTCCCTGTACAGCACTGGCTCATAGATCCTCCT CCAGCCAAACATAGCAAGAAGTGATACCTCCTTTGTGACTTC CCCAGGCCCAGTACCTGTCAGGTTGAAACAGGATTTAGAGAA GCCTCTGAACTCACCTGAACTCTGAAGCTCATCCACCAAGCA AGCACCTAGGTGCCACTGCTAGTTAGTATCCTACGCTGATAA TATGCAGAGCTGGGCCACAGAAGTCCTGGGGTGTAGGAACTG ACCAGTGACTTTTCAGTCGGCAAAGGTATGACCCCCTCAGCA GATGTAGTAATGTCCCCTTAGATCCCATCCCAGGCAGGTCTC TAAGAGGACATGGGATGAGAGATGTAGTCATGTGGCATTCCA AACACAGCTATCCACAGTGTCCCTTGCCCCTTCCACTTAGCC AGGAGGACAGTAACCTTAGCCTATCTTTCTTCCTCCCCATCC TCCCAGGACACACCCCCTGGTCTGCAGTATTCATTTCTTCCT TCACGTCCCCTCTGTGACTTCCATTTGCAAGGCTTTTGACCT CTGCAGCTGCTGGAAGATAGAGTTTGGCCCTAGGTGTGGCAA GCCATCTCAAGAGAAAGCAGACAACAGGGGGACCAGATTTTG GAAGGATCAGGAACTAAATCACTGGCGGGCCTGGGGGTAGAA AAAAGAGTGAGTGAGTCCGCTCCAGCTAAGCCAAGCTAGTCC CCGAGATACTCTGCCACAGCTGGGCTGCTCGGGGTAGCTTTA GGAATGTGGGTCTGAAAGACAATGGGATTGGAAGACATCTCT TTGAGTCTCCCCTCAACCCCACCTACAGACACACTCGTGTGT GGCCAGACTCCTGTTCAACAGCCCTCTGTGTTCTGACCACTG AGCTAGGCAACCAGAGCATGGGCCCTGTGCTGAGGATGAAGA GTTGGTTACCAATAGCAAAAACAGCAGGGGAGGGAGAACAGA GAACGAAATAAGGAAGGAAGAAGGAAAGGCCAGTCAATCAGA TGCAGTCAGAAGAGATGGGAAGCCAACACACAGCTTGAGCAG AGGAAACAGAAAAGGGAGAGATTCTGGGCATAAGGAGGCCAC AGAAAGAAGAGCCCAGGCCCCCCAAGTCTCCTCTTTATACCC TCATCCCGTCTCCCAATTAAGCCCACTCTTCTTCCTAGATCA GACCTGAGCTGCAGCGAAGAGACCCGTAGGGAGGATCACACT GGATGAAGGAGATGTGTGGAGAAGTCCAGGGAACCTAAGAGC CAGAGCCTAAAAGAGCAAGAGATAAAGGTGCTTCAAAGGTGG CCAGGCTGTGCACACAGAGGGTCGAGGACTGGTGGTAGAGCC TCAAGATAAGGATGATGCTCAGAATGGGCGGGGGGGGGGATT CTGGGGGGGGGAGAGAGAAGGTGAGAAGGAGCCTGGAACAGA GAATCTGGAAGCGCTGGAAACGATACCATAAAGGGAAGAACC CAGGCTACCTTTAGATGTAAATCATGAAAGACAGGGAGAAGG GAAGCTGGAGAGAGTAGAAGGACCCCGGGGCAAGACATTGAA GCAAGGACAAGCCAGGTTGAGCGCTCCGTGAAATCAGCCTGC TGAAGGCAGAGCCCTGGTATGAGCACCAGAACAGCAGAGGCT AGGGTTAATGTCGAGACAGGGAACAGAAGGTAGACACAGGAA CAGACAGAGACGGGGGAGCCAGGTAACAAAGGAATGGTCCTT CTCACCTGTGGCCAGAGCGTCCATCTGTGTCCACATACTCTA GAATGTTCATCAGACTGCAGGGCTGGCTTGGGAGGCAGCTGG AAAGAGTATGTGAGAGCCAGGGGAGACAAGGGGGCCTAGGAA AGGAAGAAGAGGGCAAACCAGGCCACACAAGAGGGCAGAGCC CAGAACTGAGTTAACTCCTTCCTTGTTGCATCTTCCATAGGA GGCAGTGGGAACTCTGTGACCACCATCCCCCATGAGCCCCCA CTACCCATACCAAGTTTGGCCTGAGTGGCATTCTAGGTTCCC TGAGGACAGAGCCTGGCCTTTGTCTCTTGGACCTGACCCAAG CTGACCCAATGTTCTCAGTACCTTATCATGCCCTCAAGAGCT TGAGAACCAGGCAGTGACATATTAGGCCATGGGCTAACCCTG GAGCTTGCACACAGGAGCCTCAAGTGACCTCCAGGGACACAG CTGCAGACAGGTGGCCTTTATCCCCAAAGAGCAACCATTTGG CATAGGTGGCTGCAAATGGGAATGCAAGGTTGAATCAGGTCC CTTCAAGAATACTGCATGCAAGACCTAAGACCCCTGGAGAGA GGGGTATGCTCCTGCCCCCACCCACCATAAGGGGAGTGAACT ATCCTAGGGGGCTGGCGACCTTGGGGAGACACCACATTACTG AGAGTGCTGAGCCCAGAAAAACTGACCGCCCTGTGTCCTGCC CACCTCCACACTCTAGAGCTATATTGAGAGGTGACAGTAGAT AGGGTGGGAGCTGGTAGCAGGGAGAGTGTTCCTGGGTGTGAG GGTGTAGGGGAAAGCCAGAGCAGGGGAGTCTGGCTTTGTCTC CTGAACACAATGTCTACTTAGTTATAACAGGCATGACCTGCT AAAGACCCAACATCTACGACCTCTGAAAAGACAGCAGCCCTG GAGGACAGGGGTTGTCTCTGAGCCTTGGGTGCTTGATGGTGC	34

TABLE 3-continued

PROMOTER	SEQUENCE	SEQ ID NO:
	CACAAAGGAGGGCATGAGTGTGAGTATAAGGCCCCAGGAGCG	
	TTAGAGAAGGGCACTTGGGAAGGGGTCAGTCTGCAGAGCCCC	
	TATCCATGGAATCTGGAGCCTGGGGCCAACTGGTGTAAATCT	
	CTGGGCCTGCCAGGCATTCAAAGCAGCACCTGCATCCTCTGG	
	CAGCCTGGGGAGGCGGAAGGGAGCAACCCCCCACTTATACCC	
	TTTCTCCCTCAGCCCCAGGATTAACACCTCTGGCCTTCCCCC	
	TTCCCACCTCCCATCAGGAGTGGAGGGTTGCAGAGGGAGGGT	
	AAAAACCTACATGTCCAAACATCATGGTGCACGATATATGGA	
	TCAGTATGTGTAGAGGCAAGAAAGGAAATCTGCAGGCTTAAC	
	TGGGTTAATGTGTAAAGTCTGTGTGCATGTGTGTGTGTCTGA	
	CTGAAAACGGGCATGGCTGTGCAGCTGTTCAGTTCTGTGCGT	
	GAGGTTACCAGACTGCAGGTTTGTGTGTAAATTGCCCAAGGC	
	AAAGTGGGTGAATCCCTTCCATGGTTTAAAGAGATTGGATGA	
	TGGCCTGCATCTCAAGGACCATGGAAAATAGAATGGACACTC	
	TATATGTGTCTCTAAGCTAAGGTAGCAAGGTCTTTGGAGGAC	
	ACCTGTCTAGAGATGTGGGCAACAGAGACTACAGACAGTATC	
	TGTACAGAGTAAGGAGAGAGAGGAGGGGGTGTAGAATTCTCT	
	TACTATCAAAGGGAAACTGAGTCGTGCACCTGCAAAGTGGAT	
	GCTCTCCCTAGACATCATGACTTTGTCTCTGGGGAGCCAGCA	
	CTGTGGAACTTCAGGTCTGAGAGAGTAGGAGGCTCCCCTCAG	
	CCTGAAGCTATGCAGATAGCCAGGGTTGAAAGGGGGAAGGGA	
	GAGCCTGGGATGGGAGCTTGTGTGTTGGAGGCAGGGGACAGA	
	TATTAAGCCTGGAAGAGAAGGTGACCCTTACCCAGTTGTTCA	
	ACTCACCCTTCAGATTAAAAATAACTGAGGTAAGGGCCTGGG	
	TAGGGGAGGTGGTGTGAGACGCTCCTGTCTCTCCTCTATCTG	
	CCCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACTAA	
	AAAAAGGCCATGGAGCCAGAGGGGCGAGGGCAACAGACCTTT	
	CATGGGCAAACCTTGGGGCCCTGCTGTCCTCCTGTCACCTCC	
	AGAGCCAAGGGATCAAAGGAGGAGGAGCCAGGACAGGAGGGA	
	AGTGGGAGGGAGGGTCCCAGCAGAGGACTCCAAATTTAGGCA	
	GCAGGCATATGGGATGGGATATAAAGGGGCTGGAGCACTGAG	
	AGCTGTCAGAGATTTCTCCAACCCAGGTAAGAGGGAGTTTCG	
	GGTGGGGGCTCTTCACCCACACCAGACCTCTCCCCACCTAGA	
	AGGAAACTGCCTTTCCTGGAAGTGGGGTTCAGGCCGGTCAGA	
	GATCTGACAGGGTGGCCTTCCACCAGCCTGGGAAGTTCTCAG	
	TGGCAGGAGGTTTCCACAAGAAACACTGGATGCCCCTTCCCT	
	TACGCTGTCTTCTCCATCTTCCTCCTGGGGATGCTCCTCCCC	
	GTCTTGGTTTATCTTGGCTCTTCGTCTTCAGCAAGATTTGCC	
	CTGTGCTGTCCACTCCATCTTTCTCTACTGTCTCCGTGCCTT	
	GCCTTGCCTTCTTGCGTGTCCTTCCTTTCCACCCATTTCTCA	
	CTTCACCTTTTCTCCCCTTCTCATTTGTATTCATCCTTCCTT	
	CCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTTC	
	TCCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTT	
	CCTGTGTCAGAGTGCTGAGAATCACACCTGGGGTTCCCACCC	
	TTATGTAAACAATCTTCCAGTGAGCCACAGCTTCAGTGCTGC	
	TGGGTGCTCTCTTACCTTCCTCACCCCCTGGCTTGTCCTGTT	
	CCATCCTGGTCAGGATCTCTAGATTGGTCTCCCAGCCTCTGC	
	TACTCCTCTTCCTGCCTGTTCCTCTCTCTGTCCAGCTGCGCC	
	ACTGTGGTGCCTCGTTCCAGCTGTGGTCCACATTCTTCAGGA	
	TTCTCTGAAAAGTTAACCAGGTGAGAATGTTTCCCCTGTAGA	
	CAGCAGATCACGATTCTCCCGGAAGTCAGGCTTCCAGCCCTC	
	TCTTTCTCTGCCCAGCTGCCCGGCACTCTTAGCAAACCTCAG	
	GCACCCTTACCCCACATAGACCTCTGACAGAGAAGCAGGCAC	
	TTTACATGGAGTCCTGGTGGGAGAGCCATAGGCTACGGTGTA	
	AAAGAGGCAGGGAAGTGGTGGTGTAGGAAAGTCAGGACTTCA	
	CATAGAAGCCTAGCCCACACCAGAAATGACAGACAGATCCCT	
	CCTATCTCCCCCATAAGAGTTTGAGTCGACCCGCGGCCCCGA	
	ATTG	
Chicken cardiac troponin T promoter (cTnT)	GGGATAAAAGCAGTCTGGGCTTTCACATGACAGCATCTGGGG	35
	CTGCGGCAGAGGGTCGGGTCCGAAGCGCTGCCTTATCAGCGT	
	CCCCAGCCCTGGGAGGTGACAGCTGGCTGGCTTGTGTCAGCC	
	CCTCGGGCACTCACGTATCTCCGTCCGACGGGTTTAAAATAG	
	CAAAACTCTGAGGCCACACAATAGCTTGGGCTTATATGGGCT	
	CCTGTGGGGGAAGGGGGAGCACGGAGGGGGCCGGGGCCGCTG	
	CTGCCAAAATAGCAGCTCACAAGTGTTGCATTCCTCTCTGGG	
	CGCCGGGCACATTCCTGCTGGCTCTGCCCGCCCCGGGGTGGG	
	CGCCGGGGGGACCTTAAAGCCTCTGCCCCCCAAGGAGCCCTT	
	CCCAGACAGCCGCCGGCACCCACCGCTCCGTGGGA	
Human Creatine Kinase M (hCKM)	CTCTCAGCCCTGGAAGTCCTTGCTCACAGCCGAGGCGCCGAG	36
	AGCGCTTGCTCTGCCCAGATCTGCGCGAGTCTGGCGCCCGCG	
	CTCTGAACGGCGTCGCTGCCCAGCCCCCTTCCCCGGGAGGTG	
	GGAGCGGCCACCCAGGGCCCCGTGGCTGCCCTTGTAAGGAGG	

TABLE 3-continued

PROMOTER	SEQUENCE	SEQ ID NO:
	CGAGGCCCGAGGACACCCGAGACGCCCGGTTATAATTAACCA GGACACGTGGCGAACCCCCCTCCAACACCTGCCCCCGAACCC CCCCATACCCAGCGCCTCGGGTCTCGGCCTTTGCGGCAGAGG AGACAGCAAAGCGCCCTCTAAAAATAACTCCTTTCCCGGCGA CCGAGACCCTCCCTGTCCCCCGCACAGCGGAAATCTCCCAGT GGCACCGAGGGGGCGAGGGTTAAGTGGGGGGGAGGGTGACCA CCGCCTCCCACCCTTGCCCTGAGTTTGAATCTCTCCAACTCA GCCAGCCTCAGTTTCCCCTCCACTCAGTCCCTAGGAGGAAGG GGCGCCCAAGCGCGGGTTTCTGGGGTTAGACTGCCCTCCATT GCAATTGGTCCTTCTCCCGGCCTCTGCTTCCTCCAGCTCACA GGGTATCTGCTCCTCCTGGAGCCACACCTTGGTTCCCCGAGG TGCCGCTGGGACTCGGGTAGGGGTGAGGGCCCAGGGGGCACA GGGGGAGCCGAGGGCCACAGGAAGGGCTGGTGGCTGAAGGAG ACTCAGGGGCCAGGGGACGGTGGCTTCTACGTGCTTGGGACG TTCCCAGCCACCGTCCCATGTTCCCGGCGGGGGGCCAGCTGT CCCCACCGCCAGCCCAACTCAGCACTTGGTCAGGGTATCAGC TTGGTGGGGGGGCGTGAGCCCAGCCCCTGGGGCGGCTCAGCC CATACAAGGCCATGGGGCTGGGCGCAAAGCATGCCTGGGTTC AGGGTGGGTATGGTGCGGGAGCAGGGAGGTGAGAGGCTCAGC TGCCCTCCAGAACTCCTCCCTGGGGACAACCCCTCCCAGCCA ATAGCACAGCCTAGGTCCCCCTATATAAGGCCACGGCTGCTG GCCCTTCCTTTGGGTCAGTGTCACCTCCAGGATACAGACA	
Human beta-actin (HuBa)	GCCCAGCACCCCAAGGCGGCCAACGCCAAAACTCTCCCTCCT CCTCTTCCTCAATCTCGCTCTCGCTCTTTTTTTTTTTCGCAA AAGGAGGGGAGAGGGGGTAAAAAAATGCTGCACTGTGCGGCG AAGCCGGTGAGTGAGCGGCGCGGGGCCAATCAGCGTGCGCCG TTCCGAAAGTTGCCTTTTATGGCTCGAGCGGCCGCGGCGGCG CCCTATAAAACCCAGCGGCGCGACGCGCCACCACCGCCGAGT C	37
Chicken beta-actin (CBA)	GGTCGAGGTGAGCCCCACGTTCTGCTTCACTCTCCCCATCTC CCCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTA GGTCGAGGTGAGCCCCACGTTCTGCTTCACTCTCCCCATCTC CCCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTA ATTATTTTGTGCAGCGATGGGGGCGGGGGGGGGGGGGGCGCG CGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGA GGCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCC GAAAGTTTCCTTTTATGGCGAGGCGGCGGCGGCGGCGGCCCT ATAAAAAGCGAAGCGCGCGGCGGGCGGGA	38
Cytomegalovirus (CMV)	TGGTGATGCGGTTTTGGCAGTACACCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACG TGGTGATGCGGTTTTGGCAGTACACCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACG TCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTC CAAAATGTCGTAATAACCCCGCCCCGTTGACGCAAATGGGCG GTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCGTT TAGTGAACCG	39
Cytomegalovirus (CMV) (second version)	TAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAG CCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGG CCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTC AATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTT CCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCA CTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCC TATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGC CCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACAT CTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTG GCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGG ATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTT TTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAA CTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTG GGAGGTCTATATAAGCAGAGCTGGTTTAGTGAACCGT	40
Cytomegalovirus (CMV) (third version)	CGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCC CAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCC CATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGT GGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGG TAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATG GGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGC TATTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCG TGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCC	41

TABLE 3-continued

PROMOTER	SEQUENCE	SEQ ID NO:
	CATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACG GGACTTTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCA AATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAG AGCT	
CAG promoter (first version)	ACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCC CCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAAC GCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTT ACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATAT GCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCC CGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCC TACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCAT GGTCGAGGTGAGCCCCACGTTCTGCTTCACTCTCCCCATCTC CCCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTA ATTATTTTGTGCAGCGATGGGGGCGGGGGGGGGGGGGCGCG CGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGA GGCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCC GAAAGTTTCCTTTTATGGCGAGGCGGCGGCGGCGGCGGCCCT ATAAAAAGCGAAGCGCGCGGCGGGCGG	42
CAG promoter (second version)	CGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCC CAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCC CATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGT GGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGG TAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATG GGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGC TATTACCATGTCGAGGTGAGCCCCACGTTCTGCTTCACTCTC CCCATCTCCCCCCCCTCCCCACCCCCAATTTTGTATTTATTT ATTTTTTAATTATTTTGTGCAGCGATGGGGGCGGGGGGGGGG GGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGG CGGGGCGAGGCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGG CGCGCTCCGAAAGTTTCCTTTTATGGCGAGGCGGCGGCGGCG GCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCG	43
Human EF1-alpha (EF1-α)	CAACCTTTGGAGCTAAGCCAGCAATGGTAGAGGGAAGATTCT GCACGTCCCTTCCAGGCGGCCTCCCCGTCACCACCCCCCCCA ACCCGCCCCGACCGGAGCTGAGAGTAATTCATACAAAAGGAC TCGCCCCTGCCTTGGGGAATCCCAGGGACCGTCGTTAAACTC CCACTAACGTAGAACCCAGAGATCGCTGCGTTCCCGCCCCCT CACCCGCCCGCTCTCGTCATCACTGAGGTGGAGAATAGCATG CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGC CCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAA CGGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTG ATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAG AACCGTATATAAGTGCAGTAGTCGCCGTGAACGTT	44
Human CamKIIa (CaMKIIa)	ACTTGTGGACAAAGTTTGCTCTATTCCACCTCCTCCAGGCCC TCCTTGGGTCCATCACCCCAGGGGTGCTGGGTCCATCCCACC CCCAGGCCCACACAGGCTTGCAGTATTGTGTGCGGTATGGTC AGGGCGTCCGAGAGCAGGTTTCGCAGTGGAAGGCAGGCAGGT GTTGGGGAGGCAGTTACCGGGGCAACGGGAACAGGGCGTTTT GGAGGTGGTTGCCATGGGGACCTGGATGCTGACGAAGGCTCG CGAGGCTGTGAGCAGCCACAGTGCCCTGC	48

[0161] In a certain embodiment, the vector genome comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 31. In a certain embodiment, the vector genome comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 32. In a certain embodiment, the vector genome comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 33.

[0162] Further illustrative examples of promoters are the SV40 late promoter from simian virus 40, the Baculovirus polyhedron enhancer/promoter element, Herpes Simplex Virus thymidine kinase (HSV tk), the immediate early promoter from cytomegalovirus (CMV) and various retroviral promoters including LTR elements. A large variety of other promoters are known and generally available in the art, and the sequences of many such promoters are available in sequence databases such as the GenBank database.

[0163] In some cases, vectors of the present disclosure further comprise one or more regulatory elements selected from the group consisting of an enhancer, an intron, a poly-A signal, a 2A peptide encoding sequence, a WPRE (Woodchuck hepatitis virus posttranscriptional regulatory element), and a HPRE (Hepatitis B posttranscriptional regulatory element).

[0164] In some embodiments, the vector comprises a CMV enhancer.

[0165] In certain embodiments, the vectors comprise one or more enhancers. In particular embodiments, the enhancer is a CMV enhancer sequence, a GAPDH enhancer sequence, a (3-actin enhancer sequence, or an EF1-α enhancer sequence. Sequences of the foregoing are known in the art. For example, the sequence of the CMV immediate early (IE) enhancer is SEQ ID NO: 50.

[0166] In certain embodiments, the vectors comprise one or more introns. In particular embodiments, the intron is a rabbit globin intron sequence, a chicken β-actin intron sequence, a synthetic intron sequence, an SV40 intron, or an EF1-α intron sequence.

[0167] In certain embodiments, the vectors comprise a polyA sequence. In particular embodiments, the polyA sequence is a rabbit globin polyA sequence, a human growth hormone polyA sequence, a bovine growth hormone polyA sequence, a PGK polyA sequence, an SV40 polyA sequence, or a TK polyA sequence. In some embodiments, the poly-A signal may be a bovine growth hormone polyadenylation signal (bGHpA).

[0168] In certain embodiments, the vectors comprise one or more transcript stabilizing element. In particular embodiments, the transcript stabilizing element is a WPRE sequence, a HPRE sequence, a scaffold-attachment region, a 3' UTR, or a 5' UTR. In particular embodiments, the vectors comprise both a 5' UTR and a 3' UTR.

[0169] In some embodiments, the vector comprises a 5' untranslated region (UTR) selected from Table 4. In some embodiments, the vector genome comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS 51-61.

TABLE 4

5' UNTRANSLATED REGION	SEQUENCE	SEQ ID NO:
Human beta-actin exon/intron	CGCGTCCGCCCGCGAGCACAGAGCCTCGCCTTTGCCGATC CGCCGCCCGTCCACACCCGCCGCCAGGTAAGCCCGGCCAG CCGACCGGGGCATGCGGCCGCGGCCCTTCGCCCGTGCAGA GCCGCCGTCTGGGCCGCAGCGGGGGGCGCATGGGGCGGAA CCGGACCGCCGTGGGGGGCGCGGGAGAAGCCCCTGGGCCT CCGGAGATGGGGGACACCCCACGCCAGTTCGCAGGCGCGA GGCCGCGCTCGGGCGGGCGCGCTCCGGGGGTGCCGCTCTC GGGGCGGGGGCAACCGGCGGGGTCTTTGTCTGAGCCGGGC TCTTGCCAATGGGGATCGCACGGTGGGCGCGGCGTAGCCC CCGTCAGGCCCGGTGGGGGCTGGGGCGCCATGCGCGTGCG CGCTGGTCCTTTGGGCGCTAACTGCGTGCGCGCTGGGAAT TGGCGCTAATTGCGCGTGCGCGCTGGGACTCAATGGCGCT AATCGCGCGTGCGTTCTGGGGCCCGGGCGCTTGCGCCACT TCCTGCCCGAGCCGCTGGCGCCCGAGGGTGTGGCCGCTGC GTGCGCGCGCGCGACCCGGTCGCTGTTTGAACCGGGCGGA GGCGGGGCTGGCGCCCGGTTGGGAGGGGGTTGGGGCCTGG CTTCCTGCCGCGCGCCGCGGGGACGCCTCCGACCAGTGTT TGCCTTTTATGGTAATAACGCGGCCGGCCCGGCTTCCTTT GTCCCCAATCTGGGCGCGCGCCGGCGCCCCCTGGCGGCCT AAGGACTCGGCGCGCCGGAAGTGGCCAGGGCGGCAGCGGC TGCTCTTGGCGGCCCCGAGGTGACTATAGCCTTCTTTTGT GTCTTGATAGTTCGCCAGCCTCTGCTAACCATGTTCATGC CTTCTTCTTTTTCCTACAGCTCCTGGGCAACGTGCTGGTT ATTGTGCTGTCTCATCATTTTGGCAAAGAATTC	51
Chicken beta-actin exon/intron + rabbit globin intron	GTCGCTGCGCGCTGCCTTCGCCCCGTGCCCCGCTCCGCCG CCGCCTCGCGCCGCCCGCCCCGGCTCTGACTGACCGCGTT ACTCCCACAGGTGAGCGGGCGGGACGGCCCTTCTCCTCCG GGCTGTAATTAGCGCTTGGTTTAATGACGGCTTGTTTCTT TTCTGTGGCTGCGTGAAAGCCTTGAGGGGCTCCGGGAGGG CCCTTTGTGCGGGGGGAGCGGCTCGGGGGGTGCGTGCGTG TGTGTGTGCGTGGGGAGCGCCGCGTGCGGCTCCGCGCTGC CCGGCGGCTGTGAGCGCTGCGGGCGCGGCGCGGGGCTTTG TGCGCTCCGCAGTGTGCGCGAGGGGAGCGCGGCCGGGGGC GGTGCCCCGCGGTGCGGGGGGGGCTGCGAGGGGAACAAAG GCTGCGTGCGGGGTGTGTGCGTGGGGGGGTGAGCAGGGGG TGTGGGCGCGTCGGTCGGGCTGCAACCCCCCCTGCACCCC CCTCCCCGAGTTGCTGAGCACGGCCCGGCTTCGGGTGCGG GGCTCCGTACGGGGCGTGGCGCGGGGCTCGCCGTGCCGGG CGGGGGGTGGCGGCAGGTGGGGGTGCCGGGCGGGGCGGGG CCGCCTCGGGCCGGGGAGGGCTCGGGGGAGGGGCGCGGCG GCCCCCGGAGCGCCGGCGGCTGTCGAGGCGCGGCGAGCCG CAGCCATTGCCTTTTATGGTAATCGTGCGAGAGGGCGCAG GGACTTCCTTTGTCCCAAATCTGTGCGGAGCCGAAATCTG GGAGGCGCCGCCGCACCCCCTCTAGCGGGCGCGGGGCGAA GCGGTGCGGCGCCGGCAGGAAGGAAATGGGCGGGGAGGGC CTTCGTGCGTCGCCGCGCCGCCGTCCCCTTCTCCCTCTCC AGCCTCGGGGCTGTCCGCGGGGGGACGGCTGCCTTCGGGG GGGACGGGGCAGGGCGGGGTTCGGCTTCTGGCGTGTGACC GGCGGCTCTAGAGCCTCTGCTAACCATGTTCATGCCTTCT TCTTTTTCCTACAGCTCCTGGGCAACGTGCTGGTTATTGT GCTGTCTCATCATTTTGGCAAAGAATTC	52

TABLE 4-continued

5' UNTRANSLATED REGION	SEQUENCE	SEQ ID NO:
SV40 intron (Chimeric intron sequence) Shown in FIG. 14	GGTAAGTTTAGTCTTTTTGTCTTTTATTTCAGGTCCCGGA TCCGGTGGTGGTGCAAATCAAAGAACTGCTCCTCAGTGGA TGTTGCCTTTACTTCTAGGCCTGTACGGAAGTGTTACTTC TGCTCTAAAAGCTGCGGAATTGTACCCGC	53
5'UTR-Syn1 Hs	AGTCTGCGGTGGGCAGCGGAGGAGTCGTGTCGTGCCTGAG AGCGCAGCTGTGCTCCTGGGCACCGCGCAGTCCGCCCCCG CGGCTCCTGGCCAGACCACCCCTAGGACCCCCTGCCCCAA GTCGCA	54
CMV IE exon	TCAGATCGCCTGGAGAGGCCATCCACGCTGTTTTGACCTC CATAGTGGACACCGGGACCGATCCAGCCTCCGCGGCCGGG AACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGA C	55
TPL-ePKP2 (adenovirus derived enhancer element)	CTCACTCTCTTCCGCATCGCTGTCTGCGAGGGCCAGCTGT TGGGCTCGCGGTTGAGGACAAACTCTTCGCGGTCTTTCCA GTACTCTTGGATCGGAAACCCGTCGGCCTCCGAACGGTAC TCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGA TCGGAAAACCTCTCGAGAAAGGCGTCTAACCAGTCACAGT CGCAAGGTAGGCTGAGCACCGTGGCGGGCGGCAGCGGGTG GCGGTCGGGGTTGTTTCTGGCGGAGGTGCTGCTGATGATG TAATTAAAGTAGGCGGTCTTGAGACGGCGGATGGTCGAGG TGAGGTGTGGCAGGCTTGAGATCCAGCTGTTGGGGTGAGT ACTCCCTCTCAAAAGCGGGCATTACTTCTGCGCTAAGATT GTCAGTTTCCAAAAACGAGGAGGATTTGATATTCACCTGG CCCGATCTGGCCATACACTTGAGTGACAATGACATCCACT TTGCCTTTCTCTCCACAGGTGTCCACTCCCAG	56
Human EF1-α intron/exon	CTTTTTCGCAACGGGTTTGCCGCCAGAACACAGGTAAGTG CCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTACGGGTTA TGGCCCTTGCGTGCCTTGAATTACTTCCACCTGGCTCCAG TACGTGATTCTTGATCCCGAGCTGGAGCCAGGGGCGGGCC TTGCGCTTTAGGAGCCCCTTCGCCTCGTGCTTGAGTTGAG GCCTGGCCTGGGCGCTGGGGCCGCCGCGTGCGAATCTGGT GGCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCT AGCCATTTAAAATTTTTGATGACGTGCTGCGACGCTTTTT TTCTGGCAAGATAGTCTTGTAAATGCGGGCCAGGATCTGC ACACTGGTATTTCGGTTTTTGGGCCGCGGCCGGCGACGG GGCCCGTGCGTCCCAGCGCACATGTTCGGCGAGGCGGGGC CTGCGAGCGCGGCCACCGAGAATCGGACGGGGGTAGTCTC AAGCTGGCCGGCCTGCTCTGGTGCCTGGCCTCGCGCCGCC GTGTATCGCCCCGCCCTGGGCGGCAAGGCTGGCCCGGTCG GCACCAGTTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCC CTGCTCCAGGGGGCTCAAAATGGAGGACGCGGCGCTCGGG AGAGCGGGCGGGTGAGTCACCCACACAAAGGAAAAGGGCC TTTCCGTCCTCAGCCGTCGCTTCATGTGACTCCACGGAGT ACCGGGCGCCGTCCAGGCACCTCGATTAGTTCTGGAGCTT TTGGAGTACGTCGTCTTTAGGTTGGGGGGAGGGGTTTTAT GCGATGGAGTTTCCCCACACTGAGTGGGTGGAGACTGAAG TTAGGCCAGCTTGGCACTTGATGTAATTCTCCTTGGAATT TGGCCTTTTTGAGTTTGGATCTTGGTTCATTCTCAAGCCT CAGACAGTGGTTCAAAGTTTTTTTCTTCCATTTCAG	57
HumanEF1-α, intron A	GTAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTA CGGGTTATGGCCCTTGCGTGCCTTGAATTACTTCCACCTG GCTGCAGTACGTGATTCTTGATCCCGAGCTTCGGGTTGGA AGTGGGTGGGAGAGTTCGAGGCCTTGCGCTTAAGGAGCCC CTTCGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGCGCTG GGGCCGCCGCGTGCGAATCTGGTGGCACCTTCGCGCCTGT CTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAAATTTTT GATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCT TGTAAATGCGGGCCAAGATCTGCACACTGGTATTTCGGTT TTTGGGGCCGCGGGCGGCGACGGGGCCCGTGCGTCCCAGC GCACATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCACC GAGAATCGGACGGGGGTAGTCTCAAGCTGGCCGGCCTGCT CTGGTGCCTGGCCTCGCGCCGCCGTGTATCGCCCCGCCCT GGGCGGCAAGGCTGGCCCGGTCGGCACCAGTTGCGTGAGC GGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAGCTCA AAATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGT CACCCACACAAAGGAAAAGGGCCTTTCCGTCCTCAGCCGT CGCTTCATGTGACTCCACGGAGTACCGGGCGCCGTCCAGG	58

TABLE 4-continued

5' UNTRANSLATED REGION	SEQUENCE	SEQ ID NO:
	CACCTCGATTAGTTCTCGAGCTTTTGGAGTACGTCGTCTT TAGGTTGGGGGGAGGGGTTTTATGCGATGGAGTTTCCCCA CACTGAGTGGGTGGAGACTGAAGTTAGGCCAGCTTGGCAC TTGATGTAATTCTCCTTGGAATTTGCCCTTTTTGAGTTTG GATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTCAAAG TTTTTTTCTTCCATTTCAG	
5'UTR human CamKIIa	TCAGAAGCCCCGGGCTCGTCAGTCAAACCGGTTCTCTGTT TGCACTCGGCAGCACGGGCAGGCAAGTGGTCCCTAGGTTC GGG	59
B-globin intron	GTGAGTCTATGGGACCCTTGATGTTTTCTTTCCCCTTCTT TTCTATGGTTAAGTTCATGTCATAGGAAGGGGAGAAGTAA CAGGGTACACATATTGACCAAATCAGGGTAATTTTGCATT TGTAATTTTAAAAAATGCTTTCTTCTTTTAATATACTTTT TTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCT TTCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCA CCATTCTAAAGAATAACAGTGATAATTTCTGGGTTAAGGC AATAGCAATATTTCTGCATATAAATATTTCTGCATATAAA TTGTAACTGATGTAAGAGGTTTCATATTGCTAATAGCAGC TACAATCCAGCTACCATTCTGCTTTTATTTTATGGTTGGG ATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTG CTAATCATGTTCATACCTCTTATCTTCCTCCCACAG	60
SV40 intron (long form; underlined 5' and 3' extensions)	TCTAGAGGATCCGGTACTCGAGGAACTGAAAAACCAGAAA GTTAACTGGTAAGTTTAGTCTTTTTGTCTTTTATTTCAGG TCCCGGATCCGGTGGTGGTGCAAATCAAAGAACTGCTCCT CAGTGGATGTTGCCTTTACTTCTAGGCCTGTACGGAAGTG TTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCGC	61

[0170] In some embodiments, the vector comprises a 3' untranslated region selected from Table 5. In some embodiments, the vector genome comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS 62-70.

TABLE 5

3' UNTRANSLATED REGION	SEQUENCE	SEQ ID NO:
WPRE(x) (mutated woodchuck hepatitis regulatory element - version 1)	AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTG GTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATA CGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGT ATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGC TGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACG TGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACT GGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGA CTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAACTCAT CGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTG TTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCAT CGTCCTTTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGAT TCTGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTC AATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTC TGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAG TCGGATCTCCCTTTGGGCCGCCTCCCCGC	62
WPRE(x) (mutated woodchuck hepatitis regulatory element - version 2)	TCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGT ATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACG CTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTAT GGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTG TCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTG GCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGG TTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACT TTCGCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCG CCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTT GGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCG TCCTTTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTC	63

TABLE 5-continued

3' UNTRANSLATED REGION	SEQUENCE	SEQ ID NO:
	TGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAA TCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTG CGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTC GGATCTCCCTTTGGGCCGCCTCCCCGCA	
WPRE(x) (mutated woodchuck hepatitis regulatory element - version 3)	TTCCTGTTAATCAACCTCTGGATTACAAAATTTGTGAAAG ATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTA TGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTG CTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATC CTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTC AGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAA CCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCT TTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCACGGCG GAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGG CTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGG GAAGCTGACGTCCTTTCCGCGGCTGCTCGCCTGTGTTGCC ACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCCTT CGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCT GCCGGCTCTGCGGCCTCTTCCGCCTCTTCGCCTTCGCCCT CAGACGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCCCA TGTATCTTTTTCACCTGTGCCTTGTTTTTGCCTGTGTTCC GCGTCCTACTTTTCAAGCCTCCAAGCTGTGCCTTGGGCGG CTTTGGGGCATGGACATAGATCCCTATAAAGAATTTGGTT CATCTTATCAGTTGTTGAATTTTCTTCCTTTGGAC	64
CAAX	TGTGTGATAATG	65
EES	CTGTTCTCATCACATCATATCAAGGTTATATACCATCAAT ATTGCCACAGATGTTACTTAGCCTTTTAATATTTCTCTAA TTTAGTGTATATGCAATGATAGTTCTCTGATTTCTGAGAT TGAGTTTCTCATGTGTAATGATTATTTAGAGTTTCTCTTT CATCTGTTCAAATTTTTGTCTAGTTTTATTTTTTACTGAT TTGTAAGACTTCTTTTTATAATCTGCATATTACAATTCTC TTTACTGGGGTGTTGCAAATATTTTCTGTCATTCTATGGC CTGACTTTTCTTAATGGTTTTTTAATTTTAAAAATAAGTC TTAATATTCATGCAATCTAATTAACAATCTTTTCTTTGTG GTTAGGACTTTGAGTCATAAGAAATTTTTCTCTACACTGA AGTCATGATGGCATGCTTCTATATTATTTTCTAAAAGATT TAAAGTTTTGCCTTCTCCATTTAGACTTATAATTCACTGG AATTTTTTTGTGTGTATGGTATGACATATGGGTTCCCTTT TATTTTTTACATATAAATATATTTCCCTGTTTTTCTAAAA AAGAAAAAGATCATCATTTTCCCATTGTAAAATGCCATAT TTTTTTCATAGGTCACTTACATATATCAATGGGTCTGTTT CTGAGCTCTACTCTATTTTATCAGCCTCACTGTCTATCCC CACACATCTCATGCTTTGCTCTAAATCTTGATATTTAGTG GAACATTCTTTCCCATTTTGTTCTACAAGAATATTTTTGT TATTGTCTTTGGGCTTTCTATATACATTTTGAAATGAGGT TGACAAGTTA	66
HPRE	ATAACAGGCCTATTGATTGGAAAGTTTGTCAACGAATTGT GGGTCTTTTGGGGTTTGCTGCCCCTTTTACGCAATGTGGA TATCCTGCTTTAATGCCTTTATATGCATGTATACAAGCAA AACAGGCTTTTACTTTCTCGCCAACTTACAAGGCCTTTCT CAGTAAACAGTATATGACCCTTTACCCCGTTGCTCGGCAA CGGCCTGGTCTGTGCCAAGTGTTTGCTGACGCAACCCCCA CTGGTTGGGGCTTGGCCATAGGCCATCAGCGCATGCGTGG AACCTTTGTGTCTCCTCTGCCGATCCATACTGCGGAACTC CTAGCCGCTTGTTTTGCTCGCAGCAGGTCTGGAGCAAACC TCATCGGGACCGACAATTCTGTCGTACTCTCCCGCAAGTA TACATCGTTTCCATGGCTGCTAGGCTGTGCTGCCAACTGG ATCCTGCGCGGGACGTCCTTTGTTTACGTCCCGTCGGCGC TGAATCCCGCGGACGACCCCTCCCGGGGCCGCTTGGGGCT CTACCGCCCGCTTCTCCGTCTGCCGTACCGTCCGACCACG GGGCGCACCTCTCTTTACGCGGACTCCCCGTCTGTGCCTT CTCATCTGCCGGACCGTGTGCACTTCGCTTCACCTCTGCA CGTCGCATGGAGGCCACCGTGAACGCCCACCGGAACCTGC CCAAGGTCTTGCATAAGAGGACTCTTGGACTTTCAGCAAT GTCATC	67
R2V17 (HepB derived enhancer element)	TTCCTGTAAACAGGCCTATTGATTGGAAAGTTTGTCAACG AATTGTGGGTCTTTTGGGGTTTGCTGCCCCTTTTACGCAA TGTGGATATCCTGCTTTAATGCCTTTATATGCATGTATAC AAGCAAAACAGGCTTTTACTTTCTCGCCAACTTACAAGGC	68

TABLE 5-continued

3' UNTRANSLATED REGION	SEQUENCE	SEQ ID NO:
	CTTTCTCAGTAAACAGTATATGACCCTTTACCCCGTTGCT CGGCAACGGCCTGGTCTGTGCCAAGTGTTTGCTGACGCAA CCCCCACTGGTTGGGGCTTGGCCATAGGCCATCAGCGCAT GCGTGGAACCTTTGTGTCTCCTCTGCCGATCCATACTGCG GAACTCCTAGCCGCTTGTTTTGCTCGCAGCTGGACTGGAG CAAACCTCATCGGGACCGACAATTCTGTCGTACTCTCCCG CAAGCACTCACCGTTTCCGCGGCTGCTCGCCTGTGTTGCC ACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCCTT CGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCT GCCGGCTCTGCGGCCTCTTCCGCCTCTTCGCCTTCGCCCT CAGACGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCCCA TGTATCTTTTTCACCTGTGCCTTGTTTTTGCCTGTGTTCC GCGTCCTACTTTTCAAGCCTCCAAGCTGTGCCTTGGGCGG CTTTGGGGCATGGACATAGATCCCTATAAAGAATTTGGTT CATCTTATCAGTTGTTGAATTTTCTTCCTTTGGAC	
3'UTR(globin)	GCTGGAGCCTCGGTAGCCGTTCCTCCTGCCCGCTGGGCCT CCCAACGGGCCCTCCTCCCCTCCTTGCACCGGCCCTTCCT GGTCTTTGAATAAA	69
WPRE(r)	ATTCGAGCATCTTACCGCCATTTATTCCCATATTTGTTCT GTTTTTCTTGATTTGGGTATACATTTAAATGTTAATAAAA CAAAATGGTGGGGCAATCATTTACATTTTTAGGGATATGT AATTACTAGTTCAGGTGTATTGCCACAAGACAAACATGTT AAGAAACTTTCCCGTTATTTACGCTCTGTTCCTGTTAATC AACCTCTGGATTACAAAATTTGTGAAAGATTGACTGATAT TCTTAACTATGTTGCTCCTTTTACGCTGTGTGGATATGCT GCTTTAATGCCTCTGTATCATGCTATTGCTTCCCGTACGG CTTTCGTTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTC TCTTTATGAGGAGTTGTGGCCCGTTGTCCGTCAACGTGGC GTGGTGTGCTCTGTGTTTGCTGACGCAACCCCCACTGGCT GGGGCATTGCCACCACCTGTCAACTCCTTTCTGGGACTTT CGCTTTCCCCCTCCCGATCGCCACGGCAGAACTCATCGCC GCCTGCCTTGCCCGCTGCTGGACAGGGGCTAGGTTGCTGG GCACTGATAATTCCGTGGTGTTGTCGGGGAAGGGCC	70

[0171] In some embodiments, the vector comprises a polyadenylation (polyA) signal selected from Table 6. In some embodiments, the polyA signal comprises a polynucleotide sequence at least 75%, 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any one of SEQ ID NOS 71-75.

TABLE 6

POLY-ADENYLATION SITE	SEQUENCE	SEQ ID NO:
Rabbit globin (pAGlobin-0c)	TGGCTAATAAAGGAAATTTATTTTCATTGCAATAGTGTG TTGGAATTTTTTGTGTCTCTCACTCGGAAGAACATATGG GAGGGCAAATCATTTAAAACATCAGAATGAGTATTTGGT TTAGAGTTTGGCAACATATGCCCATATGCTGGCTGCCAT GAACAAAGGTTGGCTATAAAGAGGTCATCAGTATATGAA ACAGCCCCCTGCTGTCCATTCCTTATTCCATAGAAAAGC CTTGACTTGAGGTTAGATTTTTTTTATATTTTGTTTTGT GTTATTTTTTTCTTTAACATCCCTAAAATTTTCCTTACA TGTTTTACTAGCCAGATTTTTCCTCCTCTCCTGACTACT CCCAGTCATAGCTGTCCCTCTTCTCTTATGGAGATC	71
Bovine growth hormone (pAGH-Bt - version 1)	TTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTC CTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTA ATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTG TCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAA GGGGGAGGATTGGGAATACAATAGCAGGCATGCTGGGGA TGCGGTGGGCTCTATGGGTACCCAGGTGCTGAAGAATTG ACCCGGTTCCTCCTGGG	72

TABLE 6-continued

POLY-ADENYLATION SITE	SEQUENCE	SEQ ID NO:
Bovine growth hormone (pAGH-Bt - version 2)	TTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTC CTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTA ATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTG TCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAA GGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGA TGCGGTGGGCTCTATGGGTACCCAGGTGCTGAAGAATTG ACCCGGTTCCTCCTGGG	73
Bovine growth hormone (pAGH-Bt - version 3)	CTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCT CCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCA CTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATT GTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGG GGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCA GGCATGCTGGGGATGCGGTGGGCTCTATGG	74
Human growth hormone (pAGH-Hs)	CTGCCCGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCT CTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGC CTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGAC TAGGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTG GTATGGAGCAAGGGGCCCAAGTTGGGAAGAAACCTGTAG GGCCTGC	75

[0172] Illustrative vector genomes are depicted in FIGS. **1-4** and **11-14**; and provided as SEQ ID NOs: 12-15 and 89-92. The expression cassette of each sequence is SEQ ID NOs: 8-11 or 93-96. In some embodiments, the vector genome comprises, consists essentially of, or consists of a polynucleotide sequence that shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any one of SEQ ID NOs: 12-15 and 89-92, optionally with or without the ITR sequences. In some embodiments, the vector genome comprises, consists essentially of, or consists of a polynucleotide sequence that shares at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any one of SEQ ID NOs: 8-11 and 93-96.

[0173] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; an MHCK7 promoter; a PKPa transgene; an WPRE(x) element; an pAGH-HS sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 31; any one of SEQ ID NOs: 3, 6, and 87; SEQ ID NO: 63; and SEQ ID NO: 75; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2a transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0174] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; a hTnnT2 promoter; a PKPa transgene; an WPRE(x) element; an pAGH-HS sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 32 or 33; any one of SEQ ID NOs: 3, 6, and 87; SEQ ID NO: 63; and SEQ ID NO: 75; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2a transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0175] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; an MHCK7 promoter; a PKPb transgene; an WPRE(x) element; an pAGH-HS sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 31; any one of SEQ ID NOs: 4, 7, and 88; SEQ ID NO: 63; and SEQ ID NO: 75; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2b transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0176] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; a hTnnT2 promoter; a PKPb transgene; an WPRE(x) element; an pAGH-HS sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 32 or 33; any one of SEQ ID NOs: 4, 7, and 88; SEQ ID NO: 63; and SEQ ID NO: 75; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2b transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0177] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; an MHCK7 promoter; a PKPa transgene; optionally a WPRE element; a polyadenylation sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 31; any one of SEQ ID NOs: 3, 6, and 87; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The

PKP2a transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0178] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; a hTnnT2 promoter; a PKPa transgene; optionally a WPRE element; a polyadenylation sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 32 or 33; any one of SEQ ID NOs: 3, 6, and 87; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2a transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0179] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; an MHCK7 promoter; a PKPb transgene; optionally a WPRE element; a polyadenylation sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 31; any one of SEQ ID NOs: 4, 7, and 88; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2b transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0180] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; a hTnnT2 promoter; a PKPb transgene; optionally a WPRE element; a polyadenylation sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 32 or 33; any one of SEQ ID NOs: 4, 7, and 88; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2b transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0181] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; an MHCK7 promoter; SV40 intron; a PKPa transgene; optionally a WPRE element; a polyadenylation sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 31; SEQ ID NO: 53 or 61; any one of SEQ ID NOs: 3, 6, and 87; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2a transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0182] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; a hTnnT2 promoter; SV40 intron; a PKPa transgene; optionally a WPRE element; a polyadenylation sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 32 or 33; SEQ ID NO: 53 or 61; any one of SEQ ID NOs: 3, 6, and 87; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2a transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0183] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; an MHCK7 promoter; SV40 intron; a PKPb transgene; optionally a WPRE element; a polyadenylation sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 31; SEQ ID NO: 53 or 61; any one of SEQ ID NOs: 4, 7, and 88; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2b transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0184] In a certain embodiment, the vector genome comprises, in 5' to 3' order, a 5' ITR; a hTnnT2 promoter; SV40 intron; a PKPb transgene; optionally a WPRE element; a polyadenylation sequence; and a 3' ITR. The vector genome may comprise, in 5' to 3' order, the polynucleotide sequences SEQ ID NO: 32 or 33; SEQ ID NO: 53 or 61; any one of SEQ ID NOs: 4, 7, and 88; or polynucleotide sequences sharing 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to each of the foregoing. In certain embodiments, this vector genome is packaged in an AAV9 or AAVrh74 vector. The PKP2b transgene of this embodiment is a full length transgene, i.e. a transgene encoding a PKP of at least 800 or at least 830 amino acids.

[0185] In each case the optionally WPRE element may be present or absent.

Adeno-Associated Virus Vector

[0186] AAV vectors useful in the practice of the present invention can be packaged into AAV virions (viral particles) using various systems including adenovirus-based and helper-free systems. Standard methods in AAV biology include those described in Kwon and Schaffer. *Pharm Res.* (2008) 25(3):489-99; Wu et al. *Mol. Ther.* (2006) 14(3):316-27. Burger et al. *Mol. Ther.* (2004) 10(2):302-17; Grimm et al. *Curr Gene Ther.* (2003) 3(4):281-304; Deyle D R, Russell D W. *Curr Opin Mol Ther.* (2009) 11(4):442-447; McCarty et al. *Gene Ther.* (2001) 8(16):1248-54; and Duan et al. *Mol Ther.* (2001) 4(4):383-91. Helper-free systems included those described in U.S. Pat. Nos. 6,004,797; 7,588,772; and 7,094,604;

[0187] AAV DNA in the rAAV genomes may be from any AAV variant or serotype for which a recombinant virus can be derived including, but not limited to, AAV variants or serotypes AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-11, AAV-12, AAV-13 and AAVrh10. Production of pseudotyped rAAV is disclosed in, for example, WO 01/83692. Other types of rAAV variants, for example rAAV with capsid mutations, are also contemplated. See, for example, Marsic et al., Molecular Therapy, 22(11): 1900-1909 (2014). The nucleotide sequences of the genomes of various AAV serotypes are known in the art.

[0188] In some cases, the rAAV comprises a self-complementary genome. As defined herein, an rAAV comprising a "self-complementary" or "double stranded" genome refers to an rAAV which has been engineered such that the coding region of the rAAV is configured to form an intra-molecular

double-stranded DNA template, as described in McCarty et al. Self-complementary recombinant adeno-associated virus (scAAV) vectors promoter efficient transduction independently of DNA synthesis. Gene Therapy. 8 (16): 1248-54 (2001). The present disclosure contemplates the use, in some cases, of an rAAV comprising a self-complementary genome because upon infection (such transduction), rather than waiting for cell mediated synthesis of the second strand of the rAAV genome, the two complementary halves of scAAV will associate to form one double stranded DNA (dsDNA) unit that is ready for immediate replication and transcription. It will be understood that instead of the full coding capacity found in rAAV (4.7-6 kb), rAAV comprising a self-complementary genome can only hold about half of that amount (≈2.4 kb).

[0189] In other cases, the rAAV vector comprises a single stranded genome. As defined herein, a "single standard" genome refers to a genome that is not self-complementary. In most cases, non-recombinant AAVs have singled stranded DNA genomes. There have been some indications that rAAVs should be scAAVs to achieve efficient transduction of cells. The present disclosure contemplates, however, rAAV vectors that maybe have singled stranded genomes, rather than self-complementary genomes, with the understanding that other genetic modifications of the rAAV vector may be beneficial to obtain optimal gene transcription in target cells. In some cases, the present disclosure relates to single-stranded rAAV vectors capable of achieving efficient gene transfer to anterior segment in the mouse eye. See Wang et al. Single stranded adeno-associated virus achieves efficient gene transfer to anterior segment in the mouse eye. PLoS ONE 12(8): e0182473 (2017).

[0190] In some cases, the rAAV vector is of the serotype AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAVrh10, or AAVrh74. Production of pseudotyped rAAV is disclosed in, for example, WO 01/83692. Other types of rAAV variants, for example rAAV with capsid mutations, are also contemplated. See, for example, Marsic et al., Molecular Therapy, 22(11): 1900-1909 (2014). In some cases, the rAAV vector is of the serotype AAV9. In some embodiments, said rAAV vector is of serotype AAV9 and comprises a single stranded genome. In some embodiments, said rAAV vector is of serotype AAV9 and comprises a self-complementary genome. In some embodiments, a rAAV vector comprises the inverted terminal repeat (ITR) sequences of AAV2. In some embodiments, the rAAV vector comprises an AAV2 genome, such that the rAAV vector is an AAV-2/9 vector, an AAV-2/6 vector, or an AAV-2/8 vector.

[0191] Full-length sequences and sequences for capsid genes for most known AAVs are provided in U.S. Pat. No. 8,524,446, which is incorporated herein in its entirety.

[0192] AAV vectors may comprise wild-type AAV sequence or they may comprise one or more modifications to a wild-type AAV sequence. In certain embodiments, an AAV vector comprises one or more amino acid modifications, optionally substitutions, deletions, or insertions, within a capsid protein, optionally VP1, VP2 and/or VP3. In particular embodiments, the modification provides for reduced immunogenicity when the AAV vector is provided to a subject.

[0193] Capsid proteins of a rAAV may be modified so that the rAAV is targeted to a particular target tissue of interest such as endothelial cells or more particularly endothelial tip cells. In some embodiments, the rAAV is directly injected into the intracerebroventricular space of the subject.

[0194] In some embodiments, the rAAV virion is an AAV2 rAAV virion. The capsid many be an AAV2 capsid or functional variant thereof. In some embodiments, the AAV2 capsid shares at least 98%, 99%, or 100% identity to a reference AAV2 capsid, e.g., SEQ ID NO: 76.

[0195] In some embodiments, the rAAV virion is an AAV9 rAAV virion. The capsid many be an AAV9 capsid or functional variant thereof. In some embodiments, the AAV9 capsid shares at least 98%, 99%, or 100% identity to a reference AAV9 capsid, e.g., SEQ ID NO: 77.

[0196] In some embodiments, the rAAV virion is an AAV6 rAAV virion. The capsid many be an AAV9 capsid or functional variant thereof. In some embodiments, the AAV6 capsid shares at least 98%, 99%, or 100% identity to a reference AAV6 capsid, e.g., SEQ ID NO: 78.

[0197] In some embodiments, the rAAV virion is an AAVrh.10 rAAV virion. The capsid many be an AAV9 capsid or functional variant thereof. In some embodiments, the AAVrh.10 capsid shares at least 98%, 99%, or 100% identity to a reference AAVrh.10 capsid, e.g., SEQ ID NO: 79.

[0198] In some embodiments, the capsid protein is encoded by a polynucleotide supplied on a plasmid in trans to the transfer plasmid. The polynucleotide sequence of wild-type AAVrh74 cap is provided as SEQ ID NO: 80.

[0199] The disclosure further provides protein sequences for AAVrh74 VP1, VP2, and VP3, including SEQ ID NOs: 81-83, and homologs or functional variants thereof.

[0200] In certain cases, the AAVrh74 capsid comprises the amino acid sequence set forth in SEQ ID NO: 81. In some embodiments, the rAAV vector comprises a polypeptide that comprises, or consists essentially of, or yet further consists of a sequence, e.g., at least 65%, at least 70%, at least 75%, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, or 89%, more typically 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to amino acid sequence of AAVrh74 VP1 which is set forth in SEQ ID NO: 81. In some embodiments, the rAAV vector comprises a polypeptide that comprises, or consists essentially of, or yet further consists of a sequence, e.g., at least 65%, at least 70%, at least 75%, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, or 89%, more typically 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to amino acid sequence of AAVrh74 VP2 which is set forth in SEQ ID NO: 82. In some embodiments, the rAAV vector comprises a polypeptide that comprises, or consists essentially of, or yet further consists of a sequence, e.g., at least 65%, at least 70%, at least 75%, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, or 89%, more typically 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to amino acid sequence of AAVrh74 VP3 which is set forth in SEQ ID NO: 83.

[0201] In some embodiments, the rAAV virion is an AAV-PHP.B rAAV virion or a neutrotrophic variant thereof, such as, without limitation, those disclosed in Int'l Pat. Pub. Nos. WO 2015/038958 A1 and WO 2017/100671 A1. For example, the AAV capsid may comprise at least 4 contiguous amino acids from the sequence TLAVPFK (SEQ ID NO:85) or KFPVALT (SEQ ID NO:86), e.g., inserted between a sequence encoding for amino acids 588 and 589 of AAV9.

[0202] The capsid many be an AAV-PHP.B capsid or functional variant thereof. In some embodiments, the AAV-PHP.B capsid shares at least 98%, 99%, or 100% identity to a reference AAV-PHP.B capsid, e.g., SEQ ID NO: 84.

[0203] Further AAV capsids used in the rAAV virions of the disclosure include those disclosed in Pat. Pub. Nos. WO 2009/012176 A2 and WO 2015/168666 A2.

[0204] Without being bound by theory, the present inventors have determined that an AAV9 vector, AAVrh.74, or an AAVrh.10 vector will confer desirable cardiac tropism on the vector. Without being bound by theory, the present inventors have further determined that an AAV9 vector, AAVrh.74, or an AAVrh.10 vector may provide desired specificity to cardiac cells.

[0205] In an aspect, the disclosure provides pharmaceutical compositions comprising the rAAV virion of the disclosure and one or more pharmaceutically acceptable carriers, diluents, or excipients.

[0206] For purposes of administration, optionally by injection, various solutions can be employed, such as sterile aqueous solutions. Such aqueous solutions can be buffered, if desired, and the liquid diluent first rendered isotonic with saline or glucose. Solutions of rAAV as a free acid (DNA contains acidic phosphate groups) or a pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as Poloxamer 188, e.g., at 0.001% or 0.01%. A dispersion of rAAV can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

[0207] The pharmaceutical forms suitable for injectable use include but are not limited to sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form is sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating actions of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of a dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0208] Sterile injectable solutions may be prepared by incorporating rAAV in the required amount in the appropriate solvent with various other ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the certain methods of preparation are vacuum drying and the freeze-drying technique that yield a powder of the active ingredient plus any additional desired ingredient from the previously sterile-filtered solution thereof.

[0209] In another aspect, the disclosure comprises a kit comprising an rAAV virion of the disclosure and instructions for use.

[0210] In an aspect, the disclosure provides a method of increasing PKP2 activity in a cell, comprising contacting the cell with an rAAV of the disclosure. In another aspect, the disclosure provides a method of increasing PKP2 activity in a subject, comprising administering to the subject an rAAV of the disclosure. In some embodiments, the cell and/or subject is deficient in PKP2 messenger RNA or PKP2 protein expression levels and/or activity and/or comprises a loss-of-function mutation in PKP2. The cell may be a cardiac cell, e.g. a cardiomyocyte cell. In particular embodiments, the subject is a mammal, e.g., a human.

[0211] In some embodiments, the method promotes survival of cardiac cell, e.g. a cardiomyocyte cell, in cell culture and/or in vivo. In some embodiments, the method promotes and/or restores function of the heart.

[0212] In another aspect, the disclosure provides a method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of an rAAV virion of the disclosure. In some embodiments, the disease or disorder is a cardiac disease or disorder. Illustrative cardiac disorders include heart failure, arrhythmogenic right ventricular cardiomyopathy (ARVC), Brugada syndrome (BrS) and idiopathic ventricular fibrillation. In certain embodiments, the subject suffers from or is at risk for arrhythmogenic right ventricular cardiomyopathy (ARVC). In particular embodiments, the subject is a mammal, e.g., a human, having a loss-of-function mutation in a PKP2 gene. In particular methods, treatment with the rAAV virion results in expression of the PKP2 protein encoded by the rAAV virion in the subject, e.g., in the subject's heart or cardiac tissue. In certain embodiments, treatment with the rAAV virion results in at least two-fold, at least five-fold, at least ten-fold, or more PKP2 protein levels detectable in the subject's heart.

[0213] The AAV-mediated delivery of PKP2 protein to the heart may increase life span, prevent or attenuate cardiac cell degeneration, heart failure, scarring, reduced ejection fraction, arrythmia, angina, exercise intolerance, angina (chest pain), sudden cardiac death, exertional myalgias and cramps. The AAV-mediated delivery of PKP2 protein to the heart may show improvement from, or prevent normal disease course detected by use of pathological electrocardiogram, cardiac MRI, heart biopsy, decrease in paroxysmal ventricular arrhythmias, decrease in sudden cardiac death, and/or decrease in or lack of further development of fibro-fatty deposits in right ventricular myocardium. The methods of the disclosure may prevent a decrease in, restore, and/or increase right ventricular ejection fraction (RVEF).

[0214] The methods disclosed herein may provide efficient biodistribution in the heart. They may result in sustained in expression in all, or a substantial fraction of, cardiac cells, e.g., cardiomyocytes. Notably, the methods disclosed herein may provide long-lasting expression of PKP2 protein throughout the life of the subject following AAV vector administration. In some embodiments, PKP2

protein expression in response to treatment lasts at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, or 40 years.

[0215] Combination therapies are also contemplated by the invention. Combinations of methods of the invention with standard medical treatments (e.g., corticosteroids or topical pressure reducing medications) are specifically contemplated, as are combinations with novel therapies. In some cases, a subject may be treated with a steroid and/or combination of immune suppressing agents to prevent or to reduce an immune response to administration of a rAAV described herein.

[0216] In some embodiments, the AAV vector is administered at a dose of between about 1×10^{12} and 5×10^{14} vector genomes (vg) or between about 1×10^{12} and 6×10^{14} vg of the AAV vector per kilogram (vg) of total body mass of the subject (vg/kg). In some embodiments, the AAV vector is administered at a dose of between about 1×10^{13} and 5×10^{14} vg/kg. In some embodiments, the AAV vector is administered at a dose of between about 5×10^{13} and 3×10^{14} vg/kg. In some embodiments, the AAV vector is administered at a dose of between about 5×10^{13} and 1×10^{14} vg/kg. In some embodiments, the AAV vector is administered at a dose of less than about 1×10^{12} vg/kg, less than about 3×10^{12} vg/kg, less than about 5×10^{12} vg/kg, less than about 7×10^{12} vg/kg, less than about 1×10^{13} vg/kg, less than about 3×10^{13} vg/kg, less than about 5×10^{13} vg/kg, less than about 7×10^{13} vg/kg, less than about 1×10^{13} vg/kg, less than about 3×10^{14} vg/kg, less than about 5×10^{14} vg/kg, less than about 7×10^{14} vg/kg, less than about 1×10^{15} vg/kg, less than about 3×10^{15} vg/kg, less than about 5×10^{15} vg/kg, or less than about 7×10^{15} vg/kg. In certain embodiments, the AAV vector delivered at any of these doses is an AAV9 vector or an AAV rh74 vector. In some cases, it may be advantageous to use a higher dose for an AAV rh74 vector than for an AAV9 vector.

[0217] In some embodiments, the AAV vector is administered at a dose of about 1×10^{12} vg/kg, about 3×10^{12} vg/kg, about 5×10^{12} vg/kg, about 7×10^{12} vg/kg, about 1×10^{13} vg/kg, about 3×10^{13} vg/kg, about 5×10^{13} vg/kg, about 7×10^{13} vg/kg, about 1×10^{14} vg/kg, about 3×10^{14} vg/kg, about 5×10^{14} vg/kg, about 7×10^{14} vg/kg, about 1×10^{15} vg/kg, about 3×10^{15} vg/kg, about 5×10^{15} vg/kg, or about 7×10^{15} vg/kg. In certain embodiments, the AAV vector delivered at any of these doses is an AAV9 vector or an AAV rh74 vector.

[0218] In some embodiments, the AAV vector is administered at a dose of 1×10^{12} vg/kg, 3×10^{12} vg/kg, 5×10^{12} vg/kg, 7×10^{12} vg/kg, 1×10^{13} vg/kg, 3×10^{13} vg/kg, 5×10^{13} vg/kg, 7×10^{13} vg/kg, 1×10^{14} vg/kg, 3×10^{14} vg/kg, 5×10^{14} vg/kg, 7×10^{14} vg/kg, 1×10^{15} vg/kg, 3×10^{15} vg/kg, 5×10^{15} vg/kg, or 7×10^{15} vg/kg. In certain embodiments, the AAV vector delivered at any of these doses is an AAV9 vector or an AAV rh74 vector.

[0219] In some embodiments, the AAV vector is administered systemically at a dose of between about 1×10^{12} and 5×10^{14} vector genomes (vg) of the AAV vector per kilogram (vg) of total body mass of the subject (vg/kg). In some embodiments, the AAV vector is administered systemically at a dose of between about 1×10^{13} and 5×10^{14} vg/kg. In some embodiments, the AAV vector is administered systemically at a dose of between about 5×10^{13} and 3×10^{14} vg/kg. In some embodiments, the AAV vector is administered systemically at a dose of between about 5×10^{13} and 1×10^{14} vg/kg. In some embodiments, the AAV vector is administered systemically at a dose of less than about 1×10^{12} vg/kg, less than about 3×10^{12} vg/kg, less than about 5×10^{12} vg/kg, less than about 7×10^{12} vg/kg, less than about 1×10^{13} vg/kg, less than about 3×10^{13} vg/kg, less than about 5×10^{13} vg/kg, less than about 7×10^{13} vg/kg, less than about 1×10^{14} vg/kg, less than about 3×10^{14} vg/kg, less than about 5×10^{14} vg/kg, less than about 7×10^{14} vg/kg, less than about 1×10^{15} vg/kg, less than about 3×10^{15} vg/kg, less than about 5×10^{15} vg/kg, or less than about 7×10^{15} vg/kg. In certain embodiments, the AAV vector delivered at any of these doses is an AAV9 vector or an AAV rh74 vector.

[0220] In some embodiments, the AAV vector is administered systemically at a dose of about 1×10^{12} vg/kg, about 3×10^{12} vg/kg, about 5×10^{12} vg/kg, about 7×10^{12} vg/kg, about 1×10^{13} vg/kg, about 3×10^{13} vg/kg, about 5×10^{13} vg/kg, about 7×10^{13} vg/kg, about 1×10^{14} vg/kg, about 3×10^{14} vg/kg, about 5×10^{14} vg/kg, about 7×10^{14} vg/kg, about 1×10^{15} vg/kg, about 3×10^{15} vg/kg, about 5×10^{15} vg/kg, or about 7×10^{15} vg/kg. In certain embodiments, the AAV vector delivered at any of these doses is an AAV9 vector or an AAV rh74 vector.

[0221] In some embodiments, the AAV vector is administered systemically at a dose of 1×10^{12} vg/kg, 3×10^{12} vg/kg, 5×10^{12} vg/kg, 7×10^{12} vg/kg, 1×10^{13} vg/kg, 3×10^{13} vg/kg, 5×10^{13} vg/kg, 7×10^{13} vg/kg, 1×10^{14} vg/kg, 3×10^{14} vg/kg, 5×10^{14} vg/kg, 7×10^{14} vg/kg, 1×10^{15} vg/kg, 3×10^{15} vg/kg, 5×10^{15} vg/kg, or 7×10^{15} vg/kg. In certain embodiments, the AAV vector delivered at any of these doses is an AAV9 vector or an AAV rh74 vector.

[0222] In some embodiments, the AAV vector is administered intravenously at a dose of between about 1×10^{12} and 5×10^{14} vector genomes (vg) of the AAV vector per kilogram (vg) of total body mass of the subject (vg/kg). In some embodiments, the AAV vector is administered intravenously at a dose of between about 1×10^{13} and 5×10^{14} vg/kg. In some embodiments, the AAV vector is administered intravenously at a dose of between about 5×10^{13} and 3×10^{14} vg/kg. In some embodiments, the AAV vector is administered intravenously at a dose of between about 5×10^{13} and 1×10^{14} vg/kg. In some embodiments, the AAV vector is administered intravenously at a dose of less than about 1×10^{12} vg/kg, less than about 3×10^{12} vg/kg, less than about 5×10^{12} vg/kg, less than about 7×10^{12} vg/kg, less than about 1×10^{13} vg/kg, less than about 3×10^{13} vg/kg, less than about 5×10^{13} vg/kg, less than about 7×10^{13} vg/kg, less than about 1×10^{14} vg/kg, less than about 3×10^{14} vg/kg, less than about 5×10^{14} vg/kg, less than about 7×10^{14} vg/kg, less than about 1×10^{15} vg/kg, less than about 3×10^{15} vg/kg, less than about 5×10^{15} vg/kg, or less than about 7×10^{15} vg/kg. In certain embodiments, the AAV vector delivered at any of these doses is an AAV9 vector or an AAV rh74 vector.

[0223] In some embodiments, the AAV vector is administered intravenously at a dose of about 1×10^{12} vg/kg, about 3×10^{12} vg/kg, about 5×10^{12} vg/kg, about 7×10^{12} vg/kg, about 1×10^{13} vg/kg, about 3×10^{13} vg/kg, about 5×10^{13} vg/kg, about 7×10^{13} vg/kg, about 1×10^{14} vg/kg, about 3×10^{14} vg/kg, about 5×10^{14} vg/kg, about 7×10^{14} vg/kg, about 1×10^{15} vg/kg, about 3×10^{15} vg/kg, about 5×10^{15} vg/kg, or about 7×10^{15} vg/kg.

[0224] In some embodiments, the AAV vector is administered intravenously at a dose of 1×10^{12} vg/kg, 3×10^{12} vg/kg, 5×10^{12} vg/kg, 7×10^{12} vg/kg, 1×10^{13} vg/kg, 3×10^{13} vg/kg, 5×10^{13} vg/kg, 7×10^{13} vg/kg, 1×10^{14} vg/kg, 3×10^{14} vg/kg, 5×10^{14} vg/kg, 7×10^{14} vg/kg, 1×10^{15} vg/kg, 3×10^{15} vg/kg, 5×10^{15} vg/kg, or 7×10^{15} vg/kg. In certain embodi-

ments, the AAV vector delivered at any of these doses is an AAV9 vector or an AAV rh74 vector.

[0225] Evidence of functional improvement, clinical benefit or efficacy in patients may be revealed by change in New York Heart Association functional classification (NYHA Class), pathological electrocardiogram, cardiac MRI, heart biopsy, decrease in paroxysmal ventricular arrhythmias, decrease in sudden cardiac death, and/or decrease in or lack of further development of fibro-fatty deposits in right ventricular myocardium. Benefit may be observed in electrocardiographic features normally associated with arrhythmogenic right ventricular cardiomyopathy such as T wave inversion, prolonged S-wave upstroke, localized QRS widening, and/or paroxysmal episodes of ventricular tachycardia.

[0226] In some embodiments, the method prevents or reduces a decrease in left ventricle ejection fraction percentage (LVEF %), optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the decrease observed in an untreated subject suffering from or at risk for disease or disorder related to or caused by loss of function in PKP2.

[0227] In some embodiments, the method prevents or reduces a decrease in left ventricle fractional shortening percentage (FS %), optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the decrease observed in an untreated subject suffering from or at risk for disease or disorder related to or caused by loss of function in PKP2.

[0228] In some embodiments, the method prevents or reduces an increase in right ventricle area in millimeters squared (RV Area (mm2), optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the increase observed in an untreated subject suffering from or at risk for disease or disorder related to or caused by loss of function in PKP2.

[0229] In some embodiments, the method prevents or reduces a decrease in right ventricle velocity time integral in millimeters per second (RV VTI (mm/sec), optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the decrease observed in an untreated subject suffering from or at risk for disease or disorder related to or caused by loss of function in PKP2.

[0230] In some embodiments, the method prevents or reduces an increase in left ventricle or right ventricle fibrosis, optionally by about 50%, about 60%, about 70%, about 80%, about 90%, or about 100% compared to the increase observed in an untreated subject suffering from or at risk for disease or disorder related to or caused by loss of function in PKP2.

[0231] Administration of an effective dose of the compositions may be by routes standard in the art including, but not limited to, systemic, local, direct injection, intravenous, intracardiac administration. In some cases, administration comprises systemic, local, direct injection, intravenous, intracardiac injection. Administration may be performed by cardiac catheterization.

[0232] In some embodiments, the disclosure provides for local administration and systemic administration of an effective dose of rAAV and compositions of the invention. For example, systemic administration may be administration into the circulatory system so that the entire body is affected. Systemic administration includes parental administration through injection, infusion or implantation. Routes of administration for the compositions disclosed herein include intravenous ("IV") administration, intraperitoneal ("IP") administration, intramuscular ("IM") administration, intralesional administration, or subcutaneous ("SC") administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, a depot formulation, etc. In some embodiments, the methods of the disclosure comprise administering an AAV vector of the disclosure, or pharmaceutical composition thereof by intravenous, intramuscular, intraarterial, intrarenal, intraurethral, intracardiac, intracoronary, intramyocardial, intradermal, epidural, subcutaneous, intraperitoneal, intraventricular, ionophoretic or intracranial administration.

[0233] In particular, administration of rAAV of the present invention may be accomplished by using any physical method that will transport the rAAV recombinant vector into the target tissue of an animal. Administration includes, but is not limited to, injection into the heart.

[0234] In some embodiments, the methods of the disclosure comprise intracardiac delivery. Infusion may be performed using specialized cannula, catheter, syringe/needle using an infusion pump. Administration may comprise delivery of an effective amount of the rAAV virion, or a pharmaceutical composition comprising the rAAV virion, to the heart. These may be achieved, e.g., via intravenous, intramuscular, intraarterial, intrarenal, intraurethral, intracardiac, intracoronary, intramyocardial, intradermal, epidural, subcutaneous, intraperitoneal, intraventricular, ionophoretic or intracranial administration. The compositions of the disclosure may further be administered intravenously.

[0235] The method of treatment disclosed herein may reduce and/or prevent one or more symptoms including but not limited to ventricular hypertrophy, ventricular tachycardia, exercise intolerance, angina, and reduced RVEF.

EXAMPLES

Example 1: Pre-Clinical Bioactivity and Efficacy

[0236] Vectors illustrated in FIGS. **1-4** are tested. AAV vectors or respective expression cassettes are tested in vitro using cultured cardiomyocytes (e.g., induced pluripotent stem cell cardiomyocytes, iPSC-CMs) or other cells amenable to transfection or transduction with these constructs. Expression of PKP2 is assessed by immunofluorescence and Western blot. Cell-based studies employing patient iPSC-derived cardiomyocytes will reveal benefit of overexpression of PKP2 transgene (either following AAV vector transduction and/or transfection with vector plasmids) by a decreased adipogenic potential (e.g. less lipid accumulation), decreased upregulation or abnormal peroxisome proliferator-activated receptor gamma activation, associated with increased density of PKP2.

[0237] Selected vectors are tested in vivo using mutant mouse models of cardiomyopathy (e.g., PKP2-cKO, among others). Evidence of benefit of AAV mediated overexpression of PKP2 may be revealed using a cardiomyocyte-specific, tamoxifen-activated, PKP2 knockout murine line, referred to as "PKP2-cKO". This mouse model allows control of the onset of PKP2 loss of expression, limits loss of PKP2 to adult myocytes, and initiates a progression of molecular and functional events leading to an arrhythmogenic cardiomyopathy, with right ventricular predominance in this mouse. Additional mouse models that result in similar course of pathology may also be utilized to

reveal benefit of AAV-mediated overexpression of PKP2 in cardiomyocytes. Benefit of AAV-mediated PKP2 overexpression would be evidenced by increase in survival, mitigation of the normal progression of cardiomyopathy observed on echocardiograms from left and/or right ventricle (e.g. greater left ventricular ejection fraction, greater left ventricle fractional shortening, and greater right ventricle velocity time interval, compared to PKP cKO formulation buffer control animals).

[0238] Electrophysiological evidence of functional benefit of AAV-mediated delivery of PKP2 protein is demonstrated by mitigation of disease-related disrupted calcium dynamics in affected cardiomyocytes, most notably on measures of L-type calcium current, sarcoplasmic reticulum calcium leak, diastolic calcium leak, as well as standard measures of calcium transients in affected (e.g., PKP2-deficient) cardiomyocytes such as time to peak amplitude and relaxation time constants. Histological analyses will reveal benefit of AAV-mediated PKP2 overexpression by diminished appearance of disease-related collagen deposition (e.g., via trichrome stain) in various regions of the heart including ventricles, compared to cKO formulation buffer injected controls. Additional benefit will also be revealed by evaluating cardiomyocyte ventricular proteins involved in calcium signaling pathways, measured by increased (i.e., normalized) relative levels of Casq2, and/or Trdn, and/or Cav 1.2, and/or AnkB and/or RyR2, relative to non AAV-PKP2 treated, PKP2-cKO diseased controls.

Example 2: In Vitro Testing of Adeno-Associated Virus Vectors

[0239] AAV vectors are described herein (see FIGS. **11**-**12**) were prepared and used to transduce differentiated AC16 cells, a human cardiomyocyte cell line. Expression levels of PKP2 (PKP2a isoform) were assessed by Western Blot (FIGS. **5**A-**5**B). Surprisingly, the MHCK7 promoter causes robust expression of PKP2 in cardiomyocytes, whereas the hTnnT2 promoter ("hTnT") generates marginal PKP2 levels above background under the current testing conditions. The AAVrh.74 serotype induced higher expression of PKP2 than the AAV9 serotype vector.

[0240] Based on these results, we conclude that AAV9 vectors or AAVrh74 vectors can effectively be used to express PKP2 in cardiomyocytes, and that the MHCK7 promoter is superior to the hTnnT2 promoter when solely evaluating the relative levels of PKP2 expression.

Example 3: In Vivo Efficacy of Adeno-Associated Virus Vectors

[0241] A "PKP2-cKO" mouse model of PKP2-deficiency, as described in Cerrone et al., Nat Comm., 2017 was obtained. This cardiomyocyte-specific, tamoxifen-activated PKP2 knockout murine line (aMHC-Cre-ER(T2)/Pkp2 fl/fl; referred to as "PKP2-cKO") was utilized to control the onset of PKP2 loss of expression (see Cerrone et al., Nat Comm, 2017). The conditional loss of PKP2 expression in this mouse model is limited to adult myocytes and the temporal progression of the molecular, structural and functional events as a consequence of PKP2-cKO have been established (Cerrone et al., Nat Comm, 2017). PKP2 deficiency in adult ventricular myocytes is sufficient to cause an arrhythmogenic cardiomyopathy of RV predominance, which includes the 'hallmark' functional, molecular, and structural indices consistent with the disease phenotype of ARVC.

[0242] PKP2-Cko mice were injected with tamoxifen, causing myocyte-specific knockout of PKP2. Mice were injected with AAV vectors (as described below) at 3×10^{13} vg/kg by intravenous (tail vein) injection. Four weeks later, myocyte-specific knockout of PKP2 was induced by treatment of the mice with tamoxifen. The vector genomes used were:

[0243] 5' ITR; MHCK7 promoter (with its enhancer element); SV40 intron; Kozak sequence; PKPa transgene; WPRE(x); hGH polyadenylation sequence); 3' ITR—shown in FIG. **11**

[0244] 5' ITR; hTnnT2 promoter (with exon 1); Kozak sequence; PKPa transgene; WPRE(x); hGH polyadenylation sequence); 3' ITR—shown in FIG. **12**.

[0245] Each vector genome was tested in a AAV9 serotype or AAVrh74 serotype vector.

[0246] At 21 or 28 days after tamoxifen treatment, which is 25 or 32 weeks after AAV treatment, mice were evaluated for various physiology parameters, essentially as described in Cerrone et al., Nat Comm, 2017 or using standard methodologies known in the art. Efficacy in treating disease was assessed by left ventricle ejection fraction percentage (LVEF %) (FIGS. **6**A-**6**D), left ventricle fractional shortening percentage (FS %) (FIGS. **7**A-**7**D), right ventricle area in millimeters squared (RV Area (mm^2)) (FIGS. **8**A-**8**D), right ventricle velocity time integral in millimeters per second (RV VTI (mm/sec)) (FIGS. **9**A-**9**D), and degree of fibrosis (FIGS. **10**A-**10**B). These measures are appropriate functional and morphological indices to evaluate potential efficacy of AAV-mediated PKP2 overexpression in cardiomyocytes as they are among key parameters indicative of ARVC in human disease. Generally, a right ventricle normally has slightly greater amount of fibrosis (irrespective of disease); and this is further exacerbated with lack of PKP2 in the cKO model. Progressive deterioration of these parameters was observed within 21 days of tamoxifen injection, because tamoxifen injection causes myocyte-specific knockout of the PKP gene.

[0247] Evidence for mitigation of the disease phenotype was observed following both AAV9- and AAVrh.74-mediated PKP expression, to varying degrees. With the dose studied to date (3×10^{13} vg/kg) using a pre-treatment paradigm (AAV 4 weeks prior to tamoxifen-induced PKP cKO), AAV9 surprisingly produced the most robust effects on all parameters. Nevertheless, given the cardiotropism of AAVrh74 and given that biological effects were observed with AAVrh.74-mediated overexpression of PKP2 in this model (e.g. LVEF %, FS %, and right ventricular area), optimization of the dose of AAVrh.74 in combination with the appropriate promoter (i.e., either MHCK7 or hTnnT2) could enable robust therapeutic potential for this vector.

[0248] These results demonstrate both AAV9 and AAVrh.74 can be used to treat PKP2-related diseases, such as Arrhythmogenic right ventricular cardiomyopathy (ARVC) [also known as Arrhythmogenic Right Ventricular Dysplasia (ARVD) or Arrhythmogenic Cardiomyopathy (ACM)] for which the PKP-cKO mouse is considered an appropriate model. Additionally, vectors with either MHCK7 promoter or hTnnT2 promoter have been demonstrated to be effective in treating PKP2-related disease.

SEQUENCE LISTING

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        35                  40                  45

Gln Thr Val Lys Ser Leu Arg Ile Gln Glu Gln Val Gln Gln Thr Leu
    50                  55                  60

Ala Arg Lys Gly Arg Ser Ser Val Gly Asn Gly Asn Leu His Arg Thr
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Ser Ser Val Pro Glu Tyr Val Tyr Asn Leu His Leu Val Glu Asn Asp
                85                  90                  95

Phe Val Gly Gly Arg Ser Pro Val Pro Lys Thr Tyr Asp Met Leu Lys
            100                 105                 110

Ala Gly Thr Thr Ala Thr Tyr Glu Gly Arg Trp Gly Arg Gly Thr Ala
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Gln Tyr Ser Ser Gln Lys Ser Val Glu Glu Arg Ser Leu Arg His Pro
    130                 135                 140

Leu Arg Arg Leu Glu Ile Ser Pro Asp Ser Ser Pro Glu Arg Ala His
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Tyr Thr His Ser Asp Tyr Gln Tyr Ser Gln Arg Ser Gln Ala Gly His
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            180                 185                 190

Arg Tyr Ala Arg Ser Glu Ile Val Gly Val Ser Arg Ala Gly Thr Thr
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Ser Val Ser Asp Thr Val Phe Asp Ser Ile Pro Ala Asn Pro Ala Leu
225                 230                 235                 240

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Glu Lys Glu Asn Tyr Leu Thr Ala Gly Leu Thr Val Gly Gln Val Arg
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Pro Leu Val Pro Leu Gln Pro Val Thr Gln Asn Arg Ala Ser Arg Ser
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Gly Pro Ser Val Ala Val Asp Ser Ser Gly Arg Arg Ala His Leu Thr
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Asn Val Thr Gly Cys Leu Arg Asn Met Ser Ser Ala Gly Ala Asp Gly
        515                 520                 525

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    530                 535                 540

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Ile Gln Thr Asp Asn Asn Lys Ser Ile Gly Cys Phe Gly Ser Arg Ser
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His Thr Arg Lys Met Leu His Val Gly Asp Pro Ser Val Lys Lys Thr
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Ala Ile Ser Leu Leu Arg Asn Leu Ser Arg Asn Leu Ser Leu Gln Asn
705                 710                 715                 720

Glu Ile Ala Lys Glu Thr Leu Pro Asp Leu Val Ser Ile Ile Pro Asp
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            20                  25                  30

Pro Ser Glu Ala Lys Leu Lys Leu Ala Gly Ser Ser Gly Arg Gly Gly
        35                  40                  45

Gln Thr Val Lys Ser Leu Arg Ile Gln Glu Gln Val Gln Gln Thr Leu
    50                  55                  60

Ala Arg Lys Gly Arg Ser Ser Val Gly Asn Gly Asn Leu His Arg Thr
65                  70                  75                  80

Ser Ser Val Pro Glu Tyr Val Tyr Asn Leu His Leu Val Glu Asn Asp
                85                  90                  95

Phe Val Gly Gly Arg Ser Pro Val Pro Lys Thr Tyr Asp Met Leu Lys
            100                 105                 110

Ala Gly Thr Thr Ala Thr Tyr Glu Gly Arg Trp Gly Arg Gly Thr Ala
        115                 120                 125

Gln Tyr Ser Ser Gln Lys Ser Val Glu Glu Arg Ser Leu Arg His Pro
    130                 135                 140

Leu Arg Arg Leu Glu Ile Ser Pro Asp Ser Ser Pro Glu Arg Ala His
145                 150                 155                 160

Tyr Thr His Ser Asp Tyr Gln Tyr Ser Gln Arg Ser Gln Ala Gly His
                165                 170                 175

Thr Leu His His Gln Glu Ser Arg Arg Ala Ala Leu Leu Val Pro Pro
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Ser Arg Gln Arg His Phe Asp Thr Tyr His Arg Gln Tyr Gln His Gly
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Ser Val Ser Asp Thr Val Phe Asp Ser Ile Pro Ala Asn Pro Ala Leu
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Leu Thr Tyr Pro Arg Pro Gly Thr Ser Arg Ser Met Gly Asn Leu Leu
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Ser Thr Phe Thr Asp Ser Gln Leu Gly Asn Ala Asp Met Glu Met Thr
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Leu Glu Arg Ala Val Ser Met Leu Glu Ala Asp His Met Leu Pro Ser
        355                 360                 365

Arg Ile Ser Ala Ala Ala Thr Phe Ile Gln His Glu Cys Phe Gln Lys
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Ser Glu Ala Arg Lys Arg Val Asn Gln Leu Arg Gly Ile Leu Lys Leu
385                 390                 395                 400

Leu Gln Leu Leu Lys Val Gln Asn Glu Asp Val Gln Arg Ala Val Cys
                405                 410                 415

Gly Ala Leu Arg Asn Leu Val Phe Glu Asp Asn Asp Asn Lys Leu Glu
            420                 425                 430

Val Ala Glu Leu Asn Gly Val Pro Arg Leu Leu Gln Val Leu Lys Gln
        435                 440                 445

Thr Arg Asp Leu Glu Thr Lys Lys Gln Ile Thr Asp His Thr Val Asn
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Leu Arg Ser Arg Asn Gly Trp Pro Gly Ala Val Ala His Ala Cys Asn
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Pro Ser Thr Leu Gly Gly Gln Gly Gly Arg Ile Thr Arg Ser Gly Val
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Cys Leu Arg Asn Met Ser Ser Ala Gly Ala Asp Gly Arg Lys Ala Met
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Arg Arg Cys Asp Gly Leu Ile Asp Ser Leu Val His Tyr Val Arg Gly
            580                 585                 590

Thr Ile Ala Asp Tyr Gln Pro Asp Asp Lys Ala Thr Glu Asn Cys Val
        595                 600                 605

Cys Ile Leu His Asn Leu Ser Tyr Gln Leu Glu Ala Glu Leu Pro Glu
    610                 615                 620

Lys Tyr Ser Gln Asn Ile Tyr Ile Gln Asn Arg Asn Ile Gln Thr Asp
625                 630                 635                 640

Asn Asn Lys Ser Ile Gly Cys Phe Gly Ser Arg Ser Arg Lys Val Lys
                645                 650                 655

Glu Gln Tyr Gln Asp Val Pro Met Pro Glu Glu Lys Ser Asn Pro Lys
            660                 665                 670

Gly Val Glu Trp Leu Trp His Ser Ile Val Ile Arg Met Tyr Leu Ser
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        675                 680                 685

Leu Ile Ala Lys Ser Val Arg Asn Tyr Thr Gln Glu Ala Ser Leu Gly
    690                 695                 700

Ala Leu Gln Asn Leu Thr Ala Gly Ser Gly Pro Met Pro Thr Ser Val
705                 710                 715                 720

Ala Gln Thr Val Val Gln Lys Glu Ser Gly Leu Gln His Thr Arg Lys
                725                 730                 735

Met Leu His Val Gly Asp Pro Ser Val Lys Lys Thr Ala Ile Ser Leu
            740                 745                 750

Leu Arg Asn Leu Ser Arg Asn Leu Ser Leu Gln Asn Glu Ile Ala Lys
        755                 760                 765

Glu Thr Leu Pro Asp Leu Val Ser Ile Ile Pro Asp Thr Val Pro Ser
    770                 775                 780

Thr Asp Leu Leu Ile Glu Thr Thr Ala Ser Ala Cys Tyr Thr Leu Asn
785                 790                 795                 800

Asn Ile Ile Gln Asn Ser Tyr Gln Asn Ala Arg Asp Leu Leu Asn Thr
                805                 810                 815

Gly Gly Ile Gln Lys Ile Met Ala Ile Ser Ala Gly Asp Ala Tyr Ala
            820                 825                 830

Ser Asn Lys Ala Ser Lys Ala Ala Ser Val Leu Leu Tyr Ser Leu Trp
        835                 840                 845

Ala His Thr Glu Leu His His Ala Tyr Lys Lys Ala Gln Phe Lys Lys
    850                 855                 860

Thr Asp Phe Val Asn Ser Arg Thr Ala Lys Ala Tyr His Ser Leu Lys
865                 870                 875                 880

Asp
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<210> SEQ ID NO 3
<211> LENGTH: 2511
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

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atcctgggac aactggacag ctccagcctg gcgctgccct ccgaggccaa gctgaagctg    120

gcggggagca gcggccgcgg cggccagaca gtcaagagcc tgcggatcca ggagcaggtg    180

cagcagaccc tcgcccggaa gggccgcagc tccgtgggca acggaaatct tcaccgaacc    240

agcagtgttc ctgagtatgt ctacaaccta cacttggttg aaaatgattt tgttggaggc    300

cgttcccctg ttcctaaaac ctatgacatg ctaaaggctg gcacaactgc cacttatgaa    360

ggtcgctggg gaagaggaac agcacagtac agctcccaga agtccgtgga agaaaggtcc    420

ttgaggcatc ctctgaggag actggagatt tctcctgaca gcagcccgga gagggctcac    480

tacacgcaca gcgattacca gtacagccag agaagccagg ctgggcacac cctgcaccac    540

caagaaagca ggcgggccgc cctcctagtg ccaccgagat atgctcgttc cgagatcgtg    600

ggggtcagcc gtgctggcac cacaagcagg cagcgccact ttgacacata ccacagacag    660

taccagcatg gctctgttag cgacaccgtt tttgacagca tccctgccaa cccggccctg    720

ctcacgtacc ccaggccagg gaccagccgc agcatgggca acctcttgga gaaggagaac    780

tacctgacgg cagggctcac tgtcgggcag gtcaggccgc tggtgcccct gcagcccgtc    840
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actcagaaca gggcttccag gtcctcctgg catcagagct ccttccacag cacccgcacg 900

ctgagggaag ctgggcccag tgtcgccgtg gattccagcg ggaggagagc gcacttgact 960

gtcggccagg cggccgcagg gggaagtggg aatctgctca ctgagagaag cactttcact 1020

gactcccagc tggggaatgc agacatggag atgactctgg agcgagcagt gagtatgctc 1080

gaggcagacc acatgctgcc atccaggatt tctgctgcag ctactttcat acagcacgag 1140

tgcttccaga aatctgaagc tcggaagagg gttaaccagc ttcgtggcat cctcaagctt 1200

ctgcagctcc taaaagttca gaatgaagac gttcagcgag ctgtgtgtgg ggccttgaga 1260

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gagaattgtg tgtgcattct tcataacctc tcctaccagc tggaggcaga gctcccagag 1740

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ccggaggaaa agagcaaccc caagggcgtg gagtggctgt ggcattccat tgttataagg 1920

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gtgaaaaaga cagccatctc gctgctgagg aatctgtccc ggaatctttc tctgcagaat 2160

gaaattgcca aagaaactct ccctgatttg gtttccatca ttcctgacac agtcccgagt 2220

actgaccttc tcattgaaac tacagcctct gcctgttaca cattgaacaa cataatccaa 2280

aacagttacc agaatgcacg cgaccttcta aacaccgggg gcatccagaa aattatggcc 2340

attagtgcag gcgatgccta tgcctccaac aaagcaagta aagctgcttc cgtccttctg 2400

tattctctgt gggcacacac ggaactgcat catgcctaca agaaggctca gtttaagaag 2460

acagattttg tcaacagccg gactgccaaa gcctaccact cccttaaaga c 2511

<210> SEQ ID NO 4
<211> LENGTH: 2643
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

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atcctgggac aactggacag ctccagcctg gcgctgccct ccgaggccaa gctgaagctg 120

gcggggagca gcggccgcgg cggccagaca gtcaagagcc tgcggatcca ggagcaggtg 180

cagcagaccc tcgcccggaa gggccgcagc tccgtgggca acggaaatct tcaccgaacc 240

agcagtgttc ctgagtatgt ctacaaccta cacttggttg aaaatgattt tgttggaggc 300

cgttcccctg ttcctaaaac ctatgacatg ctaaaggctg gcacaactgc cacttatgaa 360

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ggtcgctggg gaagaggaac agcacagtac agctcccaga agtccgtgga agaaaggtcc 420

ttgaggcatc ctctgaggag actggagatt tctcctgaca gcagcccgga gagggctcac 480

tacacgcaca gcgattacca gtacagccag agaagccagg ctgggcacac cctgcaccac 540

caagaaagca ggcgggccgc cctcctagtg ccaccgagat atgctcgttc cgagatcgtg 600

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tacctgacgg cagggctcac tgtcgggcag gtcaggccgc tggtgcccct gcagcccgtc 840

actcagaaca gggcttccag gtcctcctgg catcagagct ccttccacag cacccgcacg 900

ctgagggaag ctgggcccag tgtcgccgtg gattccagcg ggaggagagc gcacttgact 960

gtcggccagg cggccgcagg gggaagtggg aatctgctca ctgagagaag cactttcact 1020

gactcccagc tggggaatgc agacatggag atgactctgg agcgagcagt gagtatgctc 1080

gaggcagacc acatgctgcc atccaggatt tctgctgcag ctactttcat acagcacgag 1140

tgcttccaga aatctgaagc tcggaagagg gttaaccagc ttcgtggcat cctcaagctt 1200

ctgcagctcc taaaagttca gaatgaagac gttcagcgag ctgtgtgtgg ggccttgaga 1260

aacttagtat ttgaagacaa tgacaacaaa ttggaggtgg ctgaactaaa tggggtacct 1320

cggctgctcc aggtgctgaa gcaaaccaga gacttggaga ctaaaaaaca aataacagac 1380

catacagtca atttaagaag taggaatggc tggccgggcg cggtggctca cgcctgtaat 1440

cccagcactt tgggaggcca aggcgggcgg atcacgaggt caggagttcg agaccagcct 1500

gaccaacatg gtttgctgtg gaatttgtca tctaatgaca aactcaagaa tctcatgata 1560

acagaagcat tgcttacgct gacggagaat atcatcatcc ccttttctgg gtggcctgaa 1620

ggagactacc caaaagcaaa tggtttgctc gattttgaca tattctacaa cgtcactgga 1680

tgcctaagaa acatgagttc tgctggcgct gatgggagaa aagcgatgag aagatgtgac 1740

ggactcattg actcactggt ccattatgtc agaggaacca ttgcagatta ccagccagat 1800

gacaaggcca cggagaattg tgtgtgcatt cttcataacc tctcctacca gctggaggca 1860

gagctcccag agaaatattc ccagaatatc tatattcaaa accggaatat ccagactgac 1920

aacaacaaaa gtattggatg ttttggcagt cgaagcagga aagtaaaaga gcaataccag 1980

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aaaattatgg ccattagtgc aggcgatgcc tatgcctcca acaaagcaag taaagctgct 2520

tccgtccttc tgtattctct gtgggcacac acggaactgc atcatgccta caagaaggct 2580

cagtttaaga agacagattt tgtcaacagc cggactgcca aagcctacca ctcccttaaa 2640

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gac 2643

<210> SEQ ID NO 5
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Kozak sequence motif

<400> SEQUENCE: 5

gccaccatgg 10

<210> SEQ ID NO 6
<211> LENGTH: 2517
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polynucleotide encoding an PKP2a with Kozak sequence

<400> SEQUENCE: 6

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cagcagatcc tgggacaact ggacagctcc agcctggcgc tgccctccga ggccaagctg 120

aagctggcgg ggagcagcgg ccgcggcggc cagacagtca agagcctgcg gatccaggag 180

caggtgcagc agaccctcgc ccggaagggc cgcagctccg tgggcaacgg aaatcttcac 240

cgaaccagca gtgttcctga gtatgtctac aacctacact tggttgaaaa tgattttgtt 300

ggaggccgtt cccctgttcc taaaacctat gacatgctaa aggctggcac aactgccact 360

tatgaaggtc gctggggaag aggaacagca cagtacagct cccagaagtc cgtggaagaa 420

aggtccttga ggcatcctct gaggagactg gagatttctc ctgacagcag cccggagagg 480

gctcactaca cgcacagcga ttaccagtac agccagagaa gccaggctgg gcacaccctg 540

caccaccaag aaagcaggcg ggccgccctc ctagtgccac cgagatatgc tcgttccgag 600

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gccctgctca cgtaccccag gccagggacc agccgcagca tgggcaacct cttggagaag 780

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atgctcgagg cagaccacat gctgccatcc aggatttctg ctgcagctac tttcatacag 1140

cacgagtgct tccagaaatc tgaagctcgg aagagggtta accagcttcg tggcatcctc 1200

aagcttctgc agctcctaaa agttcagaat gaagacgttc agcgagctgt gtgtggggcc 1260

ttgagaaact tagtatttga agacaatgac aacaaattgg aggtggctga actaaatggg 1320

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acaggtttgc tgtggaattt gtcatctaat gacaaactca agaatctcat gataacagaa 1440

gcattgctta cgctgacgga gaatatcatc atccccttt ctgggtggcc tgaaggagac 1500

tacccaaaag caaatggttt gctcgatttt gacatattct acaacgtcac tggatgccta 1560

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attgactcac tggtccatta tgtcagagga accattgcag attaccagcc agatgacaag 1680

gccacggaga attgtgtgtg cattcttcat aacctctcct accagctgga ggcagagctc 1740

ccagagaaat attcccagaa tatctatatt caaaaccgga atatccagac tgacaacaac 1800

aaaagtattg gatgttttgg cagtcgaagc aggaaagtaa aagagcaata ccaggacgtg 1860

ccgatgccgg aggaaaagag caaccccaag ggcgtggagt ggctgtggca ttccattgtt 1920

ataaggatgt atctgtcctt gatcgccaaa agtgtccgca actacacaca agaagcatcc 1980

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acagttgtcc agaaggaaag tggcctgcag cacacccgaa agatgctgca tgttggtgac 2100

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cagaatgaaa ttgccaaaga aactctccct gatttggttt ccatcattcc tgacacagtc 2220

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cttctgtatt ctctgtgggc acacacggaa ctgcatcatg cctacaagaa ggctcagttt 2460

aagaagacag attttgtcaa cagccggact gccaaagcct accactccct taaagac 2517

<210> SEQ ID NO 7
<211> LENGTH: 2649
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polynucleotide encoding an PKP2b with Kozak sequence

<400> SEQUENCE: 7

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caggtgcagc agaccctcgc ccggaagggc cgcagctccg tgggcaacgg aaatcttcac 240

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ggaggccgtt cccctgttcc taaaacctat gacatgctaa aggctggcac aactgccact 360

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aggtccttga ggcatcctct gaggagactg gagatttctc ctgacagcag cccggagagg 480

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cgcacgctga gggaagctgg gcccagtgtc gccgtggatt ccagcgggag gagagcgcac 960

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atgctcgagg cagaccacat gctgccatcc aggatttctg ctgcagctac tttcatacag 1140

cacgagtgct tccagaaatc tgaagctcgg aagagggtta accagcttcg tggcatcctc 1200

aagcttctgc agctcctaaa agttcagaat gaagacgttc agcgagctgt gtgtggggcc 1260

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gtacctcggc tgctccaggt gctgaagcaa accagagact tggagactaa aaaacaaata 1380

acagaccata cagtcaattt aagaagtagg aatggctggc cgggcgcggt ggctcacgcc 1440

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cagcctgacc aacatggttt gctgtggaat ttgtcatcta atgacaaact caagaatctc 1560

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cctgaaggag actacccaaa agcaaatggt ttgctcgatt ttgacatatt ctacaacgtc 1680

actggatgcc taagaaacat gagttctgct ggcgctgatg ggagaaaagc gatgagaaga 1740

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aatctttctc tgcagaatga aattgccaaa gaaactctcc ctgatttggt ttccatcatt 2340

cctgacacag tcccgagtac tgaccttctc attgaaacta cagcctctgc ctgttacaca 2400

ttgaacaaca taatccaaaa cagttaccag aatgcacgcg accttctaaa caccgggggc 2460

atccagaaaa ttatggccat tagtgcaggc gatgcctatg cctccaacaa agcaagtaaa 2520

gctgcttccg tccttctgta ttctctgtgg gcacacacgg aactgcatca tgcctacaag 2580

aaggctcagt ttaagaagac agattttgtc aacagccgga ctgccaaagc ctaccactcc 2640

cttaaagac 2649

<210> SEQ ID NO 8
<211> LENGTH: 4081
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - MHCK7-PKP2a expression cassette

<400> SEQUENCE: 8

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ggccctgctg tctagcatgc cccactacgg gtctaggctg cccatgtaag gaggcaaggc 240

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cttcgaacaa ggctgtgggg gactgagggc aggctgtaac aggcttgggg gccagggctt 420

atacgtgcct gggactccca aagtattact gttccatgtt cccggcgaag ggccagctgt 480

cccccgccag ctagactcag cacttagttt aggaaccagt gagcaagtca gcccttgggg 540

cagcccatac aaggccatgg ggctgggcaa gctgcacgcc tgggtccggg gtgggcacgg 600

tgcccgggca acgagctgaa agctcatctg ctctcagggg cccctccctg gggacagccc 660

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ctgggacaac tggacagctc cagcctggcg ctgccctccg aggccaagct gaagctggcg 900

gggagcagcg gccgcggcgg ccagacagtc aagagcctgc ggatccagga gcaggtgcag 960

cagaccctcg cccggaaggg ccgcagctcc gtgggcaacg gaaatcttca ccgaaccagc 1020

agtgttcctg agtatgtcta caacctacac ttggttgaaa atgattttgt tggaggccgt 1080

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acgcacagcg attaccagta cagccagaga agccaggctg ggcacaccct gcaccaccaa 1320

gaaagcaggc gggccgccct cctagtgcca ccgagatatg ctcgttccga gatcgtgggg 1380

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cagcatggct ctgttagcga caccgttttt gacagcatcc ctgccaaccc ggccctgctc 1500

acgtacccca ggccagggac cagccgcagc atgggcaacc tcttggagaa ggagaactac 1560

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<220> FEATURE:
<223> OTHER INFORMATION: Made in Labe - full polynucleotide sequence of vector genome

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agttaccaga atgcacgcga ccttctaaac accgggggca tccagaaaat tatggccatt 3420

agtgcaggcg atgcctatgc ctccaacaaa gcaagtaaag ctgcttccgt ccttctgtat 3480

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gggtggaggg gggtggtatg gagcaagggg cccaagttgg gaagaaacct gtagggcctg 4380

ctacgtagat aagtagcatg gcgggttaat cattaactac aaggaacccc tagtgatgga 4440

gttggccact ccctctctgc gcgctcgctc gctcactgag gccgggcgac caaaggtcgc 4500

ccgacgcccg ggctttgccc gggcggcctc agtgagcgag cgagcgcgc 4549

<210> SEQ ID NO 15
<211> LENGTH: 4322
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Labe - full polynucleotide sequence of vector genome

<400> SEQUENCE: 15

gcgcgctcgc tcgctcactg aggccgcccg ggcaaagccc gggcgtcggg cgacctttgg 60

tcgcccggcc tcagtgagcg agcgagcgcg cagagaggga gtggccaact ccatcactag 120

gggttccttg tagttaatga ttaacccgcc atgctactta tctacgtact cagtccatta 180

ggagccagta gcctggaaga tgtctttacc cccagcatca gttcaagtgg agcagcacat 240

aactcttgcc ctctgccttc caagattctg gtgctgagac ttatggagtg tcttggaggt 300

tgccttctgc cccccaaccc tgctcccagc tggccctccc aggcctgggt tgctggcctc 360

tgctttatca ggattctcaa gagggacagc tggtttatgt tgcatgactg ttccctgcat 420

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atctgctctg gttttaaata gcttatctga gcagctggag gaccacatgg gcttatatgg 480

cgtggggtac atgttcctgt agccttgtcc ctggcacctg ccaaaatagc agccaacacc 540

ccccaccccc accgccatcc ccctgcccca cccgtcccct gtcgcacatt cctccctccg 600

cagggctggc tcaccaggcc ccagcccaca tgcctgctta aagccctctc catcctctgc 660

ctcacccagt ccccgctgag actgagcaga cgcctccagg atctgtcggc aggccaccat 720

ggcagccccc ggcgccccag ctgagtacgg ctacatccgg accgtcctgg gccagcagat 780

cctgggacaa ctggacagct ccagcctggc gctgccctcc gaggccaagc tgaagctggc 840

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gcagaccctc gcccggaagg gccgcagctc cgtgggcaac ggaaatcttc accgaaccag 960

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cctgacggca gggctcactg tcgggcaggt caggccgctg gtgcccctgc agcccgtcac 1560

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gctcccagag aaatattccc agaatatcta tattcaaaac cggaatatcc agactgacaa 2640

caacaaaagt attggatgtt ttggcagtcg aagcaggaaa gtaaaagagc aataccagga 2700

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cataatccaa aacagttacc agaatgcacg cgaccttcta aacaccgggg gcatccagaa 3180

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ctataatatt atggggtgga ggggggtggt atggagcaag gggcccaagt tgggaagaaa 4140

cctgtagggc ctgctacgta gataagtagc atggcgggtt aatcattaac tacaaggaac 4200

ccctagtgat ggagttggcc actccctctc tgcgcgctcg ctcgctcact gaggccgggc 4260

gaccaaaggt cgcccgacgc ccgggctttg cccgggcggc ctcagtgagc gagcgagcgc 4320

gc 4322

<210> SEQ ID NO 16
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Kozak sequence motif

<400> SEQUENCE: 16

gccgccrcca ugg 13

<210> SEQ ID NO 17

<400> SEQUENCE: 17

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<210> SEQ ID NO 18
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Kozak sequence motif

<400> SEQUENCE: 18

gacaccaugg 10

<210> SEQ ID NO 19

<400> SEQUENCE: 19

000

<210> SEQ ID NO 20
<211> LENGTH: 141
<212> TYPE: DNA
<213> ORGANISM: Adeno-associated virus

<400> SEQUENCE: 20

cctgcaggca gctgcgcgct cgctcgctca ctgaggccgc ccgggcaaag cccgggcgtc 60

gggcgacctt tggtcgcccg gcctcagtga gcgagcgagc gcgcagagag ggagtggcca 120

actccatcac taggggttcc t 141

<210> SEQ ID NO 21
<211> LENGTH: 168
<212> TYPE: DNA
<213> ORGANISM: Adeno-associated virus 2

<400> SEQUENCE: 21

gcgcgctcgc tcgctcactg aggccgcccg ggcaaagccc gggcgtcggg cgacctttgg 60

tcgcccggcc tcagtgagcg agcgagcgcg cagagaggga gtggccaact ccatcactag 120

gggttccttg tagttaatga ttaacccgcc atgctactta tctacgta 168

<210> SEQ ID NO 22
<211> LENGTH: 170
<212> TYPE: DNA
<213> ORGANISM: Adeno-associated virus

<400> SEQUENCE: 22

ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgacctttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtggccaa ctccatcact 120

aggggttcct tgtagttaat gattaacccg ccatgctact tatctacgta 170

<210> SEQ ID NO 23
<211> LENGTH: 145
<212> TYPE: DNA
<213> ORGANISM: Adeno-associated virus

<400> SEQUENCE: 23

ttggccactc cctctctgcg cgctcgctcg ctcactgagg ccgcccgggc aaagcccggg 60

cgtcgggcga cctttggtcg cccggcctca gtgagcgagc gagcgcgcag agagggagtg 120

gccaactcca tcactagggg ttcct 145

<210> SEQ ID NO 24

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<211> LENGTH: 141
<212> TYPE: DNA
<213> ORGANISM: Adeno-associated viurs

<400> SEQUENCE: 24

aggaacccct agtgatggag ttggccactc cctctctgcg cgctcgctcg ctcactgagg 60

ccgggcgacc aaaggtcgcc cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc 120

gagcgcgcag ctgcctgcag g 141

<210> SEQ ID NO 25
<211> LENGTH: 168
<212> TYPE: DNA
<213> ORGANISM: Adeno-associated virus 2

<400> SEQUENCE: 25

tacgtagata agtagcatgg cgggttaatc attaactaca aggaacccct agtgatggag 60

ttggccactc cctctctgcg cgctcgctcg ctcactgagg ccgggcgacc aaaggtcgcc 120

cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc gagcgcgc 168

<210> SEQ ID NO 26
<211> LENGTH: 133
<212> TYPE: DNA
<213> ORGANISM: Adeno-associated virus 2

<400> SEQUENCE: 26

aggaacccct agtgatggag actccctctc tgcgcgctcg ctcgctcact gaggccgggc 60

gaccaaaggt cgcccgacgc ccgggctttg cccgggcggc ctcagtgagc gagcgagcgc 120

gcagagaggg agt 133

<210> SEQ ID NO 27
<211> LENGTH: 124
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - vector filler sequence

<400> SEQUENCE: 27

gcggcaattc agtcgataac tataacggtc ctaaggtagc gatttaaata cgcgctctct 60

taaggtagcc ccgggacgcg tcaattgact acaaaccgag tatctgcaga gggccctgcg 120

tatg 124

<210> SEQ ID NO 28
<211> LENGTH: 84
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - vector filler sequence

<400> SEQUENCE: 28

cttctgaggc ggaaagaacc agatcctctc ttaaggtagc atcgagattt aaattaggga 60

taacagggta atggcgcggg ccgc 84

<210> SEQ ID NO 29
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Made in Lab - vector filler sequence

<400> SEQUENCE: 29

gttacccagg ctggagtgca gtggcacatt tctgctcact gcaacctcct cctccctggg 60

ttc 63

<210> SEQ ID NO 30
<211> LENGTH: 573
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in lab - CAG promoter in part Human betaherpesvirus 5

<400> SEQUENCE: 30

acttacggta aatggcccgc ctggctgacc gcccaacgac ccccgcccat tgacgtcaat 60

aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc aatgggtgga 120

gtatttacgg taaactgccc acttggcagt acatcaagtg tatcatatgc caagtacgcc 180

ccctattgac gtcaatgacg gtaaatggcc cgcctggcat tatgcccagt acatgacctt 240

atgggacttt cctacttggc agtacatcta cgtattagtc atcgctatta ccatggtcga 300

ggtgagcccc acgttctgct tcactctccc catctccccc ccctccccac ccccaatttt 360

gtatttattt atttttaat tattttgtgc agcgatgggg gcgggggggg gggggcgcg 420

cgccaggcgg ggcggggcgg ggcgaggggc ggggcggggc gaggcggaga ggtgcggcgg 480

cagccaatca gagcggcgcg ctccgaaagt ttccttttat ggcgaggcgg cggcggcggc 540

ggccctataa aaagcgaagc gcgcggcggg cgg 573

<210> SEQ ID NO 31
<211> LENGTH: 771
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - MHCK7 promoter

<400> SEQUENCE: 31

acccttcaga ttaaaaataa ctgaggtaag ggcctgggta ggggaggtgg tgtgagacgc 60

tcctgtctct cctctatctg cccatcggcc ctttggggag gaggaatgtg cccaaggact 120

aaaaaaaggc catggagcca gaggggcgag ggcaacagac ctttcatggg caaaccttgg 180

ggccctgctg tctagcatgc cccactacgg gtctaggctg cccatgtaag gaggcaaggc 240

ctggggacac ccgagatgcc tggttataat taacccagac atgtggctgc ccccccccc 300

ccaacacctg ctgcctctaa aaataaccct gtccctggtg gatcccctgc atgcgaagat 360

cttcgaacaa ggctgtgggg gactgagggc aggctgtaac aggcttgggg gccagggctt 420

atacgtgcct gggactccca aagtattact gttccatgtt cccggcgaag ggccagctgt 480

cccccgccag ctagactcag cacttagttt aggaaccagt gagcaagtca gcccttgggg 540

cagcccatac aaggccatgg ggctgggcaa gctgcacgcc tgggtccggg gtgggcacgg 600

tgcccgggca acgagctgaa agctcatctg ctctcagggg cccctccctg gggacagccc 660

ctcctggcta gtcacaccct gtaggctcct ctatataacc caggggcaca ggggctgccc 720

tcattctacc accacctcca cagcacagac agacactcag gagccagcca g 771

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<210> SEQ ID NO 32
<211> LENGTH: 544
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

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ggagcagcac ataactcttg ccctctgcct tccaagattc tggtgctgag acttatggag 120

tgtcttggag gttgccttct gccccccaac cctgctccca gctggccctc ccaggcctgg 180

gttgctggcc tctgctttat caggattctc aagagggaca gctggtttat gttgcatgac 240

tgttccctgc atatctgctc tggttttaaa tagcttatct gagcagctgg aggaccacat 300

gggcttatat ggcgtggggt acatgttcct gtagccttgt ccctggcacc tgccaaaata 360

gcagccaaca ccccccaccc ccaccgccat ccccctgccc cacccgtccc ctgtcgcaca 420

ttcctccctc cgcagggctg gctcaccagg ccccagccca catgcctgct taaagccctc 480

tccatcctct gcctcaccca gtccccgctg agactgagca gacgcctcca ggatctgtcg 540

gcag 544

<210> SEQ ID NO 33
<211> LENGTH: 502
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

ctcagtccat taggagccag tagcctggaa gatgtcttta cccccagcat cagttcaagt 60

ggagcagcac ataactcttg ccctctgcct tccaagattc tggtgctgag acttatggag 120

tgtcttggag gttgccttct gccccccaac cctgctccca gctggccctc ccaggcctgg 180

gttgctggcc tctgctttat caggattctc aagagggaca gctggtttat gttgcatgac 240

tgttccctgc atatctgctc tggttttaaa tagcttatct gagcagctgg aggaccacat 300

gggcttatat ggcgtggggt acatgttcct gtagccttgt ccctggcacc tgccaaaata 360

gcagccaaca ccccccaccc ccaccgccat ccccctgccc cacccgtccc ctgtcgcaca 420

ttcctccctc cgcagggctg gctcaccagg ccccagccca catgcctgct taaagccctc 480

tccatcctct gcctcaccca gt 502

<210> SEQ ID NO 34
<211> LENGTH: 5464
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 34

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ttcagtttcc atgccttgtt ctcacaatgc tggcctcccc agagctaatt tggactttgt 120

ttttatttca aaagggcctg aatgaggagt agatcttgtg ctacccagct ctaagggtgc 180

ccgtgaagcc ctcagacctg gagcctttgc aacagccctt taggtggaag cagaataaag 240

caattttcct taaagccaaa atcctgcctc tagactcttc ttctctgacc tcggtccctg 300

ggctctaggg tggggaggtg gggcttggaa gaagaaggtg gggaagtggc aaaagccgat 360

ccctagggcc ctgtgaagtt cggagccttc cctgtacagc actggctcat agatcctcct 420

ccagccaaac atagcaagaa gtgatacctc ctttgtgact tccccaggcc cagtacctgt 480

-continued

caggttgaaa caggatttag agaagcctct gaactcacct gaactctgaa gctcatccac 540

caagcaagca cctaggtgcc actgctagtt agtatcctac gctgataata tgcagagctg 600

ggccacagaa gtcctggggt gtaggaactg accagtgact tttcagtcgg caaaggtatg 660

acccccctcag cagatgtagt aatgtcccct tagatcccat cccaggcagg tctctaagag 720

gacatgggat gagagatgta gtcatgtggc attccaaaca cagctatcca cagtgtccct 780

tgccccttcc acttagccag gaggacagta accttagcct atctttcttc ctccccatcc 840

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tggcaagcca tctcaagaga aagcagacaa caggggggacc agattttgga aggatcagga 1020

actaaatcac tggcgggcct gggggtagaa aaaagagtga gtgagtccgc tccagctaag 1080

ccaagctagt ccccgagata ctctgccaca gctgggctgc tcggggtagc tttaggaatg 1140

tgggtctgaa agacaatggg attggaagac atctctttga gtctcccctc aaccccacct 1200

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aaacagcagg ggagggagaa cagagaacga aataaggaag gaagaaggaa aggccagtca 1380

atcagatgca gtcagaagag atgggaagcc aacacacagc ttgagcagag gaaacagaaa 1440

agggagagat tctgggcata aggaggccac agaaagaaga gcccaggccc cccaagtctc 1500

ctctttatac cctcatcccg tctcccaatt aagcccactc ttcttcctag atcagacctg 1560

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ccaggctgtg cacacagagg gtcgaggact ggtggtagag cctcaagata aggatgatgc 1740

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agatgtaaat catgaaagac agggagaagg gaagctggag agagtagaag gaccccgggg 1920

caagacattg aagcaaggac aagccaggtt gagcgctccg tgaaatcagc ctgctgaagg 1980

cagagccctg gtatgagcac cagaacagca gaggctaggg ttaatgtcga gacagggaac 2040

agaaggtaga cacaggaaca gacagagacg ggggagccag gtaacaaagg aatggtcctt 2100

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aactccttcc ttgttgcatc ttccatagga ggcagtggga actctgtgac caccatcccc 2340

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cagagcctgg cctttgtctc ttggacctga cccaagctga cccaatgttc tcagtacctt 2460

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tatccccaaa gagcaaccat ttggcatagg tggctgcaaa tgggaatgca aggttgaatc 2640

aggtcccttc aagaatactg catgcaagac ctaagacccc tggagagagg ggtatgctcc 2700

tgcccccacc caccataagg ggagtgaact atcctagggg gctggcgacc ttggggagac 2760

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ctgaacacaa tgtctactta gttataacag gcatgacctg ctaaagaccc aacatctacg 3000

acctctgaaa agacagcagc cctggaggac aggggttgtc tctgagcctt gggtgcttga 3060

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acttgggaag gggtcagtct gcagagcccc tatccatgga atctggagcc tggggccaac 3180

tggtgtaaat ctctgggcct gccaggcatt caaagcagca cctgcatcct ctggcagcct 3240

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cacctctggc cttccccctt cccacctccc atcaggagtg gagggttgca gagggagggt 3360

aaaaacctac atgtccaaac atcatggtgc acgatatatg gatcagtatg tgtagaggca 3420

agaaaggaaa tctgcaggct taactgggtt aatgtgtaaa gtctgtgtgc atgtgtgtgt 3480

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ctgcaggttt gtgtgtaaat tgcccaaggc aaagtgggtg aatcccttcc atggtttaaa 3600

gagattggat gatggcctgc atctcaagga ccatggaaaa tagaatggac actctatatg 3660

tgtctctaag ctaaggtagc aaggtctttg gaggacacct gtctagagat gtgggcaaca 3720

gagactacag acagtatctg tacagagtaa ggagagagag gagggggtgt agaattctct 3780

tactatcaaa gggaaactga gtcgtgcacc tgcaaagtgg atgctctccc tagacatcat 3840

gactttgtct ctggggagcc agcactgtgg aacttcaggt ctgagagagt aggaggctcc 3900

cctcagcctg aagctatgca gatagccagg gttgaaaggg ggaagggaga gcctgggatg 3960

ggagcttgtg tgttggaggc aggggacaga tattaagcct ggaagagaag gtgaccctta 4020

cccagttgtt caactcaccc ttcagattaa aaataactga ggtaagggcc tgggtagggg 4080

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cccctggctt gtcctgttcc atcctggtca ggatctctag attggtctcc cagcctctgc 5040

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cagctgcccg gcactcttag caaacctcag gcacccttac cccacataga cctctgacag 5280

agaagcaggc actttacatg gagtcctggt gggagagcca taggctacgg tgtaaaagag 5340

gcagggaagt ggtggtgtag gaaagtcagg acttcacata gaagcctagc ccacaccaga 5400

aatgacagac agatccctcc tatctccccc ataagagttt gagtcgaccc gcggccccga 5460

attg 5464

<210> SEQ ID NO 35
<211> LENGTH: 413
<212> TYPE: DNA
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 35

gggataaaag cagtctgggc tttcacatga cagcatctgg ggctgcggca gagggtcggg 60

tccgaagcgc tgccttatca gcgtccccag ccctgggagg tgacagctgg ctggcttgtg 120

tcagcccctc gggcactcac gtatctccgt ccgacgggtt taaaatagca aaactctgag 180

gccacacaat agcttgggct tatatgggct cctgtggggg aaggggggagc acggaggggg 240

ccggggccgc tgctgccaaa atagcagctc acaagtgttg cattcctctc tgggcgccgg 300

gcacattcct gctggctctg cccgccccgg ggtgggcgcc gggggggacct taaagcctct 360

gccccccaag gagcccttcc cagacagccg ccggcaccca ccgctccgtg gga 413

<210> SEQ ID NO 36
<211> LENGTH: 1090
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

ctctcagccc tggaagtcct tgctcacagc cgaggcgccg agagcgcttg ctctgcccag 60

atctgcgcga gtctggcgcc cgcgctctga acggcgtcgc tgcccagccc ccttccccgg 120

gaggtgggag cggccaccca gggccccgtg gctgcccttg taaggaggcg aggcccgagg 180

acacccgaga cgcccggtta taattaacca ggacacgtgg cgaacccccc tccaacacct 240

gcccccgaac ccccccatac ccagcgcctc gggtctcggc ctttgcggca gaggagacag 300

caaagcgccc tctaaaaata actcctttcc cggcgaccga gaccctccct gtcccccgca 360

cagcggaaat ctcccagtgg caccgagggg gcgagggtta agtgggggggg agggtgacca 420

ccgcctccca cccttgccct gagtttgaat ctctccaact cagccagcct cagtttcccc 480

tccactcagt ccctaggagg aaggggcgcc caagcgcggg tttctggggt tagactgccc 540

tccattgcaa ttggtccttc tcccggcctc tgcttcctcc agctcacagg gtatctgctc 600

ctcctggagc cacaccttgg ttccccgagg tgccgctggg actcgggtag gggtgagggc 660

ccaggggggca caggggggagc cgagggccac aggaagggct ggtggctgaa ggagactcag 720

gggccagggg acggtggctt ctacgtgctt gggacgttcc cagccaccgt cccatgttcc 780

cggcgggggg ccagctgtcc ccaccgccag cccaactcag cacttggtca gggtatcagc 840

ttggtggggg ggcgtgagcc cagcccctgg ggcggctcag cccatacaag gccatggggc 900

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ctcagctgcc ctccagaact cctccctggg gacaacccct cccagccaat agcacagcct 1020

aggtcccccc atataaggcc acggctgctg gcccttcctt tgggtcagtg tcacctccag 1080

gatacagaca 1090

<210> SEQ ID NO 37
<211> LENGTH: 253
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

gcccagcacc ccaaggcggc caacgccaaa actctccctc ctcctcttcc tcaatctcgc 60

tctcgctctt ttttttttcc gcaaaaggag gggagagggg gtaaaaaaat gctgcactgt 120

gcggcgaagc cggtgagtga gcggcgcggg gccaatcagc gtgcgccgtt ccgaaagttg 180

ccttttatgg ctcgagcggc cgcggcggcg ccctataaaa cccagcggcg cgacgcgcca 240

ccaccgccga gtc 253

<210> SEQ ID NO 38
<211> LENGTH: 281
<212> TYPE: DNA
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 38

ggtcgaggtg agccccacgt tctgcttcac tctccccatc tccccccccc ccccaccccc 60

aattttgtat ttatttattt tttaattatt ttgtgcagcg atgggggcgg gggggggggg 120

ggcgcgcgcc aggcggggcg gggcggggcg aggggcgggg cggggcgagg cggagaggtg 180

cggcggcagc caatcagagc ggcgcgctcc gaaagtttcc ttttatggcg aggcggcggc 240

ggcggcggcc ctataaaaag cgaagcgcgc ggcgggcggg a 281

<210> SEQ ID NO 39
<211> LENGTH: 220
<212> TYPE: DNA
<213> ORGANISM: Human betaherpesvirus 5

<400> SEQUENCE: 39

tggtgatgcg gttttggcag tacaccaatg ggcgtggata gcggtttgac tcacggggat 60

ttccaagtct ccaccccatt gacgtcaatg ggagtttgtt ttggcaccaa aatcaacggg 120

actttccaaa atgtcgtaat aaccccgccc cgttgacgca aatgggcggt aggcgtgtac 180

ggtgggaggt ctatataagc agagctcgtt tagtgaaccg 220

<210> SEQ ID NO 40
<211> LENGTH: 583
<212> TYPE: DNA
<213> ORGANISM: Human betaherpesvirus 5

<400> SEQUENCE: 40

tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata tggagttccg 60

cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc cccgcccatt 120

gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca 180

atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt atcatatgcc 240

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aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta 300

catgaccttа tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac 360

catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg actcacgggg 420

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg 480

ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg gtaggcgtgt 540

acggtgggag gtctatataa gcagagctgg tttagtgaac cgt 583

<210> SEQ ID NO 41
<211> LENGTH: 508
<212> TYPE: DNA
<213> ORGANISM: Human betaherpesvirus 5

<400> SEQUENCE: 41

cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc cccgcccatt 60

gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca 120

atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt atcatatgcc 180

aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta 240

catgaccttа tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac 300

catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg actcacgggg 360

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg 420

ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg gtaggcgtgt 480

acggtgggag gtctatataa gcagagct 508

<210> SEQ ID NO 42
<211> LENGTH: 573
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in lab - CAG promoter in part Human betaherpesvirus 5

<400> SEQUENCE: 42

acttacggta aatggcccgc ctggctgacc gcccaacgac ccccgcccat tgacgtcaat 60

aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc aatgggtgga 120

gtatttacgg taaactgccc acttggcagt acatcaagtg tatcatatgc caagtacgcc 180

ccctattgac gtcaatgacg gtaaatggcc cgcctggcat tatgcccagt acatgacctt 240

atgggacttt cctacttggc agtacatcta cgtattagtc atcgctatta ccatggtcga 300

ggtgagcccc acgttctgct tcactctccc catctccccc ccctccccac ccccaatttt 360

gtatttattt atttttaat tattttgtgc agcgatgggg gcgggggggg gggggcgcg 420

cgccaggcgg ggcggggcgg ggcgaggggc ggggcggggc gaggcggaga ggtgcggcgg 480

cagccaatca gagcggcgcg ctccgaaagt ttccttttat ggcgaggcgg cggcggcggc 540

ggccctataa aaagcgaagc gcgcggcggg cgg 573

<210> SEQ ID NO 43
<211> LENGTH: 580
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Made in lab - CAG promoter in part Human betaherpesvirus 5

<400> SEQUENCE: 43

cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc cccgcccatt 60

gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca 120

atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt atcatatgcc 180

aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta 240

catgacctta tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac 300

catgtcgagg tgagccccac gttctgcttc actctcccca tctccccccc ctccccaccc 360

ccaattttgt atttatttat tttttaatta ttttgtgcag cgatgggggc gggggggggg 420

ggggcgcgcg ccaggcgggg cggggcgggg cgaggggcgg ggcggggcga ggcggagagg 480

tgcggcggca gccaatcaga gcggcgcgct ccgaaagttt ccttttatgg cgaggcggcg 540

gcggcggcgg ccctataaaa agcgaagcgc gcggcgggcg 580

<210> SEQ ID NO 44
<211> LENGTH: 455
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

caacctttgg agctaagcca gcaatggtag agggaagatt ctgcacgtcc cttccaggcg 60

gcctccccgt caccaccccc cccaacccgc cccgaccgga gctgagagta attcatacaa 120

aaggactcgc ccctgccttg gggaatccca gggaccgtcg ttaaactccc actaacgtag 180

aacccagaga tcgctgcgtt cccgcccccc cacccgcccg ctctcgtcat cactgaggtg 240

gagaatagca tgcgtgaggc tccggtgccc gtcagtgggc agagcgcaca tcgcccacag 300

tccccgagaa gttgggggga ggggtcggca attgaacggg tgcctagaga aggtggcgcg 360

gggtaaactg ggaaagtgat gtcgtgtact ggctccgcct ttttcccgag ggtgggggag 420

aaccgtatat aagtgcagta gtcgccgtga acgtt 455

<210> SEQ ID NO 45

<400> SEQUENCE: 45

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<210> SEQ ID NO 46

<400> SEQUENCE: 46

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<210> SEQ ID NO 47

<400> SEQUENCE: 47

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<210> SEQ ID NO 48
<211> LENGTH: 281
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 48

acttgtggac aaagtttgct ctattccacc tcctccaggc cctccttggg tccatcaccc 60

caggggtgct gggtccatcc caccccccagg cccacacagg cttgcagtat tgtgtgcggt 120

atggtcaggg cgtccgagag caggtttcgc agtggaaggc aggcaggtgt tggggaggca 180

gttaccgggg caacgggaac agggcgtttt ggaggtggtt gccatgggga cctggatgct 240

gacgaaggct cgcgaggctg tgagcagcca cagtgccctg c 281

<210> SEQ ID NO 49

<400> SEQUENCE: 49

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<210> SEQ ID NO 50
<211> LENGTH: 293
<212> TYPE: DNA
<213> ORGANISM: Human betaherpesvirus 5

<400> SEQUENCE: 50

acttacggta aatggcccgc ctggctgacc gcccaacgac ccccgcccat tgacgtcaat 60

aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc aatgggtgga 120

gtatttacgg taaactgccc acttggcagt acatcaagtg tatcatatgc caagtacgcc 180

ccctattgac gtcaatgacg gtaaatggcc cgcctggcat tatgcccagt acatgacctt 240

atgggacttt cctacttggc agtacatcta cgtattagtc atcgctatta cca 293

<210> SEQ ID NO 51
<211> LENGTH: 953
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

cgcgtccgcc cgcgagcaca gagcctcgcc tttgccgatc cgccgcccgt ccacacccgc 60

cgccaggtaa gcccggccag ccgaccgggg catgcggccg cggcccttcg cccgtgcaga 120

gccgccgtct gggccgcagc ggggggcgca tggggcggaa ccggaccgcc gtgggggggcg 180

cgggagaagc ccctgggcct ccggagatgg gggacacccc acgccagttc gcaggcgcga 240

ggccgcgctc gggcgggcgc gctccggggg tgccgctctc ggggcggggg caaccggcgg 300

ggtctttgtc tgagccgggc tcttgccaat ggggatcgca cggtgggcgc ggcgtagccc 360

ccgtcaggcc cggtgggggc tggggcgcca tgcgcgtgcg cgctggtcct ttgggcgcta 420

actgcgtgcg cgctgggaat tggcgctaat tgcgcgtgcg cgctgggact caatggcgct 480

aatcgcgcgt gcgttctggg gcccgggcgc ttgcgccact tcctgcccga gccgctggcg 540

cccgagggtg tggccgctgc gtgcgcgcgc gcgacccggt cgctgtttga accgggcgga 600

ggcggggctg gcgcccggtt gggagggggt tggggcctgg cttcctgccg cgcgccgcgg 660

ggacgcctcc gaccagtgtt tgccttttat ggtaataacg cggccggccc ggcttccttt 720

gtccccaatc tgggcgcgcg ccggcgcccc ctggcggcct aaggactcgg cgcgccggaa 780

gtggccaggg cggcagcggc tgctcttggc ggccccgagg tgactatagc cttcttttgt 840

gtcttgatag ttcgccagcc tctgctaacc atgttcatgc cttcttcttt ttcctacagc 900

tcctgggcaa cgtgctggtt attgtgctgt ctcatcattt tggcaaagaa ttc 953

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<210> SEQ ID NO 52
<211> LENGTH: 1068
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - Chicken beta-actin exon/intron plus rabbit globin intron

<400> SEQUENCE: 52

gtcgctgcgc gctgccttcg ccccgtgccc cgctccgccg ccgcctcgcg ccgcccgccc 60

cggctctgac tgaccgcgtt actcccacag gtgagcgggc gggacggccc ttctcctccg 120

ggctgtaatt agcgcttggt ttaatgacgg cttgtttctt ttctgtggct gcgtgaaagc 180

cttgaggggc tccgggaggg ccctttgtgc gggggggagcg gctcgggggg tgcgtgcgtg 240

tgtgtgtgcg tggggagcgc cgcgtgcggc tccgcgctgc ccggcggctg tgagcgctgc 300

gggcgcggcg cggggctttg tgcgctccgc agtgtgcgcg aggggagcgc ggccgggggc 360

ggtgccccgc ggtgcggggg gggctgcgag gggaacaaag gctgcgtgcg gggtgtgtgc 420

gtgggggggt gagcaggggg tgtgggcgcg tcggtcgggc tgcaaccccc cctgcacccc 480

cctccccgag ttgctgagca cggcccggct tcgggtgcgg ggctccgtac ggggcgtggc 540

gcggggctcg ccgtgccggg cgggggggtgg cggcaggtgg gggtgccggg cggggcgggg 600

ccgcctcggg ccggggaggg ctcgggggag gggcgcggcg gcccccggag cgccggcggc 660

tgtcgaggcg cggcgagccg cagccattgc cttttatggt aatcgtgcga gagggcgcag 720

ggacttcctt tgtcccaaat ctgtgcggag ccgaaatctg ggaggcgccg ccgcaccccc 780

tctagcgggc gcggggcgaa gcggtgcggc gccggcagga aggaaatggg cggggagggc 840

cttcgtgcgt cgccgcgccg ccgtcccctt ctccctctcc agcctcgggg ctgtccgcgg 900

ggggacggct gccttcgggg gggacggggc agggcggggt tcggcttctg gcgtgtgacc 960

ggcggctcta gagcctctgc taaccatgtt catgccttct tctttttcct acagctcctg 1020

ggcaacgtgc tggttattgt gctgtctcat cattttggca aagaattc 1068

<210> SEQ ID NO 53
<211> LENGTH: 149
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - chimeric intron sequence

<400> SEQUENCE: 53

ggtaagttta gtctttttgt cttttatttc aggtcccgga tccggtggtg gtgcaaatca 60

aagaactgct cctcagtgga tgttgccttt acttctaggc ctgtacggaa gtgttacttc 120

tgctctaaaa gctgcggaat tgtacccgc 149

<210> SEQ ID NO 54
<211> LENGTH: 126
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

agtctgcggt gggcagcgga ggagtcgtgt cgtgcctgag agcgcagctg tgctcctggg 60

caccgcgcag tccgcccccg cggctcctgg ccagaccacc cctaggaccc cctgccccaa 120

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gtcgca 126

<210> SEQ ID NO 55
<211> LENGTH: 121
<212> TYPE: DNA
<213> ORGANISM: Human betaherpesvirus 5

<400> SEQUENCE: 55

tcagatcgcc tggagaggcc atccacgctg ttttgacctc catagtggac accgggaccg 60

atccagcctc cgcggccggg aacggtgcat tggaacgcgg attccccgtg ccaagagtga 120

c 121

<210> SEQ ID NO 56
<211> LENGTH: 512
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - adenovirus derived enhancer element

<400> SEQUENCE: 56

ctcactctct tccgcatcgc tgtctgcgag ggccagctgt tgggctcgcg gttgaggaca 60

aactcttcgc ggtctttcca gtactcttgg atcggaaacc cgtcggcctc cgaacggtac 120

tccgccaccg agggacctga gcgagtccgc atcgaccgga tcggaaaacc tctcgagaaa 180

ggcgtctaac cagtcacagt cgcaaggtag gctgagcacc gtggcgggcg gcagcgggtg 240

gcggtcgggg ttgtttctgg cggaggtgct gctgatgatg taattaaagt aggcggtctt 300

gagacggcgg atggtcgagg tgaggtgtgg caggcttgag atccagctgt tggggtgagt 360

actccctctc aaaagcgggc attacttctg cgctaagatt gtcagtttcc aaaaacgagg 420

aggatttgat attcacctgg cccgatctgg ccatacactt gagtgacaat gacatccact 480

ttgcctttct ctccacaggt gtccactccc ag 512

<210> SEQ ID NO 57
<211> LENGTH: 956
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

ctttttcgca acgggtttgc cgccagaaca caggtaagtg ccgtgtgtgg ttcccgcggg 60

cctggcctct ttacgggtta tggcccttgc gtgccttgaa ttacttccac ctggctccag 120

tacgtgattc ttgatcccga gctggagcca ggggcgggcc ttgcgcttta ggagcccctt 180

cgcctcgtgc ttgagttgag gcctggcctg ggcgctgggg ccgccgcgtg cgaatctggt 240

ggcaccttcg cgcctgtctc gctgctttcg ataagtctct agccatttaa aatttttgat 300

gacgtgctgc gacgcttttt ttctggcaag atagtcttgt aaatgcgggc caggatctgc 360

acactggtat ttcggttttt gggcccgcgg ccggcgacgg ggcccgtgcg tcccagcgca 420

catgttcggc gaggcggggc ctgcgagcgc ggccaccgag aatcggacgg gggtagtctc 480

aagctggccg gcctgctctg gtgcctggcc tcgcgccgcc gtgtatcgcc ccgccctggg 540

cggcaaggct ggcccggtcg gcaccagttg cgtgagcgga aagatggccg cttcccggcc 600

ctgctccagg gggctcaaaa tggaggacgc ggcgctcggg agagcgggcg ggtgagtcac 660

ccacacaaag gaaaagggcc tttccgtcct cagccgtcgc ttcatgtgac tccacggagt 720

-continued

accgggcgcc gtccaggcac ctcgattagt tctggagctt ttggagtacg tcgtctttag 780

gttgggggga ggggttttat gcgatggagt ttccccacac tgagtgggtg gagactgaag 840

ttaggccagc ttggcacttg atgtaattct ccttggaatt tggccttttt gagtttggat 900

cttggttcat tctcaagcct cagacagtgg ttcaaagttt ttttcttcca tttcag 956

<210> SEQ ID NO 58
<211> LENGTH: 939
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

gtaagtgccg tgtgtggttc ccgcgggcct ggcctcttta cgggttatgg cccttgcgtg 60

ccttgaatta cttccacctg gctgcagtac gtgattcttg atcccgagct tcgggttgga 120

agtgggtggg agagttcgag gccttgcgct taaggagccc cttcgcctcg tgcttgagtt 180

gaggcctggc ctgggcgctg gggccgccgc gtgcgaatct ggtggcacct tcgcgcctgt 240

ctcgctgctt tcgataagtc tctagccatt taaaattttt gatgacctgc tgcgacgctt 300

tttttctggc aagatagtct tgtaaatgcg ggccaagatc tgcacactgg tatttcggtt 360

tttggggccg cgggcggcga cggggcccgt gcgtcccagc gcacatgttc ggcgaggcgg 420

ggcctgcgag cgcggccacc gagaatcgga cgggggtagt ctcaagctgg ccggcctgct 480

ctggtgcctg gcctcgcgcc gccgtgtatc gccccgccct gggcggcaag gctggcccgg 540

tcggcaccag ttgcgtgagc ggaaagatgg ccgcttcccg gccctgctgc agggagctca 600

aaatggagga cgcggcgctc gggagagcgg gcgggtgagt cacccacaca aaggaaaagg 660

gcctttccgt cctcagccgt cgcttcatgt gactccacgg agtaccgggc gccgtccagg 720

cacctcgatt agttctcgag cttttggagt acgtcgtctt taggttgggg ggaggggttt 780

tatgcgatgg agtttcccca cactgagtgg gtggagactg aagttaggcc agcttggcac 840

ttgatgtaat tctccttgga atttgccctt tttgagtttg gatcttggtt cattctcaag 900

cctcagacag tggttcaaag ttttttttctt ccatttcag 939

<210> SEQ ID NO 59
<211> LENGTH: 83
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

tcagaagccc cgggctcgtc agtcaaaccg gttctctgtt tgcactcggc agcacgggca 60

ggcaagtggt ccctaggttc ggg 83

<210> SEQ ID NO 60
<211> LENGTH: 476
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

gtgagtctat gggacccttg atgttttctt tccccttctt ttctatggtt aagttcatgt 60

cataggaagg ggagaagtaa cagggtacac atattgacca aatcagggta attttgcatt 120

tgtaatttta aaaaatgctt tcttctttta atatactttt ttgtttatct tatttctaat 180

actttcccta atctctttct ttcagggcaa taatgataca atgtatcatg cctctttgca 240

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ccattctaaa gaataacagt gataatttct gggttaaggc aatagcaata tttctgcata 300

taaatatttc tgcatataaa ttgtaactga tgtaagaggt ttcatattgc taatagcagc 360

tacaatccag ctaccattct gcttttattt tatggttggg ataaggctgg attattctga 420

gtccaagcta ggccctttg ctaatcatgt tcatacctct tatcttcctc ccacag 476

<210> SEQ ID NO 61
<211> LENGTH: 196
<212> TYPE: DNA
<213> ORGANISM: simian virus 40

<400> SEQUENCE: 61

tctagaggat ccggtactcg aggaactgaa aaaccagaaa gttaactggt aagtttagtc 60

tttttgtctt ttatttcagg tcccggatcc ggtggtggtg caaatcaaag aactgctcct 120

cagtggatgt tgcctttact tctaggcctg tacggaagtg ttacttctgc tctaaaagct 180

gcggaattgt acccgc 196

<210> SEQ ID NO 62
<211> LENGTH: 589
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - mutated woodchuck hepatitis regulatory element

<400> SEQUENCE: 62

aatcaacctc tggattacaa aatttgtgaa agattgactg gtattcttaa ctatgttgct 60

ccttttacgc tatgtggata cgctgcttta atgcctttgt atcatgctat tgcttcccgt 120

atggctttca ttttctcctc cttgtataaa tcctggttgc tgtctcttta tgaggagttg 180

tggcccgttg tcaggcaacg tggcgtggtg tgcactgtgt ttgctgacgc aacccccact 240

ggttggggca ttgccaccac ctgtcagctc ctttccggga ctttcgcttt ccccctccct 300

attgccacgg cggaactcat cgccgcctgc cttgcccgct gctggacagg ggctcggctg 360

ttgggcactg acaattccgt ggtgttgtcg gggaaatcat cgtcctttcc ttggctgctc 420

gcctgtgttg ccacctggat tctgcgcggg acgtccttct gctacgtccc ttcggccctc 480

aatccagcgg accttccttc ccgcggcctg ctgccggctc tgcggcctct tccgcgtctt 540

cgccttcgcc ctcagacgag tcggatctcc ctttgggccg cctccccgc 589

<210> SEQ ID NO 63
<211> LENGTH: 588
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - mutated woodchuck hepatitis regulatory element

<400> SEQUENCE: 63

tcaacctctg gattacaaaa tttgtgaaag attgactggt attcttaact atgttgctcc 60

ttttacgcta tgtggatacg ctgctttaat gcctttgtat catgctattg cttcccgtat 120

ggctttcatt ttctcctcct tgtataaatc ctggttgctg tctctttatg aggagttgtg 180

gcccgttgtc aggcaacgtg gcgtggtgtg cactgtgttt gctgacgcaa cccccactgg 240

ttggggcatt gccaccacct gtcagctcct ttccgggact ttcgctttcc ccctccctat 300

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tgccacggcg gaactcatcg ccgcctgcct tgcccgctgc tggacagggg ctcggctgtt 360

gggcactgac aattccgtgg tgttgtcggg gaaatcatcg tcctttcctt ggctgctcgc 420

ctgtgttgcc acctggattc tgcgcgggac gtccttctgc tacgtccctt cggccctcaa 480

tccagcggac cttccttccc gcggcctgct gccggctctg cggcctcttc cgcgtcttcg 540

ccttcgccct cagacgagtc ggatctccct ttgggccgcc tccccgca 588

<210> SEQ ID NO 64
<211> LENGTH: 755
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - mutated woodchuck hepatitis regulatory element

<400> SEQUENCE: 64

ttcctgttaa tcaacctctg gattacaaaa tttgtgaaag attgactggt attcttaact 60

atgttgctcc ttttacgcta tgtggatacg ctgctttaat gcctttgtat catgctattg 120

cttcccgtat ggctttcatt ttctcctcct tgtataaatc ctggttgctg tctctttatg 180

aggagttgtg gcccgttgtc aggcaacgtg gcgtggtgtg cactgtgttt gctgacgcaa 240

cccccactgg ttggggcatt gccaccacct gtcagctcct ttccgggact ttcgctttcc 300

ccctccctat tgccacggcg gaactcatcg ccgcctgcct tgcccgctgc tggacagggg 360

ctcggctgtt gggcactgac aattccgtgg tgttgtcggg gaagctgacg tcctttccgc 420

ggctgctcgc ctgtgttgcc acctggattc tgcgcgggac gtccttctgc tacgtccctt 480

cggccctcaa tccagcggac cttccttccc gcggcctgct gccggctctg cggcctcttc 540

cgcctcttcg ccttcgccct cagacgagtc ggatctccct ttgggccgcc tccccgccca 600

tgtatctttt tcacctgtgc cttgtttttg cctgtgttcc gcgtcctact tttcaagcct 660

ccaagctgtg ccttgggcgg ctttggggca tggacataga tccctataaa gaatttggtt 720

catcttatca gttgttgaat tttcttcctt tggac 755

<210> SEQ ID NO 65
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CAAX motif

<400> SEQUENCE: 65

tgtgtgataa tg 12

<210> SEQ ID NO 66
<211> LENGTH: 810
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

ctgttctcat cacatcatat caaggttata taccatcaat attgccacag atgttactta 60

gccttttaat atttctctaa tttagtgtat atgcaatgat agttctctga tttctgagat 120

tgagtttctc atgtgtaatg attatttaga gtttctcttt catctgttca aatttttgtc 180

tagttttatt ttttactgat ttgtaagact tctttttata atctgcatat tacaattctc 240

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tttactgggg tgttgcaaat attttctgtc attctatggc ctgacttttc ttaatggttt 300

tttaatttta aaaataagtc ttaatattca tgcaatctaa ttaacaatct tttctttgtg 360

gttaggactt tgagtcataa gaaatttttc tctacactga agtcatgatg gcatgcttct 420

atattatttt ctaaaagatt taaagttttg ccttctccat ttagacttat aattcactgg 480

aatttttttg tgtgtatggt atgacatatg ggttcccttt tatttttttac atataaatat 540

atttccctgt ttttctaaaa aagaaaaaga tcatcatttt cccattgtaa aatgccatat 600

ttttttcata ggtcacttac atatatcaat gggtctgttt ctgagctcta ctctatttta 660

tcagcctcac tgtctatccc cacacatctc atgctttgct ctaaatcttg atatttagtg 720

gaacattctt tcccattttg ttctacaaga atatttttgt tattgtcttt gggctttcta 780

tatacatttt gaaatgaggt tgacaagtta 810

<210> SEQ ID NO 67
<211> LENGTH: 726
<212> TYPE: DNA
<213> ORGANISM: Hepatitis B virus

<400> SEQUENCE: 67

ataacaggcc tattgattgg aaagtttgtc aacgaattgt gggtcttttg gggtttgctg 60

ccccttttac gcaatgtgga tatcctgctt taatgccttt atatgcatgt atacaagcaa 120

aacaggcttt tactttctcg ccaacttaca aggcctttct cagtaaacag tatatgaccc 180

tttaccccgt tgctcggcaa cggcctggtc tgtgccaagt gtttgctgac gcaaccccca 240

ctggttgggg cttggccata ggccatcagc gcatgcgtgg aacctttgtg tctcctctgc 300

cgatccatac tgcggaactc ctagccgctt gttttgctcg cagcaggtct ggagcaaacc 360

tcatcgggac cgacaattct gtcgtactct cccgcaagta tacatcgttt ccatggctgc 420

taggctgtgc tgccaactgg atcctgcgcg ggacgtcctt tgtttacgtc ccgtcggcgc 480

tgaatcccgc ggacgacccc tcccggggcc gcttggggct ctaccgcccg cttctccgtc 540

tgccgtaccg tccgaccacg gggcgcacct ctctttacgc ggactccccg tctgtgcctt 600

ctcatctgcc ggaccgtgtg cacttcgctt cacctctgca cgtcgcatgg aggccaccgt 660

gaacgcccac cggaacctgc ccaaggtctt gcataagagg actcttggac tttcagcaat 720

gtcatc 726

<210> SEQ ID NO 68
<211> LENGTH: 755
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - HepB derived enhancer element

<400> SEQUENCE: 68

ttcctgtaaa caggcctatt gattggaaag tttgtcaacg aattgtgggt cttttggggt 60

ttgctgcccc ttttacgcaa tgtggatatc ctgctttaat gcctttatat gcatgtatac 120

aagcaaaaca ggcttttact ttctcgccaa cttacaaggc ctttctcagt aaacagtata 180

tgacccttta ccccgttgct cggcaacggc ctggtctgtg ccaagtgttt gctgacgcaa 240

cccccactgg ttggggcttg gccataggcc atcagcgcat gcgtggaacc tttgtgtctc 300

ctctgccgat ccatactgcg gaactcctag ccgcttgttt tgctcgcagc tggactggag 360

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caaacctcat cgggaccgac aattctgtcg tactctcccg caagcactca ccgtttccgc 420

ggctgctcgc ctgtgttgcc acctggattc tgcgcgggac gtccttctgc tacgtccctt 480

cggccctcaa tccagcggac cttccttccc gcggcctgct gccggctctg cggcctcttc 540

cgcctcttcg ccttcgccct cagacgagtc ggatctccct ttgggccgcc tccccgccca 600

tgtatctttt tcacctgtgc cttgtttttg cctgtgttcc gcgtcctact tttcaagcct 660

ccaagctgtg ccttgggcgg ctttggggca tggacataga tccctataaa gaatttggtt 720

catcttatca gttgttgaat tttcttcctt tggac 755

<210> SEQ ID NO 69
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

gctggagcct cggtagccgt tcctcctgcc cgctgggcct cccaacgggc cctcctcccc 60

tccttgcacc ggcccttcct ggtctttgaa taaa 94

<210> SEQ ID NO 70
<211> LENGTH: 596
<212> TYPE: DNA
<213> ORGANISM: Woodchuck hepatitis virus

<400> SEQUENCE: 70

attcgagcat cttaccgcca tttattccca tatttgttct gtttttcttg atttgggtat 60

acatttaaat gttaataaaa caaaatggtg gggcaatcat ttacattttt agggatatgt 120

aattactagt tcaggtgtat tgccacaaga caaacatgtt aagaaacttt cccgttattt 180

acgctctgtt cctgttaatc aacctctgga ttacaaaatt tgtgaaagat tgactgatat 240

tcttaactat gttgctcctt ttacgctgtg tggatatgct gctttaatgc ctctgtatca 300

tgctattgct tcccgtacgg ctttcgtttt ctcctccttg tataaatcct ggttgctgtc 360

tctttatgag gagttgtggc ccgttgtccg tcaacgtggc gtggtgtgct ctgtgtttgc 420

tgacgcaacc cccactggct ggggcattgc caccacctgt caactccttt ctgggacttt 480

cgctttcccc ctcccgatcg ccacggcaga actcatcgcc gcctgccttg cccgctgctg 540

gacaggggct aggttgctgg gcactgataa ttccgtggtg ttgtcgggga agggcc 596

<210> SEQ ID NO 71
<211> LENGTH: 387
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 71

tggctaataa aggaaattta ttttcattgc aatagtgtgt tggaattttt tgtgtctctc 60

actcggaaga acatatggga gggcaaatca tttaaaacat cagaatgagt atttggttta 120

gagtttggca acatatgccc atatgctggc tgccatgaac aaaggttggc tataaagagg 180

tcatcagtat atgaaacagc cccctgctgt ccattcctta ttccatagaa aagccttgac 240

ttgaggttag atttttttta tattttgttt tgtgttattt ttttctttaa catccctaaa 300

attttcctta catgttttac tagccagatt tttcctcctc tcctgactac tcccagtcat 360

agctgtccct cttctcttat ggagatc 387

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<210> SEQ ID NO 72
<211> LENGTH: 251
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 72

ttgccagcca tctgttgttt gcccctcccc cgtgccttcc ttgaccctgg aaggtgccac 60

tcccactgtc ctttcctaat aaaatgagga aattgcatcg cattgtctga gtaggtgtca 120

ttctattctg gggggtgggg tggggcagga cagcaagggg gaggattggg aatacaatag 180

caggcatgct ggggatgcgg tgggctctat gggtacccag gtgctgaaga attgacccgg 240

ttcctcctgg g 251

<210> SEQ ID NO 73
<211> LENGTH: 251
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 73

ttgccagcca tctgttgttt gcccctcccc cgtgccttcc ttgaccctgg aaggtgccac 60

tcccactgtc ctttcctaat aaaatgagga aattgcatcg cattgtctga gtaggtgtca 120

ttctattctg gggggtgggg tggggcagga cagcaagggg gaggattggg aagacaatag 180

caggcatgct ggggatgcgg tgggctctat gggtacccag gtgctgaaga attgacccgg 240

ttcctcctgg g 251

<210> SEQ ID NO 74
<211> LENGTH: 225
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

<400> SEQUENCE: 74

ctgtgccttc tagttgccag ccatctgttg tttgcccctc ccccgtgcct tccttgaccc 60

tggaaggtgc cactcccact gtcctttcct aataaaatga ggaaattgca tcgcattgtc 120

tgagtaggtg tcattctatt ctgggggggtg gggtggggca ggacagcaag ggggaggatt 180

gggaagacaa tagcaggcat gctggggatg cggtgggctc tatgg 225

<210> SEQ ID NO 75
<211> LENGTH: 202
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

ctgcccgggt ggcatccctg tgacccctcc ccagtgcctc tcctggccct ggaagttgcc 60

actccagtgc ccaccagcct tgtcctaata aaattaagtt gcatcatttt gtctgactag 120

gtgtccttct ataatattat ggggtggagg ggggtggtat ggagcaaggg gcccaagttg 180

ggaagaaacc tgtagggcct gc 202

<210> SEQ ID NO 76
<211> LENGTH: 735
<212> TYPE: PRT
<213> ORGANISM: Adeno-associated virus 2

<400> SEQUENCE: 76

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Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Thr Leu Ser
1               5                  10                  15

Glu Gly Ile Arg Gln Trp Trp Lys Leu Lys Pro Gly Pro Pro Pro Pro
            20                  25                  30

Lys Pro Ala Glu Arg His Lys Asp Asp Ser Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Glu Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Arg Gln Leu Asp Ser Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Pro Val Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu His Ser Pro Val Glu Pro Asp Ser Ser Ser Gly Thr Gly
145                 150                 155                 160

Lys Ala Gly Gln Gln Pro Ala Arg Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Ala Asp Ser Val Pro Asp Pro Gln Pro Leu Gly Gln Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Leu Gly Thr Asn Thr Met Ala Thr Gly Ser Gly
        195                 200                 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Met Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Ser Gln Ser Gly Ala Ser Asn Asp Asn His Tyr
            260                 265                 270

Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe His
        275                 280                 285

Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn Trp
    290                 295                 300

Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln Val
305                 310                 315                 320

Lys Glu Val Thr Gln Asn Asp Gly Thr Thr Thr Ile Ala Asn Asn Leu
                325                 330                 335

Thr Ser Thr Val Gln Val Phe Thr Asp Ser Glu Tyr Gln Leu Pro Tyr
            340                 345                 350

Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala Asp
        355                 360                 365

Val Phe Met Val Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly Ser
    370                 375                 380

Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro Ser
385                 390                 395                 400

Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe Glu
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               405                 410                 415

Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg
           420                 425                 430

Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr
       435                 440                 445

Asn Thr Pro Ser Gly Thr Thr Thr Gln Ser Arg Leu Gln Phe Ser Gln
   450                 455                 460

Ala Gly Ala Ser Asp Ile Arg Asp Gln Ser Arg Asn Trp Leu Pro Gly
465                 470                 475                 480

Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Ser Ala Asp Asn Asn
               485                 490                 495

Asn Ser Glu Tyr Ser Trp Thr Gly Ala Thr Lys Tyr His Leu Asn Gly
           500                 505                 510

Arg Asp Ser Leu Val Asn Pro Gly Pro Ala Met Ala Ser His Lys Asp
       515                 520                 525

Asp Glu Glu Lys Phe Phe Pro Gln Ser Gly Val Leu Ile Phe Gly Lys
   530                 535                 540

Gln Gly Ser Glu Lys Thr Asn Val Asp Ile Glu Lys Val Met Ile Thr
545                 550                 555                 560

Asp Glu Glu Glu Ile Arg Thr Thr Asn Pro Val Ala Thr Glu Gln Tyr
               565                 570                 575

Gly Ser Val Ser Thr Asn Leu Gln Arg Gly Asn Arg Gln Ala Ala Thr
           580                 585                 590

Ala Asp Val Asn Thr Gln Gly Val Leu Pro Gly Met Val Trp Gln Asp
       595                 600                 605

Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr
   610                 615                 620

Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys
625                 630                 635                 640

His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asn
               645                 650                 655

Pro Ser Thr Thr Phe Ser Ala Ala Lys Phe Ala Ser Phe Ile Thr Gln
           660                 665                 670

Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys
       675                 680                 685

Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn Tyr
   690                 695                 700

Asn Lys Ser Val Asn Val Asp Phe Thr Val Asp Thr Asn Gly Val Tyr
705                 710                 715                 720

Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
               725                 730                 735


<210> SEQ ID NO 77
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Adeno-associated virus 9

<400> SEQUENCE: 77

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30
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Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
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        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 78
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Adeno-associated virus 6

<400> SEQUENCE: 78

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
            20                  25                  30

Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60
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Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
        115                 120                 125

Phe Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
145                 150                 155                 160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
            180                 185                 190

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
            260                 265                 270

Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
        275                 280                 285

His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
    290                 295                 300

Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
305                 310                 315                 320

Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
                325                 330                 335

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro
            340                 345                 350

Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala
        355                 360                 365

Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly
    370                 375                 380

Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro
385                 390                 395                 400

Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe
                405                 410                 415

Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp
            420                 425                 430

Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg
        435                 440                 445

Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser
    450                 455                 460

Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
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465                 470                 475                 480

Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn
                485                 490                 495

Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn
            500                 505                 510

Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
        515                 520                 525

Asp Asp Lys Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly
    530                 535                 540

Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile
545                 550                 555                 560

Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg
                565                 570                 575

Phe Gly Thr Val Ala Val Asn Leu Gln Ser Ser Ser Thr Asp Pro Ala
            580                 585                 590

Thr Gly Asp Val His Val Met Gly Ala Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu
705                 710                 715                 720

Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
                725                 730                 735


<210> SEQ ID NO 79
<211> LENGTH: 738
<212> TYPE: PRT
<213> ORGANISM: Non-human primate Adeno-associated virus

<400> SEQUENCE: 79

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
            20                  25                  30

Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
                85                  90                  95
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Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Pro Ser Pro Gln Arg Ser Pro Asp Ser Ser Thr Gly Ile
145                 150                 155                 160

Gly Lys Lys Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln
                165                 170                 175

Thr Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro
            180                 185                 190

Pro Ala Gly Pro Ser Gly Leu Gly Ser Gly Thr Met Ala Ala Gly Gly
        195                 200                 205

Gly Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser
    210                 215                 220

Ser Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val
225                 230                 235                 240

Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His
                245                 250                 255

Leu Tyr Lys Gln Ile Ser Asn Gly Thr Ser Gly Gly Ser Thr Asn Asp
            260                 265                 270

Asn Thr Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn
        275                 280                 285

Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn
    290                 295                 300

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn
305                 310                 315                 320

Ile Gln Val Lys Glu Val Thr Gln Asn Glu Gly Thr Lys Thr Ile Ala
                325                 330                 335

Asn Asn Leu Thr Ser Thr Ile Gln Val Phe Thr Asp Ser Glu Tyr Gln
            340                 345                 350

Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe
        355                 360                 365

Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn
    370                 375                 380

Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr
385                 390                 395                 400

Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Glu Phe Ser Tyr
                405                 410                 415

Gln Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser
            420                 425                 430

Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu
        435                 440                 445

Ser Arg Thr Gln Ser Thr Gly Gly Thr Ala Gly Thr Gln Gln Leu Leu
    450                 455                 460

Phe Ser Gln Ala Gly Pro Asn Asn Met Ser Ala Gln Ala Lys Asn Trp
465                 470                 475                 480

Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser
                485                 490                 495

Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His
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            500                 505                 510

Leu Asn Gly Arg Asp Ser Leu Val Asn Pro Gly Val Ala Met Ala Thr
        515                 520                 525

His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met
    530                 535                 540

Phe Gly Lys Gln Gly Ala Gly Lys Asp Asn Val Asp Tyr Ser Ser Val
545                 550                 555                 560

Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr
                565                 570                 575

Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln Gln Gln Asn Ala Ala
            580                 585                 590

Pro Ile Val Gly Ala Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val
        595                 600                 605

Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile
    610                 615                 620

Pro His Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe
625                 630                 635                 640

Gly Leu Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val
                645                 650                 655

Pro Ala Asp Pro Pro Thr Thr Phe Ser Gln Ala Lys Leu Ala Ser Phe
            660                 665                 670

Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu
        675                 680                 685

Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr
    690                 695                 700

Ser Asn Tyr Tyr Lys Ser Thr Asn Val Asp Phe Ala Val Asn Thr Asp
705                 710                 715                 720

Gly Thr Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg
                725                 730                 735

Asn Leu


<210> SEQ ID NO 80
<211> LENGTH: 2217
<212> TYPE: DNA
<213> ORGANISM: Non-human primate adeno-associated virus

<400> SEQUENCE: 80

atggctgccg atggttatct tccagattgg ctcgaggaca acctctctga gggcattcgc     60

gagtggtggg acctgaaacc tggagccccg aaacccaaag ccaaccagca aaagcaggac    120

aacggccggg gtctggtgct tcctggctac aagtacctcg gacccttcaa cggactcgac    180

aagggggagc ccgtcaacgc ggcggacgca gcggccctcg agcacgacaa ggcctacgac    240

cagcagctcc aagcgggtga caatccgtac ctgcggtata atcacgccga cgccgagttt    300

caggagcgtc tgcaagaaga tacgtctttt gggggcaacc tcgggcgcgc agtcttccag    360

gccaaaaagc gggttctcga acctctgggc ctggttgaat cgccggttaa gacggctcct    420

ggaaagaaga gaccggtaga gccatcaccc cagcgctctc cagactcctc tacgggcatc    480

ggcaagaaag gccagcagcc cgcaaaaaag agactcaatt ttgggcagac tggcgactca    540

gagtcagtcc ccgaccctca accaatcgga gaaccaccag caggcccctc tggtctggga    600

tctggtacaa tggctgcagg cggtggcgct ccaatggcag acaataacga aggcgccgac    660
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ggagtgggta gttcctcagg aaattggcat tgcgattcca catggctggg cgacagagtc    720

atcaccacca gcacccgcac ctgggccctg cccacctaca acaaccacct ctacaagcaa    780

atctccaacg ggacctcggg aggaagcacc aacgacaaca cctacttcgg ctacagcacc    840

ccctgggggt attttgactt caacagattc cactgccact tttcaccacg tgactggcag    900

cgactcatca acaacaactg gggattccgg cccaagaggc tcaacttcaa gctcttcaac    960

atccaagtca aggaggtcac gcagaatgaa ggcaccaaga ccatcgccaa taaccttacc   1020

agcacgattc aggtctttac ggactcggaa taccagctcc cgtacgtgct cggctcggcg   1080

caccagggct gcctgcctcc gttcccggcg gacgtcttca tgattcctca gtacgggtac   1140

ctgactctga acaatggcag tcaggctgtg ggccggtcgt ccttctactg cctggagtac   1200

tttccttctc aaatgctgag aacgggcaac aactttgaat tcagctacaa cttcgaggac   1260

gtgcccttcc acagcagcta cgcgcacagc cagagcctgg accggctgat gaaccctctc   1320

atcgaccagt acttgtacta cctgtcccgg actcaaagca cgggcggtac tgcaggaact   1380

cagcagttgc tattttctca ggccgggcct aacaacatgt cggctcaggc caagaactgg   1440

ctacccggtc cctgctaccg gcagcaacgc gtctccacga cactgtcgca gaacaacaac   1500

agcaactttg cctggacggg tgccaccaag tatcatctga atggcagaga ctctctggtg   1560

aatcctggcg ttgccatggc tacccacaag gacgacgaag agcgattttt tccatccagc   1620

ggagtcttaa tgtttgggaa acagggagct ggaaaagaca acgtggacta tagcagcgtg   1680

atgctaacca gcgaggaaga aataaagacc accaacccag tggccacaga acagtacggc   1740

gtggtggccg ataacctgca acagcaaaac gccgctccta ttgtaggggc cgtcaatagt   1800

caaggagcct tacctggcat ggtgtggcag aaccgggacg tgtacctgca gggtcccatc   1860

tgggccaaga ttcctcatac ggacggcaac tttcatccct cgccgctgat gggaggcttt   1920

ggactgaagc atccgcctcc tcagatcctg attaaaaaca cacctgttcc cgcggatcct   1980

ccgaccacct tcaatcaggc caagctggct tctttcatca cgcagtacag taccggccag   2040

gtcagcgtgg agatcgagtg ggagctgcag aaggagaaca gcaaacgctg gaacccagag   2100

attcagtaca cttccaacta ctacaaatct acaaatgtgg actttgctgt caatactgag   2160

ggtacttatt ccgagcctcg ccccattggc acccgttacc tcacccgtaa tctgtaa      2217
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<210> SEQ ID NO 81
<211> LENGTH: 535
<212> TYPE: PRT
<213> ORGANISM: Non-human primate adeno-associated virus

<400> SEQUENCE: 81

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Met Ala Ala Gly Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly Ala
1               5                  10                  15

Asp Gly Val Gly Ser Ser Ser Gly Asn Trp His Cys Asp Ser Thr Trp
            20                  25                  30

Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro
        35                  40                  45

Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Asn Gly Thr Ser Gly
    50                  55                  60

Gly Ser Thr Asn Asp Asn Thr Tyr Phe Gly Tyr Ser Thr Pro Trp Gly
65                  70                  75                  80

Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp
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                85                  90                  95

Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn
            100                 105                 110

Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Gln Asn Glu Gly
        115                 120                 125

Thr Lys Thr Ile Ala Asn Asn Leu Thr Ser Thr Ile Gln Val Phe Thr
    130                 135                 140

Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly
145                 150                 155                 160

Cys Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly
                165                 170                 175

Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe
            180                 185                 190

Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn
        195                 200                 205

Phe Glu Phe Ser Tyr Asn Phe Glu Asp Val Pro Phe His Ser Ser Tyr
    210                 215                 220

Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
225                 230                 235                 240

Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln Ser Thr Gly Gly Thr Ala Gly
                245                 250                 255

Thr Gln Gln Leu Leu Phe Ser Gln Ala Gly Pro Asn Asn Met Ser Ala
            260                 265                 270

Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val
        275                 280                 285

Ser Thr Thr Leu Ser Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Gly
    290                 295                 300

Ala Thr Lys Tyr His Leu Asn Gly Arg Asp Ser Leu Val Asn Pro Gly
305                 310                 315                 320

Val Ala Met Ala Thr His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser
                325                 330                 335

Ser Gly Val Leu Met Phe Gly Lys Gln Gly Ala Gly Lys Asp Asn Val
            340                 345                 350

Asp Tyr Ser Ser Val Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr
        355                 360                 365

Asn Pro Val Ala Thr Glu Gln Tyr Gly Val Val Ala Asp Asn Leu Gln
    370                 375                 380

Gln Gln Asn Ala Ala Pro Ile Val Gly Ala Val Asn Ser Gln Gly Ala
385                 390                 395                 400

Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly Pro
                405                 410                 415

Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser Pro
            420                 425                 430

Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro Pro Gln Ile Leu Ile
        435                 440                 445

Lys Asn Thr Pro Val Pro Ala Asp Pro Pro Thr Thr Phe Asn Gln Ala
    450                 455                 460

Lys Leu Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val
465                 470                 475                 480

Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro
                485                 490                 495
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Glu Ile Gln Tyr Thr Ser Asn Tyr Tyr Lys Ser Thr Asn Val Asp Phe
            500                 505                 510

Ala Val Asn Thr Glu Gly Thr Tyr Ser Glu Pro Arg Pro Ile Gly Thr
        515                 520                 525

Arg Tyr Leu Thr Arg Asn Leu
    530                 535


<210> SEQ ID NO 82
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Non-human primate adeno-associated virus

<400> SEQUENCE: 82

Ser Thr Ile Gln Val Phe Thr Asp Ser Glu Tyr Gln Leu Pro Tyr Val
1               5                   10                  15

Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala Asp Val
            20                  25                  30

Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly Ser Gln
        35                  40                  45

Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro Ser Gln
    50                  55                  60

Met Leu Arg Thr Gly Asn Asn Phe Glu Phe Ser Tyr Asn Phe Glu Asp
65                  70                  75                  80

Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg Leu
                85                  90                  95

Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln
            100                 105                 110

Ser Thr Gly Gly Thr Ala Gly Thr Gln Gln Leu Leu Phe Ser Gln Ala
        115                 120                 125

Gly Pro Asn Asn Met Ser Ala Gln Ala Lys Asn Trp Leu Pro Gly Pro
    130                 135                 140

Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Leu Ser Gln Asn Asn Asn
145                 150                 155                 160

Ser Asn Phe Ala Trp Thr Gly Ala Thr Lys Tyr His Leu Asn Gly Arg
                165                 170                 175

Asp Ser Leu Val Asn Pro Gly Val Ala Met Ala Thr His Lys Asp Asp
            180                 185                 190

Glu Glu Arg Phe Phe Pro Ser Ser Gly Val Leu Met Phe Gly Lys Gln
        195                 200                 205

Gly Ala Gly Lys Asp Asn Val Asp Tyr Ser Ser Val Met Leu Thr Ser
    210                 215                 220

Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Gln Tyr Gly
225                 230                 235                 240

Val Val Ala Asp Asn Leu Gln Gln Gln Asn Ala Ala Pro Ile Val Gly
                245                 250                 255

Ala Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val Trp Gln Asn Arg
            260                 265                 270

Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr Asp
        275                 280                 285

Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys His
    290                 295                 300

Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asp Pro
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305                 310                 315                 320

Pro Thr Thr Phe Asn Gln Ala Lys Leu Ala Ser Phe Ile Thr Gln Tyr
                325                 330                 335

Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys Glu
            340                 345                 350

Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn Tyr Tyr
        355                 360                 365

Lys Ser Thr Asn Val Asp Phe Ala Val Asn Thr Glu Gly Thr Tyr Ser
    370                 375                 380

Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
385                 390                 395


<210> SEQ ID NO 83
<211> LENGTH: 332
<212> TYPE: PRT
<213> ORGANISM: Non-human primate adeno-associated virus

<400> SEQUENCE: 83

Arg Thr Gly Asn Asn Phe Glu Phe Ser Tyr Asn Phe Glu Asp Val Pro
1               5                   10                  15

Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn
            20                  25                  30

Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser Arg Thr Gln Ser Thr
        35                  40                  45

Gly Gly Thr Ala Gly Thr Gln Gln Leu Leu Phe Ser Gln Ala Gly Pro
    50                  55                  60

Asn Asn Met Ser Ala Gln Ala Lys Asn Trp Leu Pro Gly Pro Cys Tyr
65                  70                  75                  80

Arg Gln Gln Arg Val Ser Thr Thr Leu Ser Gln Asn Asn Asn Ser Asn
                85                  90                  95

Phe Ala Trp Thr Gly Ala Thr Lys Tyr His Leu Asn Gly Arg Asp Ser
            100                 105                 110

Leu Val Asn Pro Gly Val Ala Met Ala Thr His Lys Asp Asp Glu Glu
        115                 120                 125

Arg Phe Phe Pro Ser Ser Gly Val Leu Met Phe Gly Lys Gln Gly Ala
    130                 135                 140

Gly Lys Asp Asn Val Asp Tyr Ser Ser Val Met Leu Thr Ser Glu Glu
145                 150                 155                 160

Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Gln Tyr Gly Val Val
                165                 170                 175

Ala Asp Asn Leu Gln Gln Gln Asn Ala Ala Pro Ile Val Gly Ala Val
            180                 185                 190

Asn Ser Gln Gly Ala Leu Pro Gly Met Val Trp Gln Asn Arg Asp Val
        195                 200                 205

Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn
    210                 215                 220

Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys His Pro Pro
225                 230                 235                 240

Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asp Pro Pro Thr
                245                 250                 255

Thr Phe Asn Gln Ala Lys Leu Ala Ser Phe Ile Thr Gln Tyr Ser Thr
            260                 265                 270
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Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser
        275                 280                 285

Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn Tyr Tyr Lys Ser
    290                 295                 300

Thr Asn Val Asp Phe Ala Val Asn Thr Glu Gly Thr Tyr Ser Glu Pro
305                 310                 315                 320

Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                325                 330


<210> SEQ ID NO 84
<211> LENGTH: 743
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct - AAV9 variant

<400> SEQUENCE: 84

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285
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Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Arg Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Thr Leu Ala Val
            580                 585                 590

Pro Phe Lys Ala Gln Ala Gln Thr Gly Trp Val Gln Asn Gln Gly Ile
        595                 600                 605

Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro
    610                 615                 620

Ile Trp Ala Lys Ile Pro His Thr Asp Gly Asn Phe His Pro Ser Pro
625                 630                 635                 640

Leu Met Gly Gly Phe Gly Met Lys His Pro Pro Pro Gln Ile Leu Ile
                645                 650                 655

Lys Asn Thr Pro Val Pro Ala Asp Pro Pro Thr Ala Phe Asn Lys Asp
            660                 665                 670

Lys Leu Asn Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val
        675                 680                 685

Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro
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690 695 700

Glu Ile Gln Tyr Thr Ser Asn Tyr Tyr Lys Ser Asn Asn Val Glu Phe
705 710 715 720

Ala Val Asn Thr Glu Gly Val Tyr Ser Glu Pro Arg Pro Ile Gly Thr
725 730 735

Arg Tyr Leu Thr Arg Asn Leu
740

<210> SEQ ID NO 85
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Peptide insert

<400> SEQUENCE: 85

Thr Leu Ala Val Pro Phe Lys
1 5

<210> SEQ ID NO 86
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Peptide insert

<400> SEQUENCE: 86

Lys Phe Pro Val Ala Leu Thr
1 5

<210> SEQ ID NO 87
<211> LENGTH: 2514
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - codon optimized PKP2a polynucleotide

<400> SEQUENCE: 87

atggctgcac ctggtgcgcc tgccgaatat ggttatataa ggacagtttt gggtcaacag 60

atacttggac aacttgattc ctcttctttg gcgctccctt cagaagcaaa gttgaaattg 120

gcaggttcat caggtagagg aggacaaact gtgaaatctc tgcggattca ggaacaagta 180

caacagactt tggctagaaa gggaagatct tccgttggca atggaaattt gcatagaacg 240

agcagcgtac ctgaatacgt atacaatctc catcttgttg aaaacgattt tgtaggaggt 300

cggtctccag ttccgaaaac atatgatatg cttaaagcag gtactacagc tacatacgaa 360

ggtagatggg gaagaggaac tgcacaatat tcatctcaaa aatctgttga agaaaggtca 420

ttgcgacatc ctctcagaag gctcgaaatt tccccggatt catcacctga aagggctcat 480

tatacacaca gtgattatca atatagccaa cgatctcaag caggtcatac acttcatcat 540

caggaaagta ggcgggcggc attgcttgta ccccctcgat atgccaggtc agaaattgta 600

ggagtttcca gagcaggtac tactagtcga caaagacact ttgacacata tcataggcaa 660

tatcaacacg gtagtgtctc agacactgtt tttgattcaa taccagcaaa tccggcattg 720

ctgacgtatc ctcgacctgg tacgtcaagg agcatgggaa atcttctgga gaaagaaaat 780

tatttgactg ctgggcttac agttggacag gtacggccat tggttcctct tcaaccagtt 840

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actcagaatc gagcttccag aagctcttgg catcaatcaa gctttcattc cacaaggaca 900

ctgagagaag caggaccttc tgttgccgtt gattccagtg ggcggagagc ccaccttaca 960

gtaggtcaag cagctgccgg aggatcaggt aatttgctta cagaaaggag tacttttaca 1020

gatagccaac tcgggaatgc ggatatggaa atgacattgg agagagctgt atcaatgctg 1080

gaagcggatc atatgcttcc ttctagaatt tccgctgcgg caacttttat acagcacgaa 1140

tgttttcaaa aatccgaagc gcgaaagcgg gttaatcagc tgagaggtat tctgaaactg 1200

ttgcaacttt tgaaagtgca aaatgaagat gttcaaagag ctgtttgtgg agctcttaga 1260

aatcttgttt ttgaagataa tgataataaa ttggaagttg ctgaacttaa tggtgtacct 1320

agattgcttc aagttttgaa acaaacaaga gatttggaaa caaaaaaaca aataacagga 1380

cttttgtgga atctttcttc taatgataaa cttaaaaatt tgatgataac agaagctttg 1440

ttgacactta cagaaaatat tattatacct ttttctggat ggcctgaagg ggattatcca 1500

aaagctaatg ggttgctgga ttttgatatt ttttataatg tgacaggatg tttgaggaat 1560

atgtcctcag ctggtgctga cggtcggaaa gcaatgaggc gatgtgacgg tttgatcgat 1620

tcccttgttc attacgttag gggaacaata gctgattatc aaccagatga taaagcaaca 1680

gaaaattgtg tttgtattct tcataatctg tcttatcaat tggaagccga acttcctgaa 1740

aaatactctc aaaatatcta tattcagaat cggaacatac aaactgataa taacaaatct 1800

ataggatgtt ttggatcaag aagcagaaaa gttaaggaac aatatcaaga cgttcctatg 1860

cccgaagaaa aatcaaatcc aaagggtgta gaatggctgt ggcattctat tgttattaga 1920

atgtatttgt cactcatagc aaaatctgta cgaaattata cacaagaagc ttctttggga 1980

gcccttcaga atcttacagc aggaagtggt cctatgccta caagtgtagc gcaaacagtt 2040

gtacagaaag aatctggatt gcaacatact agaaagatgc tgcatgtagg agatccttct 2100

gttaaaaaga cagctataag cctcctgagg aacttgagtc gcaacttgtc tctccagaat 2160

gagattgcta aggaaacgct tcctgacctt gtatctatta tacctgacac ggtgccttcc 2220

acagatcttt tgattgaaac aactgcatct gcttgttata cattgaataa tatcattcaa 2280

aatagttatc agaacgcaag agatcttctg aatacaggag gtattcaaaa aataatggct 2340

atttcagcag gtgatgcata tgcttctaat aaagcgtcta aagctgcatc tgttcttttg 2400

tattctcttt gggcacatac agaacttcac catgcctaca agaaagctca attcaagaaa 2460

acagattttg ttaatagtcg cactgcaaaa gcgtatcatt cccttaagga ttaa 2514

<210> SEQ ID NO 88
<211> LENGTH: 2646
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - codon optimized PKP2b polynucleotide

<400> SEQUENCE: 88

atggccgcac ctggagctcc agctgaatat ggatatatca ggactgtctt gggtcagcag 60

attctgggcc aactggattc ttcaagtctg gccctcccga gtgaggcaaa actgaaactc 120

gcaggatcta gtggaagggg cggacagaca gtgaagtcac tcaggattca ggagcaggtc 180

caacagacac tggcaagaaa agggaggtcc agcgtcggca atggtaactt gcatagaacc 240

tcttcagtgc ctgagtacgt gtacaacctg cacctggtgg aaaacgattt tgtgggcggc 300

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agatccccgg tccctaaaac ttatgacatg ctgaaagctg gcacgacagc tacatatgaa 360

ggtagatggg gccggggcac cgcacaatat agttctcaga agtccgtgga agaaagatct 420

cttaggcacc cacttcggcg actggagata agtccagaca gcagccccga aagggcgcat 480

tatacacatt ctgactacca atacagccaa agatctcagg ctggccacac tctgcatcat 540

caggaaagta gaagggccgc ccttctcgtc cccccaagat acgcacggtc agaaatcgtg 600

ggagtgagca gagcaggtac cacctctcga cagaggcatt tcgacacata ccaccgacaa 660

taccaacatg gatcagtgtc agatactgtt tttgactcca taccagcaaa tccagcactc 720

ctgacatatc ctagaccggg gactagtcgc tccatgggga atctgctcga aaaagaaaac 780

tatctcaccg caggtctgac tgtggggcag gtaaggccgt tggtgcccct tcagcctgta 840

acgcagaata gggcttccag gtcatcctgg caccagagta gcttccactc cacaaggact 900

ctgagagagg caggccctag tgttgcagtt gatagttccg gtcgcagggc ccatcttaca 960

gttggtcaag ccgctgcagg gggtagcggt aatctgctga ccgaaagaag cacattcacg 1020

gattcccagc tcggaaatgc agacatggag atgacacttg aacgagccgt gagcatgctg 1080

gaagctgacc atatgctccc ttctagaatc tccgctgcgg ccactttcat ccagcacgag 1140

tgctttcaga aatccgaagc taggaaacgc gtgaaccagc tgaggggcat cctgaagctg 1200

ctgcagctgc ttaaggtgca gaatgaggat gtccaacgcg cagtgtgcgg tgctctgagg 1260

aacctcgtgt ttgaagataa cgataataag ttggaagtcg cagaacttaa cggggtacct 1320

cgactgctcc aggtgttgaa acagacacgg gacctggaaa cgaaaaaaca aattaccgac 1380

cacactgtga atctcagaag tcggaatggg tggcctgggg cagtagctca tgcctgtaac 1440

ccttctacat tgggtggcca aggcgggagg attaccagat caggggtacg ggatcaacct 1500

gatcagcacg ggctcctgtg gaacttgtcc tctaatgaca aactgaaaaa cctgatgata 1560

accgaggctc tgctgaccct gacagaaaac attatcatcc ccttctccgg atggccagaa 1620

ggagactatc ctaaagctaa cggcttgctg gacttcgata tcttttataa tgtcacaggg 1680

tgccttagaa atatgagtag cgccggtgcc gatggaagga aggcaatgcg ccggtgtgat 1740

ggtcttatcg attccctggt acattacgtg aggggcacca ttgccgacta ccaaccagac 1800

gataaagcaa ccgagaattg cgtgtgcatc ctgcacaatt tgagctacca actcgaagct 1860

gaactgcctg agaaatattc ccaaaatatt tatatccaga atcggaatat ccagaccgat 1920

aataacaaga gcataggatg ctttggttct agaagccgca aggtcaagga acagtaccag 1980

gatgtaccta tgccagagga aaaatcaaac cccaaaggag tggaatggct gtggcattcc 2040

atcgtgatca ggatgtacct gagtctgatt gctaagagcg tgaggaacta tacacaggag 2100

gcttcccttg gcgcactgca aaatctgacc gccggatctg ggccaatgcc aacaagcgtt 2160

gctcaaacag tagtgcaaaa ggaatctggc cttcagcaca ctaggaaaat gcttcatgtg 2220

ggagatcctt ctgtgaagaa gacggctatt agcctgctcc gcaacttgag cagaaacctt 2280

tctttgcaga atgagattgc gaaagagacg ctccctgacc tggtgtccat tataccagac 2340

acggtccctt ccacagatct tctgattgaa acgaccgctt ccgcatgtta caccctgaat 2400

aatattattc aaaactcata ccaaaatgct agagacctgc tgaacactgg ggggatccag 2460

aagattatgg caatttcagc cggcgatgcc tatgctagta ataaagcctc caaggccgcc 2520

agtgtattgc tgtatagtct gtgggcacat acagaactgc accacgcata taagaaggcc 2580

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cagtttaaaa aaaccgattt cgtaaactct cggactgcaa aagcctacca ttcactgaaa 2640

gattga 2646

<210> SEQ ID NO 89
<211> LENGTH: 4650
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - polynucleotide sequence of vector genome

<400> SEQUENCE: 89

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tcgcccggcc tcagtgagcg agcgagcgcg cagagaggga gtggccaact ccatcactag 120

gggttccttg tagttaatga ttaacccgcc atgctactta tctacgtact ctggagacgc 180

gtacccttca gattaaaaat aactgaggta agggcctggg taggggaggt ggtgtgagac 240

gctcctgtct ctcctctatc tgcccatcgg ccctttgggg aggaggaatg tgcccaagga 300

ctaaaaaaag gccatggagc cagaggggcg agggcaacag acctttcatg ggcaaacctt 360

ggggccctgc tgtctagcat gccccactac gggtctaggc tgcccatgta aggaggcaag 420

gcctggggac acccgagatg cctggttata attaacccag acatgtggct gccccccccc 480

ccccaacacc tgctgcctct aaaaataacc ctgtccctgg tggatcccct gcatgcgaag 540

atcttcgaac aaggctgtgg gggactgagg gcaggctgta acaggcttgg gggccagggc 600

ttatacgtgc ctgggactcc caaagtatta ctgttccatg ttcccggcga agggccagct 660

gtcccccgcc agctagactc agcacttagt ttaggaacca gtgagcaagt cagcccttgg 720

ggcagcccat acaaggccat ggggctgggc aagctgcacg cctgggtccg gggtgggcac 780

ggtgcccggg caacgagctg aaagctcatc tgctctcagg ggcccctccc tggggacagc 840

ccctcctggc tagtcacacc ctgtaggctc ctctatataa cccaggggca caggggctgc 900

cctcattcta ccaccacctc cacagcacag acagacactc aggagccagc cagggtaagt 960

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gctcctcagt ggatgttgcc tttacttcta ggcctgtacg gaagtgttac ttctgctcta 1080

aaagctgcgg aattgtaccc gcgccaccat ggcagccccc ggcgccccag ctgagtacgg 1140

ctacatccgg accgtcctgg gccagcagat cctgggacaa ctggacagct ccagcctggc 1200

gctgccctcc gaggccaagc tgaagctggc ggggagcagc ggccgcggcg gccagacagt 1260

caagagcctg cggatccagg agcaggtgca gcagaccctc gcccggaagg gccgcagctc 1320

cgtgggcaac ggaaatcttc accgaaccag cagtgttcct gagtatgtct acaacctaca 1380

cttggttgaa aatgattttg ttggaggccg ttcccctgtt cctaaaacct atgacatgct 1440

aaaggctggc acaactgcca cttatgaagg tcgctgggga agaggaacag cacagtacag 1500

ctcccagaag tccgtggaag aaaggtcctt gaggcatcct ctgaggagac tggagatttc 1560

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gcgccacttt gacacatacc acagacagta ccagcatggc tctgttagcg acaccgtttt 1800

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ggaggtggct gaactaaatg gggtacctcg gctgctccag gtgctgaagc aaaccagaga 2460

cttggagact aaaaaacaaa taacaggttt gctgtggaat ttgtcatcta atgacaaact 2520

caagaatctc atgataacag aagcattgct tacgctgacg gagaatatca tcatcccctt 2580

ttctgggtgg cctgaaggag actacccaaa agcaaatggt ttgctcgatt ttgacatatt 2640

ctacaacgtc actggatgcc taagaaacat gagttctgct ggcgctgatg ggagaaaagc 2700

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agattaccag ccagatgaca aggccacgga gaattgtgtg tgcattcttc ataacctctc 2820

ctaccagctg gaggcagagc tcccagagaa atattcccag aatatctata ttcaaaaccg 2880

gaatatccag actgacaaca acaaaagtat tggatgtttt ggcagtcgaa gcaggaaagt 2940

aaaagagcaa taccaggacg tgccgatgcc ggaggaaaag agcaacccca agggcgtgga 3000

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aatgccgaca tcagtggctc agacagttgt ccagaaggaa agtggcctgc agcacacccg 3180

aaagatgctg catgttggtg acccaagtgt gaaaaagaca gccatctcgc tgctgaggaa 3240

tctgtcccgg aatctttctc tgcagaatga aattgccaaa gaaactctcc ctgatttggt 3300

ttccatcatt cctgacacag tcccgagtac tgaccttctc attgaaacta cagcctctgc 3360

ctgttacaca ttgaacaaca taatccaaaa cagttaccag aatgcacgcg accttctaaa 3420

caccgggggc atccagaaaa ttatggccat tagtgcaggc gatgcctatg cctccaacaa 3480

agcaagtaaa gctgcttccg tccttctgta ttctctgtgg gcacacacgg aactgcatca 3540

tgcctacaag aaggctcagt ttaagaagac agattttgtc aacagccgga ctgccaaagc 3600

ctaccactcc cttaaagact gatcaacctc tggattacaa aatttgtgaa agattgactg 3660

gtattcttaa ctatgttgct ccttttacgc tatgtggata cgctgcttta atgcctttgt 3720

atcatgctat tgcttcccgt atggctttca ttttctcctc cttgtataaa tcctggttgc 3780

tgtctcttta tgaggagttg tggcccgttg tcaggcaacg tggcgtggtg tgcactgtgt 3840

ttgctgacgc aacccccact ggttggggca ttgccaccac ctgtcagctc ctttccggga 3900

ctttcgcttt ccccctccct attgccacgg cggaactcat cgccgcctgc cttgcccgct 3960

gctggacagg ggctcggctg ttgggcactg acaattccgt ggtgttgtcg gggaaatcat 4020

cgtcctttcc ttggctgctc gcctgtgttg ccacctggat tctgcgcggg acgtccttct 4080

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gctacgtccc ttcggccctc aatccagcgg accttccttc ccgcggcctg ctgccggctc 4140

tgcggcctct tccgcgtctt cgccttcgcc ctcagacgag tcggatctcc ctttgggccg 4200

cctccccgca tcattgcctg cccgggtggc atccctgtga cccctcccca gtgcctctcc 4260

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tcattttgtc tgactaggtg tccttctata atattatggg gtggaggggg gtggtatgga 4380

gcaaggggcc caagttggga agaaacctgt agggcctgcg ttacccaggc tggagtgcag 4440

tggcacattt ctgctcactg caacctcctc ctccctgggt tctacgtaga taagtagcat 4500

ggcgggttaa tcattaacta caaggaaccc ctagtgatgg agttggccac tccctctctg 4560

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cgggcggcct cagtgagcga gcgagcgcgc 4650

<210> SEQ ID NO 90
<211> LENGTH: 4274
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - polynucleotide sequence of vector genome

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<210> SEQ ID NO 93
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - expression cassette
polynucleotide

<400> SEQUENCE: 93

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - expression cassette
polynucleotide

<400> SEQUENCE: 94

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<210> SEQ ID NO 95
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in Lab - expression cassette polynucleotide

<400> SEQUENCE: 95

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<210> SEQ ID NO 96
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<220> FEATURE:
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1.-**91**. (canceled)

92. A method of treating arrhythmogenic right ventricular cardiomyopathy (ARVC) in a subject having a mutation in a PKP2 gene, comprising:

administering to the subject a recombinant adeno-associated virus (rAAV) vector comprising a vector genome,

wherein the vector genome comprises an expression cassette and flanking AAV inverted terminal repeats (ITRs), the expression cassette comprising a polynucleotide comprising:

a polynucleotide sequence encoding a Plakophilin-2 (PKP2);

a promoter sequence, wherein the promoter sequence is operatively linked to the polynucleotide sequence encoding the PKP2; and

a polyA sequence,

wherein the rAAV vector is an AAV9 vector, and

wherein the method treats one or more symptoms of ARVC.

93. The method of claim **92**, wherein the rAAV vector comprises a capsid protein that shares at least 95% polypeptide sequence identity to SEQ ID NO: 77.

94. The method of claim **92**, wherein the rAAV vector comprises a capsid protein that shares 99% polypeptide sequence identity to SEQ ID NO: 77.

95. The method of claim **92**, wherein the rAAV vector comprises a capsid protein that shares 100% polypeptide sequence identity to SEQ ID NO: 77.

96. The method of claim **92**, wherein the promoter is a cardiac-specific promoter.

97. The method of claim **92**, wherein the promoter is a muscle-specific promoter.

98. The method of claim **92**, wherein the promoter is a cardiomyocyte-specific promoter.

99. The method of claim **98**, wherein the promoter is a Myosin Heavy-chain Creatine Kinase 7 (MHCK7) promoter.

100. The method of claim **99**, wherein the MHCK7 promoter shares at least 90% polynucleotide sequence identity with SEQ ID NO: 31.

101. The method of claim **99**, wherein the MHCK7 promoter shares at least 95% polynucleotide sequence identity with SEQ ID NO: 31.

102. The method of claim **98**, wherein the promoter is a cardiac troponin T (hTNNT2) promoter.

103. The method of claim **102**, wherein the hTNNT2 promoter shares at least 90% polynucleotide sequence identity with SEQ ID NO: 33.

104. The method of claim **102**, wherein the hTNNT2 promoter shares at least 95% polynucleotide sequence identity with SEQ ID NO: 33.

105. The method of claim **102**, wherein the expression cassette comprises exon 1 of the cardiac troponin T (hTNNT2) gene.

106. The method of claim **105**, where the hTNNT2 promoter and exon 1 together share at least 90% polynucleotide sequence identity with SEQ ID NO: 32.

107. The method of claim **102**, wherein the polyA signal is a human growth hormone (hGH) polyA.

108. The method of claim **107**, wherein the expression cassette comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE).

109. The method of claim **102**, wherein the PKP2 is PKP2 isoform A.

110. The method of claim **109**, wherein the PKP2 isoform A shares at least 90% polypeptide sequence identity with SEQ ID NO: 1.

111. The method of claim **102**, wherein the PKP2 is PKP2 isoform B.

112. The method of claim **111**, wherein the PKP2 isoform B shares at least 90% polypeptide sequence identity with SEQ ID NO: 2.

113. The method of claim **92**, wherein the rAAV vector is administered by intravenous injection, intracardiac injection, intracardiac infusion, or cardiac catheterization.

114. The method of claim **92**, wherein the rAAV vector is administered at a dose of between about 1×10^{13} and 5×10^{14} vg/kg.

115. The method of claim **92**, wherein the rAAV vector is administered at a dose of between about 5×10^{13} and 3×10^{14} vg/kg.

116. The method of claim **92**, wherein the rAAV vector is administered at a dose of about 2×10^{14} vg/kg.

117. The method of claim **92**, wherein the method reduces a decrease in left ventricle ejection fraction percentage (LVEF %) compared to the decrease observed in an untreated subject identified as having a mutation in the PKP2 gene.

118. The method of claim **92**, wherein the method reduces a decrease in left ventricle fractional shortening percentage (FS %) compared to the decrease observed in an untreated subject identified as having a mutation in the PKP2 gene.

119. The method of claim **92**, wherein the method prevents an increase in right ventricle area in millimeters squared (RV Area (mm^2)).

120. The method of claim **92**, wherein the method increases survival compared to survival of untreated subjects identified as having a mutation in the PKP2 gene.

121. A recombinant adeno-associated virus (rAAV) vector comprising a vector genome,

wherein the vector genome comprises an expression cassette and flanking AAV inverted terminal repeats (ITRs), the expression cassette comprising a polynucleotide comprising:

a polynucleotide sequence encoding a Plakophilin-2 (PKP2);

a promoter sequence, wherein the promoter sequence is operatively linked to the polynucleotide sequence encoding the PKP2; and

a polyA sequence, and

wherein the rAAV vector is an AAV9 vector.

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