

OPTIMIZED EXPRESSION CASSETTES FOR GENE THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims the benefit of U.S. Provisional Patent Application No. 63/219,651, filed July 8, 2021, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[002] This invention relates generally to gene therapies, *e.g.*, optimized gene expression cassettes, recombinant adeno-associated virus (AAV) virions, and methods for treating and preventing heart disease using the same.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[003] The contents of the electronic sequence listing (TENA_021_02WO_SeqList_ST26.xml; Size: 430,204 bytes; and Date of Creation: July 8, 2022) are herein incorporated by reference in their entirety.

BACKGROUND

[004] Cardiomyopathy is responsible for about half of cardiac-related deaths. It is estimated that about 1 in 250 to 1 in 10,000 adults are affected by some form of cardiomyopathy (McKenna et al. *Circ Res.* 121:722-730 (2017)). Despite major efforts in screening, diagnostics, and therapeutic strategies, the prevalence of cardiomyopathies and incidence of cardiomyopathy-related deaths remains high (Brieler et al. *Am Fam Physician.* 96:640-646 (2017)).

[005] Cardiomyopathy refers to a collection of conditions of the heart that occur when its ability to pump blood is reduced. Reduction in proper functioning, such as a contractile dysfunction, of the heart muscle can lead to myocardial infarction, heart failure, blood clots, valve problems, and cardiac arrest. Cardiomyopathies can be separated into primary and secondary categories that result in varied phenotypes (McKenna et al. *Circ Res.* 121:722-730 (2017)). Primary cardiomyopathies can be genetic, acquired, or mixed in etiology. Genetic cardiomyopathies are inherited and include arrhythmogenic right ventricular dysplasia, hypertrophic, ion channel disorders, left ventricular compaction, and mitochondrial myopathies. Acquired cardiomyopathies are due primarily to non-secondary, non-genetic

causes that lead to cardiac complications and include myocarditis, peripartum, tachycardia-induced cardiomyopathy, and stress-induced cardiomyopathy. Cardiomyopathies with mixed etiology are caused by a combination of non-genetic and genetic factors, and include dilated cardiomyopathy and restrictive cardiomyopathy. Secondary cardiomyopathies refer to heart disease resulting from an extra cardiovascular cause. The underlying causes of secondary cardiomyopathies can be endocrine, infection, exposure to toxins, autoimmune related, nutritional, and/or neuromuscular.

[006] Cardiomyocytes play a central role cardiomyopathy. Cardiomyocytes, also called cardiac muscle cells, cardiac myocytes, or myocardiocytes, are cardiac cells that make up the heart muscle and are responsible for the contractile function that allows the heart to act as a pump. There are many mechanisms that reduce cardiomyocytes' ability to function properly (Dadson et al. *Clin Sci (Lond)* 131:1375-1392 (2017)). In arrhythmogenic right ventricular cardiomyopathy, progressive replacement of cardiomyocytes with fibrotic tissue results in the electrical isolation of cardiomyocytes and atrophy of the ventricular myocardium, the major structure responsible for contractile function in the heart. In mitochondrial cardiomyopathy, a deficiency in ATP production has a direct effect on contractile function in cardiomyocytes that have a high metabolic demand. Cardiomyopathies also emerge as a result of abnormal contractile function resulting from loss of normal Ca^{2+} ion-release, uptake, and sequestration processes due to loss of activity in regulatory enzymes, such as sarco/endoplasmic reticulum calcium ATPase (SERCA) (Lennon et al. *Int J Mol Med*. 7:131-41 (2001)).

[007] Treatment strategies for cardiomyopathy are needed.

[008] Gene therapy approaches for the treatment of heart disease often employ vectors configured to transduce cardiac cells and to express a transgene in a cardiac tissue-specific manner. Adeno-associated virus (AAV) vectors, cardiac-specific promoters, or both in combination, may be used to deliver a polynucleotide encoding a gene product (e.g., a therapeutic protein) to heart tissue and thereby express the gene product in that tissue to treat the heart disease.

[009] However, achieving high expression of gene products remains challenging, especially in cardiac cells.

[0010] Given these challenges, there remains a need in the art for improved gene therapy vectors, especially for heart disease.

SUMMARY

[0011] In some aspects, the present invention relates generally to vectors for delivery of a polynucleotide encoding a dwarf open reading frame (DWORF) or another transgene to cardiac cells, *e.g.*, cardiomyocytes. Disclosed herein are recombinant adeno-associated virus virions (rAAV virions), including expression cassettes and capsid proteins, that effectively deliver DWORF polynucleotides into cardiac cells, along with related compositions and methods. In any aspects described herein where DWORF transgene is referenced, DWORF can be substituted by a reference to another transgene expression of which in cardiac cells is desired. In some embodiments, where AAV-based expression vectors and virions are referenced, the disclosure also contemplates use of other viral and non-viral vectors for delivery of transgenes. In particular, any viral and non-viral vectors that can be used for delivery of transgenes into cardiac cells are provided herein.

[0012] In some aspects, provided herein is an expression cassette comprising a polynucleotide sequence comprising:

- i) one or more promoters, optionally wherein the one or more promoters are cardiac-specific promoters; and
- ii) one or more copies of a transgene, optionally wherein the transgene encodes a polypeptide for treating or preventing a heart disease or alleviating symptoms associated with a heart disease;

wherein in addition to elements (i) and (ii), the expression cassette comprises one or more of the following:

- iii) one or more enhancers, optionally wherein the one or more enhancers are cardiac-specific enhancers;
- iv) the one or more copies of a transgene is at least two copies of the transgene;
- v) the polynucleotide sequence comprises one or more introns; and/or
- vi) at least one copy of the one or more copies of the transgene is codon-optimized.

[0013] In some embodiments of the expression cassette described above, in addition to elements (i) and (ii), the expression cassette comprises one, two, three or all four of elements (iii), (iv), (v) and (vi) (any combination of elements (iii), (iv), (v) and (vi) can be used). In some embodiments of the expression cassette described above, in addition to elements (i) and (ii), the expression cassette comprises one or more enhancers, wherein the one or more enhancers are cardiac-specific enhancers, and/or the polynucleotide sequence comprises one or more introns. In some embodiments of the expression cassette described above, in addition

to elements (i) and (ii), the expression cassette comprises one or more enhancers, wherein the one or more enhancers are cardiac-specific enhancers, and the polynucleotide sequence comprises one or more introns. In some embodiments, the one or more introns improve, or can improve, the efficiency of transgene expression. In some embodiments of the expression cassette described above, in addition to elements (i) and (ii), the expression cassette comprises two copies of the transgene, wherein the two copies are not identical, optionally wherein first copy is codon-optimized and second copy is not codon-optimized nucleotide sequence encoding the transgene. In some embodiments of the expression cassette described above, in addition to elements (i) and (ii), the expression cassette comprises two copies of the transgene, wherein the two copies are not identical to each other, optionally wherein first copy is codon-optimized and second copy is not codon-optimized nucleotide sequence encoding the transgene, and further the polynucleotide sequence comprises one or more introns. In some embodiments of the expression cassette described above, in addition to elements (i) and (ii), the expression cassette comprises two copies of the transgene, wherein the two copies are not identical to each other, optionally wherein first copy is codon-optimized and second copy is not codon-optimized nucleotide sequence encoding the transgene, and further the polynucleotide sequence comprises one or more introns, and further the polynucleotide sequence comprises one or more enhancers (e.g., wherein the one or more enhancers are cardiac-specific enhancers). In some embodiments, the one or more introns improve, or can improve, the efficiency of transgene expression. In some embodiments where two copies of the transgene are used, two copies of the promoters are also used.

[0014] In some embodiments of the expression cassette, the polynucleotide sequence comprises one or more promoters, wherein the one or more promoters are cardiac-specific enhancers. In some embodiments of the expression cassette, at least one promoter is a cardiac-specific promoter, or all of the promoters are cardiac-specific promoters. In some embodiments of the expression cassette, the polynucleotide sequence comprises a single promoter. In some embodiments of the expression cassette, the polynucleotide sequence comprises two promoters. In some embodiments of the expression cassette, at least one promoter of the one or more promoters is a chicken cTnT promoter. In some embodiments, the chicken cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 11. In some embodiments, the chicken cTnT promoter comprises SEQ ID NO: 11. In some embodiments of the expression cassette, at least one promoter of the one or more promoters is a human cTnT promoter. In some embodiments, the human cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 12 or SEQ ID NO: 13. In some

embodiments, the human cTnT promoter comprises SEQ ID NO: 12 or SEQ ID NO: 13. In some embodiments, the expression cassette comprises a chicken cTnT promoter and a human cTnT promoter.

[0015] In some embodiments of the expression cassette, the polynucleotide sequence comprises one or more copies of a transgene, wherein the transgene encodes a polypeptide for treating or preventing a heart disease or alleviating symptoms associated with a heart disease.

[0016] In some embodiments of the expression cassette, one or more copies of a transgene is at least two copies of the transgene. In some embodiments of the expression cassette, one or more copies of a transgene is two copies of the transgene. In some embodiments, one or more copies of a transgene is at least two copies of the transgene, and wherein the polynucleotide sequence comprises at least two promoters each operably linked to the at least two copies of the transgene. In some embodiments, one or more copies of a transgene is two copies of the transgene, and wherein the polynucleotide sequence comprises two promoters each operably linked to the two copies of the transgene. In some embodiments of the expression cassette comprising two copies of the transgene, the two “copies” are not identical. While not being bound by any theory, using two nucleic acid sequences encoding a polypeptide that are not identical may prevent DNA recombination within the vector. In some embodiments, the expression cassette comprises one copy of the transgene that has the original DNA sequence encoding a polypeptide and one copy of the transgene that has a codon optimized DNA sequence encoding the polypeptide. In some embodiments of the expression cassette comprising two copies of the transgene, the first copy of the transgene is sufficiently different from the second copy of the transgene to prevent DNA recombination.

[0017] In some embodiments of the expression cassette, the polynucleotide sequence comprises one or more enhancers, optionally wherein the one or more enhancers are cardiac-specific enhancers. In some embodiments of the expression cassette, the polynucleotide sequence comprises two or more enhancers (e.g., 2, 3, or 4 enhancers). In some embodiments of the expression cassette, one or more enhancers are cardiac-specific enhancers (e.g., at least one enhancer is a cardiac-specific enhancer, or 2, 3, or 4, or all of the enhancers are cardiac-specific enhancers). In some embodiments of the expression cassette, the polynucleotide sequence comprises one enhancer. In some embodiments of the expression cassette, the polynucleotide sequence comprises no enhancers. In some embodiments, the one or more cardiac-specific enhancers are selected from a ACTC1 enhancer and a α MHC enhancer. In some embodiments, the ACTC1 enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 78. In some embodiments, the ACTC1 enhancer comprises SEQ ID

NO: 78. In some embodiments, the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79. In some embodiments, the α MHC enhancer comprises SEQ ID NO: 79. In some embodiments, the expression cassette comprises an α MHC enhancer and an ACTC1 enhancer. In some embodiments of the expression cassette, the enhancer sequence comprises an α MHC enhancer followed by an ACTC1 enhancer. In some embodiments of the expression cassette, the enhancer sequence comprises an ACTC1 enhancer followed by an α MHC enhancer.

[0018] In some embodiments of the expression cassette, the polynucleotide sequence comprises one or more introns. In some embodiments of the expression cassette, the polynucleotide sequence comprises one intron. In some embodiments of the expression cassette, the polynucleotide sequence comprises two introns. In some embodiments of the expression cassette, the polynucleotide sequence comprises more than two introns. In some embodiments of the expression cassette, one or more introns are the same. In some embodiments of the expression cassette, one or more introns are different from each other. In some embodiments, the expression cassette comprises an intron and the intron is selected from a CMV intron and a chimeric intron. In some embodiments, the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 80. In some embodiments, the CMV intron comprises SEQ ID NO: 80. In some embodiments, the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81. In some embodiments, the chimeric intron comprises SEQ ID NO: 81. In some embodiments, the expression cassette comprises a CMV intron and a chimeric intron. In some embodiments, the expression cassette does not comprise an intron (e.g., does not comprise a CMV intron or a chimeric intron).

[0019] In some embodiments of the expression cassette, at least one copy of the one or more copies of the transgene is codon-optimized (e.g., codon-optimized for optimum human expression). In some embodiments of the expression cassette, two copies of the transgene are codon-optimized. In some embodiments of the expression cassette, first copy of the transgene is codon-optimized and second copy of the transgene is not codon optimized (e.g., original DNA sequence) or is otherwise different from the first copy. In some embodiments of the expression cassette, the first copy of the transgene is sufficiently different from the second copy of the transgene to prevent DNA recombination.

[0020] In some embodiments, the expression cassette further comprises one or more (e.g., two) post-transcriptional regulatory elements ("PTRE"). In some embodiments, the expression cassette further comprises one or more (e.g., two) WPRE sequences. In some embodiments, the expression cassette comprises one WPRE sequence. In some embodiments, the WPRE

sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26. In some embodiments, the WPRE sequence comprises SEQ ID NO: 26. In some embodiments, the expression cassette does not comprise a WPRE sequence.

[0021] In some embodiments, the expression cassette further comprises one or more polyadenylation sequences ("p(A)"). In some embodiments, the expression cassette comprises one polyadenylation sequence. In some embodiments, the expression cassette comprises two polyadenylation sequences. In some embodiments, the polyadenylation sequence is selected from a BGH polyadenylation sequence and a SV40 polyadenylation sequence. In some embodiments, the BGH polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 27. In some embodiments, the BGH polyadenylation sequence comprises SEQ ID NO: 27. In some embodiments, the SV40 polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 28. In some embodiments, the SV40 polyadenylation sequence comprises SEQ ID NO: 28. In some embodiments, the expression cassette comprises a BGH polyadenylation sequence and a SV40 polyadenylation sequence.

[0022] In some embodiments, the expression cassette comprises 5' to 3' arrangement of elements selected from any one of the following:

- (i) 5'-promoter-intron-transgene-PTRE -p(A)-3';
- (ii) 5'-promoter-transgene- PTRE -p(A)-promoter-transgene- PTRE -p(A);
- (iii) 5'-enhancer-promoter-transgene-PTRE-p(A)-3';
- (iv) 5'-enhancer-promoter-intron-transgene-PTRE-p(A)-3';
- (v) 5'-enhancer-enhancer-promoter-transgene-PTRE-p(A)-3';
- (vi) 5'-enhancer-enhancer-promoter-intron-transgene-PTRE-p(A)-3';
- (vii) 5'-enhancer-promoter-intron-transgene-PTRE-p(A)-p(A)-transgene-intron-promoter-enhancer-3';
- (viii) 5'-enhancer-promoter-intron-transgene-PTRE-p(A)-enhancer-promoter-intron-transgene-p(A)-3';
- (ix) 5'-p(A)-PTRE-transgene-intron-promoter-enhancer-enhancer-promoter-intron-transgene-p(A)-3';
- (x) 5'-promoter-intron-transgene-PTRE-p(A)-p(A)-transgene-intron-promoter-3';
- (xi) 5'-promoter-intron-transgene-PTRE-p(A)-promoter-intron-transgene-p(A)-3'; and
- (xii) 5'-p(A)-PTRE-transgene-intron-promoter-promoter-intron-transgene-p(A)-3'.

[0023] In some embodiments of the expression cassette, the transgene has an increased expression level compared to an expression cassette comprising a polynucleotide having an

arrangement of elements from 5' to 3' comprising: 5'-promoter-transgene-WPRE-p(A)-3'. In some embodiments, the increased expression level is between about 1.5-fold and about 150-fold. In some embodiments, the increased expression level is at least 2 fold, at least 5 fold, at least 10 fold, at least 25 fold, at least 50 fold, at least 75 fold, or at least 100 fold.

[0024] In some embodiments, the expression cassette is flanked by ITRs. In some embodiments, the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15. In some embodiments, the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.

[0025] In some embodiments, the expression cassette comprises from about 1.9kb to about 3.7kb. In some embodiments, the expression cassette comprises from about 2.5kb to about 3.7kb, optionally from about 2.8 kb to about 3.6 kb.

[0026] In some embodiments, the transgene in the expression cassette encodes a polypeptide useful in the treatment of a heart disease or disorder, optionally when a wild type copy of the gene is introduced to a subject. In some embodiments, the transgene in the expression cassette encodes a polypeptide which is associated with a heart disease (e.g., where loss of function mutations in the gene encoding the polypeptide are associated with heart disease).

[0027] In some embodiments, the transgene in the expression cassette encodes a polypeptide selected from: DWORF, JPH2, BAG3, CRYAB, Lamin A isoform of LMNA, Lamin C isoform of LMNA, TNNT3, PLN, LAMP2a, LAMP2b, LAMP2c, DPI isoform of DSP, DPII isoform of DSP, DSG2, and JUP. In some embodiments, the expression cassette comprises a transgene which shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:201, SEQ ID NO:203, SEQ ID NO:205, SEQ ID NO:207, SEQ ID NO:209, SEQ ID NO:211, SEQ ID NO:213, SEQ ID NO:215, SEQ ID NO:217, SEQ ID NO:219, SEQ ID NO:221, SEQ ID NO:223, SEQ ID NO:225, SEQ ID NO:227, or SEQ ID NO:229. In some embodiments, the polypeptide shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:202, SEQ ID NO:204, SEQ ID NO:206, SEQ ID NO:208, SEQ ID NO:210, SEQ ID NO:212, SEQ ID NO:214, SEQ ID NO:216, SEQ ID NO:218, SEQ ID NO:220, SEQ ID NO:222, SEQ ID NO:224, SEQ ID NO:226, SEQ ID NO:228, or SEQ ID NO:230.

[0028] In some embodiments, the transgene in the expression cassette encodes a DWORF polypeptide. In some embodiments, the transgene shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:33, SEQ ID NO:44, SEQ ID NO:76, or SEQ ID NO:77. In some embodiments, the polypeptide shares at least 75%, 80%, 90%, 95%, 96%,

97%, 98%, 99% or 100% sequence identity to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:32, or SEQ ID NO:43.

[0029] In some embodiments, the expression cassette comprises a 5' to 3' arrangement of elements selected from any one of the following:

- (i) 5'-human or chicken TnT promoter-chimeric intron-transgene-WPRE-p(A)-3';
- (ii) 5'- first human or chicken TnT promoter-first copy of transgene-WPRE-p(A)- second human or chicken TnT promoter – second copy of transgene-WPRE-p(A), optionally where the first and second promoter sequences and the first and second copies of the transgene are in the same forward orientation;
- (iii) 5'- human TnT promoter-CMV intron-transgene-WPRE-bGHpA-3';
- (iv) 5'-ACTC1e enhancer-cardiac- human TnT promoter -transgene-WPRE-bGHpA-3';
- (v) 5'- α MHCe enhancer- human TnT promoter -transgene-WPRE-bGHpA-3';
- (vi) 5'-ACTC1e enhancer- human TnT promoter -CMV intron-transgene-WPRE-bGHpA-3';
- (vii) 5'- α MHCe enhancer- human TnT promoter -CMV intron-transgene-WPRE-bGHpA-3';
- (viii) 5'-ACTC1e enhancer- α MHCe enhancer-human TnT promoter-transgene-WPRE-bGHpA-3';
- (ix) 5'- α MHCe enhancer -ACTC1e enhancer-human TnT promoter-transgene-WPRE-bGHpA-3';
- (x) 5'- ACTC1e enhancer- α MHCe enhancer-human TnT promoter-CMV intron-transgene-WPRE- bGHpA-3';
- (xi) 5'- α MHCe enhancer- ACTC1e enhancer- human TnT promoter-CMV intron-transgene-WPRE-bGHpA-3';
- (xii) 5'- human TnT promoter-transgene with a codon-optimized polynucleotide sequence-WPRE-bGHpA-3';
- (xiii) 5'- α MHCe enhancer- human TnT promoter -CMV intron-first transgene-WPRE-bGHpA-SV40pA-second transgene (e.g., with a codon-optimized polynucleotide sequence)-chimeric intron- chicken TnT promoter - ACTC1e enhancer-3', optionally wherein the first transgene and the human TnT promoter are in a forward orientation, and the second transgene and the chicken TnT promoter are in a reverse orientation;
- (xiv) 5'- α MHCe enhancer- human TnT promoter -CMV intron-first transgene-WPRE-bGHpA- ACTC1e enhancer- chicken TnT promoter-chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene, the human TnT promoter, the second transgene and the chicken TnT promoter are in a forward orientation;

(xv) 5'-bGHpA-WPRE-first transgene-CMV intron-human TnT promoter- α MHCe enhancer- ACTC1e enhancer- chicken TnT promoter-chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene and the human TnT promoter are in a reverse orientation, and the second transgene and the chicken TnT promoter are in a forward orientation;

(xvi) 5'-human TnT promoter -CMV intron-first transgene-WPRE-bGHpA-pSV40pA-second transgene (e.g., with a codon-optimized polynucleotide sequence)-chimeric intron- chicken TnT promoter-3', optionally wherein the first transgene and the human TnT promoter are in a forward orientation, and the second transgene and the chicken TnT promoter are in a reverse orientation; and

(xvii) 5'- huma TnT promoter-CMV intron-first transgene-WPRE-bGHpA-chicken TnT promoter- chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)- SV40pA-3', optionally wherein the first transgene, the human TnT promoter, the second transgene and the chicken TnT promoter are in a forward orientation; and (xix) 5'- bGHpA- WPRE- first transgene- CMV intron-human TnT promoter- chicken TnT promoter- chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene and the human TnT promoter are in a reverse orientation, and the second transgene and the chicken TnT promoter are in a forward orientation.

[0030] In some embodiments, the expression cassette comprises 5' to 3' arrangement of elements selected from any one of the following:

(i) 5'- ACTC1e enhancer- α MHCe enhancer-human TnT promoter-CMV intron-transgene-WPRE- bGHpA-3';

(ii) 5'- α MHCe enhancer- ACTC1e enhancer- human TnT promoter-CMV intron-transgene-WPRE-bGHpA-3';

(iii) 5'- α MHCe enhancer- human TnT promoter -CMV intron-first transgene-WPRE-bGHpA-SV40pA-second transgene (e.g., with a codon-optimized polynucleotide sequence)-chimeric intron- chicken TnT promoter - ACTC1e enhancer-3', optionally wherein the first transgene and the human TnT promoter are in a forward orientation, and the second transgene and the chicken TnT promoter are in a reverse orientation;

(iv) 5'- α MHCe enhancer- human TnT promoter -CMV intron-first transgene-WPRE-bGHpA- ACTC1e enhancer- chicken TnT promoter-chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene,

the human TnT promoter, the second transgene and the chicken TnT promoter are in a forward orientation;

(v) 5'-bGHpA-WPRE-first transgene-CMV intron-human TnT promoter- α MHCe enhancer-ACTC1e enhancer- chicken TnT promoter-chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene and the human TnT promoter are in a reverse orientation, and the second transgene and the chicken TnT promoter are in a forward orientation;

(vi) 5'-human TnT promoter -CMV intron-first transgene-WPRE-bGHpA-pSV40pA-second transgene (e.g., with a codon-optimized polynucleotide sequence)-chimeric intron- chicken TnT promoter-3', optionally wherein the first transgene and the human TnT promoter are in a forward orientation, and the second transgene and the chicken TnT promoter are in a reverse orientation; (vii) 5'- huma TnT promoter-CMV intron-first transgene-WPRE-bGHpA-chicken TnT promoter- chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)- SV40pA-3', optionally wherein the first transgene, the human TnT promoter, the second transgene and the chicken TnT promoter are in a forward orientation; and

(viii) 5'- bGHpA- WPRE- first transgene- CMV intron-human TnT promoter- chicken TnT promoter- chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene and the human TnT promoter are in a reverse orientation, and the second transgene and the chicken TnT promoter are in a forward orientation.

[0031] In some embodiments, the expression cassette is a recombinant expression cassette.

[0032] In some aspects, provided herein is a recombinant vector comprising any of the expression cassettes described herein. In some embodiments, the vector is a viral vector. In some embodiments, the vector is a non-viral vector.

[0033] In some aspects, provided herein is a recombinant adeno-associated virus (rAAV) virion, comprising a capsid protein and a viral genome comprising any of the expression cassettes described herein, wherein the expression cassette is flanked by inverted terminal repeats (ITRs). In some embodiments, the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15. In some embodiments, the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15. In some embodiments, the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV9 capsid protein (SEQ ID NO: 143). In some embodiments, the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV5 capsid protein (SEQ ID NO: 144). In some embodiments, the capsid protein is a

chimeric capsid protein. In some embodiments, the capsid protein is an AAV5/AAV9 chimeric capsid protein. In some embodiments, the capsid protein is selected from any one of SEQ ID NOs: 145-200.

[0034] In some aspects, provided herein is a pharmaceutical composition comprising any of the vectors described herein or any of the rAAV virions described herein, and a pharmaceutically acceptable carrier.

[0035] In some aspects, provided herein is a kit comprises any of the pharmaceutical compositions described herein, or any components of such pharmaceutical compositions (e.g., a vector or an rAAV virion).

[0036] In some aspects, provided herein is a method of increasing expression of a polypeptide in a cardiac cell or cardiac tissue comprising contacting a cell with any vector described herein, any rAAV virion described herein, or any pharmaceutical composition described herein. In some embodiments, the cardiac cell is a cardiomyocyte. In some embodiments, the cardiac tissue is heart tissue. In some embodiments, the polypeptide expression is increased between about 1.5-fold and 150-fold. In some embodiments, the polypeptide expression is increased at least 2 fold, at least 5 fold, at least 10 fold, at least 25 fold, at least 50 fold, at least 75 fold, or at least 100 fold. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*.

[0037] In some aspects, provided herein is a method of increasing polypeptide expression in a subject comprising administering to the subject any vector described herein, any rAAV virion described herein, or any pharmaceutical composition described herein. In some embodiments, the subject is a mammal. In some embodiments, the subject is a human. In some embodiments, following administering, the polypeptide expression is increased in the heart of the subject. In some embodiments, the subject being treated has a heart disease or is at risk of a heart disease. In some embodiments, the subject being treated has borderline or reduced ejection fraction. In some embodiments, the subject being treated has normal ejection fraction. In some embodiments, wherein the subject being treated has a genetic mutation associated with a heart disease (e.g., a mutation in a *PLN* gene). In some embodiments, the subject has a low or undetectable level of expression of the polypeptide encoded by the transgene, compared to a healthy subject.

[0038] In some aspects, provided herein is a method of treating or preventing a heart disease or disorder in a subject in need thereof comprising administering to the subject any vector described herein, any rAAV virion described herein, or any pharmaceutical composition described herein. In some embodiments, the subject being treated has a heart disease or

disorder. In some embodiments, the subject being treated is a risk of developing a heart disease or disorder. In some embodiments, the heart disease or disorder is cardiomyopathy. In some embodiments, the cardiomyopathy is dilated cardiomyopathy. In some embodiments, the heart disease or disorder is myocardial infarction. In some embodiments, the myocardial infarction is chronic myocardial infarction. In some embodiments, the subject has an inherited risk allele for a heart disease or disorder. In some embodiments, the subject has an inherited risk allele for a heart disease or disorder due to a genetic mutation. In some embodiments, the subject has an inherited risk allele for a heart disease or disorder due to a genetic mutation in a *PLN* gene (for example, one or more mutations in the *PLN* gene described herein or known in the art). In some embodiments, the heart disease or disorder is with reduced ejection fraction (HFrEF). In some embodiments, the heart disease or disorder is with preserved ejection fraction (HFpEF). In some embodiments, the method leads to expression of the polypeptide encoded by the transgene in the heart of the subject. In some embodiments, the method leads to expression of the polypeptide encoded by the transgene in cardiomyocytes of the subject. In some embodiments, the method causes no detectable expression of the polypeptide encoded by the transgene in the muscles of the subject except the heart, in the liver of the subject, and/or in the cardiac fibroblasts of the subject. In some embodiments, the method improves one or more measures of cardiac function, optionally fraction shortening and/or left ventricular internal dimension (LVID). In some embodiments, the improvement in cardiac function is observed at or later than week 2, week 4, week 6, week 8, week 10, week 12, week 14, week 16, week 18, week 20, week 22, and/or week 24, after the administering. In some embodiments, the administering is systemic administration. In some embodiments, the systemic administration is selected from intravenous or intracoronary injection. In some embodiments, when an rAAV virion is administered, it is administered as a unit dose. In some embodiments, the unit dose comprises about 3×10^{14} vg/kg or less, about 2×10^{14} vg/kg or less, about 1×10^{14} vg/kg or less, about 9×10^{13} vg/kg or less, about 8×10^{13} vg/kg or less, about 7×10^{13} vg/kg or less, about 6×10^{13} vg/kg or less, about 5×10^{13} vg/kg or less, about 4×10^{13} vg/kg or less, about 3×10^{13} vg/kg or less, about 2×10^{13} vg/kg or less, or about 1×10^{13} vg/kg or less. In some embodiments, the subject being treated is a mammal. In some embodiments, the subject being treated is a human.

[0039] In one aspect, the disclosure provides a recombinant adeno-associated virus (rAAV) virion, comprising a capsid protein and a viral genome comprising an expression cassette comprising a polynucleotide sequence encoding a dwarf open reading frame (DWORF)

polypeptide operatively linked to a promoter, the expression cassette flanked by inverted terminal repeats.

[0040] In some embodiments, the DWORF polypeptide shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to a sequence selected from SEQ ID NOs: 1, 3, 4, 7, 9, 23, and 43. In some embodiments, the DWORF polypeptide is selected from SEQ ID NOs: 1, 3, 4, 7, 9, 23, and 43.

[0041] In some embodiments, the promoter is a chicken cTnT promoter. In some embodiments, the chicken cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 11. In some embodiments, the chicken cTnT promoter comprises SEQ ID NO: 11. In some embodiments, the promoter is a human cTnT promoter. In some embodiments, the human cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 12 or SEQ ID NO: 13. In some embodiments, the human cTnT promoter comprises SEQ ID NO: 12 or SEQ ID NO: 13.

[0042] In some embodiments, the expression cassette further comprises one or more enhancers. In some embodiments, the enhancer the one or more enhancers are selected from a ACTC1 cardiac enhancer and a α MHC enhancer. In some embodiments, the ACTC1 cardiac enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 78. In some embodiments, the ACTC1 cardiac enhancer comprises SEQ ID NO: 78. In some embodiments, the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79. In some embodiments, the α MHC enhancer comprises SEQ ID NO: 79.

[0043] In some embodiments, the expression cassette further comprises an intron. In some embodiments, the intron is selected from a CMV intron and a chimeric intron. In some embodiments, the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 80. In some embodiments, the CMV intron comprises SEQ ID NO: 80. In some embodiments, the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81. In some embodiments, the chimeric intron comprises SEQ ID NO: 81.

[0044] In some embodiments, the expression cassette further comprises a WPRE sequence. In some embodiments, the WPRE sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26. In some embodiments, the WPRE sequence comprises SEQ ID NO: 26.

[0045] In some embodiments, the expression cassette further comprises a polyadenylation sequence. In some embodiments, the polyadenylation sequence is selected from a BGH polyadenylation sequence and a SV40 polyadenylation sequence. In some embodiments, the BGH polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to

SEQ ID NO: 27. In some embodiments, the BGH polyadenylation sequence comprises SEQ ID NO: 27. In some embodiments, the SV40 polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 28. In some embodiments, the SV40 polyadenylation sequence comprises SEQ ID NO: 28.

[0046] In some embodiments, the expression cassette is flanked by ITRs. In some embodiments, the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15. In some embodiments, the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.

[0047] In some embodiments, the expression cassette comprises a single promoter. In some embodiments, the expression cassette comprises two promoters. In some embodiments, the expression cassette comprises a single copy a sequence encoding the DWORF polypeptide. In some embodiments, the expression cassette comprises two copies of a sequence encoding the DWORF polypeptide. In some embodiments, where the expression cassette comprises two copies of a sequence encoding the DWORF polypeptide, the two “copies” are not identical. While not being bound by any theory, using two nucleic acid sequences encoding a polypeptide that are not identical may prevent DNA recombination within the vector. In some embodiments, the expression cassette comprises one copy that has the original DNA sequence encoding the DWORF polypeptide and one copy that has a codon optimized DNA sequence encoding the DWORF polypeptide. In some embodiments, the expression cassette comprises two copies of a sequence encoding the DWORF polypeptide, wherein one copy is codon-optimized and one copy is not codon optimized. In some embodiments, the expression cassette comprises one, two, three, or four enhancers. In some embodiments, the expression cassette comprises one or two introns. In some embodiments, the expression cassette comprises one or two WPRE sequences. In some embodiments, the expression cassette comprises one or two polyadenylation sequences.

[0048] In some embodiments, the expression cassette comprises about 3.2 kb, about 3.3 kb, about 3.4 kb, about 3.5 kb, about 3.6 kb, about 3.7 kb, or less. In some embodiments, the expression cassette comprises about 1.9 kb, about 2.1 kb, about 2.2 kb, about 2.3 kb, about 2.4 kb, about 2.5 kb, about 2.6 kb, about 2.7 kb, about 2.8 kb, about 2.9 kb, about 3.0 kb, about 3.1 kb, about 3.2 kb, or more.

[0049] In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75. In some embodiments, wherein the expression cassette comprises any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75. In some

embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 61. In some embodiments, the expression cassette comprises SEQ ID NO: 61. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 62. In some embodiments, the expression cassette comprises SEQ ID NO: 62. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 63. In some embodiments, the expression cassette comprises SEQ ID NO: 63.

[0050] In some embodiments, the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV9 capsid protein (SEQ ID NO: 143). In some embodiments, the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV5 capsid protein (SEQ ID NO: 144). In some embodiments, the capsid protein is a chimeric capsid protein. In some embodiments, the capsid protein is an AAV5/AAV9 chimeric capsid protein. In some embodiments, the capsid protein is selected from any one of SEQ ID NOs: 145-200.

[0051] In one aspect, the disclosure provides an expression cassette comprising polynucleotide sequence encoding a dwarf open reading frame (DWORF) polypeptide operatively linked to a promoter. In some embodiments, the DWORF polypeptide shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOs: 1, 3, 4, 7, 9, 23, and 43. In some embodiments, the DWORF polypeptide is selected from SEQ ID NOs: 1, 3, 4, 7, 9, 23, and 43.

[0052] In some embodiments, the promoter is a chicken cTnT promoter. In some embodiments, the chicken cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 11. In some embodiments, the chicken cTnT promoter comprises SEQ ID NO: 11. In some embodiments, the promoter is a human cTnT promoter. In some embodiments, the human cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 12 or SEQ ID NO: 13. In some embodiments, the human cTnT promoter comprises SEQ ID NO: 12 or SEQ ID NO: 13.

[0053] In some embodiments, the expression cassette further comprises one or more enhancers. In some embodiments, the enhancer the one or more enhancers are selected from a ACTC1 cardiac enhancer and a α MHC enhancer. In some embodiments, the ACTC1 cardiac enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 78. In some embodiments, the ACTC1 cardiac enhancer comprises SEQ ID NO: 78. In some embodiments, the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79. In some embodiments, the α MHC enhancer comprises SEQ ID NO: 79.

[0054] In some embodiments, the expression cassette further comprises an intron. In some embodiments, the intron is selected from a CMV intron and a chimeric intron. In some embodiments, the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 80. In some embodiments, the CMV intron comprises SEQ ID NO: 80. In some embodiments, the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81. In some embodiments, the chimeric intron comprises SEQ ID NO: 81.

[0055] In some embodiments, the expression cassette further comprises a WPRE sequence. In some embodiments, the WPRE sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26. In some embodiments, the WPRE sequence comprises SEQ ID NO: 26.

[0056] In some embodiments, the expression cassette further comprises a polyadenylation sequence. In some embodiments, the polyadenylation sequence is selected from a BGH polyadenylation sequence and a SV40 polyadenylation sequence. In some embodiments, the BGH polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 27. In some embodiments, the BGH polyadenylation sequence comprises SEQ ID NO: 27. In some embodiments, the SV40 polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 28. In some embodiments, the SV40 polyadenylation sequence comprises SEQ ID NO: 28.

[0057] In some embodiments, the expression cassette is flanked by ITRs. In some embodiments, the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15. In some embodiments, the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.

[0058] In some embodiments, the expression cassette comprises a single promoter. In some embodiments, the expression cassette comprises two promoters. In some embodiments, the expression cassette comprises a single copy a sequence encoding the DWORF polypeptide. In some embodiments, the expression cassette comprises two copies of a sequence encoding the DWORF polypeptide. In some embodiments, the expression cassette comprises one, two, three, or four enhancers. In some embodiments, the expression cassette comprises one or two introns. In some embodiments, the expression cassette comprises one or two WPRE sequences. In some embodiments, the expression cassette comprises one or two polyadenylation sequences.

[0059] In some embodiments, the expression cassette comprises about 3.2 kb, about 3.3 kb, about 3.4 kb, about 3.5 kb, about 3.6 kb, about 3.7 kb, or less. In some embodiments, the expression cassette comprises about 1.9 kb, about 2.1 kb, about 2.2 kb, about 2.3 kb, about 2.4

kb, about 2.5 kb, about 2.6 kb, about 2.7 kb, about 2.8 kb, about 2.9 kb, about 3.0 kb, about 3.1 kb, about 3.2 kb, or more.

[0060] In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75. In some embodiments, the expression cassette comprises any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 61. In some embodiments, the expression cassette comprises SEQ ID NO: 61. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 62. In some embodiments, the expression cassette comprises SEQ ID NO: 62. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 63. In some embodiments, the expression cassette comprises SEQ ID NO: 63.

[0061] In some embodiments, the expression cassette comprises a 5' inverted terminal repeat and a 3' inverted terminal repeat.

[0062] In one aspect, the disclosure provides a pharmaceutical composition comprising the rAAV virion disclosed herein and an pharmaceutically acceptable diluent. In another aspect, the disclosure provides a kit comprising a pharmaceutical composition provided herein.

[0063] In one aspect, the disclosure provides a method of increasing DWORF expression in a cell comprising contacting a cell with the rAAV virion disclosed herein or the pharmaceutical composition disclosed herein. In some embodiments, the cell is a cardiac cell. In some embodiments, the cardiac cell is a cardiomyocyte. In some embodiments, DWORF expression is increased between about 1.5-fold and 150-fold. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo.

[0064] In one aspect, the disclosure provides a method of increasing DWORF expression in a tissue comprising contacting the tissue with the rAAV virion disclosed herein or the pharmaceutical composition disclosed herein. In some embodiments, the tissue is cardiac tissue. In some embodiments, DWORF expression is increased between about 1.5-fold and 150-fold. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo.

[0065] In one aspect, the disclosure provides a method of increasing DWORF expression in an organ comprising contacting the organ with the rAAV virion disclosed herein or the

pharmaceutical composition disclosed herein. In some embodiments, DWORF expression is increased between about 1.5-fold and 150-fold.

[0066] In some embodiments, the organ is a heart. In some embodiments, the heart is diseased or is at risk of heart disease. In some embodiments, the heart has reduced or borderline ejection fraction. In some embodiments, the heart has a normal ejection fraction.

[0067] In some embodiments, the heart comprises a genetic mutation associated with a heart disease. In some embodiments, the genetic mutation is a PLN mutation. In some embodiments, the heart has low or undetectable DWORF expression compared to a healthy heart. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo.

[0068] In one aspect, the disclosure provides a method of increasing DWORF expression in a subject comprising administering to the subject the rAAV virion disclosed herein or the pharmaceutical composition disclosed herein. In some embodiments, the subject is an animal. In some embodiments, the subject is a human. In some embodiments, DWORF expression is increased in the heart of the subject. In some embodiments, the subject has a heart disease or is at risk of a heart disease. In some embodiments, the subject has borderline or reduced ejection fraction. In some embodiments, the subject has normal ejection fraction. In some embodiments, the subject has a genetic mutation associated with a heart disease. In some embodiments, the genetic mutation is a PLN mutation. In some embodiments, the subject has a low or undetectable level of DWORF expression compared to a healthy subject.

[0069] In one aspect, the disclosure provides a method of treating a heart disease or disorder in a subject in need thereof comprising administering to the subject the rAAV virion disclosed herein or the pharmaceutical composition disclosed herein.

[0070] In some embodiments, the subject has a heart disease or disorder. In some embodiments, the subject is at risk of developing a heart disease or disorder. In some embodiments, the heart disease or disorder is cardiomyopathy. In some embodiments, the heart disease or disorder is dilated cardiomyopathy. In some embodiments, the heart disease or disorder is myocardial infarction. In some embodiments, the heart disease or disorder is chronic myocardial infarction. In some embodiments, the heart disease or disorder is acute myocardial infarction.

[0071] In some embodiments, the subject has an inherited risk allele for a heart disease or disorder. In some embodiments, the inherited risk allele comprises a mutation to the PLN gene. In some embodiments, the mutation to the PLN gene is a PLN promoter mutation. In some embodiments, the mutation to the PLN gene is a PLNL39stop mutation. In some embodiments, the mutation to the PLN gene is a RC9 mutation. In some embodiments, the mutation to the

PLN gene is a R9L mutation. In some embodiments, the mutation to the PLN gene is a PLN gene duplication. In some embodiments, the mutation to the PLN gene is a R14del mutation.

[0072] In some embodiments, the heart disease or disorder is with reduced ejection fraction (HFrEF). In some embodiments, the heart disease or disorder is with preserved ejection fraction (HFpEF).

[0073] In some embodiments, the method causes expression of the DWORF polypeptide in the heart of the subject. In some embodiments, the method causes expression of the DWORF polypeptide in cardiomyocytes.

[0074] In some embodiments, the method causes no detectable expression of the DWORF polypeptide in the muscles of the subject except the heart. In some embodiments, the method causes no detectable expression of the DWORF polypeptide in the liver of the subject. In some embodiments, the method causes no detectable expression of the DWORF polypeptide in cardiac fibroblasts.

[0075] In some embodiments, the method improves one or more measures of cardiac function, optionally fraction shortening and/or left ventricular internal dimension (LVID). In some embodiments, the improvement in cardiac function is observed at weeks 2 through week 16. In some embodiments, the method reduces cardiac remodeling. In some embodiments, the method counteracts a decrease in DWORF expression in subjects suffering from or at risk of a heart disease.

[0076] In some embodiments, the rAAV virion is administered by systemic administration. In some embodiments, the systemic administration is selected from intravenous or intracoronary injection.

[0077] In some embodiments, the rAAV is administered as a unit dose. In some embodiments, the unit dose comprises about 3×10^{14} vg/kg or less, about 2×10^{14} vg/kg or less, about 1×10^{14} vg/kg or less, about 9×10^{13} vg/kg or less, about 8×10^{13} vg/kg or less, about 7×10^{13} vg/kg or less, about 6×10^{13} vg/kg or less, about 5×10^{13} vg/kg or less, about 4×10^{13} vg/kg or less, about 3×10^{13} vg/kg or less, about 2×10^{13} vg/kg or less, or about 1×10^{13} vg/kg or less.

[0078] In one aspect, the disclosure provides a method of alleviating one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion disclosed herein or the pharmaceutical composition disclosed herein.

[0079] In one aspect, the disclosure provides a method of improving one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion disclosed herein or the pharmaceutical composition disclosed herein.

[0080] In one aspect, the disclosure provides a method of preventing one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion disclosed herein or the pharmaceutical composition disclosed herein.

[0081] In one aspect, the disclosure provides an expression cassette comprising a polynucleotide comprising a 5' to 3' arrangement of elements, wherein the elements comprise: i) one or more promoters; ii) optionally one or more enhancers; iii) optionally one or more introns; iv) one or more transgenes; v) optionally one or more WPRE sequences; and vi) optionally one or more polyadenylation sequences, p(A). In some embodiments, the 5' to 3' arrangement of elements is selected from: i) 5'-promoter-intron-transgene-WPRE-p(A)-3'; ii) 5'-enhancer-promoter-transgene-WPRE-p(A)-3'; iii) 5'-enhancer-enhancer-promoter-transgene-WPRE-p(A)-3'; iv) 5'-enhancer-enhancer-promoter-intron-transgene-WPRE-p(A)-3'; v) 5'-enhancer-enhancer-promoter-intron-transgene-WPRE-p(A)-3'; vi) 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-enhancer-3'; vii) 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-enhancer-promoter-intron-transgene-p(A)-3'; viii) 5'-p(A)-WPRE-transgene-intron-promoter-enhancer-enhancer-promoter-intron-transgene-p(A)-3'; ix) 5'-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-3'; x) 5'-promoter-intron-transgene-WPRE-p(A)-promoter-intron-transgene-p(A)-3'; and xi) 5'-p(A)-WPRE-transgene-intron-promoter-promoter-intron-transgene-p(A)-3'. In some embodiments, the transgene has an increased expression level compared to a second expression cassette comprising a polynucleotide having an arrangement of elements from 5' to 3' comprising: 5'-promoter-transgene-WPRE-p(A)-3'. In some embodiments, the increased expression level is between about 1.5-fold and about 150-fold compared to the second expression cassette.

[0082] In one aspect, the disclosure provides a recombinant adeno-associated virus (rAAV) virion, comprising a capsid protein and a viral genome comprising an expression cassette of any one of disclosed herein, the expression cassette flanked by inverted terminal repeats. In some embodiments, the expression cassette comprises a transgene, wherein the transgene encodes a polypeptide use for treating or a preventing a heart disease, or alleviating symptoms associated with a heart disease. In some embodiments, the capsid protein is selected from any one of SEQ ID NOs: 145-200.

BRIEF DESCRIPTIONS OF DRAWINGS

[0083] **FIG. 1** shows a diagram of illustrative embodiments of expression cassettes comprising a polynucleotide encoding a promoter, a DWORF polypeptide, a WPRE sequence, and a poly(A) signal sequence flanked by AAV inverted terminal repeats.

[0084] **FIG. 2** is a graph showing expression of GFP delivered to human induced pluripotent stem cell derived cardiomyocytes *in vitro* using an embodiment of an expression cassette packaged into an rAAV virion.

[0085] **FIG. 3** is a graph showing expression of human DWORF polypeptide delivered *in vivo* in a murine model using an embodiment of an expression cassette packed into an rAAV virion using an AAV9 capsid protein.

[0086] **FIG. 4A** is a graph showing expression of human DWORF in induced pluripotent stem cell derived cardiomyocytes using an embodiment of an expression cassette packaged into an rAAV virion one of several AAV protein capsid proteins described herein.

[0087] **FIG. 4B** is a series of images showing expression of GFP using an embodiment of an expression cassette described herein packaged into an rAAV virion one of several AAV protein capsid proteins described herein.

[0088] **FIG. 5A** is a graph showing DWORF RNA expression in heart tissue from animals treated with rAAV virions containing an embodiment of an expression cassette packaged with one of five chimeric capsid proteins or the AAV9 capsid protein.

[0089] **FIG. 5B** is an immunoblot showing DWORF protein levels in heart tissue from animals treated with rAAV virions containing an embodiment of an expression cassette packaged with one of four chimeric capsid proteins or the AAV9 capsid protein.

[0090] **FIG. 6A** is a graph showing improved ejection fraction in a PLN-R14^Δ mouse model following treatment with an embodiment of an expression cassette packaged into an rAAV virion using AAV9 protein capsid.

[0091] **FIG. 6B** is a graph showing improved fractional shortening in a PLN-R14^Δ mouse model following treatment with an embodiment of an expression cassette packaged into an rAAV virion using AAV9 protein capsid.

[0092] **FIG. 7A** shows a diagram of an illustrative expression cassette orientation comprising a polynucleotide encoding a promoter, a DWORF polypeptide, a WPRE sequence, and a poly(A) signal sequence flanked by AAV inverted terminal repeats.

[0093] **FIG. 7B** shows a diagram of illustrative expression cassette orientations comprising a polynucleotide encoding a promoter, one or more enhancers, an intron, a DWORF polypeptide, a WPRE sequence, and a poly(A) signal sequence flanked by AAV inverted terminal repeats.

[0094] **FIG. 7C** shows a diagram of illustrative expression cassette orientations comprising a polynucleotide encoding a promoter, one or more enhancers, an intron, a DWORF polypeptide, a WPRE sequence, and a poly(A) signal sequence flanked by AAV inverted terminal repeats.

[0095] **FIG. 8A** is a schematic diagram which outlines the strategy for assessing the expression of DWORF in cardiomyocytes mice retro-orbitally injected with AAV9:DWORF constructs containing various regulatory elements and arrangements *in vivo*.

[0096] **FIG. 8B** is a western blot which demonstrates the expression of DWORF and GAPDH in cardiomyocytes mice retro-orbitally injected with AAV9:DWORF constructs containing various regulatory elements and arrangements *in vivo*.

[0097] **FIG. 8C** is a chart showing the DWORF expression level in an animal model achieved using a panel of rAAV virions comprising expression cassettes encoding a DWORF polypeptide.

[0098] **FIG. 9** is a plot showing improved ejection fraction in an animal model of cardiomyopathy treated with a panel of rAAV virions comprising expression cassettes encoding a DWORF polypeptide.

[0099] **FIG. 10** is a plot showing preserved ejection fraction in an animal model of cardiomyopathy treated with a panel of rAAV virions comprising expression cassettes encoding a DWORF polypeptide.

[00100] **FIG. 11A** is a schematic diagram of DWORF gene therapy efficacy study in the MLP-KO DCM mouse model.

[00101] **FIGS. 11B and 11C** demonstrate that AAV9:DWORF constructs containing novel promoters improve the ejection fraction relative to a saline control in the MLP-KO DCM mouse model.

[00102] **FIGS. 11D and 11E** demonstrate that AAV9:DWORF constructs improved exercise capacity, including running distance and time to exhaustion, in the MLP-KO DCM mouse model 26 weeks post-treatment.

[00103] **FIG. 12A** is a schematic diagram of detailing DWORF gene therapy tolerability study in naïve mice.

[00104] **FIG. 12B** demonstrates that AAV9:pHZ21 is well tolerated in naïve mice up to 2×10^{14} vg/kg dose with no difference in body weight, ejection fraction, heart rate, and left ventricular mass (LV mass).

DETAILED DESCRIPTION

[00105] In some aspects, described herein are optimized gene therapy expression cassettes, and their use in the treatment of heart disease. In some aspects, described herein are gene therapy expression cassettes that are able to mediate high expression of transgenes. In some embodiments, described herein are cardiac-specific gene therapy expression cassettes that are able to mediate significantly higher expression of a transgene than can be achieved using a cTnT promoter alone (e.g., a chicken cTnT promoter alone and/or a human cTnT promoter alone) or using the expression cassette depicted in FIG. 7A. In some aspects, described herein are gene therapy expression cassettes that allow to lower the viral load while achieving desired expression of a transgene. In some aspects, described herein are gene therapy expression cassettes that allow to achieve durable expression of a transgene. In some embodiments, described herein are gene therapy expression cassettes that allow to achieve expression of a transgene for at least, or more than, 12 weeks, 16 weeks, 18 weeks, 20 weeks, 22 weeks, 24 weeks, or 26 weeks, after administration of a gene therapy expression cassette comprising the transgene to a subject. In some embodiments, described herein are gene therapy expression cassettes that allow to achieve expression of a transgene for at least, or more than, 24 weeks or at least 6 months after administration of a gene therapy expression cassette comprising the transgene to a subject. In some aspects, administration of a gene therapy expression cassette described herein to a subject results in one or more improvements in cardiac function (e.g., an improvement in ejection fraction or an improvement in exercise capacity). In some embodiments, administration of a gene therapy expression cassette described herein to a subject results in a durable improvement in cardiac function (e.g., a durable improvement in ejection fraction or a durable improvement in exercise capacity). In some embodiments, administration of a gene therapy expression cassette described herein to a subject results in one or more improvements in cardiac function for at least, or more than, 12 weeks, 16 weeks, 18 weeks, 20 weeks, 22 weeks, 24 weeks, or 26 weeks after the administration. In some embodiments, administration of a gene therapy expression cassette described herein to a subject results in one or more improvements in cardiac function for at least, or more than, 24 weeks or at least 6 months after the administration. In some embodiments, a gene therapy expression cassette described herein allows for cardiac cell-specific expression of a transgene (e.g., cardiomyocyte-specific expression of a transgene).

[00106] In some aspects, the present disclosure provides a viral or a non-viral vector comprising an expression cassette encoding a gene product, and methods of use thereof. In

some embodiments, the expression cassettes described herein comprise a polynucleotide encoding a gene product operably linked to a cardiac cell-specific promoter and/or enhancer (such as any combination of cardiac cell-specific promoters and enhancers described herein, in any orientation as described herein). In some embodiments, the expression cassettes described herein comprise two copies of a polynucleotide encoding a gene product and a cardiac cell-specific promoter (such as any combination of such sequences, in any orientation as described herein). In some embodiments, the expression cassettes described herein comprise a polynucleotide encoding a gene product operably linked to a cardiac cell-specific promoter and/or enhancer (such as one promoter, or any combination of cardiac cell-specific promoters and enhancers described herein, in any orientation as described herein), a WPRE sequence, and/or one or two copies of a polyA sequence (such as any combination of such sequences, in any orientation as described herein). In some embodiments, the expression cassettes described herein comprise a polynucleotide encoding a gene product operably linked to a cardiac cell-specific promoter and/or an intron. In some embodiments, the expression cassettes described herein comprise one or two copies of a polynucleotide encoding a gene product, one or two copies of a cardiac cell-specific promoter, one, two or more copies of a cardiac-specific enhancer, and/or one or more intron sequences (such as any combination of such sequences, in any orientation as described herein). In some embodiments, the expression cassettes described herein comprise one or two copies of a polynucleotide encoding a gene product, one or two copies of a cardiac cell-specific promoter, one, two or more copies of a cardiac-specific enhancer, one or more intron sequences (such as any combination of such sequences, in any orientation as described herein), a WPRE sequence, and one or two copies of a polyA sequence (such as any combination of such sequences, in any orientation as described herein). In some embodiments, the vectors comprising the expression cassettes described herein may, for example, transduce cardiac cells. In some embodiments, targeted cardiac cells express the gene product, e.g., provide a high level of expression of the gene product. In some aspects, the present disclosure provides pharmaceutical compositions comprising the vectors described herein. In some aspects, the disclosure provides methods for treating a subject diagnosed with or at risk of a heart disease (e.g., cardiomyopathy) using the vectors and pharmaceutical compositions of the disclosure.

[00107] In some aspects, the present disclosure provides recombinant adeno-associated virus (rAAV) virions as a vector for the expression cassette described herein.

[00108] Abnormal calcium handling is a universal characteristic of cardiomyopathy, and reduced sarco/endoplasmic reticulum calcium ATPase (SERCA) activity plays a central role

in both the initiation and progression of the disease. SERCA is a calcium pump that promotes the uptake, maintenance, and cycling of Ca^{2+} ions in cardiac cells, such as cardiomyocytes. SERCA activity is regulated by an inhibitory peptide, phospholamban. There is significant interest in increasing the activity of SERCA by increasing the abundance of a polypeptide called Dwarf Open Reading Frame (DWORF) that enhances SERCA activity through its direct displacement of the SERCA inhibitory peptide phospholamban. Contacting SERCA with DWORF is a strategy for increasing SERCA activity in a cell.

[00109] In some aspects, the present disclosure provides recombinant adeno-associated virus (rAAV) virions comprising a polynucleotide encoding a DWORF polypeptide, or a functional variant thereof, and methods of use thereof. In some embodiments, the rAAV virions described herein comprise a polynucleotide encoding a DWORF polypeptide, or a functional variant thereof, operably linked to a cardiac cell-specific promoter and/or enhancer (such as any combination of cardiac cell-specific promoters and enhancers described herein, in any orientation as described herein). In some embodiments, the rAAV virions described herein comprise one or two copies of a polynucleotide encoding a DWORF polypeptide, or a functional variant thereof, a WPRE sequence, and one or two copies of a polyA sequence (such as any combination of such sequences, in any orientation as described herein). In some embodiments, the rAAV virions described herein comprise a polynucleotide encoding a DWORF polypeptide operably linked to a cardiac cell-specific promoter and/or an intron. In some embodiments, the rAAV virions described herein comprise one or two copies of a polynucleotide encoding DWORF, one or two copies of a cardiac cell-specific promoter, one, two or more copies of a cardiac-specific enhancer, and/or one or more intron sequences (such as any combination of such sequences, in any orientation as described herein). In some embodiments, the rAAV virions described herein comprise one or two copies of a polynucleotide encoding DWORF, one or two copies of a cardiac cell-specific promoter, one, two or more copies of a cardiac-specific enhancer, one or more intron sequences (such as any combination of such sequences, in any orientation as described herein), a WPRE sequence, and one or two copies of a polyA sequence (such as any combination of such sequences, in any orientation as described herein). In some embodiments, the rAAV virions described herein may, for example, transduce cardiac cells with a polynucleotide with a sequence encoding DWORF polypeptide operatively linked to a cardiac cell-specific promoter region into the host cell genome. In some embodiments, targeted cardiac cells express the DWORF polypeptide and may have increased SERCA activity. Also provided in the disclosure are pharmaceutical compositions comprising the rAAV virions described herein. In an aspect, the disclosure

provides methods for treating a subject diagnosed with or at risk of cardiomyopathy using the rAAV virions and pharmaceutical compositions of the disclosure.

TERMINOLOGY

[00110] Unless the context indicates otherwise, the features of the invention can be used in any combination. Any feature or combination of features set forth can be excluded or omitted. Certain features of the invention, which are described in separate embodiments may also be provided in combination in a single embodiment. Features of the invention, which are described in a single embodiment may also be provided separately or in any suitable sub-combination.

[00111] Generally, 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 belongs. The detailed description is divided into sections only for the reader's convenience and disclosure found in any section may be combined with that in another section.

[00112] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of tissue culture, immunology, molecular biology, cell biology and recombinant DNA, which are within the skill of the art. *See, e.g.*, Sambrook and Russell eds. (2001) *Molecular Cloning: A Laboratory Manual*, 3rd edition; Ausubel et al. eds. (2007) *Current Protocols in Molecular Biology*; *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson et al. (1991) *PCR 1: A Practical Approach* (IRL Press at Oxford University Press); MacPherson et al. (1995) *PCR 2: A Practical Approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Pat. No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation*; IRL Press (1986) *Immobilized Cells and Enzymes*; Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); Herzenberg et al. eds (1996) *Weir's Handbook of Experimental Immunology*; *Manipulating the Mouse Embryo: A Laboratory Manual*, 3rd edition (2002) Cold Spring Harbor Laboratory Press; Sohail (2004) *Gene Silencing by RNA Interference: Technology and Application* (CRC Press); and Sell (2013) *Stem Cells Handbook*.

[00113] The conjunction “and/or” means both “and” and “or,” and lists joined by “and/or” encompasses all possible combinations of one or more of the listed items.

[00114] As used herein, the term “about,” when used to modify a numeric value, indicates that deviations of up to 10% above and below the numeric value remain within the intended meaning of the recited value.

[00115] “AAV” is an abbreviation for adeno-associated virus. The term covers all subtypes of AAV, except where a subtype is indicated, and to both naturally occurring and recombinant forms. The abbreviation “rAAV” refers to recombinant adeno-associated virus. “AAV” includes AAV or any subtype. “AAV5” refers to AAV subtype 5. “AAV9” refers to AAV subtype 9. The genomic sequences of various serotypes of AAV, as well as the sequences of the native inverted terminal repeats (ITRs), Rep proteins, and capsid subunits may be found in the literature or in public databases such as GenBank. *See, e.g.*, GenBank Accession Numbers NC_002077 (AAV1), AF063497 (AAV1), NC_001401 (AAV2), AF043303 (AAV2), NC_001729 (AAV3), NC_001829 (AAV4), U89790 (AAV4), NC_006152 (AAV5), AF513851 (AAV7), AF513852 (AAV8), NC_006261 (AAV8), and AY530579 (AAV9). Publications describing AAV include Srivistava et al. (1983) *J. Virol.* 45:555; Chiorini et al. (1998) *J. Virol.* 71:6823; Chiorini et al. (1999) *J. Virol.* 73:1309; Bantel-Schaal et al. (1999) *J. Virol.* 73:939; Xiao et al. (1999) *J. Virol.* 73:3994; Muramatsu et al. (1996) *Virol.* 221:208; Shade et al. (1986) *J. Virol.* 58:921; Gao et al. (2002) *Proc. Nat. Acad. Sci. USA* 99: 11854; Moris et al. (2004) *Virology* 33:375-383; Int’l Pat. Publ Nos. WO2018/222503A1, WO2012/145601A2, WO2000/028061A2, WO1999/61601A2, and WO1998/11244A2; U.S. Pat. Appl. Nos. 15/782,980 and 15/433,322; and U.S. Pat. Nos. 10,036,016, 9,790,472, 9,737,618, 9,434,928, 9,233,131, 8,906,675, 7,790,449, 7,906,111, 7,718,424, 7,259,151, 7,198,951, 7,105,345, 6,962,815, 6,984,517, and 6,156,303.

[00116] An “rAAV virion” refers to a viral particle including at least one viral capsid protein (*e.g.* VP1) and an encapsidated rAAV vector (or fragment thereof).

[00117] An “infectious” virion or viral particle is one that comprises a competently assembled viral capsid and is capable of delivering a polynucleotide component into a cell for which the virion is tropic.

[00118] “Packaging” refers to a series of intracellular events that result in the assembly of an rAAV virion including encapsidation of the rAAV vector. AAV “*rep*” and “*cap*” genes refer to polynucleotide sequences encoding replication and encapsidation proteins of adeno-associated virus. AAV *rep* and *cap* are referred to herein as AAV “packaging genes.” Packaging requires either a helper virus itself or, more commonly in recombinant systems,

helper virus function supplied by a helper-free system (*i.e.* one or more helper plasmids). A “helper virus” for AAV refers to a virus that allows AAV (*e.g.* wild-type AAV) to be replicated and packaged by a mammalian cell. The helper viruses may be an adenovirus, herpesvirus or poxvirus, such as vaccinia.

[00119] The term “inverted terminal repeats” or “ITRs” as used herein refers to AAV viral cis-elements named so because of their symmetry. These elements are essential for efficient multiplication of an AAV genome. In some embodiments, the minimal elements indispensable for ITR function are a Rep-binding site and a terminal resolution site plus a variable palindromic sequence allowing for hairpin formation.

[00120] The terms “parental capsid” or “parental sequence” refer to a reference sequence from which a particle capsid or sequence is derived. Unless otherwise specified, parental sequence refers to the sequence of the wild-type capsid protein of the same serotype as the engineered capsid protein.

[00121] “Recombinant,” as applied to a polynucleotide means that the polynucleotide is distinct from a polynucleotide found in nature (*e.g.*, the polynucleotide is the product of various combinations of cloning, restriction or ligation steps, and other procedures, or the polynucleotide is assembled from synthetic oligonucleotides. A “recombinant” protein is a protein produced from a recombinant polypeptide. A recombinant virion is a virion that comprises a recombinant polynucleotide and/or a recombinant protein, *e.g.* a recombinant capsid protein.

[00122] As used herein, the term “percent sequence identity,” and the term “identity” when it is used to refer to % sequence identity, with respect to a reference nucleic acid or amino acid sequence is the percentage of nucleic acid bases or amino acid residues in a candidate sequence that are identical with the nucleic acid bases or amino acid residues in the reference sequence, respectively, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Methods of sequence alignment are well known in the art. Sequences can be aligned using various computer programs, such BLAST, available at ncbi.nlm.nih.gov. Alignments can be made using publicly available computer software such as BLASTp, BLASTn, BLAST-2, ALIGN or MegAlign Pro (DNASTAR) software. Other techniques for alignment are described in *Methods in Enzymology*, vol. 266: *Computer Methods for Macromolecular Sequence Analysis* (1996); and *Meth. Mol. Biol.* 70: 173-187 (1997); *J. Mol. Biol.* 48: 44. Skill artisans are capable of choosing an appropriate alignment method depending on various factors including sequence length, divergence, and the presence of absence of insertions or deletions with respect to the reference sequence.

[00123] The terms "operably linked" and "operatively linked" refer to a nucleic acid sequence placed into a functional relationship with another nucleic acid sequence. These terms, as used herein, have a meaning commonly known in the art. For example, a promoter is operably linked to a gene when that promoter is placed in a location that permits that promoter to initiate transcription of that gene. An enhancer is operably linked to a gene when that enhancer, when bound by an appropriate transcription factor, can regulate (e.g., enhance) expression of that gene.

[00124] "Treatment," "treating," and "treat" are defined as acting upon a disease, disorder, or condition with an agent to reduce or ameliorate harmful or any other undesired effects of the disease, disorder, or condition and/or its symptoms.

[00125] As used herein the term "effective amount" and the like in reference to an amount of a composition refers to an amount that is sufficient to induce a desired physiologic outcome (e.g., treatment of a disease). An effective amount can be administered in one or more administrations, applications or dosages. Such delivery is dependent on a number of variables including the time period which the individual dosage unit is to be used, the bioavailability of the composition, the route of administration, etc. It is understood, however, that specific amounts of the compositions (e.g., rAAV virions) for any particular subject depends upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the composition combination, severity of the particular disease being treated and form of administration.

[00126] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00127] The terms "individual," "subject," and "patient" are used interchangeably herein, and refer to a mammal, including, but not limited to, human and non-human primates (e.g., simians); mammalian sport animals (e.g., horses); mammalian farm animals (e.g., sheep, goats, etc.); mammalian pets (e.g., dogs, cats, etc.); and rodents (e.g., mice, rats, etc.).

[00128] As used herein, the term "cardiomyopathy" refers to any disease or dysfunction that affects myocardium directly. The etiology of the disease or disorder may be, for example, inflammatory, metabolic, toxic, infiltrative, fibroplastic, hematological, genetic, or unknown in origin. Two fundamental forms are recognized (1) a primary type, consisting of heart muscle

disease of unknown cause; and (2) a secondary type, consisting of myocardial disease of known cause or associated with a disease involving other organ systems. “Specific cardiomyopathy” refers to heart diseases associated with certain systemic or cardiac disorders; examples include hypertensive and metabolic cardiomyopathy. The cardiomyopathies include dilated cardiomyopathy (DCM), a disorder in which left and/or right ventricular systolic pump function is impaired, leading to progressive cardiac enlargement; hypertrophic cardiomyopathy, characterized by left ventricular hypertrophy without obvious causes such as hypertension or aortic stenosis; and restrictive cardiomyopathy, characterized by abnormal diastolic function and excessively rigid ventricular walls that impede ventricular filling. Cardiomyopathies also include left ventricular non-compaction, arrhythmogenic right ventricular cardiomyopathy, and arrhythmogenic right ventricular dysplasia.

[00129] “Heart failure” refers to the pathological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or allows the heart to do so only from an abnormally elevated diastolic volume. Heart failure includes systolic and diastolic failure. Patients with heart failure are classified into those with low cardiac output (typically secondary to ischemic heart disease, hypertension, dilated cardiomyopathy, and/or valvular or pericardial disease) and those with elevated cardiac output (typically due to hyperthyroidism, anemia, pregnancy, arteriovenous fistulas, beriberi, and Paget’s disease). Heart failure includes heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

[00130] The term “therapeutic gene” as used herein refers to a gene that, when expressed, confers a beneficial effect on the cell or tissue in which it is present, or on a mammal in which the gene is expressed. Examples of beneficial effects include amelioration of a sign or symptom of a condition or disease, prevention or inhibition of a condition or disease, or conferral of a desired characteristic. Therapeutic genes include genes that partially or wholly correct a genetic deficiency in a cell or mammal.

[00131] As used herein the term “cardiac cell” refers to any cell present in the heart that provides a cardiac function, such as heart contraction or blood supply, or otherwise serves to maintain the structure of the heart. Cardiac cells as used herein encompass cells that exist in the epicardium, myocardium or endocardium of the heart. Cardiac cells also include, for example, cardiac muscle cells or cardiomyocytes, and cells of the cardiac vasculatures, such as cells of a coronary artery or vein. Other non-limiting examples of cardiac cells include epithelial cells, endothelial cells, fibroblasts, cardiac stem or progenitor cells, cardiac

conducting cells and cardiac pacemaking cells that constitute the cardiac muscle, blood vessels and cardiac cell supporting structure. Cardiac cells may be derived from stem cells, including, for example, embryonic stem cells or induced pluripotent stem cells.

EXPRESSION CASSETTES

Expression Cassette Overview

[00132] The vectors of the disclosure may comprise any expression cassette described herein. In some aspects, the rAAV virions of the disclosure comprise a viral genome comprising an expression cassette as shown in **FIG. 1**, **FIGs. 7A-7C**, or variations thereof. The expression cassette may comprise a polynucleotide encoding any gene product described herein, or functional variant thereof, optionally operatively linked to a promoter, optionally an intron, optionally a polyadenylation (poly(A)) signal, optionally a woodchuck hepatitis virus post-transcriptional element (WPRE), and optionally a transcription termination signal. The expression cassette may be flanked by inverted terminal repeats (ITRs). These components provide the function of expressing the transgene after a host cell is targeted by, e.g., the rAAV virion. The promoter sequence, when present, controls expression of the polynucleotide encoding a gene product.

[00133] The expression cassette may comprise a polynucleotide encoding a DWORF polypeptide, or functional variant thereof, optionally operably linked to a promoter, optionally an intron, optionally a polyadenylation (poly(A)) signal, optionally a woodchuck hepatitis virus post-transcriptional element (WPRE), and optionally a transcription termination signal. The promoter sequence, when present, controls expression of the polynucleotide encoding the DWORF polypeptide, or functional variant thereof. The promoter sequence can be a cardiac cell-specific promoter. The promoter sequence can be further operably linked to an enhancer, such as any cardiac cell-specific enhancer described herein.

[00134] In any constructs shown in **FIG. 1** and **FIGs. 7A-7C**, DWORF nucleotide sequence can be replaced by a nucleotide sequence encoding another gene product or polypeptide, such as any gene product or polypeptide described herein (e.g., see the description of transgenes and gene products encoded by such transgenes below). Accordingly, in some embodiments, provided herein is any expression cassette shown in **FIG. 1** and **FIGs. 7A-7C** wherein the DWORF nucleotide sequence is replaced by a nucleotide sequence encoding another gene product or polypeptide.

[00135] Also, in any expression cassettes shown in Table 1, DWORF nucleotide sequence can be replaced by a nucleotide sequence encoding another gene product or

polypeptide, such as any gene product or polypeptide described herein (e.g., see the description of transgenes and gene products encoded by such transgenes below). Further, in any expression cassette shown in Table 1, the ITR sequences can be omitted. Accordingly, in some embodiments, provided herein is any expression cassette shown in Table 1 wherein the DWORF nucleotide sequence is replaced by a nucleotide sequence encoding another gene product or polypeptide, and/or wherein the specified ITR sequence is not present.

Transgenes

[00136] In some embodiments, the expression cassette of the disclosure comprises a transgene. Transgenes can include nucleotide sequences encoding any polypeptide for use in treating or preventing a heart disease or disorder, or alleviating symptoms therefrom. The promoters, enhancers and combinations thereof described herein are operably linked to a transgene encoding a product. A transgene can be a gene or nucleotide sequence that encodes a product, or functional fragment thereof. A product can be, for example, a polypeptide or a non-coding nucleotide. By non-coding nucleotide, it is meant that the sequence transcribed from the transgene or nucleotide sequence is not translated into a polypeptide. In some embodiments, the product encoded by the transgene or nucleotide operably linked to an enhancer described herein is a non-coding polynucleotide. A non-coding polynucleotide can be an RNA, such as for example a microRNA (miRNA or miR), short hairpin RNA (shRNA), long non-coding RNA (lncRNA), and/or a short interfering RNA (siRNA). In some embodiments, the transgene encodes a product natively expressed by a cardiac cell, e.g., a cardiomyocyte. In some embodiments, the transgene encodes a product natively expressed in a cell type other than a cardiac cell. Without limitation, cell types other than cardiac fibroblasts can be from any multicellular organism, single-celled organism, or microorganism.

[00137] In some embodiments, the transgene encodes a polypeptide. In some embodiments, the transgene encodes a non-coding polynucleotide such as, for example, a microRNA (miRNA or miR).

[00138] In some embodiments, the transgene comprises a sequence encoding a product selected from cadherins, connexins, Cx43, growth factors such as fibroblast growth factor (FGF)-2 and transforming growth factor- β , cytokines such as interleukin (IL)-1 β and the IL-6 family, leukemia inhibitory factor, cardiotrophin-1, cardiogenic transcription factors, insulin-like growth factor, GATA4, MEF2C, TBX5, ESRRG, MESP1, MYOCD, ZFPM2, HAND2, miR-1, miR-133, Oct4, Sox2, Klf4, c-Myc, SRF, SMARCD3, Nkx2-5, Akt, PKB, Baf60c, BMP4, miR-208, and miR-499.

[00139] In some embodiments, the transgene encodes a functional cardiac protein. In some embodiments, the gene product is a genome-editing endonuclease (optionally with a guide RNA, single-guide RNA, and/or repair template) that replaces or repairs a non-functional cardiac protein into a functional cardiac protein. Functional cardiac proteins include, but are not limited to cardiac troponin T; a cardiac sarcomeric protein; β -myosin heavy chain; myosin ventricular essential light chain 1; myosin ventricular regulatory light chain 2; cardiac α -actin; α -tropomyosin; cardiac troponin I; cardiac myosin binding protein C; four-and-a-half LIM protein 1; titin; 5'-AMP-activated protein kinase subunit gamma-2; troponin I type 3; myosin light chain 2; actin α cardiac muscle 1; cardiac LIM protein; caveolin 3 (CAV3); galactosidase α (GLA); lysosomal-associated membrane protein 2 (LAMP2); mitochondrial transfer RNA glycine (MTTG); mitochondrial transfer RNA isoleucine (MTTI); mitochondrial transfer RNA lysine (MTTK); mitochondrial transfer RNA glutamine (MTTQ); myosin light chain 3 (MYL3); troponin C (TNNC1); transthyretin (TTR); sarcoendoplasmic reticulum calcium-ATPase 2a (SERCA2a); stromal-derived factor-1 (SDF-1); adenylyl cyclase-6 (AC6); beta-ARKct (β -adrenergic receptor kinase C terminus); fibroblast growth factor (FGF); platelet-derived growth factor (PDGF); vascular endothelial growth factor (VEGF); hepatocyte growth factor; hypoxia inducible growth factor; thymosin β 4 (TMSB4X); nitric oxide synthase-3 (NOS3); unc-119 (UCN3); melusin; apolipoprotein-E (ApoE); superoxide dismutase (SOD); and S100A1 (a small calcium binding protein; *see, e.g.,* Ritterhoff and Most (2012) *Gene Ther.* 19:613; Kraus et al. (2009) *Mol. Cell. Cardiol.* 47:445).

[00140] In some embodiments, the transgene can treat or prevent coronary heart disease. In some embodiments, the transgene comprises a sequence encoding a product selected from vascular endothelial growth factor (VEGF), a VEGF isoform, VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-D^{dNdC}, VEGF-A_{116A}, VEGF-A₁₆₅, VEGF-A₁₂₁, VEGF-2, placenta growth factor (PIGF), fibroblast growth factor 4 (FGF-4), human growth factor (HGF), human granulocyte colony-stimulating factor (hGCSF), and hypoxia inducible factor 1 α (HIF-1 α).

[00141] In some embodiments, the transgene can treat or prevent heart failure. In some embodiments, the transgene can treat or prevent chronic heart failure. In some embodiments, the transgene comprises a sequence encoding a product selected from SERCA2a, stromal cell-derived factor-1 (SDF-1), adenylyl cyclase type 6, S100A1, miRNA-17-92, miR-302-367, anti-miR-29a, anti-miR-30a, anti-miR-141, cyclin A2, cyclin-dependent kinase 2, Tbx20, miRNA-590, miRNA-199, anti-sense oligonucleotide against Lp(a), interfering RNA against PCSK9, anti-sense oligonucleotide against apolipoprotein C-III, lipoprotein lipase^{S447X}, anti-

sense oligonucleotide against apolipoprotein B, anti-sense oligonucleotide against c-myc, and E2F oligonucleotide decoy.

[00142] In some embodiments, the transgene encodes a gene product whose expression complements a defect in a gene responsible for a genetic disorder. The disclosure polynucleotides encoding one or more of the following—*e.g.*, for use, without limitation, in the disorder indicated in parentheses, or for other disorders caused by each: TAZ (Barth syndrome); FXN (Freidrich's Ataxia); CASQ2 (CPVT); FBN1 (Marfan); RAF1 and SOS1s (Noonan); SCN5A (Brugada); KCNQ1 and KCNH2s (Long QT Syndrome); DMPK (Myotonic Dystrophy 1); LMNA (Limb Girdle Dystrophy Type 1B); JUP (Naxos); TGFBR2 (Loeys-Dietz); EMD (X-Linked EDMD); and ELN (SV Aortic Stenosis). In some embodiments, a polynucleotide encodes one or more of: cardiac troponin T (TNNT2); BAG family molecular chaperone regulator 3 (BAG3); myosin heavy chain (MYH7); tropomyosin 1 (TPM1); myosin binding protein C (MYBPC3); 5'-AMP-activated protein kinase subunit gamma-2 (PRKAG2); troponin I type 3 (TNNI3); titin (TTN); myosin, light chain 2 (MYL2); actin, alpha cardiac muscle 1 (ACTC1); potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1); myocyte enhancer factor 2c (MEF2C); and cardiac LIM protein (CSRP3).

[00143] In some embodiments, the transgene comprises a nucleotide sequence encoding a protein selected from DWORF, junctophilin (*e.g.*, JPH2), BAG family molecular chaperone regulator 3 (BAG3), phospholamban (PLN), alpha-crystallin B chain (CRYAB), LMNA (such as Lamin A and Lamin C isoforms), troponin I type 3 (TNNI3), lysosomal-associated membrane protein 2 (LAMP2, such as LAMP2a, LAMP2b and LAMP2c isoforms), desmoplakin (DSP, such as DPI and DPII isoforms), desmoglein 2 (DSG2), and junction plakoglobin (JUP). In some embodiments, the transgene comprises a nucleotide sequence encoding a human protein. In some embodiments, the transgene comprises a human nucleotide sequence (a human DNA sequence). In some embodiments, the transgene comprises a DNA sequence that has been codon-optimized. In some embodiments, the transgene comprises a nucleotide sequence encoding a wild-type protein, or a functionally active fragment thereof.

[00144] In some embodiments, the transgene comprises a polynucleotide sequence encoding a DWORF polypeptide.

[00145] In some embodiments, the transgene comprises a polynucleotide sequence encoding a junctophilin 2 (JPH2) polypeptide. In some embodiments, the transgene comprises a polynucleotide sequence encoding a full-length JPH2 polypeptide. In some embodiments, the transgene comprises a polynucleotide sequence encoding an N-terminal fragment of the

JPH2 polypeptide. In some embodiments, the transgene comprises a polynucleotide sequence encoding an N-terminal fragment of the JPH2 polypeptide, which retains the JPH2 activity.

[00146] In some embodiments, the transgene comprises a polynucleotide sequence encoding a BAG3 polypeptide.

[00147] In some embodiments, the transgene comprises a polynucleotide sequence encoding a CRYAB polypeptide.

[00148] In some embodiments, the transgene comprises a polynucleotide sequence encoding a LMNA polypeptide. In some embodiments, the transgene comprises a polynucleotide sequence encoding the LaminA isoform of LMNA. In some embodiments, the transgene comprises a polynucleotide sequence encoding the LaminC isoform of LMNA.

[00149] In some embodiments, the transgene comprises a polynucleotide sequence encoding a TNNT3 polypeptide.

[00150] In some embodiments, the transgene comprises a polynucleotide sequence encoding a PLN polypeptide.

[00151] In some embodiments, the transgene comprises a polynucleotide sequence encoding a LAMP2 polypeptide. In some embodiments, the transgene comprises a polynucleotide sequence encoding the LAMP2a isoform. In some embodiments, the transgene comprises a polynucleotide sequence encoding the LAMP2b isoform. In some embodiments, the transgene comprises a polynucleotide sequence encoding the LAMP2c isoform.

[00152] In some embodiments, the transgene comprises a polynucleotide sequence encoding a DSP polypeptide. In some embodiments, the transgene comprises a polynucleotide sequence encoding the DPI isoform of DSP. In some embodiments, the transgene comprises a polynucleotide sequence encoding the DPII isoform of DSP.

[00153] In some embodiments, the transgene comprises a polynucleotide sequence encoding a DSG2 polypeptide.

[00154] In some embodiments, the transgene comprises a polynucleotide sequence encoding a JUP polypeptide.

[00155] It is appreciated that the transgenes described herein are non-limiting and transgenes useful for treating a heart disease may be discovered for use in the expression cassettes described herein.

DWORF Transgene

[00156] In some embodiments, the expression cassette of the present disclosure comprises a polynucleotide sequence encoding a DWORF polypeptide. In some embodiments, the expression cassette provides increased expression of a DWORF polypeptide in cardiac cell.

In some embodiments, the cardiac cell is a cardiomyocyte. In some embodiments, expression of the DWORF polypeptide may be increased 5%, 10%, 15%, 20%, or 25% compared to expression of the DWORF polypeptide factor in an untreated subject. In some embodiments, expression of the DWORF polypeptide may be increased 1-fold, 2-fold, 3-fold, 4-fold, or 5-fold compared to expression of the DWORF polypeptide in an untreated subject. In some embodiments, the DWORF polypeptide may be expressed at any detectable level in the cardiac cell, whereas the DWORF polypeptide may not be expressed, or expressed at undetectable levels, in an untreated subject. Put another way, the cardiac cell to which the rAAV virion is administered may express a DWORF polypeptide in higher abundance than in a cardiac cell that has only endogenous (*i.e.*, native) expression of the DWORF polypeptide.

[00157] DWORF polypeptide is an endogenous enhancer of SERCA calcium pump activity, a desirable drug target for regulation of cardiac contractility. DWORF is also an unusually small protein, which makes it a good candidate for delivery to a target cell or tissue by rAAV virions. Because DWORF is an endogenous protein, expression of DWORF in humans would not be immunogenic, allowing for long-term dosing and expression. The structural features of DWORF polypeptides are as follows. First, the polypeptides may have 5 to 35 consecutive residues of the Dwarf Open Reading Frame (DWORF), located on chromosome 3 of a mammalian species, including mouse and human (Nelson et al. *Science*. 351: 271–275 (2016); U.S. Pat. No. 10,570,183). Thus, the term “a peptide having no more than X consecutive residues,” even when including the term “comprising,” cannot be understood to comprise a greater number of consecutive residues. In general, the peptides will be 35 residues or less, again, comprising no more than 20 consecutive residues of DWORF. The overall length may be 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 residues. Ranges of peptide length of 5-34/35 residues, 6-34/35 residues, 7-50 residues, 7-25, residues, 5-20 residues, 6-20 residues, 7-20 residues, and 7-15 residues are contemplated. The number of consecutive DWORF residues may be 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. Ranges of consecutive residues of 5-20 residues, 5-20 residues, 6-20 residues, 7-20 residues and 5-15 residues, 5-15, residues, 6-15 residues or 7-15 residues are contemplated. Illustrative DWORF sequences can be found in Table 2a.

[00158] In some embodiments, DWORF polypeptide is human DWORF polypeptide. In some embodiments, the expression cassette comprises a single polynucleotide sequence encoding a dwarf open reading frame (DWORF) polypeptide. In some embodiments, the polynucleotide sequence encoding DWORF is codon optimized. In some embodiments, the

DWOLF polypeptide comprises a polypeptide sequence that shares at least 95% identity to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In some embodiments, the DWOLF polypeptide comprises a polypeptide sequence that shares at least 98% identity to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In some embodiments, the DWOLF polypeptide comprises the polypeptide sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9.

Table 2a: Illustrative DWOLF Sequences

DWOLF Variant	DWOLF Polypeptide	Nucleotide (Open Reading Frame)
Mouse Variant	MAEKESTSPHLMVPILLVGVIV GCIIVYIVFF (SEQ ID NO: 1)	ATGGCTGAGAAAGAGTCAACATCACCACACCT CATGGTCCCATTTCTCTCCTGGTTGGATGGATT GTAGGCTGCATCATCGTTATTTACATTGTCTTCT TCTAA (SEQ ID NO: 2)
Human Variant	MAEKAGSTFSLHVPILLIGWIV GCIIMYVFFS (SEQ ID NO: 3)	ATGGCTGAGAAAAGCGGGGTCTACATTTTCACAC CTTCTGGTTCCATTCTTCTCCTGATTGGCTGGA TTGTGGGCTGCATCATAATGATTTATGTTGTCTT CTCTTAG (SEQ ID NO: 4)
Artificial	MAEKAEESTSPHLMVPILLVGVIV VGCIIVYIVFF (SEQ ID NO: 5)	ATGGCTGAGAAAGCAGAGTCAACATCACCACA CCTCATGGTTCCCATTTCTCTCCTGGTTGGATGG ATTGTAGGCTGCATCATCGTTATTTACATTGTCT TCTTCTAA (SEQ ID NO: 6)
Artificial	MAEKESTSPHLIVPILLVGVIVG CIIVYIVFF (SEQ ID NO: 7)	ATGGCTGAGAAAGAGTCAACATCACCACACCT CATTGTTCCCATTTCTCTCCTGGTTGGATGGATT GTAGGCTGCATCATCGTTATTTACATTGTCTTCT TCTAA (SEQ ID NO: 8)
Artificial	MAEKAEESTSPHLIVPILLVGVIV GCIIVYIVFF (SEQ ID NO: 9)	ATGGCTGAGAAAGCAGAGTCAACATCACCACA CCTCATTGTTCCCATTTCTCTCCTGGTTGGATGG ATTGTAGGCTGCATCATCGTTATTTACATTGTCT TCTTCTAA (SEQ ID NO: 10)
Human Variant	MAEKESTSPHLMVPILLVGVIV GCIIVYIVFF (SEQ ID NO: 32)	ATGGCAGAGAAAGGCTGGAAGCACTTTCTCTCA CCTGCTCGTGCCGATTTTGCTTTTGATTGGGTG GATAGTTGGCTGTATCATAATGATCTACGTTGT CTTTTCATAG (SEQ ID NO: 33)
Human Variant	MAEKGSTFSLHVPILLIGWIVG CIIMYVFFS (SEQ ID NO: 43)	ATGGCCGAGAAAGGCGAGCACCTTCAGCCACCT GCTGGTGCCCATCCTGCTGCTGATCGGCTGGAT CGTGGGCTGCATCATCATGATCTACGTGGTGT CAGC (SEQ ID NO: 44)
Codon Optimized Mouse DWOLF	MAEKESTSPHLMVPILLVGVIV GCIIVYIVFF (SEQ ID NO: 1)	ATGGCCGAGAAAGGAATCTACCAGCCCCACCT GATGGTGCCTATTCTGCTGCTGGTGGGCTGGAT CGTCGGCTGCATCATCGTGATCTACATCGTGT CTTCTGA (SEQ ID NO: 76)
Codon Optimized Human DWOLF	MAEKAGSTFSLHVPILLIGWIV GCIIMYVFFS (SEQ ID NO: 3)	ATGGCCGAGAAAGGCCGATCTACCTTCAGCCA CCTGCTGGTCCCTATTCTGCTGCTGATCGGCTG GATCGTGGGCTGCATCATCATGATCTACGTGGT GTTCAGCTGA (SEQ ID NO: 77)

Other Exemplary Transgenes

[00159] In some embodiments, the expression cassette of the present disclosure comprises a polynucleotide sequence encoding another gene product (not DWOLF), for example, a polypeptide selected from JPH2, BAG3, CRYAB, LMNA (e.g., Lamin A or Lamin C isoform), TNIN3, PLN, LAMP2 (e.g., LAMP2a, LAMP2b or LAMP2c isoform), DSP (e.g.,

DPI or DPII isoform), desmoglein 2 (DSG2), and junction plakoglobin (JUP). In some embodiments, the expression cassette provides increased expression of the gene product in a cardiac cell. In some embodiments, the cardiac cell is a cardiomyocyte. In some embodiments, expression of the polypeptide encoded by the polynucleotide sequence may be increased 5%, 10%, 15%, 20%, or 25% compared to expression in an untreated subject. In some embodiments, expression of the polypeptide encoded by the polynucleotide sequence may be increased 1-fold, 2-fold, 3-fold, 4-fold, or 5-fold compared to expression in an untreated subject. In some embodiments, the polypeptide encoded by the polynucleotide sequence may be expressed at any detectable level in the cardiac cell, whereas it may not be expressed, or expressed at undetectable levels, in an untreated subject. In some embodiments, the cardiac cell to which a vector described herein is administered may express a polypeptide encoded by the polynucleotide sequence in higher abundance than in a cardiac cell that has only endogenous (*i.e.*, native) expression of the polypeptide.

[00160] In some embodiments, the polypeptide is a human polypeptide. In some embodiments, the polynucleotide sequence encoding the polypeptide is codon optimized. In some embodiments, the expression cassette comprises a single polynucleotide sequence encoding a polypeptide. In some embodiments, the expression cassette comprises two polynucleotide sequences encoding a polypeptide. In some embodiments, the expression cassette comprises two polynucleotide sequences encoding a polypeptide, wherein at least one of the sequences is codon-optimized.

[00161] In some embodiments, a polynucleotide sequence encodes JPH2, e.g., human JPH2. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:201. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding JPH2, e.g., human JPH2. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is JPH2, e.g., human JPH2. In some embodiments, the JPH2 polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:202.

[00162] In some embodiments, a polynucleotide sequence encodes an N-terminal fragment of JPH2, e.g., human JPH2. In some embodiments, a polynucleotide sequence of an N-terminal fragment of JPH2 has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:227. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding an N-terminal fragment of JPH2, e.g., human JPH2. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is an N-terminal fragment of JPH2, e.g., human JPH2. In some embodiments,

the N-terminal fragment of JPH2 polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:228. The human sequences of an N-terminal fragment of JPH2 correspond to the mouse JPH2 N-terminal peptide with amino acids 1-565, generated by a Calpain cleavage (see Guo et al., 2018, Science 362, doi: 10.1126/science.aan3303).

[00163] In some embodiments, a polynucleotide sequence encodes BAG3, e.g., human BAG3. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:203. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding BAG3, e.g., human BAG3. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is BAG3, e.g., human BAG3. In some embodiments, the BAG3 polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:204.

[00164] In some embodiments, a polynucleotide sequence encodes CRYAB, e.g., human CRYAB. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:205. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding CRYAB, e.g., human CRYAB. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is CRYAB, e.g., human CRYAB. In some embodiments, the CRYAB polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:206.

[00165] In some embodiments, a polynucleotide sequence encodes LMNA, e.g., human LMNA. In some embodiments, a polynucleotide sequence encodes Lamin A isoform of LMNA, e.g., human Lamin A. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:207. In some embodiments, a polynucleotide sequence encodes Lamin C isoform of LMNA, e.g., human Lamin C. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:209. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding an LMNA polypeptide. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding Lamin A or Lamin C, e.g., human Lamin A or Lamin C. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is LMNA, e.g., human LMNA. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is Lamin A isoform of LMNA, e.g., human.

In some embodiments, the Lamin A polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:208. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is Lamin C isoform of LMNA, e.g., human. In some embodiments, the Lamin C polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:210.

[00166] In some embodiments, a polynucleotide sequence encodes TNNI3, e.g., human TNNI3. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:211. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding TNNI3, e.g., human TNNI3. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is TNNI3, e.g., human TNNI3. In some embodiments, the TNNI3 polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:212.

[00167] In some embodiments, a polynucleotide sequence encodes PLN, e.g., human PLN. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:229. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding PLN, e.g., human PLN. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is PLN, e.g., human PLN. In some embodiments, the PLN polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:230.

[00168] In some embodiments, a polynucleotide sequence encodes LAMP2, e.g., human LAMP2. In some embodiments, a polynucleotide sequence encodes LAMP2a isoform of LAMP2, e.g., human LAMP2a. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:213. In some embodiments, a polynucleotide sequence encodes LAMP2b isoform of LAMP, e.g., human LAMP2b. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:215. In some embodiments, a polynucleotide sequence encodes LAMP2c isoform of LAMP, e.g., human LAMP2c. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:217. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding LAMP2, e.g., human LAMP2. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding LAMP2a, LAMP2b or LAMP2c. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is a LAMP2

polypeptide, e.g., human LAMP2. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is LAMP2a isoform of LAMP2, e.g., human. In some embodiments, the LAMP2a polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:214. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is LAMP2b isoform of LAMP2, e.g., human. In some embodiments, the LAMP2b polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:216. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is LAMP2c isoform of LAMP2, e.g., human. In some embodiments, the LAMP2c polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:218.

[00169] In some embodiments, a polynucleotide sequence encodes DSP, e.g., human DSP. In some embodiments, a polynucleotide sequence encodes DPI isoform of DSP, e.g., human DPI. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:219. In some embodiments, a polynucleotide sequence encodes DPII isoform of DSP, e.g., human DPII. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:221. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding a DSP polypeptide. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding DPI or DPII, e.g., human DPI or DPII. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is DSP, e.g., human DSP. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is DPI isoform of DSP, e.g., human. In some embodiments, the DPI polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:220. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is DPII isoform of DSP, e.g., human. In some embodiments, the DPII polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:222.

[00170] In some embodiments, a polynucleotide sequence encodes DSG2, e.g., human DSG2. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:223. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding DSG2, e.g., human DSG2. In some embodiments, the gene product or polypeptide expressed using any expression

construct described herein is DSG2, e.g., human DSG2. In some embodiments, the DSG2 polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:224.

[00171] In some embodiments, a polynucleotide sequence encodes JUP, e.g., human JUP. In some embodiments, a polynucleotide sequence has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:225. In some embodiments, a polynucleotide sequence is a codon-optimized sequence encoding JUP, e.g., human JUP. In some embodiments, the gene product or polypeptide expressed using any expression construct described herein is JUP, e.g., human JUP. In some embodiments, the JUP polypeptide has at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to SEQ ID NO:226.

[00172] In some embodiments, any other polynucleotide sequence described herein can be used in any expression construct described herein. In some embodiments, such polynucleotide sequence encodes any gene product or polypeptide described herein. The polynucleotide sequence can be sequence-optimized (such as for expression in a human). In some embodiments, the sequence encodes a human polypeptide. The sequences of the polynucleotides and polypeptides described herein are known in the art. Sequences that have at least 75%, 80%, 85%, 90%, 95%, 98%, 99% or 100% sequence identity to such sequence are also contemplated herein. Illustrative sequences can be found in Table 2b.

Table 2b: Illustrative Gene product Sequences

Transgene	Polypeptide	Nucleotide (Open Reading Frame)
Human JPH2 (the N-terminal part of the sequence that, in some instances, can be used on its own, as an alternative to the full-length JPH2, is shown in bold)	MSGGRFDFDDGGAYCGGWEG GKAHGHGLCTGPKGQGEYSGS WNFGFEVAGVYTWPSGNTFEG YWSQGRHGLGIETKGRWLYK GEWTHGFKGRYGIQSSSSGAK YEGTWNNGLQDGYGTETYADG GTYQGQFTNGMRHGYGVRQSV PYGMVVVRSPLRTSLSSLRSE HSNGTVAPDSPASDGPALPS PAIPRGGFALSLLANAEAAARAP KGGGLFQRGALLGKLRRAESR TSVGSQRSRVSLKSDLSSGASD AASTASLGEAAEGADEAAPFEA DIDATTTETYMG EWKNDKRSR FGVSRSSGLRYEGEWLDNLRH GYGCTTLPDGHREEGKYRHN LVKDTKRRMLQLKSNKVRQKV EHSVEGAQRAAAIARQKAEIAA SRTSHAKAKAEAAEQAALAN QESNIARTLARELAPDFYQPGPE YQKRRLQEIENSESLLEPPDR GAGAAGLPQPPRESPQLHERET PRPEGGSPSPAGTPPQPKRPRPG VSKDGLLSPGAWNGEPSGEGSR	ATGAGTGGGGGCGCTTCGACTTTGATGATG GAGGGGCGTACTGCGGGGCTGGGAGGGG GGAAAGGCCCATGGGCATGGACTGTGCACA GGCCCCAAGGGCCAGGGCGAATACTCTGGC TCCTGGAACTTTGGCTTTGAGGTGGCAGGTG TCTACACCTGGCCCAGCGGAAACACCTTTGA GGGATACTGGAGCCAGGGCAAACGGCATGG GCTGGGCATAGAGACCAAGGGGCGCTGGCT CTACAAGGGCGAGTGGACACATGGCTTCAA GGGACGCTACGGAATCCGGCAGAGCTCAAG CAGCGGTGCCAAGTATGAGGGCACCTGGAA CAATGGCCTGCAAGACGGCTATGGACCCGA GACCTATGCTGATGGAGGGACGTACCAAGG CCAGTTCACCAACGGCATGCGCCATGGCTAC GGAGTACGCCAGAGCGTGCCCTACGGGATG GCCGTGGTGGTGCCTCGCCGCTGCGCACG TCGCTGTCTCCCTGCGCAGCGAGCACAGC AACGGCACGGTGGCCCCGACTCTCCCGCC TCGCCGGCTCCGACGGCCCCGCGCTGCC TCGCCCGCCATCCCGCGTGGCGGCTTCGCG CTCAGCCTCCTGGCCAATGCCGAGGCGGCC GCGCGGGCGCCCAAGGGCGGCGGCTCTTC CAGCGGGCGCGCTGCTGGGCAAGCTGCGG CGCGCAG

	SVTPSEGAGRRSPARPATERMAI EALQAPPAPSREPEVALYQGYH SYAVRTTPEPPPFEDQPEPEVSGS ESAPSSPATAPLQAPTLRGPEPAR ETPAKLEPKPIIPKAEPRAKARKTE ARGLTKAGAKKKARKEAALAAE AEVEVEEVPNTILICMVILLNIGLA ILFVHLLT (SEQ ID NO: 202)	AGTCGCGCACGTCCGTGGGTAGCCAGCGCA GCCGTGTCAGCTTCCTTAAGAGCGACCTCAG CTCGGGCGCCAGCGACGCCGCTCCACCGC CAGCCTGGGAGAGGCCGCCGAGGGCGCCGA CGAGGCCGCACCCTTCGAGGCCGATATCGA CGCCACCACCACCGAGACCTACATGGGCGA GTGGAAGAACGACAAACGCTCGGGCTTCGG CGTGAGCGAACGCTCCAGTGGCCTCCGCTA CGAGGGCGAGTGGCTGGACAACCTGCGCCA CGGCTATGGCTGCACCACGCTGCCCCGACGG CCACCGCGAGGAGGGCAAGTACCGCCACAA CGTGCTGGTCAAGGACACCAAGCGCCGCAT GCTGCAGCTCAAGAGCAACAAGGTCCGCCA GAAAGTGGAGCACAGTGTGGAGGGTGCCCA GCGCGCCGCTGCTATCGCGCGCCAGAAGGC CGAGATTGCCGCCTCCAGGACAAGCCACGC CAAGGCCAAAGCTGAGGCAGCGGAACAGGC CGCCCTGGCTGCCAACCAGGAGTCCAACATT GCTCGCACTTTGGCCAGGGAGCTGGCTCCG GACTTCTACCAGCCAGGTCCGGAATATCAGA AGCGCCGGCTGCTGCAGGAGATCCTGGAGA ACTCGGAGAGCCTGCTGGAGCCCCCGACC GGGGCGCCGGCGCAGCGGGCCTCCACAGC CGCCCCGCGAGAGCCCGCAGCTGCACGAGC GTGAGACCCCTCGGCCCGAGGGTGGCTCCC CGTACCGGCCCGGACGCCCCCGAGCCCA AGCGGCCCGAGGCCCGGGGTGTCCAAGGACG GCCTGCTGAGCCCAGGCGCTGGAACGGCG AGCCCAGCGGTGAGGGCAGCCGGTCAGTCA CTCCGTCCGAGGGCGCGGGCCGCCGAGCC CCGCGCGTCCAGCCACCGAGCGCATGGCCA TCGAGGCTCTGCAGGCACCGCCTGCGCCGT CGCGGGAGCCGGAGGTGGCGCTTTACCAGG GCTACCACAGCTATGCTGTGCGCACCCACGCC GCCCGAGCCCCACCTTTGAGGACCAGCCCG AGCCCGAGGTCTCCGGGTCCGAGTCCGCGCCCT CGTCCCCGGCCACCGCCCCGCTGCAGGCCCCCA CGCTCCGAGGCCCGAGCCTGCACGCGAGACC CCCGCCAAGCTGGAGCCCAAGCCCATCATCCCC AAAGCCGAGCCAGGGCCAAGGCCCGCAAGAC TGAGGCTCGAGGGCTGACCAAGGCGGGGCCA AGAAGAAGGCGCGGAAGGAGCCGCACTGGC GGCAGAGGCGGAGGTGGAGGTGGAAGAGGTCC CCAACACCATCCTCATCTGCATGGTGATCCTGC TGAACATCGGCCTGGCCATCCTCTTTGTTACC TCCTGACCTGA (SEQ ID NO: 201)
Human BAG3	MSAATHSPMMQVASNGDRDPL PPGWEIKIDPQTGWPFVDHNSRT TTWNDPRVPSEGPKETPSSANGPS REGSRLPPAREGHPVYPQLRPGYI PIPVLHEGAENRQVHPFHVYPQPG MQRFRTEAAAAAPQRSQSPLRGM PETTQPDKQCGQVAAAAAQP SHGPERSQSPAASDCSSSSSASLP SSGRSSLGSHQLPRGYISIPVIEHQ NVTRPAAQPSFHQAQKTHYPAQQ GEYQTHQPVYHKIQGDDWEPRPL RAASPRSSVQGASSREGSPARSS TPLHSPSPIRVHTVVDPRPQQPMTH RETAPVSQPENKPESKPGPVGP	ATGAGCGCCGCCACCACTCGCCCATGATGCA GGTGGCGTCCGGCAACGGTGACCGCGACCTTT GCCCCCGGATGGGAGATCAAGATCGACCCGC AGACCGGCTGGCCCTTCTTCGTGGACCACAACA GCCGCACCACTACGTGGAACGACCCGCGCTG CCCTCTGAGGGCCCCAAGGAGACTCCATCCTCT GCCAATGGCCCTTCCCGGAGGGCTCTAGGCTG CCGCTGCTAGGGAAGGCCACCTGTGTACCCC CAGCTCCGACCAGGCTACATTCCTCTCTGTG CTCCATGAAGGCGCTGAGAACCAGGAGGTGCA CCCTTTCCATGTCTATCCCCAGCCTGGGATGCA GCGATTCCGAAGTGGGCGGAGCAGCGGCTC CTCAGAGGTCCCAGTCACCTCTGCGGGGCATGC CAGAAACCACTCAGCCAGATAAACAGTGTGGA

	PPGHIPIQVIRKEVDSKPVSKPPP PSEKVEVKVPPAPVPCPPSPGPS AVPSSPKSVATEERAAPSTAPAEA TPPKPGAEAPPKHPGVLKVEAIL EKVQGLEQAVDNFEGKKTDKKY LMIEEYLTKEALLDSVDPEGRA DVRQARRDGVRKVQTILEKLEQK AIDVPGQVQVYELQPSNLEADQP LQAIMEMGAVAADKGKKNAGN AEDPHTETQQPEATAAATSNPSS MTDTPGNPAAP (SEQ ID NO: 204)	CAGGTGGCAGCGGCGGGCAGCCCAGCCCC AGCCTCCACGGACCTGAGCGGTCCCAGTCTCC AGCTGCCTCTGACTGCTCATCTCATCTCCTC GGCCAGCCTGCCTTCTCCGGCAGGAGCAGCCT GGGCAGTCAACAGCTCCCGCGGGGTACATCT CCATTCCGGTGATACACGAGCAGAACGTTACCC GGCCAGCAGCCCAGCCCTCCTTCCACCAAGCCC AGAAGACGCACTACCCAGCGCAGCAGGGGGAG TACCAGACCCACCAGCCTGTGTACCACAAGATC CAGGGGGATGACTGGGAGCCCCGGCCCCCTGCG GGCGGCATCCCCGTTCAAGTTCATCTGTCCAGGG TGCATCGAGCCGGGAGGGCTCACCAGCCAGGA GCAGCAGCCACTCCACTCCCCCTCGCCCATCC GTGTGCACACCGTGGTCGACAGGCCTCAGCAG CCCATGACCCATCGAGAACTGCACCTGTTTCC CAGCCTGAAAAACAAACCAGAAAGTAAGCCAGG CCCAGTTGGACCAGAACTCCCTC CTGGACACATCCCAATTCAAGTGATCCGCAA GAGGTGGATTCTAAACCTGTTTCCAGAAGCCC CCACCTCCCTCTGAGAAAGGTAGAGGTGAAAAGT TCCCCCTGCTCCAGTTCCTTGCTCCTCCTCCAGC CCTGGCCCTTCTGCTGTCCCTCTTCCCCAAG AGTGTGGCTACAGAAGAGAGGGCAGCCCCCAG CACTGCCCCCTGCAGAAGCTACACCTCCAAAACC AGGAGAAGCCGAGGCTCCCCCAAAACATCCAG GAGTGCTGAAAGTGGAAGCCATCCTGGAGAAG GTACAGGGGCTGGAGCAGGCTGTAGACAACTT TGAAGGCAAGAAGACTGACAAAAAG TACCTGATGATCGAAGAGTATTGACCAAAGA GCTGCTGGCCCTGGATTCAAGTGGACCCCGAGG GACGAGCCGATGTGCGTCAGGCCAGGAGAGAC GGTGTACAGGAAGGTTACAGACCATCTTGAAAA ACTTGAACAGAAAGCCATTGATGTCCAGGTC AAGTCCAGGTCTATGAACTCCAGCCCAGCAAC CTTGAAGCAGATCAGCCACTGCAGGCAATCAT GGAGATGGGTGCCGTGGCAGCAGACAAGGGCA AGAAAAATGCTGGAAATGCAGAAGATCCCCAC ACAGAAACCCAGCAGCCAGAAGCCACAGCAGC AGCGACTTCAAACCCAGCAGCATGACAGACA CCCCTGGTAACCCAGCAGCACCCGTAG (SEQ ID NO:203)
Human CRYAB	MDIAIHHPWIRRPFFPHSPSRLFD QFFGEHLLSDLFPTSTLSPFYLR PPSFLRAPSWFDTGLSEMRLEKDR FSVNLDVKHFSPEELKVKVLGDVI EVHGKHEERQDEHGFISREFHRK YRIPADVDPITITSSLDGVLTVN GPRKQVSGPERTIPITREEKPAVT AAPKK (SEQ ID NO: 206)	ATGGACATCGCCATCCACCACCCCTGGATCCGC CGCCCCCTTCTTTCTTTTCCACTCCCCAGCCGCC TCTTTGACCAGTTCTTCGGAGAGCACCTGTTGG AGTCTGATCTTTTCCCGACGTCTACTTCCCTGA GTCCCTTCTACCTTCGGCCACCCTCCTTCTGCG GGCACCCAGCTGGTTTGACACTGGACTCTCAGA GATGCGCCTGGAGAAGGACAGGTTCTCTGTCA ACCTGGATGTGAAGCACTTCTCCCCAGAGGAA CTCAAAGTTAAGGTGTTGGGAGATGTGATTGA GGTGCATGGAAAACATGAAGAGCGCCAGGATG AACATGGTTTTCATCTCCAGGGAGTTCCACAGGA AATACCGGATCCCAGCTGATGTAGACCTCTCA CCATTACTTCATCCCTGTCATCTGATGGGGTCC TCACTGTGAATGGACCAAGGAAACAGGTCTCT GGCCCTGAGCGCACCATTCCTCATCACCCGTGAA GAGAAGCCTGCTGTACCCGAGCCCCCAAGAA ATAG (SEQ ID NO: 205)

Human LMNA LaminA	METPSQRRATRSGAQASSTPLSPT RITRLQEKEDLQELNDRLAVYIDR VRSLETENAGLRRLRITESEEVVSR EVSGIKAAEYAEELGDARKTLDSEV AKERARLQELSKVREEFKELKA RNTKKEGDLIAAQARLKDLEALL NSKEAALSTALSEKRTLEGELHDL RGQVAKLEAALGEAKKQLQDEM LRRVDAENRLQTMKEELDFQKNI YSEELRETKRRHETRLVEIDNGKQ REFESRLADALQELRAQHEDQVE QYKKELEKTYSAKLDNARQSAER NSNLVGAAHEELQQSRIRIDSLSA QLSQLQKQLAAKEAKLRDLEDSL ARERDTSRLLAEKEREMAEMRA RMQQQLDEYQELLDIKLALDMEI HAYRKLLEGEERLRLSPSPTSQR SRGRASSHSQTQGGGSVTKKRK LESTESRSSFSQHARTSGRVAVEE VDEEGKFVRLRNKSNEDQSMGN WQIKRQNGDDPLLTYRFPKFTL KAGQVVTIWAAGAGATHSPPTDL VWKAQNTWGCNSLRTALINST GEEVAMRKLVRSVTVVEDDEDE DGDDLLHHHHGSHCSSGDPAEY NLRSRTVLCGTCGQPADKASASG SGAQVGGPISSGSSASSVTVTRSY RSVGGSGGGSFGDNLVTRSYLLG NSSPRTQSPQNC SIM (SEQ ID NO: 208)	ATGGAGACCCCGTCCCAGCGGCGGCCACCCG CAGCGGGGCGCAGGCCAGCTCCACTCCGCTGT CGCCACCCGCATCACCCGGCTGCAGGAGAAG GAGGACCTGCAGGAGCTCAATGATCGCTTGGC GGTCTACATCGACCGTGTGCGCTCGCTGGAAAC GGAGAACGCAGGGCTGCGCCTTCGCATCACCG AGTCTGAAGAGGTGGTCAGCCGCGAGGTGTCC GGCATCAAGGCCCGCTACGAGGCCGAGCTCGG GGATGCCCCGAAGACCCTTGACTCAGTAGCCA AGGAGCGCGCCCGCTGCAGCTGGAGCTGAGC AAAGTGCGTGAGGAGTTTAAGGAGCTGAA AGCGCGCAATACCAAGAAGGAGGGTGACCTGA TAGCTGCTCAGGCTCGGCTGAAGGACCTGGAG GCTCTGCTGAACTCCAAGGAGGCCGCACTGAG CACTGCTCTCAGTGAGAAGCGCACGCTGGAGG GCGAGCTGCATGATCTGCGGGGCCAGGTGGCC AAGCTTGAGGCAGCCCTAGGTGAGGCCAAGAA GCAACTTCAGGATGAGATGCTGCGCGGCTGG ATGCTGAGAACAGGCTGCAGACCATGAAGGAG GAACTGGACTTCCAGAAGAATCTACAGTGA GGAGCTGCGTGAGACCAAGCGCCGTCATGAGA CCCGACTGGTGGAGATTGACAATGGGAAGCAG CGTGAGTTTGAGAGCCGGCTGGCGGATGCGCT GCAGGAACTGCGGGCCCAGCATGAGGACCAGG TGGAGCAGTATAAGAAGGAGCTGGAGAAGACT TATTCTGCCAAGCTGGACAATGCCAGGCAGTCT GCTGAGAGGAACAGCAACCTGGTGGGGGCTGC CCACGAGGAGCTGCAGCAGTCGCGCATCCGCA TCGACAGCCTCTCTGCCAGCTCAGCCAGCTCC AGAAGCAGCTGGCAGCCAAGGAGGCGAAGCTT CGAGACCTGGAGGACTCACTGGCCCGTGAGCG GGACACCAGCCGCGGCTGCTGGCGGAAAAGG AGCGGGAGATGGCCGAGATGCGGGCAAGGATG CAGCAGCAGCTGGACGAGTACCAGGAGCTTCT GGACATCAAGCT GGCCCTGGACATGGAGATCCACGCCTACCGCA AGCTCTTGAGGGCGAGGAGGAGAGGCTACGC CTGTCCCCCAGCCCTACCTCGCAGCGCAGCCGT GGCCGTGCTTCCTCTCACTCATCCAGACACAG GGTGGGGGCAGCGTCACCAAAAAGCGCAAACCT GGAGTCCACTGAGAGCCGCGAGCAGCTTCTCAC AGCACGCACGCACTAGCGGGCGCGTGGCCGTG GAGGAGGTGGATGAGGAGGGCAAGTTTGTCCG GCTGCGCAACAAGTCCAATGAGGACCAGTCCA TGGGCAATTGGCAGATCAAGCGCCAGAATGGA GATGATCCCTTGCTGACTTACCGTTCC CACCAAAGTTACCCCTGAAGGCTGGGCAGGTG GTGACGATCTGGGCTGCAGGAGCTGGGGCCAC CCACAGCCCCCTACCGACCTGGTGTGGAAGG CACAGAACACCTGGGGCTGCGGGAACAGCCTG CGTACGGCTCTCATCACTCCACTGGGGAAGA AGTGGCCATGCGCAAGCTGGTGCCTCAGTGA CTGTGGTTGAGGACGACGAGGATGAGGATGGA GATGACCTGCTCCATACCAACACGGCTCCAC TGCAGCAGCTCGGGGACCCGCTGAGTACAA CCTGCGCTCGCGCACCGTGCTGTGCGGGACCTG CGGGCAGCCTGCCGACAAGGCATCTGCCAGCG GCTCAGGAGCCCAGGTGGGCGGACCCATCTCC TCTGGCTCTTCTGCCTCCAGTGTACCGTCACT CGCAGCTACCGCAGTGTGGGGGCGAGTGGGGG
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		TGGCAGCTTCGGGGACAATCTGGTCAACCGCTC CTACCTCCTGGGCAACTCCAGCCCCGAACCA GAGCCCCAGAACTGCAGCATCATGTAA (SEQ ID NO: 207)
Human LMNA LaminC	METPSQRRATRSGAQASSTPLSPT RITRLQEKEDLQELNDRLAVYIDR VRSLETENAGRLRLRITESEEVVS EVSGIKAAAYEALGDARKTLDV AKERARLQLELSKVREEFKELKA RNTKKEGDLIAAQARLKDLEALL NSKEAALSTALSEKRTLEGELHDL RGQVAKLEAALGEAKKQLQDEM LRRVDAENRLQTMKEELDFQKNI YSEELRETKRRHETRLVEIDNGKQ REFESRLADALQELRAQHEDQVE QYKKELEKTYSAKLDNARQSAER NSNLVGAHEELQSRIRIDSLSA QLSQLQKQLAAKEAKLRDLEDSL ARERDTSRLLAEKEREMAEMRA RMQQQLDEYQELLDIKLALDMEI HAYRKLLEGEERLRLSPSPTSQR SRGRASSHSSQTQGGGSVTKKRK LESTESRSSFSQHARTSGRVAVEE VDEEGKFVRLRNKSNEQSMGN WQIKRQNGDDPLLTYRFPKFTL KAGQVVTIWAAGAGATHSPPTDL VWKAQNTWGCNSLRTALINST GEEVAMRKLVRSTVVEDDEDE DGDDLLHHHHVSGSRR (SEQ ID NO: 210)	ATGGAGACCCCGTCCCAGCGGCGGCCACCCG CAGCGGGGCGCAGGCCAGCTCCACTCCGCTGT CGCCCACCCGCATCACCCGGCTGCAGGAGAAG GAGGACCTGCAGGAGCTCAATGATCGCTTGGC GGTCTACATCGACCGTGTGCGCTCGCTGGAAAC GGAGAACGCAGGGCTGCGCCTTCGCATCACCG AGTCTGAAGAGGTGGTCAGCCGCGAGGTGTCC GGCATCAAGGCCGCTACGAGGCCGAGCTCGG GGATGCCCCGAAGACCCTTGACTCAGTAGCCA AGGAGCGCGCCCGCTGCAGCTGGAGCTGAGC AAAGTGCGTGAGGAGTTTAAGGAGCTGAA AGCGCGCAATACCAAGAAGGAGGGTGACCTGA TAGCTGCTCAGGCTCGGCTGAAGGACCTGGAG GCTCTGCTGAAGTCCAGGAGGCCGACTGAG CACTGCTCTCAGTGAGAAGCGCACGCTGGAGG GCGAGCTGCATGATCTGCGGGGCCAGGTGGCC AAGCTTGAGGCAGCCCTAGGTGAGGCCAAGAA GCAACTTCAGGATGAGATGCTGCGGCGGTGG ATGCTGAGAACAGGCTGCAGACCATGAAGGAG GAACTGGACTTCCAGAAGAATCTACAGTGA GGAGCTGCGTGAGACCAAGCGCCGTCATGAGA CCCGACTGGTGAGATTGACAAATGGGAAGCAG CGTGAGTTTGAGAGCCGGCTGGCGGATGCGCT GCAGGAACTGCGGGCCAGCATGAGGACCAGG TGGAGCAGTATAAGAAGGAGCTGGAGAAGACT TATTCTGCCAAGCTGGACAATGCCAGGCAGTCT GCTGAGAGGAACAGCAACCTGGTGGGGGCTGC CCACGAGGAGCTGCAGCAGTCGCGCATCCGCA TCGACAGCCTCTCTGCCCAGCTCAGCCAGCTCC AGAAGCAGCTGGCAGCCAAGGAGGCGAAGCTT CGAGACCTGGAGGACTCACTGGCCCGTGAGCG GGACACCAGCCGGCGGCTGCTGGCGGAAAAGG AGCGGGAGATGGCCGAGATGCGGGCAAGGATG CAGCAGCAGCTGGACGAGTACCAGGAGCTTCT GGACATCAAGCTGGCCCTGGACATGGAGATCC ACGCCTACCGCAAGCTCTTGAGAGGGCGAGGAG GAGAGGCTACGCCTGTCCCCAGCCCTACCTCG CAGCGCAGCCGTGGCCGTGCTTCTCTCACTCA TCCCAGACACAGGGTGGGGGCAGCGTCACCAA AAAGCGCAAACTGGAGTCCACTGAGAGCCGCA GCAGCTTCTCACAGCACGCACGCACTAGCGGG CGCGTGGCCGTGGAGGAGGTGGATGAGGAGGG CAAGTTTGTCCGGCTGCGCAACAAGTCCAATGA GGACCAGTCCATGGGCAATTGGCAGATCAAGC GCCAGAAATGGAGATGATCCCTTGCTGACTTACC GGTTCC CACCAAAGTTACCCCTGAAGGTGGGCAGGTG GTGACGATCTGGGCTGCAGGAGCTGGGGCCAC CCACAGCCCCCTACCGACCTGGTGTGGAAGG CACAGAACACCTGGGGCTGCGGGAACAGCCTG CGTACGGCTCTCATCACTCCACTGGGGAAGA AGTGGCCATGCGCAAGCTGGTGGCTCAGTGA CTGTGGTTGAGGACGACGAGGATGAGGATGGA GATGACCTGCTCCATCACCACCACGTGAGTGGT AGCCGCCGCTGA (SEQ ID NO: 209)

Human TNNT3	MADGSSDAAREPRPAPAPIRRRSS NYRAYATEPHAHKKKSKISASRKL QLKTLQLQIAKQELEREAEERRGE KGRALSTRCQPLELAGLGFELQ DLCRQLHARVVDKVDDEERYDIEAK VTKNITEIADLTQKIFDLRGKFKR PTLRRVRISADAMMQALLGARAK ESLDLRAHLKQVKKEDTEKENRE VGDWRKNIDALSGMEGRKKKFE S (SEQ ID NO: 212)	ATGGCGGATGGGAGCAGCGATGCGGCTAGGGA ACCTCGCCCTGCACCAGCCCCAATCAGACGCCG CTCTCCAACCTACCGCGCTTATGCCACGGAGCC GCACGCCAAGAAAAAATCTAAGATCTCCGCT CGAGAAAATTGCAGCTGAAGACTCTGCTGCTG CAGATTGCAAAGCAAGAGCTGGAGCGAGAGGC GGAGGAGCGGCGCGGAGAGAAGGGGCGCGCT CTGAGCACCCGCTGCCAGCCGCTGGAGTTGGCC GGGCTGGGCTTCGCGGAGCTGCAGGACTTGTG CCGACAGCTCCACGCCCGTGTGGACAAGGTGG ATGAAGAGAGATACGACATAGAGGCAAAAGTC ACCAAGAACATCACGGAGATTGCAGATCTGAC TCAGAAAGATCTTTGACCTTCGAGGCAAGTTAA GCGGCCACCCTGCGGAGAGTGAGGATCTCTG CAGATGCCATGATGCAGGCGCTGCTGGGGGCC CGGGCTAAGGAGTCCCTGGACCTGCGGGCCCA CCTCAAGCAGGTGAAGAAGGAGGACACCGAGA AGGAAAACCGGGAGGTGGGAGACTGGCGCAA GAACATCGATGCACTGAGTGGAATGGAGGGCC GCAAGAAAAAGTTTGAGAGCTGA (SEQ ID NO: 211)
Human LAMP2a	MVCFRLFPVPGSLVLVCLVLGA VRSYALELNLTDSENATCLYAKW QMNFTVRYETTNKYKTVTISDH GTVTYNGSICGDDQNGPKIAVQF GPGFSWIANFTKAASTYSIDSVSF SYNTGDNTTFDAEDKGILTVDL LAIRIPLNDFRCNSLSTLEKNDV VQHYWDVLVQAFVQNGTVSTNE FLCDKDKTSTVAPTIHTTVSPPT TPTPKEKPEAGTYSVNNGNDTCL LATMGLQLNITQDKVASVININPN TTHSTGSCRSHALLRLNSSTIKY LDFVFAVKNNRFLYKEVNISM LVNGSVFSIANNLSYWDAPLGS SYMCKEQTVSVSGAFQINTFDL RVQPFNVQTQGYSTAQDCSADD DNFLVPIAVGAALAGVLILVLLAY FIGLKHHAAGYEQF (SEQ ID NO: 214)	ATGGTGTGCTTCCGCTCTTCCCGTTCCGGGC TCAGGGCTCGTTCTGGTCTGCCTAGTCTGGGA GCTGTGCGGTCTTATGCATTGGAACCTTAATTTG ACAGATTGAGAAAATGCCACTTGCCTTTATGCA AAATGGCAGATGAATTTACAGTACGCTATGA AACTACAAATAAAACTTATAAACTGTAACCA TTTCAGACCATGGCACTGTGACATATAATGGAA GCATTTGTGGGGATGATCAGAAATGGTCCCAAA ATAGCAGTGCACTTCGGACCTGGCTTTTCCTGG ATTGCGAATTTTACCAAGGCAGCATCTACTTAT TCAATTGACAGCGTCTCATTTTCTACAACT GGTGATAACACAACATTTCTGATGCTGAAGAT AAAGGAATCTTACTGTTGATGAACCTTTTGCC ATCAGAAATCCATTGAATGACCTTTTTAGATGC AATAGTTTATCACTTTGGAAAAGAATGATGTT GTCCAACACTACTGGGATGTTCTTGTAACAGCT TTTGTCCAAAATGGCACAGTGAGCACAATGA GTTCTGTGTGATAAAGACAAAACCTCAACAGT GGCACCACCATACACCACTGTGCCATCTCC TACTACAACACCTACTCCAAAGGAAAAACCAG AAGCTGGAACCTATTCAAGTTAATAATGGCAATG ATACTTGTCTGCTGGCTACCATGGGGCTGCAGC TGAACATCACTCAGGATAAGGTTGCTTCAGTTA TTAACATCAACCCCAATACAACCTCACTCCACAG GCAGCTGCCGTTCTCACACTGCTCTACTTAGAC TCAATAGCAGCACCATTAAAGTATCTAGACTTGT TCTTTGCTGTGAAAAATGAAAACCGATTTTATC TGAAGGAAGTGAACATCAGCATGTATTTGGTTA ATGGCTCCGTTTTCAGCATTGCAATAAACAATC TCAGCTACTGGGATGCCCCCTGGGAAGTTCTT ATATGTGCAACAAAGAGCAGACTGTTTCAGTGT CTGGAGCATTTTCAGATAAATACCTTTGATCTAA GGGTTCAAGCTTTCAATGTGACACAAGGAAAG TATTCTACAGCTCAAGACTGCAGTGACAGATGAC GCAACTTCCTTGTGCCCATAGCGGTGGGAGCT GCCTTGGCAGGAGTACTTATTCTAGTGTGCTG GCTTATTTTATTTGCTCAAGCACCATCATGCT GGATATGAGCAATTTTAG (SEQ ID NO: 213)

Human LAMP2b	MVCFRLFPVPGSLVLVCLVLGA VRSYALELNLTDSENATCLYAKW QMNFTVRYETTINKTYKTVTISDH GTVTYNGSICGDDQNGPKIAVQF GPGFSWIANFTKAASTYSIDSVSF SYNTGDNTTFPDAEDKGILTVDL LAIRIPLNDFRCNSLSTLEKNDV VQHYWDVLVQAFVQNGTVSTNE FLCDKDKTSTVAPTIHTTVPSPTT TPTPKEKPEAGTYSVNNGNDTCL LATMGLQLNITQDKVASVININPN TTHSTGSCRSHALLRLNSSTIKY LDFVFAVKNNRNFYLKEVNISM LVNGSVFSIANNLSYWDAPLGS SYMCKNEQTVSVSGAFQINTFDL RVQPFNVQKGKYSTAQECSLDD TILIPVAVGAGSLIIVIVIAVYVIGR RKSYAGYQTL (SEQ ID NO: 216)	ATGGTGTGCTTCCGCCTCTTCCCGGTTCCGGGC TCAGGGCTCGTTCTGGTCTGCCTAGTCTGGGA GCTGTGCGGTCTTATGCATTGGAACCTAATTG ACAGATTGAGAAAATGCCACTTGCCTTTATGCA AAATGGCAGATGAATTTACAGTACGCTATGA AACTACAAATAAACTTATAAACTGTAAACCA TTTCAGACCATGGCACTGTGACATATAATGGAA GCATTTGTGGGGATGATCAGAATGGTCCCAA ATAGCAGTGCAGTTCGGACCTGGCTTTTCTCGG ATTGCGAATTTTACCAAGGCAGCATCTACTTAT TCAATTGACAGCGTCTCATTTTCTTACAACACT GGTGATAACACAACATTTCTGTATGCTGAAGAT AAAGGAATTCTTACTGTTGATGAACCTTTGGCC ATCAGAATTCCATTGAATGACCTTTTTAGATGC AATAGTTTATCAACTTTGGAAAAAGAAATGATGTT GTCCAACACTACTGGGATGTTCTTGTACAAGCT TTTGTCCAAAATGGCACAGTGAGCACAAATGA GTTCTGTGTGATAAAAGACAAAACCTTCAACAGT GGCACCCACCATAACACACCACTGTGCCATCTCC TACTACAACACCTACTCCAAAGGAAAAACCAG AAGCTGGAACCTATTCAGTTAATAATGGCAATG ATACTTGTCTGCTGGCTACCATGGGGCTGCAGC TGAACATCACTCAGGATAAGGTTGCTTCAGTTA TTAACATCAACCCCAATACAACCTACTCCACAG GCAGCTGCCGTTTCTCACACTGCTCTACTTAGAC TCAATAGCAGCACCATTAAAGTATCTAGACTTTG TCTTTGCTGTGAAAAATGAAAACCGATTTTATC TGAAGGAAGTGAACATCAGCATGTATTTGGTTA ATGGCTCCGTTTTTACGATTGCAAATAACAATC TCAGCTACTGGGATGCCCCCTGGGAAGTTCTT ATATGTGCAACAAAGAGCAGACTGTTTCAAGTGT CTGGAGCATTTTCAAGATAAATACCTTTGATCTAA GGGTTTCAAGCTTTTCAATGTGACACAAGGAAAG TATTCTACAGCCCAAGAGTGTTCGCTGGATGAT GACACCATTTCTAATCCCAATTATAGTTGGTGC GGTCTTTCAAGCTTGATTATCGTTATAGTGATT GCTTACGTAATTGGCAGA AGAAAAAGTTATGCTGGATATCAGACTCTGTA A (SEQ ID NO: 215)
Human LAMP2c	MVCFRLFPVPGSLVLVCLVLGA VRSYALELNLTDSENATCLYAKW QMNFTVRYETTINKTYKTVTISDH GTVTYNGSICGDDQNGPKIAVQF GPGFSWIANFTKAASTYSIDSVSF SYNTGDNTTFPDAEDKGILTVDL LAIRIPLNDFRCNSLSTLEKNDV VQHYWDVLVQAFVQNGTVSTNE FLCDKDKTSTVAPTIHTTVPSPTT TPTPKEKPEAGTYSVNNGNDTCL LATMGLQLNITQDKVASVININPN TTHSTGSCRSHALLRLNSSTIKY LDFVFAVKNNRNFYLKEVNISM LVNGSVFSIANNLSYWDAPLGS SYMCKNEQTVSVSGAFQINTFDL RVQPFNVQKGKYSTAECSADSD LNFLIPVAVGVALGFLIIVVFISYM IGRRKSRTGYQSV (SEQ ID NO: 218)	ATGGTGTGCTTCCGCCTCTTCCCGGTTCCGGGC TCAGGGCTCGTTCTGGTCTGCCTAGTCTGGGA GCTGTGCGGTCTTATGCATTGGAACCTAATTG ACAGATTGAGAAAATGCCACTTGCCTTTATGCA AAATGGCAGATGAATTTACAGTACGCTATGA AACTACAAATAAACTTATAAACTGTAAACCA TTTCAGACCATGGCACTGTGACATATAATGGAA GCATTTGTGGGGATGATCAGAATGGTCCCAA ATAGCAGTGCAGTTCGGACCTGGCTTTTCTCGG ATTGCGAATTTTACCAAGGCAGCATCTACTTAT TCAATTGACAGCGTCTCATTTTCTTACAACACT GGTGATAACACAACATTTCTGTATGCTGAAGAT AAAGGAATTCTTACTGTTGATGAACCTTTGGCC ATCAGAATTCCATTGAATGACCTTTTTAGATGC AATAGTTTATCAACTTTGGAAAAAGAAATGATGTT GTCCAACACTACTGGGATGTTCTTGTACAAGCT TTTGTCCAAAATGGCACAGTGAGCACAAATGA GTTCTGTGTGATAAAAGACAAAACCTTCAACAGT GGCACCCACCATAACACACCACTGTGCCATCTCC TACTACAACACCTACTCCAAAGGAAAAACCAG AAGCTGGAACCTATTCAGTTAATAATGGCAATG

		ATACTTGTCTGCTGGCTACCATGGGGCTGCAGC TGAACATCACTCAGGATAAGGTTGCTTCAGTTA TTAACATCAACCCCAATACAACCTCACTCCACAG GCAGCTGCCGTTCTCACACTGCTCTACTTAGAC TCAATAGCAGCACCATTAAAGTATCTAGACTTTG TCTTTGCTGTGAAAAATGAAAAACCGATTTTATC TGAAGGAAGTGAACATCAGCATGTATTTGGTTA ATGGCTCCGTTTTTCAGCATTGCAAATAACAATC TCAGCTACTGGGATGCCCCCTGGGAAGTTCTT ATATGTGCAACAAAGAGCAGACTGTTTCAGTGT CTGGAGCATTTTCAGATAAAATACCTTTGATCTAA GGGTTTCAGCCTTTCAATGTGACACAAGGAAAG TATTCTACAGCTGAAGAATGTTCTGCTGACTCT GACCTCAACTTTCTTATTCTGTGTCAGTGGGT GTGGCCTTGGGCTTCCTTATAATTGTTGCTTTA TCTCTTATATGATTGGAAGAAGGAAAAGTCGTA CTGGTTATCAGTCTGTGTAA (SEQ ID NO: 217)
Human DSP_DPI	MSCNGGSHPRINTLGRMIRAESGP DLRYEVTSGGGGTSRMYYSRRG VITDQNSDGYCQTGTMSRHQNN NTIQELLQNCSDCLMRAELIVQPE LKYGDGIQLTRSREDECFAQAN DQMEILDSLIREMRQMGQPCDAY QKRLQLQEQMRALYKAISVPRV RRASSKGGGGYTCQSGSGWDEFT KHVTSECLGWMRQRAEMDMV AWGVDLASVEQHINSHRGIHNSI GDYRWQLDKIKADLREKSAIYQL EEEEYENLLKASFERMDHLRQLQN IIQATSREIMWINDCEEEELLYDW SDKNTNIAQKQEAFSIRMSQLEVK EKELNKLKQESDQLVLNQHPASD KIEAYMDTLQTQWSW ILQITKCIDVHLKENAAYFQFFEE AQSTEAYLKLGLQDSIRKKYPCDK NMPLQHLLEQIKELEKEREKILEY KRQVQNLVNSKKIVQLKPRNPD YRSNKPILRALCDYKQDQKIVHK GDECILKDNNSERSKYVTGPGGV DMLVPSVGLIIPPNPLAVDLCKI EQYYEAILALWNQLYINMKSLVS WHYCMIDIEKIRAMTIAKLKTMR QEDYMKTIADLELHYQEFIRNSQ GSEMFQDDDKRKIQSQFTDAQKH YQTLVIQLPGYPQHQTVTTEITH HGTCQDVNHNKVIETNRENDKQE TWMLMELQKIRRQIEHCEGRMTL KNLPLADQGSSHITVKINELKSV QNDSQAI AEVLNQLKDMLANFRG SEKYCYLQNEVFGLFQKLENG VTDGYLNSLCTVRALLQAILQTE DMLKVYEARL TEEETVCLDLKV EAYRCGLKKIKNDLNLKSSLAT MKTELQKAQQIHS QTSQQYPLYDLGLKFGEKVTQL TDRWQRIDKQIDFRLWDLEKQIK QLRNYRDNYQAFCKWLYDAKRR QDSLES MKFGDSNTVMRFLNEQK NLHSEISGRDKSEEVQKIAELCA NSIKDYELQLASYTSGLTLLNPI	ATGAGCTGCAACGGAGGCTCCACCCGCGGAT CAACACTCTGGGCCGCGATGATCCGCGCCGAGTC TGGCCCGGACCTGCGCTACGAGGTGACCAGCG GCGGCGGGGGCACCAGCAGGATGTACTATTCT CGGCGCGGCGTGATCACCAGCAGAACTCGGA CGGCTACTGTCAAACCGGCACGATGTCCAGGC ACCAGAACAGAACACCATCCAGGAGCTGCTG CAGAACTGCTCCGACTGCTGTGATGCGAGCAGA GCTCATCGTGCAGCCTGAATTGAAGTATGGAG ATGGAATACAACCTGACTCGGAGTCGAGAATTG GATGAGTGTTTTGCCAGGCCAATGACCA AATGGAAATCCTCGACAGCTTGATCAGAGAGA TGCGGCAGATGGGCCAGCCCTGTGATGCTTACC AGAAAAGGCTTCTTCAGCTCCAAGAGCAAATG CGAGCCCTTTATAAAGCCATCAGTGTCCCTCGA GTCCGCAGGGCCAGCTCCAAGGGTGGTGAGG CTACACTTGTCAGAGTGGCTCTGGCTGGGATGA GTTACCAAACATGTCACCAGTGAATGTTTGGG GTGGATGAGGCAGCAAAGGGCGGAGATGGACA TGGTGGCTGGGGTGTGGACCTGGCCTCAGTGG AGCAGCACATTAACAGCCACCGGGGCATCCAC AACTCCATCGGCGACTATCGCTGGC AGCTGGACAAAATCAAAGCCGACCTGCGCGAG AAATCTGCGATCTACCAGTTGGAGGAGGAGTA TGAAAACCTGTGTAAGCGTCCTTTGAGAGGA TGGATCACCTGCGACAGCTGCAGAACATCATTG AGGCCACGTCCAGGGAGATCATGTGGATCAAT GACTGCGAGGAGGAGGAGCTGCTGTACGACTG GAGCGACAAGAACACCAACATCGCTCAGAAAC AGGAGGCCTTCTCCATACGCATGAGTCAACTGG AAGTTAAAGAAAAAGAGCTCAATAAGCTGAAA CAAGAAAGTGACCAACTTGTCTCAATCAGCAT CCAGCTTCAGACAAAATTGAGGCCTATATGGA CACTCTGCAGACGAGTGGAGTTGGATTCTTCA GATCACCAAGTGCAATTGATGTTTATCTGAAAGA AAATGCTGCCTACTTTTCAGTTTTTTGAAGAGGC GCAGTCTACTGAAGCATACCTGAAGGGGCTCC AGGACTCCATCAGGAAGAAGTACCCCTGCGAC AAGAACATGCCCCTGCAGCACCTGCTGGAACA GATCAAGGAGCTGGAGAAAGAACGAGAGAAA ATCCTTGAATACAAGCGTCAGGTGCAGAACTTG GTAACAAGTCTAAGAAGATTGTACAGCTGAA

KRTMIQSPSGVILQEAAADVHARYI ELLTRSGDYRFLSEMLKSLEDL KLKNTKIEVLEEELRLARDANSEN CNKNKFLDQNLQKYQAECSQFK AKLASLEELKRQAELDGKSAKQN LDKCYGQIKELNEKITRLTYEIED EKRRRSVEDRFDQQKN DYDQL QKARQCEKENLGWQKLESEKAIK EKEYEIERLRVLLQEEGTRKREYE NELAKVRNHYNEEMSNLRNKYE TEINITKTIKEISMQKEDDSKNLR NQLDRLSRENRLKDEIVRLNDSI LQATEQRRRAEENALQQKACGSE IMQKKQHLEIELKQVMQQRSEDN ARHKQSLEEAATIQDKNKEIERL KAEFQEEAKRRWEYENELSKVRN NYDEEIIISLKNQFETEINITKTIHQ LTMQKEEDTSYRAQIDNLTREN RSLSEEIKRLKNTLTQTENLRRV EEDIQQQKATGSEVSQRKQQLLEV ELRQVTQMRTEESVRYKQSLDDA AKTIQDKNKEIERLKQLIDKETND RKCLEDENARLQRVQYDLQKAN SSATETINKLVQEQLTRLRIDY ERSVQERTVKDQDITRFQNSLKL QLQKQKVEEELNRLKRTASEDS KRKKLEEELEGMRRSLKEQAIIK NLTQQLEQASIVKKRSEDDLRQQ RDVLDGHLREKQRTQEELRRLSS EVEALRRQLLQEQESVKQAHLRN EHFQKAIEDKSRSLSNESKIEIERLQ SLTENLTKEHLMLEEELRNLRLEY DDLRRGRSEADSDKNATILELRSQ LQISNNRTLELQGLINDLQREREN LRQEIEKFQKQALEASNRIQESKN QCTQVVQERESLLVKIKVLEQDK ARLQRLLEDELNRAKSTLEAETRV KQRLCEKQQIQNDLNQWKTQY SRKEEAIRKIESEREKSEREKNSLR SEIERLQAEIKRIEERCRRKLEDST RETQSQLETERSRYQREIDKLRRQ PYGSHRETQTECEWTVDTSKLVF DGLRKKVTAMQLYECQLIDKTTL DKLLKGKKSVEEVASEIQPFLRGA GSIAGASASPKEYSLVEAKRKK LISPESTVMLLEAQAATGGIIPHR NEKLTVDSAIARDLIDFDDRQIY AAEKAITGFDDPFGKTVSVSEAI KKNLIDRETGMRLLEAQIASGGV VDPVNSVFLPKDVALARGLIDRD LYR SLNDPRDSQKNFVDPVTKKKVSY VQLKERCRIEPTGLLLSVQKRS MSFQGIRQPVTVTELVDSGILRPS TVNELESGQISYDEVGERIKDFLQ GSSCIAGIYNETTKQLGIYEAMK I GLVRPGTALELLEAQAATGFIVDP VSNLRLPVEEAYKRGLVGIEFKEK LLSAERA VTGYNDPETGNIISLFQ	GCCTCGTAACCCAGACTACAGAAGCAATAAAC CCATTATTCTCAGAGCTCTCTG TGACTACAAACAAGATCAGAAAAATCGTGATA AGGGGGATGAGTGTATCCTGAAGGACAACAAC GAGCGCAGCAAGTGGTACGTGACGGGCCCGGG AGGCGTTGACATGCTTGTTCCTCTGTGGGGCT GATCATCCCTCCTCCGAACCCACTGGCCGTGGA CCTCTCTTGCAAGATTGAGCAGTACTACGAAGC CATCTTGGCTCTGTGGAACCAGCTCTACATCAA CATGAAGAGCCTGGTGTCTCGGCACTACTGCAT GATTGACATAGAGAAGATCAGGGCCATGACAA TCGCCAAGCTGAAAACAATGCGGCAGGAAGAT TACATGAAGACGATAGCCGACCTTGAGTTACAT TACCAAGAGTTCATCAGAAATAGCCAAGGCTC AGAGATGTTTGAGATGATGACAAGCGGAAAA TACAGTCTCAGTTCACCGATGCCAGAAGCATT ACCAGACCCTGGTCATTACAGCTCCCTGGCTATC CCCAGCACCAGACAGTGACCAACTGAAATC ACTCATCATGGAACCTGCCAAGATGTCAACCAT AATAAAGTAATTGAAACCAACAGAGAAAAATGA CAAGCAAGAAACATGGATGCTGATGGAGCTGC AGAAGATTGCGAGGCAGATAGAGCACTGCCGAG GGCAGGATGACTCTCAAAAACCTCCCTCTAGCA GACCAGGGATCTTCTCACCACATCACAGTGAA AATTAACGAGCTTAAGAGTGTGCGAATGATT CACAAGCAATTGCTGAGGTTCTCAACCAAGCTTA AAGATATGCTTGCCAACTCAGAGGTTCTGAAA AGTACTGCTATTTACAGAATGAAGTATTTGGAC TATTTACAGAACTGGAAAATATCAATGGTGTTA CAGATGGCTACTTAAATAGCTTATGCACAGTAA GGGCACTGCTCCAGGCTATTCTCCAAACAGAA GACATGTTAAAGGTTTATGAAGCCAGGCTCACT GAGGAGGAAACTGTCTGCCTGGACCTGGATAA AGTGGAAGCTTACCGCTGTGGACTGAAGAAAA TAAAAAATGA CTTGAACCTGAAGAAGTCGTTGTTGGCCACTAT GAAGACAGAACTACAGAAAGCCCAGCAGATCC ACTCTCAGACTTCACAGCAGTATCCACTTTATG ATCTGGACTTGGGCAAGTTCGGTGAAAAAGTC ACACAGCTGACAGACCGCTGGCAAAGGATAGA TAAACAGATCGACTTTAGGTTATGGGACCTGGA GAAACAAATCAAGCAATTGAGGAATTATCGTG ATAACTATCAGGCTTTCTGCAAGTGGCTCTATG ATGCTAAACGCCGCCAGGATTCTTAGAATCCA TGAAATTTGGAGATTCCAACACAGTCATGCGGT TTTTGAATGAGCAGAAGAAGCTTGC ACAGTGAAATATCTGGCAAACGAGACAAATCA GAGGAAGTACAAAAAATTGCTGAACTTTGCGC CAATTCAATTAAGGATTATGAGCTCCAGCTGGC CTCATACACCTCAGGACTGGAAGACTCTGTGTA CATACCTATCAAGAGGACCATGATTCAGTCCCC TTCTGGGGTGATTCTGCAAGAGGCTGCAGATGT TCATGCTCGGTACATTGAACTACTTACAAGATC TGGAGACTATTACAGGTTCTTAAGTGAGATGCT GAAGAGTTTGGAAGATCTGAAGCTGAAAAATA CCAAGATCGAAGTTTTGGAAGAGGAGCTCAGA CTGGCCCCGAGATGCCAACTCGGAAAACTGTAA TAAGAACAAATTCCTGGATCAGAACTGCGAGA AATACCAGGCAGAGTGTTCCCAAGTTCAAAGCG AAGCTTGCGAGCCTGGAGGAGCTGAAGAGACA
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AMNKELIEKGHGIRLLEAQIATGG IIDPKESHRLPVDIA YKRGYFNEEL SEILSDPSDDTKGFFDPNTEENLT YLQLKERCIKDEETGLCLLPLKEK KKQVQTSQKNLTKRRRVVIVDPE TNKEMSVQEAYKKGLIDYETFKE LCEQECEWEEITITGSDGSTRVVL VDRKTGSQYDIQDAIDKGLVDRK FFDQYRSGSLSLTQFADMISLKNG VGTSSSMGSGVSDDVFSSSRHESV SKISTISSVRNL TIRSSSFSDTLEES SPIAAIFDTENLEKISITEGIERGIV DSITGQRLLEAQACTGGIHPPTG QKLSLQDAVSQGVIDQDMATRLK PAQKAFIGFEGVKGKKKMSAAEA VKEKWLPYEAGQRFLEFYQYLTGG LVDPEVHGRISTEEAIRKFIDGR AAQRLQDTSSYAKILTCPKTKLKI SYKDAINRSMVEDITGLRLLEAAS VSSKGLPSPYNMSSAPGSRSGSRS GSRSGSRSGSRSGSRSGSFDATGN SSYSYSYSFSSSSIGH (SEQ ID NO: 220)	GGCTGAGCTGGATGGGAAGTCGGCTAAGCAAA ATCTAGACAAGTGCTACGGCCAAATAAAGAA CTCAATGAGAAGATCACCCGACTGACTTATGA GATTGAAGATGAAAAGAGAAGAAGAAAATCTG TGGAAGACAGATTTGACCAACAGAAGAATGAC TATGACCAACTGCAGAAAGCAAGGCAATGTGA AAAGGAGAACCTTGTTGGCAGAAATTAGAGT CTGAGAAAAGCCATCAAGGAGAAGGAGTACGAG ATTGAAAGGTTGAGGGTTCTACTGCAGGAAGA AGGCACCC GGAAGAGAGAATATGAAAATGAGCTGGCAAAG GTAAGAAACCACTATAATGAGGAGATGAGTAA TTTAAGGAACAAGTATGAAACAGAGATTAAACA TTACGAAGACCACCATCAAGGAGATATCCATG CAAAAAGAGGATGATTCCAAAAATCTTAGAAA CCAGCTTGATAGACTTTCAAGGGAAAAATCGAG ATCTGAAGGATGAAATTGTGAGGCTCAATGAC AGCATCTTGACGGCCACTGAGCAGCGAAGGCG AGCTGAAGAAAAACGCCCTTCAGCAAAAGGCCT GTGGCTCTGAGATAATGCAGAAGAAGCAGCAT CTGGAGATAGAAGTGAAGCAGGTCATGCAGCA GCGCTCTGAGGACAATGCCCGGCACAAGCAGT CCCTGGAGGAGGCTGCCAAGACCATTGAGGAC AAAAATAAGGAGATCGAGAGACTCAAAGCTGA GTTTCAGGAGGAGGCCAAGCGCCGCTGGGAAT ATGAAAATGAACTGAGTAAGGTAAGAAACAAT TATGATGAGGAGATCATTAGCTTAAAAAATCA GTTTGAGACCGAGATCAACATCACCAAGACCA CCATCCACCAGCTCACCATGCAGAAGGAAGAG GATACCAGTGGCTACCGGGCTCAGATAGACAA TCTCACCCGAGAAAACAGGAGCTTATCTGAAG AAATAAAGAGGCTGAAGAACAACCTCTAACCAG ACCACAGAGAATCTCAGGAGGGTGGAAGAAGA CATCCAACAGCAAAAGGCCACTGGCTCTGAGG TGTCTCAGAGGAAACAGCAGCTGGAGGTTGAG CTGAGACAAGTCACTCAGATGCGAACAGAGGA GAGCGTAAGATATAAGCAATCTCTGATGATGC TGCCAAAACCATCCAGGATAAAAAACAAGGAGA TAGAAAAGGTTAAAAACAACCTGATCGACAAAGAA ACAAATGACCGGAAATGCCTGGAAGATGAAAA CGCGAGATTACAAAGGGTCCAGTATGACCTGC AGAAAGCAAACAGTAGTGCGACGGAGACAATA AACAAACTGAAGGTTGAGGAGCAAGAAGTAC ACGCCTGAGGATCGACTATGAAAGGGTTTCCC AGGAGAGGACTGTGAAGGACCAGGATATCACG CGGTTCCAGAACTCTCTGAAAGAGCTGCAGCTG CAGAAAGCAGAAGGTGGAAGAGGAGCTGAATCG GCTGAAGAGGACCGCGTCAGAAGACTCCTGCA AGAGGAAGAAGCTGGAGGAAGAGCTGGAAGG CATGAGGAGGTCGCTGAAGGAGCAAGCCATCA AAATCACCAACCTGACCCAGCAGCTGGAGCAG GCATCCATTGTTAAGAAGAGGAGTGAGGATGA CCTCCGGCAGCAGAGGGACGTGCTGGATGGCC ACCTGAGGGAAAAAGCAGAGGACCCAGGAAGA GCTGAGGAGGCTCTCTTCTGAGGTCGAGGCCCT GAGGCGGCAGTTACTCCAGGAACAGGAAAGTG TCAAAACAAGCTCACTTGAGGAATGAGCATTTCC AGAAGGCGATAGAAGATAAAAGCAGAAGCTTA AATGAAAGCAAAATAGAAATTGAGAGGCTGCA GTCTCTCACAGAGAACCTGACCAAGGAGCA
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	CTTGATGTTAGAAGAAGAACTGCGGAACCTGA GGCTGGAGTACGATGACCTGAGGAGAGGACGA AGCGAAGCGGACAGTGATAAAAAATGCAACCAT CTTGGAACCTAAGGAGCCAGCTGCAGATCAGCA ACAACCGGACCCTGGAAGTGCAGGGGCTGATT AATGATTTACAGAGAGAGAGGGAAAAATTGAG ACAGGAAATTGAGAAATTCAAAAGCAGGCTT TAGAGGCATCTAATAGGATTCAGGAATCAAAG AATCAGTGTACTCAGGTGGTACAGGAAAGAGA GAGCCTTCTGGTGAAGTCAAAGTCTCTGGAGC AAGACAAGGCAAGGCTGCAGAGGCTGGAGGAT GAGCTGAATCGTGCAAAATCAACTCTAGAGGC AGAAACAGGGTGAAACAGCGCCTGGAGTGTG AGAAACAGCAAATTCAGAATGACCTGAATCAG TGGAAGACTCAATATTCCCGCAAGGAGGAGGC TATTAGGAAGATAGAATCGGAAAGAGAAAAGA GTGAGAGAGAGAAGAACAGTCTTAGGAGTGAG ATCGAAAGACTCCAAGCAGAGATCAAGAGAAT TGAAGAGAGGTGCAGGCGTAAGCTGGAGGATT CTACCAGGGAGACACAGTCACAGTTAGAAACA GAACGCTCCCGATATCAGAGGGAGATTGATAA ACTCAGACAGCGCCATATGGGTCCCATCGAG AGACCCAGACTGAGTGTGAGTGGACCGTTGAC ACCTCCAAGCTGGTGTGTTGATGGGCTGAGGAA GAAGGTGACAGCAATGCAGCTCTATGAGTGTG AGCTGATCGACAAAACAACCTTGGACAACTA TTGAAGGGGAAGAAGTCAGTGGAAGAAGTTGC TTCTGAAATCCAGCCATTCTTCGGGGTGCAGG ATCTATCGCTGGAGCATCTGCTTCTCCTAAGGA AAAATACTCTTTGGTAGAGGCCAAGAGAAAAGA AATTAATCAGCCCAGAATCCACAGTCATGCTTC TGGAGGCCCAGGCAGCTACAGGTGGTATAATT GATCCCCATCGGAATGAGAAGCTGACTGTGGA CAGTGCCATAGCTCGGGACCTATTGACTTCGA TGACCGTCAGCAGATATATGCAGCAGAAAAAG CTATCACTGGTTTTGATGATCCATTTTCAGGCA AGACAGTATCTGTTTCAGAAGCCATCAAGAAA AATTTGATTGATAGAGAAACCGGAATGCGCCT GCTGGAAGCCCAGATTGCTTCAGGGGGTGTAG TAGACCCTGTGAACAGTGTCTTTTTGCCAAAAG ATGTCGCTTGGCCCGGGGCTGATTGATAGAG ATTTGTATCGATCCCTGAATGATCCCCGAGATA GTCAGAAAACTTTGTGGATCCAGTCACCAAA AAGAAAGGTCAGTTACGTGCAGCTGAAGGAACG GTGCAGAATCGAACCACATACTGGTCTGCTCTT G CTTTCAGTACAGAAGAGAAGCATGTCCTTCCAA GGAATCAGACAACCTGTGACCGTCACTGAGCT AGTAGATTCTGGTATATTGAGACCGTCCACTGT CAATGAACTGGAATCTGGTCAGATTTCTTATGA CGAGGTTGGTGAGAGAATTAAGGACTTCCTCC AGGGTTCAAGCTGCATAGCAGGCATATACAAT GAGACCACAAAACAGAAGCTTGGCATTATGA GGCCATGAAAAATTGGCTTAGTCCGACCTGGTAC TGCTCTGGAGTTGCTGGAAGCCCAAGCAGCTAC TGGCTTTATAGTGGATCCTGTTAGCAACTTGAG GTTACCAAGTGGAGGAAGCCTACAAGAGAGGTC TGGTGGGCATTGAGTTCAAAGAGAAGCTCCTGT CTGCAGAACGAGCTGTCACTGGGTATAATGATC CTGAAACAGGAAACATCATCTCTTTGTTCCAAG
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		CCATGAATAAGGAACTCATCGAAAAGGGCCAC GGTATTTCGCTTATTAGAAGCACAGATCGCAACC GGGGGATCATTGACCCAAAGGAGAGCCATCG TTTACCAGTTGACATAGCATATAAGAGGGGCTA TTTCAATGAGGAACTCAGTGAGATTCTCTCAGA TCCAAGTGATGATACCAAAGGATTTTTTGACCC CAACACTGAAGAAAATCTTACCTATCTGCAACT AAAAGAAAGATGCATTAAGGATGAGGAAACAG GGCTCTGTCTTCTGCCTCTGAAAGAAAAGAAGA AACAGGTGCAGACATCACAAAAGAATACCCTC AGGAAGCGTAGAGTGGTCATAGTTGACCCAGA AACCAATAAAGAAATGTCTGTTGAGGAGGCCT ACAAGAAGGGCCTAATTGATTATGAAACCTTC AAAGAACTGTGTGAGCAGGAATGTGAATGGGA AGAAATAACCATCACGGGATCAGATGGCTCCA CCAGGGTGGTCTGGTAGATAGAAAGACAGGC AGTCAGTATGATATTCAAGATGCTATTGACAAG GGCCTTGTTGACAGGAAGTTCTTTGATCAGTAC CGATCCGGCAGCCTCAGCCTCACTCAATTTGCT GACATGATCTCCTTGAAAAATGGTGTGCGGCACC AGCAGCAGCATGGGCAGTGGTGTGACGGATGA TGTTTTTAGCAGCTCCCGACATGAATCAGTAAG TAAGATTTCCACCATATCCAGCGTCAGGAATTT AACCATAAGGAGCAGCTCTTTTTCAGACACCCT GGAAGAAATCGAGCCCCATTGCAGCCATCTTTGA CACAGAAAACCTGGAGAAAATCTCCATTACAG AAGGTATAGAGCGGGGCATCGTTGACAGCATC ACGGGTCAGAGGCTT CTGGAGGCTCAGGCCTGCACAGGTGGCATCAT CCACCCAACCACGGGCCAGAAAGCTGTCACTTC AGGACGCAGTCTCCAGGGTGTGATTGACCAA GACATGGCCACCAGGCTGAAGCCTGCTCAGAA AGCCTTCATAGGCTTCGAGGGTGTGAAGGGAA AGAAAGATGTGACAGCAGAGGCGAGTGAAA GAAAAATGGCTCCCGTATGAGGCTGGCCAGCG CTTCTGGAGTTCCAGTACCTCACGGGAGGTCT TGTTGACCCGGAAGTGCATGGGAGGATAAGCA CCGAAGAAGCCATCCGGAAGGGGTTTCATAGAT GGCCGCGCCGCACAGAGGCTGCAAGACACCAG CAGCTATGCCAAAATCCTGACCTGCCCCAAAAC CAAATTAATAATATCTATAAGGATGCCATAA ATCGCTCCATGGTAGAAGATATCACTGGGCTGC GCCTTCTGGAAGCCGCTCCGTGTCTGTTCAAGG GCTTACCCAGCCCTTACAACATGTCTTCGGCTC CGGGGTCCCGCTCCGGCTCCCGCTCGGGATCTC GCTCCGGATCTCGCTCCGGGTCCCGCAGTGGGT CCCGGAGAGGAAGCTTTGACGCCACAGGGAAT TCTTCTACTCTTATTCCTACTCATTTAGCAGTA GTTCTATTGGGCACTAG (SEQ ID NO: 219)
Human DSP DPII isoform	MSCNNGSHPRINTLGRMIRAESGP DLRYEVTSGGGTSMYYSRRG VITDQNSDGYCQTGTMSRHQNP NTIQELLQNCSDCLMRAELIVQPE LKYGDGIQLTRSREDECFAQAN DQMEILDSLIREMRQMGQPCDAY QKRLQLQEQRALYKAISVPRV RRASSKGGGGYTCQSGSGWDEFT KHVTSECLGWMRQRAEMDMV AWGVDLASVEQHINSHRGIHNSI GDYRWQLDKIKADLREKSAIYQL	ATGAGCTGCAACGGAGGCTCCACCCGCGGAT CAACACTCTGGGCCGCGATGATCCGCGCCGAGTC TGGCCCGGACCTGCGCTACGAGGTGACCAGCG GCGGCGGGGGCACCAGCAGGATGTACTATTCT CGGCGCGGCGTGATCACCGACCAGAACTCGGA CGGCTACTGTCAAACCGGCACGATGTCCAGGC ACCAGAACCAGAACCATCCAGGAGCTGCTG CAGAACTGCTCCGACTGCTTGATGCGAGCAGA GCTCATCGTGCAGCCTGAATTGAAGTATGGAG ATGGAATACAACCTGACTCGGAGTCGAGAATTG GATGAGTGTTTTGCCAGGCCAATGACCAAATG

EEEYENLLKASFERMDHLRQLQN IIQATSREIMWINDCEEEELLYDW SDKNTNIAQKQEAFSIRMSQLEV EKELNKLKQESDQLVLNQHPASD KIEAYMDTLQTQWSW ILQITKCIDVHLKENAAYFQFFEE AQSTEAYLKLQDSIRKKYPCDK NMPLQHLLLEQIKELEKEREKILEY KRQVQNLVNSKKIVQLKPRNPD YRSNKPILRALCDYKQDQKIVHK GDECILKDNNSKWKYVTPGGV DMLVPSVGLIIPPNPLAVDLSCKI EQYYEAILALWNQLYINMKSLVS WHYCMIDIEKIRAMTIKLTMR QEDYMKTIADLELHYQEFIRNSQ GSEMFQDDDKRKIQSQFTDAQKH YQTLVIQLPGYPQHQTVTTEITH HGTCQDVNHNKVIETNRENDKQE TWMLMELQKIRRQIEHCEGRMTL KNLPLADQSSHHITVKINELKSV QNDSQAIAEVLNQLKDMLANFRG SEKCYLQNEVFGLFQKLENING VTDGYLNSLCTVRALLQAILQTE DMLKVYEARLTEEETVCLDLKV EAYRCGLKKIKNDLNLKSSLAT MKTELQKAQIHS QTSQQYPLYDLDLGKFGKVTQL TDRWQRIDKQIDFRLWDLEKQIK QLRNYRDNYQAFCKWLYDAKRR QDSLESMMKFGDSNTVMRFLNEQK NLHSEISGKRDKSEEVQKIAELCA NSIKDYELQLASYTSGLTLLNPI KRTMIQSPSGVILQEADVHARYI ELLTRSGDYRFLSEMLKLEDL KLKNTKIEVLEELRLARDANSEN CNKNKFLDQNLQKYQAECQFK AKLASLEELKRQAEIDGKSAKQN LDKCYGQIKELNEKITRLTYEIED EKRRRSVEDRFDQKNDYDQL QKARQCEKENLGWQKLESEKAIK EKEYEIERLRVLLQEEGTRKREYE NELAKASNRIQESKNQCTQVVQE RESLLVKIKVLEQDKARLQRLD ELNRAKSTLEAETRVKQRLCEK QQ IQNDLNQWKTYQSRKEEAIRKIES EREKSEREKNLSRSEIERLQAEIKR IEERCRRKLED STRETQSQLETERSRYQREIDKL RRPYGSHRETQTECEWTVDTSKL VFDGLRKKVTAMQLYECQLIDKT TLDKLLKGKKSVEEVASEIQPFLR GAGSIAGASASPKEKYSLVEAKR KKLISPESTVMLLEAQAATGGIID PHRNEKLTVDSAIARDLIDFDDRQ QIYAAEKAITGFDDPFSGKTVSVS EAIKKNLIDRETGMRLLEAQIASG GVVDPVNSVFLPKDVALARGLID RDLYRSLNDPRDSQKNFVDPVTK KKVSIVQLKERCRIEPHTGLLLLS	GAAATCCTCGACAGCTTGATCAGAGAGATGCG GCAGATGGGCCAGCCCTGTGATGCTTACCAGA AAAGGCTTCTTCAGCTCCAAGAGCAAATGCGA GCCCTTTATAAAGCCATCAGTGTCCCTCGAGTC CGCAGGGCCAGCTCCAAGGGTGGTGGAGGCTA CACTTGTCAGAGTGGCTCTGGCTGGGATGAGTT CACCAAACATGTCAACAGTGAATGTTTGGGGTG GATGAGGCAGCAAAGGGCGGAGATGGACATGG TGGCCTGGGGTGTGGACCTGGCCTCAGTGGAG CAGCACATTAACAGCCACCGGGGCATCCACAA CTCCATCGGCGACTATCGCTGGC AGCTGGACAAAATCAAAGCCGACCTGCGCGAG AAATCTGCGATCTACCAGTTGGAGGAGGAGTA TGAAAACCTGCTGAAAGCGTCTTTGAGAGGA TGGATCACCTGCGACAGCTGCAGAACATCATT AGGCCACGTCCAGGGAGATCATGTGGATCAAT GACTGCGAGGAGGAGGAGTGTGTACGACTG GAGCGACAAGAACACCAACATCGCTCAGAAAC AGGAGGCCTTCTCCATACGCATGAGTCAACTGG AAGTTAAAGAAAAAGAGCTCAATAAGCTGAAA CAAGAAAAGTGACCAACTTGTCTCAATCAGCAT CCAGCTTCAGACAAAATTGAGGCTATATGGA CACTCTGCAGACGCAGTGGAGTTGGATTCTTCA GATCACCAAGTGCATTGATGTTTATCTGAAAGA AAATGCTGCCTACTTTCAGTTTTTTGAAGAGGC GCAGTCTACTGAAGCATACCTGAAGGGGCTCC AGGACTCCATCAGGAAGAAGTACCCCTGCGAC AAGAACATGCCCCTGCAGCACCTGCTGGAACA GATCAAGGAGCTGGAGAAAGAACGAGAGAAA ATCCTTGAATACAAGCGTCAGGTGCAGAACTTG GTAAACAAGTCTAAGAAGATTGTACAGCTGAA GCCTCGTAACCCAGACTACAGAAGCAATAAAC CCATTATTCTCAGAGCTCTCTG TGACTACAAACAAGATCAGAAAATCGTGCATA AGGGGGATGAGTGTATCCTGAAGGACAACAAC GAGCGCAGCAAGTGGTACGTGACGGGCCCGGG AGGCGTTGACATGCTTGTTCCTCTGTGGGGCT GATCATCCCTCCTCCGAACCCACTGGCCGTGGA CCTCTCTTGCAAGATTGAGCAGTACTACGAAGC CATCTTGGCTCTGTGGAACACAGCTCTACATCAA CATGAAGAGCCTGGTGTCTGGCACTACTGCAT GATTGACATAGAGAAGATCAGGGCCATGACAA TCGCCAAGCTGAAAACAATGCGGCAGGAAGAT TACATGAAGACGATAGCCGACCTTGAGTTACAT TACCAAGAGTTCATCAGAAATAGCCAAGGCTC AGAGATGTTTGGAGATGATGACAAGCGGAAAA TACAGTCTCAGTTACCCGATGCCAGAAGCATT ACCAGACCCTGGTCATTACAGCTCCCTGGCTATC CCCAGCACCAGACAGTGACCACAACCTGAAATC ACTCATCATGGAACCTGCCAAGATGTCAACCAT AATAAAGTAATTGAAACCAACAGAGAAAATGA CAAGCAAGAAACATGGATGCTGATGGAGCTGC AGAAGATTGCGAGGCAGATAGAGCACTGCGAG GGCAGGATGACTCTCAAAAACCTCCTCTAGCA GACCAGGGATCTTCTACCACATCACAGTGAA AATTAACGAGCTTAAGAGTGTGCAGAAATGATT CACAAGCAATTGCTGAGGTTCTCAACCAGCTTA AAGATATGCTTGCCAACCTCAGAGGTTCTGAAA AGTACTGCTATTTACAGAATGAAGTATTTGGAC TATTTACAGAACTGGAAAATATCAATGGTGTTA
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VQKRSMFQGIQPVTVTELVD GILRPSTVNELESGQISYDEVGERI KDFLQGSSCIAGIYNETTKQLGI YEAMKIGLVRPGTALELLEAQAA TGFIVDPVSNLRLPVEEAYKRGLV GIEFKEKLLSAERAVTGYNDPETG NIISLFQAMNKELIEKGHGRLLLEA QIATGGIIDPKESHRLPVDIAYKRG YFNEELSEILSDPSDDTKGFFDPNT EENLTYLQLKERCIKDEETGLCLL PLKEKKKQVQTSQKNLTKRRRVV IVDPETNKEMSVQEAYKKGLIDY ETFKELCEQECWEIITITGSDGST RVVLVDRKTGSQYDIQDAIDKGL VDRKFFDQYRSGSLSLTQFADMIS LKNVGTSSSMGSGVSDDVSSS RHESVSKISTISSVRNLTRSSFS TLEESSPIAAIFDTENLEKISITEGIE RGIVDSITGQRLLEAQAQTGGIHP TTGQKLSLQDAVSQGVIDQDMAT RLKPAQKAFIGFEGVKGKKKMSA AEAVKEKWLPEYAGQRFLEFQYL TGGLVDPEVHGRISTEEAIRKGF DGRAAQRLQDTSSYAKILTCPKT KLKISYKDAINRSMVEDITGLRLL EASVSXKGLPSPYNMSSAPGSR GSRSGSRSGSRSGSRSGSRSGSFD ATGNSSYSYSFSSSSIGH (SEQ ID NO: 222)	CAGATGGCTACTTAAATAGCTTATGCACAGTAA GGGCACTGCTCCAGGCTATTCTCCAAACAGAA GACATGTTAAAGGTTTATGAAGCCAGGCTCACT GAGGAGGAAACTGTCTGCCTGGACCTGGATAA AGTGGAAGCTTACCGCTGTGGACTGAAGAAAA TAAAAAATGA (SEQ ID NO:221) CTTGAACCTGAAGAAGTCGTTGTTGGCCACTAT GAAGACAGAACTACAGAAAGCCAGCAGATCC ACTCTCAGACTTCACAGCAGTATCCACTTTATG ATCTGGACTTGGGCAAGTTCGGTGAAAAAGTC ACACAGCTGACAGACCGCTGGCAAAGGATAGA TAAACAGATCGACTTTAGGTTATGGGACCTGGA GAAACAAATCAAGCAATTGAGGAATTATCGTG ATAACTATCAGGCTTTCTGCAAGTGGCTCTATG ATGCTAAACGCCGCCAGGATTCTTAGAATCCA TGAAATTTGGAGATTCACACAGTCATGCGGT TTTTGAATGAGCAGAAGAAGCTTGC ACAGTGAAATATCTGGCAAACGAGACAAATCA GAGGAAGTACAAAAAATTGCTGAACCTTTCGCGC CAATTCAATTAAGGATTATGAGCTCCAGCTGGC CTCATAACCTCAGGACTGGAAACTCTGTGTA CATACCTATCAAGAGGACCATGATTCAGTCCCC TTCTGGGGTGATTCTGCAAGAGGCTGCAGATGT TCATGCTCGGTACATTGAACCTTACAAGATC TGGAGACTATTACAGGTTCTTAAGTGAGATGCT GAAGAGTTTGGAAAGATCTGAAGCTGAAAAATA CCAAGATCGAAGTTTTGGAAAGAGGAGCTCAGA CTGGCCCCGAGATGCCAACTCGGAA AACTGTAATAAGAACAAATTCCTGGATCAGAA CCTGCAGAAATACCAGGCAGAGTGTCCCAAGT CAAAGCGAAGCTTGCGAGCCTGGAGGAGCTGA AGAGACAGGCTGAGCTGGATGGGAAGTCGGCT AAGCAAAATCTAGACAAGTGCTACGGCCAAAT AAAAGAACTCAATGAGAAGATCACCCGACTGA CTTATGAGATTGAAGATGAAAAGAGAAGAAGA AAATCTGTGGAAGACAGATTTGACCAACAGAA GAATGACTATGACCAACTGCAGAAAGCAAGGC AATGTGAAAAGGAGAACCTTGGTTGGCAGAAA TTAGAGTCTGAGAAAGCCATCAAGGAGAAGGA GTACGAGATTGAAAGGTTGAGGGTTCTACTGC AGGAAGAAGGCACCC GGAAGAGAGAATATGAAAATGAGCTGGCAAAG GCATCTAATAGGATTACAGGAATCAAAGAATCA GTGTACTCAGGTGGTACAGGAAAGAGAGAGCC TTCTGGTGAAAATCAAAGTCCTGGAGCAAGAC AAGGCAAGGCTGCAGAGGCTGGAGGATGAGCT GAATCGTGCAAAATCAACTCTAGAGGCAGAAA CCAGGGTGAAACAGCGCCTGGAGTGTGAGAAA CAGCAAATTCAGAATGACCTGAATCAGTGGA GACTCAATATTTCCCGCAAGGAGGAGGCTATTA GGAAGATAGAATCGGAAAGAGAAAAGAGTGA GAGAGAGAAGAACAGTCTTAGGAGTGAGATCG AAAGACTCCAAGCAGAGATCAAGAGAATTGAA GAGAGGTGCAGGCGTAAGCTGGAGGATTCTAC CAGGGAGACACAGTCACAGTTAGAAACAGAAC GCT CCCGATATCAGAGGGAGATTGATAAACTCAGA CAGCGCCCATATGGGTCCCATCGAGAGACCCA GACTGAGTGTGAGTGGACCGTTGACACCTCCA AGCTGGTGTTTGATGGGCTGAGGAAGAAGGTG
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		ACAGCAATGCAGCTCTATGAGTGTGACGTGATC GACAAAAACAACCTTGGACAAACTATTGAAGGG GAAGAAAGTCAGTGGAAGAAGTTGCTTCTGAAA TCCAGCCATTCTTCGGGGTGCAGGATCTATCG CTGGAGCATCTGCTTCTCCTAAGGAAAAATACT CTTTGGTAGAGGCCAAGAGAAAAGAAATTAATC AGCCCAGAATCCACAGTCATGCTTCTGGAGGCC CAGGCAGCTACAGGTGGTATAATTGATCCCCAT CGGAATGAGAAGCTGACTGTGACAGTGCCAT AGCTCGGGACCTCATTGACTTCGATGACCGTCA GCAGATATATGCAGCAGAAAAAGCTATCACTG GTTTTGATGATCCATTTTCAGGCAAGACAGTAT CTGTTTCAGAAGCCATCAAGAAAAATTTGATTG ATAGAGAAACCGGAATGCGCCTGCTGGAAGCC CAGATTGCTTCAGGGGGTGTAGTAGACCCTGTG AACAGTGTCTTTTTGCCAAAAGATGTGCGCTTG GCCCCGGGGCTGATTGATAGAGATTGTATCGA TCCCTGAATGATCCCCGAGATAGTCAGAAAAA CTTTGTGGATCCAGTCACCAAAAAGAAGGTCA GTTACGTGCAGCTGAAGGAACGGTGCAGAAATC GAACACATACTGGTCTGCTCTTGCTTTCAGTA CAGAAGAGAAGCATGTCTTCCAAGGAATCAG ACAACCTGTGACCGTCACTGAGCTAGTAGATT TGGTATATTGAGACCGTCCACTGTCAATGAACT GGAATCTGGTCAAGTTTCTTATGACGAGGTTGG TGAGAGAATTAAGGACTTCTCCAGGGTTCAA GCTGCATAGCAGGCATATACAATGAGACCACA AAACAGAAGCTTGGCATTATGAGGCCATGAA AATTGGCTTAGTCCGACCTGGTACTGCTCTGGA GTTGCTGGAAGCCCAAGCAGCTACTGGCTTTAT AGTGGATCCTGTTAGCAACTTGAGGTTACCAGT GGAGGAAGCCTACAAGAGAGGTCTGGTGGGCA TTGAGTTCAAAGAGAAGCTCCTGTCTGCAGAAC GAGCTGTCACTGGGTATAATGATCCTGAAACA GGAAACATCATCTCTTTGTTCCAAGCCATGAAT AAGGAACTCATCGAAAAGGGCCACGGTATTCTG CTTATTAGAAGCACAGATCGCAACCGGGGGGA TCATTGACCCAAAGGAGAGCCATCGTTTACCAG TTGACATAGCATATAAGAGGGGCTATTTCAATG AG GAACTCAGTGAGATTCTCTCAGATCCAAGTGAT GATACCAAAGGATTTTTTGACCCCAACTGAA GAAAATCTTACCTATCTGCAACTAAAAGAAAG ATGCATTAAGGATGAGGAAACAGGGCTCTGTC TTCTGCCTCTGAAAAGAAAAGAAGAACAGGTG CAGACATCACAAAAGAATACCCTCAGGAAGCG TAGAGTGGTCATAGTTGACCCAGAAACCAATA AAGAAATGTCTGTTTCAAGAGGCCTACAAGAAG GGCCTAATTGATTATGAAACCTTCAAAGAAGT TGTGAGCAGGAATGTGAATGGGAAGAAATAAC CATCACGGGATCAGATGGCTCCACCAGGGTGG TCCTGGTAGATAGAAAGACAGGCAGTCAGTAT GATATTCAAGATGCTATTGACAAGGGCCTTGTT GACAGGAAGTTCTTTGATCAGTACCGATCCGGC AGCCTCAGCCTCACTCAATTTGCTGACATGATC TCCTTGAAAAATGGTGTGCGCACCCAGCAGCAG CATGGGCAGTGGTGTGAGCGATGATGTTTTAG CAGCTCCCGACATGAATCAGTAAGTAAGATTT CACCATATCCAGCGTCAGGAATTTAACATAAG GAGCAGCTCTTTTTCAGACACCCTGGAAGAATC
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		GAGCCCCATTGCAGCCATCTTTGACACAGAAA ACCTGGAGAAAAATCTCCA TTACAGAAGGTATAGAGCGGGGCATCGTTGAC AGCATCACGGGTGAGAGGCTTCTGGAGGCTCA GGCCTGCACAGGTGGCATCATCCACCCAACCA CGGGCCAGAAAGCTGTCACTTCAGGACGCAGTC TCCCAGGGTGTGATTGACCAAGACATGGCCAC CAGGCTGAAGCCTGCTCAGAAAGCCTTCATAG GCTTCGAGGGTGTGAAGGGAAGAAGAAGATG TCAGCAGCAGAGGCAGTGAAAGAAAAATGGCT CCCGTATGAGGCTGGCCAGCGCTTCCTGGAGTT CCAGTACCTCACGGGAGGTCTTGTGACCCGGA AGTGCATGGGAGGATAAGCACCGAAGAAGCCA TCCGGAAGGGGTTCATAGATGGCCGCGCCGCA CAGAGGCTGCAAGACACCAGCAGCTATGCCAA AATCCTGACCTGCCCCAAAACCAAAATAAAAA TATCCTATAAGGATGCCATAAATCGCTCCATGG TAGAAGATATCACTGGGCTGCGCCTTCTGGAAG CCGCCTCCGTGTCGTCCAAGGGCTTACCCAGCC CTTACAACATGTCTTCGGCTCCGGGGTCCCGCT CCGGCTCCCGCTCGGGATCTCGCTCCGGATCTC GCTCCGGGTCCCGCAGTGGGTCCCGGAGAGGA AGCTTTGACGCCACAGGGAATTCTTCTACTCT TATTCTACTCATTTAGCAGTAGTTCTATTGGG CACTAG (SEQ ID NO: 221)
Human DSG2	MARSPGRAYALLLLICFNVGSG LHLQVLSTRNENKLLPKHPLVR QKRAWITAPVALREGEDLSKKNP IAKIHSDLAEEERGLKITYKYTGKG ITEPPFGIFVFNKDTGELNVTSLD REETPFLLTGALDARGNNVEK PLELRIKVLINDNEPVFTQDVV GSVEELSAHTLVMKINATDADE PNTLNSKISYRIVSLEPAYPPVYL NKDTGEIYTTSVTLDREEHSSYTL TVEARDGNGEVTDPVKQAQVQI RILDVNDNIPVVENK VLEGMVEE NQVNVEVTRIKVFDADAEIGSDNW LANFTFASGNEGGYFHIEDAQT NEGIVTLIKEVDYEEMKNLDFSVI VANKAAFHKSIRSKYKPTPIPIKV KVKNVKEGIHFKSSVISIYVSESM DRSSKGQIIGNFQAFDEDTGLPAH ARYVKLEDRDNWISVDSVTSEIK LAKLPDFESRYVQNGTYTVKIVAI SEDYPRKTITGTVLINVEDINDNC PTLIEPVQTICHDAEYVNVTAE DL DGHPNSGPF SFSVIDKPPGMAEK WKIARQUESTSVLLQQSEKLGSR EIQLISDNQGFSCPEKQVLT LTV ECLHSGCREAQHDSYVGLGPAA IALMILAFLLLLVPLLLLMCHCG KGAKGFTPIPGTIEMLHPWNNEG APPEDKVVPSFLPVDQGGSLVGR NGVGGMAKEATMKGSSSASIVK GQHEMSEMDGRWEEHRSLLSGR ATQFTGATGAIMTTETTKTARAT GASRDMAGAQA AVALNEEFLR NYFTDKAASYTEEDENHTAKDCL LVYSQEETESLNASIGCCSFIEGEL	ATGGCGCGGAGCCCGGGACGCGCGTACGCCCT GCTGCTTCTCCTGATCTGCTTTAACGTTGGAAG TGGACTTCACCTACAGGTCTTAAGCACAAGAAA TGAAAATAAGCTGCTTCTAAACATCCTCATTT AGTGCGGCAAAAAGCGCGCCTGGATCACCGCCC CCGTGGCTCTTCGGGAGGGAGAGGATCTGTCC AAGAAAGAAATCCAATTGCCAAGATACATTCTGA TCTTGCAAGAAGAAAGAGGACTCAAAATTACTT ACAAATACACTGGAAGGGATTACAGAGCCA CCTTTTGGTATATTTGTCTTTAAACAAAGATACT GGAGAACTGAATGTTACCAGCATTCTTGATCGA GAAGAAACACCATTTTTTCTGCTAACAGGTTAC GCTTTGGATGCAAGAGGAAACAATGTAGAGAA ACCCTTAGAGCTACGCATTAAGGTTCTTGATAT CAATGACAACGAACAGTGTTACACACAGGATG TCTTTGTTGGGTCTGTTGAAGAGTTGAGTGCAG CACATACTCTTGATGAAAAATCAATGCAACAG ATGCAGATGAGCCCAATACCCTGAATTCGAAA ATTCCTATAGAATCGTATCTCTGGAGCCTGCT TATCCTCCAGTGTCTACCTAAATAAAGATACA GGAGAGATTTATACAACCAAGTGTACCTTGGAC AGAGAGGAACACAGCAGCTACACTTTGACAGT AGAAGCAAGAGATGGCAATGGAGAAGTTACAG ACAAACCTGTAAAACAAGCTCAAGTTCAGATT CGTATTTTGGATGTCAATGACAATATACCTGTA GTAGAAAATAAAGTGCTTGAAGGGATGGTTGA AGAAAATCAAGTCAACGTAGAAGTTACGCGCA TAAAAGTGTTTCGATGCAGATGAAATAGGTTCTG ATAATTGGCTGGCAAATTTTACATTTGCATCAG GAAATGA AGGAGGTTATTTCCACATAGAAACAGATGCTC AAACTAACGAAGGAATTGTGACCCCTATTAAAG GAAGTAGATTATGAAGAAATGAAGAATCTTGA CTTCAGTGTTATGTGCGTAATAAAGCAGCTTT TCACAAGTCGATTAGGAGTAAATACAAGCCTA

	DDRFLDDLGLKFKTLAEVCLGQK IDINKEIEQRQKPATETSMNTASH SLCEQTMVNSENTYSSGSSFPVK SLQEANA EKVTQEIVTERS VSSRQ AQKVATPLPDPMASRNVIA TETS YVTGSTMPPTTVILGPSQPQSLIVT ERVYAPASTLVDQPYANEGTVVV TERVIQPHGGGSPLEGTQHLQD VPYVMVRERESFLAPSSGVQPTL AMPNIAVGQNVTVTERVLAPAST LQSSYQIPTENSMTARNTTVSGAG VPGPLPDFGLEESGHSNSTITTSST RVTKHSTVQHSYS (SEQ ID NO: 224)	CACCCATTCCCATCAAGGTCAAAAGTGAAAAAT GTGAAAGAAGGCATTCAATTTAAAAAGCAGCGT CATCTCAATTTATGTTAGCGAGAGCATGGATAG ATCAAGCAAAGGCCAAATAATTGGAAATTTTC AAGCTTTTGATGAGGACACTGGACTACCAGCCC ATGCAAGATATGTAAAAATTAGAAGATAGAGAT AATTGGATCTCTGTGGATTCTGTACATCTGAA ATTAAACTTGCAAAACTTCCTGATTTTGAATCT AGATATGTTCAAAATGGCACATACACTGTAAA GATTGTGGCCATATCAGAAGATTATCCTAGAAA AACCATCACTGGCACAGTCTTATCAATGTTGA AGACATCAACGACAACGTGCCACACTGATAG AGCCTGTGCAGACAATCTGTACAGATGCAGAG TATGTGAATGTTACTGCAGAGGACCTGGATGG ACACCCAAACAGTGGCCCTTCAGTTTCTCCGT CATTGACAAACCACCTGGCATGGCAGAAAAAT GGAAAAATAGCACGCCAAGAAAGTACCAGTGTG CTGCTGCAACAAAGTGAGAAAAAGCTTGGGAG AAGTGAAATTCAGTTCCTGATTTTCAACAATCA GGGTTTTAGTTGTCTGAAAAAGCAGGTCCTTAC ACTCACAGTTTGTGAGTGTCTGCATGGCAGCGG CTGCAGGGAAGCACAGCATGACTCCTATGTGG GCCTGGGACCCGCAGCAATTGCGCTCATGATTT TGGCCTTTCTGCTCCTGCTATTGGTACCACTTTT ACTGCTGA TGTGCCATTGCGGAAAGGGCGCCAAAGGCTTT ACCCCCATACCTGGCACCATAGAGATGCTGCAT CCTTGGAATAATGAAGGAGCACCACTGAAGA CAAGGTGGTGCCATCATTCTGCCAGTGGATCA AGGGGGCAGTCTAGTAGGAAGAAATGGAGTAG GAGGTATGGCCAAGGAAGCCACGATGAAAGGA AGTAGCTCTGCTTCCATTGTCAAAGGGCAACAT GAGATGTCCGAGATGGATGGAAGGTGGGAAGA ACACAGAAGCCTGCTTTCTGGTAGAGCTACCCA GTTTACAGGGGGCCACAGGCGCTATCATGACCA CTGAAACCACGAAGACCGCAAGGGCCACAGGG GCTTCCAGAGACATGGCCGGAGCTCAGGCAGC TGCTGTTGCACTGAACGAAGAATTCTTAAGAAA TTATTTCACTGATAAAGCGGCCTCTTACACTGA GGAAGATGAAAAATCACACAGCCAAAGATTGCC TTCTGGTTTTATTCTCAGGAAGAACTGAATCGC TGAATGCTTCTATTGGTTGTTGCAGTTTATTGA AGGAGAGCTAGATGACCGCTTCTTAGATGATTT GGGACTTAAATTCAAGACACTAGCTGAAGTTTG CCTGGGTCAAAAAATAGATATAAATAAGGAAA TTGAGCAGAGACAAAAACCTGCCACAGAAACA AGTATGAACACAGCTTC ACATTCACCTCTGTGAGCAAACATATGGTTAATTC AGAGAATACCTACTCCTCTGGCAGTAGCTTCCC AGTTCCAAAATCTTTGCAAGAAGCCAATGCAG AGAAAGTAACTCAGGAAATAGTCACTGAAAGA TCTGTGTCTTCTAGGCAGGCGCAAAAGGTAGCT ACACCTCTTCTGACCCAATGGCTTCTAGAAAT GTGATAGCAACAGAAACTTCTATGTACAGG GTCCACTATGCCACCAACCACTGTGATCCTGGG TCCTAGCCAGCCACAGAGCCTTATTGTGACAGA GAGGGTGTATGCTCCAGCTTCTACCTTGGTAGA TCAGCCTTATGCTAATGAAGGTACAGTTGTGGT CACTGAAAGAGTAATACAGCCTCATGGGGGTG GATCGAATCCTCTGGAAGGCACTCAGCATCTTC
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		AAGATGTACCTTACGTCATGGTGAGGGAAAAGA GAGAGCTTCCTTGCCCCAGCTCAGGTGTGCAG CCTACTCTGGCCATGCCTAATATAGCAGTAGGA CAGAATGTGACAGTGACAGAAAGAGTTCTAGC ACCTGCTTCCACTCTGCAATCCAGTTACCAGAT TCCCACTGAAAATTCTATGACGGCTAGGAACAC CACGGTGTCTGGAGCTGGAGTCCCTGGCC CTCTGCCAGATTTTGGTTTAGAGGAATCTGGTC ATTCTAATTCTACCATAACCACATCTTCCACCA GAGTTACCAAGCATAGCACTGTACAGCATTCTT ACTCCTAA (SEQ ID NO: 223)
Human JUP	MEVMNLMEQPIKVTEWQQTYTY DSGIHSGANTCVPSVSSKGIMEED EACGRQYTLKKTTTYTQGVPPSQ GDLEYQMSSTARAKRVREAMCP GVSGEDSSLLLATQVEGQATNLQ RLAEPSSLKSAIVHLINYQDDAE LATRALPELTKLLNDEDPVVVTK AAMIVNQLSKKEASRRALMGSPQ LVAAVVRTMQNTSDDLTAARCTTS ILHNLSSHREGLLAIFKSGGIPALV RMLSSPVESVLFYAITTLHNLLY QEGAKMAVRLADGLQKMVPLLN KNNPKFLAITTDCLQLLAYGNQE SKLIILANGGPQALVQIMRNYSE KLLWTTSRVLKVLVSVCPSPKPAIV EAGGMQALGKHLTSNSPRLVQN CLWTLRNLSDVATKQEGLESVLK ILVNQLSVDDVNVLTCAATGTLN LTCNNSKNKTLVTQNSGVEALIH AILRAGDKDDITEPAVCLRLHTS RHPEAEMAQNSVRLNY GIPAIVKLLNQPNQWPLVKATIGL IRNLALCPANHAPLQEAAPVIRLV QLLVKAHQDAQRHVAAGTQQPY TDGVRMEEIVEGCTGALHILARD PMNRMEIFRLNTIPLFVQLLYSSV ENIQRVAAGVLCELAQDKEAADA IDAEGASAPLMELLHSRNEGAT YAAAVLFRISEDKNPDYRKRVSV ELTNSLFKHDPAAWEAAQSMIPIN EPYGDDMDATYRPMYSSDVPLDP LEMHMDMDGDYPIDTYSGLRPP YPTADHMLA (SEQ ID NO: 226)	ATGGAGGTGATGAACCTGATGGAGCAGCCTAT CAAGGTGACTGAGTGGCAGCAGACATACACCT ACGACTCGGGTATCCACTCGGGCGCCAACACCT GCGTGCCCTCCGTCAGCAGCAAGGGCATCATG GAGGAGGATGAGGCCTGCGGGCGCCAGTACAC GCTCAAGAAAACCACTTACACCCAGGGG TGCCCCCAGCCAAGGTGATCTGGAGTACCAG ATGTCCACAACAGCCAGGGCCAAACGGGTGCG GGAGGCCATGTGCCCTGGTGTGTCAGGCGAGG ACAGCTCGCTTCTGCTGGCCACCCAGGTGGAGG GGCAGGCCACCAACCTGCAGCGACTGGCCGAG CCGTCCCAGCTGCTCAAGTCGGCCATTGTGCAT CTCATCAACTACC AGGACGATGCCGAGCTGGCCACTCGCGCCCTG CCCAGCTCACCAAACTGCTCAACGACGAGGA CCCGGTGGTGGTGACCAAGGCGGCCATGATTG TGAACCAGCTGTGCAAGAAGGAGGCGTCGCGG CGGGCCCTGATGGGCTCGCCCCAGCTGGTGGCC GCTGTGCTGCGTACCATGCAGAATACCAGCGA CCTGGACACAGCCCGCTGCACCACCAGCATCCT GCACAACCTCTCCCAACCAACCGGAGGGGCTGC TCGCCATCTTCAAGTCGGGTGGCATCCCTGCTC TGGTCCGCTGCTCAGCTCCCTGTGGAGTCGG TCCTGTTCTATGCCATCACACGCTGCACAACC TGCTCCTGTACCAGGAGGGCGCCAAGATGGCC GTGCGCTGGCCGACGGGCTGCAAAAGATGGT GCCCTGCTCAACAAGAACAACCCCAAGTTCCT GGCCATCACCAACGACTGCCTGCAGCTCCTGGC CTACGGCAACCAAGGAGAGCAAGCTGATCATCC TGGCCAATGGTGGGCCCCAGGCCCTCGTGCAG ATCATGCGTAACTACAGTTATGAAAAGCTGCTC TGGACCACAGTCTGTGTCTCAAGGTGCTATCC GTGTGTCCCAGCAATAAGCCTGCCATTGTGGAG GCTGGTGGGATGCAGGCCCTGGGCAAGCACCT GACCAGCAACAGCCCCCGCTGGTGCAGAACT GCCTGTGGACCCTGCGCAACCTCTCAGATGTGG CCACCAAGCAGGAGGGCCTGGAGAGTGTGCTG AAGATTCTGGTGAATCAGCTGAGTGTGGATGA CGTCAACGTCCTACCTGTGCCACGGGCACACT CTCCAACCTGACATGCAACAACAGCAAGAACA AGACGCTGGTGACACAGAACAGCGGTGTGGAG GCTCTCATCCATGCCATCCTGCGTGTGGTGAC AAGGACGACATCACGGAGCCTGCCGTCTGCGC TCTGCGCCACCTCACTAGCCGCCACCTGAGGC CGAGATGGCCCCAGAACTCTGTGCGTCTCAACTA TGGCATCCCAGCCATCGTGAAGCTGCTCAACCA GCCCAACCAAGTGGCCACTGGTCAAGGCAACCA TCGGCTTGATCAGGAATCTGGCCCTGTGCCAG CCAACCATGCCCCGCTGCAGGAGGCGAGCGGTC

		ATCCCCCGCCTCGTCCAACTGCTGGTGAAGGCC CACCAGGATGCCCAGCGCCACGTAGCTGCAGG CACACAGCAGCCCTACACGGATGGTGTGAGGA TGGAGGAGATTGTGGAGGGCTGCACCGGAGCA CTGCACATCCTCGCCCGGACCCCATGAACCGC ATGGAGATCTTCCGGCTCAACACCATTCCCCTG TTTGTGCAGCTCCTGTACTCGTCGGTGGAGAAC ATCCAGCGCGTGGCTGCCGGGGTGTGTGTGA GCTGGCCCAGGACAAGGAGGGCGGCCGACGCCA TTGATGCAGAGGGGGCTCGGCCCACTCATG GAGTTGCTGCACTCCCGCAACGAGGGCACTGC CACCTACGCTGTGCCGTCTGTTCGCATCTC CGAGGACAAGAACCAGACTACCGGAAGCGCG TGTCCGTGGAGCTCACCAACTCCCTCTTCAAGC ATGACCCGGCTGCCTGGGAGGCTGCCAGAGC ATGATTCCCATCAATGAGCCCTATGGAGATGAC ATGGATGCCACCTACCGCCCATGTACTCCAGC GATGTGCCCCTTGACCCGCTGGAGATGCACATG GACATGGATGGAGACTACCCCATCGACACCTA CAGCGACGGCCTCAGGCCCCCTGACCCCACTGC AGACCACATGCTGGCCTAG (SEQ ID NO: 225)
Human JPH2 N- terminal fragment	MSGGRFDFDDGGAYCGGWEGGK AHGHGLCTGPKGQGEYSGSWNF GFEVAGVYTWPSTNTFEGYWSQ GKRHGLGIETKGRWLYKGEWTH GFKGRYGIRQSSSSGAKYEGTWN NGLQDGYGTETYADGGTYQGQF TNGMRHGYGVRQSVPYGMAVV VRSPLRTSLSSLRSEHSNGTVAPD SPASPASDGPALPSAIPRGGFALS LLANAEAAARAPKGGGLFQORGA LLGKLRRRAESRTSVGSQRSRVSL KSDLSSGASDAASTASLGAAEG ADEAAPFEADIDATTETYMGEW KNDKRSFGVSRSSGLRYEGEW LDNLRHGYGCTTLPDGHREEGKY RHNVLVKDTKRRMLQLKSNKVR QKVEHSVEGAQRAAAIARQKAEI AASRTSHAKAKAEAAEQALAA NQESNIARTLARELAPDFYQPGPE YQKRLLQEILENSESLEPPDRG AGAAGLPQPPRESPQLHERETPRP EGGSPSPAGTPPQPKRPRPGVSKD GLLSPGAWNGEPSGEGSRSVTPSE GAGRRSPARPATERMAIEALQAP PAPSREPEVALYQGYHSYAVR (SEQ ID NO:228)	ATGAGTGGGGGGCCGCTTCGACTTTGATGATGGA GGGGCGTACTGCGGGGGCTGGGAGGGGGGAA GGCCCATGGGCATGGACTGTGCACAGGCCCA AGGGCCAGGGCGAATACTCTGGCTCTGGAAC TTTGGCTTTGAGGTGGCAGGTGTCTACACTGG CCCAGCGGAAACACCTTTGAGGGATCTGGAG CCAGGGCAAACGGCATGGGCTGGGCATAGAGA CCAAGGGGCGCTGGCTCTACAAGGGCGAGTGG ACACATGGCTTCAAGGGACGCTACGGAATCCG GCAGAGCTCAAGCAGCGGTGCCAAGTATGAGG GCACCTGGAACAATGGCCTGCAAGACGGCTAT GGCACCGAGACCTATGCTGATGGAGGGACGTA CCAAGGCCAGTTCACCAACGGCATGCGCCATG GCTACGGAGTACGCCAGAGCGTGCCCTACGGG ATGGCCGTGGTGGTGGCTCGCCGCTGCGCACG TCGCTGTCTGTCCTCGCGCAGCAGCAGCAAC GGCACGGTGGCCCCGGAATCTCCCGCTCGCCG GCCTCCGACGGCCCCGCGCTGCGCTCGCCCGC ATCCCGCGTGGCGGCTTCGCGCTCAGCCTCCTG GCCAATGCCGAGGCGGCGCGCGGGCGCCCA GGGCGGCGGCGCTCTTCCAGCGGGCGCGTGC TGGGCAAGCTGCGGCGCGCAGAGTCGCGCACG TCCGTGGGTAGCCAGCGCAGCCGTGTCAGCTTC CTTAAGAGCGACCTCAGCTCGGGCGCCAGCGA CGCCGCGTCCACCGCCAGCCTGGGAGAGGCCG CCGAGGGCGCCGACGAGGCCGACCCCTTCGAG GCCGATATCGACGCCACCACCACCGAGACCTA CATGGGCGAGTGGAAGAACGACAAACGCTCGG GCTTCGGCGTGAGCGAACGCTCCAGTGGCCTCC GCTACGAGGGCGAGTGGCTGGACAACCTGCGC CACGGCTATGGCTGCACCACGCTGCCCGACGG CCACCGCGAGGAGGGCAAGTACCGCCACAACG TGCTGGTCAAGGACACCAAGCGCCGATGCTG CAGCTCAAGAGCAACAAGGTCCGCCAGAAAGT GGAGCACAGTGTGGAGGGTGCCAGCGCGCGG CTGCTATCGCGCGCCAGAAGGCCGAGATTGCC GCCTCCAGGACAAGCCACGCCAAGGCCAAAGC TGAGGCAGCGGAACAGGCCGCGCTGGCTGCCA ACCAGGAGTCCAACATTGCTCGCACTTTGGCCA

		GGGAGCTGGCTCCGGACTTCTACCAGCCAGGTC CGGAATATCAGAAGCGCCGGCTGCTGCAGGAG ATCCTGGAGAACTCGGAGAGCCTGCTGGAGCC CCCCGACCGGGGCGCCGGCGCAGCGGGCCTCC CACAGCCGCCCCGCGAGAGCCCGCAGCTGCAC GAGCGTGAGACCCCTCGGCCCGAGGGTGGCTC CCCGTCACCGGCCGGGACGCCCCCGCAGCCCA AGCGGCCCCAGGCCCGGGGTGTCCAAGGACGGC CTGCTGAGCCCAGGCGCCTGGAACGGCGAGCC CAGCGGTGAGGGGAGCCGGTCAGTCACTCCGT CCGAGGGCGCGGGGCCCGCAGCCCCGCGCGT CCAGCCACCGAGCGCATGGCCATCGAGGCTCT GCAGGCACCGCCTGCGCCGTCGCGGGAGCCGG AGGTGGCGCTTTACCAGGGCTACCACAGCTATG CTGTGCGC (SEQ ID NO:227)
Human PLN	MEKVQYLTRSAIRRASTIEMPQQ ARQKLQNLFINFCLILICLLLIIV MLL (SEQ ID NO:230)	ATGGAGAAAGTCCAATACCTCACTCGCTCAGCT ATAAGAAGAGCCTCAACCATTGAAATGCCTCA ACAAGCACGTCAAAAAGCTACAGAATCTATTTAT CAATTTCTGTCTCATCTTAATATGTCTCTTGCTG ATCTGTATCATCGTGATGCTTCTCTGA (SEQ ID NO:229)

Promoters and Enhancers

[00173] In some embodiments, the expression cassette of the disclosure comprises a promoter. The term “promoter” as used herein refers to a DNA sequence that directs the binding of RNA polymerase and thereby promotes RNA synthesis. Promoters and corresponding protein or polypeptide expression may be ubiquitous, meaning strongly active in a wide range of cells, tissues and species or cell-type specific, tissue-specific, or species specific. Examples of ubiquitous promoters include the CAG promoter and CMB promoter (Yue et al. *BioTechniques* 33:672-678 (2002)). Promoters may be “constitutive,” meaning continually active, or “inducible,” meaning the promoter can be activated or deactivated by the presence or absence of biotic or abiotic factors. Also included in the nucleic acid constructs or vectors of the invention are enhancer sequences that may or may not be contiguous with the promoter sequence. Enhancer sequences influence promoter-dependent gene expression and may be located in the 5′ or 3′ regions of the native gene.

[00174] Various promoters may be used. The promoter may be cell-type specific. Constitutive promoters are used in expression cassettes and can be, for example, the cytomegalovirus enhancer fused to the chicken β -actin promoter (CAG), simian virus 40 (SV40) promoter, and the herpes simplex virus thymidine kinase (HSV-TK) promoter (Damdindorj et al. *PLoS One*. 9:e106472 (2014)). Other cell-type specific promoters may also be used. Cardiac cell specific promoters can be, for example, the MLC2v promoter (Phillips et al. *Hypertension* 39:651-5 (2002)) and the cardiac Troponin-T (cTnT) promoter (Konkalmatt

et al. *Circ Cardiovasc Imaging*. 6:478–486 (2013)). The transgene polynucleotide sequence in an expression cassette can be, for example, an open reading frame encoding a protein. The ITRs in an expression cassette serve as markers used for viral packaging of the expression cassette (Clark et al. *Hum Gene Ther*. 6:1329-41 (1995)).

[00175] Advantageously, the promoter, optionally in conjunction with an enhancer, enables expression of the polynucleotide encoding a polypeptide (e.g., a DWORF polypeptide), or functional variant thereof, in a target cell.

[00176] In some embodiments, the expression cassette comprises a single promoter. In some embodiments, the expression cassette comprises at least one promoter. In some embodiments, the expression cassette comprises two promoters. In some embodiments, the expression cassette comprises a ubiquitous promoter. In some embodiments, the expression cassette comprises an inducible promoter. In some embodiments, the expression cassette comprises a cell-type specific promoter. In some embodiments, the promoter specifically promotes expression of the polynucleotide encoding a polypeptide, or functional variant thereof, in a cardiac cell (e.g., a cardiomyocyte). In some embodiments, the promoter specifically promotes expression of the polynucleotide encoding the DWORF polypeptide, or functional variant thereof, in a cardiac cell. In some embodiments, the promoter specifically promotes expression of the polynucleotide encoding the DWORF polypeptide, or functional variant thereof, in a cardiomyocyte. Illustrative promoter and enhancer sequences are provided in Table 3.

[00177] In some embodiments, the promoter is a chicken cardiac troponin-T (cTnT or ccTnT) promoter. In some embodiments, the chicken cTnT promoter comprises a polynucleotide sequence that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 11. In some embodiments, the chicken cTnT promoter comprises SEQ ID NO: 11.

[00178] In some embodiments, the promoter is a human cTnT promoter. In some embodiments, the promoter is a short human cTnT promoter. In some embodiments, the short human cTnT promoter comprises a polynucleotide sequence that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 12. In some embodiments, the short human cTnT promoter comprises SEQ ID NO: 12. In some embodiments, the promoter is a long human cTnT promoter. In some embodiments, the long human cTnT promoter comprises a polynucleotide sequence that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 13. In some embodiments, the long human cTnT promoter comprises SEQ ID NO: 13.

[00179] The expression cassette can include one or more enhancers. The term “enhancer” as used herein refers to a DNA sequence that directs the binding of transcriptional regulatory proteins (*e.g.*, transcriptional machinery) and RNA polymerase, and thereby promotes RNA synthesis. The enhancer can be operably linked to a promoter and modulate the expression of a transgene operably linked to a promoter. The presence of an enhancer can modulate transgene expression by, for example, increasing expression or decreasing expression. An enhancer can modulate transgene expression by, for example, increasing expression levels in a desired cell type, for example, a cardiac cell. An enhancer can modulate transgene expression by, for example, decreasing expression levels in an “off-target” cell type, or a cell type in which expression is not desired.

[00180] In some embodiments, the expression cassette comprises a single enhancer. In some embodiments, the expression cassette comprises at least one enhancer. In some embodiments, the expression cassette comprises two enhancers. In some embodiments, the expression cassette comprises three enhancers. In some embodiments, the expression cassette comprises four enhancers. In some embodiments, the expression cassette comprises an enhancer that is operably linked to a promoter. For example, a ACTC1 cardiac enhancer can be linked to a human cTnT promoter. In some embodiments, the expression cassette comprises an enhancer that is operably linked to another enhancer. For example, a ACTC1 cardiac enhancer can be operably linked to an α MHC enhancer. In some embodiments, the expression cassette comprises an enhancer that is operably linked to a promoter and operably linked to another enhancer.

[00181] In some embodiments, the enhancer comprises an ACTC1 cardiac enhancer (ACTC1e). In some embodiments, the ACTC1 cardiac enhancer shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 78. In some embodiments, the ACTC1 cardiac enhancer comprises SEQ ID NO: 78. In some embodiments, the enhancer comprises an α MHC enhancer (α MHCe). In some embodiments, the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 79. In some embodiments, the α MHC enhancer comprises SEQ ID NO: 79.

Table 3: Illustrative Promoter and Enhancer Sequences

Promoter/ Enhancer Name	Sequences
Chicken cTnT	GGGATAAAAGCAGTCTGGGCTTTCACATGACAGCATCTGGGGCTGCGGCAGAGG GTCGGGTCCGAAGCGCTGCCTTATCAGCGTCCCCAGCCCTGGGAGGTGACAGCTG GCTGGCTTGTGTCAGCCCCTCGGGCACTCACGTATCTCCGTCCGACGGGTTAAAA TAGCAAACTCTGAGGCCACACAATAGCTTGGGCTTATATGGGCTCCTGTGGGGG AAGGGGAGCACGGAGGGGGCCGGGGCCGCTGCTGCCAAATAGCAGCTCACAA

	GTGTTGCATTCTCTCTGGGCGCCGGGCACATTCTGCTGGCTCTGCCCCCCCCGG GGTGGGCGCCGGGGGGACCTTAAAGCCTCTGCCCCCAAGGAGCCCTTCCCAGAC AGCCGCGGCACCCACCGCTCCGTGGGA (SEQ ID NO: 11)
Short Human cTnT	GTCATGGAGAAGACCCACCTTGCAGATGTCCTCACTGGGGCTGGCAGAGCCGGCA ACCTGCCTAAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTA CCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAG ATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCC TGCTCCCAGCTGGCCCTCCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGATTC TCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATCTGCTCTGGT TTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGGCTTATATGGCGTGGGG TACATGTTCTGTAGCCTTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCC CACCCCCACCGCATCCCCCTGCCCCACCCGTCCTGTCGCACATTCTCCCTCC GCAGGGCTGGCTCACCAGGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATC CTCTGCCTCACCAGTCCCCGCTGAGACTGAGCAGACGCCTCCA (SEQ ID NO: 12)
Long Human cTnT	AGAGGACCCTTCAAGGACATTAGTGGTGGAGGCAGCATAGTAGCTCCCAAGGCA GAGGGATTGAGAGAAGAGTTTGGAGCTGGGAAGGCGGGACACATGATTGGGTG ATGGGAGAAGGGGGCAGAGAATAGCGAGATTGCTTTCTTTGCCCCACGGAGAAAC AGAGGAGTGTGGATCATGAATGGGCAAGATCTTTAAGTGCCAGGGGGGGTCTAG GAGGAGGGGAGGGCCTGCTCCAGAGGAGGACCATTCCTGCTTCAGAGCCAAGCA GGACCTAGGCTGTGAAGATTCCGAGAAAAGAGATGGAGGGGAGAGTCAGCTCAGC TGCTTACTGGCTTGCTTTCTCTCTCTTTTCAATTTTATAATCTACCAAACCTG CAATGGGCCAGCCTTGAACATACAAGTGCATGTGCATGGTCAGACACAGGCAAGC AAGCAAGACCCCTAGGCCTGACCTATGCATCTGCAATCTAGTAGGTTTAGCAGAT CATAGCCCCGACTGCTTGATTTAAAGCCGTTAGGGGATGACCTTTGACAGTCCG CATCACCCCTCTCACACAACGAGCGCCTGTTCAAGGTTCTTGAAGGTTTCTAC CTTGATCTGGCCTCCTGTAGCAGTTTCACTCCATTCCCTGTGAGGAGGGGTGTC ACATGGCTTTGGGGGTGATGGAGAAGACCCACCTTGCAGATGCTCCTCACTGGGC TGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCT GGAAGATGTCTTTACCCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTGTC CCTCTGCCTTCCAAGATTCTGGTGCTGAGACTTATGGAGTGTCTTGGAGGTTGCCT TCTGCCCCCAACCTGCTCCAGCTGGCCCTCCCAGGCCTGGGTTGCTGGCCTCT GCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTG CATATCTGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGGCT TATATGGCGTGGGGTACATGTTCCCTGTAGCCTTGTCCCTGGCACCTGCCAAAATAG CAGCCAACACCCCCACCCCCACCGCCATCCCCCTGCCCCACCCGTCCTGTCGC ACATTCTCCCTCCGAGGGCTGGCTCACCAGGCCCCAGCCACATGCCTGCTTAA AGCCCTCTCCATCCTCTGCCTCACCAGTCCCCGCTGAGACTGAGCAGACGCCTCC AGGATCTGTGGCAGCTGCTGTTCTGAGGTAAGGCTCGGGCAGGGCTCTGGGGAA GAGGAGAGCAGAGAATGGACGGGGAGATGTGAGGGTCTTGGGCCCTGGCATATT TACCCAGAGTCTGCCTGTGTCCGAGAAAGTCCATGGCCCCCTCTGGTGGAGGCCA CACTTCAGAGGACAGGTTGCCAGGTCTGGGCTCCAAGATTGGTACAATAGAGCAG AGAGA (SEQ ID NO: 13)
ACTC1 cardiac enhancer (ACTC1e)	AACTGGCCTGCCCAGACCAAACGTGCGGAACGTAGTTAAGTGTAGAGGTAGG ATTTGAAGCCTGTCGATCATTCGATTCTCCTTTTCTCTACGCTGCTTCTGTCAA TGGGCATCCTCACTGTCAAATGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGG CAGGCCTCTCCCCAGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCA TCCCAAACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGCCCCCTG AAGATAATCAGCAGTCTGTCTCAGCATATCAATCCAAGCCACTCTAGACAGAGA TGCCGGTGCCAGTTTCTATTTTTAACTGGTGTGAACTGAAGGAAAAGCACAGC ATTAGAAGTCCAAGCA (SEQ ID NO: 78)
α MHC cardiac enhancer (α MHCe)	CCTTCAGATTAAAAATAACTAAGGTAAGGGCCATGTGGGTAGGGGAGGTGGTGTG AGACGGTCTGTCTCTCTCTATCTGCCATCGGCCCTTTGGGGAGGAGGAATGTG CCCAAGGACTAAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTT CATGGGCAAACCTCAGGGCTGCTGTC (SEQ ID NO: 79)

Introns

[00182] The expression cassette can include an intron sequence, for example, a synthetic or chimeric intron sequence. The intron sequence can be used to adjust the length (*i.e.*, size) of

the expression cassette for improving recombinant AAV packaging. The intron sequence can be used to improve the efficiency of transgene expression (*i.e.*, mRNA production or transcription) in a host cell containing the expression cassette. In some embodiments, the expression cassette comprises an intron. In some embodiments, the intron comprises the CMV intron (CMVint). In some embodiments, the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 80. In some embodiments, the CMV intron comprises SEQ ID NO: 80. In some embodiments, the intron comprises a chimeric intron. In some embodiments, the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 81. In some embodiments, the chimeric intron comprises SEQ ID NO: 81.

Table 9. Illustrative Intron Sequences

Intron	Intron Sequence
CMV intron	GTAAGTACCGCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTAT GCATGCTGACAGACTAACAGACTGTTCTTTCTGGGTCTTTCTGCA G (SEQ ID NO: 80)
Chimeric Intron (Chimint)	GTAAGTATCAAGGTTACAAGACAGGTTTAAGGAGACCAATAGAAAC TGGGCTTGTCGAGACAGAGAAGACTCTTGCCTTCTGATAGGCACCT ATTGGTCTTACTGACATCCACTTTGCCTTCTCTCCACAG (SEQ ID NO: 81)

WPRES Sequences and Other Post-Transcriptional Elements

[00183] In some embodiments, the expression cassette comprises a posttranscriptional regulatory element.

[00184] In some embodiments, the expression cassette comprises a woodchuck hepatitis virus post-transcriptional element (WPRES). The WPRES sequence can be inserted, for example, proximal to on the 3' end of a transgene in a viral vector to, for example, optimize gene expression in a viral vector (Lee et al. *Exp Physiol.* 90:33-37 (2005)). In some embodiments, the WPRES comprises a polynucleotide sequence that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 26. In some embodiments, the WPRES comprises SEQ ID NO: 26.

Table 4: Illustrative WPRES Sequence

WPRES Sequence
TCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACATGTTGCTCCTTTACGC TATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTTATTTCTCCT CCTTGATAAATCCTGGTTGCTGTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGT GGTGTGCACTGTGTTTGTGCTGACGCAACCCCACTGGTTGGGGCATTGCCACCACTGTGAGTCCTT TCCGGGACTTTTCGCTTTCCCTCCCTATTGCCACGGCGGAACATCGCCGCTGCTTGCCCGCTG CTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTGTCGGGGAAATCATCGTCCTTT CCTTGGCTGCTCGCTGTGTTGCCACCTGGATTCTGCGGGGACGCTTCTGCTACGTCCTTCGGC

CCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCG (SEQ ID NO: 26)

Poly Adenylation Sequences

[00185] In some embodiments, the expression cassette comprises a poly(A) signal sequence. In some embodiments, the poly(A) signal is a BGH poly(A) sequence. In some embodiments, the BGH poly(A) signal sequence comprises the polynucleotide sequence that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 27. In some embodiments, the poly(A) signal is an SV40 poly(A) signal. In some embodiments, the SV40 poly(A) signal sequence comprises the polynucleotide sequence that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 28.

Table 5: Illustrative Poly(A) Sequences

Poly(A) Sequence	Sequence
BGH	GCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCCTGCTTTCCTAATAAAATGAGGAAATGTCATCGCATTGTCTGAGTAGGTGTCTATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGA (SEQ ID NO: 27)
SV40	GATCCAGACATGATAAGATACATTGATGAGTTTGACAAACCACAAGTAGAATGCAGTGAAAAAATGCTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATATAAGCTGCAATAACAAGT (SEQ ID NO: 28)

Inverted Terminal Repeat Sequences

[00186] In some embodiments, the expression cassette is flanked by AAV inverted terminal repeats (ITRs). In some embodiments, the ITRs comprise the polynucleotide sequence that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 14 and/or SEQ ID NO: 15.

Table 6: Illustrative ITR Sequences

ITR Sequences
CTGCGCGCTCGCTCGCTCACTGAGGCCGCGCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGAGAGGGAGTGGCCAACCTCCATCACTAGGGGTTCT (SEQ ID NO: 14)
AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCGCGAGCGCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 15)

Illustrative Expression Cassettes

[00187] The disclosure provides expression cassettes comprising a polynucleotide comprising a 5' to 3' arrangement (sometimes referred to as an orientation) of elements. In some embodiments, the elements comprise one or more promoters; optionally one or more enhancers; optionally one or more introns; one or more transgenes; optionally one or more WPRE sequences; and optionally one or more polyadenylation sequences (p(A)). Illustrative

order of the elements in the polynucleotide are shown in FIG. 1, FIG. 7A, FIG. 7B, FIG. 7C and Table 1. Illustrative orientations of the elements on the polynucleotide are also shown in FIG. 1, FIG. 7A, FIG. 7B, FIG. 7C and Table 1. In some embodiments, the 5' to 3' arrangement of elements is selected from:

- [00188] 5'-promoter-transgene-WPRE-p(A)-3';
- [00189] 5'-promoter-intron-transgene-WPRE-p(A)-3';
- [00190] 5'-promoter-transgene-WPRE-p(A)-promoter-transgene-WPRE-p(A);
- [00191] 5'-enhancer-promoter-transgene-WPRE-p(A)-3';
- [00192] 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-3';
- [00193] 5'-enhancer-enhancer-promoter-transgene-WPRE-p(A)-3';
- [00194] 5'-enhancer-enhancer-promoter-intron-transgene-WPRE-p(A)-3';
- [00195] 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-enhancer-3';
- [00196] 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-enhancer-promoter-intron-transgene-p(A)-3';
- [00197] 5'-p(A)-WPRE-transgene-intron-promoter-enhancer-enhancer-promoter-intron-transgene-p(A)-3';
- [00198] 5'-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-3';
- [00199] 5'-promoter-intron-transgene-WPRE-p(A)-promoter-intron-transgene-p(A)-3';
- and
- [00200] 5'-p(A)-WPRE-transgene-intron-promoter-promoter-intron-transgene-p(A)-3'.

[00201] In some embodiments, the expression cassettes described herein achieve an increased expression level of the transgene compared to a second expression cassette comprising a polynucleotide having an arrangement of elements from 5' to 3' comprising: 5'-promoter-transgene-WPRE-p(A)-3'. In some embodiments, the expression level is increased between about 1.5-fold and about 150-fold compared the second expression cassette.

[00202] In some embodiments, the expression cassettes provided herein comprise the following elements (where the elements can be those described herein, e.g., the sequences of which are provided herein):

- [00203] 5'-promoter-transgene-WPRE-p(A)-3';
- [00204] 5'-promoter-intron-transgene-WPRE-p(A)-3';
- [00205] 5'-promoter-transgene-WPRE-p(A)-promoter-transgene-WPRE-p(A);
- [00206] 5'-enhancer-promoter-transgene-WPRE-p(A)-3';
- [00207] 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-3';

- [00208] 5'-enhancer-enhancer-promoter-transgene-WPRE-p(A)-3';
- [00209] 5'-enhancer-enhancer-promoter-intron-transgene-WPRE-p(A)-3';
- [00210] 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-enhancer-3';
- [00211] 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-enhancer-promoter-intron-transgene-p(A)-3';
- [00212] 5'-p(A)-WPRE-transgene-intron-promoter-enhancer-enhancer-promoter-intron-transgene-p(A)-3';
- [00213] 5'-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-3';
- [00214] 5'-promoter-intron-transgene-WPRE-p(A)-promoter-intron-transgene-p(A)-3';
- or
- [00215] 5'-p(A)-WPRE-transgene-intron-promoter-promoter-intron-transgene-p(A)-3'.
- [00216] In the expression cassettes described herein (such as those listed above), the orientation of the promoter, enhancer, transgene and poly(A) elements can be forward or reverse (e.g., in cases where there are more than one promoters, one promoter, optionally enhancer, and operably linked transgene can be oriented in a forward direction, and another promoter, optionally enhancer, and operably linked transgene can be oriented in a reverse direction).
- [00217] In some embodiments, the expression cassettes provided herein comprise the following elements:
- [00218] 5'-cardiac-specific promoter-transgene-WPRE-p(A)-3';
- [00219] 5'-cardiac-specific promoter-intron (e.g., chimeric intron)-transgene-WPRE-p(A)-3';
- [00220] 5'-cardiac-specific promoter-transgene-WPRE-p(A)-promoter-transgene-WPRE-p(A), where both promoters and transgene sequences are in the same, forward orientation;
- [00221] 5'-cardiac-specific promoter-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00222] 5'-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00223] 5'-enhancer (e.g., ACTC1e)-cardiac-specific promoter-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00224] 5'-enhancer (e.g., α MHCe)-cardiac-specific promoter-transgene-WPRE-p(A) (e.g., bGHpA)-3';

- [00225] 5'-enhancer (e.g., ACTC1e)-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00226] 5'-enhancer (e.g., α MHCe)-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00227] 5'-enhancer (e.g., ACTC1e)-enhancer (e.g., α MHCe)-cardiac-specific promoter-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00228] 5'-enhancer (e.g., α MHCe)-enhancer (e.g., ACTC1e)-cardiac-specific promoter-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00229] 5'-enhancer (e.g., ACTC1e)-enhancer (e.g., α MHCe)-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00230] 5'-enhancer (e.g., α MHCe)-enhancer (e.g., ACTC1e)-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-3';
- [00231] 5'-cardiac-specific promoter-transgene with a codon-optimized polynucleotide sequence-WPRE-p(A) (e.g., bGHpA)-3';
- [00232] 5'-enhancer (e.g., α MHCe)-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-p(A) (e.g., SV40pA)-transgene (e.g., with a codon-optimized polynucleotide sequence)-intron (e.g., chimeric intron)-cardiac-specific promoter-enhancer (e.g., ACTC1e)-3', optionally wherein the first in order transgene and the promoter/enhancer sequences operably linked thereto are in a forward orientation, and the second in order transgene and the promoter/enhancer sequences operably linked thereto are in a reverse orientation;
- [00233] 5'-enhancer (e.g., α MHCe)-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-enhancer (e.g., ACTC1e)-cardiac-specific promoter-intron (e.g., chimeric intron)-transgene (e.g., with a codon-optimized polynucleotide sequence)-p(A) (e.g., SV40pA)-3', optionally wherein both the first and the second in order transgenes and the promoter/enhancer sequences operably linked thereto are in a forward orientation;
- [00234] 5'-p(A) (e.g., bGHpA)-WPRE-transgene-intron (e.g., CMV intron)-cardiac-specific promoter-enhancer (e.g., α MHCe)-enhancer (e.g., ACTC1e)-cardiac-specific promoter-intron (e.g., chimeric intron)-transgene (e.g., with a codon-optimized polynucleotide sequence)-p(A) (e.g., SV40pA)-3', optionally wherein the first in order transgene and the promoter/enhancer sequences operably linked thereto are in a reverse orientation, and the second in order transgene and the promoter/enhancer sequences operably linked thereto are in a forward orientation;

[00235] 5'-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-p(A) (e.g., SV40pA)-transgene (e.g., with a codon-optimized polynucleotide sequence)-intron (e.g., chimeric intron)-cardiac-specific promoter-3', optionally wherein the first in order transgene and the promoter/enhancer sequences operably linked thereto are in a forward orientation, and the second in order transgene and the promoter/enhancer sequences operably linked thereto are in a reverse orientation;

[00236] 5'-cardiac-specific promoter-intron (e.g., CMV intron)-transgene-WPRE-p(A) (e.g., bGHpA)-cardiac-specific promoter-intron (e.g., chimeric intron)-transgene (e.g., with a codon-optimized polynucleotide sequence)-p(A) (e.g., SV40pA)-3', optionally wherein both the first and the second in order transgenes and the promoter/enhancer sequences operably linked thereto are in a forward orientation; or

[00237] 5'-p(A) (e.g., bGHpA)-WPRE-transgene-intron (e.g., CMV intron)-cardiac-specific promoter-cardiac-specific promoter-intron (e.g., chimeric intron)-transgene (e.g., with a codon-optimized polynucleotide sequence)-p(A) (e.g., SV40pA)-3', optionally wherein the first in order transgene and the promoter/enhancer sequences operably linked thereto are in a reverse orientation, and the second in order transgene and the promoter/enhancer sequences operably linked thereto are in a forward orientation.

[00238] In the expression cassettes described herein (such as those listed above), the cardiac-specific promoter can be a short human cTnT promoter (such as hcTnTp) or chicken cTnT promoter (such as ccTnTp). The more specific examples of the expression cassettes described above can be found in, e.g., FIG. 1, FIG. 7A, FIG. 7B, FIG. 7C and Table 1.

[00239] In some embodiments, the expression cassettes described herein enable an increased expression level of the transgene compared to a second expression cassette comprising a polynucleotide having an arrangement of elements from 5' to 3' comprising: 5'-promoter-transgene-WPRE-p(A)-3'. In some embodiments, the expression level is increased between about 1.5-fold and about 150-fold compared the second expression cassette.

[00240] In some embodiments, one or more (e.g., one, two, three or four) elements of the expression cassettes described herein can be omitted.

[00241] In some embodiments, one or more (e.g., one, two, three or four) elements of the expression cassettes described herein can be replaced by other elements, such as functionally equivalent elements.

[00242] In some embodiments of the expression cassettes provided herein, the WPRE element is replaced by any other post-transcriptional regulatory element known in the art. In some embodiments, the expression cassettes provided herein comprise any post-transcriptional

regulatory element known in the art. In some embodiments, the expression cassettes provided herein do not comprise a post-transcriptional regulatory element (e.g., do not comprise the WPRE element). In some embodiments, the expression cassettes provided herein comprise WPRE.

[00243] In some embodiments of the expression cassettes provided herein, the bGHpA and/or SV40pA poly(A) element is replaced by any other poly(A) element known in the art. In some embodiments, the expression cassettes provided herein comprise any poly(A) element known in the art. In some embodiments, the expression cassettes provided herein do not comprise a poly(A) element. In some embodiments, the expression cassettes provided herein do not comprise bGHpA. In some embodiments, the expression cassettes provided herein do not comprise SV40pA. In some embodiments, the expression cassettes provided herein do not comprise bGHpA or SV40pA. In some embodiments, the expression cassettes provided herein comprise one or both of bGHpA and SV40pA.

[00244] In some embodiments of the expression cassettes provided herein, the CMV intron and/or chimeric intron element is replaced by any other intron element known in the art. In some embodiments, the expression cassettes provided herein comprise any intron element known in the art. In some embodiments, the expression cassettes provided herein do not comprise an intron. In some embodiments, the expression cassettes provided herein do not comprise a CMV intron. In some embodiments, the expression cassettes provided herein do not comprise a chimeric intron (e.g., do not comprise Chim int). In some embodiments, the expression cassettes provided herein do not comprise CMV intron or Chim int. In some embodiments, the expression cassettes provided herein comprise one or both of CMV intron and Chim int.

[00245] It should be understood that the illustrative orientations of the expression cassette can include flanking inverted terminal repeat (ITR) sequences on the 5' and 3' ends of the expression cassette. It should be understood that the ITR sequences can be optional. In some embodiments, the expression cassettes described herein do not include the ITR sequences (e.g., non-AAV, such as DNA plasmid-based, expression cassettes).

[00246] Operably linked elements, such as those in the illustrative orientations above, can be on one or both strands of the polynucleotide.

[00247] In some embodiments, the expression cassette comprises one copy of a sequence encoding a polypeptide (i.e., one copy of a transgene). In some embodiments, the expression cassette comprises two copies of a sequence encoding a polypeptide (i.e., two copies of a transgene). In some embodiments, where the expression cassette comprises two copies of

a sequence encoding a polypeptide, the two “copies” are not identical. While not being bound by any theory, using two sequences encoding a polypeptide that are not identical may prevent DNA recombination within the vector. In some embodiments, the expression cassette comprises one copy that has the original DNA sequence encoding a polypeptide and one copy that has a codon optimized DNA sequence encoding the polypeptide. In some embodiments, where the expression cassette comprises two copies of a sequence encoding a polypeptide, the two copies are identical.

[00248] In some embodiments, the expression cassette comprises one or more promoters described herein (with or without one or more enhancers described herein) driving one or more copies of a transgene (such as any transgene described herein). In some embodiments, the expression cassette does not comprise an enhancer (e.g., α MHCe and/or ACTC1e). In some embodiments, the expression cassette comprises one or more enhancers such as cardiac-specific enhancers (e.g., α MHCe and/or ACTC1e). In some embodiments, the expression cassette comprises α MHCe enhancer (and, optionally, does not comprise ACTC1e enhancer). In some embodiments, the expression cassette comprises ACTC1e enhancer (and, optionally, does not comprise α MHCe enhancer). In some embodiments, the expression cassette comprises at least two enhancers in the order of first α MHCe and then ACTC1e. In some embodiments, the expression cassette comprises at least two enhancers in the order of first ACTC1e and then α MHCe. In some embodiments, the expression cassette comprises an intron element, e.g., a CMV intron element and/or a chimeric intron (such as Chim int described herein). In some embodiments, the expression cassette comprises an intron element but does not comprise an enhancer. In some embodiments, the expression cassette comprises an intron element (e.g., CMV intron and/or a chimeric intron) and further comprises an enhancer (e.g., α MHCe and/or ACTC1e). In some embodiments, the expression cassette comprises a transgene with a codon-optimized polynucleotide sequence. In some embodiments, the expression cassette comprises a transgene with a codon-optimized polynucleotide sequence but does not comprise an enhancer. In some embodiments, the expression cassette comprises a transgene with a codon-optimized polynucleotide sequence and further comprises an enhancer (e.g., α MHCe and/or ACTC1e). In some embodiments, the expression cassette comprises one or more promoters described herein and one, two or more enhancers described herein (e.g., comprises an α MHCe and/or ACTC1e enhancer) driving the expression of one or more copies of a transgene (without or without CMV intron or chimeric intron elements). In some embodiments, the promoter is a cardiac-specific promoter, e.g., a human cTnT promoter (such as a short human promoter, hcTnTp) and/or a chicken cTnT promoter (such as ccTnTp). In

some of the embodiments, the enhancer is a cardiac-specific enhancer, e.g., α MHCe and/or ACTC1e. In some embodiments, two or more cardiac-specific enhancers are used, where the two or more of the enhancers can be the same or different (e.g., both or all α MHCe, both or all ACTC1e, or at least one α MHCe and at least one ACTC1e). In some embodiments, two cardiac-specific enhancers are used, where the two enhancers can be the same or different (e.g., both α MHCe, both ACTC1e, or one α MHCe and one ACTC1e). In some embodiments, the transgene comprises a non-codon-optimized polynucleotide sequence encoding a gene product. In some embodiments, the order of the elements is as shown in any of the expression cassettes depicted in FIG1, FIG. 7A, FIG. 7B, FIG. 7C and Table 1. For example, (i) the order of the promoter and transgene elements can be as shown in FIG1, FIG. 7A, FIG. 7B, FIG. 7C or Table 1, (ii) the order of promoter, enhancer and transgene elements can be as shown in FIG1, FIG. 7A, FIG. 7B, FIG. 7C or Table 1, (iii) the order of promoter, transgene, WPRE and poly(A) elements can be as shown in FIG1, FIG. 7A, FIG. 7B, FIG. 7C or Table 1, optionally with or without enhancer elements being in the same order as shown in FIG1, FIG. 7A, FIG. 7B, FIG. 7C or Table 1, or (iv) the order of promoter, transgene, WPRE, poly(A), CMV intron (such as CMVint) elements can be as shown in FIG1, FIG. 7A, FIG. 7B, FIG. 7C or Table 1, optionally with or without enhancer elements being in the same order as shown in FIG1, FIG. 7A, FIG. 7B, FIG. 7C or Table 1. In some embodiments, the orientation of any of the elements is as shown in any of the expression cassettes depicted in FIG1, FIG. 7A, FIG. 7B, FIG. 7C and Table 1. The sequences of individual expression cassette elements discussed herein (such as promoters, enhancers, transgenes, WPRE, poly(A), CMV intron and chimeric intron) can be any of the sequences of such elements provided herein or any sequences with at least, e.g., 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% sequence identity thereto.

[00249] In some embodiments, the expression cassette comprises one promoter described herein (with or without one or more enhancers described herein) driving one copy of a transgene (such as any transgene described herein). In some embodiments, the expression cassette comprises one promoter described herein, without any enhancer (e.g., without any enhancer described herein, e.g., without α MHCe and/or without ACTC1e) driving one copy of a transgene, optionally, such an expression cassette comprises an intron element, e.g., a CMV intron element and/or a chimeric intron (such as Chim int described herein), and/or comprises a transgene with a codon-optimized polynucleotide sequence. In some embodiments, the expression cassette comprises one promoter described herein, without any enhancer (e.g., without any enhancer described herein, e.g., without α MHCe and/or without ACTC1e) driving one copy of a transgene, and further comprises a CMV intron and/or a chimeric intron (such as

Chim int). In some embodiments, the expression cassette comprises one promoter described herein, without any enhancer (e.g., without any enhancer described herein, e.g., without α MHCe and/or without ACTC1e) driving one copy of a transgene, and further comprises a CMV intron. In some embodiments, the expression cassette comprises one promoter described herein, without any enhancer (e.g., without any enhancer described herein, e.g., without α MHCe and/or without ACTC1e) driving one copy of a transgene, wherein the transgene comprises a codon-optimized polynucleotide sequence. In some embodiments, the expression cassette comprises one promoter described herein and one, two or more enhancers described herein (e.g., comprises an α MHCe and/or ACTC1e enhancer) driving the expression of one copy of a transgene. In some embodiments, the expression cassette comprises one promoter described herein and one enhancer described herein (e.g., α MHCe or ACTC1e enhancer) driving the expression of one copy of a transgene. In some embodiments, the expression cassette comprises one promoter described herein and two enhancers described herein (e.g., both α MHCe, both ACTC1e, or one α MHCe and one ACTC1e) operably linked to one copy of a transgene. In some embodiments, the promoter is a cardiac-specific promoter, e.g., a human cTnT promoter (such as a short human promoter, hcTnTp) and/or a chicken cTnT promoter (such as ccTnTp). In some of the embodiments where one or more enhancers are used, the enhancer is a cardiac-specific enhancer, e.g., α MHCe and/or ACTC1e. In some embodiments, two or more cardiac-specific enhancers are used, where the two or more of the enhancers can be the same or different (e.g., both or all α MHCe, both or all ACTC1e, or at least one α MHCe and at least one ACTC1e). In some embodiments, two cardiac-specific enhancers are used, where the two enhancers can be the same or different (e.g., both α MHCe, both ACTC1e, or one α MHCe and one ACTC1e). In some embodiments, the expression cassette comprises at least two enhancers in the order of first α MHCe and then ACTC1e. In some embodiments, the expression cassette comprises at least two enhancers in the order of first ACTC1e and then α MHCe. In some embodiments, the transgene comprises a non-codon-optimized polynucleotide sequence encoding a gene product. In some embodiments, the transgene comprises a codon-optimized polynucleotide sequence encoding the gene product. In some embodiments, one or more intron elements are also used in addition to promoter and enhancer elements. In some embodiments, a CMV intron element is used. In some embodiments, a chimeric intron element (Chim int) is used. In some embodiments, both a CMV intron and a chimeric intron (Chim int) are used. In some embodiments where one promoter is used, the order of the elements is as shown in any of the expression cassettes depicted in FIG. 7B. For example, (i) the order of the promoter and transgene elements can be

as shown in FIG. 7B, (ii) the order of promoter, enhancer and transgene elements can be as shown in FIG. 7B, (iii) the order of promoter, transgene, WPRE and poly(A) elements can be as shown in FIG. 7B, optionally with or without enhancer elements being in the same order as shown in FIG. 7B, or (iv) the order of promoter, transgene, WPRE, poly(A), CMV intron (such as CMVint) elements can be as shown in FIG. 7B, optionally with or without enhancer elements being in the same order as shown in FIG. 7B. In some embodiments where one promoter is used, the orientation of any of the elements is as shown in any of the expression cassettes depicted in FIG. 7B. In some embodiments, the orientation of the elements is forward orientation. In some embodiments, the orientation of the elements is reverse orientation. The sequences of individual expression cassette elements discussed herein (such as promoters, enhancers, transgenes, WPRE, poly(A), CMV intron and chimeric intron) can be any of the sequences of such elements provided herein or any sequences with at least, e.g., 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% sequence identity thereto.

[00250] In some embodiments, the expression cassette comprises two promoters described herein (with or without one or more enhancers described herein) driving the expression of two copies of a transgene (such as any transgene described herein). In some embodiments, the expression cassette comprises two promoters described herein (with or without one or more enhancers described herein) each promoter operably linked to one copy of a transgene (such as any transgene described herein). In some embodiments, the expression cassette comprises two promoters described herein, without any enhancer (e.g., without any enhancer described herein, e.g., without α MHCe and/or without ACTC1e) driving the expression of two copies of a transgene. In some embodiments, the expression cassette comprises two promoters described herein and one, two or more enhancers described herein (e.g., comprising an α MHCe and/or ACTC1e enhancer) driving the expression of two copies of a transgene. In some embodiments, the expression cassette comprises two promoters described herein and two enhancers described herein (e.g., comprising an α MHCe and/or ACTC1e enhancer) operably linked to two copies of a transgene, where each transgene is operably linked to one promoter and one enhancer. In some embodiments, the promoter is a cardiac-specific promoter, e.g., a human cTnT promoter (such as a short human promoter, hcTnTp) and/or a chicken cTnT promoter (such as ccTnTp). In the embodiments where two promoters are used, the two promoters can be the same or different. In some embodiments, where the two promoters drive the expression of two copies of a transgene (each promoter driving expression of one copy of the transgene), both promoters can be cardiac-specific promoters, either the same cardiac-specific promoters or different from each other. In some

embodiments, both promoters can be human cTnT promoters (e.g., both can be a short human promoter, hcTnTp). In some embodiments, both promoters can be chicken cTnT promoters (such as ccTnT). In some embodiments, the two promoters are different, e.g., one is a human cTnT promoter (such as a short human cTnT promoter, hcTnTp) and one is a chicken cTnT promoter (such as ccTnT). In some embodiments where two promoters and two transgenes are used, the two transgenes can be the same or different (such as the same or different variants of the same transgene). For example, the first copy of the transgene can be a non-codon-optimized polynucleotide sequence encoding a gene product, and the second copy of the transgene can be a codon-optimized polynucleotide sequence encoding the gene product. In some embodiments, both copies of the transgene used in an expression cassette are the same. In some of the embodiments where one or more enhancers are used, the enhancer is a cardiac-specific enhancer, e.g., α MHCe and/or ACTC1e. In some embodiments, two or more cardiac-specific enhancers are used, where the two or more of the enhancers can be the same or different (e.g., both or all α MHCe, both or all ACTC1e, or at least one α MHCe and at least one ACTC1e). In some embodiments, two cardiac-specific enhancers are used, where the two enhancers can be the same or different (e.g., both α MHCe, both ACTC1e, or one α MHCe and one ACTC1e). In some embodiments where two promoters are used, two cardiac-specific enhancers operably linked to the transgene are used as well, optionally wherein one enhancer is α MHCe and another is ACTC1e. In some embodiments, the expression cassette comprises at least two enhancers in the order of first α MHCe and then ACTC1e. In some embodiments, the expression cassette comprises at least two enhancers in the order of first ACTC1e and then α MHCe. In some embodiments where two promoters are used, one or more intron elements are also used. In some embodiments where two promoters are used, a CMV intron element is also used. In some embodiments where two promoters are used, a chimeric intron element (Chim int) is also used. In some embodiments where two promoters are used, a CMV intron and a chimeric intron (Chim int) are used. In some embodiments where two promoters are used, the order of the elements is as shown in any of the expression cassettes depicted in FIG. 7C. For example, (i) the order of the promoter and transgene elements can be as shown in FIG. 7C, (ii) the order of promoter, enhancer and transgene elements can be as shown in FIG. 7C, (iii) the order of promoter, transgene, WPRE and poly(A) elements can be as shown in FIG. 7C, optionally with or without enhancer elements being in the same order as shown in FIG. 7C, or (iv) the order of promoter, transgene, WPRE, poly(A), CMV intron (such as CMVint) and chimeric intron (such as Chim int) elements can be as shown in FIG. 7C, optionally with or without enhancer elements being in the same order as shown in FIG. 7C. In some embodiments

where two promoters are used, the first promoter and the associated transgene (and, optionally an enhancer) are oriented in a forward 5' to 3' direction, and the second promoter and the associated transgene (and, optionally an enhancer) are oriented in a reverse direction. In some embodiments where two promoters are used, the first promoter and the associated transgene (and, optionally an enhancer) are oriented in reverse relative to 5' to 3' direction, and the second promoter and the associated transgene (and, optionally an enhancer) are oriented in a forward direction. In some embodiments where two promoters are used, both promoters and the associated transgenes (and, optionally an enhancer) are oriented in a forward 5' to 3' direction. In some embodiments where two promoters are used, both promoters and the associated transgenes (and, optionally an enhancer) are oriented in reverse relative to the 5' to 3' direction. In some embodiments where two promoters are used, the orientation of any of the elements (such forward or reverse orientation in 5' to 3' direction) is as shown in any of the expression cassettes depicted in FIG. 7C. In some embodiments where two promoters are used, the orientation of promoters, enhancers if any, transgenes, WPRE, poly(A), CMV intron and chimeric intron elements (such forward or reverse orientation in 5' to 3' direction) is as shown in any of the expression cassettes depicted in FIG. 7C. The sequences of individual expression cassette elements discussed herein (such as promoters, enhancers, transgenes, WPRE, poly(A), CMV intron and chimeric intron) can be any of the sequences of such elements provided herein or any sequences with at least, e.g., 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% sequence identity thereto.

[00251] Expression cassette sequences of the disclosure can be found, without limitation, in Table 1. In some embodiments, the expression cassette comprises about 3.2 kilobases (kb), 3.3 kb, 3.4 kb, 3.5 kb, 3.6 kb, 3.7 kb, or less. In some embodiments, the expression cassette comprises about 1.9 kb, 2.1 kb, 2.2 kb, 2.3 kb, 2.4 kb, 2.5 kb, 2.6 kb, 2.7 kb, 2.8 kb, 2.9 kb, 3.0 kb, 3.1 kb, 3.2 kb, or more.

[00252] In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NOs: 20-24 and SEQ ID NOs: 45-63. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NOs: 64-75. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 61. In some embodiments, the expression cassette comprises SEQ ID NO: 61. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or

100% identity to SEQ ID NO: 62. In some embodiments, the expression cassette comprises SEQ ID NO: 62. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 63. In some embodiments, the expression cassette comprises SEQ ID NO: 63. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 49. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 51. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 55. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 56. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 57. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 58. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 59. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 60. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 67. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 69. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 74. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 75. In some of these embodiments, the sequence encoding DWORF (the DWORF open reading frame) can be replaced by a sequence encoding another polypeptide described herein, and the sequence identity referenced above does not take into account the part of the polynucleotide sequence encoding DWORF (the DWORF open reading frame).

[00253] In some embodiments, the transgene in the expression cassette encodes a polypeptide for use in treating or preventing a heart disease or disorder. In some embodiments,

the transgene in the expression cassette encodes a polypeptide selected from: DWORF, junctophilin (e.g., JPH2), BAG family molecular chaperone regulator 3 (BAG3), alpha-crystallin B chain (CRYAB), LMNA (such as Lamin A and Lamin C isoforms), troponin I type 3 (TNNI3), phospholamban (PLN), lysosomal-associated membrane protein 2 (LAMP2, such as LAMP2a, LAMP2b and LAMP2c isoforms), desmoplakin (DSP, such as DPI and DPII isoforms), desmoglein 2 (DSG2), and junction plakoglobin (JUP), or a variant of any of these polypeptides (e.g., having at least 75%, at least 85%, at least 95%, at least 97% or at least 99% sequence identity thereto). In some embodiments, the transgene in the expression cassette encodes DWORF (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes JPH2 (e.g., a full-length JPH2 or an N-terminal fragment of JPH2) (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes BAG3 (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes CRYAB (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes LMNA Lamin A isoform (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes LMNA Lamin C isoform (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes TNNI3 (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes PLN (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes LAMP2a (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes LAMP2b (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes LAMP2c (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes DSP DPI isoform (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes DSP DPII isoform (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes DSG2 (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes JUP (or a variant thereof). In some embodiments, the transgene in the expression cassette encodes a human polypeptide (such as any human polypeptide described herein).

[00254] In some embodiments, the expression cassettes described herein lead to cardiac cell-specific expression of a transgene. In some embodiments, the expression cassettes described herein lead to cardiomyocyte-specific expression of a transgene. In some embodiments, the expression cassettes described herein allow high expression of a transgene in a cardiac cell (e.g., a cardiomyocyte) and low or no expression in other cells (e.g., low or no expression in liver cells, low or no expression in muscle cells except for muscle cells of the heart, low or no expression in cardiac fibroblasts). In some embodiments, the expression

cassettes described herein allow high expression of a transgene in heart tissue of a subject (e.g., in human heart). In some embodiments, the expression cassettes described herein allow no or low expression of a transgene in tissues of a subject other than the heart (e.g., in liver or in muscles except those of the heart). “High” and “low” can be relative to each other, for example, the expression of a transgene in cardiac cells (e.g., cardiomyocytes) and/or heart tissue can be at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, 50 fold, 100 fold, 150 fold, or 200 fold higher than its expression in other cells and tissues (e.g., liver, muscle except for the heart).

Table 1. Illustrative Expression Cassette Sequences

Expression Cassette	Sequence
pCR-MD1 distinct sequence elements are indicated in bold, starting with ITR, hcTnTp, DWORF (which is also underlined), WPRE, polyA (hGHpA), ITR	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGG GCGTCGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTTCCTTGT <i>AGTTAATGATTAAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA</i> <i>GATCGGAATTCGCCCTTAAGGTCATGGAGAAGACCCACCTTGAGAT</i> GTCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCT CAGTCCATTAGGAGCCAGTAGCCTGGAAAGATGTCTTTACCCCCAG CATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGCCTTCC AAGATTCTGGTGCTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT CTGCCCCCAACCCTGCTCCAGCTGGCCCTCCAGGCCTGGGTT GCTGGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTT ATGTTGCATGACTGTTCCCTGCATATCTGCTCTGGTTTTAAATAGC TTATCTGAGCAGCTGGAGGACCACATGGGCTTATATGGCGTGGGG TACATGTTCCCTGTAGCCTTGTCCTGGCACCTGCCAAAATAGCAG CCAACACCCCCACCCCCACCGCCATCCCCCTGCCCCACCCGTCC CCTGTGCGACATTCTCCCTCCGCAGGGCTGGCTCACCAGGCCCC AGCCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCACCCA GTCCCCGCTGAGACTGAGCAGACGCCTCCAGCGGCCGCCGCCACC <u>ATGGCTGAGAAAGAGTCAACATCACCAACCTCATGGTTCCCAT</u> <u>CTTCTCTGGTTGGATGGATTGTAGGCTGCATCATCGTTATTTACA</u> <u>TTGTCTTCTCTAA</u> <i>AAGCTTTGGATCCAATCAACCTCTGGATTACAAA</i> ATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTA CGCTATGTGGATACGCTGCTTTAATGCCCTTGTATATATGCTTGC TTCCCGTATGGCTTTTCATTTCTCCTCCTTGTATAAATCCTGGTTG CTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGC GTGGTGTGCACTGTGTTTGTGACGCAACCCCCACTGGTTGGGGC ATTGCCACCACCTGTCACTCCTTTCCGGGACTTTTCGCTTTCCCCC TCCCTATTGCCACGGCGGAATCATCGCCGCTGCCTTGCCCCGCT GCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATCCGTTGGTGT TGTGGGGAAATCATCGTCTTTCCTTGGCTGCTCGCCTGTGTTG CCACCTGGATTCTGCGCGGGACGTCTCTCTGCTACGTCCCTTCGG CCCTCAATCCAGCGGACCTTCTTCCCGCGGCTGCTGCCGGCTC TGCGGCCTCTTCCGCTCTTTCGAGATCTGCCTCGACTGTGCCTTCT AGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTGCCTTCTTGA CCCTGGAAGGTGCCACTCCCACTGTCTTTCTAATAAAATGAGG AAATTGCATCGCATTGTCTGAGTAGGTGTATTCTATTCTGGGGG GTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAAT AGCAGGCATGCTGGGGACTCGAGTTAAGGGCGAATCCCGATTAGGAT CTTCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAA TACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCG CTCGCTCGCTCACTGAGGCCGGGCGACCAAGGTCGCCCCAGCGC CGGGCTTTGCCCGGGCGGCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 20)
pCR-MD2	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGT CGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAG

	AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTTCGCCCTTAAGAGAGGACCCTTTCAAGGACATTAGTGGTGGAGGC AGCATAGTAGCTCCCAAGGCAGAGGGATTGAGAGAAGAGTTTGAGGA CTGGGAAGGCGGGACACATGATTGGGTGATGGGAGAAGGGGGCAGAG AATAGCGAGATTGCTTTCTTTGCCACGGAGAAAACAGAGGAGTGTGGA TCATGAATGGGCAAGATCTTTAAGTGCCAGGGGGGGTCTAGGAGGAG GGGAGGGCCTGCTCCAGAGGAGGACCATTCTGCTTCAGAGCCAAAGC AGGACCTAGGCTGTGAAGATTCCGAGAAAAGAGATGGAGGGGAGAGTC AGCTCAGCTGCTTACTGGCTTGCTTTCCTCCTGTCTCTTTTATTTTATA ATCTACCAAACCTGCAATGGGCCAGCCTTGAACATACAAGTGCATGT GCATGGTCAGACACAGGCAAGCAAGCAAGACCCCTAGGCCGTGACCTA TGCATCTGCAATCTAGTAGGTTTAGCAGATCATAGCCCCGCACTGCTT GATTTTAAAGCCGTTAGGGGATGACCTTTGACAGTCCGCATCACCCCT CTCACACAACGAGCGCTGTTCAAGGTTCTTGACTGGAAGTTCTACCT TGTATCTGGCCTCCTGTAGCAGTTTTCAGTCCATTCCCTGTGAGGAGGGT GTGCCACATGGCTTTGGGGTTCATGGAGAAGACCCACCTTGCAGATGT CCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCCTAAGGCTGCTCAGTC CATTAGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTT CAAGTGGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGG TGCTGAGACTTATGGAGTGTCTTGAGGTTGCCTTCTGCCCCCAACCC TGCTCCAGCTGGCCCTCCAGGCCTGGGTTGCTGGCCTCTGCTTTATC AGGATTCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTG CATATCTGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCA CATGGGCTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGG CACCTGCCAAAATAGCAGCCAACACCCCCACCCCCACCGCCATCCCC CTGCCCCACCCGTCCCCTGTGCGACATTCTCCCTCCGCAAGGCTGGCT CACCAGGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTG CCTCACCCAGTCCCCGCTGAGACTGAGCAGACGCCTCCAGGATCTGTC GGCAGCTGCTGTTCTGAGGTAAGGCTCGGGCAGGGCTCTGGGGAAGA GGAGAGCAGAGAATGGACGGGGAGATGTGAGGGTCTTGGGCCCTGGC ATATTTACCCAGAGTCTGCCTGTGTCCGAGAAGTCCATGGCCCTCCT GGTGGAGGCCACACTTCAGAGGACAGGTTGCCAGGTCTGGGCTCCAA GATTGGTACAATAGAGCAGAGAGAGGAGTGCCTGCGACGCTGCCTTC GCCCCGTGCCCCGCTCCGCCGCCGCTCGCGCCGCCGCCGCCGCTCT GACTGACCGGTTACTCCCACAGGTGAGCGGGCGGACGGCCCTTCTC CTCCGGGCTGTAATTAGCGCTTGGTTTAATGACGGCTTGTTCTTTTCT GTGGCTGCGTGAAAGCCTTGAGGGGCTCCGGGAGCTAGAGCCTCTGCT AACCATGTTTCATGCCTTCTCTTTTCTTACAGCTCCTGGGCAACGTGC TGGTTATTGTGCTGTCTCATCATTTTGGCAAAGAATTCCCAATCGATAC CCAATCGATACAGATCTAGCGGCCGCGCCGCCACCATGAGTGAGAAA GAGTCAACATCACACACCTCATGGTTCCCATTTCTCCTGCTGGAT GGATTGTAGGCTGCATCATCGTTATTTACATTGTCTTCTTCTAACAG GGTTGATTGGATCCAAGCTTTGGATCCAATGGATCCAATCAACCTCTG GATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTC CTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTAT TGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGATAAATCCTGGTTGC TGTCTCTTATGAGGAGTTGTGGCCGTTGTCAGGCAACGTGGCGTGG TGTGCACTGTGTTTGTGACGCAACCCCCACTGGTTGGGGCATTGCCA CCACCTGTCAGCTCCTTTCCGGGACTTTGCTTTCCCCCTCCCTATTGC CACGGCGGAACTCATCGCCGCTGCCTTGCCCGCTGTGGACAGGGGC TCGGCTGTTGGGCACTGACAATTCCGTGGTGTGTGCGGGGAAATCATC GTCTTTCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGG ACGTCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCT CCCGCGCCTGCTGCCGGCTCTGCGGCCTCTCCGCGTCTTCGAGATCT GCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCC CCGTGCCTTCTTGACCCTGGAAGGTGCCACTCCCCTGCTCTTCTCTA ATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTAT TCTGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAA GACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCGAATTCCCCGA
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	TTAGGATCTTCCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGT TAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCT CTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCC GACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGC AG (SEQ ID NO: 21)
pCR-HD1	CTGCGCGCTCGCTCGCTCACTGAGGCCGCGCGGCAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGGTCATGGAGAAGACCCACCTTGCAGATGTCTCA CTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATTA GGAGCCAGTAGCCTGGAAGATGTCTTTACCCCAAGCATCAGTTCAAGT GGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCTGCTC CCAGCTGGCCCTCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCCCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAACACCCCCACCCCCACCGCATCCCCCTGCCC CACCCGTCCCTGTGCGACATTCTCCCTCCGCAGGGCTGGCTCACCA GGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCTCTGCCTCAC CCAGTCCCGCTGAGACTGAGCAGACGCCTCCAGCGGCCCGCCCGCAC CATGGCAGAGAAGGCTGGAAGCACTTTCTCTCACCTGTCTGTCGGAT TTTGCTTTTGATTGGGTGGATAGTTGGCTGTATCATAATGATCTACGTT GTCTTTTCATAGAAGCTTTGGATCCAATCAACCTCTGGATTACAAAATT TGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTAT GTGGATACGCTGCTTAAATGCCTTGTATCATGCTATTGCTCCCGTAT GGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATG AGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGT TTGCTGACGCAACCCCCACTGTTGGGGCATTGCCACCACCTGTCAGC TCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAAC CATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGG CACTGACAATTCCGTGGTGTGTCGGGGAAATCATCGTCCTTTCTTGG CTGCTCGCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCT ACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGCGGCCTGCT GCCGGCTCTGCGGCCTCTTCCGCGCTTTCGAGATCTGCCTCGACTGTGC CTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTCCCTTCTG ACCCTGGAAGGTGCCACTCCCACTGTCTTTCTTAATAAAATGAGGAA ATTGCATCGATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGG GTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGC ATGCTGGGACTCGAGTTAAGGGCGAATTCCCGATTAGGATCTTCTTA GAGCATGGCTACGTAGATAAAGTAGCATGGCGGGTTAATCATTAACTAC AAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGC TCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCGACGCCCGGGCTTT GCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 22)
pCR-HD2	CTGCGCGCTCGCTCGCTCACTGAGGCCGCGCGGCAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGAGAGGACCTTTCAAGGACATTAGTGGTGGAGGC AGCATAGTAGTCCCAAGGCAGAGGGATTGAGAGAAGGTTTGAGGA CTGGGAAGGCGGGACACATGATTGGGTGATGGGAGAAGGGGGCAGAG AATAGCGAGATTGCTTTCTTTGCCACGGAGAAACAGAGGAGTGTGGA TCATGAATGGGCAAGATCTTTAAGTGCCAGGGGGGTCATGGAGGAG GGGAGGGCCTGTCCAGAGGAGGACCATTCCTGCTTCAGAGCCAAGC AGGACCTAGGCTGTGAAGATTTCGAGAGAAAGAGATGGAGGGGAGAGTC AGCTCAGCTGCTTACTGGCTTGCTTTCTCCTGTCTCTTTTCATTTTCATA ATCTACCAAACCCTGCAATGGGCCAGCCTTGAACATACAAGTGCATGT GCATGGTCAGACACAGGCAAGCAAGCAAGACCCCTAGGCCTGACCTA TGCATCTGCAATCTAGTAGGTTTAGCAGATCATAGCCCCGCACTGCTT

	GATTTTAAAGCCGTTAGGGGATGACCTTTGACAGTCCGCATCACCCCT CTCACACAACGAGCGCCTGTTCAAGGTTCTTGAAGTTCTACCT TGTATCTGGCCTCCTGTAGCAGTTTCAGTCCATTCCCTGTGAGGAGGT GTGCCACATGGCTTTGGGGTTCATGGAGAAGACCCACCTTGAGATGT CCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTC CATTAGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTT CAAGTGGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGG TGCTGAGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCC TGCTCCCAGCTGGCCCTCCCAGGCCTGGGTTGCTGGCCTCTGCTTTATC AGGATTCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTG CATATCTGCTCTGGTTTAAATAGCTTATCTGAGCAGCTGGAGGACCA CATGGGCTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGG CACCTGCCAAAATAGCAGCCAAACACCCCCACCCCCACGCCATCCCC CTGCCCCACCCGTCCCCTGTGCGACATTCTCCCTCCGAGGGCTGGCT CACCAGGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCTCTG CCTCACCCAGTCCCCGCTGAGACTGAGCAGACGCCTCCAGGACTGTGTC GGCAGCTGCTGTTCTGAGGTAAGGCTCGGGCAGGGCTCTGGGAAGA GGAGAGCAGAGAATGGACGGGGAGATGTGAGGGTCTTGGGCCCTGGC ATATTTACCCAGAGTCTGCCTGTGTCCGCAGAAGTCCATGGCCCTCTCT GGTGGAGGCCACACTTCAGAGGACAGGTTGCCAGGTCTGGGCTCCAA GATTGGTACAATAGAGCAGAGAGAGGAGTGCCTGCGACGCTGCCTTC GCCCCGTGCCCCGCTCCGCCGCCGCTCGCGCCGCCCGCCCGCTCT GACTGACCGCTTACTCCACAGGTGAGCGGGCGGGACGGCCCTTCTC CTCCGGGCTGTAATTAGCGCTTGGTTTAATGACGGCTTGTCTTTCT GTGGCTGCGTGAAAGCCTTGAGGGGCTCCGGGAGTAGAGCCTCTGCT AACCATGTTTCATGCCTTCTCTTTTCTACAGCTCTGGGCAACGTGC TGGTTATTGTGCTGTCTCATCATTTTGGCAAAGAATTTCCCAATCGATAC CCAATCGATACAGATCTAGCGGCCGCGCCGCCACCATGGCAGAGAAG GCTGGAAGCACTTCTCTCACCTGCTCGTGCCGATTTTGCTTTTGATG GGTGGATAGTTGGCTGTATCATAATGATCTACGTTGTCTTTTCATAGCC AGAGGTTGATTGGATCCAAGCTTTGGATCCAATGGATCCAATCAACCT CTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAAGCTATGTTG CTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGC TATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTGTATAAATCCTGGT TGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTGAGGCAACGTGGCG TGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTG CCACCACCTGTGAGCTCCTTTCCGGGACTTTCGCTTTCCCGCTCCCTAT TGCCACGGCGGAATCATCGCCGCTGCCTTGCCCGCTGCTGGACAGG GGCTCGGCTGTGGGCACTGACAATCCGTGGTGTGTGCGGGGAAATC ATCGTCTTTCTTTGGCTGCTCGCCTGTGTGCCACCTGGATTCTGCGC GGGACGTCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTC CTTCCCGCGGCTGCTGCCGGCTCGCGGCTCTTCCCGCTCTTCCGAGA TCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCT CCCCGTGCCTTCTTTGACCCTGGAAGGTGCCACTCCACTGTCTTTCT CTAATAAAATGAGGAAATTCATCGCATTGTCTGAGTAGGTGTCAATC TATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGAGGATTGGG AAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCGAATTCCC GATTAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGG GTAAATCATTAATAACAAGGAACCCCTAGTGATGGAGTTGGCCACTCC CTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGTCCG CCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGC GCAG (SEQ ID NO: 23)
	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTCCGCCGGCCTCAGTGAGCGAGCGGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCGCCATGCTACTTATCTACCAGGGTAATGGGGATCCTCTAGAA CTATAGCTAGAATTCGCCCTTACGGGCCCCCCTCGAGGTGGGATAA AAGCAGTCTGGGCTTTCACATGACAGCATCTGGGGCTGCGGCAGAGG GTCGGGTCCGAAGCGCTGCCTTATCAGCGTCCCCAGCCCTGGGAGGTG ACAGCTGGCTGGCTTGTGTACGCCCTCGGGCACTCACGTATCTCCGT

	CCGACGGGTTTAAAAATAGCAAAACTCTGAGGCCACACAATAGCTTGG GCTTATATGGGCTCCTGTGGGGGAAGGGGGAGCACGGAGGGGGCCGG GGCCGCTGTGCCAAAATAGCAGCTCACAAGTGTTCATTCTCTCTG GGCGCCGGGCACATTCTGCTGGCTCTGCCCCCGGGGTGGGCGCC GGGGGGACCTTAAAGCCTCTGCCCCCAAGGAGCCCTTCCAGACAGC CGCCGGCACCCACCGCTCCGTGGGACGATCCCCGAAGCTCTAGAGCTT TATTGCGGTAGTTTATCACAGTTAAATTGCTAACGCAGTCAGTGCTTCT GACACAACAGTCTCGAACTTAAGCTGCAGAAGTTGGTCTGTGAGGCAC GGGCAGGTAAGTATCAAGGTTACAAGACAGGTTTAAAGGAGACCAATA GAAACTGGGCTTGTGAGACAGAGAAGACTCTTGCGTTTCTGATAGGC ACCTATTGGTCTTACTGACATCCACTTTGCCTTTCTCTCCACAGGTGTC CACTCCCAGTTCAATTACAGCTCTTAAGGCTAGAGTACTTAATACGAC TCACTATAGGCTAGCCGCCACCATGGCTGAGAAAGAGTCAACATCAC ACACCTCATGGTTCCCATTTCTCTCTGGTTGGATGGATTGTAGGCTGC ATCATCGTTATTTACATTGTCTTCTTAACGGCCGCGCGGATCCAGAC ATGATAAGATACATTGATGAGTTTGGACAAACCACAACCTAGAATGCA GTGAAAAAATGCTTTATTTGTGAAATTTGTGATGCTTATGCTTTATT GTAACCATTAATAAGCTGCAATAAAACAAGTTAAACAACAACATTGCATT CATTTTATGTTTCAGGTTCAAGGGGAGGTGTGGGAGGTTTTTATGTCG ACCCGGGCGGCCCTCGAGGACGGGGTGAACCTACGCCTGAGGATCCGAT CTTTTTCCCTCTGCCAAAAATTATGGGGACATCATGAAGCCCTTGAG CATCTGACTTCTGGCTAATAAAGGAAATTTATTTTCTGCAATAGTGT GTTGGAATTTTTGTGTCTCTCACTCGGAAGCAATTCGTTGATCTGAAT TTCGACCACCCATAATACCCATTACCCTGGTAGATAAGTAGCATGGCG GGTTAATCATTAACACAAGGAACCCCTAGTGATGGAGTTGGCCACTC CCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAGGTCTG CCCGACGCCCGGGCTTTGCCCGGGCGGCCCTAGTGAGCGAGCGAGCG CGCAG (SEQ ID NO: 24)
pHZ15	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCGGCCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTTAGGAAAGATCGG AATTCGCCCTTAAGAACTGGCCTGCCCGAGACCAACGTGCGGAACGT AGTTAAGTGTAGAGGTAGGATTTGAAGCCTGTCGATCATTCTGATTC TCCTTTTCTCTACGTCTGCTTCTGTCAATGGGCATCCTCACTGTCAAAA TGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGCAGGCCCTCTCCCC AGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGGCCC CTGAAGATAATCAGCAGTCTCTGCTCAGCATATCAATCCAAGCCCACT TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTAACTGGTGTGAACT GAAGGAAAAGCACAGCATTAGAAGTCCAAGCAGTCATGGAGAAGACC CACCTTGACAGATGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCT AAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTAC CCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGCC TTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT CTGCCCCCAACCCTGCTCCCAGCTGGCCCTCCAGGCCCTGGGTTGCT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCCTGCATATCTGCTCTGGTTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCCCTG TAGCCTTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCCACC CCCACCGCAATCCCCCTGCCCAACCGTCCCCTGTCTGCACATTCCTCCC TCCGCAGGGCTGGCTCACCAGGCCCCAGCCACATGCCTGCTTAAAGC CCTCTCCATCCTCTGCCTCACCAGTCCCCGCTGAGACTGAGCAGACG CCTCCAGCGGCCGCCGCCACCATGGCTGAGAAAGAGTCAACATCACCC ACACCTCATGGTTCCCATTTCTCTCTGGTTGGATGGATTGTAGGCTGC ATCATCGTTATTTACATTGTCTTCTTCTAAAAGCTTTGGATCCAATCAA CCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACATATG TTGCTCCTTTTACGCTATGTGGATACGCTGCTTAATGCCTTTGTATCA TGCTATGTCTTCCCGTATGGCTTTCATTTCTCTCTCTGTATAAATCCT GGTTGCTGTCTTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTG

	GCGTGGTGTGCACTGTGTTTGTGACGCAACCCCCACTGGTTGGGGCA TTGCCACCACCTGTCTAGCTCCTTTCCGGGACTTTTCGCTTTCCCCCTCCC TATTGCCACGGCGGAACTCATCGCCGCTGCCTTGCCCGCTGCTGGAC AGGGGCTCGGCTGTTGGGCACTGACAATCCGTGGTGTGTCGGGGAA ATCATCGTCCTTTTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTG CGCGGGACGTCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGAC CTTCTTCCCGCGGCCTGCTGCCGGCTCTGCCGCCTCTTCCGCGTCTTC GAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGC CCTCCCCCGTGCTTCTTGAACCTGGAAGGTGCCACTCCCCTGTCC TTTCTAATAAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTC ATTCTATTCTGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGAT TGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCGAAT TCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGCATG GCGGGTTAATCATTAATACTACAAGGAACCCCTAGTGATGGAGTTGGCCA CTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAG TCGCCGACGCCCCGGGCTTTGCCGGGCGGCCTCAGTGAGCGAGCGAG CGCGCAG (SEQ ID NO: 45)
pHZ16	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTGCGCCTTAAGAACTGGCCTGCCGAGACCAACCGTGCAGAACGT AGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGTCGATCATTCTGATTC TCCTTTTCTCTACGTCTGCTTCTGTCAATGGGCATCCTCACTGTCAA TGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGAGGCCTCTCCCC AGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCAGCCCGGCCCT CTGAAGATAATCAGCAGTCTGCTCAGCATATCAATCCAAGCCCACTC TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTAACTGGTGTGAACT GAAGGAAAAGCACAGCATTAGAAGTCCAAGCACCTTCAGATTAAAAA TAACTAAGGTAAGGGCCATGTGGGTAGGGGAGGTGGTGTGAGACGGT CCTGTCTCTCTCTATCTGCCCATCGGCCCTTTGGGGAGGAGGAATGTG CCAAGGACTAAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGC AGACCTTTCATGGGCAACCTCAGGGCTGCTGTCGTCATGGAGAAGAC CCACCTTGCAATGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGCC TAAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTA CCCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGGCCCTGTC CTTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCC TCTGCCCCCAACCCTGCTCCAGCTGGCCCTCCCAGGCCTGGGTTGCT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCCTGCATATCTGCTCTGGTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCTG TAGCCTTGTCCTTGGCACCTGCCAAAATAGCAGCCAACACCCCCCACC CCCACCGCCATCCCCCTGCCCAACCGTCCCCTGTCGCACATTCTCCC TCCGCAGGGCTGGCTCACCAGGCCCCAGCCACATGCCTGCTTAAAGC CCTCTCCATCCTCTGCCTCACCAGTCCCGCTGAGACTGAGCAGACG CCTCCAGCGGCCGCCGCCACCATGGCTGAGAAAGAGTCAACATCACC ACACCTCATGGTTCCCATTCTCTCTGGTTGGATGGATTGTAGGCTGC ATCATCGTATTTACATTGTCTTCTTCTAAAAGCTTTGGATCCAATCAA CCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAATATG TTGCTCCTTTTACGCTATGTGGATACGCTGCTTAAATGCCTTTGTATCA TGCTATTGCTTCCCGTATGGCTTTTCAATTTCTCCTCTGTATAAATCCT GGTTGCTGTCTTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTG GCGTGGTGTGCACTGTGTTTGTGACGCAACCCCCACTGGTTGGGGCA TTGCCACCACCTGTCTAGCTCCTTTCCGGGACTTTTCGCTTTCCCCCTCCC TATTGCCACGGCGGAACTCATCGCCGCTGCCTTGCCCGCTGCTGGAC AGGGGCTCGGCTGTTGGGCACTGACAATCCGTGGTGTGTCGGGGAA ATCATCGTCCTTTTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTG CGCGGGACGTCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGAC CTTCTTCCCGCGGCCTGCTGCCGGCTCTGCCGCCTCTTCCGCGTCTTC

	GAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGC CCCTCCCCCGTGCTTCCTTGACCCTGGAAGGTGCCACTCCCAGTGTCC TTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTC ATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGAT TGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCGAAT TCCCGATTAGGATCTTCCTAGAGCATGGCTACGTAGATAAGTAGCATG GCGGGTTAATCATTAATACTACAAGGAACCCCTAGTGATGGAGTTGGCCA CTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAGG TCGCCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAG CGCGCAG (SEQ ID NO: 46)
pHZ17	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCCTTGTAAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGCCTTCAGATTAAAAATAACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCCTGTCTCTCTCTATCTGC CCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACTAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTTTCATGGGCAAAC CTCAGGGCTGCTGTCTCATGGAGAAGACCCACCTTGAGATGTCCTC ACTGGGGCTGGCAGAGCCGCAACCTGCCTAAGGCTGCTCAGTCCATT AGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTTCAAG TGGAGCAGCATAAATCTTGGCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCCCTGCTC CCAGCTGGCCCTCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGCTCCTGGCACCTG CCAAAATAGCAGCCAAACACCCCCACCCCCACCGCCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCCCTCCGACGGGCTGGCTCACCA GGCCCCAGGCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCAGCGGCCCGCCGCCAC CATGGCTGAGAAAGAGTCAACATCACACACCTCATGGTTCCCATTTCT TCTCCTGGTTGGATGGATTGTAGGCTGCATCATCGTTATTTACATTGTC TTCTTCTAAAAGCTTTGGATCCAATCAACCTCTGGATTACAAAATTTGT GAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTG GATACGCTGCTTAAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGC TTTCATTTTCTCCTCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAGG AGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTG CTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCC TTTCCGGGACTTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAATCAT CGCCGCTGCTTGGCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCAC TGACAATTCCGTGGTGTTGTGCGGGGAAATCATCGTCTTTCCTTGGCTG CTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACG TCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCTGCTGCC GGCTCTGCGGCCCTTTCGCGTCTTCGAGATCTGCCTCGACTGTGCCTT CTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCGTGCCTTTCCTTGAC CCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAAT TGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGT GGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGACTCGAGTTAAGGGCGAATTCCCGATTAGGATCTTCCTAGA GCATGGCTACGTAGATAAAGTAGCATGGCGGGTTAATCATTAACATAAA GGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTC GCTCACTGAGGCCGGGCGACCAAGGTGCGCCGACGCCCGGGCTTTGCG CCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 47)
pHZ18	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCCTTGTAAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGCCTTCAGATTAAAAATAACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCCTGTCTCTCTCTATCTGC

	CCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACTAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTTCATGGGCAAAC CTCAGGGCTGCTGTCAACTGGCCTGCCGAGACCAAACGTGCGGAAC TAGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGTCGATCATTCTGATT CTCCTTTCTCTACGCTGCTTCCTGTCAATGGGCATCCTCACTGTCAA ATGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGCAGGCCTCTCCC CAGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGGCC CTGAAGATAATCAGCAGTCCTGCTCAGCATATCAATCCAAGCCCACTC TAGACAGAGATGCCGGTGCCCAAGTTTTCTATTTTAACTGGTGTGAAC GAAGGAAAAGCACAGCATTAGAAGTCCAAGCAGTCATGGAGAAGACC CACCTTGCAGATGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGTAC AAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGGAAGATGTCTTTAC CCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGCC TTCCAAGATTCTGGTGCTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT CTGCCCCCAACCTGCTCCAGCTGGCCCTCCCAGGCCTGGGTTGCT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCTGCATATCTGCTCTGGTTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCTG TAGCCTTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCCACC CCCACCGCCATCCCCCTGCCCCACCCGTCCCCTGTGCGACATTCTCTCC TCCGACGGGCTGGCTCACCAGGCCCCAGCCACATGCTGTCTTAAAGC CCTCTCCATCCTCTGCCTCACCCAGTCCCCGCTGAGACTGAGCAGACG CCTCCAGCGCCGCCGCCACCATGGCTGAGAAAGAGTCAACATCACC ACACCTCATGTTTCCATTCTCTCTGGTTGGATGGATTGTAGGCTGC ATCATCGTTATTTACATTGTCTTCTTCTAAAAGCTTTGGATCCAATCAA CCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATG TTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCA TGCTATTGCTTCCCGTATGGCTTTCATTTCTCTCTCTGTATAAATCCT GGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTACAGGCAACGTG GCGTGGTGTGCACTGTGTTTGTGACGCAACCCCACTGGTTGGGGCA TTGCCACCACCTGTGAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCC TATTGCCACGGCGGAACATCATCGCCGCCTGCCTTGCCCGCTGCTGGAC AGGGGCTCGGCTGTGGGGCACTGACAATTCGTGGTGTGTGCGGGGAA ATCATCGTCTTTTCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTG CGCGGGACGTCTTCTGTACGTCCCTTCGGCCCTCAATCCAGCGGAC CTTCTTCCCGCGGCCTGCTGCGGCTCTGCGGCCTCTTCCGCTCTTC GAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGC CCCTCCCCCGTGCCTTCTTGACCCTGGAAGGTGCCACTCCCACTGTCC TTTCTAATAAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTC ATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGAT TGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCGAAT TCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGCATG GCGGGTTAATCATTAATACTACAAGGAACCCCTAGTGATGGAGTTGGCCA CTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGG TCGCCCAGCGCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAG CGCGCAG (SEQ ID NO: 48)
pHZ19 distinct sequence elements are indicated in bold, starting with ITR, enhancer/promoter combo (αMHCe, followed by ACTC1e, followed by hcTnTp), DWORF (which is also underlined), WPRE, poly A (hGHpA), ITR	CTGCGGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCG GCGTCGGGCGACCTTTGGTTCGCCCGCCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGT <i>AGTTAATGATTAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA</i> <i>GATCGGAATTCGCCCTTAAGCCTTCAGATTAAAAATACTAAGGTAAG</i> GGCCATGTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCC TCTATCTGCCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGG ACTAAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACC TTTCATGGGCAACCTCAGGGCTGCTGTCAACTGGCCTGCCCGAG ACCAAACGTGCGGAACGTAGTTAAGTGTTAGAGGTAGGATTGAA GCCTGTGCATATTCTGATTCTCCTTTTCTCTACGTCTGCTTCTG TCAATGGGCATCCTCACTGTCAAATGCAGATGGTACAGCAGGGCT TGGTCTCAGCCAGGCAGGCCTCTCCCCAGTCTCCATGGCTCAGCT

	GTCCAGCAGTTTCATCCCTAGACCATCCCAAACATGGTTGAGAAG CTCTGAGGGGAGGACCCAGCACTGCCCCGGCCCCCTGAAGATAATCA GCAGTCCTGCTCAGCATATCAATCCAAGCCCACTCTAGACAGAGA TGCCGGTGCCAGTTTTCTATTTTTAACTGGTGTGAAGTGAAGGAA AAGCACAGCATTAGAAGTCCAAGCAGTCATGGAGAAGACCCACCT TGCAGATGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCTAA GGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTA CCCCCAGCATCAGTTCAAGTGGAGCAGCACATAAATCTTTGCCCTC TGCCTTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAG GTTGCCTTCTGCCCCCAACCCTGCTCCCAGCTGGCCCTCCCAGG CCTGGGTGCTGGCCTCTGCTTTATCAGGATTCTCAAGAGGGACA GCTGGTTTATGTTGCATGACTGTTCCCTGCATATCTGCTCTGGTTT TAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGGCTTATATG GCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTGCCAA AATAGCAGCCAACACCCCCACCCCCACCGCCATCCCCCTGCCCC ACCCGTCCCCCTGTGCGACATTCTCCCTCCCGAGGGCTGGCTCAC CAGGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCTCTG CCTCACCCAGTCCCCGCTGAGACTGAGCAGACCGCTCCATAACTG GTAAGTACCGCTATAGACTCTATAGGCACACCCCTTTGGCTCTTA TGCATGCTGACAGACTAACAGACTGTTCTTTCTGGGTCTTTTCT GCAGGCCTGTACGGAAGTGTACTTCTGCTCTAAAAGCTGCGGAA TTGTACCGCGGGCGATCCAATCGATACAGATCTAGCGGCCGCC GCCACCATGGCTGAGAAAGAGTCAACATCACACACCTCATGGTTC CCATTCTTCTCCTGGTTGGATGGATTGTAGGCTGCATCATCGTTAT TTACATTGCTCTTCTCTAAAGCTTTGGATCCAATCAACCTCTGGATT ACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCC TTTTACGCTATGTGGATACGCTGCTTTAATGCCCTTGTATCATGCT ATTGCTTCCCGTATGGCTTTTCAATTTCTCCTCTGTATAAATCCT GGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTGACGGCAAC GTGGCGTGGTGTGCACTGTGTTGTGACGCAACCCCCCACTGGTT GGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACCTTTCGCTT TCCCCCTCCCTATTGCCACGGCGGAACATCATCGCCGCTCCTTG CCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCG TGGTGTGTGCGGGGAAATCATCGTCTTTCTTGGCTGCTCGCCT GTGTTGCCACCTGGATTCTGCGCGGGACGTCTTCTGCTACGTCC CTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGGCGCTGCTGC CGGCTCTGCGGCTCTTCCGCGTCTTCGAGATCTGCCTCGACTGTG CCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTGCCTT CCTTGACCCTGGAAGGTGCCACTCCCACTGTCTTTCTTAATAAAAA TGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTG GGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAG ACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCGAATTCCCGAT TAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTA ATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCT CTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCTG CCCGACGCCCCGGGCTTTGCCCGGGCGGCTCAGTGAGCGAGCGA GCGCGCAG (SEQ ID NO: 49)
pHZ20	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAGCCCGGGCGT CGGGCGACCTTTGGTGCCTCGGCGCTCAGTGAGCGAGCGGCGCAG AGAGGGAGTGGCCAATCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGGTCTAGGAGAAGACCCACCTTGCAGATGTCTCA CTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATTA GGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTTCAAGT GGAGCAGCACATAACTCTTGCCTCTGCCTTCCAAGATTCTGGTGTCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCCAACCTGCTC CCAGCTGGCCCTCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG

	CAAAAATAGCAGCCAACACCCCCACCCCCACCGCCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCCCTCCGCAGGGCTGGCTCACCA GGCCCCAGCCCATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAACTGGTAAGTACC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTGACA GACTAACAGACTGTTCCTTTCTGGGTCTTTCTGCAGGCCTGTACGGA AGTGTTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCGCGGCCGATC CAATCGATACAGATCTAGCGGCCGCCGCCACCATGGCTGAGAAAAGA GTCAACATCACCAACCTCATGGTTCCCATTCTTCTCTGGTTGGATGG ATTGTAGGCTGCATCATCGTTATTTACATTGTCTCTTCTAAAAGCTTT GGATCCAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGT ATTCTTAACATATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTAA TGCCCTTGTATCATGCTATTGCTTCCCGTATGGCTTTTCATTTTCTCCTCC TTGTATAAATCCTGGTTGCTGCTCTTTATGAGGAGTTGTGGCCCGTTG TCAGGCAACGTGGCGTGGTGTGCACTGTGTTGCTGACGCAACCCCCA CTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCCG TTTCCCCCTCCCTATTGCCACGGCGGAATCATCGCCGCTGCTTGGC CGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCGTTGGT TTGTCGGGGAATCATCGTCTTTCTTGGCTGCTCGCCTGTGTTGCCA CCTGGATTCTGCGCGGGACGTCTTCTGCTACGTCCCTTCGGCCCTCAA TCCAGCGGACCTTCTTCCCGCGCCTGCTGCCGGCTCTGCGGCCTCTT CCGCGTCTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATC TGTGTTTGCCCCCTCCCCCGTGCCTTCTTGACCCTGGAAGGTGCCACT CCCACTGTCTTTCTTAATAAAATGAGGAAATTGCATCGCATTGTCTG AGTAGGTGTCTATTCTTCTGGGGGGTGGGGTGGGGCAGGACAGCAA GGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGTT AAGGGCGAATTCGCGATTAGGATCTTCTAGAGCATGGCTACGTAGAT AAGTAGCATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGATG GAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGG CGACCAAAGGTCGCCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTG AGCGAGCGAGCGCGCAG (SEQ ID NO: 50)
pHZ21 distinct sequence elements are indicated in bold, starting with ITR, enhancer/promoter combo (ACTC1e, followed by αMHCE, followed by hcTnTp), DWORF (which is also underlined), WPRE, polyA (hGHPA), ITR	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCG GCGTCGGGCGACCTTTGGTCGCCCGGCCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTT<i>GT</i> <i>AGTTAATGATTAAACCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA</i> <i>GATCGGAATTCGCCCTTAAGAACTGGCCTGCCCGAGACCAAAACGTGC</i> GGAACGTAGTTAAGTGTTAGAGGTAGGATTGAAGCCTGTCCGATC ATTCTGATTCTCTTTTCTCTACGCTGCTTCTGTCAATGGGCAT CCTCACTGTCAAATGCAGATGGTACAGCAGGGCTTGGTCTCAGCC AGGCAGGCCTCTCCCCAGTCTCCATGGCTCAGCTGTCCAGCAGTT TCATCCCTAGACCATCCCAAACATGGTTGAGAAGCTCTGAGGGGA GGACCCAGCACTGCCCGGCCCTGAAGATAATCAGCAGTCTCGT CAGCATATCAATCCAAGCCCACTCTAGACAGAGATGCCGGTGCCC AGTTTTCTATTTTAACTGGTGTGAAGTGAAGGAAAAGCACAGCAT TAGAAGTCCAAGCACCTTCAAGATTAAAAATAACTAAGGTAAGGGC CATGTGGGTAGGGAGGTGGTGTGAGACGGTCTGTCTCTCCTCT ATCTGCCCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACT AAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTT CATGGGCAAACCTCAGGGCTGCTGTCTCATGGAGAAGACCCACC TTGCAGATGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCTA AGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTT ACCCCCAGCATCAGTTCAAGTGAGCAGCACATAACTCTTGCCCT CTGCCCTTCCAAGATTCTGGTGCTGAGACTTATGGAGTGTCTTGA GGTTGCCTTCTGCCCCCAACCTGCTCCAGCTGGCCCTCCAG GCCTGGGTGCTGGCCTCTGCTTTATCAGGATTCTCAAGAGGGAC AGCTGGTTTATGTTGCATGACTGTTCCCTGCATATCTGCTCTGGTT TTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGGCTTATAT GGCGTGGGGTACATGTTCTGTAGCCTGTCCCTGGCACCTGCCA AAATAGCAGCCAACACCCCCACCCCCACCGCCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCCCTCCGCAGGGCTGGCTCA

	CCAGGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCCTCT GCCTCACCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAACT GGTAAGTACCGCCTATAGACTCTATAGGCACACCCCTTTGGCTCTT ATGCATGCTGACAGACTAACAGACTGTTCTTTCTGGGTCTTTTC TGCAGGCCTGTACGGAAGTGTACTTCTGCTCTAAAAGCTGCGGA ATTGTACCCGCGGCCGATCCAATCGATACAGATCTAGCGGCCGCC GCCACCATGGCTGAGAAAGAGTCAACATCACCACACCTCATGGTTC <u>CCATTCTTCTCCTGGTTGGATGGATTGTAGGCTGCATCATCGTTAT</u> <u>TTACATTGTCTTCTCTAA</u>⁴<u>AGCTTTGGATCCAATCAACCTCTGGATT</u> ACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCC TTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCT ATTGCTTCCCGTATGGCTTTCATTTTCTCCTCTTTGTATAAATCT GGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTACAGGCAAC GTGGCGTGGTGTGCACTGTGTTTGTGACGCAACCCCCACTGGTT GGGGCATTGCCACCACCTGTCAGCTCCTTTCGGGACTTTCGCTT TCCCCCTCCCTATTGCCACGGCGGAACATCGCCGCTGCCTTG CCCGCTGTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCG TGGTGTGTGCGGGAAATCATCGTCTTTCCTTGGCTGCTCGCCT GTGTTGCCACCTGGATTCTGCGGGGACGTCCTTCTGCTACGTCC CTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGCGGCTGCTGC CGGCTCTGCGGCCTCTTCCGCGTCTTCGAGATCTGCCTCGACTGTG CCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCCTCCCCGCTGCTT CCTTGACCCTGGAAGGTGCCACTCCCACTGTCTTTCTAATAAAAA TGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTG GGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAG ACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCGAATTCGGATT AGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATC ATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCT GCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAGGTGCCCC GACGCCCCGGCTTTGCCCGGGCGGCCCTCAGTGAGCGAGCGAGCG CGCAG (SEQ ID NO: 51)
pH22	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGAACTGGCCTGCCCCGAGACCAACGTGCGGAACGT AGTTAAGTGTAGAGGTAGGATTTGAAGCCTGTGATCATCTGTATT TCCTTTTCTCTACGTCTGCTTCTGTCAATGGGCATCCTCACTGTCAAA TGCAGATGGTACAGCAGGCTTGGTCTCAGCCAGGAGGCTCTCCCC AGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGGCC CTGAAGATAATCAGCAGTCTGCTCAGCATATCAATCCCAAGCCCACT TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTAACTGGTGTGAAC GAAGGAAAAGCACAGCATTAGAAGTCCAAGCAGTCATGGAGAAGACC CACCTTGACAGATGTCCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCT AAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGCTTTTAC CCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGCC TTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT CTGCCCCCAACCCTGCTCCAGCTGGCCCTCCAGGCCTGGGTGCT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCCTGCATATCTGCTCTGGTTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCTGT TAGCCTTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCACC CCCACCGCAATCCCCCTGCCCAACCGTCCCCTGTGCGACATTCTCTCC TCCGACAGGGCTGGCTACACAGGCCCCAGCCACATGCCTGCTTAAAGC CCTCTCCATCCTCTGCCTCACCCAGTCCCCGCTGAGACTGAGCAGACG CCTCCATAACTGGTAAGTACCGCCTATAGACTCTATAGGCACACCCCT TTGGCTCTTATGCATGCTGACAGACTAACAGACTGTTCTTTCTGGGT CTTTTCTGAGGCCTGTACGGAAGTGTACTTCTGCTCTAAAAGCTGCG GAATTGTACCCGCGGCCGATCCAATCGATACAGATCTAGCGGCCGCC

	GCCACCATGGCTGAGAAAAGAGTCAACATCACCACACCTCATGGTTCCC ATTCTTCTCCTGGTTGGATGGATTGTAGGCTGCATCATCGTTATTTACA TTGTCTTCTTCTAAAAGCTTTGGATCCAATCAACCTCTGGATTACAAAA TTTGTGAAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCT ATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGT ATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTA TGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGT GTTTGTCTGACGCAACCCCACTGGTTGGGGCATTGCCACCACCTGTCA GCTCCTTTCGGGACTTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAA CTCATCGCCGCTGCCTTGCCGCTGCTGGACAGGGGCTCGGCTGTTG GGCACTGACAATTCCGTGGTGTGTGCGGGGAAATCATCGTCCTTTTCCTT GGCTGCTCGCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTG CTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCCTTCCCGCGGCTG CTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGAGATCTGCCTCGACTGT GCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCTCCCCCGTGCCTTCC TTGACCCTGGAAGGTGCCACTCCCACTGTCTTTCTAATAAAATGAG GAAATTGCATCGCATTGTCTGAGTAGGTGTCTATTCTTTCGGGGGT GGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCA GGCATGCTGGGGACTCGAGTTAAGGGCGAATCCCGATTAGGATCTTC CTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAAC TACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCT CGCTCGCTCACTGAGGCCGGGCGACCAAGGTCGCCCGACGCCCGGG CTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 52)
pHZ23	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTGCCCCTTAAGCCTTCAGATTAAAAATAACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCTCTATCTGC CCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACTAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTTCATGGGCAAAC CTCAGGGCTGCTGTCTCATGGAGAAGACCCACCTTGCAGATGTCTC ACTGGGGCTGGCAGAGCCGCAACCTGCCTAAGGCTGCTCAGTCCATT AGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTTCAAG TGGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCCGCTC CCAGCTGGCCCTCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAAACACCCCCACCCCCACCGCCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCTCCCTCCGCAGGGCTGGCTACCA GGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAACTGGTAAGTACC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTGACA GACTAACAGACTGTTCCTTTCTGGGTCTTTTCTGCAGGCCTGTACGGA AGTGTTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCGCGGCCGATC CAATCGATACAGATCTAGCGGCCGCCGCCACCATGGCTGAGAAAGA GTCAACATCACCACACCTCATGGTTCCCATTTCTCTCCTGGTTGGATGG ATTGTAGGCTGCATCATCGTTATTTACATTGTCTCTTCTAAAAGCTTT GGATCCAATCAACCTCTGGATTACAAAATTTGTGAAAAGATTGACTGGT ATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAA TGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTTCATTTCTCCTCC TTGTATAAATCCTGGTTGCTGTCTTTTATGAGGAGTTGTGGCCCGTTG TCAGGCAACGTGGCGTGGTGTGCACTGTGTTTGTGACGCAACCCCCA CTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTTCGC TTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCTGCCTTGCC CGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTG TTGTCGGGGAAATCATCGTCCTTTTCCTTGGCTGCTCGCCTGTGTTGCCA

	CCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAA TCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTT CCGCGTCTTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATC TGTTGTTTGCCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACT CCCACTGTCTTTTCTAATAAAATGAGGAAATTGCATCGCATTGTCTG AGTAGGTGTCAATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAA GGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGTT AAGGGCGAATTCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGAT AAGTAGCATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGATG GAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGG CGACCAAAGTTCGCCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTG AGCGAGCGAGCGCGCAG (SEQ ID NO: 53)
pHZ24	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGCCTCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCCGG AATTGCGCCTTAAGGTCAATGGAGAAGACCCACCTTGCAGATGTCTCA CTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATTA GGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTTCAAGT GGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCCCTGCTC CCAGCTGGCCCTCCAGGCCTGGGTTGCTGGCCTCTGCTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAACACCCCCACCCCCACCGCATCCCCCTGCCC CACCCGTCCCTGTGCACATTCTCCCTCCGAGGGCTGGCTCACA GGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCAGCGCGCCGCCGCCAC CATGGCCGAGAAGGAATCTACAGCCCCACCTGATGGTGCTATTCT GCTGCTGGTGGGCTGGATCGTGGCTGCATCATCGTGATCTACATCGT GTTCTTCTGAAAGCTTTGGATCCAATCAACCTCTGGATTACAAAATTTG TGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGT GGATACGCTGCTTAAATGCCTTTGTATCATGCTATTGCTTCCCGTATGG CTTTCATTTTCTCCTCCTTGTATAAAATCCTGGTTGCTGTCTTTATGAG GAGTTGTGGCCCGTTGTGAGGCAACGTGGCGTGGTGTGCACTGTGTTT GCTGACGCAACCCCCACTGTTGGGGCATTGCCAACCTGTGCACTC CTTTCCGGGACTTTGCTTTCCCCCTCCCTATTGCCACGGCGGAACCTCA TCGCCGCTGCTTGGCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCA CTGACAATTCCGTGGTGTGTCGGGGAAATCATCGTCTTTTCTTGGCT GCTCGCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTAC GTCCCTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGCGGCTGCTGC CGGCTCTGCGGCCTCTTCCGCGTCTTCGAGATCTGCCTCGACTGTGCCT TCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTGCCTTCTTGA CCCTGGAAGGTGCCACTCCCCTGCTCTTCTAATAAAATGAGGAAA TTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGT GGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCAT GCTGGGGACTCGAGTTAAGGGCGAATTCCCGATTAGGATCTTCTTAGA GCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAACTACAA GGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTC GCTCACTGAGGCCGGGCGACCAAAGGTGCCCCGAGCCCCGGGCTTTGC CCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 54)
pHZ25 distinct sequence elements are indicated in bold, starting with ITR, promoter/enhancer combo (αMHCe, followed by hcTnTp), DWORF (which	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGG GCGTGGGGCGACCTTTGGTTCGCCCGGCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGT <i>AGTTAATGATTAAACCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA</i> <i>GATCGGAATTCGCCCTTAAGCCTTCAGATTAAAAATACTAAGGTAAG</i> GGCCATGTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCC TCTATCTGCCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGG ACTAAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACC

is also underlined), WPRE, polyA (hGHpA), SV40pA, optimized DWORF (which is also underlined), promoter/enhancer combo (ccTnTp, followed by ACTC1e), ITR

TTTCATGGGCAAACCTCAGGGCTGCTGTCGTCATGGAGAAGACCC
 ACCTTGACAGATGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGC
 CTAAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAAGATGTC
 TTTACCCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGC
 CCTCTGCCTTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTG
 GAGGTTGCCTTCTGCCCCCAACCTGCTCCAGCTGGCCCTCCC
 AGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGATTCTCAAGAGGG
 ACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATCTGCTCTGG
 TTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGGCTTAT
 ATGGCGTGGGGTACATGTTCCTGTAGCCTTGTCCCTGGCACCTGC
 CAAAATAGCAGCCAACACCCCCACCCCCACCGCCATCCCCCTGC
 CCCACCCGTCCCCGTGTCGCACATTCTCCCTCCGACGGGCTGGCT
 CACCAGGCCCCAGCCCACATGCCTGCTTAAAGCCCTCTCCATCCT
 CTGCCTCACCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAA
 CTGGTAAGTACCGCTATAGACTCTATAGGCACACCCCTTTGGCT
 CTTATGCATGCTGACAGACTAACAGACTGTTCTTTCTGGGTCTT
 TTCTGCAGGCCTGTACGGAAGTGTTACTTCTGCTCTAAAGCTGC
 GGAATTGTACCCGCGGCCGATCCAATCGATAACAGTACGCGGCC
 GCCCGCCACCATGGCTGAGAAAGAGTCAACATCACCACACCTCATG
GTTCCCATCTCTCTCTGGTTGGATGGATTGTAGGCTGCATCATCG
TTATTTACATTGCTCTCTCTAAAGCTTTGGATCCAATCAACCTCTG
 GATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTTGTG
 CTCTTTTACGCTATGTGGATACGCTGCTTAAATGCCTTTGTATCA
 TGCTATTGCTTCCCGTATGGCTTTTCAATTTCTCTCTTGTATAAA
 TCCTGGTTGCTGTCTCTTATGAGGAGTTGTGGCCCGTTGTACAG
 CAACGTGGCGTGGTGTGCACTGTGTTTGTGACGCAACCCCCACT
 GGTTGGGGCATTTGCCACCACCTGTACGCTCCTTTCCGGACTTTT
 GCTTTCCCCCTCCCTATTGCCACGGCGGAACATCGCCGCTGC
 CTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAAT
 TCCGTGGTGTGTGCGGGAAATCATCGTCTTTCTTTGGCTGCTC
 GCCTGTGTTGCCACCTGGATTCTGCGCGGGACGCTCTTCTGCTAC
 GTCCCTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGCGGCTG
 CTGCCGGCTCTGCGGCCCTTCCCGCTCTTCGAGATCTGCCTCGAC
 TGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTG
 CCTTCTTGACCCTGGAAGGTGCCACTCCCACTGTCTTTTCTTAAT
 AAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCTATTCTAT
 TCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGCGAGGATTGGG
 AAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCAGCCAGAA
 GTCAGATGCTCAAGGGGCTTCATGATGTCCCCATAATTTTGGCAGAGGGA
 AAAAGATCGGATCCTCAGGCGTAGTTACCCCCGTCTCGAGGCGCGCCGG
 GTCGACTAAAAAACCTCCACACCTCCCCCTGAACCTGAAACATAAAATGAA
 TGCAATTGTTGTTGTTAACTTGTTTATTGACGCTTATAATGGTTACAA
 ATAAAGCAATAGCATCACAAATTTACAAATAAAGCATTTTTTTTCA
 CTGCATTCTAGTTGTGGTTTGTCCAAACTCATCAATGTATCTTATC
 ATGTCTGGATCCGCGCGGCCGTCAGAAGAACACGATGTAGATCACC
ATGATGCAGCCGACGATCCAGCCCACCAGCAGCAGAATAGGCACC
ATCAGGTGGGGCTGGTAGATTCTCTCTCGGCCATGGTGGCGGCTA
 GCCTATAGTGAGTCTATTAAAGTACTCTAGCCTTAAGAGCTGTAATTG
 AACTGGGAGTGGACACCTGTGGAGAGAAAGGCAAGTGGATGTC
 AGTAAGACCAATAGGTGCCTATCAGAAACGCAAGACTCTTCTCTG
 TCTCGACAAGCCCAGTTTCTATTGGTCTCTTAAACCTGTCTTGT
 ACCTTGATACTTACCTGCCCAGTGCCTCACGACCAACTTCTGCAGC
 TTAAGTTCGAGACTGTTGTGTCAGAAGCACTGACTGCGTTAGCAA
 TTTAACTGTGATAAACTACCGCAATAAAGCTCTAGAGCTTCGGGG
 ATCGTCCCACGGAGCGGTGGGTGCCGGCGGCTGTCTGGGAAGGG
 CTCCTTGGGGGGCAGAGGCTTAAAGTCCCCCGGCGGCCACCCC
 GGGGCGGGCAGAGCCAGCAGGAATGTGCCCGGCGCCAGAGAGG
 AATGCAACACTTGTGAGCTGCTATTTTGGCAGCAGCGCCCCCGGC
 CCCCTCCGTGCTCCCCCTTCCCCACAGGAGCCCATATAAGCCCA
 AGCTATTGTGTGGCCTCAGAGTTTGTCTATTTTAAACCCGTCGGAC

	GGAGATACGTGAGTGCCCCGAGGGGCTGACACAAGCCAGCCAGCT GTCACCTCCCAGGGCTGGGGACGCTGATAAGGCAGCGCTTCGGAC CCGACCCCTCTGCCGACGCCCCAGATGCTGTCATGTGAAAAGCCAG ACTGCTTTTATCCCTGCTTGGACTTCTAATGCTGTGCTTTTCCTTC AGTTACACACCAGTTAAAAATAGAAAAGTGGGCACCGGCATCTCTG TCTAGAGTGGGCTTGGATTGATATGCTGAGCAGGACTGCTGATTA TCTTCAGGGGGCCGGGCAGTGCTGGGTCCTCCCTCAGAGCTTCTC AACCATGTTTGGGATGGTCTAGGGATGAAACTGCTGGACAGCTGA GCCATGGAGACTGGGGAGAGGCCTGCCTGGCTGAGACCAAGCCC TGCTGTACCATCTGCATTTGACAGTGAGGATGCCATTGACAGGA AGCAGACGTAGAGAAAAGGAGAATCAGAATGATCGACAGGCTTCA AATCCTACCTCTAACACTTAACCTACGTTCCGCACGTTTGGTCTCGG GCAGGCCAGTTGAATTCCCGATTAGGATCTTCTAGAGCATGGCTACGTA GATAAGTAGCATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGA TGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGG CCGGGCGACCAAAGGTCGCCCCACGCCCGGGCTTTGCCCGGGCG GCCTCAGTGAGCGAGCGCGCGAG (SEQ ID NO: 55)
pH233 distinct sequence elements are indicated in bold, starting with ITR, promoter/enhancer combo (αMHCe, followed by hcTnTp), DWORF (which is also underlined), WPRE, poly A (hGHPA), promoter/enhancer combo (CTC1e, followed by ccTnTp), optimized DWORF (which is also underlined), SV40pA, ITR	CTGCGCGCTCGCTCGCTCACTGAGCCCGCCGGGCAAAGCCCGG GCGTCGGGCGACCTTTGGTCGCCCCGCCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGT AGTTAATGATTAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA GATCGGAATTGCCCCCTTAAGCCTTCAGATTAAAAATAACTAAGGTAAG GGCCATGTGGGTAGGGAGGGTGGTGTGAGACGGTCTGTCTCTCC TCTATCTGCCCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGG ACTAAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACC TTTCATGGGCAAACCTCAGGGCTGCTGTGCTCATGGAGAAGACCC ACCTTGCAGATGTCTCACTGGGGCTGGCAGCGCCGCAACCTGC CTAAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTC TTTACCCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGC CCTCTGCCTTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTG GAGGTGCTTCTGCCCCCAACCCTGCTCCAGCTGGCCCTCCC AGGCCTGGGTGTGCTGGCCTCTGCTTTATCAGGATTCTCAAGAGGG ACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATCTGCTCTGG TTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGGCTTAT ATGGCGTGGGGTACATGTTCCTGTAGCCTTGTCCCTGGCACCTGC CAAAATAGCAGCAACACCCCCACCCCCACCGCCATCCCCCTGC CCCACCCGTCCCCCTGTGCGACATTCTCCCTCCGAGGGCTGGCT CACCAGGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCCT CTGCCTACCCAGTCCCCGCTGAGACTGAGCAGACGCCCTCCATAA CTGGTAAGTACCGCTATAGACTCTATAGGCACACCCCTTTGGCT CTTATGCATGCTGACAGACTAACAGACTGTTCTTTCTGGGTCTT TTCTGCAGGCCTGTACGGAAGTGTTACTTCTGCTCTAAAAGCTGC GGAATTGTACCCGCGGCGATCCAATCGATACAGATCTAGCGGCC GCCCCGCCACCATGGCTGAGAAAGAGTCAACATCACACACCTCATG GTTCCCATCTCTCTCTGGTTGGATGGATTGTAGGCTGCATCATCG TTATTTACATTGTCTTCTCTAAAGCTTTGGATCCAATCAACCTCTG GATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTG CTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCA TGCTATTGCTTCCCGTATGGCTTTTCAATTTCTCCTCCTTGATAAA TCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAAG CAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCACT GGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTT GCTTTCCCCCTCCCTATTGCCACGGCGGAACCTCATCGCCGCTGC CTTGCCCGCTGCTGGACAGGGGCTCGGCTGTGGGGCACTGACAAT TCCGTGGTGTGTCGGGGAAATCATCGTCCTTTCTTTGGCTGCTC GCCTGTGTTGCCACCTGGATTCTGCGCGGGACCTCTCTGCTAC GTCCCTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGCGGGCTG CTGCCGGCTCTGCGGCCCTTCCCGCTCTTCGAGATCTGCTCGAC TGTGCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTG CCTTCCTTGACCTGGAAGGTGCCACTCCCACTGTCCTTTCTTAAT

	AAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTAT TCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGG AAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCAGCCAGAA <i>GTCAGATGCTCAAGGGGCTTCATGATGTCCCCATAATTTTGGCAGAGGGA</i> <i>AAAAGATCGGATCCTCAGGCGTAGTTCACCCCGTCTCGAGGCCGCCCCG</i> <i>GTCGACTAAAAACCTCCCACCTCCCCCTGAACCTGAAACATAAAATGAA</i> <i>TGCAATTGTTGTTAACTGGCCTGCCCCGAGACCAACGTCGCGA</i> ACGTAGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGTCCGATCATT CTGATTCTCCTTTTCTCTACGTCTGCTTCCTGTCAATGGGCATCCT CACTGTCAAATGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGG CAGGCCTCTCCCCAGTCTCCATGGCTCAGCTGTCCAGCAGTTTCA TCCCTAGACCATCCCAACATGTTGAGAAGCTCTGAGGGGAGGA CCCAGCACTGCCCGGCCCTGAAGATAATCAGCAGTCTGCTCAG CATATCAATCCAAGCCCCTCTAGACAGAGATGCCGGTGCCAGT TTTCTATTTTAACTGGTGTGAACCTGAAGGAAAAGCACAGCATTAG AAGTCCAAGCAGGGATAAAAGCAGTCTGGGCTTTCACATGACAGC ATCTGGGGCTGGCAGAGGGTCGGGTCCGAAGCGCTGCCTTATC AGCGTCCCCAGCCCTGGGAGGTGACAGCTGGCTGGCTTGTGTACG CCCCTCGGGCACTCACGTATCTCCGTCCGACGGGTTTAAATAGC AAAACCTCTGAGGCCACACAATAGCTTGGGCTTATATGGGCTCCTG TGGGGGAAGGGGAGCACGGAGGGGGCCGGGGCCGCTGCTGCCA AAATAGCAGCTACAAGTGTTGCATTCTCTCTGGGCGCCGGGCA CATTCTGTGCTGCTCTGCCCCGCCCGGGTGGGCGCCGGGGGA CCTTAAAGCCTCTGCCCCCAAGGAGCCCTTCCAGACAGCCGCC GGCACCCACCGCTCCGTGGGACGATCCCCGAAGCTCTAGAGCTTT ATTGCGGTAGTTTATCACAGTTAAATTGCTAACGCAGTCAGTGCTT CTGACACAACAGTCTCGAACTTAAGCTGCAGAAGTTGGTCTGTAG GCCTGGGCAGGTAAGTATCAAGGTTACAAGACAGGTTTAAGGAG ACCAATAGAACTGGGCTTGTGAGACAGAGAAGACTCTTGCGTT TCTGATAGGCACCTATTGGTCTTACTGACATCCACTTTGCCTTTCT CTCCACAGGTGTCCACTCCAGTTCAATTACAGTCTTAAGGCTAG AGTACTTAATACGACTCACTATAGGCTAGCCGCCACCATGGCCGAGAAG GAATCTACCAGCCCCACCTGATGGTGCTATTCTGCTGCTGGTG GGCTGGATCGTCGGCTGCATCATCGTGATCTACATCGTGTCTTCT GACGGCCGCGCGGATCCAGACATGATAAGATACATTGATGAGTTTG GACAAACCACAACCTAGAATGCAGTGAAAAAATGCTTTATTTGTG AAATTTGTGATGCTATTGCTTTATTTGTAACCATTAAGCTGCAA TAAACAAGTGAATCCCGATTAGGATCTTCCTAGAGCATGGCTACGTAGA TAAGTAGCATGGCGGGTAAATCATTAACTACAAGGAACCCCTAGTGATG GAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGC CTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 56)
pHZ34 distinct sequence elements are indicated in bold, starting with ITR, poly A (hGHpA), WPRE, DWORF (which is also underlined), promoter/enhancer combo (hcTnTp, followed by αMHCE, followed by ACTC1e, followed by ccTnTp), optimized DWORF (which is also underlined), SV40pA, ITR	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCG GCGTCGGGCGACCTTTGGTCCGCCGGCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTTCTTGT <i>AGTTAATGATTAAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA</i> <i>GATCGGAATTCTCCCCAGCATGCCTGCTATTGTCTTCCCAATCCTCC</i> CCCTTGCTGTCTTGGCCCCACCCACCCCCAGAATAGAATGACAC CTACTCAGACAATGCGATGCAATTTCTCATTATTTATTAGGAAAGGA CAGTGGGAGTGGCACCTTCCAGGGTCAAGGAAGGCACGGGGGAG GGGCAAAACAACAGATGGCTGGCAACTAGAAGGCACAGTCGAGGCA <i>GATCTCGAAGACGCGGAAGAGGCCGAGAGCCGGCAGCAGGCCGC</i> GGGAAGGAAGGTCCGCTGGATTGAGGGCCGAAGGGACGTAGCAG AAGGACGTCCCGCGCAGAATCCAGGTGGCAACACAGGCGAGCAG CCAAGGAAAGGACGATGATTTCCCCGACAACACCACGGAATTGTC AGTGCCCAACAGCCGAGCCCCGTGTCCAGCAGCGGGCAAGGCAGG CGGCGATGAGTTCCGCCGTGGCAATAGGGAGGGGGAAAGCGAAA GTCCCGGAAAGGAGCTGACAGGTGGTGGCAATGCCCCAACCAGT GGGGGTGCGCTCAGCAAAACACAGTGCACACCACGCCACGTTGCCT GACAACGGGCCACAACCTCTCATAAAGAGACAGCAACCAGGATTT

	ATACAAGGAGGAGAAAAATGAAAGCCATACGGGAAGCAATAGCATG ATACAAAGGCATTAAAGCAGCGTATCCACATAGCGTAAAAAGGAGC AACATAGTTAAGAATACCAGTCAATCTTTACAAAATTTTGTAAATCC AGAGGTTGATTGGATCCAAAGCTTTTAGAAGAAGACAATGTAAATAA CGATGATGCAGCCTACAATCCATCCAACCAGGAGAAGAATGGGAA CCATGAGGTGTGGTGATGTTGACTCTTTCTCAGCCATGGTGGCGGG CGGCCGCTAGATCTGTATCGATTGGATCGGCCGCGGTACAATTC CGCAGCTTTTAGAGCAGAAGTAACACTTCCGTACAGGCCTGCAGA AAAGACCCAGGAAAGGAACAGTCTGTAGTCTGTGTCAGCATGCATA AGAGCCAAAGGGGTGTGCCTATAGAGTCTATAGGCGGTACTTACC AGTTATGGAGGCGTCTGCTCAGTCTCAGCGGGGACTGGGTGAGGC AGAGGATGGAGAGGGCTTTAAGCAGGCATGTGGCTGGGGCCTG GTGAGCCAGCCCTGCGGAGGGAGGAATGTGCGACAGGGGACGGG TGGGGCAGGGGGATGGCGGTGGGGGTGGGGGTGTTGGCTGCTA TTTTGGCAGGTGCCAGGGACAAGGCTACAGGAACATGTACCCAC GCCATATAAGCCCATGTGGTCTCCAGCTGCTCAGATAAGCTATTT AAAACCAGAGCAGATATGCAGGGAACAGTCATGCAACATAAACCA GCTGTCCCTCTTGAGAATCCTGATAAAGCAGAGGCCAGCAACCCA GGCCTGGGAGGGCCAGCTGGGAGCAGGGTTGGGGGGCAGAAGGC AACCTCCAAGACACTCCATAAGTCTCAGCACCAGAATCTTGGAAG GCAGAGGGCAAGAGTTATGTGCTGCTCCACTTGAATGATGTGCG GGGTAAAGACATCTTCCAGGCTACTGGCTCCTAATGGACTGAGCA GCCTTAGGCAGGTTGCCGGCTCTGCCAGCCCCAGTGAGGACATCT GCAAGGTGGGTCTTCTCCATGACGACAGCAGCCCTGAGGTTTGCC CATGAAAGGTCTGCTGCCCTCGCCCCCTCTGGCTCCAGGGCCTTTT TTAGTCCTTGGGCACATTCTCTCTCCCCAAAGGGCCGATGGGCA GATAGAGGAGAGACAGGACCGTCTCACACCACCTCCCCTACCCAC ATGGCCCTTACCTTAGTTATTTTAACTCTGAAGGCTCGAGTTAAGGG CAGCCAGAAAGTCAGATGCTCAAGGGGCTTCATGATGTCCCATATTTTG GCAGAGGGAAAAAGATCGGATCCTCAGGCGTAGTTCACCCCGTCTCGAG GCCGCCCGGGTCGACTAAAAAACCTCCACACCTCCCCCTGAACCTGAAAC ATAAAATGAATGCAATTGTTGTTAACTGGCCTGCCCGAGACCAAA CGTGCGGAACGTAGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGT CGATCATTCTGATTCTCCTTTTCTCTACGTCTGCTTCTGTCAATG GGCATCTCACTGTCAAATGCAGATGGTACAGCAGGGCTTGGTCT CAGCCAGGACGGCTCTCCCCAGTCTCCATGGCTCAGTGTCCAG CAGTTTCATCCCTAGACCATCCCAAACATGGTTGAGAAGCTTGA GGGGAGGACCCAGCACTGCCCCGGCCCCCTGAAGATAATCAGCAGTC CTGCTCAGCATATCAATCCAAGCCACTCTAGACAGAGATGCCGG TGCCAGTTTTCTATTTTAACTGGTGTGAACGAAGGAAAAGCAC AGCATTAGAAGTCCAAGCAGGGATAAAAGCAGTCTGGGCTTTTAC ATGACAGCATCTGGGGCTGCGGCAGAGGGTCCGGTCCGAAGCGC TGCCTTATCAGCGTCCCCAGCCCTGGGAGGTGACAGCTGGCTGGC TTGTGTGAGCCCCCTCGGGCACTCACGTATCTCCGTCCGACGGGTT TAAATAGCAAACTCTGAGGCCACACAATAGCTTGGGCTTATAT GGGCTCCTGTGGGGGAAGGGGGAGCACGGAGGGGGCGGGGGCC GCTGCTGCCAAAATAGCAGCTCACAAGTGTGCAATTCCTCTCTGG GCGCCGGGCACATTCTGCTGGCTCTGCCCCCCCCGGGGTGGGC GCCGGGGGGACCTTAAAGCCTCTGCCCCCAAGGAGCCCTTCCCA GACAGCCGCCGGCACCACCGCTCCGTGGGACGATCCCCGAAGCT CTAGAGCTTTATTGCGGTAGTTTATCACAGTTAAATTGTCTAACGCA GTCAGTGCTTCTGACACAACAGTCTCGAACTTAAGCTGCAGAAGT TGGTCGTGAGGCACTGGGCAGGTAAGTATCAAGGTTACAAGACAG GTTTAAGGAGACCAATAGAAACTGGGCTGTGCGAGACAGAGAAGA CTCTTGCGTTTCTGATAGGCACCTATTGGTCTTACTGACATCCACT TTGCCTTTCTCTCCACAGGTGTCCACTCCAGTTCAATTACAGCTC TTAAGGCTAGAGTACTTAATACGACTCACTATAGGCTAGCCGCCACCAT GGCCGAGAAGGAATCTACCAGCCCCACCTGATGGTGCCTATTCT GCTGCTGGTGGGCTGGATCGTGGCTGCATCATCGTGATCTACAT CGTGTTCTTCTGACGGCCGCGCGATCCAGACATGATAAGATACAT
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	TGATGAGTTTGGACAAACCACAACCTAGAATGCAGTGAAAAAAATG CTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTAA TAAGCTGCAATAAACCAAGTGAATTCCCGATTAGGATCTTCTAGAGCAT GGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAACTACAAGGAACC CCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCT CACTGAGGCCGGGCGACCAAAGTCTGCCCCGACGCCCGGGCTTTG CCCCGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 57)
pH269 distinct sequence elements are indicated in bold, starting with ITR, hcTnTp, DWORF (which is also underlined), WPRE, poly A (hGHpA), SV40pA, optimized DWORF (which is also underlined), ccTnTp, ITR	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCCGG GCGTCGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACCTCCATCACTAGGGGTTTCCTTGT AGTTAATGATTAAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA GATCGGAATTCGCCCTTAAGGTTCATGGAGAAGACCCACCTTGAGAT GTCTTCACTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCT CAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAG CATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGCCTTCC AAGATTCTGGTGTCTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT CTGCCCCCAACCTGTCTCCAGCTGGCCCTCCAGGCCCTGGGTT GCTGGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTT ATGTTGCATGACTGTTCCCTGCATATCTGCTCTGGTTTTAAATAGC TTATCTGAGCAGCTGGAGGACCACATGGGCTTATATGGCGTGGGG TACATGTTCCCTGTAGCCTTGTCCCTGGCACCTGCCAAAATAGCAG CCAACACCCCCACCCCCACCGCCATCCCCCTGCCCCACCCCTCC CCTGTGCGACATTCTCCCTCCGCGAGGGCTGGCTCACCAGGCCCC AGCCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCACCCA GTCCCCGCTGAGACTGAGCAGACGCCCTCCATAACTGGTAAGTACC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGTCTG ACAGACTAACAGACTGTTCTTTTCTGGGTCTTTCTGAGGCCCTG TACGGAAGTGTTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCG CGGCCGATCCAATCGATACAGATCTAGCGGCCGCCGCCACCATGG CTGAGAAAGAGTCAACATCACCAACCTCATGGTTCCCATTTCTCT CCTGGTTGGATGGATTGTAGGCTGCATCATCGTTATTTACATTGTCT TTCTTCTA~~AAAGCTTTGGATCCAATCAACCTCTGGATTACAAAATTTG~~ TGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTA TGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCC GTATGGCTTTTCAATTTCTCCCTCTGTATAAATCCTGGTTGCTGTC TCTTTATGAGGAGTTGTGGCCGTTGTGAGGCAACGTTGGCGTGGT GTGCACTGTGTTTGTCTGACGCAACCCCCACTGGTTGGGGCTTGC CACCACCTGTGAGCTCCTTTCCGGGACTTTTCGCTTTCCCCCTCCCT ATTGCCACGGCGGAACCTCATCGCCGCTGCTTGGCCGCTGCTGG ACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTTGGTGTGTCG GGGAAATCATCGTCTTTCTTGGCTGCTCGCTGTGTTGCCACCT GGATTCTGCGCGGGACGTCTTCTGCTACGTCCCTTCGCGCCCTCA ATCCAGCGGACCTTCTTCCCGCGGCTGCTGCCGGCTCTGCGGC CTCTTCCGCGTCTTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGC CAGCCATCTGTTGTTGGCCCTCCCCCGTGCTTCTTACCCCTGG AAGGTGCCACTCCCCTGCTCTTCTTAATAAAATGAGGAAATTGC ATCGCATTGTCTGAGTAGGTGTATTCTATTCTGGGGGGTGGGGT GGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGC ATGCTGGGGACTCGAGTTAAGGGCAGCCAGAAGTCAGATGCTCAAGGGG CTTCATGATGTCCCATAAATTTTGGCAGAGGGAAGGATCGGATCCTCAG GCGTAGTTACCCCGTCTCTGAGGCCGCCGGGTCGACTAAAAAACCTCC CACACCTCCCCCTGAACCTGAAACATAAAATGAATGCAATTGTTGTTAA CTTGTATTATGCAGCTTATAATGGTTACAAATAAAGCAATAGCATC ACAAATTTACAAATAAAGCATTTTTTTCACTGCATCTAGTTGTG GTTTGTCCAACTCATCAATGTATCTTATCATGTCTGGATCCGCGC GGCCGTCAGAAGAACACGATGTAGATCACGATGATGCAGCCGACG ATCCAGCCCACCAGCAGCAGAATAGGCACCATCAGGTGGGGGCTG GTAGATTCTTCTCGGCCATGGTGGCGGCTAGCCTATAGTGAGTCGTA TTAAGTACTCTAGCCTTAAAGAGCTGTAATTGAACTGGGAGTGGACA CCTGTGGAGAGAAAGGCAAAGTGGATGTCAGTAAGACCAATAGGT

	GCCTATCAGAAACGCAAGAGTCTTCTCTGTCTCGACAAGCCCACT TTCTATTGGTCTCCCTTAAACCTGTCTTGTAACCTTGATACTTACCT GCCCAGTGCCTCAGGACCAACTTCTGCAGCTTAAAGTTTCGAGACTG TTGTGTCAGAAGCACTGACTGCGTTAGCAATTTAACTGTGATAAAC TACCGCAATAAAGCTCTAGAGCTTCGGGGATCGTCCCACGGAGCG GTGGGTGCCGGCGGCTGTCTGGGAAGGGCTCCTTGGGGGGCAGA GGCTTTAAGGTCCCCCGGGCGCCACCCCGGGGCGGGCAGAGCC AGCAGGAATGTGCCCCGGCGCCAGAGAGGAATGCAACACTTGTGA GCTGCTATTTTGGCAGCAGCGCCCCGGCCCCCTCCGTGCTCCCC CTTCCCCACAGGAGCCCATATAAGCCCAAGCTATTGTGTGGCCT CAGAGTTTGTCTATTTTAAACCGTTCGGACGGAGATACGTGAGTG CCCGAGGGGCTGACACAAGCCAGCCAGCTGTCACCTCCAGGGCT GGGGACGCTGATAAGGCAGCGCTTCGGACCCGACCTCTGCCGCA GCCCCAGATGCTGTCTATGTGAAAGCCAGACTGCTTTTATCCCGAA TTCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGCATGGC GGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACT CCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGCGACCAAAG GTCGCCCCGACGCCGGGCTTTGCCCGGGCGGCTCAGTGAGCGA GCGAGCGCGCAG (SEQ ID NO: 58)
pHZ72 distinct sequence elements are indicated in bold, starting with ITR, hcTnTp, DWORF (which is also underlined), WPRE, poly A (hGHPA), ccTnTp, optimized DWORF (which is also underlined), SV40pA, ITR	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCCGG GCGTCGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTCTGT AGTTAATGATTAAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA GATCGGAATTCGCCCTTAAAGGTCATGGAGAAGACCCACCTTGCAGAT GTCTCACTGCGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCT CAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCAAG CATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGCCTTCC AAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT CTGCCCCCAACCTGCTCCCAGCTGGCCCTCCAGGCCCTGGGTT GCTGGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTT ATGTTGCATGACTGTTCCCTGCATATCTGCTCTGGTTTTAAATAGC TTATCTGAGCAGCTGGAGGACCACATGGGCTATATGGCGTGGGG TACATGTTCCCTGTAGCCTTGTCCCTGGCACCTGCCAAAATAGCAG CCAACACCCCCACCCCCACCGCCATCCCCCTGCCCAACCCGTCC CCTGTGCGACATTCTCCCTCCGCAGGGCTGGCTCACCAGGCCCC AGCCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCACC GTCCCCGCTGAGACTGAGCAGACGCCCTCCATAAGTAACTAGC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTG ACAGACTAACAGACTGTTCTTTCTGGGTCTTTTCTGCAGGCCTG TACGGAAGTGTTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCG CGGCCGATCCAATCGATACAGATCTAGCGGCCGCCGCCACCATGG CTGAGAAAAGAGTCAACATCACCACACCTCATGGTTCCCATCTTCT CCTGGTTGGATGGATTGTAGGCTGCATCATCGTTATTTACATTGTC TTCTTCTAAAGCTTTGGATCCAATCAACCTCTGGATTACAAAATTG TGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTA TGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCC GTATGGCTTTTCAATTTCTCCTCCTGTATAAATCCTGGTTGCTGTC TCTTTATGAGGAGTTGTGGCCCGTTGTGAGGCAACGTGGCGTGGT GTGCACTGTGTTTGTGACGCAACCCCCCACTGGTTGGGGCATTC CACCACCTGTGAGCTCCTTTCCGGGACTTTTCGCTTTCCCCCTCCCT ATTGCCACGGCGGAACCTCATCGCCGCTGCTTGGCCGCTGCTGG ACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTGTGCG GGGAAATCATCGTCTTTTCTTGGCTGCTCGCCTGTGTTGCCACCT GGATTCTGCGCGGGACGTCTTCTGCTACGTCCCTTCGGCCCTCA ATCCAGCGGACCTTCTTCCCGCGGCTGCTGCCGGCTCTGCGGC CTCTTCCGCGTCTTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGC CAGCCATCTGTTGTTTGGCCCTCCCCCGTGCCTTCTTGAACCTGG AAGGTGCCACTCCCACTGTCTTTTCTAATAAAATGAGGAAATTGC ATCGCATTGTCTGAGTAGGTGTCTTCTATTCTGGGGGGTGGGGT GGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGC

	ATGCTGGGGACTCGAGTTAAGGGCAGCCAGAAAGTCAGATGCTCAAGGGG <i>CTTCATGATGTCCCATTAATTTTGGCAGAGGGAAAAAGATCGGATCCTCAG</i> <i>GCGTAGTTCACCCCGTCTCGAGGCCGCCGGGTCGACTAAAAACCTCC</i> <i>CACACCTCCCCCTGAACCTGAAACATAAAATGAATGCAATTGTTGTTAG</i> GGATAAAAGCAGTCTGGGCTTTCACATGACAGCATCTGGGGCTGC GGCAGAGGGTCGGGTCCGAAGCGCTGCCTTATCAGCGTCCCCAGC CCTGGGAGGTGACAGCTGGCTGGCTTGTGTCAGCCCCTCGGGCAC TCACGTATCTCCGTCCGACGGGTTTAAATAGCAAAACTCTGAGG CCACACAATAGCTTGGGCTTATATGGGCTCCTGTGGGGGAAGGGG GAGCACGGAGGGGGCCGGGGCCGCTGCTGCCAAAATAGCAGCTC ACAAGTGTTCATTCTCTCTGGGCGCCGGGCACATTCTGTCTGG CTCTGCCCGCCCCGGGGTGGGCGCCGGGGGGACCTTAAAGCCTC TGCCCCCAAGGAGCCCTTCCCAGACAGCCGCCGGCACCCACCGC TCCGTGGGACGATCCCCGAAGCTCTAGAGCTTTATTGCGGTAGTT TATCACAGTTAAATTGCTAACGCAGTCAGTGCTTCTGACACAACAG TCTCGAACTTAAGCTGCAGAAGTTGGTCGTGAGGCATGGGCAGG TAAGTATCAAGGTTACAAGACAGGTTTAAGGAGACCAATAGAAAC TGGGCTTGTCGAGACAGAGAAGACTCTTGCGTTTCTGATAGGCAC CTATTGGTCTTACTGACATCCACTTTGCCTTTCTCTCCACAGGTGT CCACTCCCAGTTCAATTACAGCTCTTAAGGCTAGAGTACTTAATACG <i>ACTCACTATAGGCTAGCCGCCACC</i>ATGGCCGAGAAGGAATCTACCAGC CCCCACCTGATGGTGCCCTATTCTGCTGCTGGTGGCTGGATCGTC GGCTGCATCATCGTGATCTACATCGTGTCTCTGACGGCCGCGCG GATCCAGACATGATAAGATACATTGATGAGTTTGGACAAACCACA ACTAGAATGCAGTGAAAAAAATGCTTTATTTGTGAAATTTGTGATG CTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAAACAAGTGAAT <i>TCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGCATGGCG</i> <i>GGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTC</i> CCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGG TCGCCCCAGCCCCGGGCTTTGCCCGGGCGGCCCTCAGTGAGCGAG CGAGCGCGCAG (SEQ ID NO: 59)
pHZ75 distinct sequence elements are indicated in bold, starting with ITR, polyA (hGHpA), WPRE, DWORF(which is also underlined), hcTnTp/ ccTnTp combo, optimized DWORF (which is also underlined), SV40pA, ITR	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCCGG GCGTCGGGCGACCTTTGGTCGCCCGGCCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAACCTCCATCACTAGGGGTTCTTGT <i>AGTTAATGATTAAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAA</i> <i>GATCGGAATTC</i>TCCCCAGCATGCCTGCTATTGTCTTCCCAATCCTCC CCCTTGCTGTCTGCCCCACCCACCCCAAGGAGCAATAGACAC CTACTCAGACAATGCGATGCAATTTCTCATTTTATTAGGAAAGGA CAGTGGGAGTGGCACCCTCCAGGGTCAAGGAAGGCACGGGGGAG GGGCAAAACAAGATGGCTGGCAACTAGAAGGCACAGTCGAGGCA <i>GATCTCGAAGACGCGGAAGAGGCCGAGAGCCGGCAGCAGGCCCGC</i> GGGAAGGAAGTCCCGCTGGATTGAGGGCCGAAGGGACGTAGCAG AAGGACGTCCCGCGCAGAATCCAGGTGGCAACACAGGCGAGCAG CCAAGGAAAGGACGATGATTTCCCCGACAACACCACGGAATTGTC AGTGCCCAACAGCCGAGCCCCTGTCCAGCAGCGGGCAAGGCAGG CGGCGATGAGTTCCGCGTGGCAATAGGGAGGGGGAAAGCGAAA GTCCCGAAAGGAGCTGACAGGTGGTGGCAATGCCCAACCACT GGGGGTTGCGTCAGCAAAACACAGTGCACACCACGCCACGTTGCT GACAACGGGGCCACAACCTCCTCATAAAGAGACAGCAACCAGGATTT ATACAAGGAGGAGAAAAATGAAAGCCATACGGGAAGCAATAGCATG ATACAAAGGCATTAAAGCAGCGTATCCACATAGCGTAAAGGAGC AACATAGTTAAGAATACCAGTCAATCTTTCACAAATTTTGTAATCC AGAGGTTGATTGGATCCAAAGCTTTAGAGAAGACAATGTAAATAA CGATGATGCAGCCTACAATCCATCCAACCAGGAGAAAGAAATGGGAA CCATGAGGTGTGGTGATGTTGACTCTTCTCAGCCATGGTGGCGG <i>GCGGCCGCTAGATCTGTATCGATTGGATCGGCCGCGGGTACAATTC</i> CGCAGCTTTTAGAGCAGAAGTAACACTTCCGTACAGGCCTGCAGA AAAGACCCAGGAAAGGAACAGTCTGTAGTCTGTACGATGCATA AGAGCCAAAGGGGTGTGCCATAGAGTCTATAGGCGGTACTTACC AGTTATGGAGGCGTCTGCTCAGTCTCAGCGGGGACTGGGTGAGGC

	AGAGGATGGAGAGGGCTTTAAGCAGGCATGTGGGCTGGGGCCTG GTGAGCCAGCCCTGCGGAGGGAGGAATGTGCGACAGGGGACGGG TGGGGCAGGGGATGGCGGTGGGGGTGGGGGGTGTGGCTGCTA TTTTGGCAGGTGCCAGGGACAAGGCTACAGGAACATGTACCCAC GCCATATAAGCCCATGTGGTCCTCCAGCTGCTCAGATAAGCTATTT AAAACCAGAGCAGATATGCAGGGAACAGTCAATGCAACATAAACCA GCTGTCCCTCTTGAGAATCCTGATAAAGCAGAGGCCAGCAACCCA GGCCTGGGAGGGCCAGCTGGGAGCAGGGTTGGGGGGCAGAAGGC AACCTCCAAGACACTCCATAAGTCTCAGCACCAGAATCTTGGAAG GCAGAGGGCAAGAGTTATGTGCTGCTCCACTTGAAGTATGCTGG GGGTAAAGACATCTTCCAGGCTACTGGCTCCTAATGGACTGAGCA GCCTTAGGCAGGTTGCCGGCTCTGCCAGCCCCAGTGAGGACATCT GCAAGGTGGGTCTTCTCCATGACCTCGAGTTAAGGGCAGCCAGAAGTC AGATGCTCAAGGGGCTTCATGATGTCCCATATAATTTTGGCAGAGGGAAAA AGATCGGATCCTCAGGCGTAGTTCACCCCGTCCCTCAGAGGCCCGGGGTC GACTAAAAAACCTCCACACCTCCCCCTGAACCTGAAACATAAAATGAATGC AATTGTTGTTGTTAGGGATAAAAAGCAGTCTGGGCTTTCACATGACAG CATCTGGGGCTGCGGCAGAGGGTCCGGTCCGAAGCGCTGCTTAT CAGCGTCCCCAGCCCTGGGAGGTGACAGCTGGCTGGCTTGTGTCA GCCCCCTCGGGCACTCACGTATCTCCGTCCGACGGGTTTAAAATAG CAAACTCTGAGGCCACACAATAGCTTGGGCTTATATGGGCTCTCT GTGGGGGAAGGGGGAGCACGGAGGGGGCGGGGGCGCTGCTGC CAAAATAGCAGCTCACAAGTGTTCATTCTCTCTGGGCGCCGGG CACATTCTGCTGGCTCTGCCCCCCCCGGGGTGGGCGCCGGGGG GACCTTAAAGCCTCTGCCCCCAAGGAGCCCTTCCAGACAGCCG CCGGCACCCACCGCTCCGTGGGACGATCCCCGAAGCTCTAGAGCTTTA TTGCGGTAGTTTATCAGAGTTAAATTGCTAACGCAGTCAGTCTGCTGACAC AACAGTCTCGAACTTAAGCTGCAGAAGTTGGTCTGAGGCACTGGGCAGGT AAGTATCAAGGTTACAAGACAGGTTAAGGAGACCAATAGAACTGGGCTT GTGAGACAGAGAAGACTCTTGCGTTTCTGATAGGCACCTATTGGTCTTACT GACATCCACTTTGCCCTTCTCTCCACAGGTGTCCACTCCAGTTCAATTACA GCTCTTAAGGCTAGAGTACTTAATACGACTCACTATAGGCTAGCCGCCACC <u>ATGGCCGAGAAGGAATCTACCAGCCCCACCTGATGGTGCCTATT</u> <u>CTGCTGCTGGTGGGCTGGATCGTCCGCTGCATCATCGTGATCTAC</u> <u>ATCGTGTCTTCTGACGGCCGCGCGGATCCAGACATGATAAGATAC</u> ATTGATGAGTTTGGACAAACCACAATAAGATGCAAGTGAACAAAAA TGCTTTTATTGTGAAATTTGTGATGCTATTGCTTTATTGTAAACCA TTATAAGCTGCAATAAACAAGTGAATTCCCGATTAGGATCTTCCTAG AGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTC GCTCGCTCACTGAGCCGGGCGACCAAAGGTGCCCCGACGCCCG GGCTTTGCCCCGGCGGCTCAGTGAGCGAGCGAGCGCGAG (SEQ ID NO: 60)
pHZ51 (human DWORF version of pHZ15)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAAGCCCGGGCGT CGGGCGACCTTTGGTGCCTCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACCTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCCGCCCTTAAGAACTGGCCTGCCCCGAGACCAACGTCGCGAACGT AGTTAAGTGTAGAGGTAGGATTTGAAGCCTGTCGATCATTCTGATTC TCCTTTTCTCTACGTCTGCTTCTGTCAATGGGCATCCTCACTGTCAAA TGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGCAAGCCCTCTCCCC AGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGGCC CTGAAGATAATCAGCAGTCTGCTCAGCATATCAATCCAAGCCCACTC TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTAACTGGTGTGAAC GAAGGAAAAGCACAGCATTAGAAGTCCAAGCAGTCATGGAGAAGACC CACCTTGACAGATGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCT AAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTAC CCCCAGCATCAGTTCAAGTGAGCAGCACATAACTCTTGCCCTCTGCC TTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT

	CTGCCCCCAACCCTGCTCCCAGCTGGCCCTCCCAGGCCTGGGTTGCT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCTGCATATCTGCTCTGGTTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCTG TAGCCTTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCCACC CCCACCGCATCCCCCTGCCCAACCGTCCCCTGTCGCACATTCTCCC TCCGCAGGGCTGGCTCACCAGGCCCCAGCCACATGCCTGCTTAAAGC CCTCTCCATCCTCTGCCTCACCAGTCCCCGCTGAGACTGAGCAGACG CCTCCAGCGCCGCCGCCACCATGGCTGAAAAAGCGGGGTCTACATT TTCACACCTTCTGGTTCTATTCTTCTCCTGATTGGCTGGATTGTGGGC TGCATCATAATGATTTATGTTGTCTTCTCTTAGAAGCTTTGGATCCAAT CAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAAC TATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGT ATCATGCTATTGCTTCCCGTATGGCTTTTCATTTTCTCCTCCTTGATAAA TCCTGGTTGCTGTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAAC GTGGCGTGGTGTGCACTGTGTTTGTGACGCAACCCCCACTGGTTGGG GCATTGCCACCACTGTGAGCTCCTTTCCGGGACTTTCCGCTTTCCCCCT CCCTATTGCCACGGCGGAATCATCGCCGCTGCCTTGCCCGCTGCTG GACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTGTGCGGG GAAATCATCGTCCTTTCCCTGGCTGCTCGCCTGTGTGCCACCTGGATT CTGCGCGGGACGTCTTCTGCTACGTCCCTTCCGGCCCTCAATCCAGCG GACCTTCTTCCCGCGGCCTGTGCGGCTCTGCGGCCTTCCCGCTC TTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTT TGCCCCCCCCCGTGCTTCTTGACCCTGGAAGGTGCCACTCCCCTG TCCTTCTCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGT GTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAG GATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCG AATTCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGC ATGGCGGGTTAATCATTAACACAAGGAACCCCTAGTGATGGAGTTGG CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAA AGGTGCGCCGACGCCCCGGCTTTGCCCGGGCGGCTCAGTGAGCGAGC GAGCGCGCAG (SEQ ID NO: 61)
pHZ100 (human DWORF version of pHZ72)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGCAAAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTGCCCCTTAAGGTCATGGAGAAGACCCACCTTGCAGATTGCGCTCA CTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATTA GGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTTCAAGT GGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCTGCTC CCAGCTGGCCCTCCAGGCCTGGGTTGCTGGCCTTATTCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAACACCCCCACCCCCACCGCATCCCCCTGCC CACCCGTCCCCTGTCGCACATTCTCCCTCCGCAGGGCTGGCTACCA GGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAACTGGTAAGTACC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTGACA GACTAACAGACTGTTCTTTCTGGGTCTTTTCTGCAGGCCTGTACGGA AGTGTTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCGCGGCCGATC CAATCGATACAGATCTAGCGGCCGCCGCCACCATGGCTGAAAAAGC GGGGTCTACATTTTACACCTTCTGGTTCTTCTTCTCTCTGATTGGCT GGATTGTGGGCTGCATCATAATGATTTATGTTGTCTTCTTAGAAGCT TTGGATCCAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTG GTATTCTTAACATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTT AATGCCTTGTATCATGCTATTGCTTCCCGTATGGCTTTTCAATTTCTCCT CCTTGATAAAATCCTGGTTGCTGTCTTTATGAGGAGTTGTGGCCCGT TGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTGCTGACGCAACCCC

	CACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTC GCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCTGCCTTG CCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATCCGTGG TGTTGTCGGGGAAATCATCGTCCTTTCCCTGGCTGCTCGCCTGTGTGC CACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTC AATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCT CTTCCGCGTCTTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCC ATCTGTTGTTTGCCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCC ACTCCCACTGTCCTTTCTAATAAAATGAGGAAATTGCATCGCATTGTC TGAGTAGGTGTCAATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCA AGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGT TAAGGGCAGCCAGAAGTCAGATGCTCAAGGGGCTTCATGATGTCCCCA TAATTTTGGCAGAGGGAAAAAGATCGGATCCTCAGGCGTAGTTCACC CCGTCTCGAGGCCCGCGGGTCTGACTAAAAAACCTCCCACACCTCCC CCTGAACCTGAAACATAAAATGAATGCAATTGTTGTTGTTAGGGATAA AAGCAGTCTGGGCTTTCACATGACAGCATCTGGGGCTGCGGCAGAGG GTCGGGTCCGAAGCGCTGCCTTATCAGCGTCCCCAGGCTGAGGAGTG ACAGCTGGCTGGCTTGTGTCAGCCCCCTCGGGCACTACGTATCTCCGT CCGACGGGTTAAAAATAGCAAACTCTGAGGCCACACAATAGCTTGG GCTTATATGGGCTCCTGTGGGGGAAGGGGGAGCACGGAGGGGGCCGG GGCCGCTGCTGCCAAAATAGCAGCTCACAAGTGTTCATTCTCTCTG GGCGCCGGGCACATTCTGCTGGCTCTGCCCGCCCCGGGGTGGGCGCC GGGGGGACCTTAAAGCCTCTGCCCCCAAGGAGCCCTTCCAGACAGC CGCCGGCACCCACCGCTCCGTGGGACGATCCCCGAAGCTCTAGAGCTT TATTGCGGTAGTTTATCACAGTTAAATTGCTAACGCAGTCAGTGCTTCT GACACAACAGTCTCGAACTTAAGCTGCAGAAGTTGGTCGTGAGGCACT GGGCAGGTAAGTATCAAGGTTACAAGACAGGTTTAAAGGAGACCAATA GAAACTGGGCTTGTGAGACAGAGAAGACTCTTGCGTTTCTGATAGGC ACCTATTGGTCTTACTGACATCCACTTTGCCTTCTCTCCACAGGTGTC CACTCCAGTTCAATTACAGCTCTTAAGGCTAGAGTACTTAATACGAC TCACTATAGGCTAGCCGCCACCATGGCCGAGAAGGCCGGATCTACCTT CAGCCACCTGCTGGTCCCTATTCTGCTGCTGATCGGCTGGATCGTGGG CTGCATCATCATGATCTACGTGGTGTTCAGCTGACGGCCGCGCGGATC CAGACATGATAAGATACATTGATGAGTTTGGACAAACCACAACCTAGA ATGCAGTGAAAAAAATGCTTTATTTGTGAAAATTTGTGATGCTATTGCTT TATTTGTAACCATTATAAGCTGCAATAAACAAGTGAATCCCGATTAG GATCTTCCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAAT CATTAACACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCT GCGCGCTCGTCTGCTCACTGAGGCCGGGCGACCAAGGTTCGCCCGAC GCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 62)
pHZ101 (human DWORF version of pHZ75)	CTGCGCGCTCGCTCGTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGCCTCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCTCCCAGCATGCCTGCTATTGTCTTCCCAATCCTCCCCCTTGCT GTCCTGCCCCACCCCAACCCCAAGAAATAGAAATGACACCTACTCAGACA ATGCGATGCAATTTCTCATTTTATTAGGAAAGGACAGTGGGAGTGGC ACCTTCCAGGGTCAAGGAAGGCACGGGGGAGGGGCAAACAACAGATG GCTGGCAACTAGAAGGCACAGTCGAGGCAGATCTCGAAGACGCGGAA GAGGCCGCAGAGCCGGCAGCAGGCCGCGGGAAGGAAGTCCGCTGGA TTGAGGGCCGAAGGGACGTAGCAGAAGGACGTCCCGCGCAGAATCCA GGTGGCAACACAGGCGAGCAGCCAAGGAAAGGACGATGATTTCCCCG ACAACACCACGGAATTGTCAGTGCCCAACAGCCGAGCCCTGTCCAGC AGCGGGCAAGGCAGGCGGCGATGAGTTCCGCCGTGGCAATAGGGAGG GGGAAAGCGAAAAGTCCCGGAAAGGAGCTGACAGTGGTGGCAATGCC CCAACCAGTGGGGGTTGCGTCAGCAAAACACAGTGCACACCACGCCAC GTTGCCTGACAACGGGCCACAACCTCCTCATAAAGAGACAGCAACCAG GATTTATACAAGGAGGAGAAAATGAAAGCCATACGGGAAGCAATAGC ATGATACAAAGGCATTAAAGCAGCGTATCCACATAGCGTAAAGGAG

	CAACATAGTTAAGAATACCAGTCAATCTTTCACAAATTTTGTAAATCCA GAGGTTGATTGGATCCAAAGCTTCTAAGAGAAGACAACATAAATCATT ATGATGCAGCCCAACAATCCAGCCAATCAGGAGAAGAATAGGAACCG AAGGTGTGAAAATGTAGACCCCGCTTTTTCAGCCATGGTGGCGGGCGG CCGCTAGATCTGTATCGATTGGATCGGCCGCGGGTACAATTCGCGCAGC TTTTAGAGCAGAAAGTAACTTCCGTACAGGCCTGCAGAAAAAGACCCA GGAAAGGAACAGTCTGTAGTCTGTCAGCATGCATAAGAGCCAAAGG GGTGTGCCTATAGAGTCTATAGGCGGTACTTACCAGTTATGGAGGCGT CTGCTCAGTCTCAGCGGGGACTGGGTGAGGCAGAGGATGGAGAGGGC TTTAAGCAGGCATGTGGGCTGGGGCCTGGTGAGCCAGCCCTGCGGAG GGAGGAATGTGCGACAGGGGACGGGTGGGGCAGGGGGATGGCGGTG GGGGTGGGGGTGTTGGCTGCTATTTTGGCAGGTGCCAGGGACAAGG CTACAGGAACATGTACCCACGCCATATAAGCCCATGTGTCTCCAG CTGCTCAGATAAGCTATTTAAAACCAGAGCAGATATGCAGGGAACAG TCATGCAACATAAACAGCTGTCCCTCTTGAGAATCCTGATAAAGCAG AGGCCAGCAACCCAGGCCTGGGAGGGCCAGCTGGGAGCAGGGTGGG GGGCAGAAGGCAACCTCCAAGACACTCCATAAGTCTCAGCACCAGAA TCTTGGAAGGCAGAGGGCAAGAGTTATGTGCTGCTCCACTTGAACGA TGCTGGGGGTAAAGACATCTTCCAGGCTACTGGCTCCTAATGGACTGA GCAGCCTTAGGCAGGTTGCCGGCTCTGCCAGCCCCAGTGAGGACATCT GCAAGGTGGGTCTTCTCCATGACCTCGAGTTAAGGGCAGCCAGAAGTC AGATGCTCAAGGGGCTCATGATGTCCCAATAATTTTGGCAGAGGGA AAAAGATCGGATCCTCAGGCGTAGTTCACCCCGTCTCGAGGCCGCC GGGTGCACTAAAAACCTCCACACCTCCCCCTGAACCTGAAACATAA AATGAATGCAATTGTTGTTGTTAGGGATAAAAGCAGTCTGGGCTTCA CATGACAGCATCTGGGGCTGCGGCAGAGGGTGGGTCCGAAGCGCTG CCTTATCAGCGTCCCAGCCCTGGGAGGTGACAGCTGGCTGGCTTGTG TCAGCCCCCTCGGGCACTCACGTATCTCCGTCCGACGGGTTAAAAATAG CAAACTCTGAGGCCACACAATAGCTTGGGCTTATATGGGCTCCTGTG GGGGAAGGGGAGCAGGAGGGGGCCGGGGCCGCTGCTGCCAAAT AGCAGCTCACAAGTGTTGCATTCTCTCTGGGCGCCGGGCACATTCT GCTGGCTCTGCCCGCCCCGGGGTGGGCGCCGGGGGACCTTAAAGCCT CTGCCCCCAAGGAGCCCTTCCCAGACAGCCGCCGGCACCCACCGCTC CGTGGGACGATCCCCGAAGCTCTAGAGCTTTATTGCGGTAGTTTATCA CAGTTAAATTGCTAACGCAGTCAGTGCTTCTGACACAACAGTCTCGAA CTTAAGCTGCAGAAAGTTGGTCTGAGGCACTGGGCAGGTAAAGTATCAA GGTTACAAGACAGGTTTAAAGGAGACCAATAGAACTGGGCTTGTGCA GACAGAGAAGACTCTTGCGTTTCTGATAGGCACCTATTGGTCTTACTG ACATCCACTTTGCCTTTCTCTCCACAGGTGTCCACTCCAGTTCAATTA CAGCTCTTAAGGCTAGAGTACTTAATACGACTCACTATAGGCTAGCCG CCACCATGGCCGAGAAGGCCGGATCTACCTTCAGCCACCTGCTGGTCC CTATTCTGCTGCTGATCGGCTGGATCGTGGGCTGCATCATGATCTA CGTGGTGTTCAGCTGACGGCCGCGCGGATCCAGACATGATAAGATACA TTGATGAGTTTGACAAACCACAACCTAGAATGCAGTGAAAAAATGC TTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATATAA GCTGCAATAAACAAAGTGAATTCCCGATTAGGATCTTCTAGAGCATGG CTACGTAGATAAGTAGCATGGCGGGTTAATCATTAACATAAGGAACC CCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGTCACT GAGGCCGGGCGACCAAGGTGCGCCGACGCGCGGGCTTTGCCCCGGC GGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 63)
pHZ52 (human DWORF version of pHZ16)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAAGCCGGGCGT CGGGCGACCTTTGGTGCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGAACTGGCCTGCCCCGAGACCAACGTGCGGAACGT AGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGTGATCATTCTGATTC TCCTTTTCTCTACGTCTGCTTCTGTCAATGGGCATCCTCACTGTCAAA TGCAGATGGTACAGCAGGCTTGGTCTCAGCCAGGAGGCTCTCCCC AGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGGCC

	CTGAAGATAATCAGCAGTCCTGCTCAGCATATCAATCCAAGCCCACTC TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTAACTGGTGTGAAC GAAGGAAAAGCACAGCATTAGAAGTCCAAGCACCTTCAGATTAAAAA TAACTAAGGTAAGGGCCATGTGGGTAGGGGAGGTGGTGTGAGACGGT CCTGTCTCTCTCTATCTGCCCATCGGCCCTTTGGGGAGGAGGAATGTG CCCAAGGACTAAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGC AGACCTTTCATGGGCAAACCTCAGGGCTGCTGTCGTATGGAGAAGAC CCACCTTGACAGATGTCTCACTGGGGCTGGCAGAGCCCGGCAACCTGCC TAAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTA CCCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGC CTTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGAGGTTGCT TCTGCCCCCAACCTGTCTCCAGCTGGCCCTCCAGGCCCTGGGTGTGCT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCCTGCATATCTGCTCTGGTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCCCTG TAGCCTTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCCACC CCCACCGCATCCCCCTGCCCAACCGTCCCCTGTGCGACATGCTTCCC TCCGCAGGGCTGGCTCACCAGGCCCGAGCCACATGCTGCTTAAAGC CCTCTCCATCCTCTGCCTCACCAGTCCCCGCTGAGACTGAGCAGACG CCTCCAGCGCGCGCCCGCCACCATGGCTGAAAAAGCGGGGTCTACATT TTCACACCTTCTGGTTCCTATTCTTCTCTGATTGGCTGGATTGTGGGC TGCATCATAATGATTTATGTTGTCTTCTCTTAGAAGCTTGGATCCAAAT CAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAAC TATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTAAATGCCTTTGT ATCATGCTATTGCTTCCCGTATGGCTTTCATTTCTCCTCCTTGTATAAA TCCTGGTTGCTGTCTCTTATGAGGAGTTGTGGCCCGTGTGACGGCAAC GTGGCGTGGTGGCACTGTGTTTGTGCTGACGCAACCCCACTGGTTGGG GCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCT CCCTATTGCCACGGCGGAACATCGCCGCTGCTTGGCCGCTGCTG GACAGGGGCTCGGCTGTGGGCACTGACAATCCGTGGTGTGTGCGGG GAAATCATCGTCTTTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATT CTGCGCGGGACGTCCTTCTGCTACGTCCTTCCGGCCCTCAATCCAGCG GACCTTCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTC TTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTT TGCCCCCTCCCCCGTGCCTTCTTGACCCTGGAAGGTGCCACTCCCCTG TCCTTCTCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGT GTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAG GATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCG AATTCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGC ATGGCGGGTTAATCATTAATACTACAAGGAACCCCTAGTGATGGAGTTGG CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGCCGGGCGACCAA AGGTGCGCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAG GAGCGCGCAG (SEQ ID NO: 64)
pHZ53 (human DWORF version of pHZ17)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGCCTCGCCGCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCCGCCCTTAAGCCTTCAGATTAAAAATACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCTCTATCTGC CCATCGGCCCTTTGGGGAGGAGGAATGTGCCAAGGACTAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTTCATGGGCAAAAC CTCAGGGCTGCTGTGCTCATGGAGAAGACCCACCTTGAGATGTCTCTC ACTGGGGCTGGCAGAGCCGCAACCTGCCTAAGGCTGCTCAGTCCATT AGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCGAGCATCAGTTCAAG TGGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGTGCT AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCTGCTC CCAGCTGGCCCTCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCTGGCACCTG

	CAAAAATAGCAGCCAAACACCCCCACCCCCACCGCCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCCCTCCGACGGGTGGCTCACCA GGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCAGCGGCCGCCGCCAC CATGGCTGAAAAAGCGGGGTCTACATTTTACACCTTCTGGTTCTATT CTTCTCCTGATTGGCTGGATTGTGGGTGCATCATAATGATTTATGTTG TCTTCTCTTAGAAGCTTTGGATCCAATCAACCTCTGGATTACAAAATTT GTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATG TGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATG GCTTTCATTTTCTCCTCCTTGTATAAAATCCTGGTTGCTGTCTCTTATGA GGAGTTGTGGCCCGTTGTGAGGCAACGTGGCGTGGTGTGCACTGTGTT TGCTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCT CCTTCCGGGACTTTTCGCTTTCCCTCCCTATTGCCACGGCGGAATC ATCGCCGCTGCCTTGGCCGCTGCTGGACAGGGGCTCGGCTGTTGGGC ACTGACAATTCCGTGGTGTGTGCGGGAAATCATCGTCTTCTCTTGGC TGCTCGCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTA CGTCCCTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGCGGCTGTG CCGGCTCTGCGGCTCTTCCGCTCTTCGAGATCTGCTCGACTGTGCC TTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCGTGCCCTCCTTG ACCCTGGAAGGTGCCACTCCCACTGTCTTCTCTAATAAAATGAGGAA ATTGCATCGCATTGTCTGAGTAGGTGTCTATTCTATTTCTGGGGGTGGG GTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGC ATGCTGGGGACTCGAGTTAAGGGGCAATTCCCGATTAGGATCTTCTTA GAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAACCTAC AAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGC TCGCTCACTGAGGCCGGGCGACCAAAGGTGCCCCGACGCCCGGGCTTT GCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 65)
pHZ54 (human DWORF version of pHZ18)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCGGGCGT CGGGCGACCTTTGGTGCCTCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTGCGCCCTTAAAGCCTTCAGATTAAAAATAACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCTCTATCTGC CCATCGGCCCTTTGGGGAGGAGGAATGTGCCAAGGACTAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTTCATGGGCAAAAC CTCAGGGCTGCTGTCAACTGGCCTGCCGAGACCAACGTCGGAACG TAGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGTGATCTTCTGATT CTCCTTTTCTCTACGTCTGCTTCTGTCAATGGGCATCCTCACTGTCAA ATGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGCAGGCCTCTCCC CAGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGGCC CTGAAGATAATCAGCAGTCTGCTCAGCATATCAATCCAAGCCCACTC TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTAACTGGTGTGAAC GAAGGAAAAGCACAGCATTAGAAGTCCAAGCAGTCATGGAGAAGACC CACCTTGACAGATGTCCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCT AAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGCTTTTAC CCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTTGGCCTCTGCC TTCCAAGATTCTGGTGCTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT CTGCCCCCAACCTGCTCCAGCTGGCCCTCCCAGGCCTGGGTGCT GGCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTCCCTGCATATCTGCTCTGGTTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCTG TAGCCTTGTCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCACC CCCACCGCAATCCCCCTGCCCAACCGTCCCCTGTGCGACATTCTCCC TCCGACAGGGCTGGCTACCCAGGCCCCAGCCACATGCCTGCTTAAAGC CCTCTCCATCCTCTGCCTCACCCAGTCCCCGCTGAGACTGAGCAGACG CCTCCAGCGGCCGCCGCCACCATGGCTGAAAAAGCGGGGTCTACATT TTCACACCTTCTGGTTCTATTCTTCTCTGATTGGCTGGATTGTGGGC TGCATCATAATGATTTATGTTGTCTTCTCTAGAAGCTTTGGATCCAAT CAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAAC

	TATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGT ATCATGCTATTGCTTCCCGTATGGCTTTTCATTTTCTCCTCCTTGTATAAA TCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTGAGGCAAC GTGGCGTGGTGTGCACTGTGTTTGTGACGCAACCCCCACTGGTTGGG GCATTGCCACCACCTGTCAGCTCCTTTCGGGACTTTCGCTTTCCCCCT CCCTATTGCCACGGCGGAACATCGCCGCTGCTTGGCCGCTGCTG GACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTGTGCGGG GAAATCATCGTCCTTTCCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATT CTGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCG GACCTTCCCTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTCCGCGTC TTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGT TGCCCCCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCCTG TCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGT GTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAG GATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGTTAAGGGCG AATTCGCGATTAGGATCTTCTAGAGCATGGCTACGTAGATAAGTAGC ATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGG CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCGGGCGACCAA AGGTGCGCCGACGCGCGGCTTTGCCCGGGCGGCTCAGTGAGCGAGC GAGCGCGCAG (SEQ ID NO: 66)
pHZ55 (human DWORF version of pHZ19)	CTGCGCGCTCGCTCGCTCACTGAGGCGCCCGGGCAAAGCCGGGCGT CGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCCTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGCCTTCAGATTAAAAATAACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCTCTATCTGC CCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACTAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTTCATGGGCAAAC CTCAGGGCTGCTGTCAACTGGCCTGCCGAGACCAAACGTGCGGAACG TAGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGTGATCATTCTGATT CTCCTTTTCTCTACGTCTGCTTCTGTCAATGGGCATCCTCACTGTCAA ATGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGCAGGCCTCTCCC CAGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGGCC CTGAAGATAATCAGCAGTCTGCTCAGCATATCAATCCAAGCCCACTC TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTAACTGGTGTGAAC GAAGGAAAAGCAGCAGCATTAGAAGTCCAAGCAGTCATGGAGAAGACC CACCTTGCAAGTGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGCCT AAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTAC CCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGCC TTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCCTT CTGCCCCCAACCTGTCTCCAGCTGGCCCTCCAGGCCTGGGTGTGT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCTGCATATCTGCTCTGGTTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCTGT TAGCCTTGTCCCTGGCACCTGCCAAAATAGCAGCCAAACCCCCCACC CCCACCGCCATCCCCCTGCCCAACCGTCCCCTGTGCGACATTCTCCC TCCGAGGGCTGGCTACCCAGGCCCCAGCCACATGCCTGCTTAAAGC CCTCTCCATCCTCTGCCTACCCAGTCCCCGCTGAGACTGAGCAGACG CCTCCATAACTGGTAAGTACCGCCTATAGACTCTATAGGCACACCCCT TTGGCTCTTATGCATGCTGACAGACTAACAGACTGTTCTTTCTGGGT CTTTTCTGAGGCCTGTACGGAAGTGTTACTTCTGCTCTAAAAGCTGCG GAATTGTACCCGCGCCGATCCAATCGATACAGATCTAGCGGCCGCCC GCCACCATGGCTGAAAAAGCGGGGTCTACATTTTACACCTTCTGGTT CCTATTCTTCTCTGATTGGCTGGATTGTGGGCTGCATCATAATGATTT ATGTTGTCTTCTCTAGAAGCTTTGGATCCAATCAACCTCTGGATTACA AAATTTGTGAAAGATTGACTGGTATTCTTAAGTATGTTGCTCCTTTTAC GCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC CGTATGGCTTTCATTTTCTCCTCTGTATAAATCCTGGTGTGCTCTCT TTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCAC

	TGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTG TCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCACGGCG GAACTCATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTG TTGGGCACTGACAATTCCGTGGTGTGTGCGGGGAAATCATCGTCTTTTC CTTGGCTGCTCGCCTGTGTGCCACCTGGATTCTGCGCGGGACGTCCTT CTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGC CTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGAGATCTGCCTCGAC TGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCTCCCCCGTGCCT TCCTTGACCCTGGAAGGTGCCACTCCCACTGTCTTTCTTAATAAAATG AGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGG GTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAG CAGGCATGCTGGGGACTCGAGTTAAGGGCGAATCCCCGATTAGGATCT TCCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATT ACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCG CTCGCTCGCTCACTGAGGCCGGGCGACCAAAGTTCGCCCCGACGCCCGG GCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 67)
pHZ56 (human DWORF version of pHZ20)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCCTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTGCGCCCTTAAGGTCTATGGAGAAGACCCACCTTGAGATGTCTCA CTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATTA GGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTTCAAGT GGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCTGCTC CCAGCTGGCCCTCCAGGCCTGGGTTGTGGCCTCTGCCTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAACACCCCCACCCCCACCGCATCCCCCTGCC CACCCGTCCCTGTGCGACATTCCCTCCCTCCGAGGGCTGGCTCACCA GGCCCCAGCCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAACTGGTAAGTACC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTGACA GACTAACAGACTGTTCTTTCTGGGTCTTTTCTGCAGGCCTGTACGGA AGTGTTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCGCGCCGATC CAATCGATACAGATCTAGCGGCCGCCGCCACCATGGCTGAAAAAGC GGGGTCTACATTTTACACCTTCTGGTTCTTCTTCTCTCTGATTGGCT GGATTGTGGGCTGCATCATAATGATTTATGTTGTCTTCTCTTAGAAGCT TTGGATCCAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTG GTATTCTTAACATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTT AATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTTCTCTCTCT CCTTGATAAAATCCTGGTTGCTGTCTTTATGAGGAGTTGTGGCCCGT TGTCAAGCAACGTGGCGTGGTGTGCACTGTGTTGCTGACGCAACCCC CACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTC GCTTTCCCCCTCCCTATTGCCACGGCGGAATCATCGCCGCTGCCTTG CCCCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGG TGTTGTGCGGGGAAATCATCGTCTTTCCTTGGCTGCTCGCCTGTGTTGC CACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCTTTCGGCCCTC AATCCAGCGGACCTTCTTCCCGCGGCTGCTGCCGCTCTGCGGCCT CTTCCGCGTCTTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCC ATCTGTTGTTTGGCCCTCCCCGTGCCTTCTTGACCCTGGAAGGTGCC ACTCCCACTGTCTTTCTTAATAAAATGAGGAAATTGCATCGCATTGTC TGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCA AGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGT TAAGGGCGAATTCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGA TAAGTAGCATGGCGGGTTAATCATTAATACTACAAGGAACCCCTAGTGAT GGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGG

	GCGACCAAAGGTCGCCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAG (SEQ ID NO: 68)
pHZ57 (human DWORF version of pHZ21)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGAACTGGCCTGCCCCGAGACCAAACGTGCGGAACGT AGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGTCGATCATTCTGATTC TCCTTTTCTCTACGTCTGCTTCCTGTCAATGGGCATCCTCACTGTCAAA TGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGCAGGCCTCTCCCC AGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGGCCC CTGAAGATAATCAGCAGTCCTGCTCAGCATATCAATCCAAGCCCACTC TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTTAACTGGTGTGAAC GAAGGAAAAGCACAGCATTAGAAGTCCAAGCACCTTCAGATTAAAAA TAACTAAGGTAAGGGCCATGTGGGTAGGGGAGGTGGTGTGAGACGGT CCTGTCTCTCTCTATCTGCCCCATCGGCCCTTTGGGGAGGAGGAATGTG CCCAAGGACTAAAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGC AGACCTTTCATGGGCAAACCTCAGGGCTGCTGTGTCATGGAGAAGAC CCACCTTGCGATGTCCTCACTGGGGCTGGCAGAGCCGGCAACCTGCC TAAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTA CCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGC CTTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCC TCTGCCCCCAACCCTGCTCCCAGCTGGCCCTCCCAGGCCTGGGTTGCT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCCTGCATATCTGCTCTGGTTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCTCTG TAGCCTTGTCCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCCACC CCCACCGCATCCCCCTGCCCCACCCGTCCTCTGCGCACATTCTCTCC TCCGCAGGGCTGGCTCACCAGGCCCCAGCCCATGCCTGCTTAAAGC CCTCTCCATCCTCTGCCTCACCCAGTCCCCGCTGAGACTGAGCAGACG CCTCCATAACTGGTAAGTACCGCCTATAGACTCTATAGGCACACCCCT TTGGCTCTTATGCATGCTGACAGACTAACAGACTGTTCTTTCTGGGT CTTTTCTGCAGGCCTGTACGGAAGTGTACTTCTGCTCTAAAAGCTGCG GAATTGTACCCGCGGCCGATCCAATCGATACAGATCTAGCGGCCGCC GCCACCATGGCTGAAAAAGCGGGGTCTACATTTTACACACCTTCTGGTT CCTATTCTTCTCTGATTGGCTGGATTGTGGGCTGCATCAATGATTT ATGTTGTCTTCTCTTAGAAGCTTTGGATCCAATCAACCTCTGGATTACA AAATTTGTGAAAGATTGACTGGTATTCTTAATATGTTGCTCCTTTTAC GCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC CGTATGGCTTTTCAATTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCT TTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCAC TGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTG TCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCACGGCG GAACTCATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTG TTGGGCACTGACAATTCCGTGGTGTGTCGGGGAAATCATCGTCTTTTC CTTGGCTGCTCGCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTT CTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCTTCCCCGGGC CTGCTGCCGCTCTGCGGCCTCTCCGCGTCTTCGAGATCTGCCTCGAC TGTGCCCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTGCC TCCTTGACCTTGGAAGGTGCCACTCCCACTGTCTTCTTAATAAAAATG AGGAAATTGCATCGCATTGTCTGAGTAGGTGTCAATTCTATTCTGGGGG GTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAG CAGGCATGCTGGGGACTCGAGTTAAGGGCGAATCCCGATTAGGATCT TCCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATT ACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCG CTCGCTCGCTCACTGAGGCCGGGCGACCAAAGTTCGCCCCGACGCCCG GCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 69)

pHZ58 (human DWORF version of pHZ22)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGC GCCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACCTCCATCACTAGGGGTTCCCTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGAACTGGCCTGCCGAGACCAAACGTGCGGAACGT AGTTAAGTGTAGAGGTAGGATTTGAAGCCTGTCGATCATTCTGATTC TCCTTTTCTCTACGTCTGCTTCCTGTCAATGGGCATCCTCACTGTCAAA TGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGCAGGCCTCTCCCC AGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCATCCCA AACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCCGCCCC CTGAAGATAATCAGCAGTCTGTCTCAGCATATCAATCCAAGCCCACTC TAGACAGAGATGCCGGTGCCAGTTTTCTATTTTAACTGGTGTGAACT GAAGGAAAAGCACAGCATTAGAAGTCCAAGCACCTTCAGATTAAAAA TAACTAAGGTAAGGGCCATGTGGGTAGGGGAGGTGGTGTGAGACGGT CCTGTCTCTCCTCTATCTGCCCATCGGCCCTTTGGGGAGGAGGAATGTG CCCAAGGACTAAAAAAGGCCCTGGAGCCAGAGGGGCGAGGGCAGC AGACCTTTCATGGGCAAACCTCAGGGCTGCTGTCTCATGGAGAAGAC CCACCTTGACAGATGTCTCACTGGGGCTGGCAGAGCCGGCAACCTGCC TAAGGCTGCTCAGTCCATTAGGAGCCAGTAGCCTGGAAGATGTCTTTA CCCCCAGCATCAGTTCAAGTGGAGCAGCACATAACTCTTGCCCTCTGC CTTCCAAGATTCTGGTGTGAGACTTATGGAGTGTCTTGGAGGTTGCC TCTGCCCCCAACCTGTCTCCAGCTGGCCCTCCAGGCCTGGGTGTCT GGCCTCTGCTTTATCAGGATTCTCAAGAGGGACAGCTGGTTTATGTTG CATGACTGTTCCCTGCATATCTGCTCTGGTTTTAAATAGCTTATCTGAG CAGCTGGAGGACCACATGGGCTTATATGGCGTGGGGTACATGTTCCCTG TAGCCTTGTCCTGGCACCTGCCAAAATAGCAGCCAACACCCCCCACC CCCACCGCCATCCCCCTGCCCAACCGTCCCTGTGCGACATTCTCTCC TCCGCAGGGCTGGCTCACCAGGCCCCAGCCACATGCCTGCTTAAAGC CCTCTCCATCCTCTGCCTCACCAGTCCCCGCTGAGACTGAGCAGACG CCTCCATAACTGGTAAGTACCGCTATAGACTCTATAGGCACACCCCT TTGGCTCTTATGCATGCTGACAGACTAACAGACTGTTCCCTTCTGGGT CTTTTCTGCAGGCCTGTACGGAAGTGTTACTTCTGCTCTAAAGCTGCG GAATTGTACCCGCGGCCGATCCAATCGATACAGATCTAGCGGCCGCCC GCCACCATGGCTGAAAAAGCGGGGTCTACATTTTCACACCTTCTGGTT CCTATTCTTCTCCTGATTGGCTGGATTGTGGGCTGCATCATAATGATT ATGTTGCTTCTCTTAGAAGCTTTGGATCCAATCAACCTCTGGAATTACA AAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCTTTTAC GCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCC CGTATGGCTTTCATTTTCTCCTCCTTGATAAATCCTGGTGTCTGTCTCT TTATGAGGAGTTGTGGCCCGTTGTCAAGCAACGTGGCGTGGTGTGCAC TGTGTTTGTGACGCAACCCCCACTGGTTGGGGCATTTGCCACCACTG TCAGTCTCTTCCGGGACTTTCGCTTTCCCTCCCTATTGCCACGGCG GAACTCATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTG TTGGGCACTGACAATTCCGTGGTGTGTGCGGGGAAATCATCGTCTTTCT CTTGGCTGCTCGCCTGTGTGCCACCTGGATTCTGCGCGGGACGTCTCT CTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGCGGC CTGTGCGCGCTCTGCGGCCTCTTCCGCGTCTTCGAGATCTGCCTCGAC TGTGCCCTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGTGCCT TCCTTGACCCTGGAAGGTGCCACTCCCACTGTCTTTCTTAATAAAATG AGGAAATTGCATCGCATTGTCTGAGTAGGTGTCTATTCTATCTGGGG GTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAG CAGGCATGCTGGGGACTCGAGTTAAGGGCGAATTTCCCGATTAGGATCT TCCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATT ACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCG CTCGCTCGCTCACTGAGGCCGGGCGACCAAAGTGCCTCGCCGACGCCCG GCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 70)
pHZ59 (human DWORF version of pHZ23)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGC GCCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACCTCCATCACTAGGGGTTCCCTGTAGTTAATGAT

	TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGCCTTCAGATTAAAAATAACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCTCTATCTGC CCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACTAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTTCATGGGCAAAC CTCAGGGCTGCTGTCTCATGGAGAAGACCCACCTTGAGATGTCTC ACTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATT AGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTTCAAAG TGGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCCTGCTC CCAGCTGGCCCTCCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAAACCCCCCACCCTCCAGCCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCCCTCCGCAGGGCTGGCTCACCA GGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCTCTGCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAACTGGTAAGTACC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTGACA GACTAACAGACTGTTCCTTTCTGGGTCTTTTCTGCAGGCCTGTACGGA AGTGTTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCGCGGCCGATC CAATCGATACAGATCTAGCGGCCGCCGCCACCATGGCTGAAAAAGC GGGGTCTACATTTTACACCTTCTGGTTCTTCTTCTCTGATTGGCT GGATTGTGGGCTGCATCATAATGATTATGTTGTCTTCTCTTAGAAGCT TTGGATCCAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTG GTATTCTTAAGTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTT AATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCT CCTTGTATAAATCCTGGTTGCTGTCTCTTATGAGGAGTTGTGGCCCGT TGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTGCTGACGCAACCCC CACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTC GCTTTCCCCCTCCCTATTGCCACGGCGGAACCTATCGCCGCTGCCTTG CCCCGTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGG TGTTGTGCGGGAAATCATCGTCCTTTCTTGGCTGCTCGCCTGTGTTGC CACCTGGATTCTGCGCGGGACGTCTCTGCTACGTCCCTTCGGCCCTC AATCCAGCGGACCTTCCTTCCCGCGCCTGCTGCGGGCTCTGCGGCCT CTTCCGCTCTTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCC ATCTGTTGTTTGCCCTCCCCCGTGCCTTCCTTGACCTTGAAGGTGCC ACTCCCACTGTCCTTTCTAATAAAATGAGGAAATTGCATCGCATTGTC TGAGTAGGTGTATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCA AGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGT TAAGGGCGAATTCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGA TAAGTAGCATGGCGGGTTAATCATTAACATAAGGAACCCCTAGTGAT GGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGG GCGACCAAAGGTGCGCCGACGCGCGGCTTTGCCCGGGCGGCCCTCAGT GAGCGAGCGAGCGCGCAG (SEQ ID NO: 71)
pHZ60 (human DWORF version of pHZ24)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTCGCCCCGCCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGGTCATGGAGAAGACCCACCTTGAGATGTCTCA CTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATTA GGAGCCAGTAGCCTGGAAGATGTCTTTACCCCCAGCATCAGTTCAAGT GGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCCTGCTC CCAGCTGGCCCTCCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAAACCCCCCACCCTCCAGCCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCCCTCCGCAGGGCTGGCTCACCA

	GGCCCCAGCCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCAGCGGCCGCCGCCAC CATGGCCGAGAAGGCCGGATCTACCTTCAGCCACCTGCTGGTCCCTAT TCTGCTGCTGATCGGCTGGATCGTGGGCTGCATCATGATCTACGT GGTGTTCAGCTGAAAGCTTTGGATCCAATCAACCTCTGGATTACAAAA TTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTACGCT ATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGT ATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGCTCTTTA TGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGT GTTTGTGACGCAACCCCACTGGTTGGGGCATTGCCACCACCTGTCA GCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAA CTCATCGCCGCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTGT GGCACTGACAATTCCGTGGTGTGTCGGGGAAATCATCGTCTTTCCTT GGCTGCTCGCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTG CTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTG CTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGAGATCTGCCTCGACTGT GCCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCGTCCTTCC TTGACCCTGGAAGGTGCCACTCCCACTGTCTTTCTAATAAAATGAG GAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGT GGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCA GGCATGCTGGGGACTCGAGTTAAGGGCGAATCCCCGATTAGGATCTTC CTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAAC TACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCT CGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCCGACGCCGGG CTTGCCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 72)
pHZ61 (human DWORF version of pHZ25)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGT CGGGCGACCTTTGGTGCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCGCCCTTAAGCCTTCAGATTAAAAATAACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCCTCTATCTGC CCATCGGCCCTTTGGGGAGGAGGAATGTGCCCAAGGACTAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGCAGACCTTTCATGGGCAAAC CTCAGGGCTGCTGTCTCATGGAGAAGACCCACCTTGCAGATGTCTCT ACTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATT AGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCAAGCATAGTTCAAG TGGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCTGCTC CCAGCTGGCCCTCCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCATGAGC CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAAACACCCCCACCCCCACCGCCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCCTCCCTCCGCAGGGCTGGCTACCA GGCCCCAGCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAACTGGTAAGTACC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTGACA GACTAACAGACTGTTCCTTTCCTGGGTCTTTTCTGCAGGCCTGTACGGA AGTGTTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCGCGGCCGATC CAATCGATACAGATCTAGCGGCCGCCGCCACCATGGCTGAAAAAGC GGGGTCTACATTTTCACACCTTCTGGTTCTTCTTCTCTGATTGGCT GGATTGTGGGCTGCATCATAATGATTTATGTTGTCTTCTTTAGAAGCT TTGGATCCAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTG GTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTT AATGCCTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCT CCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGT TGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTGCTGACGCAACCCC CACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTC GCTTCCCCCTCCCTATTGCCACGGCGGAACATCGCCGCGCTGCCTTG

	CCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGG TGTGTGCGGGGAAATCATCGTCCTTTCTTGGCTGCTCGCCTGTGTTGC CACCTGGATTCTGCGCGGGACGTCCCTTCTGCTACGTCCCTTCGGCCCTC AATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCGGGCTCTGCGGCCT CTTCCGCGTCTTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCC ATCTGTGTTTGGCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCC ACTCCCACTGTCCTTTCCTAATAAAAATGAGGAAATTGCATCGCATTGTC TGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCA AGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGT TAAGGGCAGCCAGAAGTCAGATGCTCAAGGGGCTTCATGATGTCCCA TAATTTTGGCAGAGGGAAAAAGATCGGATCCTCAGGCGTAGTTCACC CCGTCCTCGAGGCCGCGGGTCTGACTAAAAAACCTCCCACACCTCCC CCTGAACCTGAAACATAAAAATGAATGCAATTGTTGTTAACTTGTTT ATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCATCACAAATTC ACAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGTTTGTCCAAAC TCATCAATGTATCTTATCATGTCTGGATCCGCGCGGCCGTCAGCTGAA CACCAGTAGATCATGATGATGCAGCCACGATCCAGCCGATCAGCAG CAGAATAGGGACCAGCAGGTGGCTGAAGGTAGATCCGGCCTTCTCGG CCATGGTGGCGGCTAGCCTATAGTGAGTCGTATTAAGTACTCTAGCCT TAAGAGCTGTAATTGAACTGGGAGTGGACACCTGTGGAGAGAAAGGC AAAGTGGATGTCAGTAAGACCAATAGGTGCCTATCAGAAACGCAAGA GTCTTCTGTCTCGACAAGCCAGTTTCTATTGGTCTCCTTAAACCTG TCTTGTAACTTGATACCTTACCTGCCAGTGCCTCACGACCAACTTCTG CAGCTTAAGTTCGAGACTGTTGTGTCAGAAGCACTGACTGCGTTAGCA ATTTAACTGTGATAAACTACCGCAATAAAGCTCTAGAGCTTCGGGGAT CGTCCACGGAGCGGTGGGTGCCGGCGGGCTGTCTGGGAAGGGCTCCTT GGGGGGCAGAGGCTTTAAGGTCCCCCGGCGCCACCCCGGGCGGG CAGAGCCAGCAGGAATGTGCCCGGCGCCAGAGAGGAATGCAACACT TGTGAGCTGCTATTTTGGCAGCAGCGGCCCGGCCCCCTCCGTGCTCC CCCTTCCCCACAGGAGCCCATATAAGCCCAAGCTATTGTGTGGCCTC AGAGTTTTGCTATTTTAAACCCGTCGGACGGAGATACGTGAGTGCCCG AGGGGCTGACACAAGCCAGCCAGCTGTACCTCCAGGGCTGGGGAC GCTGATAAGGCAGCGCTTCGGACCCGACCCTCTGCCGAGCCCCAGAT GCTGTCTGTGAAAGCCCAGACTGCTTTATCCCTGCTGGACTTCTAA TGCTGTGCTTTTCTTCAGTTCACACCAGTTAAAAATAGAAAACTGGG CACCGGCATCTCTGTCTAGAGTGGGCTTGGATTGATGTGAGCAGG ACTGCTGATTATCTTCAGGGGCGGGCAGTGCTGGGTCTCTCCCTCAG AGCTTCTCAACCATGTTTGGGATGGTCTAGGGATGAAACTGCTGGACA GCTGAGCCATGGAGACTGGGGAGAGGCCTGCCTGGCTGAGACCAAGC CCTGCTGTACCATCTGCATTTGACAGTGAGGATGCCATTGACAGGAA GCAGACGTAGAGAAAAGGAGAATCAGAATGATCGACAGGCTTCAAAT CCTACCTCTAACACTTAACTACGTTCGCGACGTTTGGTCTCGGGCAGG CAGTTGAATTCCCGATTAGGATCTTCTAGAGCATGGCTACGTAGATA AGTAGCATGGCGGGTTAATCATTAACCTACAAGGAACCCCTAGTGATGG AGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGC GACCAAAGGTGCGCCGACGCCCGGGCTTTGCCCGGGCGGCTCAGTGA GCGAGCGAGCGCGCAG (SEQ ID NO: 73)
pHZ62 (human DWORF version of pHZ33)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCGCGGCAAGCCCGGGCGT CGGGCGACCTTTGGTGCCTCGCGGCTCAGTGAGCGAGCGGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTGCGCCTTAAGCCTTCAGATTAAAAATAACTAAGGTAAGGGCCAT GTGGGTAGGGGAGGTGGTGTGAGACGGTCTGTCTCTCTCTATCTGC CCATCGGCCCTTTGGGGAGGAGGAATGTGCCAAGGACTAAAAAAAAG GCCCTGGAGCCAGAGGGGCGAGGGCAGACCTTTTCATGGGCAAC CTCAGGGCTGCTGTCTCATGGAGAAGACCCACCTTGAGATGTCTCTC ACTGGGGCTGGCAGAGCCGGCAACCTGCCTAAGGCTGCTCAGTCCATT AGGAGCCAGTAGCCTGGAAGATGTCTTTACCCCGAGCATCAGTTCAAG TGGAGCAGCACATAACTCTTGCCCTCTGCCTTCCAAGATTCTGGTGCTG AGACTTATGGAGTGTCTTGGAGGTTGCCTTCTGCCCCCAACCTGCTC

	CCAGCTGGCCCTCCCAGGCCTGGGTTGCTGGCCTCTGCTTTATCAGGAT TCTCAAGAGGGACAGCTGGTTTATGTTGCATGACTGTTCCCTGCATATC TGCTCTGGTTTTAAATAGCTTATCTGAGCAGCTGGAGGACCACATGGG CTTATATGGCGTGGGGTACATGTTCTGTAGCCTTGTCCCTGGCACCTG CCAAAATAGCAGCCAACACCCCCACCCCCACCGCATCCCCCTGCC CACCCGTCCCCTGTGCGACATTCTCCCTCCGCAGGGCTGGCTCACCA GGCCCCAGCCCACATGCCTGCTTAAAGCCCTCTCCATCCTCTGCCTCAC CCAGTCCCCGCTGAGACTGAGCAGACGCCTCCATAAAGGTAAGTACC GCCTATAGACTCTATAGGCACACCCCTTTGGCTCTTATGCATGCTGACA GACTAACAGACTGTTCTTTCTGGGTCTTTTCTGCAGGCCTGTACGGA AGTGTACTTCTGCTCTAAAAGCTGCGGAATTGTACCCGCGGCCGATC CAATCGATACAGATCTAGCGGCCGCCGCCACCATGGCTGAAAAAGC GGGGTCTACATTTTACACCTTCTGGTTCTTCTTCTCCTGATTGGCT GGATTGTGGGCTGCATCATAATGATTTATGTTGTCTTCTCTTAGAAGCT TTGGATCCAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTG GTATTTCTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTT AATGCCTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTCTCCT CCTGTATAAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGTGGCCCGT TGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTGCTGACGCAACCCC CACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTC GCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCTGCCTTG CCCGCTGTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCGCTGG TGTTGTGCGGGAAATCATCGTCCTTTCTTGGCTGCTCGCCTGTGTTGC CACCTGGATTCTGCGCGGGACGTCTTCTGCTACGTCCCTTCGGCCCTC AATCCAGCGGACCTTCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCT CTTCCGCTCTTCGAGATCTGCCTCGACTGTGCCTTCTAGTTGCCAGCC ATCTGTTGTTGCCCTCCCCCGTGCCTTCTTGACCCTGGAAGGTGCC ACTCCCACTGTCTTTCTAATAAAATGAGGAAATTGCATCGCATTGTC TGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCA AGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGACTCGAGT TAAGGGCAGCCAGAAGTCAGATGCTCAAGGGGCTTCATGATGTCCCA TAATTTTGGCAGAGGGAAAAAGATCGGATCCTCAGGCGTAGTTCCAC CCGTCTCGAGGCCGCCGGGTGCGACTAAAAAACCTCCACACCTCCC CCTGAACCTGAAACATAAAATGAATGCAATTGTTGTTGTTAACTGGC CTGCCCGAGACCAAAACGTGCGGAACGTAGTTAAGTGTAGAGGTAGG ATTTGAAGCCTGTCGATCATTCTGATTCTCCTTTCTCTACGTCTGCTC CTGTCAATGGGCATCTCCTACTGTCAAATGCAGATGGTACAGCAGGGCT TGGTCTCAGCCAGGCAGGCCTCTCCCCAGTCTCCATGGCTCAGCTGTC CAGCAGTTTCATCCCTAGACCATCCCAAACATGGTTGAGAAGCTCTGA GGGGAGGACCCAGCACTGCCCGGCCCTGAAGATAATCAGCAGTCCT GCTCAGCATATCAATCCAAGCCCACTCTAGACAGAGATGCCGGTGCC AGTTTTCTATTTTAACTGGTGTGAAGTGAAGGAAAAGCACAGCATT GAAGTCCAAGCAGGGATAAAAGCAGTCTGGGCTTTCACATGACAGCA TCTGGGGTGCAGCAGAGGGTCCGAGCGCTGCCCTATCAGCG TCCCCAGCCCTGGGAGGTGACAGCTGGCTGGCTTGTGTACGCCCTCG GGCACTCACGTATCTCCGTCCGACGGGTTTAAAAATAGCAAACTCTGA GGCCACACAATAGCTTGGGCTTATATGGGCTCCTGTGGGGGAAGGGG GAGCACGGAGGGGGCCGGGGCCGCTGCTGCCAAAATAGCAGCTCACA AGTGTGCAATTCCTCTCTGGGCGCCGGGCACATTCTGCTGGCTCTGCC CGCCCCGGGGTGGGCGCCGGGGGACCTTAAAGCCTCTGCCCCCCAA GGAGCCCTTCCCAGACAGCCGCCGGCACCCACCGCTCCCGTGGGACGAT CCCCGAAGCTCTAGAGCTTTATTGCGGTAGTTTATCACAGTTAAATTGC TAACGCAGTCAGTGCTTCTGACACAACAGTCTCGAACTTAAGCTGCAG AAGTTGGTCTGTAGGCACTGGGCAGGTAAGTATCAAGGTTACAAGAC AGGTTTAAAGGAGACCAATAGAACTGGGCTTGTGAGACAGAGAAGA CTTTGCGTTTCTGATAGGCACCTATTGGTCTTACTGACATCCACTTTG CCTTTCTCTCCACAGGTGTCCACTCCCAGTTCAATTACAGCTCTTAAGG CTAGAGTACTTAATACGACTCACTATAGGCTAGCCGCCACCATGGCCG AGAAGGCCGGATCTACCTTCAGCCACCTGCTGGTCCCTATTCTGCTGCT GATCGGCTGGATCGTGGGCTGCATCATCATGATCTACGTGGTGTTCAG
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	CTGACGGCCGCGCGGATCCAGACATGATAAGATACATTGATGAGTTTG GACAAACCACAAGTGAATGCAGTGAAAAAATGCTTTATTTGTGAA ATTTGTGATGCTATTGCTTTATTTGTAACCAATTATAAGCTGCAATAAAC AAGTGAATCCCCGATTAGGATCTTCCTAGAGCATGGCTACGTAGATAA GTAGCATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGA GTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCG ACCAAAGGTCGCCCCAGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAG CGAGCGAGCGCGCAG (SEQ ID NO: 74)
pHZ63 (human DWORF version of pHZ34)	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAGCCCCGGGCGT CGGGCGACCTTTGGTTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAG AGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTTGTAGTTAATGAT TAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGGAAGATCGG AATTCTCCCCAGCATGCCTGCTATTGTCTTCCCAATCCTCCCCCTTGCT GTCCTGCCCCACCCACCCCCCAGAATAGAATGACACCTACTCAGACA ATGCGATGCAATTTCTCATTATTATTAGGAAAGGACAGTGGGAGTGGC ACCTTCCAGGGTCAAGGAAGGCACGGGGGAGGGGCAAAACAACAGATG GCTGGCAACTAGAAGGCACAGTCGAGGCAGATCTCGAAGACGCGGAA GAGGCCGAGAGCCGGCAGCAGGCCGCGGGAGGAAGGTAAGTCCGCTGGA TTGAGGGCCGAAGGGACGTAGCAGAAGGACGTCCCGCGCAGAATCCA GGTGGCAACACAGGCGAGCAGCCAAGGAAAGGACGATGATTTCCCCG ACAACACCACGGAATTGTCAAGTGCCTAACAGCCGAGCCCCCTGTCCAG AGCGGGCAAGGCAGGCGGGCGATGAGTTCCGCGGTGCAATTCGCGAGG GGGAAAGCGAAAGTCCCGGAAAGGAGCTGACAGGTGGTGGCAATGCC CCAACCAAGTGGGGGTTGCGTCAGCAAACACAGTGCACACCACGCCAC GTTGCCTGACAACGGGGCCACAACCTCCTCATAAAGAGACAGCAACCAG GATTTATACAAGGAGGAGAAAAATGAAAGCCATACGGGAAGCAATAGC ATGATACAAAAGGCATTAAAGCAGCGTATCCACATAGCGTAAAGAGGAG CAACATAGTTAAGAATACCAGTCAATCTTTCACAAATTTTGTAAATCCA GAGGTTGATTGGATCCAAAGCTTCTAAGAGAAGACAACATAAATCATT ATGATGCAGCCCAATCCAGCCAATCAGGAGAAGAATAGGAACCCAG AAGGTGTGAAAATGTAGACCCCGCTTTTTTCAGCCATGGTGGCGGGCGG CCGCTAGATCTGTATCGATTGGATCGGCCGCGGGTACAATTCCGCAGC TTTTAGAGCAGAAGTAACACTTCCGTACAGGCCTGCAGAAAAGACCCA GGAAAGGAACAGTCTGTTAGTCTGTCAGCATGCATAAGAGCCAAAGG GGTGTGCCTATAGAGTCTATAGGCGGTACTTACCAGTTATGGAGGCGT CTGCTCAGTCTCAGCGGGGACTGGGTGAGGCAGAGGATGGAGAGGGC TTTAAGCAGGCATGTGGGCTGGGGCCTGGTGAGCCAGCCCTGCGGAG GGAGGAATGTGCGACAGGGGACGGGTGGGGCAGGGGGATGGCGGTG GGGGTGGGGGGTGTGGCTGCTATTTTGGCAGGTGCCAGGGACAAGG CTACAGGAACATGTACCCACGCCATATAAGCCCATGTGGTCTCTCCAG CTGCTCAGATAAGCTATTTAAACCAGAGCAGATATGCAGGGAACAG TCATGCAACATAAAACCAGCTGTCCCTCTTGAGAATCTGTATAAAGCAG AGGCCAGCAACCCAGGCCTGGGAGGGCCAGCTGGGAGCAGGGTTGGG GGGCAGAAGGCAACCTCCAAGACACTCCATAAGTCTCAGACCAGAA TCTTGGAAGGCAGAGGGCAAGAGTTATGTGCTGCTCCACTTGAAGTGA TGCTGGGGGTAAAGACATCTTCCAGGCTACTGGCTCCTAATGGACTGA GCAGCCTTAGGCAGGTTGCCGGCTCTGCCAGCCCCAGTGAGGACATCT GCAAGGTGGGTCTTCTCCATGACGACAGCAGCCCTGAGGTTTGGCCAT GAAAGGTCTGTGCCCTCGCCCCCTCTGGCTCCAGGGCCTTTTTTTAGTC CTTGGGCACATTCTCTCCCCAAAGGGCCGATGGGCAGATAGAGGAG AGACAGGACCGTCTCACACCACCTCCCCTACCCACATGGCCCTTACCT TAGTTATTTTTAATCTGAAGGCTCGAGTTAAGGGCAGCCAGAAGTCAG ATGCTCAAGGGGCTTCATGATGTCCCCATAATTTTTTGGCAGAGGGAAA AAGATCGGATCCTCAGGCGTAGTTCACCCCGTCTCGAGGCCGCCCCG GTCGACTAAAAAACCTCCCACACCTCCCCCTGAACCTGAAACATAAAA TGAATGCAATTGTTGTTGTTAAACTGGCCTGCCCGAGACCAAAACGTGC GGAACGTAGTTAAGTGTTAGAGGTAGGATTTGAAGCCTGTGATCATT CTGATTCTCTTTTCTACGTCTGCTTCTGTCAATGGGCATCCTCACT GTCAAATGCAGATGGTACAGCAGGGCTTGGTCTCAGCCAGGCAGGCCT CTCCCCAGTCTCCATGGCTCAGCTGTCCAGCAGTTTCATCCCTAGACCA

	TCCCAAACATGGTTGAGAAGCTCTGAGGGGAGGACCCAGCACTGCCC GGCCCCTGAAGATAATCAGCAGTCCTGCTCAGCATATCAATCCAAGCC CACTCTAGACAGAGATGCCGGTGCCAGTTTTCTATTTTTAACTGGTGT GAACTGAAGGAAAAGCACAGCATTAGAAGTCCAAGCAGGGATAAAAG CAGTCTGGGCTTTCACATGACAGCATCTGGGGCTGCGGCAGAGGGTGC GGTCCGAAGCGCTGCCTTATCAGCGTCCCCAGCCCTGGGAGGTGACAG CTGGCTGGCTTGTGTCAGCCCCCTCGGGCACTCACGTATCTCCGTCGAC GGTTTTAAAAATAGCAAACTCTGAGGCCACACAATAGCTTGGGCTTAT ATGGGCTCCTGTGGGGGAAGGGGAGCACGGAGGGGGCCGGGGCCGC TGCTGCCAAAATAGCAGCTCACAAGTGTTGCATTCTCTCTGGCGCC GGGCACATTCTGCTGGCTCTGCCCCCCCCGGGGTGGGCGCCGGGGGG ACCTTAAAGCCTCTGCCCCCAAGGAGCCCTTCCCAGACAGCCGCCGG CACCACCGCTCCGTGGGACGATCCCCGAAGCTCTAGAGCTTTATTGC GGTAGTTTATCACAGTTAAATTGCTAACGCAGTCAGTGCTTCTGACAC AACAGTCTCGAACTTAAGCTGCAGAAGTTGGTCGTGAGGCACTGGGCA GGTAAGTATCAAGGTTACAAGACAGGTTTAAGGAGACCAATAGAAAC TGGGCTTGTGAGACAGAGAAGACTCTTGCGTTTCTGATAGGCACCTA TTGGTCTTACTGACATCCACTTTGCCTTTCTCTCCACAGGTGTCCACTC CCAGTTCAATTACAGCTCTTAAGGCTAGAGTACTTAATACGACTCACT ATAGGCTAGCCGCCACCATGGCCGAGAAGGCCGGATCTACCTTCAGCC ACCTGCTGGTCCCTATTCTGCTGCTGATCGGCTGGATCGTGGGCTGCAT CATCATGATCTACGTGGTGTTCAGCTGACGGCCGCGCGGATCCAGACA TGATAAGATACATTGATGAGTTTGGACAAACCACAAGTGAATGCAGT GAAAAAATGCTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGT AACCATTATAAGCTGCAATAAACAAGTGAATCCCCGATTAGGATCTTC CTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAAAC TACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCT CGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCCGACGCCCGGG CTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAG (SEQ ID NO: 75)
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VECTORS

[00255] In some aspects, the disclosure provides vectors comprising the expression cassettes provided herein. The vector can be any viral vector or any non-viral vector known in the art or described herein.

[00256] In some embodiments, the vector is a viral vector. In some embodiments the viral vector is an adeno-associated virus vector (AAV), an adenoviral vector (AV), a lentiviral vector (LV), a retroviral vector (RV), a herpes simplex virus vector (HSV), or a poxvirus vector.

[00257] In some embodiments, provided herein is an AAV comprising any expression cassette described herein. In some embodiments, provided herein is an AV comprising any expression cassette described herein. In some embodiments, provided herein is an LV comprising any expression cassette described herein. In some embodiments, provided herein is an RV comprising any expression cassette described herein. In some embodiments, provided herein is an HSV comprising any expression cassette described herein. In some embodiments, provided herein is a poxvirus-based vector comprising any expression cassette described herein.

[00258] In some embodiments, the vector is a non-viral vector. In some embodiments, the non-viral vector is a naked DNA (e.g., a DNA plasmid). In some embodiments, the non-viral vector is a plasmid. In some embodiments, the non-viral vector is a liposome or lipid vector comprising plasmid DNA and a lipid solution.

[00259] For example, viral and non-viral vectors and delivery systems are described in Sung & Kim 2019, Biomaterials Research 23:8; Mali, 2013, Indian Journal of Human Genetics, 19(1):3-8; Hardee et al., 2017, Genes 8:65; Bulcha et al., 2020, Signal Transduction and Targeted Therapy; Ghosh et al., 2020, Applied Biosafety: Journal of ABSA International 25(1):7-18, the disclosures of each of which are hereby incorporated by reference herein in their entireties.

[00260] In some embodiments, the vectors are recombinant vectors.

[00261] In some embodiments, the vectors described herein comprise an expression cassette comprising a polynucleotide encoding any gene product described herein. In some embodiments, the expression cassette comprises a sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NOS: 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225,

[00262] In some embodiments, the vectors described herein comprise an expression cassette comprising a polynucleotide encoding DWORF. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NOS: 20-24 and SEQ ID NOS: 45-75.

[00263] In some aspects of the disclosure, a vector is used to deliver the expression cassettes described herein to cardiac cells of a subject, e.g., to treat cardiomyopathy. In some embodiments, the disclosure provides a viral vector comprising an expression cassette comprising a polynucleotide encoding a gene product (such as any gene product described herein, e.g., a DWORF polypeptide) operatively linked to a promoter and a pharmaceutically acceptable carrier. In some embodiments, the disclosure provides a virion comprising a capsid and an expression cassette comprising a polynucleotide encoding a gene product (such as any gene product described herein, e.g., a DWORF polypeptide) operatively linked to a promoter and a pharmaceutically acceptable carrier. In some embodiments, the disclosure provides a plasmid comprising an expression cassette comprising a polynucleotide encoding a gene product (such as any gene product described herein, e.g., a DWORF polypeptide) operatively linked to a promoter and a pharmaceutically acceptable carrier.

[00264] In some embodiments, the viral vectors described herein are replication incompetent, in that it cannot independently further replicate and package its genome. For

example, when a cardiac cell is targeted with a virion, the transgene is expressed in the targeted cardiac cell, however, due to the fact that the targeted cardiac cell lacks packaging and accessory function genes, the virion is not able to replicate. In some embodiments, the viral vectors described herein are replication-competent.

[00265] In some embodiments, the vectors described herein are capable of being delivered to both dividing and non-dividing cells. In some embodiments, the vectors described herein are capable of being delivered to non-dividing cells. In some embodiments, the vectors described herein are capable of being delivered to dividing cells.

[00266] In some embodiments, the vectors comprising the expression cassettes described herein lead to cardiac cell-specific expression of a transgene. In some embodiments, the vectors comprising the expression cassettes described herein lead to cardiomyocyte-specific expression of a transgene. In some embodiments, the vectors comprising the expression cassettes described herein allow high expression of a transgene in a cardiac cell (e.g., a cardiomyocyte) and low or no expression in other cells (e.g., low or no expression in liver cells, low or no expression in muscle cells except for muscle cells of the heart, low or no expression in cardiac fibroblasts). In some embodiments, the vectors comprising the expression cassettes described herein allow high expression of a transgene in heart tissue of a subject (e.g., in human heart). In some embodiments, the vectors comprising the expression cassettes described herein allow no or low expression of a transgene in tissues of a subject other than the heart (e.g., in liver or in muscles except those of the heart). “High” and “low” can be relative to each other, for example, the expression of a transgene in cardiac cells (e.g., cardiomyocytes) and/or heart tissue can be at least 2 fold, 5 fold, 10 fold, 15 fold, 20 fold, 50 fold, 100 fold, 150 fold, or 200 fold higher than its expression in other cells and tissues (e.g., liver, muscle except for the heart).

RECOMBINANT AAV VIRIONS

[00267] In some aspects, the disclosure provides recombinant AAV (rAAV) virions comprising the expression cassettes provided herein. In some embodiments, the rAAV virion comprises a capsid protein and an expression cassette. In some embodiments, the expression cassette comprises a polynucleotide encoding any gene product described herein.

[00268] In some embodiments, the expression cassette comprises a polynucleotide encoding DWORF. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to

SEQ ID NOs: 20-24 and SEQ ID NOs: 45-63. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 61. In some embodiments, the expression cassette comprises SEQ ID NO: 61. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 62. In some embodiments, the expression cassette comprises SEQ ID NO: 62. In some embodiments, the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 63. In some embodiments, the expression cassette comprises SEQ ID NO: 63.

[00269] In some aspects of the disclosure, an rAAV virion is used to deliver the expression cassettes described herein to cardiac cells of a subject, *e.g.*, to treat cardiomyopathy. Accordingly, the disclosure provides an rAAV virion, the rAAV virion comprising an AAV capsid and an expression cassette comprising a polynucleotide encoding a DWORF polypeptide operatively linked to a promoter and a pharmaceutically acceptable carrier.

[00270] The rAAV virions of the disclosure comprise a capsid protein. Capsid proteins are structural proteins that make up the assembled icosahedral packaging of the rAAV virion that contains the expression cassette. Capsid proteins are classified by the serotype. Wild type capsid serotypes in rAAV virions can be, for example, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, or AAV12 (Naso et al. *BioDrugs* 31:317–334 (2017)). Engineered capsid types include chimeric capsids and mosaic capsids (Choi et al. *Curr Gene Ther.* 5: 299–310 (2005)). Capsids are selected for rAAV virions based on their ability to transduce specific tissue or cell types (Liu et al. *Curr Pharm Des.* 21:3248-56 (2015)).

[00271] Any capsid protein that can facilitate rAAV virion transduction into cardiac cells for delivery of a transgene, as described herein, can be used. Capsid proteins used in rAAV virions for transgene delivery to cardiac cells that result in high expression can be, for example, AAV4, AAV6, AAV7, AAV8, and AAV9 (Zincarelli et al. *Mol. Ther.* 16:P1073-1080 (2008)). Artificial capsids, such as chimeric capsids generated through combinatorial libraries, can also be used for transgene delivery to cardiac cells that results in high expression (see US 63/012,703, the contents of which are herein incorporated by reference). Other capsid proteins with various features can also be used in the rAAV virions of the disclosure. AAV vectors and capsids are provided in U.S. Pat. Pub. Nos. US10011640B2; US7892809B2, US8632764B2, US8889641B2, US9475845B2, US10889833B2, US10480011B2, and US10894949B2, the contents of which are herein incorporated by reference; and Int'l Pat. Pub. Nos. WO2020198737A1, WO2019028306A2, WO2016054554A1, WO2018152333A1,

WO2017106236A1, WO2008124724A1, WO2017212019A1, WO2020117898A1, WO2017192750A1, WO2020191300A1, and WO2017100671A1, the contents of which are herein incorporated by reference.

[00272] In some embodiments, the rAAV virions of the disclosure comprise an engineered capsid protein. Engineered capsid proteins can be derived from a parental, *e.g.*, wild type, capsid and include, for example, variant polypeptide sequence with respect to a parental capsid sequence at one or more sites. For example, variant sites of the parental capsid can occur at the VR-IV site, VR-V site, VR-VII site and/or VR-VIII site (see, *e.g.*, Büning and Srivastava. *Mol Ther Methods Clin Dev.* 12:248-265 (2019)).

[00273] In some embodiments, the capsid protein is an AAV5/AAV9 chimeric capsid protein. In some embodiments, the chimeric capsid protein comprises at least 1, 2, 3, 4, 5 or more polypeptide segments that are derived from AAV5 capsid protein (SEQ ID NO: 144). In some embodiments, the chimeric capsid protein comprises at least 1, 2, 3, 4, 5 or more polypeptide segments that are derived from AAV9 capsid protein (SEQ ID NO: 143). In some embodiments, at least one polypeptide segment is derived from the AAV5 capsid protein and at least one polypeptide segment is derived from the AAV9 capsid protein.

[00274] In some embodiments, the capsid protein is a combinatory capsid proteins. As used herein, “combinatory capsid protein” refers to a AAV5/AAV9 chimeric capsid protein, which further comprises amino acid variations with respect to the chimeric parental sequence at one or more sites. In some embodiments, the one or more sites of the chimeric parental sequence are selected from those equivalent to the VR-IV site, the VR-V site, the VR-VII site and the VR-VIII site of the AAV9 capsid protein.

[00275] In some embodiments, the rAAV virions comprise an engineered capsid protein selected from Table 7.

Table 7. Engineered Capsid Proteins

Engineered Capsid	SEQ ID NO:
CR9-01	145
CR9-07	146
CR9-08	147
CR9-09	148
CR9-10	149
CR9-11	150
CR9-13	151
CR9-14	152
CR9-15	153
CR9-16	154

Engineered Capsid	SEQ ID NO:
CR9-17	155
CR9-20	156
CR9-21	157
CR9-22	158
ZC23	159
ZC24	160
ZC25	161
ZC26	162
ZC27	163
ZC28	164

Engineered Capsid	SEQ ID NO:
ZC29	165
ZC30	166
ZC31	167
ZC32	168
ZC33	169
ZC34	170
ZC35	171
ZC40	172
ZC41	173
ZC42	174
ZC43	175
ZC44	176
ZC45	177
ZC46	178
ZC47	179
ZC48	180
ZC49	181
ZC50	182

Engineered Capsid	SEQ ID NO:
TN47-07	183
TN47-10	184
TN47-13	185
TN47-14	186
TN47-17	187
TN47-22	188
TN40-07	189
TN40-10	190
TN40-13	191
TN40-14	192
TN40-17	193
TN40-22	194
TN44-07	195
TN44-10	196
TN44-13	197
TN44-14	198
TN44-17	199
TN44-22	200

[00276] In some embodiments, the rAAV is replication defective, in that the rAAV virion cannot independently further replicate and package its genome. For example, when a cardiac cell is targeted with rAAV virions, the transgene is expressed in the targeted cardiac cell, however, due to the fact that the targeted cardiac cell lacks AAV rep and cap genes and accessory function genes, the rAAV is not able to replicate.

[00277] In some embodiments, rAAV virions of the present disclosure encapsulating the expression cassettes as described herein, can be produced using helper-free production. rAAVs are replication-deficient viruses and normally require components from a live helper virus, such as adenovirus, in a host cell for packaging of infectious rAAV virions. rAAV helper-free production systems allow the production of infectious rAAV virions without the use of a live helper virus. In the helper-free system, a host packaging cell line is co-transfected with three plasmids. A first plasmid may contain adenovirus gene products (*e.g.*, E2A, E4, and VA RNA genes) needed for the packaging of rAAV virions. A second plasmid may contain required AAV genes (*e.g.*, REP and CAP genes). A third plasmid contains the polynucleotide sequence encoding the transgene of interest and a promoter flanked by ITRs. A host packaging cell line can be, for example, AAV-293 host cells. Suitable host cells contain additional components required for packaging infectious rAAV virions that are not supplied by the plasmids. In some

embodiments, the CAP genes can encode, for example, AAV capsid proteins as described herein.

[00278] In some embodiments, the CAP genes can encode, for example, AAV capsid proteins as described herein. In some embodiments, the promoter is a promoter sequence as described herein. In some embodiments, the promoter sequence is a cTnT promoter sequence. In some embodiments, the polypeptide of interest is a DWORF polypeptide.

[00279] The expression cassettes, enhancers and/or promoters described herein with respect to AAV virions need not be limited to their use in AAV virions and can be incorporated in essentially any other construct where expression of a polynucleotide encoding a gene product is desired.

[00280] rAAV virions can deliver transgenes to cells in a subject that are, in turn, expressed in the cell. A transgene delivered by an rAAV virion may be incorporated into the genome of the targeted cell, allowing for potential long-term expression of the transgene product. Compared to other viral transgene delivery systems, such as adenoviruses, rAAV virions have the advantage of low immunogenicity. rAAV virions can be used to transduce and deliver transgenes to many cells types, including eye, blood, liver, heart, joint tissue, muscle, brain kidney or lung cells (U.S. Pat. No. 10,308,957; U.S. Pat. No. 9,803,218). rAAV virions can contain genomes up to about 5.2 kilobases (kb), limiting the size of the polynucleotide that can be integrated into the host cell to about 4.4 kb (Choi et al. *Mol Brain*. 7:1 (2014)).

METHODS OF USE

Methods of Increasing Polypeptide Expression

[00281] The disclosure provides methods of increasing polypeptide expression in a cell comprising contacting the cell with any vector or virion (e.g., rAAV virion) described herein. In some embodiments, the cell is a cardiac cell. In some embodiments, the cell is a cardiomyocyte. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*. In some embodiments, the polypeptide is any polypeptide for use in treating or preventing a heart disease. In some embodiments, the polypeptide is any polypeptide described herein. In some embodiments, the polypeptide is encoded by any transgene described herein.

[00282] The disclosure provides methods of increasing polypeptide expression in a tissue comprising contacting the tissue with any vector or virion (e.g., rAAV virion) described herein. In some embodiments, the tissue is cardiac tissue. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*.

[00283] The disclosure provides methods of increasing polypeptide expression in an organ comprising contacting the organ with any vector or virion (e.g., rAAV virion) described herein. In some embodiments, the organ is a heart. In some embodiments, the heart is diseased or at risk of disease. In some embodiments, the heart has borderline or reduced ejection fraction. In some embodiments, the heart has a normal ejection fraction. In some embodiments, the heart comprises a genetic mutation associated with a heart disease. In some embodiments, the genetic mutation is a *PLN* mutation. In some embodiments, the heart has low or undetectable polypeptide expression compared to a healthy heart. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*.

[00284] The disclosure provides methods of increasing polypeptide expression in a subject comprising administering to the subject any vector or virion (e.g., rAAV virion) described herein. In some embodiments the subject is an animal. An animal can be, without limitation, a mouse, rat, dog, or non-human primate. In some embodiments, the subject is a human. In some embodiments, the increased polypeptide expression is in the heart of the subject. In some embodiments, the subject has a heart disease or is at risk of a heart disease. In some embodiments, the subject has borderline or reduced ejection fraction. In some embodiments, the subject has a normal ejection fraction. In some embodiments, the subject has a genetic mutation associated with a heart disease. In some embodiments, the genetic mutation is a *PLN* mutation. In some embodiments, the subject has low or undetectable level of DWORF expression compared to a healthy subject.

[00285] In some embodiments, the polypeptide is expressed in a cell, tissue, organ, or subject at a desired level of expression. A “desired level of expression” can be selected such that the level of expression is relative to the polypeptide expression in a healthy or diseased cell, tissue, organ, or subject. For example, an increased level in polypeptide expression relative to a diseased cardiac cell, cardiac tissue, heart, or subject with a heart disease or disorder can be a desired level of expression. The desired level of expression can be expressed relative to the difference in expression achieved between different vector or virions (e.g., rAAV virions) containing different expression cassettes. For example, a vector or virion (e.g., rAAV virion) comprising an expression cassette comprising a promoter and an enhancer may achieve a desired level of expression compared to a vector or virion (e.g., rAAV virion) comprising only a promoter.

[00286] The polypeptide expression level achieved by any vector or virion (e.g., rAAV virion) comprising an expression cassette can be described as a “fold” change (*i.e.*, increase or decrease) compared to basal polypeptide expression. The polypeptide expression level

achieved by a vector or virion (e.g., rAAV virion) comprising an expression cassette can be described as a “fold change” compared to polypeptide expression achieved by an expression cassette comprising a single promoter, no enhancers, and a sequence encoding the polypeptide. Fold change is a relative quantity, such that the levels of expression between the expression level achieved by an expression cassette and reference expression level are expressed as a ratio. It is understood that when describing fold change of polypeptide expression, “about” refers to ± 0.5 -fold. Polypeptide expression levels can be categorized as “low expression”, “medium expression”, or “high expression.” “Low expression” is meant to include expression levels between about 1.5-fold and 20-fold increase in polypeptide expression. “Medium expression” is meant to include expression levels between about 20-fold increase and about 60-fold increase in polypeptide expression. “High expression” is meant to include expression levels between about 60-fold and 140-fold increase in polypeptide expression.

[00287] In some embodiments, the polypeptide expression level is between about a 1.5-fold and 150-fold increase. In some embodiments, the polypeptide expression level is increased at least about 1.5-fold, about 3.5-fold, about 5.5-fold, about 7.5-fold, about 9.5-fold, about 11.5-fold, about 13.5-fold, about 15.5-fold, about 17.5-fold, about 19.5-fold, about 21.5-fold, about 23.5-fold, about 25.5-fold, about 27.5-fold, about 29.5-fold, about 31.5-fold, about 33.5-fold, about 35.5-fold, about 37.5-fold, about 39.5-fold, about 41.5-fold, about 43.5-fold, about 45.5-fold, about 47.5-fold, about 49.5-fold, about 51.5-fold, about 53.5-fold, about 55.5-fold, about 57.5-fold, about 59.5-fold, about 61.5-fold, about 63.5-fold, about 65.5-fold, about 67.5-fold, about 69.5-fold, about 71.5-fold, about 73.5-fold, about 75.5-fold, about 77.5-fold, about 79.5-fold, about 81.5-fold, about 83.5-fold, about 85.5-fold, about 87.5-fold, about 89.5-fold, about 91.5-fold, about 93.5-fold, about 95.5-fold, about 97.5-fold, about 99.5-fold, about 101.5-fold, about 103.5-fold, about 105.5-fold, about 107.5-fold, about 109.5-fold, about 111.5-fold, about 113.5-fold, about 115.5-fold, about 117.5-fold, about 119.5-fold, about 121.5-fold, about 123.5-fold, about 125.5-fold, about 127.5-fold, about 129.5-fold, about 131.5-fold, about 133.5-fold, about 135.5-fold, about 137.5-fold, about 139.5-fold, about 141.5-fold, about 143.5-fold, about 145.5-fold, about 147.5-fold, or about 149.5-fold.

[00288] In some embodiments, the polypeptide expression level is increased at least or more than about 5-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 10-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 15-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 25-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 35-fold. In some embodiments, the

polypeptide expression level is increased at least or more than about 50-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 60-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 75-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 85-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 100-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 110-fold. In some embodiments, the polypeptide expression level is increased at least or more than about 125-fold.

[00289] In some embodiments, the fold increase is relative to an expression cassette comprising a single promoter, no enhancers, and a sequence encoding the polypeptide. In some embodiments, the fold increase is relative to a healthy cell, tissue, organ, or subject. In some embodiments, the fold increase is relative to a diseased cell, tissue, organ, or subject.

Methods of Increasing DWORF Expression

[00290] The disclosure provides methods of increasing DWORF expression in a cell comprising contacting the cell with the rAAV virions described herein. In some embodiments, the cell is a cardiac cell. In some embodiments, the cell is a cardiomyocyte. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*.

[00291] The disclosure provides methods of increasing DWORF expression in a tissue comprising contacting the tissue with the rAAV virions described herein. In some embodiments, the tissue is cardiac tissue. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*.

[00292] The disclosure provides methods of increasing DWORF expression in an organ comprising contacting the organ with the rAAV virions described herein. In some embodiments, the organ is a heart. In some embodiments, the heart is diseased or at risk of disease. In some embodiments, the heart has borderline or reduced ejection fraction. In some embodiments, the heart has a normal ejection fraction. In some embodiments, the heart comprises a genetic mutation associated with a heart disease. In some embodiments, the genetic mutation is a *PLN* mutation. In some embodiments, the heart has low or undetectable DWORF expression compared to a healthy heart. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*.

[00293] The disclosure provides methods of increasing DWORF expression in a subject comprising administering to the subject the rAAV virions described herein. In some embodiments the subject is an animal. An animal can be, without limitation, a mouse, rat, dog, or non-human primate. In some embodiments, the subject is a human. In some embodiments,

the increased DWORF expression is in the heart of the subject. In some embodiments, the subject has a heart disease or is at risk of a heart disease. In some embodiments, the subject has borderline or reduced ejection fraction. In some embodiments, the subject has a normal ejection fraction. In some embodiments, the subject has a genetic mutation associated with a heart disease. In some embodiments, the genetic mutation is a *PLN* mutation. In some embodiments, the subject has low or undetectable level of DWORF expression compared to a healthy subject.

[00294] In some embodiments, DWORF is expressed in a cell, tissue, organ, or subject at a desired level of expression. A “desired level of expression” can be selected such that the level of expression is relative to DWORF expression in a healthy or diseased cell, tissue, organ, or subject. For example, an increased level in DWORF expression relative to a diseased cardiac cell, cardiac tissue, heart, or subject with a heart disease or disorder can be a desired level of expression. The desired level of expression can be expressed relative to the difference in expression achieved between different rAAV virions containing different expression cassettes. For example, an rAAV virion comprising an expression cassette comprising a promoter and an enhancer may achieve a desired level of expression compared to an rAAV virion comprising only a promoter.

[00295] The DWORF expression level achieved by an rAAV virion comprising an expression cassette can be described as a “fold” change (*i.e.*, increase or decrease) compared to basal DWORF expression. The DWORF expression level achieved by an rAAV virion comprising an expression cassette can be described as a “fold change” compared to DWORF expression achieved by an expression cassette comprising a single promoter, no enhancers, and a sequence encoding DWORF. Fold change is a relative quantity, such that the levels of expression between the expression level achieved by an expression cassette and reference expression level are expressed as a ratio. It is understood that when describing fold change of DWORF expression, “about” refers to ± 0.5 -fold. DWORF expression levels can be categorized as “low expression”, “medium expression”, or “high expression.” “Low expression” is meant to include expression levels between about 1.5-fold and 20-fold increase in DWORF expression. “Medium expression” is meant to include expression levels between about 20-fold increase and about 60-fold increase in DWORF expression. “High expression” is meant to include expression levels between about 60-fold and 140-fold increase in DWORF expression.

[00296] In some embodiments, the DWORF expression level is between about a 1.5-fold and 150-fold increase. In some embodiments, the DWORF expression level is increased about 1.5-fold, about 3.5-fold, about 5.5-fold, about 7.5-fold, about 9.5-fold, about 11.5-fold,

about 13.5-fold, about 15.5-fold, about 17.5-fold, about 19.5-fold, about 21.5-fold, about 23.5-fold, about 25.5-fold, about 27.5-fold, about 29.5-fold, about 31.5-fold, about 33.5-fold, about 35.5-fold, about 37.5-fold, about 39.5-fold, about 41.5-fold, about 43.5-fold, about 45.5-fold, about 47.5-fold, about 49.5-fold, about 51.5-fold, about 53.5-fold, about 55.5-fold, about 57.5-fold, about 59.5-fold, about 61.5-fold, about 63.5-fold, about 65.5-fold, about 67.5-fold, about 69.5-fold, about 71.5-fold, about 73.5-fold, about 75.5-fold, about 77.5-fold, about 79.5-fold, about 81.5-fold, about 83.5-fold, about 85.5-fold, about 87.5-fold, about 89.5-fold, about 91.5-fold, about 93.5-fold, about 95.5-fold, about 97.5-fold, about 99.5-fold, about 101.5-fold, about 103.5-fold, about 105.5-fold, about 107.5-fold, about 109.5-fold, about 111.5-fold, about 113.5-fold, about 115.5-fold, about 117.5-fold, about 119.5-fold, about 121.5-fold, about 123.5-fold, about 125.5-fold, about 127.5-fold, about 129.5-fold, about 131.5-fold, about 133.5-fold, about 135.5-fold, about 137.5-fold, about 139.5-fold, about 141.5-fold, about 143.5-fold, about 145.5-fold, about 147.5-fold, or about 149.5-fold.

[00297] In some embodiments, the DWORF expression level is increased at least or more than about 5-fold. In some embodiments, the DWORF expression level is increased at least or more than about 10-fold. In some embodiments, the DWORF expression level is increased at least or more than about 15-fold. In some embodiments, the DWORF expression level is increased at least or more than about 25-fold. In some embodiments, the DWORF expression level is increased at least or more than about 35-fold. In some embodiments, the DWORF expression level is increased at least or more than about 50-fold. In some embodiments, the DWORF expression level is increased at least or more than about 60-fold. In some embodiments, the DWORF expression level is increased at least or more than about 75-fold. In some embodiments, the DWORF expression level is increased at least or more than about 85-fold. In some embodiments, the DWORF expression level is increased at least or more than about 100-fold. In some embodiments, the DWORF expression level is increased at least or more than about 110-fold. In some embodiments, the DWORF expression level is increased at least or more than about 125-fold.

[00298] In some embodiments, the fold increase is relative to an expression cassette comprising a single promoter, no enhancers, and a sequence encoding DWORF. In some embodiments, the fold increase is relative to a healthy cell, tissue, organ, or subject. In some embodiments, the fold increase is relative to a diseased cell, tissue, organ, or subject.

Methods of Treatment

[00299] In an aspect, any vector comprising an expression cassette described herein may be used for treating disease, such as heart disease.

[00300] In an aspect, rAAV virions comprising an expression cassette described herein may be used for treating disease (Wang et al. *Nat Rev Drug Discov.* 18:358–378 (2019)). For treatment, rAAV virions have been used to deliver transgenes encoding polypeptides such as microdystrophin (Chamberlain et al. *Mol Ther.* 25:1125-1131 (2017)), glial cell line-derived neurotrophic factor (McFarthing et al. *J Parkinsons Dis.* 9:251–264 (2019)), and Factor IX (Nathwani et al. *N Engl J Med.* 371:1994–2004 (2014)).

[00301] A variety of strategies for treating heart failure using rAAV-based delivery of a transgene have been pursued *in vivo*. In a pig model of heart failure, β -adrenergic receptor, a regulator of contractility, has been targeted by delivery of a small polypeptide, β ARKct that indirectly prevents disruption of β -adrenergic receptor signaling (Raake et al. *Eur Heart J.* 34:1437–47 (2013)). In a canine model, cardiomyocyte viability was enhanced by rAAV-based delivery of a vascular endothelial growth factor (VEGF) isoform. In human clinical trials, rAAV-based delivery of an isoform of the SERCA calcium pump, SERCA2a, to the heart was tested as a treatment for heart failure. SERCA, or sarco/endoplasmic reticulum Ca^{2+} -ATPase, or SR Ca^{2+} -ATPase, is a calcium ATPase-type P-ATPase. SERCA resides in the sarcoplasmic reticulum (SR) within muscle cells. It is a Ca^{2+} ATPase that transfers Ca^{2+} from the cytosol of the cell to the lumen of the SR at the expense of ATP hydrolysis during muscle relaxation. SERCA activity is necessary for proper contractile function of the heart. However, direct replacement of SERCA activity by rAAV-based delivery of the SERCA2a isoform failed to show a significant effect in clinical trials (Bass-Stringer et al. *Heart, Lung and Circulation.* 27:1285–1300 (2018)). Enhancing SERCA activity using alternative strategies is desired for treating diseases of the heart, *e.g.*, heart failure and cardiomyopathy.

[00302] There are three major domains on the cytoplasmic face of SERCA: the phosphorylation and nucleotide-binding domains, which form the catalytic site, and the actuator domain, which is involved in the transmission of major conformational changes. The rate at which SERCA moves Ca^{2+} across the SR membrane can be controlled by the regulatory protein phospholamban (PLN). SERCA is normally inhibited by PLN, with which it is closely associated. Increased β -adrenergic stimulation reduces the association between SERCA and PLN by the phosphorylation of PLN by PKA. When PLN is associated with SERCA, the rate of Ca^{2+} movement is reduced; upon dissociation of PLN, Ca^{2+} movement increases.

[00303] An alternative strategy to enhancing SERCA activity by delivering a SERCA2a isoform is to enhance activity of natively expressed SERCA by displacing PLN. Contacting SERCA with the DWORF polypeptide, described in detail above, can displace PLN and enhance SERCA activity.

[00304] In some embodiments, the disclosure provides a method of treating a heart disease or disorder in a subject in need thereof, the method comprising administering an effective amount of a vector comprising an expression cassette comprising a polynucleotide encoding a therapeutic polypeptide operatively linked to a promoter, wherein the therapeutic polypeptide can be any polypeptide useful for treating heart disease. As described herein, the vector can be any viral or non-viral vector.

[00305] In some embodiments, the disclosure provides a method of treating a heart disease or disorder in a subject in need thereof, the method comprising administering an effective amount of a recombinant adeno-associated virus (rAAV) virion, the rAAV virion comprising an AAV capsid and an expression cassette comprising a polynucleotide encoding a DWORF polypeptide operatively linked to a promoter.

[00306] In a method of treating a subject as described herein, “treating” or “treatment of a condition or subject in need thereof” refers to (1) taking steps to obtain beneficial or desired results, including clinical results such as the reduction of symptoms; (2) inhibiting the disease, for example, arresting or reducing the development of the disease or its clinical symptoms; (3) relieving the disease, for example, causing regression of the disease or its clinical symptoms; or (4) delaying the disease. For purposes of the methods described herein, beneficial or desired clinical results include, but are not limited to, reduction of symptoms associated with heart failure, cardiomyopathy, dilated cardiomyopathy, myocardial infarction, acute myocardial infarction, and chronic myocardial infarction.

[00307] In other aspects, the disclosure provides a method of preventing a heart disease or disorder in a subject in need thereof, the method comprising administering an effective amount of a vector comprising an expression cassette comprising a polynucleotide encoding a therapeutic polypeptide operatively linked to a promoter, wherein the therapeutic polypeptide can be any polypeptide useful for preventing heart disease. As described herein, the vector can be any viral or non-viral vector. In some embodiments, prevention of a disease causes the clinical symptoms of the disease not to develop in a patient that may be predisposed to the disease, but does not yet experience or display symptoms of the disease.

[00308] Subjects in need of treatment using the compositions and methods of the present disclosure include, but are not limited to, a subject suffering from or being at risk of heart failure. A subject “suffering from” heart failure is considered to have symptoms associated with or a confirmed diagnosis of any of the heart diseases described herein. A subject “at risk of” heart failure is considered to have one or more risk factors associated with any of the heart diseases described herein.

[00309] In some embodiments, the methods described herein are useful to treat heart disease or disorder with reduced ejection fraction (HFrEF). In some embodiments, the methods described herein are useful to treat heart disease or disorder with preserved ejection fraction (HFpEF).

[00310] In some embodiments, the methods described herein are useful to treat cardiomyopathy. In some embodiments, a method described herein is useful to treat dilated cardiomyopathy. In some embodiments, the subject suffers from or is at risk for cardiomyopathy. In some embodiments, the cardiomyopathy is dilated cardiomyopathy (DCM). In some embodiments, the DCM is genetic DCM (e.g., DCM associated with a *PLN* mutation in a subject to be treated). In some embodiments, the methods described herein are useful to treat *PLN* mutation-associated cardiomyopathy. In some embodiments, the DCM is non-genetic DCM. In some embodiments, subject suffers from or is at risk for myocardial infarction. In some embodiments, the myocardial infarction is chronic myocardial infarction. In some embodiments, the myocardial infarction is acute myocardial infarction.

[00311] Cardiomyopathy phenotypes can manifest in a subject through a multitude of molecular mechanisms. Transgenic animals have been developed to investigate the molecular pathophysiology of specific mechanisms and the efficacy of potential therapeutic and prevention strategies for cardiomyopathy phenotypes (Law et al. *J Clin Med.* 9:520 (2020)). These animal models can be used to evaluate aspects of the rAAV viral genomes, rAAV virions, and compositions thereof described herein. The *MLP*^{-/-} transgenic mouse model, for example, recapitulates the phenotype of dilated cardiomyopathy by knocking out the muscle LIM protein, a positive regulator of myogenic differentiation associated with the actin-based cytoskeleton. The absence of LIM protein results in a disruption of cytoskeletal architecture and decreased Ca²⁺ cycling (Minamisawa et al. *Cell.* 99:313-22 (1999)). Artificial replacement with a phosphomimetic *PLN* transgene delivered by rAAV reduced DCM symptoms in the animals, including improved ejection fraction (Iwanaga Y et al. *J Clin Invest.* 113:727-736 (2004)). While the *MLP*^{-/-} model recapitulates DCM phenotype in a general way, other transgenic mouse models of DCM are more appropriate for specific DCM phenotypes, such as those driven by a mutation to the *PLN* gene. For example, a transgenic mouse model to recapitulate the clinically observed *PLN*-R14Del mutation has been developed (Haghighi et al. *Proc. Natl. Acad. Sci. U.S.A* 103:1388-1393 (2006)). It is expected that mouse models with different transgenic modifications to induce a DCM phenotype are not interchangeable for the purpose of evaluating the efficacy of a given therapeutic or prevention strategy, and that each model provides different information about the translation of a therapy.

[00312] In some embodiments, the subject in need of treatment has an inherited risk allele (*i.e.*, mutation) for a heart disease or disorder. A risk allele can be, for example, a mutation to the *PLN* gene. Mutations to the *PLN* gene can cause a dysfunctional inhibitory effect on SERCA activity. Clinically observable mutations in the *PLN* gene and protein include a mutation in the *PLN* promoter, a truncation resulting in a $PLN^{L39stop}$ mutant, aberrant R9C, R9L, and R9H mutations, *PLN* gene duplications, and deletion of arginine 14 (R14del) in the regulatory domain of PLN. Each of these mutations have been directly linked to dilated cardiomyopathy, hypertrophic cardiomyopathy, or arrhythmic right ventricular cardiomyopathy (Table 8.) (Landstrom et al. *Am Heart J.* 161:165-171 (2011), Lee et al. *Cardiol Young.* 24:953-954 (2014); Haghighi et al. *J. Clin. Invest.* 111:869-876 (2003); Schmitt et al. *Science* 299:1410-1413 (2003); Haghighi et al. *Proc. Natl. Acad. Sci. U.S.A* 103:1388-1393 (2006); Medeiros A et al. *Am. Heart J.* 162:1088-1095 (2011)).

Table 8. PLN mutations and associated heart diseases

PLN Mutation	Associated Heart Disease
<i>PLN</i> promoter mutation	Dilated Cardiomyopathy; Hypertrophic Cardiomyopathy
$PLN^{L39stop}$	Dilated Cardiomyopathy; Hypertrophic Cardiomyopathy
R9C	Dilated Cardiomyopathy
R9L	Dilated Cardiomyopathy
R9H	Dilated Cardiomyopathy
<i>PLN</i> gene duplication	Dilated Cardiomyopathy
R14del	Dilated Cardiomyopathy; Arrhythmic Right Ventricular Cardiomyopathy

[00313] The various mutations in PLN have different mechanisms of inducing a cardiomyopathy phenotype. For example, the R9C mutation indirectly blocks the phosphorylation of PLN by PKA and prevents the formation of monomeric PLN that can bind to SERCA. In some embodiments, the subject in need of treatment has a *PLN* promoter mutation. In some embodiments, the subject in need of treatment has a $PLN^{L39stop}$ mutation. In some embodiments, the subject in need of treatment has a R9C mutation. In some embodiments, the subject in need of treatment has a R9L mutation. In some embodiments, the subject in need of treatment has a R9H mutation. In some embodiments, the subject in need of treatment has a *PLN* gene duplication. In some embodiments, the subject in need of treatment has a R14del mutation.

[00314] Mutations can be detected by many types of genetic analysis known in the art. Genetic analysis can be, for example, direct sequencing, fluorescent *in situ* hybridization assays, polymerase chain reaction-based assays, nucleotide microarray assays, or any other technique known in the art to determine the sequence characteristics of polynucleotides sampled from a subject. For example, DNA was isolated from the peripheral blood samples patients diagnosed with either dilated cardiomyopathy (DCM) or arrhythmic right ventricular cardiomyopathy (ARVC). The coding region of the *PLN* gene in the isolated DNA was sequenced using a BigDye Terminator DNA sequencing kit (version 2.0) on a 3730 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Patients diagnosed with either DCM or ARVC both carried the PLN R14del mutation (van der Zwaag et al. *Eur J Heart Fail.* 14:1199-1207 (2012)).

Methods of Reducing, Improving, and Preventing Symptoms

[00315] In some embodiments, the disclosure provides a method of reducing one or more symptoms of a heart disease or disorder in a subject comprising administration of any vector comprising an expression cassette described herein. In some embodiments, the symptoms are reduced compared to the symptoms of the heart disease or disorder prior to administration of the vector comprising an expression cassette described herein to the subject. In some embodiments, the disclosure provides a method of reducing one or more symptoms of a heart disease or disorder in a subject comprising administration of an rAAV virion described herein. In some embodiments, the symptoms are reduced compared to the symptoms of the heart disease or disorder prior to administration of the rAAV virion to the subject. In some embodiments, the heart disease or disorder is heart failure. In some embodiments, the heart disease or disorder is cardiomyopathy. In some embodiments, the heart disease or disorder is dilated cardiomyopathy. In some embodiments, the heart disease or disorder is myocardial infarction. In some embodiments, the heart disease or disorder is chronic myocardial infarction. In some embodiments, the heart disease or disorder is acute myocardial infarction.

[00316] In some embodiments, the disclosure provides a method of improving one or more symptoms of a heart disease or disorder in a subject comprising administration of a vector comprising an expression cassette described herein. In some embodiments, the symptoms are improved compared to the symptoms of the heart disease or disorder prior to administration of the vector to the subject. In some embodiments, the disclosure provides a method of improving one or more symptoms of a heart disease or disorder in a subject comprising administration of an rAAV virion described herein. In some embodiments, the symptoms are improved compared to the symptoms of the heart disease or disorder prior to administration of the rAAV virion to

the subject. In some embodiments, the heart disease or disorder is heart failure. In some embodiments, the heart disease or disorder is cardiomyopathy. In some embodiments, the heart disease or disorder is dilated cardiomyopathy. In some embodiments, the heart disease or disorder is myocardial infarction. In some embodiments, the heart disease or disorder is chronic myocardial infarction. In some embodiments, the heart disease or disorder is acute myocardial infarction.

[00317] In some embodiments, the disclosure provides a method of preventing one or more symptoms of a heart disease or disorder in a subject comprising administration of a vector comprising an expression cassette described herein. In some embodiments, the disclosure provides a method of preventing one or more symptoms of a heart disease or disorder in a subject comprising administration of the rAAV virion described herein. In some embodiments, the symptoms are prevented in a subject considered to be at-risk of the heart disease or disorder. In some embodiments, the heart disease or disorder is heart failure. In some embodiments, the heart disease or disorder is cardiomyopathy. In some embodiments, the heart disease or disorder is dilated cardiomyopathy. In some embodiments, the heart disease or disorder is myocardial infarction. In some embodiments, the heart disease or disorder is chronic myocardial infarction. In some embodiments, the heart disease or disorder is acute myocardial infarction.

[00318] In some embodiments, the symptoms are reduced compared to the symptoms of the heart disease or disorder prior to administration of the vector to the subject. In some embodiments, the symptoms are reduced compared to the symptoms of the heart disease or disorder prior to administration of the rAAV virion to the subject. In some embodiments, the heart disease or disorder is heart failure. In some embodiments, the heart disease or disorder is cardiomyopathy. In some embodiments, the heart disease or disorder is dilated cardiomyopathy. In some embodiments, the heart disease or disorder is myocardial infarction. In some embodiments, the heart disease or disorder is chronic myocardial infarction. In some embodiments, the heart disease or disorder is acute myocardial infarction.

[00319] As used herein, “symptoms” include any of the diagnostic criteria or symptoms associated with, e.g., heart diseases described herein. Severity and changes of symptoms and diagnostic results are determined by a medical professional qualified to deliver assessments and analyze the results of such assessments.

[00320] Common symptoms in subjects with or at risk of developing heart disease are fatigue, dyspnea, edema, chest pain, arrhythmias, blood clots, impaired heart valve function, and heart murmur. In some embodiments, the subject experiences reduced symptoms

associated with the heart diseases described herein following administration of the vector, an rAAV virion or compositions of the disclosure. In some embodiments, the improved symptoms are one or more of enhanced contractility; reduced fatigue; reduced dyspnea; reduced edema; reduced chest pain; reduced arrhythmias; reduced blood clots; improved heart valve function; and reduced heart murmur. In some embodiments, the symptom is a change in 6 minute walk distance. In some embodiments, symptoms are determined by the Minnesota Living with Heart Failure Questionnaire. In some embodiments, the symptom is an abnormal level of B-type natriuretic peptide (*i.e.*, BNP, NT-proBNP). In some embodiments, the severity of symptoms are determined by measuring LV remodeling. In some embodiments of the method described herein improves one or more measures of cardiac function. In some embodiments, the measures of cardiac function comprise fractional shortening and/or left ventricular internal dimension (LVID). In some embodiments, the measures of cardiac function comprises left ventricular end-systolic volume (LVESV). In some embodiments, the improvement in cardiac function is ejection fraction. In some embodiments, improvement in cardiac function is observed at weeks 2 through 12. In some embodiments, the method reduces cardiac remodeling. In some embodiments, the method counteracts a decrease in DWORF expression in subjects suffering from myocardial infarction.

[00321] Ejection fraction is a measurement of the percentage of blood leaving the heart each time it contracts. The ejection fraction is determined using the stroke volume (SV) and the end-diastolic volume (EDV), calculated as: $EF(\%) = (SV/EDV) \times 100$. Ejection fraction can be measured in a subject with imaging tests, including echocardiogram, cardiac catheterization, magnetic resonance imaging (MRI), computerized tomography (CT), and/or nuclear medicine scan. A normal ejection fraction is between about 50% and about 75%. A “borderline” ejection fraction can range between about 41% and about 50%. A reduced ejection fraction is less than about 41%. A borderline or reduced ejection fraction can be used as a symptom in diagnosing a heart disease or disorder. It is understood that the cutoff values between normal, borderline, and reduced ejection fraction are approximate and one skilled in the art, *e.g.*, a cardiologist, will ultimately make the determination.

[00322] In some embodiments of the methods provided herein, it may be desirable to improve ejection fraction. Ejection fraction can be considered to be improved if the ejection fraction percentage increases. In some embodiments, the ejection fraction

[00323] In some embodiments of the methods provided herein, it may be desirable to preserve ejection fraction. Preserving ejection fraction can be used to prevent the onset of a heart disease or disorder in a subject at risk thereof, prevent the progression of a heart disease

or disorder, or prevent worsening of symptoms associated with a heart disease or disorder in a subject at risk of or suffering therefrom.

[00324] The disclosure provides methods of improving ejection fraction in a subject at risk or suffering from a heart disease or disorder. In some embodiments, ejection fraction is improved (*i.e.*, increased) in the subject following administration of a vector comprising an expression cassette described herein. In some embodiments, ejection fraction is improved (*i.e.*, increased) in the subject following administration of a vector or an rAAV virion described herein. In some embodiments, ejection fraction is improved about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 22 weeks or about 24 weeks following administration of the vector or the rAAV virion to the subject. In some embodiments, ejection fraction is improved about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20% following administration of the vector or the rAAV virion to the subject.

[00325] The disclosure provides methods of preserving ejection fraction in a subject at risk or suffering from a heart disease or disorder. For example, the subject may maintain an ejection fraction that would otherwise be expected to reduce in the absence of administration of the vector or the rAAV virion or pharmaceutical composition of the disclosure. In some embodiments, ejection fraction is preserved in the subject following administration of the vector or the rAAV virion of the disclosure. In some embodiments, ejection fraction is preserved about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 22 weeks or about 24 weeks following administration of the vector or rAAV virion to the subject. In some embodiments, ejection fraction is preserved by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20% following administration of the vector or rAAV virion to the subject.

[00326] Assessment of heart contractility can be used to assess acute and chronic forms of heart failure. Heart contractility may be monitored by using invasive hemodynamic monitoring, continuous ECG monitoring, central venous pressure, kidney function, pulse

oximetry, arterial pressure monitoring, pulmonary artery catheter, and/or transeophageal echocardiography (Kuhn C, Werdan K. *Surgical Treatment: Evidence-Based and Problem-Oriented*. Munich: Zuckschwerdt; 2001. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK6895/>).

[00327] Dyspnea and fatigue associated with heart disease described herein can be measured using questionnaires. The Modified Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M)¹⁰ (Huang et al. *Am J Crit Care*. 17:436–442 (2008)) and Minnesota Living with Heart Failure Questionnaire (MLHFQ)¹¹ (Bilbao et al. *Health Qual Life Outcomes*. 14:23 (2016)), for example, can be used to measure subjects with a heart disease as described herein. The questionnaires are self-administered and allow a score to be derived that is used to assess symptom severity for dyspnea, fatigue, and other heart-health related symptoms.

[00328] Cardiomyopathy, myocardial infarction and heart valve function may be assessed using one or more of an exercise stress test, electrocardiogram, echocardiogram, chest X-ray, cardiac CT scan, or angiogram with cardiac catheterization, cardiac MRI, B-type natriuretic peptide (BNP) levels in the blood, and/or genetic screening. Further testing is required to diagnose specific types of cardiomyopathy, myocardial infarction, or heart valve dysfunction.

[00329] In some aspects, administration of a vector comprising an expression cassette described herein to a subject results in an improvement in exercise capacity of the subject (e.g., improvement in running distance and/or time to exhaustion). In some aspects, administration of an rAAV comprising an expression cassette described herein encoding DWORF to a subject results in an improvement in exercise capacity of the subject (e.g., improvement in running distance and/or time to exhaustion).

[00330] Dilated cardiomyopathy (DCM) is a progressive disease of heart muscle characterized by chamber enlargement and contractile dysfunction of the left ventricle in the absence of chronic pressure and/or volume overload. DCM is diagnosed primarily using echocardiography.

[00331] Echocardiography with a PLAX view in 2D/M-mode is used to measure several parameters, including ejection fraction, LVIDd/s, IVSd, LVPWd, and fractional shortening. These parameters are used to assess the left ventricle cavity size, wall thickness, and radial function. Diagnostic criterion for DCM includes LVIDd/s greater than 112% (2 S.D) corrected for age and body surface area (BSA). Fractional shortening less than 25% is a criterion for the

diagnosis of DCM in the presence of a dilated ventricle (Mathew et al. *Echo Res Pract.* 4:G1–G13 (2017)).

[00332] Qualitative assessment of left and right ventricular structure and function with special reference to radial and longitudinal function and regional wall motion abnormalities are assessed by echocardiography in the apical four-chamber (A4C) view in 2D mode. Ejection fraction (EF) can be estimated using, for example, biplane Simpsons method. EF of less than 45% is a diagnostic criterion for DCM in the presence of dilated ventricle (Mathew et al. *Echo Res Pract.* 4: G1–G13 (2017)).

ADMINISTRATION

[00333] In some embodiments, the vectors and compositions of the present disclosure can be administered to a subject in need thereof by systemic application, *e.g.*, by intravenous, intra-arterial or intraperitoneal delivery. In some embodiments, the rAAV virion and compositions of the present disclosure can be administered to a subject in need thereof by systemic application, *e.g.*, by intravenous, intra-arterial or intraperitoneal delivery of a vector in analogy to what has been shown in animal models (Katz et al., *Gene Ther* 19:659-669 (2012)). In some embodiments, the vectors, rAAV virions and compositions of the present disclosure treat or prevent heart failure. In some embodiments, the cardiomyopathy, wherein the vector is administered systemically. In some embodiments, the rAAV virion is administered by intravenous or intracoronary injection.

[00334] The disclosure provides methods for expressing a polypeptide in a cell *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, the disclosure provides methods for expressing a DWORF polypeptide in a cell *in vitro*, *ex vivo*, or *in vivo*. The method comprises, for example, exposing a target cell to the vectors, rAAV virions or pharmaceutical compositions described herein. A target cell can be, for example and without limitation, a cardiac cell, a muscle cell, an induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM), and/or a cardiomyocyte. In some embodiments, a method of expressing a polypeptide (*e.g.*, DWORF polypeptide) in a cell comprises transfecting or transducing (alternating referred to as “infecting”) a target cell or population of target cells with a vector described herein. In some embodiments, a method of expressing a polypeptide (*e.g.*, DWORF polypeptide) in a cell comprises transducing (alternating referred to as “infecting”) a target cell or population of target cells with an rAAV virion or pharmaceutical compositions described herein. In some embodiments, the rAAV transduces cardiac cells. In some embodiments, the rAAV transduces cardiomyocytes. In some

embodiments, the rAAV transduces induced pluripotent stem cell-derived cardiomyocytes (iPSC-CM).

[00335] In some embodiments, the vector transfection or transduction increases polypeptide expression in the heart of the subject. In some embodiments, the rAAV transduction increases DWORF polypeptide expression in the heart of the subject. “Increased polypeptide expression” typically refers to expression at least 5%, 10%, 15%, 20% or more compared to a control subject or tissue not treated with the vector. “Increased DWORF polypeptide expression” typically refers to expression at least 5%, 10%, 15%, 20% or more compared to a control subject or tissue not treated with the vector. In some embodiments, detectable expression means expression at 1.5-fold, 2-fold, 2.5-fold, or 3-fold greater than a no-vector control. Expression can be assessed by Western blot, as described in the example that follows, or enzyme-linked immunosorbent assay (ELISA), or other methods known in the art. In some cases, expression is measured quantitatively using a standard curve. Standard curves can be generated using purified protein, *e.g.*, purified DWORF polypeptide, by methods described in the examples or known in the art. Alternatively, expression of the therapeutic gene product can be assessed by quantification of the corresponding mRNA. In some embodiments, the method causes the expression of the polypeptide (*e.g.*, DWORF polypeptide) in the heart of the subject.

[00336] In some embodiments, the method causes no detectable expression of the polypeptide in the muscles of the subject except the heart, in the liver of the subject, and/or in cardiac fibroblasts. In some embodiments, the method causes expression of the polypeptide in cardiomyocytes.

[00337] In some embodiments, the method causes no detectable expression of the DWORF polypeptide in the muscles of the subject except the heart. In some embodiments, the method causes no detectable expression of the DWORF polypeptide in the liver of the subject. In some embodiments, the method causes expression of the DWORF polypeptide in cardiomyocytes. In some embodiments, the method causes no detectable expression of the DWORF polypeptide in cardiac fibroblasts.

[00338] In some embodiments, the increased polypeptide expression in heart tissue occurs at doses, in vector genomes (vg) per kilogram weight of subject (kg), of 3×10^{14} vg/kg or less, 2×10^{14} vg/kg or less, 1×10^{14} vg/kg or less, 9×10^{13} vg/kg or less, 8×10^{13} vg/kg or less, 7×10^{13} vg/kg or less, 6×10^{13} vg/kg or less, 5×10^{13} vg/kg or less, 4×10^{13} vg/kg or less, 3×10^{13} vg/kg or less, 2×10^{13} vg/kg or less, or 1×10^{13} vg/kg or less.

[00339] In some embodiments, the increased DWORF expression in heart tissue occurs at doses, in vector genomes (vg) per kilogram weight of subject (kg), of 3×10^{14} vg/kg or less, 2×10^{14} vg/kg or less, 1×10^{14} vg/kg or less, 9×10^{13} vg/kg or less, 8×10^{13} vg/kg or less, 7×10^{13} vg/kg or less, 6×10^{13} vg/kg or less, 5×10^{13} vg/kg or less, 4×10^{13} vg/kg or less, 3×10^{13} vg/kg or less, 2×10^{13} vg/kg or less, or 1×10^{13} vg/kg or less.

PHARMACEUTICAL COMPOSITIONS AND KITS

[00340] The vectors of the disclosure are generally delivered to the subject as a pharmaceutical composition. In some embodiments, the rAAV virion of the disclosure is delivered to the subject as a pharmaceutical composition. Pharmaceutical compositions comprise a pharmaceutically acceptable solvent (*e.g.*, water, etc.) and one or more excipients. In some embodiments, the pharmaceutical compositions comprise a buffer at about neutral pH (pH 5, 6, 7, 8, or 9). In some embodiments, the pharmaceutical composition comprises phosphate buffered saline (*e.g.*, PBS at pH of about 7). The pharmaceutical compositions may comprise a pharmaceutically acceptable salt. The concentration of the salt may be selected to ensure that the pharmaceutical composition is isotonic to, or nearly isotonic to, the target tissue.

[00341] In various embodiments, the compositions described herein contain vehicles (*e.g.*, carriers, diluents and excipients) that are pharmaceutically acceptable for a formulation capable of being injected. These may be in particular isotonic, sterile, saline solutions (monosodium or disodium phosphate, sodium, potassium, calcium or magnesium chloride and the like or mixtures of such salts), or dry, especially freeze-dried compositions which upon addition, depending on the case, of sterilized water or physiological saline, permit the constitution of injectable solutions. Illustrative pharmaceutical forms suitable for injectable use include, *e.g.*, sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions.

[00342] In various embodiments, the pharmaceutical compositions of the disclosure comprise about 1×10^8 genome copies per milliliter (GC/mL), about 5×10^8 GC/mL, about 1×10^9 GC/mL, about 5×10^9 GC/mL, about 1×10^{10} GC/mL, about 5×10^{10} GC/mL, about 1×10^{11} GC/mL, about 5×10^{11} GC/mL, about 1×10^{12} GC/mL, about 5×10^{12} GC/mL, about 5×10^{13} GC/mL, about 1×10^{14} GC/mL, or about 5×10^{14} GC/mL of the viral vector (*e.g.*, rAAV virion).

[00343] In various embodiments, the pharmaceutical compositions of the disclosure comprise about 1×10^8 viral genomes per milliliter (vg/mL), about 5×10^8 vg/mL, about 1×10^9 vg/mL, about 5×10^9 vg/mL, about 1×10^{10} vg/mL, about 5×10^{10} vg/mL, about 1×10^{11} vg/mL,

about 5×10^{11} vg/mL, about 1×10^{12} vg/mL, about 5×10^{12} vg/mL, about 5×10^{13} vg/mL, about 1×10^{14} vg/mL, or about 5×10^{14} vg/mL of the viral vector (*e.g.*, rAAV virion).

[00344] In some embodiments, the pharmaceutical compositions of the disclosure are administered in a total volume of about 1 mL, 5 mL, 10 mL, about 20 mL, about 25 mL, about 30 mL, about 35 mL, about 40 mL, about 45 mL, about 50 mL, about 55 mL, about 60 mL, 65 mL, about 70 mL, about 75 mL, about 80 mL, about 85 mL, about 90 mL, about 95 mL, about 100 mL, about 105 mL, about 110 mL, about 115 mL, about 120 mL, about 125 mL, about 130 mL, about 135 mL, about 140 mL, about 145 mL, about 150 mL, about 155 mL, about 160 mL, about 165 mL, about 170 mL, about 175 mL, about 180 mL, about 185 mL, about 190 mL, about 200 mL, about 205 mL, about 210 mL, about 215 mL, or about 220 mL.

[00345] Genome copies per milliliter can be determined by quantitative polymerase chain reaction (qPCR) using a standard curve generated with a reference sample having a known concentration of the polynucleotide genome of the virus. For AAV, the reference sample used is often the transfer plasmid used in generation of the rAAV virion but other reference samples may be used.

[00346] Alternatively or in addition, the concentration of a viral vector can be determined by measuring the titer of the vector on a cell line. Viral titer is typically expressed as viral particles (vp) per unit volume (*e.g.*, vp/mL). In various embodiments, the pharmaceutical compositions of the disclosure comprise about 1×10^8 viral particles per milliliter (vp/mL), about 5×10^8 vp/mL, about 1×10^9 vp/mL, about 5×10^9 vp/mL, about 1×10^{10} vp/mL, about 5×10^{10} vp/mL, about 1×10^{11} vp/mL, about 5×10^{11} vp/mL, about 1×10^{12} vp/mL, about 5×10^{12} vp/mL, about 5×10^{13} vp/mL, or about 1×10^{14} vp/mL, or about 5×10^{14} of the viral vector (*e.g.*, rAAV virion).

[00347] In some embodiments, the present disclosure provides a kit comprising a container housing a pharmaceutical composition as described herein.

NUMBERED EMBODIMENTS OF THE INVENTION I

[00348] Embodiment 1: A recombinant adeno-associated virus (rAAV) virion, comprising a capsid protein and a viral genome comprising an expression cassette comprising a polynucleotide sequence encoding a dwarf open reading frame (DWORF) polypeptide operatively linked to a promoter, the expression cassette flanked by inverted terminal repeats.

[00349] Embodiment 2: The rAAV virion of embodiment 1, wherein the DWORF polypeptide shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to a sequence selected from SEQ ID NOs: 1, 3, 4, 7, 9, 23, and 43.

- [00350] Embodiment 3: The rAAV virion of embodiment 1, wherein the DWORF polypeptide is selected from SEQ ID NOs: 1, 3, 4, 7, 9, 23, and 43.
- [00351] Embodiment 4: The rAAV virion of embodiment 1 or 2, wherein the promoter is a chicken cTnT promoter.
- [00352] Embodiment 5: The rAAV virion of embodiment 4, wherein the chicken cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 11.
- [00353] Embodiment 6: The rAAV virion of embodiment 4, wherein the chicken cTnT promoter comprises SEQ ID NO: 11.
- [00354] Embodiment 7: The rAAV virion of embodiment 1 or 2, wherein the promoter is a human cTnT promoter.
- [00355] Embodiment 8: The rAAV virion of embodiment 7, wherein the human cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 12 or SEQ ID NO: 13.
- [00356] Embodiment 9: The rAAV virion of embodiment 7, wherein the human cTnT promoter comprises SEQ ID NO: 12 or SEQ ID NO: 13.
- [00357] Embodiment 10: The rAAV virion of any one of embodiments 1 to 9, wherein the expression cassette further comprises one or more enhancers.
- [00358] Embodiment 11: The rAAV virion of embodiment 10, wherein the enhancer the one or more enhancers are selected from a ACTC1 cardiac enhancer and a α MHC enhancer.
- [00359] Embodiment 12: The rAAV virion of embodiment 11, wherein the ACTC1 cardiac enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 78.
- [00360] Embodiment 13: The rAAV virion of embodiment 11, wherein the ACTC1 cardiac enhancer comprises SEQ ID NO: 78.
- [00361] Embodiment 14: The rAAV virion of embodiment 11, wherein the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79.
- [00362] Embodiment 15: The rAAV virion of embodiment 11, wherein the α MHC enhancer comprises SEQ ID NO: 79.
- [00363] Embodiment 16: The rAAV virion of any one of embodiments 1 to 15, wherein the expression cassette further comprises an intron.
- [00364] Embodiment 17: The rAAV virion of embodiment 16, wherein the intron is selected from a CMV intron and a chimeric intron.
- [00365] Embodiment 18: The rAAV virion of embodiment 17, wherein the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 80.

- [00366] Embodiment 19: The rAAV virion of embodiment 17, wherein the CMV intron comprises SEQ ID NO: 80.
- [00367] Embodiment 20: The rAAV virion of embodiment 17, wherein the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81.
- [00368] Embodiment 21: The rAAV virion of embodiment 17, wherein the chimeric intron comprises SEQ ID NO: 81.
- [00369] Embodiment 22: The rAAV virion of any one of embodiments 1 to 21, wherein the expression cassette further comprises a WPRE sequence.
- [00370] Embodiment 23: The rAAV virion of embodiment 22, wherein the WPRE sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26.
- [00371] Embodiment 24: The rAAV virion of embodiment 22, wherein the WPRE sequence comprises SEQ ID NO: 26.
- [00372] Embodiment 25: The rAAV virion of any one of embodiments 1 to 24, wherein the expression cassette further comprises a polyadenylation sequence.
- [00373] Embodiment 26: The rAAV virion of embodiment 25, wherein the polyadenylation sequence is selected from a BGH polyadenylation sequence and a SV40 polyadenylation sequence.
- [00374] Embodiment 27: The rAAV virion of embodiment 26, wherein the BGH polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 27.
- [00375] Embodiment 28: The rAAV virion of embodiment 26, wherein the BGH polyadenylation sequence comprises SEQ ID NO: 27.
- [00376] Embodiment 29: The rAAV virion of embodiment 26, wherein the SV40 polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 28.
- [00377] Embodiment 30: The rAAV virion of embodiment 26, wherein the SV40 polyadenylation sequence comprises SEQ ID NO: 28.
- [00378] Embodiment 31: The rAAV virion of any one of embodiments 1 to 30, wherein the expression cassette is flanked by ITRs.
- [00379] Embodiment 32: The rAAV virion of embodiment 31, wherein the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
- [00380] Embodiment 33: The rAAV virion of embodiment 31, wherein the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.

- [00381] Embodiment 34: The rAAV virion of any one of embodiments 1 to 33, wherein the expression cassette comprises a single promoter.
- [00382] Embodiment 35: The rAAV virion of any one of embodiments 1 to 33, wherein the expression cassette comprises two promoters.
- [00383] Embodiment 36: The rAAV virion of any one of embodiments 1 to 35 wherein the expression cassette comprises a single copy a sequence encoding the DWORF polypeptide.
- [00384] Embodiment 37: The rAAV virion of any one of embodiments 1 to 35 wherein the expression cassette comprises two copies of a sequence encoding the DWORF polypeptide.
- [00385] Embodiment 38: The rAAV virion of any one of embodiments 1 to 37 wherein the expression cassette comprises one, two, three, or four enhancers.
- [00386] Embodiment 39: The rAAV virion of any one of embodiments 1 to 38 wherein the expression cassette comprises one or two introns.
- [00387] Embodiment 40: The rAAV virion of any one of embodiments 1 to 39 wherein the expression cassette comprises one or two WPRE sequences.
- [00388] Embodiment 41: The rAAV virion of any one of embodiments 1 to 40 wherein the expression cassette comprises one or two polyadenylation sequences.
- [00389] Embodiment 42: The rAAV virion of any one of embodiments 1 to 41 wherein the expression cassette comprises about 3.2 kb, about, about 3.3 kb, about 3.4 kb, about 3.5 kb, about 3.6 kb, about 3.7 kb, or less.
- [00390] Embodiment 43: The rAAV virion of any one of embodiments 1 to 41 wherein the expression cassette comprises about 1.9 kb, about 2.1 kb, about 2.2 kb, about 2.3 kb, about 2.4 kb, about 2.5 kb, about 2.6 kb, about 2.7 kb, about 2.8 kb, about 2.9 kb, about 3.0 kb, about 3.1 kb, about 3.2 kb, or more.
- [00391] Embodiment 44: The rAAV virion of embodiment 1, wherein the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75.
- [00392] Embodiment 45: The rAAV virion of embodiment 1, wherein the expression cassette comprises any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75.
- [00393] Embodiment 46: The rAAV virion of embodiment 1, wherein the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 61.
- [00394] Embodiment 47: The rAAV virion of embodiment 1, wherein the expression cassette comprises SEQ ID NO: 61.

[00395] Embodiment 48: The rAAV virion of embodiment 1, wherein the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 62.

[00396] Embodiment 49: The rAAV virion of embodiment 1, wherein the expression cassette comprises SEQ ID NO: 62.

[00397] Embodiment 50: The rAAV virion of embodiment 1, wherein the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 63.

[00398] Embodiment 51: The rAAV virion of embodiment 1, wherein the expression cassette comprises SEQ ID NO: 63.

[00399] Embodiment 52: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV9 capsid protein (SEQ ID NO: 143).

[00400] Embodiment 53: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV5 capsid protein (SEQ ID NO: 144).

[00401] Embodiment 54: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein is a chimeric capsid protein.

[00402] Embodiment 55: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein is an AAV5/AAV9 chimeric capsid protein.

[00403] Embodiment 56: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein is selected from any one of SEQ ID NOs: 145-200.

[00404] Embodiment 57: An expression cassette comprising polynucleotide sequence encoding a dwarf open reading frame (DWORF) polypeptide operatively linked to a promoter.

[00405] Embodiment 58: The expression cassette of embodiment 57, wherein the DWORF polypeptide is selected from SEQ ID NOs: 1, 3, 4, 7, 9, 23, and 43.

[00406] Embodiment 59: The expression cassette of embodiment 57 or 58, wherein the promoter is a chicken cTnT promoter.

[00407] Embodiment 60: The expression cassette of embodiment 59, wherein the chicken cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 11.

[00408] Embodiment 61: The expression cassette of embodiment 59, wherein the chicken cTnT promoter comprises SEQ ID NO: 11.

[00409] Embodiment 62: The expression cassette of embodiment 57 or 58, wherein the promoter is a human cTnT promoter.

[00410] Embodiment 63: The expression cassette of embodiment 62, wherein the human cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 12 or SEQ ID NO: 13.

[00411] Embodiment 64: The expression cassette of embodiment 62, wherein the human cTnT promoter comprises SEQ ID NO: 12 or SEQ ID NO: 13.

[00412] Embodiment 65: The expression cassette of any one of embodiments 57 to 64, wherein the expression cassette further comprises one or more enhancers.

[00413] Embodiment 66: The expression cassette of embodiment 65, wherein the enhancer the one or more enhancers are selected from a ACTC1 cardiac enhancer and a α MHC enhancer.

[00414] Embodiment 67: The expression cassette of embodiment 66, wherein the ACTC1 cardiac enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 78.

[00415] Embodiment 68: The expression cassette of embodiment 66, wherein the ACTC1 cardiac enhancer comprises SEQ ID NO: 78.

[00416] Embodiment 69: The expression cassette of embodiment 66, wherein the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79.

[00417] Embodiment 70: The expression cassette of embodiment 66, wherein the α MHC enhancer comprises SEQ ID NO: 79.

[00418] Embodiment 71: The expression cassette of any one of embodiments 57 to 70, wherein the expression cassette further comprises an intron.

[00419] Embodiment 72: The expression cassette of any one of embodiments 57 to 70, wherein the intron is selected from a CMV intron and a chimeric intron.

[00420] Embodiment 73: The expression cassette of embodiment 72, wherein the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 80.

[00421] Embodiment 74: The expression cassette of embodiment 72, wherein the CMV intron comprises SEQ ID NO: 80.

[00422] Embodiment 75: The expression cassette of embodiment 72, wherein the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81.

- [00423] Embodiment 76: The expression cassette of embodiment 72, wherein the chimeric intron comprises SEQ ID NO: 81.
- [00424] Embodiment 77: The expression cassette of any one of embodiments 57 to 76, wherein the expression cassette further comprises a WPRE sequence.
- [00425] Embodiment 78: The expression cassette of embodiment 77, wherein the WPRE sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26.
- [00426] Embodiment 79: The expression cassette of embodiment 77, wherein the WPRE sequence comprises SEQ ID NO: 26.
- [00427] Embodiment 80: The expression cassette of any one of embodiments 57 to 79, wherein the expression cassette further comprises a polyadenylation sequence.
- [00428] Embodiment 81: The expression cassette of embodiment 80, wherein the polyadenylation sequence is selected from a BGH polyadenylation sequence and a SV40 polyadenylation sequence.
- [00429] Embodiment 82: The expression cassette of embodiment 81, wherein the BGH polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 27.
- [00430] Embodiment 83: The expression cassette of embodiment 81, wherein the BGH polyadenylation sequence comprises SEQ ID NO: 27.
- [00431] Embodiment 84: The expression cassette of embodiment 81, wherein the SV40 polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 28.
- [00432] Embodiment 85: The expression cassette of embodiment 81, wherein the SV40 polyadenylation sequence comprises SEQ ID NO: 28.
- [00433] Embodiment 86: The expression cassette of any one of embodiments 57 to 85, wherein the expression cassette is flanked by ITRs.
- [00434] Embodiment 87: The expression cassette of embodiment 86, wherein the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
- [00435] Embodiment 88: The expression cassette of embodiment 86, wherein the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
- [00436] Embodiment 89: The expression cassette of any one of embodiments 57 to 88 comprising a single promoter.

- [00437] Embodiment 90: The expression cassette of any one of embodiments 57 to 88 comprising two promoters.
- [00438] Embodiment 91: The expression cassette of any one of embodiments 57 to 90 comprising a single copy a sequence encoding the DWORF polypeptide.
- [00439] Embodiment 92: The expression cassette of any one of embodiments 57 to 90 comprising two copies of a sequence encoding the DWORF polypeptide.
- [00440] Embodiment 93: The expression cassette of any one of embodiments 57 to 92 comprising one, two, three, or four enhancers.
- [00441] Embodiment 94: The expression cassette of any one of embodiments 57 to 93 comprising one or two introns.
- [00442] Embodiment 95: The expression cassette of any one of embodiments 57 to 94 comprising one or two WPRE sequences.
- [00443] Embodiment 96: The expression cassette of any one of embodiments 57 to 95 comprising one or two polyadenylation sequences.
- [00444] Embodiment 97: The expression cassette of any one of embodiments 57 to 96 comprising about 3.2 kb, about 3.3 kb, about 3.4 kb, about 3.5 kb, about 3.6 kb, about 3.7 kb, or less.
- [00445] Embodiment 98: The expression cassette of any one of embodiments 57 to 96 comprising about 1.9 kb, about 2.1 kb, about 2.2 kb, about 2.3 kb, about 2.4 kb, about 2.5 kb, about 2.6 kb, about 2.7 kb, about 2.8 kb, about 2.9 kb, about 3.0 kb, about 3.1 kb, about 3.2 kb, or more.
- [00446] Embodiment 99: The expression cassette of embodiment 1, comprising a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75.
- [00447] Embodiment 100: The expression cassette of embodiment 57, comprising any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75.
- [00448] Embodiment 101: The expression cassette of embodiment 57, comprising a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 61.
- [00449] Embodiment 102: The expression cassette of embodiment 57, comprising SEQ ID NO: 61.
- [00450] Embodiment 103: The expression cassette of embodiment 57, comprising a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 62.

- [00451] Embodiment 104: The expression cassette of embodiment 57, comprising SEQ ID NO: 62.
- [00452] Embodiment 105: The expression cassette of embodiment 57, comprising a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 63.
- [00453] Embodiment 106: The expression cassette of embodiment 57, comprising SEQ ID NO: 63.
- [00454] Embodiment 107: The expression cassette of any one of embodiments 57 to 98, further comprising a 5' inverted terminal repeat and a 3' inverted terminal repeat.
- [00455] Embodiment 108: A pharmaceutical composition comprising the rAAV virion of any one of embodiments 1 to 56 and an pharmaceutically acceptable diluent.
- [00456] Embodiment 109: A kit comprising the pharmaceutical composition of embodiment 108.
- [00457] Embodiment 110: A method of increasing DWORF expression in a cell comprising contacting a cell with the rAAV virion of any one of embodiments 1 to 56 or the composition of embodiment 108.
- [00458] Embodiment 111: The method of embodiment 110, wherein the cell is a cardiac cell.
- [00459] Embodiment 112: The method of embodiment 111, wherein the cardiac cell is a cardiomyocyte.
- [00460] Embodiment 113: The method of any one of embodiments 110 to 112, wherein DWORF expression is increased between about 1.5-fold and 150-fold.
- [00461] Embodiment 114: The method of any one of embodiments 110 to 113, wherein the contacting is *in vitro*.
- [00462] Embodiment 115: The method of any one of embodiments 110 to 113, wherein the contacting is *in vivo*.
- [00463] Embodiment 116: A method of increasing DWORF expression in a tissue comprising contacting the tissue with the rAAV virion of any one of embodiments 1 to 56 or the composition of embodiment 108.
- [00464] Embodiment 117: The method of embodiment 116, wherein the tissue is cardiac tissue.
- [00465] Embodiment 118: The method of embodiment 116 or 117, wherein DWORF expression is increased between about 1.5-fold and 150-fold.

- [00466] Embodiment 119: The method of any one of embodiments 116 to 118, wherein the contacting is *in vitro*.
- [00467] Embodiment 120: The method of embodiment 116 or 118, wherein the contacting is *in vivo*.
- [00468] Embodiment 121: A method of increasing DWORF expression in an organ comprising contacting the organ with the rAAV virion of any one of embodiments 1 to 56 or the composition of embodiment 108.
- [00469] Embodiment 122: The method of embodiment 121, wherein the organ is a heart.
- [00470] Embodiment 123: The method of embodiment 122, wherein the heart is diseased or is at risk of disease.
- [00471] Embodiment 124: The method of embodiment 122 or embodiment 123, wherein the heart has reduced or borderline ejection fraction.
- [00472] Embodiment 125: The method of embodiment 122 or embodiment 123, wherein the heart has a normal ejection fraction.
- [00473] Embodiment 126: The method of any one of embodiments 122 to 125, wherein the heart comprises a genetic mutation associated with a heart disease.
- [00474] Embodiment 127: The method of embodiment 126, wherein the genetic mutation is a *PLN* mutation.
- [00475] Embodiment 128: The method of any one of embodiments 121 to 127, wherein the heart has low or undetectable DWORF expression compared to a healthy heart.
- [00476] Embodiment 129: The method of any one of embodiments 121 to 128, wherein DWORF expression is increased between about 1.5-fold and 150-fold.
- [00477] Embodiment 130: The method of any one of embodiments 121 to 129, wherein the contacting is *in vitro*.
- [00478] Embodiment 131: The method of any one of embodiments 121 to 129, wherein the contacting is *in vivo*.
- [00479] Embodiment 132: A method of increasing DWORF expression in a subject comprising administering to the subject the rAAV virion of any one of embodiments 1 to 56 or the composition of embodiment 108.
- [00480] Embodiment 133: The method of embodiment 132, wherein the subject is an animal.
- [00481] Embodiment 134: The method of embodiment 132, wherein the subject is a human.

- [00482] Embodiment 135: The method of any one of embodiments 132 to 134, wherein DWORF expression is increased in the heart of the subject.
- [00483] Embodiment 136: The method of any one of embodiments 132 to 135, wherein subject has a heart disease or is at risk of a heart disease.
- [00484] Embodiment 137: The method of any one of embodiments 132 to 136, wherein subject has borderline or reduced ejection fraction.
- [00485] Embodiment 138: The method of any one of embodiments 132 to 136, wherein the subject has normal ejection fraction.
- [00486] Embodiment 139: The method of any one of embodiments 132 to 138, wherein the subject has a genetic mutation associated with a heart disease.
- [00487] Embodiment 140: The method of embodiment 139, wherein the genetic mutation is a *PLN* mutation.
- [00488] Embodiment 141: The method of any one of embodiments 132 to 140, wherein the subject has a low or undetectable level of DWORF expression compared to a healthy subject.
- [00489] Embodiment 142: A method of treating a heart disease or disorder in a subject in need thereof comprising administering to the subject the rAAV virion of any one of embodiments 1 to 56 or the composition of embodiment 108.
- [00490] Embodiment 143: The method of embodiment 142, wherein the subject has a heart disease or disorder.
- [00491] Embodiment 144: The method of embodiment 142, wherein the subject is a risk of developing a heart disease or disorder.
- [00492] Embodiment 145: The method or any one of embodiments 142 to 144, wherein the heart disease or disorder is cardiomyopathy.
- [00493] Embodiment 146: The method of any one of embodiments 142 to 144, wherein the heart disease or disorder is dilated cardiomyopathy.
- [00494] Embodiment 147: The method of any one of embodiments 142 to 144, wherein the heart disease or disorder is myocardial infarction.
- [00495] Embodiment 148: The method of any one of embodiments 142 to 144, wherein the heart disease or disorder is chronic myocardial infarction.
- [00496] Embodiment 149: The method of any one of embodiments 142 to 144, wherein the heart disease or disorder is acute myocardial infarction.
- [00497] Embodiment 150: The method of any one of embodiments 142 to 149, wherein the subject has an inherited risk allele for a heart disease or disorder.

- [00498] Embodiment 151: The method of any one of embodiments 142 to 150, wherein the inherited risk allele comprises a mutation to the *PLN* gene.
- [00499] Embodiment 152: The method of embodiment 151, wherein the mutation to the *PLN* gene is a *PLN* promoter mutation.
- [00500] Embodiment 153: The method of embodiment 151, wherein the mutation to the *PLN* gene is a $PLN^{L39stop}$ mutation.
- [00501] Embodiment 154: The method of embodiment 151, wherein the mutation to the *PLN* gene is a RC9 mutation.
- [00502] Embodiment 155: The method of embodiment 151, wherein the mutation to the *PLN* gene is a R9L mutation.
- [00503] Embodiment 156: The method of embodiment 151, wherein the mutation to the *PLN* gene is a *PLN* gene duplication.
- [00504] Embodiment 157: The method of embodiment 151, wherein the mutation to the *PLN* gene is a R14del mutation.
- [00505] Embodiment 158: The method of any one of embodiments 142 to 157, wherein the heart disease or disorder is with reduced ejection fraction (HFrEF).
- [00506] Embodiment 159: The method of any one of embodiments 142 to 157, wherein the heart disease or disorder is with preserved ejection fraction (HFpEF).
- [00507] Embodiment 160: The method of any one of embodiments 142 to 159, wherein the method causes expression of the DWORF polypeptide in the heart of the subject.
- [00508] Embodiment 161: The method of any one of embodiments 142 to 160, wherein the method causes expression of the DWORF polypeptide in cardiomyocytes.
- [00509] Embodiment 162: The method of any one of embodiments 142 to 161, wherein the method causes no detectable expression of the DWORF polypeptide in the muscles of the subject except the heart.
- [00510] Embodiment 163: The method of any one of embodiments 142 to 162, wherein the method causes no detectable expression of the DWORF polypeptide in the liver of the subject.
- [00511] Embodiment 164: The method of any one of embodiments 142 to 163, wherein the method causes no detectable expression of the DWORF polypeptide in cardiac fibroblasts.
- [00512] Embodiment 165: The method of any one of embodiments 142 to 164, wherein the method improves one or more measures of cardiac function, optionally fraction shortening and/or left ventricular internal dimension (LVID).

[00513] Embodiment 166: The method of any one of embodiments 142 to 165, wherein the improvement in cardiac function is observed at weeks 2 through week 16.

[00514] Embodiment 167: The method of any one of embodiments 142 to 166, wherein the method reduces cardiac remodeling.

[00515] Embodiment 168: The method of any one of embodiments 142 to 166, wherein the method counteracts a decrease in DWORF expression in subjects suffering from or at risk of a heart disease.

[00516] Embodiment 169: The method of any one of embodiments 142 to 168, wherein the rAAV virion is administered by systemic administration.

[00517] Embodiment 170: The method of embodiment 169, wherein the systemic administration is selected from intravenous or intracoronary injection.

[00518] Embodiment 171: The method of embodiment 169 or 170, wherein the rAAV is administered as a unit dose.

[00519] Embodiment 172: The method of embodiment 171, wherein the unit dose comprises about 3×10^{14} vg/kg or less, about 2×10^{14} vg/kg or less, about 1×10^{14} vg/kg or less, about 9×10^{13} vg/kg or less, about 8×10^{13} vg/kg or less, about 7×10^{13} vg/kg or less, about 6×10^{13} vg/kg or less, about 5×10^{13} vg/kg or less, about 4×10^{13} vg/kg or less, about 3×10^{13} vg/kg or less, about 2×10^{13} vg/kg or less, or about 1×10^{13} vg/kg or less.

[00520] Embodiment 173: A method of alleviating one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion of any one of embodiments 1 to 56 or the composition of embodiment 108.

[00521] Embodiment 174: A method of improving one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion of any one of embodiments 1 to 56 or the composition of embodiment 108.

[00522] Embodiment 175: A method of preventing one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion of any one of embodiments 1 to 56 or the composition of embodiment 108.

[00523] Embodiment 176: An expression cassette comprising a polynucleotide comprising a 5' to 3' arrangement of elements, wherein the elements comprise:

- i. one or more promoters;
- ii. optionally one or more enhancers;
- iii. optionally one or more introns;

- iv. one or more transgenes;
- v. optionally one or more WPRE sequences; and
- vi. optionally one or more polyadenylation sequences, p(A).

[00524] Embodiment 177: The expression cassette of embodiment 176, wherein the 5' to 3' arrangement of elements is selected from:

- i. 5'-promoter-intron-transgene-WPRE-p(A)-3';
- ii. 5'-enhancer-promoter-transgene-WPRE-p(A)-3';
- iii. 5'-enhancer-enhancer-promoter-transgene-WPRE-p(A)-3';
- iv. 5'-enhancer-enhancer-promoter-intron-transgene-WPRE-p(A)-3';
- v. 5'-enhancer-enhancer-promoter-intron-transgene-WPRE-p(A)-3';
- vi. 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-enhancer-3';
- vii. 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-enhancer-promoter-intron-transgene-p(A)-3';
- viii. 5'-p(A)-WPRE-transgene-intron-promoter-enhancer-enhancer-promoter-intron-transgene-p(A)-3';
- ix. 5'-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-3';
- x. 5'-promoter-intron-transgene-WPRE-p(A)-promoter-intron-transgene-p(A)-3'; and
- xi. 5'-p(A)-WPRE-transgene-intron-promoter-promoter-intron-transgene-p(A)-3'.

[00525] Embodiment 178: The expression cassette of embodiment 176 or embodiment 177, wherein the transgene has an increased expression level compared to a second expression

cassette comprising a polynucleotide having an arrangement of elements from 5' to 3' comprising: 5'-promoter-transgene-WPRE-p(A)-3'.

[00526] Embodiment 179: The expression cassette of embodiment 178, wherein the increased expression level is between about 1.5-fold and about 150-fold compared to the second expression cassette.

[00527] Embodiment 180: A recombinant adeno-associated virus (rAAV) virion, comprising a capsid protein and a viral genome comprising an expression cassette of any one of embodiments 176 to 179, the expression cassette flanked by inverted terminal repeats.

[00528] Embodiment 181: The rAAV of embodiment 180, wherein the expression cassette comprises a transgene, wherein the transgene encodes a polypeptide use for treating or a preventing a heart disease, or alleviating symptoms associated with a heart disease.

[00529] Embodiment 182: The rAAV of embodiment 180 or embodiment 181, wherein the capsid protein is selected from any one of SEQ ID NOs: 145-200.

NUMBERED EMBODIMENTS OF THE INVENTION II

[00530] Embodiment 1: A recombinant adeno-associated virus (rAAV) virion, comprising a capsid protein and a viral genome comprising an expression cassette comprising a polynucleotide sequence encoding a polypeptide operatively linked to a promoter, the expression cassette flanked by inverted terminal repeats, optionally wherein the polypeptide is for expression in a cardiac cell or tissue and/or for use in treating or a preventing a heart disease.

[00531] Embodiment 2: The rAAV virion of embodiment 1, wherein the polypeptide is selected from DWORF, JPH2, BAG3, CRYAB, Lamin A isoform of LMNA, Lamin C isoform of LMNA, TNNI3, PLN, LAMP2a, LAMP2b, LAMP2c, DPI isoform of DSP, DPII isoform of DSP, DSG2, and JUP.

[00532] Embodiment 3: The rAAV virion of embodiment 1 or 2, wherein the polypeptide shares at least 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to a sequence selected from polypeptide sequences in Tables 2a and 2b.

[00533] Embodiment 4: The rAAV virion of any one of embodiments 1-3, wherein the promoter is a chicken cTnT promoter.

[00534] Embodiment 5: The rAAV virion of embodiment 4, wherein the chicken cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 11.

[00535] Embodiment 6: The rAAV virion of embodiment 4, wherein the chicken cTnT promoter comprises SEQ ID NO: 11.

- [00536] Embodiment 7: The rAAV virion of any one of embodiments 1-3, wherein the promoter is a human cTnT promoter.
- [00537] Embodiment 8: The rAAV virion of embodiment 7, wherein the human cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 12 or SEQ ID NO: 13.
- [00538] Embodiment 9: The rAAV virion of embodiment 7, wherein the human cTnT promoter comprises SEQ ID NO: 12 or SEQ ID NO: 13.
- [00539] Embodiment 10: The rAAV virion of any one of embodiments 1 to 9, wherein the expression cassette further comprises one or more enhancers.
- [00540] Embodiment 11: The rAAV virion of embodiment 10, wherein the enhancer the one or more enhancers are selected from a ACTC1 cardiac enhancer and a α MHC enhancer.
- [00541] Embodiment 12: The rAAV virion of embodiment 11, wherein the ACTC1 cardiac enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 78.
- [00542] Embodiment 13: The rAAV virion of embodiment 11, wherein the ACTC1 cardiac enhancer comprises SEQ ID NO: 78.
- [00543] Embodiment 14: The rAAV virion of embodiment 11, wherein the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79.
- [00544] Embodiment 15: The rAAV virion of embodiment 11, wherein the α MHC enhancer comprises SEQ ID NO: 79.
- [00545] Embodiment 16: The rAAV virion of any one of embodiments 1 to 15, wherein the expression cassette further comprises an intron.
- [00546] Embodiment 17: The rAAV virion of embodiment 16, wherein the intron is selected from a CMV intron and a chimeric intron.
- [00547] Embodiment 18: The rAAV virion of embodiment 17, wherein the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 80.
- [00548] Embodiment 19: The rAAV virion of embodiment 17, wherein the CMV intron comprises SEQ ID NO: 80.
- [00549] Embodiment 20: The rAAV virion of embodiment 17, wherein the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81.
- [00550] Embodiment 21: The rAAV virion of embodiment 17, wherein the chimeric intron comprises SEQ ID NO: 81.
- [00551] Embodiment 22: The rAAV virion of any one of embodiments 1 to 21, wherein the expression cassette further comprises a WPRE sequence.

- [00552] Embodiment 23: The rAAV virion of embodiment 22, wherein the WPRE sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26.
- [00553] Embodiment 24: The rAAV virion of embodiment 22, wherein the WPRE sequence comprises SEQ ID NO: 26.
- [00554] Embodiment 25: The rAAV virion of any one of embodiments 1 to 24, wherein the expression cassette further comprises a polyadenylation sequence.
- [00555] Embodiment 26: The rAAV virion of embodiment 25, wherein the polyadenylation sequence is selected from a BGH polyadenylation sequence and a SV40 polyadenylation sequence.
- [00556] Embodiment 27: The rAAV virion of embodiment 26, wherein the BGH polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 27.
- [00557] Embodiment 28: The rAAV virion of embodiment 26, wherein the BGH polyadenylation sequence comprises SEQ ID NO: 27.
- [00558] Embodiment 29: The rAAV virion of embodiment 26, wherein the SV40 polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 28.
- [00559] Embodiment 30: The rAAV virion of embodiment 26, wherein the SV40 polyadenylation sequence comprises SEQ ID NO: 28.
- [00560] Embodiment 31: The rAAV virion of any one of embodiments 1 to 30, wherein the expression cassette is flanked by ITRs.
- [00561] Embodiment 32: The rAAV virion of embodiment 31, wherein the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
- [00562] Embodiment 33: The rAAV virion of embodiment 31, wherein the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
- [00563] Embodiment 34: The rAAV virion of any one of embodiments 1 to 33, wherein the expression cassette comprises a single promoter.
- [00564] Embodiment 35: The rAAV virion of any one of embodiments 1 to 33, wherein the expression cassette comprises two promoters.
- [00565] Embodiment 36: The rAAV virion of any one of embodiments 1 to 35, wherein the expression cassette comprises a single copy a sequence encoding the polypeptide.
- [00566] Embodiment 37: The rAAV virion of any one of embodiments 1 to 35, wherein the expression cassette comprises two copies of a sequence encoding the polypeptide.

[00567] Embodiment 38: The rAAV virion of any one of embodiments 1 to 37, wherein the expression cassette comprises one, two, three, or four enhancers.

[00568] Embodiment 39: The rAAV virion of any one of embodiments 1 to 38, wherein the expression cassette comprises one or two introns.

[00569] Embodiment 40: The rAAV virion of any one of embodiments 1 to 39, wherein the expression cassette comprises one or two WPRE sequences.

[00570] Embodiment 41: The rAAV virion of any one of embodiments 1 to 40, wherein the expression cassette comprises one or two polyadenylation sequences.

[00571] Embodiment 42: The rAAV virion of any one of embodiments 1 to 41, wherein the expression cassette comprises about 3.2 kb, about 3.3 kb, about 3.4 kb, about 3.5 kb, about 3.6 kb, about 3.7 kb, or less.

[00572] Embodiment 43: The rAAV virion of any one of embodiments 1 to 42, wherein the expression cassette comprises about 1.9 kb, about 2.1 kb, about 2.2 kb, about 2.3 kb, about 2.4 kb, about 2.5 kb, about 2.6 kb, about 2.7 kb, about 2.8 kb, about 2.9 kb, about 3.0 kb, about 3.1 kb, about 3.2 kb, or more.

[00573] Embodiment 44: The rAAV virion of any one of embodiments 1-3, wherein the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to a sequence within any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75 where the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00574] Embodiment 45: The rAAV virion of any one of embodiments 1-3, wherein the expression cassette comprises any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence within any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75 where the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF)

are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00575] Embodiment 46: The rAAV virion of any one of embodiments 1-3, wherein the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59 and SEQ ID NO: 60, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence sharing at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59 and SEQ ID NO: 60 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00576] Embodiment 47: The rAAV virion of any one of embodiments 1-3, wherein the expression cassette comprises any one of SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59 and SEQ ID NO: 60, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence of SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59 and SEQ ID NO: 60 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00577] Embodiment 48: The rAAV virion of any one of embodiments 1-3, wherein the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some

embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence sharing at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00578] Embodiment 49: The rAAV virion of any one of embodiments 1-3, wherein the expression cassette comprises any one of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence of any one of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00579] Embodiment 50: The rAAV virion of any one of embodiments 1-3, wherein the expression cassette comprises a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, and SEQ ID NO: 75, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence sharing at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, and SEQ ID NO: 75 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00580] Embodiment 51: The rAAV virion of any one of embodiments 1-3, wherein the expression cassette comprises any one of SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, and SEQ ID NO: 75, optionally without the sequence or

sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence of any one of SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, and SEQ ID NO: 75 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00581] Embodiment 52: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV9 capsid protein (SEQ ID NO: 143).

[00582] Embodiment 53: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV5 capsid protein (SEQ ID NO: 144).

[00583] Embodiment 54: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein is a chimeric capsid protein.

[00584] Embodiment 55: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein is an AAV5/AAV9 chimeric capsid protein.

[00585] Embodiment 56: The rAAV virion of any one of embodiments 1 to 51, wherein the capsid protein is selected from any one of SEQ ID NOs: 145-200.

[00586] Embodiment 57: An expression cassette comprising a polynucleotide sequence encoding a polypeptide operatively linked to a promoter, optionally wherein the polypeptide is for expression in a cardiac cell or tissue and/or for use in treating or preventing a heart disease.

[00587] Embodiment 58: The expression cassette of embodiment 57, wherein the polypeptide is selected from DWORF, JPH2, BAG3, CRYAB, Lamin A isoform of LMNA, Lamin C isoform of LMNA, TNNI3, PLN, LAMP2a, LAMP2b, LAMP2c, DPI isoform of DSP, DPII isoform of DSP, DSG2, and JUP, optionally wherein the polypeptide shares at least 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to a sequence selected from polypeptide sequences in Tables 2a and 2b.

[00588] Embodiment 59: The expression cassette of embodiment 57 or 58, wherein the promoter is a chicken cTnT promoter.

[00589] Embodiment 60: The expression cassette of embodiment 59, wherein the chicken cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 11.

- [00590] Embodiment 61: The expression cassette of embodiment 59, wherein the chicken cTnT promoter comprises SEQ ID NO: 11.
- [00591] Embodiment 62: The expression cassette of embodiment 57 or 58, wherein the promoter is a human cTnT promoter.
- [00592] Embodiment 63: The expression cassette of embodiment 62, wherein the human cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 12 or SEQ ID NO: 13.
- [00593] Embodiment 64: The expression cassette of embodiment 62, wherein the human cTnT promoter comprises SEQ ID NO: 12 or SEQ ID NO: 13.
- [00594] Embodiment 65: The expression cassette of any one of embodiments 57 to 64, wherein the expression cassette further comprises one or more enhancers.
- [00595] Embodiment 66: The expression cassette of embodiment 65, wherein the enhancer the one or more enhancers are selected from a ACTC1 cardiac enhancer and a α MHC enhancer.
- [00596] Embodiment 67: The expression cassette of embodiment 66, wherein the ACTC1 cardiac enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 78.
- [00597] Embodiment 68: The expression cassette of embodiment 66, wherein the ACTC1 cardiac enhancer comprises SEQ ID NO: 78.
- [00598] Embodiment 69: The expression cassette of embodiment 66, wherein the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79.
- [00599] Embodiment 70: The expression cassette of embodiment 66, wherein the α MHC enhancer comprises SEQ ID NO: 79.
- [00600] Embodiment 71: The expression cassette of any one of embodiments 57 to 70, wherein the expression cassette further comprises an intron.
- [00601] Embodiment 72: The expression cassette of any one of embodiments 57 to 70, wherein the intron is selected from a CMV intron and a chimeric intron.
- [00602] Embodiment 73: The expression cassette of embodiment 72, wherein the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 80.
- [00603] Embodiment 74: The expression cassette of embodiment 72, wherein the CMV intron comprises SEQ ID NO: 80.

[00604] Embodiment 75: The expression cassette of embodiment 72, wherein the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81.

[00605] Embodiment 76: The expression cassette of embodiment 72, wherein the chimeric intron comprises SEQ ID NO: 81.

[00606] Embodiment 77: The expression cassette of any one of embodiments 57 to 76, wherein the expression cassette further comprises a WPRE sequence.

[00607] Embodiment 78: The expression cassette of embodiment 77, wherein the WPRE sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26.

[00608] Embodiment 79: The expression cassette of embodiment 77, wherein the WPRE sequence comprises SEQ ID NO: 26.

[00609] Embodiment 80: The expression cassette of any one of embodiments 57 to 79, wherein the expression cassette further comprises a polyadenylation sequence.

[00610] Embodiment 81: The expression cassette of embodiment 80, wherein the polyadenylation sequence is selected from a BGH polyadenylation sequence and a SV40 polyadenylation sequence.

[00611] Embodiment 82: The expression cassette of embodiment 81, wherein the BGH polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 27.

[00612] Embodiment 83: The expression cassette of embodiment 81, wherein the BGH polyadenylation sequence comprises SEQ ID NO: 27.

[00613] Embodiment 84: The expression cassette of embodiment 81, wherein the SV40 polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 28.

[00614] Embodiment 85: The expression cassette of embodiment 81, wherein the SV40 polyadenylation sequence comprises SEQ ID NO: 28.

[00615] Embodiment 86: The expression cassette of any one of embodiments 57 to 85, wherein the expression cassette is flanked by ITRs.

[00616] Embodiment 87: The expression cassette of embodiment 86, wherein the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15.

[00617] Embodiment 88: The expression cassette of embodiment 86, wherein the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.

- [00618] Embodiment 89: The expression cassette of any one of embodiments 57 to 88 comprising a single promoter.
- [00619] Embodiment 90: The expression cassette of any one of embodiments 57 to 88 comprising two promoters.
- [00620] Embodiment 91: The expression cassette of any one of embodiments 57 to 90 comprising a single copy a sequence encoding the polypeptide.
- [00621] Embodiment 92: The expression cassette of any one of embodiments 57 to 90 comprising two copies of a sequence encoding the polypeptide.
- [00622] Embodiment 93: The expression cassette of any one of embodiments 57 to 92 comprising one, two, three, or four enhancers.
- [00623] Embodiment 94: The expression cassette of any one of embodiments 57 to 93 comprising one or two introns.
- [00624] Embodiment 95: The expression cassette of any one of embodiments 57 to 94 comprising one or two WPRE sequences.
- [00625] Embodiment 96: The expression cassette of any one of embodiments 57 to 95 comprising one or two polyadenylation sequences.
- [00626] Embodiment 97: The expression cassette of any one of embodiments 57 to 96 comprising about 3.2 kb, about 3.3 kb, about 3.4 kb, about 3.5 kb, about 3.6 kb, about 3.7 kb, or less.
- [00627] Embodiment 98: The expression cassette of any one of embodiments 57 to 97 comprising about 1.9 kb, about 2.1 kb, about 2.2 kb, about 2.3 kb, about 2.4 kb, about 2.5 kb, about 2.6 kb, about 2.7 kb, about 2.8 kb, about 2.9 kb, about 3.0 kb, about 3.1 kb, about 3.2 kb, or more.
- [00628] Embodiment 99: The expression cassette of embodiment 57 or 58, comprising a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to a sequence of any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00629] Embodiment 100: The expression cassette of embodiment 57 or 58, comprising a polynucleotide sequence of any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises any one of SEQ ID NOs: 20-24 or SEQ ID NOs: 45-75 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00630] Embodiment 101: The expression cassette of embodiment 57 or 58, comprising a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00631] Embodiment 102: The expression cassette of embodiment 57 or 58, comprising a polynucleotide sequence of any one of SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence of any one of SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than

DWOLF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00632] Embodiment 103: The expression cassette of embodiment 57 or 58, comprising a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, optionally without the sequence or sequences encoding DWOLF (open reading frame or open reading frames encoding DWOLF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWOLF, the polynucleotide sequence shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58 in which the sequence or sequences encoding DWOLF (open reading frame or open reading frames encoding DWOLF) are replaced by a sequence or sequences encoding the polypeptide other than DWOLF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00633] Embodiment 104: The expression cassette of embodiment 57, comprising any one of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, optionally without the sequence or sequences encoding DWOLF (open reading frame or open reading frames encoding DWOLF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWOLF, the polynucleotide sequence comprises a sequence of any one of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58 in which the sequence or sequences encoding DWOLF (open reading frame or open reading frames encoding DWOLF) are replaced by a sequence or sequences encoding the polypeptide other than DWOLF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00634] Embodiment 105: The expression cassette of embodiment 57 or 58, comprising a polynucleotide sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, and SEQ ID NO: 75, optionally without the sequence or sequences encoding DWOLF (open reading frame or open reading frames encoding DWOLF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWOLF, the polynucleotide sequence comprises a sequence that shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, and SEQ ID NO: 75 in which the sequence or sequences encoding DWOLF (open reading frame or open reading frames encoding

DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00635] Embodiment 106: The expression cassette of embodiment 57 or 58, comprising any one of SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, and SEQ ID NO: 75, optionally without the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF). In some embodiments, where the expression cassette is for expression of a polypeptide other than DWORF, the polynucleotide sequence comprises a sequence of any one of SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, and SEQ ID NO: 75 in which the sequence or sequences encoding DWORF (open reading frame or open reading frames encoding DWORF) are replaced by a sequence or sequences encoding the polypeptide other than DWORF (e.g., any polypeptide described herein, such as any polypeptide listed in Table 2b which also provide sequences of such polypeptides).

[00636] Embodiment 107: The expression cassette of any one of embodiments 99 to 106, wherein the expression cassette does not comprise a 5' inverted terminal repeat and a 3' inverted terminal repeat of the polynucleotide sequence.

[00637] Embodiment 108: A pharmaceutical composition comprising the rAAV virion of any one of embodiments 1 to 56 and a pharmaceutically acceptable carrier, or a pharmaceutical composition comprising a vector comprising the expression cassette of any of embodiments 57 to 107 and a pharmaceutically acceptable carrier.

[00638] Embodiment 109: A kit comprising the pharmaceutical composition of embodiment 108.

[00639] Embodiment 110: A method of increasing a polypeptide expression in a cell comprising contacting a cell with the rAAV virion of any one of embodiments 1 to 56, a vector comprising the expression cassette of any one of embodiments 57-107, or the composition of embodiment 108.

[00640] Embodiment 111: The method of embodiment 110, wherein the cell is a cardiac cell.

[00641] Embodiment 112: The method of embodiment 111, wherein the cardiac cell is a cardiomyocyte.

[00642] Embodiment 113: The method of any one of embodiments 110 to 112, wherein the polypeptide expression is increased between about 1.5-fold and 150-fold.

- [00643] Embodiment 114: The method of any one of embodiments 110 to 113, wherein the contacting is *in vitro*.
- [00644] Embodiment 115: The method of any one of embodiments 110 to 113, wherein the contacting is *in vivo*.
- [00645] Embodiment 116: A method of increasing a polypeptide expression in a tissue comprising contacting the tissue with the rAAV virion of any one of embodiments 1 to 56, a vector comprising the expression cassette of any one of embodiments 57-107, or the composition of embodiment 108.
- [00646] Embodiment 117: The method of embodiment 116, wherein the tissue is cardiac tissue.
- [00647] Embodiment 118: The method of embodiment 116 or 117, wherein polypeptide expression is increased between about 1.5-fold and 150-fold.
- [00648] Embodiment 119: The method of any one of embodiments 116 to 118, wherein the contacting is *in vitro*.
- [00649] Embodiment 120: The method of embodiment 116 or 118, wherein the contacting is *in vivo*.
- [00650] Embodiment 121: A method of increasing a polypeptide expression in an organ comprising contacting the organ with the rAAV virion of any one of embodiments 1 to 56, a vector comprising the expression cassette of any one of embodiments 57-107, or the composition of embodiment 108.
- [00651] Embodiment 122: The method of embodiment 121, wherein the organ is a heart.
- [00652] Embodiment 123: The method of embodiment 122, wherein the heart is diseased or is at risk of disease.
- [00653] Embodiment 124: The method of embodiment 122 or embodiment 123, wherein the heart has reduced or borderline ejection fraction.
- [00654] Embodiment 125: The method of embodiment 122 or embodiment 123, wherein the heart has a normal ejection fraction.
- [00655] Embodiment 126: The method of any one of embodiments 122 to 125, wherein the heart comprises a genetic mutation associated with a heart disease.
- [00656] Embodiment 127: The method of embodiment 126, wherein the genetic mutation is a *PLN* mutation.
- [00657] Embodiment 128: The method of any one of embodiments 121 to 127, wherein the heart has low or undetectable polypeptide expression compared to a healthy heart.

[00658] Embodiment 129: The method of any one of embodiments 121 to 128, wherein the polypeptide expression is increased between about 1.5-fold and 150-fold.

[00659] Embodiment 130: The method of any one of embodiments 121 to 129, wherein the contacting is *in vitro*.

[00660] Embodiment 131: The method of any one of embodiments 121 to 129, wherein the contacting is *in vivo*.

[00661] Embodiment 132: A method of increasing a polypeptide expression in a subject comprising administering to the subject the rAAV virion of any one of embodiments 1 to 56, a vector comprising the expression cassette of any one of embodiments 57-107, or the composition of embodiment 108.

[00662] Embodiment 133: The method of embodiment 132, wherein the subject is an animal.

[00663] Embodiment 134: The method of embodiment 132, wherein the subject is a human.

[00664] Embodiment 135: The method of any one of embodiments 132 to 134, wherein the polypeptide expression is increased in the heart of the subject.

[00665] Embodiment 136: The method of any one of embodiments 132 to 135, wherein subject has a heart disease or is at risk of a heart disease.

[00666] Embodiment 137: The method of any one of embodiments 132 to 136, wherein subject has borderline or reduced ejection fraction.

[00667] Embodiment 138: The method of any one of embodiments 132 to 136, wherein the subject has normal ejection fraction.

[00668] Embodiment 139: The method of any one of embodiments 132 to 138, wherein the subject has a genetic mutation associated with a heart disease.

[00669] Embodiment 140: The method of embodiment 139, wherein the genetic mutation is a *PLN* mutation.

[00670] Embodiment 141: The method of any one of embodiments 132 to 140, wherein the subject has a low or undetectable level of the polypeptide expression compared to a healthy subject.

[00671] Embodiment 142: A method of treating a heart disease or disorder in a subject in need thereof comprising administering to the subject the rAAV virion of any one of embodiments 1 to 56, a vector comprising the expression cassette of any one of embodiments 57-107, or the composition of embodiment 108.

- [00672] Embodiment 143: The method of embodiment 142, wherein the subject has a heart disease or disorder.
- [00673] Embodiment 144: The method of embodiment 142, wherein the subject is a risk of developing a heart disease or disorder.
- [00674] Embodiment 145: The method or any one of embodiments 142 to 144, wherein the heart disease or disorder is cardiomyopathy.
- [00675] Embodiment 146: The method of any one of embodiments 142 to 144, wherein the heart disease or disorder is dilated cardiomyopathy.
- [00676] Embodiment 147: The method of any one of embodiments 142 to 144, wherein the heart disease or disorder is myocardial infarction.
- [00677] Embodiment 148: The method of any one of embodiments 142 to 144, wherein the heart disease or disorder is chronic myocardial infarction.
- [00678] Embodiment 149: The method of any one of embodiments 142 to 144, wherein the heart disease or disorder is acute myocardial infarction.
- [00679] Embodiment 150: The method of any one of embodiments 142 to 149, wherein the subject has an inherited risk allele for a heart disease or disorder.
- [00680] Embodiment 151: The method of any one of embodiments 142 to 150, wherein the inherited risk allele comprises a mutation to the *PLN* gene.
- [00681] Embodiment 152: The method of embodiment 151, wherein the mutation to the *PLN* gene is a *PLN* promoter mutation.
- [00682] Embodiment 153: The method of embodiment 151, wherein the mutation to the *PLN* gene is a *PLN*^{L39stop} mutation.
- [00683] Embodiment 154: The method of embodiment 151, wherein the mutation to the *PLN* gene is a RC9 mutation.
- [00684] Embodiment 155: The method of embodiment 151, wherein the mutation to the *PLN* gene is a R9L mutation.
- [00685] Embodiment 156: The method of embodiment 151, wherein the mutation to the *PLN* gene is a *PLN* gene duplication.
- [00686] Embodiment 157: The method of embodiment 151, wherein the mutation to the *PLN* gene is a R14del mutation.
- [00687] Embodiment 158: The method of any one of embodiments 142 to 157, wherein the heart disease or disorder is with reduced ejection fraction (HFrEF).
- [00688] Embodiment 159: The method of any one of embodiments 142 to 157, wherein the heart disease or disorder is with preserved ejection fraction (HFpEF).

- [00689] Embodiment 160: The method of any one of embodiments 142 to 159, wherein the method causes expression of the polypeptide in the heart of the subject.
- [00690] Embodiment 161: The method of any one of embodiments 142 to 160, wherein the method causes expression of the polypeptide in cardiomyocytes.
- [00691] Embodiment 162: The method of any one of embodiments 142 to 161, wherein the method causes no detectable expression of the polypeptide in the muscles of the subject except the heart.
- [00692] Embodiment 163: The method of any one of embodiments 142 to 162, wherein the method causes no detectable expression of the polypeptide in the liver of the subject.
- [00693] Embodiment 164: The method of any one of embodiments 142 to 163, wherein the method causes no detectable expression of the polypeptide in cardiac fibroblasts.
- [00694] Embodiment 165: The method of any one of embodiments 142 to 164, wherein the method improves one or more measures of cardiac function, optionally fraction shortening and/or left ventricular internal dimension (LVID).
- [00695] Embodiment 166: The method of any one of embodiments 142 to 165, wherein the improvement in cardiac function is observed at weeks 2 through week 24.
- [00696] Embodiment 167: The method of any one of embodiments 142 to 166, wherein the method reduces cardiac remodeling.
- [00697] Embodiment 168: The method of any one of embodiments 142 to 166, wherein the method counteracts a decrease in the polypeptide expression in subjects suffering from or at risk of a heart disease.
- [00698] Embodiment 169: The method of any one of embodiments 142 to 168, wherein the administering is by systemic administration.
- [00699] Embodiment 170: The method of embodiment 169, wherein the systemic administration is selected from intravenous or intracoronary injection.
- [00700] Embodiment 171: The method of embodiment 169 or 170, wherein the rAAV is administered as a unit dose.
- [00701] Embodiment 172: The method of embodiment 171, wherein the unit dose comprises about 3×10^{14} vg/kg or less, about 2×10^{14} vg/kg or less, about 1×10^{14} vg/kg or less, about 9×10^{13} vg/kg or less, about 8×10^{13} vg/kg or less, about 7×10^{13} vg/kg or less, about 6×10^{13} vg/kg or less, about 5×10^{13} vg/kg or less, about 4×10^{13} vg/kg or less, about 3×10^{13} vg/kg or less, about 2×10^{13} vg/kg or less, or about 1×10^{13} vg/kg or less.
- [00702] Embodiment 173: A method of alleviating one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion of

any one of embodiments 1 to 56, a vector comprising the expression cassette of any one of embodiments 57-107, or the composition of embodiment 108.

[00703] Embodiment 174: A method of improving one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion of any one of embodiments 1 to 56, a vector comprising the expression cassette of any one of embodiments 57-107, or the composition of embodiment 108.

[00704] Embodiment 175: A method of preventing one or more symptoms of a heart disease or disorder in a subject in need thereof comprising administering the rAAV virion of any one of embodiments 1 to 56, a vector comprising the expression cassette of any one of embodiments 57-107, or the composition of embodiment 108.

[00705] Embodiment 176: An expression cassette comprising a polynucleotide comprising:

- i. one or more promoters;
- ii. optionally one or more enhancers;
- iii. optionally one or more introns;
- iv. one or more transgenes, optionally wherein the one or more transgenes encode one or more polypeptides for use in treating or preventing a heart disease;
- v. optionally one or more WPRE sequences; and
- vi. optionally one or more polyadenylation sequences, p(A).

[00706] Embodiment 177: The expression cassette of embodiment 176, wherein the 5' to 3' arrangement of elements is selected from:

- (i) 5'-promoter-transgene-WPRE-p(A)-3';
- (ii) 5'-promoter-intron-transgene-WPRE-p(A)-3';
- (iii) 5'-promoter-transgene-WPRE-p(A)-promoter-transgene-WPRE-p(A);
- (iv) 5'-enhancer-promoter-transgene-WPRE-p(A)-3';
- (v) 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-3';
- (vi) 5'-enhancer-enhancer-promoter-transgene-WPRE-p(A)-3';
- (vii) 5'-enhancer-enhancer-promoter-intron-transgene-WPRE-p(A)-3';

- (viii) 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-enhancer-3';
 - (ix) 5'-enhancer-promoter-intron-transgene-WPRE-p(A)-enhancer-promoter-intron-transgene-p(A)-3';
 - (x) 5'-p(A)-WPRE-transgene-intron-promoter-enhancer-enhancer-promoter-intron-transgene-p(A)-3';
 - (xi) 5'-promoter-intron-transgene-WPRE-p(A)-p(A)-transgene-intron-promoter-3';
 - (xii) 5'-promoter-intron-transgene-WPRE-p(A)-promoter-intron-transgene-p(A)-3'; and
 - (xiii) 5'-p(A)-WPRE-transgene-intron-promoter-promoter-intron-transgene-p(A)-3';
- wherein optionally the transgene encodes a polypeptide for use in treating or a preventing a heart disease.

[00707] Embodiment 178: The expression cassette of embodiment 176 or embodiment 177, wherein the transgene has an increased expression level compared to a second expression cassette comprising a polynucleotide having an arrangement of elements from 5' to 3' comprising: 5'-promoter-transgene-WPRE-p(A)-3'.

[00708] Embodiment 179: The expression cassette of embodiment 178, wherein the increased expression level is between about 1.5-fold and about 150-fold compared to the second expression cassette.

[00709] Embodiment 180: A recombinant adeno-associated virus (rAAV) virion, comprising a capsid protein and a viral genome comprising an expression cassette of any one of embodiments 176 to 179, the expression cassette flanked by inverted terminal repeats.

[00710] Embodiment 181: The rAAV of embodiment 180, wherein the expression cassette comprises a transgene, wherein the transgene encodes a polypeptide for use in treating or a preventing a heart disease, or alleviating symptoms associated with a heart disease.

[00711] Embodiment 182: The rAAV of embodiment 180 or embodiment 181 wherein the capsid protein is selected from any one of SEQ ID NOs: 145-200.

EXAMPLES

EXAMPLE 1: NOVEL EXPRESSION CASSETTES

[00712] The purpose of this study was to evaluate several engineered expression cassettes for their ability to express a transgene in human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM) and a mouse model.

[00713] The human DWORF (hDWORF) polynucleotide (SEQ ID NO: 33) was inserted into expression cassettes designed to induce strong cardiomyocyte-specific expression while maintaining a total size of 3-4.7 kbp in length. Three unique expression cassettes were generated, pCR-HD1 (SEQ ID NO: 22), pCR-HD2 (SEQ ID NO: 23), and pCR-HD3. **FIG. 1** shows an illustrative embodiment of each expression cassette, which contained iterations of a cardiac Troponin T promoter (see Table 3), WPRE (SEQ ID NO: 26) and BGH poly(A) signal (SEQ ID NO: 27). To evaluate expression of a transgene encoded by each expression cassette in hiPSC-CMs, the DWORF transgene was replaced with GFP in each expression cassettes, designated CR-G1, CR-G2, and CR-G3 corresponding to pCR-HD1, pCR-HD2, and pCR-HD3, respectively. The CR-G1, CR-G2, and CR-G3 expression cassettes were packaged into rAAV virions using an AAV6 capsid (SEQ ID NO: 39) protein. Cells were infected with each rAAV virion containing the expression cassette variants at an MOI of 50,000, and GFP expression was quantified by flow cytometry. **FIG. 2** shows the pCR-G1, pCR-G2, and pCR-G3 expression cassettes showed high levels of expression in hiPSC-CMs. Surprisingly, the double transgene construct exhibited lower expression, likely due to the homologous recombination between the tandem repeat sequences. Next, the expression cassettes containing hDWORF, pCR-HD1 and pCR-HD2 were evaluated in a wild type CD1 mouse model. Each cassette was packaged into rAAV virions using an AAV9 capsid protein. The rAAV virions (5×10^{11} vg) were administered systemically by retro-orbital injection into wild type CD1 mice (N=2). Two weeks following injection, animals were sacrificed and hDWORF expression was assessed in hearts. **FIG. 3** shows the pCR-HD2 expression cassette results in about a 2-fold increase in hDWORF expression. It was concluded that increasing the length of the canonical hTNNT2 promoter from 600 bp to 1.5 kb, increasing total vector size from 1.9 kb to 3.2 kb, and/or inserting an intron surprisingly doubles gene expression.

EXAMPLE 2: EVALUATION IN HIPSC-CMs

[00714] The purpose of this study was to evaluate the ability of chimeric capsid proteins to facilitate infection of hiPSC-CMs with an rAAV virion containing an expression cassette encoding an HA-tagged hDWORF protein and the chimeric capsid protein.

[00715] Expression cassettes encoding an HA-tagged hDWORF protein were packaged into rAAV virions with using a one of five chimeric capsid proteins. The chimeric capsid proteins tested include CR9-01 (SEQ ID NO: 29), CR9-10 (SEQ ID NO: 19), CR9-14 (SEQ ID NO: 30), TN44-07 (SEQ ID NO: 31), or TN47-10 (SEQ ID NO: 18), and the AAV9 capsid protein (SEQ ID NO: 16) was used as a control. Wild type hiPSC-CMs were infected at a MOI

of 3,900. Five days following infection, cells were fixed and stained for SERCA2a and HA-tagged hDWORF. Stained cells were imaged (**FIG. 4B**) and quantified (**FIG. 4A**) using a cytation imager, and expression was normalized to AAV9. **FIG. 4A** shows HA-tagged hDWORF expression in hiPSC-CM cell cultures infected with rAAV virions containing the CR9-01, CR9-10, CR9-14, or TN44-07 chimeric capsid proteins. Each of these capsids performed as well or better than the AAV9 capsid protein in delivering a functional expression cassette.

EXAMPLE 3: EVALUATION IN A MURINE MODEL

[00716] The purpose of this study was to evaluate the ability of chimeric capsid proteins to facilitate infection of heart tissue in wildtype mice with an rAAV virion containing an expression cassette encoding an HA-tagged hDWORF protein and the chimeric capsid protein.

[00717] Expression cassettes encoding an HA-tagged hDWORF protein were packaged into rAAV virions with using one of five chimeric capsid proteins. The chimeric capsid proteins tested include CR9-01 (SEQ ID NO: 29), CR9-10 (SEQ ID NO: 19), CR9-14 (SEQ ID NO: 30), TN44-07 (SEQ ID NO: 31), or TN47-10 (SEQ ID NO: 18), and the AAV9 capsid protein (SEQ ID NO: 16) was used as a control. The rAAV virions were delivered by retro-orbital injection into wildtype mice at a dose of 5×10^{11} vg/mouse (N=3). Fourteen days following injection, animals were sacrificed, and heart tissue was collected for RNA and protein analysis. **FIG. 5A** shows hDWORF RNA expression in heart tissue infected with the indicated capsid. All expression levels were normalized to the expression levels in the AAV9 group. The results indicate that *in vivo* delivery of rAAV virions packaged with the CR9-01, CR9-10, CR9-14, TN44-07, and TN47-10 each showed increased hDWORF expression compared to parental AAV9. The rAAV virions containing the CR9-10 and TN47-10 capsids showed the highest levels of expression compared to the other tested capsids (~9-fold and ~11-fold increased, respectively). **FIG. 5B** shows that hDWORF protein expression confirmed the RNA expression levels in the heart tissue, indicating that hDWORF RNA was translated to protein in the infected cells and that the modified capsids dramatically increased protein expression.

EXAMPLE 4: DWORF GENE THERAPY IN A PLN-R14^{ΔA} MODEL

[00718] The purpose of this study was to evaluate the ability of rAAV virions containing an expression cassette encoding an mDWORF protein to reduce symptoms associated with cardiomyopathy in mice harboring the PLN-R14 deletion mutation.

[00719] Transgenic mice expressing a homozygous PLN gene harboring the arginine 14 deletion (PLN-R14^{ΔΔ}) recapitulates human cardiomyopathy, exhibiting similar histopathologic abnormalities and premature death (Haghighi K et al. *Proc. Natl. Acad. Sci. U.S.A* 103:1388-1393 (2006)). In particular, the transgenic mice can be used as a model of dilated cardiomyopathy. The model is significantly more severe than a *MLP*^{-/-} knockout and clinically relevant, as there are no known MLP knockout cardiomyopathy patients.

[00720] In this study, three-week-old homozygous PLN-R14del animals were injected with either Hank's Balanced Salt Solution (HBSS) as sham control or rAAV virions comprised of the pCR-MD1 expression cassette (SEQ ID NO: 20) and the AAV9 capsid protein. PLN-R14^{ΔΔ} mice were administered rAAV virions by retro-orbital injection with a dose ranging from 5×10^{12} vg/kg to 5×10^{13} vg/kg (N=7-8/group). Ejection fraction and fractional shortening were assessed by echocardiography as markers of cardiac function at 6.5 weeks of age. **FIG. 6A** show a dose-dependent improvement in ejection fraction compared to sham control ($p=0.035$). **FIG. 6B** shows a dose-dependent improvement in fractional shortening compared to sham control ($p=0.028$).

[00721] Together these results indicate systemic administration of rAAV virions expressing DWORF improves cardiac function in an animal model of cardiomyopathy. Observation of this effect in mice treated at three weeks of age demonstrates that this gene therapy can both treat and prevent development of hypertrophic cardiomyopathy (HCM).

EXAMPLE 5: RAAV-MEDIATED DWORF EXPRESSION

[00722] Expression cassettes were packaged with AAV9 capsid into rAAV virions and injected into 4 week old wildtype C57Bl6 mice at a dose of 5×10^{13} vg/kg (N=4). Mouse hearts were harvested at 3 weeks following injection. DWORF protein expression was determined by Western blots and quantified (**FIG. 8C**, Table 10). A transgenic mouse (Tg-dworf) with a high DWORF expression level was used as a positive control.

[00723] The results show that combinations of specific promoters and enhancers and their orientation in the expression cassette lead to different levels of DWORF expression. The specific expression cassettes used in this example and the associated elements and their orientation are shown in **FIG. 7A-7C**. DWORF expression was increased with added elements compared to promoter alone, but the extent of increased DWORF expression was not predictable based on elements and orientation alone.

[00724] **FIG. 8A** shows the strategy for evaluating the expression of transgene (DWORF) in cardiomyocytes of naïve mice. Three weeks post-injection, animals were

sacrificed and DWORF expression was assessed in hearts. **FIG. 8B** shows expression analysis results for 16 AAV constructs with various regulatory elements and arrangements to increase CM-selective expression of transgene (DWORF). In particular, **FIG. 8B** shows the expression of DWORF in wild type C57BL6 mouse cardiomyocytes harvested three weeks after retro-orbital inject with AAV9:DWORF vectors as assessed by western blot; the lower western blot panels display the expression of GAPDH as a positive control. Quantification of these data in **FIG. 8C** revealed that combinations of specific promoters and enhancers and their orientation in the expression cassette result in different levels of transgene expression. A transgenic mouse (Tg-dworf) with a high DWORF expression level was used as a positive control in this example.

[00725] For each expression cassette, DWORF expression was normalized to the observed level for the pCRmD1 expression cassette, which has only the human cTnT promoter without added enhancer elements. Adding the ACTC1 enhancer (pHZ15) or α MHC enhancer (pHZ17) increased DWORF expression about 3-fold to about 4-fold relative to pCRmD1. Adding the CMV intron (pHZ20) was observed to increase DWORF expression about 5-fold. Combining the promoter, a single enhancer, and an intron (pHZ22 and pHZ23) did not significantly increase DWORF expression compared to any element alone. Combining both enhancers with the promoter only marginally increased DWORF expression to about 6- to 8-fold compared to promoter alone. Surprising, the combination of both enhancers, a promoter, and an intron increased DWORF expression about 10- to 16-fold. Interestingly, the 5' to 3' order of enhancers plays a fine-tune role in regulating protein expression. Orienting the ACTC1 enhancer 5' to the second enhancer (pHZ16 or pHZ21) appears to increase DWORF expression compared to orienting the ACTC1 enhancer 3' to the second enhancer (pHZ18 or pHZ19). Including a codon optimized DWORF transgene (pHZ24) also increased expression.

Table 10. DWORF Expression

Expression Cassette	DWORF Expression Fold Increase over Promoter Only
pCRmD1	1.0
pHZ15	3.9
pHZ16	8.2
pHZ17	3.3
pHZ18	6.0
pHZ19	10.0

pHZ20	4.8
pHZ21	16.6
pHZ22	5.0
pHZ23	6.5
pHZ24	8.2
pHZ25	108.0
pHZ33	94.2
pHZ34	112.6
pHZ69	139.3
pHZ72	41.2
pHZ75	60.6
Tg-DWOLF (Positive Control)	113.7

[00726] Although adding various regulatory elements greatly increased DWORF expression, adding more copies of the transgene (pHZ25, pHZ33, pHZ34, pHZ69, pHZ72 and pHZ75) has an unexpected synergistic impact on DWORF levels. We used different enhancers, promoters, introns, and codon-optimized DWORF in each copy to avoid the homologous recombination between the tandem repeat sequences. The dual copies vectors have about 40- to 140-fold more expression than DWORF under transcriptional control of the promoter alone. Surprisingly, the orientation of the two copies has an unexpected role in regulating gene expression. For example, a tail-to-tail orientation shows the best expression, followed by head-to-head and head-to-tail arrangements. The results also suggest that different arrangements of the two copies of the transgene can be used to fine-tune the transgene expression.

EXAMPLE 6: EFFECT OF DWORF EXPRESSION ON EJECTION FRACTION

[00727] The effect of rAAV mediated DWORF expression on ejection fraction was determined in an MLP knockout (MLP-KO) dilated cardiomyopathy (DCM) model. Three of the rAAV virions were tested, including those with vector genomes having a single copy expression cassettes pHZ19 and pHZ21, and one having a dual copy expression cassette pHZ34. MLP-KO mice were dosed with either pHZ19 at 5×10^{13} vg/kg, pHZ21 at 5×10^{13} vg/kg, or pHZ34 at 1×10^{13} vg/kg. Virions were delivered by retro-orbital injection at 6 weeks of age, at which time the mice were presenting with moderate heart failure. Cardiac functions were accessed by echocardiography at 3, 6, 9, 12, 16 and 20 weeks post-treatment. As shown in **FIG. 9**, pHZ21 at a 5×10^{13} vg/kg dose significantly improved ejection fraction (14.4%) by 16 weeks

post-virus injection compared to the HBSS group. Although pHZ21 only has a 1.6 fold more DWORF expression than the pHZ19, this modest improvement in expression seems to have a very profound effect on improving cardiac function. The dose of pHZ34 is five times lower than the pHZ19 and pHZ21, but it achieved similar improvement as the pHZ21 and better improvement than pHZ19, highlight the importance of DWORF expression.

[00728] Three of the DWORF expression cassettes were tested in another well characterized DCM model, the BAG3 cardiac conditional knock-out (BAG3-cKO) model. DWORF expression cassettes were tested in this model included one single copy vector, the pHZ21, and two dual-copy vectors, pHZ72 and pHZ75. BAG3-cKO mice were dosed with either 5×10^{13} vg/kg AAV9-pHZ21, AAV9-pHZ72 and AAV9-pHZ75. Virions were delivered by retro-orbital injection at 8 weeks of age when the mice have already developed moderate heart failure. Cardiac functions were accessed by echocardiography at 3 and 6 weeks post-treatment. As shown in **FIG. 10**, pHZ72 at a 5×10^{13} vg/kg dose substantially improved ejection fraction (7.4%) by 6 weeks post-virus injection compared to the HBSS group, suggesting that such optimized DWORF gene therapy can improve cardiac function in this model.

***EXAMPLE 7: EFFECT OF DWORF CONSTRUCTS IN A SEVERE MLP-KO DCM
MOUSE MODEL***

[00729] The purpose of this study was to test how optimized DWORF vectors can improve heart function and exercise capacity in a well-characterized MLP knockout (MLP-KO) dilated cardiomyopathy model.

[00730] **FIG. 11A** is the schematic diagram of the study design. Three of the rAAV virions were tested, including those with vector genomes having a single copy expression cassettes pHZ19 and pHZ21, and one having a dual copy expression cassette pHZ34. MLP-KO mice were dosed with either pHZ19 at 5×10^{13} vg/kg, pHZ21 at 5×10^{13} vg/kg, or pHZ34 at 1×10^{13} vg/kg. Virions were delivered by retro-orbital injection at 6 weeks of age, at which time the mice were presenting with moderate heart failure. Cardiac functions were accessed by echocardiography 3-4 weeks and up to 24 weeks post-treatment. MLP-KO mice have limited exercise capacity compared to their wild-type littermates. To assess how much DWORF gene therapy can improve exercise capacity in MLP-KO mice, mice were allowed to run on a rodent treadmill and their running duration was monitored at 26 weeks.

[00731] As shown in **FIG. 11B** and **FIG. 11C**, pHZ21 at a 5×10^{13} vg/kg dose significantly improved ejection fraction (14.3%) by 24 weeks post-virus injection compared to the HBSS group. Although pHZ21 only has a 1.6 fold more DWORF expression than the

pHZ19, this modest improvement in expression seems to have a very profound effect on improving cardiac function. The dose of pHZ34 is five times lower than the pHZ19 and pHZ21, but it achieved similar improvement as the pHZ21 and better improvement than pHZ19, highlighting the importance of DWORF expression. **FIG. 11D** and **FIG. 11E** show that MLP-KO mice have limited exercise capacity compared to their wild-type littermates. pHZ21, the best DWORF vector to improve ejection fraction, also significantly improved exercise capacity, including running distance and time to exhaustion, in the MLP KO DCM mouse model 26 weeks post-treatment relative to the saline control.

[00732] Overall, this study shows that AAV-delivered DWORF mitigated the contractile dysfunction and improved exercise capacity in this MLP-KO DCM model. AAV:DWORF cassettes expressed higher levels of DWORF, supporting the most significant degree of efficacy that was durable out to 24 weeks. These results show that DWORF gene therapy can be used for normalizing calcium homeostasis and limiting disease progression.

EXAMPLE 8: TOLERABILITY OF DWORF GENE THERAPY IN NAÏVE MICE

[00733] The purpose of this study was to evaluate the tolerability of DWORF gene therapy in naïve mice. **FIG. 12A** is the schematic diagram of the study design. Naïve mice were dosed with either HBSS saline control or AAV9:pHZ21 vector at two doses: 5×10^{13} vg/kg and 2×10^{14} vg/kg. Viruses were delivered via intraperitoneal (IP) injection at postnatal day 3 (P3). Cardiac functions were evaluated by echocardiography 4 weeks after viral injection.

[00734] **FIG. 12B** shows that AAV9:pHZ21 is well tolerated in wild-type mice up to 2×10^{14} vg/kg. Compared with the saline control group, there are no differences in body weight, ejection fraction, heart rate, and left ventricular mass (LV mass) for those groups that were dosed with AAV9:pHZ21.

INCORPORATION BY REFERENCE

[00735] Various references such as patents, patent applications, and publications are cited herein, the disclosures of which are hereby incorporated herein by reference in their entireties. Also, all references mentioned herein are specifically incorporated by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

What is claimed is:

1. An expression cassette comprising a polynucleotide sequence comprising:
 - i) one or more promoters, optionally wherein the one or more promoters are cardiac-specific promoters; and
 - ii) one or more copies of a transgene, wherein the transgene encodes a polypeptide for treating or preventing a heart disease or alleviating symptoms associated with a heart disease;wherein the expression cassette comprises one or more of:
 - iii) the polynucleotide sequence further comprises one or more enhancers;
 - iv) the one or more copies of a transgene is at least two copies of the transgene;
 - v) the polynucleotide sequence further comprises one or more introns; and/or
 - vi) at least one copy of the one or more copies of the transgene is codon-optimized.
2. The expression cassette of claim 1, wherein the polynucleotide sequence further comprises one or more enhancers, optionally wherein the one or more enhancers are cardiac-specific enhancers.
3. The expression cassette of claim 1 or 2, wherein the one or more copies of a transgene is two copies of the transgene, optionally wherein the one or more promoters is two promoters, and further optionally wherein the two copies of the transgene are not identical.
4. The expression cassette of any one of claims 1-3, wherein the polynucleotide sequence further comprises one or more introns, optionally wherein the one or more introns improve the efficiency of transgene expression.
5. The expression cassette of any one of claims 1-4, wherein at least one copy of the one or more copies of the transgene is codon-optimized, optionally wherein the one or more copies of the transgene are two copies of the transgene and wherein one copy of the transgene is not codon-optimized.

6. The expression cassette of any one of claims 1-5, wherein the polynucleotide sequence further comprises:
 - i) one or more post-transcriptional regulatory elements ("PTRE"), optionally wherein the one or more post-transcriptional regulatory elements are WPRE; and/or
 - ii) one or more polyadenylation sequences ("p(A)").
7. The expression cassette of any one of claims 1-6, which comprises 5' to 3' arrangement of elements selected from:
 - (i) 5'-promoter-intron-transgene-PTRE -p(A)-3';
 - (ii) 5'-promoter-transgene- PTRE -p(A)-promoter-transgene- PTRE -p(A);
 - (iii) 5'-enhancer-promoter-transgene-PTRE-p(A)-3';
 - (iv) 5'-enhancer-promoter-intron-transgene-PTRE-p(A)-3';
 - (v) 5'-enhancer-enhancer-promoter-transgene-PTRE-p(A)-3';
 - (vi) 5'-enhancer-enhancer-promoter-intron-transgene-PTRE-p(A)-3';
 - (vii) 5'-enhancer-promoter-intron-transgene-PTRE-p(A)-p(A)-transgene-intron-promoter-enhancer-3';
 - (viii) 5'-enhancer-promoter-intron-transgene-PTRE-p(A)-enhancer-promoter-intron-transgene-p(A)-3';
 - (ix) 5'-p(A)-PTRE-transgene-intron-promoter-enhancer-enhancer-promoter-intron-transgene-p(A)-3';
 - (x) 5'-promoter-intron-transgene-PTRE-p(A)-p(A)-transgene-intron-promoter-3';
 - (xi) 5'-promoter-intron-transgene-PTRE-p(A)-promoter-intron-transgene-p(A)-3'; and
 - (xii) 5'-p(A)-PTRE-transgene-intron-promoter-promoter-intron-transgene-p(A)-3'.
8. The expression cassette of any one of claims 1-7, wherein the transgene has an increased expression level compared to an expression cassette comprising a polynucleotide having an arrangement of elements from 5' to 3' comprising: 5'-promoter-transgene-WPRE-p(A)-3'.
9. The expression cassette of claim 8, wherein the increased expression level is between about 1.5-fold and about 150-fold, optionally wherein the increased expression level is at

least 2 fold, at least 5 fold, at least 10 fold, at least 25 fold, at least 50 fold, at least 75 fold, or at least 100 fold.

10. The expression cassette of any one of claims 1-9, wherein at least one promoter of the one or more promoters is a chicken cTnT promoter.
11. The expression cassette of claim 10, wherein the chicken cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 11.
12. The expression cassette of claim 10, wherein the chicken cTnT promoter comprises SEQ ID NO: 11.
13. The expression cassette of any one of claims 1-12, wherein at least one promoter of the one or more promoters is a human cTnT promoter.
14. The expression cassette of claim 13, wherein the human cTnT promoter shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 12 or SEQ ID NO: 13.
15. The expression cassette of claim 13, wherein the human cTnT promoter comprises SEQ ID NO: 12 or SEQ ID NO: 13.
16. The expression cassette of any one of claims 1-15, wherein the one or more enhancers are one or more cardiac-specific enhancers.
17. The expression cassette of claim 16, wherein the one or more cardiac-specific enhancers are selected from a ACTC1 cardiac enhancer and a α MHC enhancer.
18. The expression cassette of claim 17, wherein the ACTC1 cardiac enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 78.
19. The expression cassette of claim 17, wherein the ACTC1 cardiac enhancer comprises SEQ ID NO: 78.
20. The expression cassette of claim 17, wherein the α MHC enhancer shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79.
21. The expression cassette of claim 17, wherein the α MHC enhancer comprises SEQ ID NO: 79.

22. The expression cassette of any one of claims 1-21, wherein the intron is selected from a CMV intron and a chimeric intron.
23. The expression cassette of claim 22, wherein the CMV intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 80.
24. The expression cassette of claim 22, wherein the CMV intron comprises SEQ ID NO: 80.
25. The expression cassette of claim 22, wherein the chimeric intron shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81.
26. The expression cassette of claim 22, wherein the chimeric intron comprises SEQ ID NO: 81.
27. The expression cassette of any one of claims 1-26, wherein the expression cassette comprises a WPRE sequence.
28. The expression cassette of claim 27, wherein the WPRE sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26.
29. The expression cassette of claim 27, wherein the WPRE sequence comprises SEQ ID NO: 26.
30. The expression cassette of any one of claims 1-29, wherein the expression cassette comprises a polyadenylation sequence.
31. The expression cassette of claim 30, wherein the polyadenylation sequence is selected from a BGH polyadenylation sequence and a SV40 polyadenylation sequence.
32. The expression cassette of claim 31, wherein the BGH polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 27.
33. The expression cassette of claim 31, wherein the BGH polyadenylation sequence comprises SEQ ID NO: 27.
34. The expression cassette of claim 31, wherein the SV40 polyadenylation sequence shares at least 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 28.

35. The expression cassette of claim 31, wherein the SV40 polyadenylation sequence comprises SEQ ID NO: 28.
36. The expression cassette of any one of claims 1-35, wherein the expression cassette is flanked by ITRs.
37. The expression cassette of claim 36, wherein the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
38. The expression cassette of claim 36, wherein the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
39. The expression cassette of any one of claims 1 to 38 comprising a single promoter.
40. The expression cassette of any one of claims 1 to 38 comprising two promoters.
41. The expression cassette of any one of claims 1 to 40, comprising from about 1.9 kb to about 3.7 kb.
42. The expression cassette of any one of claims 1 to 40, comprising about 2.5 kb to about 3.7 kb, optionally from about 2.8 kb to about 3.6 kb.
43. The expression cassette of any one of claims 1 to 42, wherein the transgene encodes a polypeptide selected from: DWORF, JPH2, BAG3, CRYAB, Lamin A isoform of LMNA, Lamin C isoform of LMNA, TNNI3, PLN, LAMP2a, LAMP2b, LAMP2c, DPI isoform of DSP, DPII isoform of DSP, DSG2, and JUP.
44. The expression cassette of any one of claims 1-43, wherein the transgene shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:201, SEQ ID NO:203, SEQ ID NO:205, SEQ ID NO:207, SEQ ID NO:209, SEQ ID NO:211, SEQ ID NO:213, SEQ ID NO:215, SEQ ID NO:217, SEQ ID NO:219, SEQ ID NO:221, SEQ ID NO:223, SEQ ID NO:225, SEQ ID NO:227, or SEQ ID NO:229.
45. The expression cassette of any one of claims 1-44, wherein the polypeptide shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:202, SEQ ID NO:204, SEQ ID NO:206, SEQ ID NO:208, SEQ ID NO:210, SEQ ID NO:212, SEQ ID NO:214, SEQ ID NO:216, SEQ ID NO:218, SEQ ID NO:220, SEQ ID NO:222, SEQ ID NO:224, SEQ ID NO:226, SEQ ID NO:228, or SEQ ID NO:230.

46. The expression cassette of any one of claims 1 to 43, wherein the transgene encodes a DWORF polypeptide.
47. The expression cassette of claim 46, wherein the transgene shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:33, SEQ ID NO:44, SEQ ID NO:76, or SEQ ID NO:77.
48. The expression cassette of claim 46, wherein the polypeptide shares at least 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:32, or SEQ ID NO:43.
49. The expression cassette of any one of claims 43-48, wherein the transgene comprises a codon-optimized nucleic acid sequence.
50. The expression cassette of any one of claims 1-49, which comprises 5' to 3' arrangement of elements selected from:
- (i) 5'-human or chicken TnT promoter-chimeric intron-transgene-WPRE-p(A)-3';
 - (ii) 5'- first human or chicken TnT promoter-first copy of transgene-WPRE-p(A)- second human or chicken TnT promoter – second copy of transgene-WPRE-p(A), optionally where the first and second promoter sequences and the first and second copies of the transgene are in the same forward orientation;
 - (iii) 5'- human TnT promoter-CMV intron-transgene-WPRE-bGHpA-3';
 - (iv) 5'-ACTC1e enhancer-cardiac- human TnT promoter -transgene-WPRE-bGHpA-3';
 - (v) 5'- α MHCe enhancer- human TnT promoter -transgene-WPRE-bGHpA-3';
 - (vi) 5'-ACTC1e enhancer- human TnT promoter -CMV intron-transgene-WPRE-bGHpA-3';
 - (vii) 5'- α MHCe enhancer- human TnT promoter -CMV intron-transgene-WPRE-bGHpA-3';
 - (viii) 5'-ACTC1e enhancer- α MHCe enhancer-human TnT promoter-transgene-WPRE-bGHpA-3';
 - (ix) 5'- α MHCe enhancer -ACTC1e enhancer-human TnT promoter-transgene-WPRE-bGHpA-3';
 - (x) 5'- ACTC1e enhancer- α MHCe enhancer-human TnT promoter-CMV intron-transgene-WPRE- bGHpA-3';
 - (xi) 5'- α MHCe enhancer- ACTC1e enhancer- human TnT promoter-CMV intron-transgene-WPRE-bGHpA-3';

- (xii) 5'- human TnT promoter-transgene with a codon-optimized polynucleotide sequence-WPRE-bGHpA-3';
- (xiii) 5'- α MHCe enhancer- human TnT promoter -CMV intron-first transgene-WPRE-bGHpA-SV40pA-second transgene (e.g., with a codon-optimized polynucleotide sequence)-chimeric intron- chicken TnT promoter - ACTC1e enhancer-3', optionally wherein the first transgene and the human TnT promoter are in a forward orientation, and the second transgene and the chicken TnT promoter are in a reverse orientation;
- (xiv) 5'- α MHCe enhancer- human TnT promoter -CMV intron-first transgene-WPRE-bGHpA- ACTC1e enhancer- chicken TnT promoter-chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene, the human TnT promoter, the second transgene and the chicken TnT promoter are in a forward orientation;
- (xv) 5'-bGHpA-WPRE-first transgene-CMV intron-human TnT promoter- α MHCe enhancer- ACTC1e enhancer- chicken TnT promoter-chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene and the human TnT promoter are in a reverse orientation, and the second transgene and the chicken TnT promoter are in a forward orientation;
- (xvi) 5'-human TnT promoter -CMV intron-first transgene-WPRE-bGHpA-pSV40pA-second transgene (e.g., with a codon-optimized polynucleotide sequence)-chimeric intron- chicken TnT promoter-3', optionally wherein the first transgene and the human TnT promoter are in a forward orientation, and the second transgene and the chicken TnT promoter are in a reverse orientation;
- (xvii) 5'- huma TnT promoter-CMV intron-first transgene-WPRE-bGHpA-chicken TnT promoter- chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)- SV40pA-3', optionally wherein the first transgene, the human TnT promoter, the second transgene and the chicken TnT promoter are in a forward orientation; and
- (xviii) 5'- bGHpA- WPRE- first transgene- CMV intron-human TnT promoter- chicken TnT promoter- chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene and the human TnT promoter are in a reverse orientation, and the second transgene and the chicken TnT promoter are in a forward orientation.

51. The expression cassette of claim 50, which comprises 5' to 3' arrangement of elements selected from:

- (i) 5'- ACTC1e enhancer- α MHCe enhancer-human TnT promoter-CMV intron-transgene-WPRE- bGHpA-3';
- (ii) 5'- α MHCe enhancer- ACTC1e enhancer- human TnT promoter-CMV intron-transgene-WPRE-bGHpA-3';
- (iii) 5'- α MHCe enhancer- human TnT promoter -CMV intron-first transgene-WPRE-bGHpA-SV40pA-second transgene (e.g., with a codon-optimized polynucleotide sequence)-chimeric intron- chicken TnT promoter - ACTC1e enhancer-3', optionally wherein the first transgene and the human TnT promoter are in a forward orientation, and the second transgene and the chicken TnT promoter are in a reverse orientation;
- (iv) 5'- α MHCe enhancer- human TnT promoter -CMV intron-first transgene-WPRE-bGHpA- ACTC1e enhancer- chicken TnT promoter-chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene, the human TnT promoter, the second transgene and the chicken TnT promoter are in a forward orientation;
- (v) 5'-bGHpA-WPRE-first transgene-CMV intron-human TnT promoter- α MHCe enhancer- ACTC1e enhancer- chicken TnT promoter-chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene and the human TnT promoter are in a reverse orientation, and the second transgene and the chicken TnT promoter are in a forward orientation;
- (vi) 5'-human TnT promoter -CMV intron-first transgene-WPRE-bGHpA-pSV40pA-second transgene (e.g., with a codon-optimized polynucleotide sequence)-chimeric intron-chicken TnT promoter-3', optionally wherein the first transgene and the human TnT promoter are in a forward orientation, and the second transgene and the chicken TnT promoter are in a reverse orientation;
- (vii) 5'- huma TnT promoter-CMV intron-first transgene-WPRE-bGHpA-chicken TnT promoter- chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)- SV40pA-3', optionally wherein the first transgene, the human TnT promoter, the second transgene and the chicken TnT promoter are in a forward orientation; and
- (viii) 5'- bGHpA- WPRE- first transgene- CMV intron-human TnT promoter- chicken TnT promoter- chimeric intron-second transgene (e.g., with a codon-optimized polynucleotide sequence)-SV40pA-3', optionally wherein the first transgene and the human TnT promoter are in a reverse orientation, and the second transgene and the chicken TnT promoter are in a forward orientation.

52. The expression cassette of any one of claims 1-51, which is a recombinant expression cassette.
53. A recombinant vector comprising the expression cassette of any one of claims 1-52.
54. A recombinant adeno-associated virus (rAAV) virion, comprising a capsid protein and a viral genome comprising the expression cassette of any one of claims 1-52, wherein the expression cassette is flanked by inverted terminal repeats (ITRs).
55. The rAAV virion of claim 54, wherein the ITRs share at least 90%, 95%, 96%, 97%, 98%, or 99% identity to one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
56. The rAAV virion of claim 54, wherein the ITRs comprise one or more of SEQ ID NO: 14 and SEQ ID NO: 15.
57. The rAAV virion of any one of claims 54-56, wherein the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV9 capsid protein (SEQ ID NO: 143).
58. The rAAV virion of any one of claims 54-56, wherein the capsid protein shares at least 98%, at least 99%, or 100% identity to an AAV5 capsid protein (SEQ ID NO: 144).
59. The rAAV virion of any one of claims 54-56, wherein the capsid protein is a chimeric capsid protein.
60. The rAAV virion of any one of claims 54-56, wherein the capsid protein is an AAV5/AAV9 chimeric capsid protein.
61. The rAAV virion of any one of claims 54-56, wherein the capsid protein is selected from any one of SEQ ID NOs: 145-200.
62. A pharmaceutical composition comprising the vector of claim 53, or the rAAV virion of any one of claims 54-61, and a pharmaceutically acceptable carrier.
63. A kit comprising the pharmaceutical composition of claim 62.
64. A method of increasing expression of a polypeptide in a cardiac cell or cardiac tissue comprising contacting a cell with the vector of claim 53, the rAAV virion of any one of claims 54-61, or the composition of claim 62.

65. The method of claim 64, wherein the cardiac cell is a cardiomyocyte.
66. The method of claim 64, wherein the cardiac tissue is heart tissue.
67. The method of any one of claims 64-66, whereby the polypeptide expression is increased between about 1.5-fold and 150-fold.
68. The method of any one of claims 64-67, wherein the contacting is *in vitro*.
69. The method of any one of claims 64-67, wherein the contacting is *in vivo*.
70. A method of increasing polypeptide expression in a subject comprising administering to the subject the vector of claim 53, the rAAV virion of any one of claims 54-61, or the composition of claim 62.
71. The method of claim 70, wherein the subject is a mammal.
72. The method of claim 70, wherein the subject is a human.
73. The method of any one of claims 70-72, whereby the polypeptide expression is increased in the heart of the subject.
74. The method of any one of claims 70-73, wherein subject has a heart disease or is at risk of a heart disease.
75. The method of any one of claims 70-74, wherein subject has borderline or reduced ejection fraction.
76. The method of any one of claims 70-74, wherein the subject has normal ejection fraction.
77. The method of any one of claims 70-76, wherein the subject has a genetic mutation associated with a heart disease, optionally wherein the genetic mutation is a mutation in PLN.
78. The method of any one of claims 70-77, wherein the subject has a low or undetectable level of the polypeptide expression compared to a healthy subject.

79. A method of treating or preventing a heart disease or disorder in a subject in need thereof comprising administering to the subject the vector of claim 53, the rAAV virion of any one of claims 54-61, or the composition of claim 62.
80. The method of claim 79, wherein the subject has a heart disease or disorder.
81. The method of claim 79, wherein the subject is at risk of developing a heart disease or disorder.
82. The method or any one of claims 79-81, wherein the heart disease or disorder is cardiomyopathy.
83. The method of claim 82, wherein the cardiomyopathy is dilated cardiomyopathy.
84. The method of any one of claims 79-81, wherein the heart disease or disorder is myocardial infarction.
85. The method of claim 84, wherein the myocardial infarction is chronic myocardial infarction.
86. The method of claim 84, wherein the myocardial infarction is acute myocardial infarction.
87. The method of any one of claims 79-86, wherein the subject has an inherited risk allele for a heart disease or disorder.
88. The method of claim 87, wherein the inherited risk allele comprises a mutation in the *PLN* gene, optionally wherein the mutation in the *PLN* gene is a *PLN* promoter mutation, a *PLN* gene duplication, a R14del mutation.
89. The method of any one of claims 79 to 88, wherein the heart disease or disorder is with reduced ejection fraction (HFrEF).
90. The method of any one of claims 79 to 88, wherein the heart disease or disorder is with preserved ejection fraction (HFpEF).
91. The method of any one of claims 79 to 90, wherein the method leads to expression of the polypeptide in the heart of the subject.

92. The method of any one of claims 79 to 91, wherein the method leads to expression of the polypeptide in cardiomyocytes of the subject.
93. The method of any one of claims 79 to 92, wherein the method causes no detectable expression of the polypeptide in the muscles of the subject except the heart, in the liver of the subject, and/or in the cardiac fibroblasts of the subject.
94. The method of any one of claims 79 to 93, wherein the method improves one or more measures of cardiac function, optionally fraction shortening and/or left ventricular internal dimension (LVID).
95. The method of claim 94, wherein the improvement in cardiac function is observed at or later than week 2, week 4, week 6, week 8, week 10, week 12, week 14, week 16, week 18, week 20, week 22, and/or week 24, after the administering.
96. The method of any one of claims 79 to 95, wherein the administering is systemic administration.
97. The method of claim 96, wherein the systemic administration is selected from intravenous or intracoronary injection.
98. The method of claim 96 or 97, wherein the rAAV virion is administered as a unit dose.
99. The method of claim 98, wherein the unit dose comprises about 3×10^{14} vg/kg or less, about 2×10^{14} vg/kg or less, about 1×10^{14} vg/kg or less, about 9×10^{13} vg/kg or less, about 8×10^{13} vg/kg or less, about 7×10^{13} vg/kg or less, about 6×10^{13} vg/kg or less, about 5×10^{13} vg/kg or less, about 4×10^{13} vg/kg or less, about 3×10^{13} vg/kg or less, about 2×10^{13} vg/kg or less, or about 1×10^{13} vg/kg or less.
100. The method of any one of claims 79 to 99, wherein the subject is a mammal.
101. The method of any one of claims 79 to 99, wherein the subject is a human.