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(54) Title: COMPOSITIONS AND METHODS FOR TREATING LAMINOPATHIES

(57) Abstract: The present disclosure provides compositions and methods for treating, preventing, or inhibiting laminopathies. In one aspect, the disclosure provides nucleic acid constructs and/or vectors comprising a nucleotide sequence encoding lamin A and/or lamin C.



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COMPOSITIONS AND METHODS FOR TREATING LAMINOPATHIES

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of priority from U.S. Provisional Application No. 62/812,021, filed on February 28, 2019. The foregoing applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE DISCLOSURE

[1] The *LMNA* gene encodes at least three isoforms (lamin A, lamin C, and lamin A Δ 10) as a result of normal alternative splicing. The two main isoforms, lamin A and lamin C, are constitutive components of the fibrous nuclear lamina, a complex molecular interface located between the inner membrane of the nuclear envelope and DNA. Lamin A and lamin C have diverse physiological roles, ranging from mechanical nuclear membrane maintenance to gene regulation. Numerous mutations in the *LMNA* gene give rise to a spectrum of diseases known as laminopathies. These diseases include at least eight well-characterized phenotypes, some of which are confined to the skeletal muscles or skin, while others are multisystemic.

[2] Dilated cardiomyopathy is one of the diseases amongst the large families of *LMNA*-related diseases. Prevalence of dilated cardiomyopathy ranges from 1:2500 individuals to 1:250 individuals. Dilated cardiomyopathy is characterized by dilation and impaired contraction of the left ventricle or both ventricles and impaired systolic function. Despite being a rare disease, dilated cardiomyopathy represents a serious health burden, often leading to arrhythmias, thromboembolism and sudden death at any stage of disease. There is no specific treatment for dilated cardiomyopathy or the other *LMNA*-related laminopathies.

[3] There is a need for novel treatments for laminopathies (*e.g.*, dilated cardiomyopathy).

SUMMARY OF THE DISCLOSURE

[4] Provided herein are compositions and methods, that, in some embodiments, may be used for treatment of laminopathies such as dilated cardiomyopathy.

[5] In some embodiments, the disclosure provides a nucleic acid construct comprising a nucleotide sequence encoding (a) a lamin A polypeptide, (b) a lamin C polypeptide, or (c) a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or fragment of any of (a) – (c) operably linked to a regulatory element having less than 500 bp. In some embodiments, the disclosure provides a nucleic acid construct comprising a

nucleotide sequence encoding (a) a lamin A polypeptide, (b) a lamin C polypeptide, or (c) a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or fragment of any one of (a) – (c), wherein the nucleotide sequence comprises at least one, but not all, of the non-coding sequences of the LMNA gene. In certain embodiments, the non-coding sequence is an intron. In certain embodiments, the nucleotide sequence comprises at least one, but not all, of the introns corresponding to introns 1-11 of a wild-type human *LMNA* gene. In certain embodiments, the nucleotide sequence comprises the intron corresponding to intron 10 of the wildtype-human *LMNA* gene. In certain embodiments, the intron corresponding to intron 10 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 79, or a fragment thereof. In certain embodiments, the nucleotide sequence comprises the intron corresponding to intron 8 of the wildtype-human *LMNA* gene. In certain embodiments, the intron corresponding to intron 8 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 77, or a fragment thereof. In certain embodiments, the nucleotide sequence comprises the intron corresponding to intron 9 of the wildtype-human *LMNA* gene. In certain embodiments, the intron corresponding to intron 9 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 78, or a fragment thereof. In certain embodiments, the nucleotide sequence comprises the intron corresponding to intron 11 of the wildtype-human *LMNA* gene. In certain embodiments, the intron corresponding to intron 11 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 80, or a fragment thereof. In certain embodiments, the nucleotide sequence comprises the introns corresponding to introns 9 and 10 of the wildtype-human *LMNA* gene. In certain embodiments, the nucleotide sequence comprises the introns corresponding to introns 8, 9, 10 and 11 of the wildtype-human *LMNA* gene. In certain embodiments, the nucleic acid construct comprises at least one intron corresponding to introns 8-11 of the wildtype human *LMNA* gene, and lacks at least one intron corresponding to introns 1-7 of the wildtype human *LMNA* gene. In certain embodiments, the nucleic acid construct comprises the intron corresponding to intron 10 of the wildtype human *LMNA* gene, and lacks at least one intron corresponding to introns 1-7 of the wildtype human *LMNA* gene. In certain embodiments, the nucleic acid construct comprises the introns corresponding to introns 8-11 of the wildtype

human *LMNA* gene, and lacks the introns corresponding to introns 1-7 of the wildtype human *LMNA* gene. In certain embodiments, the nucleic acid construct comprises the introns corresponding to introns 9 and 10 of the wildtype human *LMNA* gene, and lacks the introns corresponding to introns 1-8 and 11 of the wildtype human *LMNA* gene. In certain embodiments, the nucleic acid construct comprises the intron corresponding to intron 10 of the wildtype human *LMNA* gene, and lacks the introns corresponding to introns 1-9 and 11 of the wildtype human *LMNA* gene. In certain embodiments, the nucleotide sequence is operably linked to a regulatory element. In certain embodiments, the nucleotide sequence is operably linked to a regulatory element having less than or equal to 400 base pairs (bp), 300bp, 250bp, 200bp, 150bp, 140bp, 130bp, 120bp, 110bp, 100bp, 70bp, or 50bp. In certain embodiments, the regulatory element is any one of or combination of: any one of SEQ ID NOs: 30-58, CBA, CMV, SCP, SERpE_TTR, Proto1, minCMV, UCL-HLP, CMVe, CAG, or EFS. In certain embodiments, the regulatory element is any one of or combination of SEQ ID NO: 31, SEQ ID NO: 33, CBA, or minCMV. In certain embodiments, the regulatory element is SEQ ID NO: 33. In certain embodiments, the regulatory element is CBA. In certain embodiments, the regulatory element is minCMV. In certain embodiments, the regulatory element is cell-type selective. In certain embodiments, the regulatory element is selectively expressed in cardiomyocytes. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 80% identical to the nucleotide sequence of any one of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 90% identical to the nucleotide sequence of any one of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 95% identical to the nucleotide sequence of any one of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is the sequence of any one of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleotide sequence encodes a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 12, or a biologically active fragment thereof. In certain embodiments, the nucleotide sequence encodes a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%,

99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, or a biologically active fragment thereof. In certain embodiments, the nucleotide sequence encodes a lamin C polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof. In certain embodiments, the nucleotide sequence encodes a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 12, or a biologically active fragment thereof, and a lamin C polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof. In certain embodiments, the nucleotide sequence encodes a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, or a biologically active fragment thereof, and a lamin C polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof. In certain embodiments, the nucleotide sequence further comprises a polyadenylation signal.

[6] In some embodiments, the disclosure provides for a nucleic acid construct comprising a nucleotide sequence encoding a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or fragment thereof, wherein said construct comprises at least intron 8 or intron 11 of the wildtype-human LMNA gene. In some embodiments, intron 8 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 77, or a fragment thereof. In some embodiments, intron 11 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 80, or a fragment thereof. In some embodiments, the nucleotide sequence further comprises intron 10 of the wildtype-human LMNA gene. In some embodiments, intron 10 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 79, or a fragment thereof. In some embodiments, the nucleotide sequence further comprises intron 9 of the wildtype-human LMNA gene. In some embodiments, intron 9 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 78, or a fragment

thereof. In some embodiments, the nucleotide sequence comprises introns 8 and 11 of the wildtype-human *LMNA* gene. In some embodiments, the nucleotide sequence comprises intron 8 of the wildtype-human *LMNA* gene. In some embodiments, the nucleotide sequence comprises intron 11 of the wildtype-human *LMNA* gene. In some embodiments, the nucleotide sequence further comprises introns 9 and 10 of the wildtype-human *LMNA* gene. In some embodiments, the nucleotide sequence comprises introns 8, 9, 10 and 11 of the wildtype-human *LMNA* gene. In some embodiments, the nucleic acid construct lacks at least one intron corresponding to introns 1-7 of the wildtype human *LMNA* gene. In some embodiments, the nucleic acid construct lacks introns 1-7 of the wildtype human *LMNA* gene. In some embodiments, the nucleic acid construct further comprises intron 9 of the wildtype human *LMNA* gene, and lacks at least one intron corresponding to introns 1-7 of the wildtype human *LMNA* gene. In some embodiments, the nucleic acid construct further comprises intron 10 of the wildtype human *LMNA* gene, and lacks at least one intron corresponding to introns 1-7 of the wildtype human *LMNA* gene. In some embodiments, the nucleic acid construct comprises introns 8-11 of the wildtype human *LMNA* gene, and lacks introns 1-7 of the wildtype human *LMNA* gene. In some embodiments, the regulatory element has less than or equal to 500 base pairs. In some embodiments, the regulatory element has less than or equal to 900 base pairs. In some embodiments, the regulatory element has less than or equal to 800 base pairs (bp), 700 bp, 600 bp, 500 bp, 400 bp, 300bp, 250bp, 200bp, 150bp, 140bp, 130bp, 120bp, 110bp, 100bp, 70bp, or 50bp. In some embodiments, the regulatory element is any one of or combination of: any one of SEQ ID NOs: 30-58, SEQ ID NO: 102, CBA, CMV, SCP, SERpE_TTR, Proto1, minCMV, UCL-HLP, CMVe, Myh6, Desmin, cTnT, α -MHC, MLC-2, CAG, or EFS. In some embodiments, the regulatory element is any one of or combination of SEQ ID NO: 31, SEQ ID NO: 33, CBA, or minCMV. In some embodiments, the regulatory element is SEQ ID NO: 33. In some embodiments, the regulatory element is CBA. In some embodiments, the regulatory element is minCMV. In some embodiments, the regulatory element is cell-type selective. In some embodiments, the regulatory element is selectively expressed in cardiomyocytes. In some embodiments, the regulatory element is any one of or combination of Myh6, Desmin, cTnT, α -MHC, or MLC-2. In some embodiments, the regulatory element is cTNT. In some embodiments, the cTNT regulatory element comprises SEQ ID NO: 101. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 80%

identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 90% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is the sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence encodes a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 12, or a biologically active fragment thereof, and a lamin C polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof. In some embodiments, the nucleotide sequence encodes a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, or a biologically active fragment thereof, and a lamin C polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof. In some embodiments, the nucleotide sequence further comprises a polyadenylation signal.

[7] In some embodiments, the disclosure provides for a nucleotide construct comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type LMNA gene; and (b) intron 8 of a wild-type LMNA gene. In some embodiments, the disclosure provides for a nucleotide construct comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type LMNA gene; and (b) intron 11 of a wild-type LMNA gene. In some embodiments, the disclosure provides for a nucleotide construct comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type LMNA gene; and (b) intron 8 and intron 11 of a wild-type LMNA gene. In some embodiments, the nucleotide sequence further encodes one or more of introns 9 and 10 of a wild-type LMNA gene. In some embodiments, the disclosure provides for a nucleotide construct comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type LMNA gene; and (b) introns 8-11 of a wild-type LMNA gene. In some embodiments, the nucleotide

sequence is at least 80% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence is at least 90% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence is at least 95% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence is the sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence encodes: a) a lamin A polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 12, and b) a lamin C polypeptide having an amino acid sequence at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13. In some embodiments, the nucleotide sequence encodes: a) a lamin A polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, and b) a lamin C polypeptide having an amino acid sequence at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13. In some embodiments, the nucleotide sequence encodes a polypeptide having the amino acid sequence of any one or more of SEQ ID NO: 12-19, or 21. In some embodiments, the nucleotide sequence does not comprise the nucleotide sequence corresponding to introns 1-7 of a wild-type LMNA gene. In some embodiments, the nucleotide sequence is operably linked to a regulatory element. In some embodiments, the nucleotide sequence is operably linked to a regulatory element having less than 900 bp. In some embodiments, the nucleotide sequence is operably linked to a regulatory element having less than or equal to 900bp, 800bp, 700bp, 600bp, 500bp, 400bp, 300bp, 250bp, 200bp, 150bp, 140bp, 130bp, 120bp, 110bp, 100bp, 70bp, or 50bp. In some embodiments, the regulatory element is any one of or combination of any one of SEQ ID NOs: 30-58, SEQ ID NO: 102, CBA, CMV, SCP, SERpE_TTR, Proto1, minCMV, UCL-HLP, CMVe, Myh6, Desmin, cTnT, α -MHC, MLC-2, CAG, or EFS.

[8] In some embodiments, the disclosure provides for a viral vector comprising any of the nucleic acid constructs provided herein. In certain embodiments, the viral vector comprises a nucleotide sequence encoding (a) a lamin A polypeptide, (b) a lamin C polypeptide, or (c) a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or

fragment of any one of (a) – (c). In certain embodiments, the nucleotide sequence comprises at least one non-coding region of the LMNA gene. In certain embodiments, the non-coding region is an intron. In certain embodiments, the viral vector comprises a nucleotide sequence encoding: (a) exons 1-12 of a wild-type *LMNA* gene; and (b) intron 10 of a wild-type *LMNA* gene. In certain embodiments, the viral vector comprises a nucleic acid construct provided herein, wherein the nucleotide sequence further encodes one or more of introns 8, 9, and 11 of a wild-type *LMNA* gene. In some embodiments, the disclosure provides a viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type *LMNA* gene; and (b) introns 9 and 10 of a wild-type *LMNA* gene. In some embodiments, the disclosure provides a viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type *LMNA* gene; and (b) introns 8-11 of a wild-type *LMNA* gene. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 80% identical to the nucleotide sequence of any one of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 90% identical to the nucleotide sequence of any one of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 95% identical to the nucleotide sequence of any one of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is the sequence of any one of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 12, or a biologically active fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, or a biologically active fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a lamin C polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding (a) a lamin A polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99%

or 100% identical to the amino acid sequence of SEQ ID NO: 12, and (b) a lamin C polypeptide having an amino acid sequence at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13. In certain embodiments, the viral vector comprises a nucleotide sequence encoding (a) a lamin A polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, and (b) a lamin C polypeptide having an amino acid sequence at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO: 12-21 or 24. In certain embodiments, the viral vector comprises a nucleotide sequence does not comprise the nucleotide sequence corresponding to introns 1-7 of a wild-type *LMNA* gene. In certain embodiments, the viral vector comprises a nucleotide sequence that is operably linked to a regulatory element. In certain embodiments, the viral vector comprises a nucleotide sequence that is operably linked to a regulatory element having less than or equal to 400bp, 300bp, 250bp, 200bp, 150bp, 140bp, 130bp, 120bp, 110bp, 100bp, 70bp, or 50bp. In certain embodiments, the viral vector comprises a regulatory element that is any one of or combination of any one of SEQ ID NOs: 30-58, CBA, CMV, SCP, SERpE_TTR, Proto1, minCMV, UCL-HLP, CMVe, CAG, or EFS. In certain embodiments, the viral vector comprises a regulatory element that is any one of or combination of SEQ ID NO: 31, SEQ ID NO: 33, CBA, or minCMV. In certain embodiments, the viral vector comprises a regulatory element that is SEQ ID NO: 33. In certain embodiments, the viral vector comprises a regulatory element that is CBA. In certain embodiments, the viral vector comprises a regulatory element that is minCMV. In certain embodiments, the viral vector comprises a regulatory element that is cell-type selective. In certain embodiments, the viral vector comprises a regulatory element that is selectively expressed in neuronal cells, retinal cells, renal cells, skeletal muscle cells, adipocytes, or cardiomyocytes. In certain embodiments, the viral vector comprises a regulatory element that is selectively expressed in cardiomyocytes. In certain embodiments, the viral vector comprises a nucleotide sequence further comprising a polyadenylation signal. In certain embodiments, the viral vector is an adeno-associated virus (AAV) vector. In certain embodiments, the AAV vector is AAV6, AAV9, scAAV6, or scAAV9. In certain embodiments, the AAV vector comprises a nucleotide sequence further comprising a 5' AAV inverted terminal repeat (ITR) sequence and a 3' AAV ITR sequence.

[9] In some embodiments, the disclosure provides for a viral vector comprising a nucleotide sequence encoding a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or fragment thereof, wherein said nucleotide sequence comprises at least intron 8 or intron 11 of the wildtype-human LMNA gene. In some embodiments, the disclosure provides for a viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type LMNA gene; and (b) intron 8 of a wild-type LMNA gene. In some embodiments, the disclosure provides for a viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type LMNA gene; and (b) intron 11 of a wild-type LMNA gene. In some embodiments, the disclosure provides for a viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type LMNA gene; and (b) intron 8 and intron 11 of a wild-type LMNA gene. In some embodiments, the nucleotide sequence further encodes one or more of introns 9 and 10 of a wild-type LMNA gene. In some embodiments, the disclosure provides for a viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type LMNA gene; and (b) introns 8-11 of a wild-type LMNA gene. In some embodiments, the nucleotide sequence is at least 80% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence is at least 90% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence is at least 95% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence is the sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleotide sequence encodes: a) a lamin A polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 12, and b) a lamin C polypeptide having an amino acid sequence at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13. In some embodiments, the nucleotide sequence encodes: a) a lamin A polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, and b) a lamin C polypeptide having an amino acid sequence at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13. In some embodiments, the nucleotide sequence encodes a

polypeptide having the amino acid sequence of any one or more of SEQ ID NO: 12-19, or 21. In some embodiments, the nucleotide sequence does not comprise the nucleotide sequence corresponding to introns 1-7 of a wild-type LMNA gene. In some embodiments, the nucleotide sequence is operably linked to a regulatory element. In some embodiments, the nucleotide sequence is operably linked to a regulatory element having less than 500 bp. In some embodiments, the nucleotide sequence is operably linked to a regulatory element having less than 900 bp. In some embodiments, the nucleotide sequence is operably linked to a regulatory element having less than or equal to 800bp, 700bp, 600bp, 500bp, 400bp, 300bp, 250bp, 200bp, 150bp, 140bp, 130bp, 120bp, 110bp, 100bp, 70bp, or 50bp. In some embodiments, the regulatory element is any one of or combination of any one of SEQ ID NOs: 30-58, SEQ ID NO: 102, CBA, CMV, SCP, SERpE_TTR, Proto1, minCMV, UCL-HLP, CMVe, Myh6, Desmin, cTnT, α -MHC, MLC-2, CAG, or EFS. In some embodiments, the regulatory element is any one of or combination of SEQ ID NO: 31, SEQ ID NO: 33, CBA, or minCMV. In some embodiments, the regulatory element is SEQ ID NO: 33. In some embodiments, the regulatory element is CBA. In some embodiments, the regulatory element is minCMV. In some embodiments, the regulatory element is cell-type selective. In some embodiments, the regulatory element is selectively expressed in neuronal cells, retinal cells, renal cells, skeletal muscle cells, adipocytes, or cardiomyocytes. In some embodiments, the regulatory element is selectively expressed in cardiomyocytes. In some embodiments, the regulatory element is any one of or combination of Myh6, Desmin, cTnT, α -MHC, or MLC-2. In some embodiments, the regulatory element is cTNT. In some embodiments, the cTNT regulatory element comprises SEQ ID NO: 101. In some embodiments, the nucleotide sequence further comprises a polyadenylation signal. In some embodiments, the viral vector is an adeno-associated virus (AAV) vector. In some embodiments, the AAV vector is AAV1, AAV2, AAV5, AAV6, AAV8, AAV9, scAAV1, scAAV2, scAAV5, scAAV6, scAAV8, or scAAV9. In some embodiments, the nucleotide sequence further comprises a 5' AAV inverted terminal repeat (ITR) sequence and a 3' AAV ITR sequence.

[10] In some embodiments, the disclosure provides a viral particle comprising any of the viral vectors as provided herein. In certain embodiments, the viral particle comprises capsid proteins of an AAV. In certain embodiments, the capsid proteins of an AAV is an AAV6 or AAV9.

[11] In some embodiments, the disclosure provides a host cell comprising any of the nucleic acid constructs, viral vectors, or viral particles as provided herein.

[12] In some embodiments, the disclosure provides pharmaceutical composition comprising any of the nucleic acid constructs, viral vectors, viral particles, or host cells as provided herein; and one or more pharmaceutically acceptable excipients.

[13] In some embodiments, the disclosure provides a method for treating a laminopathy in a subject comprising administering a therapeutically effective amount of any of the nucleic acid constructs, viral vectors, viral particles, host cells, or pharmaceutical compositions as provided herein to a subject in need thereof.

[14] In some embodiments, the disclosure provides a method for expressing (a) a lamin A polypeptide, (b) a lamin C polypeptide, or (c) a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or a fragment of any one of (a) – (c) in a subject comprising administering to said subject a therapeutically effective amount of any of the nucleic acid constructs, viral vectors, viral particles, host cells, or pharmaceutical compositions as provided herein.

[15] In some embodiments, the disclosure provides a method for increasing expression of (a) a functional lamin A polypeptide, (b) a functional lamin C polypeptide, or (c) a functional lamin A polypeptide and a functional lamin C polypeptide, or a biologically active variant and/or a fragment of any one of (a) – (c) in a subject comprising administering to said subject a therapeutically effective amount of any of the nucleic acid constructs, viral vectors, viral particles, host cells, or pharmaceutical compositions as provided herein.

[16] In certain embodiments, the subject treated in accordance with any of the methods disclosed herein is suffering from a laminopathy. In certain embodiments, the laminopathy is any one or more of: Charcot-Marie-Tooth disease, Emery-Dreifuss muscular dystrophy, familial partial lipodystrophy, Hutchinson-Gilford progeria syndrome, limb-girdle muscular dystrophy, *LMNA*-related congenital muscular dystrophy, mandibuloacral dysplasia, arrhythmogenic right ventricular cardiomyopathy, familial atrial fibrillation, left ventricular noncompaction, or dilated cardiomyopathy. In certain embodiments, the laminopathy is dilated cardiomyopathy. In certain embodiments, any of the nucleic acid constructs, viral vectors, viral particles, host cells, or pharmaceutical compositions provided herein is administered intramyocardially, intravenously, intramuscularly, intrathecally, subcutaneously, systemically, or locally into the myocardium. In certain embodiments, any

of the nucleic acid constructs, viral vectors, viral particles, host cells, or pharmaceutical compositions provided herein is administered intravenously or systemically.

BRIEF DESCRIPTION OF THE DRAWINGS

[17] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[18] FIG. 1 illustrates a vector map of a full viral vector genome construct for expression of lamin A. The viral vector comprises an adeno-associated viral (AAV) vector comprising a CMV promoter, an enhancer having SEQ ID NO: 31, a lamin isoform A insert comprising exons 1-12 of lamin A, and a polyadenylation sequence signal.

[19] FIG. 2 illustrates a vector map of a full viral vector genome construct for expression of lamin C. The viral vector comprises an adeno-associated viral (AAV) vector comprising a CMV promoter, an enhancer having SEQ ID NO: 31, a lamin isoform C insert comprising exons 1-10 of lamin C, and a polyadenylation sequence signal.

[20] FIG. 3 illustrates a vector map of a full viral vector genome construct (minigene 1) for expression of lamin A and lamin C. The viral vector comprises an adeno-associated viral (AAV) vector comprising a CMV promoter, an enhancer having SEQ ID NO: 31, a lamin isoform A/C insert comprising exons 1-12 of lamin A/C, introns 8-11 of lamin A/C, and a polyadenylation sequence signal.

[21] FIG. 4 illustrates a vector map of a full viral vector genome construct (minigene 2) for expression of lamin A and lamin C. The viral vector comprises an adeno-associated viral (AAV) vector comprising a CMV promoter, an enhancer having SEQ ID NO: 31, a lamin isoform A/C insert comprising exons 1-12 of lamin A/C, intron 9 and 10 of lamin A/C, and a polyadenylation sequence signal.

[22] FIG. 5 illustrates a vector map of a full viral vector genome construct (minigene 3) for expression of lamin A and lamin C. The viral vector comprises an adeno-associated viral (AAV) vector comprising a CMV promoter, an enhancer having SEQ ID NO: 31, a lamin isoform A/C insert comprising exons 1-12 of lamin A/C, intron 10 of lamin A/C, and a polyadenylation sequence signal.

[23] FIG. 6 is a western blot showing that Lamin A and Lamin C isoforms are both produced from LMNA minigene construct 1 in HEK293 cells.

[24] FIG. 7 is a graph of mRNA expression levels demonstrating that the LMNA minigene construct is able to express both Lamin A and Lamin C in both HEK293T cells (left) and iPS cardiomyocytes (right).

[25] FIG. 8 is a western blot showing that Lamin A and Lamin C isoforms are both produced from minigene construct 1 *in vitro* (293T cells), and *in vivo* in heart and liver tissues (bottom panels heart tissue from wildtype and heterozygous *Lmna*^{+/-} male mouse model animals at 24 weeks old).

[26] FIG. 9 is a graph showing rescue of disease phenotype in LMNA^{-/-} KO mice when dosed with AAV virus carrying minigene construct 1.

[27] FIG. 10A and FIG. 10B show *in vivo* expression of Lamin A and Lamin C isoforms in mice treated with AAV9 carrying minigene construct 1 when measured by RNAseq. FIG. 10A shows the expression of Lamin A and Lamin C in the heart and liver under the control of a ubiquitous promoter. FIG. 10B shows the expression of Lamin A and Lamin C in the heart and liver under the control of a heart-specific promoter (cTNT).

[28] Fig 11A-11C are simplified schematics of several different constructs each incorporating the chicken beta actin promoter. In Fig. 11A, the construct comprises a CBA promoter, a lamin isoform A/C insert comprising exons 1-12 of lamin A/C, introns 8-11 of lamin A/C, and a polyadenylation sequence signal. In Fig. 11B, the construct comprises a CBA promoter, a lamin isoform A/C insert comprising exons 1-12 of lamin A/C, intron 9 and 10 of lamin A/C, and a polyadenylation sequence signal. In Fig. 11C, the construct comprises a CBA promoter, a lamin isoform A/C insert comprising exons 1-12 of lamin A/C, intron 10 of lamin A/C, and a polyadenylation sequence signal.

[29] FIG. 12 is a western blot showing expression of Lamin A and Lamin C isoforms in LMNA minigene constructs encoding Lamin A and/or Lamin C in HEK293 cells.

[30] Fig 13 is a graph of mRNA expression levels demonstrating that an LMNA minigene construct encoding Lamin A and/or Lamin C under the CMV promoter is able to express Lamin A and/or Lamin C in HEK293T cells. In particular an LMNA minigene encoding Lamin A and Lamin C expressed both Lamin A and Lamin C in HEK293T cells.

DETAILED DESCRIPTION OF THE DISCLOSURE

[31] Lamin A and lamin C are constitutive components of the fibrous nuclear lamina, a complex molecular interface located between the inner membrane of the nuclear envelope and DNA. Lamin A and lamin C have diverse physiological roles, ranging from mechanical nuclear membrane maintenance to gene regulation. The *LMNA* gene encodes at least three isoforms (lamin A, lamin C, and lamin AΔ10) as a result of normal alternative splicing. *LMNA* contains twelve exons, which yield transcripts for lamin C and prelamin A (the precursor to mature lamin A) by alternative splicing of exon 10. Both isoforms are identical for the first 566 amino acids (encoded by exons 1-10), but their carboxyl terminal sequences diverge. Prelamin A contains an extra 98 unique amino acids at the C terminus (encoded by exons 11-12), while lamin C terminates with exon 10 sequences and has 6 unique C-terminal amino acids. Prelamin A is processed to form lamin A, a 646 amino acids long protein. Meanwhile, lamin C is composed of 572 amino acids.

[32] *LMNA* mutations in humans result in a variety of diseases, including cardiomyopathy, muscular dystrophy, and progeria disorders. More than 500 disease-causing mutations have been identified, some of which result in diseases such as dilated cardiomyopathy. Dilated cardiomyopathy is characterized by dilation and impaired contraction of the left ventricle or both ventricles and impaired systolic function. The prevalence of dilated cardiomyopathy ranges from 1:2500 individuals to 1:250 individuals. Despite being a rare disease, dilated cardiomyopathy represents a serious health burden, often leading to arrhythmias, thromboembolism and sudden death at any stage of disease. As of 2014, 165 dilated cardiomyopathy associated mutations had been identified in the *LMNA* gene (Tesson F. *Cardiol J.* 2014;21(4):331-42). These mutations included missense/nonsense mutations, splicing mutations, small deletions, small insertions, small indel, gross deletions, or gross insertions. The majority of *LMNA* mutations leading to dilated cardiomyopathy are autosomal dominant missense mutations found throughout the gene that generate mutated lamin A/C proteins.

[33] The present disclosure contemplates compositions and methods for treating, preventing, or inhibiting dilated cardiomyopathy and other laminopathies. In one aspect, the disclosure provides a viral vector, viral particle, host cell, or pharmaceutical composition comprising a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or a codon-optimized variant and/or fragment of any of the foregoing. In one aspect, the disclosure provides a viral vector, viral

particle, host cell, or pharmaceutical composition comprising a nucleotide sequence encoding (a) a biologically active fragment of a lamin A polypeptide; (b) a biologically active fragment of a lamin C polypeptide; (c) a biologically active fragment of a lamin A and a biologically active fragment of a lamin C polypeptide; or a codon-optimized variant and/or fragment of any of the foregoing. In another aspect, the disclosure provides a nucleic acid comprising a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A polypeptide and a lamin C polypeptide, or a codon-optimized variant thereof and/or fragment thereof operably linked to any one of or combination of: SEQ ID NO: 31, SEQ ID NO: 33, CBA, and/or minCMV. In another aspect, the disclosure provides a nucleic acid comprising a nucleotide sequence encoding (a) a biologically active fragment of a lamin A polypeptide; (b) a biologically active fragment of a lamin C polypeptide; (c) a biologically active fragment of a lamin A polypeptide and a biologically active fragment of a lamin C polypeptide, or a codon-optimized variant thereof and/or fragment thereof operably linked to any one of or combination of: SEQ ID NO: 31, SEQ ID NO: 33, CBA, and/or minCMV. In another embodiment, the disclosure provides a method for treating a laminopathy in a subject comprising administering one or more of any of the nucleic acids, viral vectors, viral particles, host cells, or pharmaceutical compositions disclosed herein.

[34] A wide variety of laminopathies may be treated or prevented using the nucleic acids, viral vectors, viral particles, host cells, pharmaceutical compositions, and methods provided herein. Laminopathies that may be treated or prevented using the nucleic acids, viral vectors, viral particles, host cells, pharmaceutical compositions, and methods of the disclosure include but are not limited to Charcot-Marie-Tooth disease, Emery-Dreifuss muscular dystrophy, familial partial lipodystrophy, Hutchinson-Gilford progeria syndrome, limb-girdle muscular dystrophy, LMNA-related congenital muscular dystrophy, mandibuloacral dysplasia, arrhythmogenic right ventricular cardiomyopathy, familial atrial fibrillation, left ventricular noncompaction, and dilated cardiomyopathy.

A. General Techniques

[35] Unless otherwise defined herein, scientific and technical terms recited herein shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, pharmacology, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, genetics and protein and nucleic acid chemistry,

described herein, are those well-known and commonly used in the art. In case of conflict, the present specification, including definitions, will control.

[36] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, *Molecular Cloning: A Laboratory Manual*, second edition (Sambrook et al., 1989) Cold Spring Harbor Press; *Oligonucleotide Synthesis* (M.J. Gait, ed., 1984); *Methods in Molecular Biology*, Humana Press; *Cell Biology: A Laboratory Notebook* (J.E. Cellis, ed., 1998) Academic Press; *Animal Cell Culture* (R.I. Freshney, ed., 1987); *Introduction to Cell and Tissue Culture* (J.P. Mather and P.E. Roberts, 1998) Plenum Press; *Cell and Tissue Culture: Laboratory Procedures* (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-1998) J. Wiley and Sons; *Methods in Enzymology* (Academic Press, Inc.); *Gene Transfer Vectors for Mammalian Cells* (J.M. Miller and M.P. Calos, eds., 1987); *Current Protocols in Molecular Biology* (F.M. Ausubel et al., eds., 1987); *PCR: The Polymerase Chain Reaction*, (Mullis et al., eds., 1994); Sambrook and Russell, *Molecular Cloning: A Laboratory Manual*, 3rd. ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (2001); Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (2002); Harlow and Lane *Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1998); Coligan et al., *Short Protocols in Protein Science*, John Wiley & Sons, NY (2003); *Short Protocols in Molecular Biology* (Wiley and Sons, 1999).

[37] Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, biochemistry, immunology, molecular biology, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, and chemical analyses.

B. Definitions

[38] Throughout this specification and embodiments, the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

[39] It is understood that wherever embodiments are described herein with the language “comprising,” otherwise analogous embodiments described in terms of “consisting of” and/or “consisting essentially of” are also provided.

[40] The term “including” is used to mean “including but not limited to.” “Including” and “including but not limited to” are used interchangeably.

[41] Any example(s) following the term “*e.g.*” or “for example” is not meant to be exhaustive or limiting.

[42] Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[43] By way of example, “an element” means one element or more than one element.

[44] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the disclosure are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Moreover, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a stated range of “1 to 10” should be considered to include any and all subranges between (and inclusive of) the minimum value of 1 and the maximum value of 10; that is, all subranges beginning with a minimum value of 1 or more, *e.g.*, 1 to 6.1, and ending with a maximum value of 10 or less, *e.g.*, 5.5 to 10.

[45] Where aspects or embodiments of the disclosure are described in terms of a Markush group or other grouping of alternatives, the present disclosure encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, but also the main group absent one or more of the group members. The present disclosure also envisages the explicit exclusion of one or more of any of the group members in the disclosure.

[46] As used herein, the singular forms “a”, “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms “including”, “includes”, “having”, “has”, “with”, or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term “comprising”.

[47] Unless otherwise indicated, the term “lamin A” is used herein to refer to prelamin A polypeptides and/or mature lamin A polypeptides. The term covers all lamin A polypeptides formed as a result of posttranslational modifications of prelamin A (e.g. removal of the 18 amino acids from the carboxyl terminus of prelamin A to form mature lamin A). The term includes all biologically active lamin A proteins, fragments or variants thereof.

[48] The term “AAV” is an abbreviation for adeno-associated virus and may be used to refer to the virus itself or a derivative thereof. The term covers all serotypes, subtypes, and both naturally occurring and recombinant forms, except where required otherwise. The abbreviation “rAAV” refers to recombinant adeno-associated virus. The term “AAV” includes AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, rh10, and hybrids thereof, avian AAV, bovine AAV, canine AAV, equine AAV, primate AAV, non-primate AAV, and ovine AAV. The genomic sequences of various serotypes of AAV, as well as the sequences of the native terminal repeats (TRs), Rep proteins, and capsid subunits are known in the art. Such sequences may be found in the literature or in public databases such as GenBank. A “rAAV vector” as used herein refers to an AAV vector comprising a polynucleotide sequence not of AAV origin (i.e., a polynucleotide heterologous to AAV), typically a sequence of interest for the genetic transformation of a cell. In general, the heterologous polynucleotide is flanked by at least one, and generally by two, AAV inverted terminal repeat sequences (ITRs). An ITR sequence is a term well understood in the art and refers to relatively short sequences found at the termini of viral genomes which are in opposite orientation. An rAAV vector may either be single-stranded (ssAAV) or self-complementary (scAAV). An “AAV virus” or “AAV viral particle” refers to a viral particle composed of at least one AAV capsid protein and an encapsidated polynucleotide rAAV vector. If the particle comprises a heterologous polynucleotide (i.e., a polynucleotide other than a wild-type AAV genome such as a transgene to be delivered to a mammalian cell), it is typically referred to as an “rAAV viral particle” or simply an “rAAV particle”.

[49] The term “about” or “approximately” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, “about” can mean within one or more than one standard deviation, per the

practice in the art. Alternatively, “about” can mean a range of up to 20%, up to 15%, up to 10%, up to 5%, or up to 1% above and/or below a given value.

[50] The terms “determining”, “measuring”, “evaluating”, “assessing”, “assaying”, “analyzing”, and their grammatical equivalents can be used interchangeably herein to refer to any form of measurement and include determining if an element is present or not (for example, detection). These terms can include both quantitative and/or qualitative determinations. Assessing may be relative or absolute.

[51] An “expression cassette” refers to a nucleic molecule comprising one or more regulatory elements operably linked to a coding sequence (*e.g.*, a gene or genes) for expression.

[52] The term “effective amount” or “therapeutically effective amount” refers to that amount of a composition described herein that is sufficient to affect the intended application, including but not limited to disease treatment, as defined below. The therapeutically effective amount may vary depending upon the intended treatment application (in a cell or in vivo), or the subject and disease condition being treated, *e.g.*, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in a target cell. The specific dose will vary depending on the particular composition chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[53] A “fragment” of a nucleotide or peptide sequence refers to a fragment of the sequence that is shorter than the full-length or reference DNA or protein sequence.

[54] The term “biologically active” as used herein when referring to a molecule such as a protein, polypeptide, nucleic acid, and/or polynucleotide means that the molecule retains at least one biological activity (either functional or structural) that is substantially similar to a biological activity of the full-length or reference protein, polypeptide, nucleic acid, and/or polynucleotide. For example, a “biologically active” lamin A or lamin C protein, or fragment or variant thereof, would retain at least one activity that is substantially similar to a full-length or reference wild-type lamin A or lamin C protein, respectively.

[55] The terms “host cell,” “host cell line,” and “host cell culture” are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced,

including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[56] The term "human derived" as used herein refers to sequences that are found in a human genome (or a human genome build), or sequences homologous thereto. A homologous sequence may be a sequence which has a region with at least 80% sequence identity (*e.g.*, as measured by BLAST) as compared to a region of the human genome. For example, a sequence that has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identity to a human sequence is deemed human derived. In some cases, a regulatory element contains a human derived sequence and a non-human derived sequence such that overall the regulatory element has low sequence identity to the human genome, while a part of the regulatory element has 100% sequence identity (or local sequence identity) to a sequence in the human genome.

[57] The term "in vitro" refers to an event that takes places outside of a subject's body. For example, an in vitro assay encompasses any assay run outside of a subject. In vitro assays encompass cell-based assays in which cells alive or dead are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

[58] The term "in vivo" refers to an event that takes place in a subject's body.

[59] An "isolated" nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally, at a chromosomal location that is different from its natural chromosomal location, or contains only coding sequences.

[60] As used herein, "operably linked", "operable linkage", "operatively linked", or grammatical equivalents thereof refer to juxtaposition of genetic elements, *e.g.*, a promoter, an enhancer, a polyadenylation sequence, etc., wherein the elements are in a relationship permitting them to operate in the expected manner. For instance, a regulatory element, which can comprise promoter and/or enhancer sequences, is operatively linked to a coding region if

the regulatory element helps initiate transcription of the coding sequence. There may be intervening residues between the regulatory element and coding region so long as this functional relationship is maintained.

[61] A “pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation or composition, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[62] The terms “pharmaceutical formulation” or “pharmaceutical composition” refer to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[63] The term “regulatory element” refers to a nucleic acid sequence or genetic element which is capable of influencing (*e.g.*, increasing, decreasing, or modulating) expression of an operably linked sequence, such as a gene. Regulatory elements include, but are not limited to, promoter, enhancer, repressor, silencer, insulator sequences, an intron, UTR, an inverted terminal repeat (ITR) sequence, a long terminal repeat sequence (LTR), stability element, posttranslational response element, or a polyA sequence, or a combination thereof. Regulatory elements can function at the DNA and/or the RNA level, *e.g.*, by modulating gene expression at the transcriptional phase, post-transcriptional phase, or at the translational phase of gene expression; by modulating the level of translation (*e.g.*, stability elements that stabilize mRNA for translation), RNA cleavage, RNA splicing, and/or transcriptional termination; by recruiting transcriptional factors to a coding region that increase gene expression; by increasing the rate at which RNA transcripts are produced, increasing the stability of RNA produced, and/or increasing the rate of protein synthesis from RNA transcripts; and/or by preventing RNA degradation and/or increasing its stability to facilitate protein synthesis. In some embodiments, a regulatory element refers to an enhancer, repressor, promoter, or a combination thereof, particularly an enhancer plus promoter combination or a repressor plus promoter combination. In some embodiments, the regulatory element is derived from a human sequence.

[64] The terms “subject” and “individual” are used interchangeably herein to refer to a vertebrate, preferably a mammal, more preferably a human. The methods described herein

can be useful in human therapeutics, veterinary applications, and/or preclinical studies in animal models of a disease or condition.

[65] As used herein, the terms “treat”, “treatment”, “therapy” and the like refer to obtaining a desired pharmacologic and/or physiologic effect, including, but not limited to, alleviating, delaying or slowing progression, reducing effects or symptoms, preventing onset, preventing reoccurrence, inhibiting, ameliorating onset of a diseases or disorder, obtaining a beneficial or desired result with respect to a disease, disorder, or medical condition, such as a therapeutic benefit and/or a prophylactic benefit. “Treatment,” as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease or at risk of acquiring the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease. A therapeutic benefit includes eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. In some cases, for prophylactic benefit, the compositions are administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made. The methods of the present disclosure may be used with any mammal. In some cases, the treatment can result in a decrease or cessation of symptoms. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[66] A “variant” of a nucleotide sequence refers to a sequence having a genetic alteration or a mutation as compared to the most common wild-type DNA sequence (*e.g.*, cDNA or a sequence referenced by its GenBank accession number) or a specified reference sequence.

[67] A “vector” as used herein refers to a nucleic acid molecule that can be used to mediate delivery of another nucleic acid molecule to which it is linked into a cell where it can be replicated or expressed. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has

been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as “expression vectors.” Other examples of vectors include plasmids and viral vectors.

[68] In general, “sequence identity” or “sequence homology”, which can be used interchangeably, refer to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Two or more sequences (polynucleotide or amino acid) can be compared by determining their “percent identity”, also referred to as “percent homology”. The percent identity to a reference sequence (*e.g.*, nucleic acid or amino acid sequence) may be calculated as the number of exact matches between two optimally aligned sequences divided by the length of the reference sequence and multiplied by 100. Conservative substitutions are not considered as matches when determining the number of matches for sequence identity. It will be appreciated that where the length of a first sequence (A) is not equal to the length of a second sequence (B), the percent identity of A:B sequence will be different than the percent identity of B:A sequence. Sequence alignments, such as for the purpose of assessing percent identity, may be performed by any suitable alignment algorithm or program, including but not limited to the Needleman-Wunsch algorithm (see, *e.g.*, the EMBOSS Needle aligner available on the world wide web at ebi.ac.uk/Tools/psa/emboss_needle/), the BLAST algorithm (see, *e.g.*, the BLAST alignment tool available on the world wide web at blast.ncbi.nlm.nih.gov/Blast.cgi), the Smith-Waterman algorithm (see, *e.g.*, the EMBOSS Water aligner available on the world wide web at ebi.ac.uk/Tools/psa/emboss_water/), and Clustal Omega alignment program (see *e.g.*, the world wide web at clustal.org/omega/ and F. Sievers et al., *Mol Sys Biol.* 7: 539 (2011)). Optimal alignment may be assessed using any suitable parameters of a chosen algorithm, including default parameters. The BLAST program is based on the alignment method of Karlin and Altschul, *Proc. Natl. Acad. Sci. USA* 87:2264-2268 (1990) and as discussed in Altschul, et al., *J. Mol. Biol.* 215:403-410 (1990); Karlin and Altschul, *Proc. Natl. Acad. Sci. USA* 90:5873-5877 (1993); and Altschul et al., *Nucleic Acids Res.* 25:3389-3402 (1997).

[69] Unless otherwise indicated, all terms used herein have the same meaning as they would to one skilled in the art and the practice of the present invention will employ, conventional techniques of molecular biology, microbiology, and recombinant DNA technology, which are within the knowledge of those of skill of the art.

C. Nucleic acid constructs

1. *Lamin Constructs*

[70] Provided herein are nucleic acid constructs comprising a nucleotide sequence encoding lamin A, lamin C, lamin A and lamin C (or biologically active variants or fragments thereof), or a codon-optimized variant and/or fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A (or a biologically active variant or fragment thereof) or a codon-optimized variant and/or fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin C (or a biologically active variant or fragment thereof) or a codon-optimized variant and/or fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding both lamin A and lamin C (or biologically active variants or fragments thereof) or a codon-optimized variant and/or fragment thereof.

[71] In some embodiments, the nucleic acid construct comprises a transgene operably linked to a regulatory element, wherein the transgene encodes (a) lamin A (or a biologically active variant or fragment thereof); (b) lamin C (or a biologically active variant or fragment thereof); (c) both lamin A and lamin C (or biologically active variants or fragments thereof), or a codon-optimized variant and/or fragment thereof. In certain embodiments, the transgene comprises a nucleotide sequence encoding lamin A (or a biologically active variant or fragment thereof) or a codon-optimized variant and/or fragment thereof. In certain embodiments, the transgene comprises a nucleotide sequence encoding lamin C (or a biologically active variant or fragment thereof) or a codon-optimized variant and/or fragment thereof. In certain embodiments, the transgene comprises a nucleotide sequence encoding both lamin A and lamin C (or biologically active variants or fragments thereof) or a codon-optimized variant and/or fragment thereof.

[72] In some cases, the nucleic acid construct comprises a nucleic acid coding sequence which is operatively linked to regulatory components in a manner which permits transcription, translation, and/or expression of a transgene in a target cell (*e.g.* a cardiomyocyte or myocardiocyte, which terms are used interchangeably herein). The transgene (heterologous nucleic acid sequence) can be derived from any organism. In certain embodiments, the transgene is derived from a human. In certain embodiments, the transgene encodes a mature form of lamin A (or a biologically active variant or fragment thereof). In certain embodiments, the transgene encodes prelamin A (or a biologically active variant or

fragment thereof). In certain embodiments, the transgene encodes lamin C (or a biologically active variant or fragment thereof). In certain embodiments, the transgene encodes both lamin A and lamin C (or biologically active variants or fragments thereof). In certain embodiments, the transgene encodes both prelamin A and lamin C (or biologically active variants or fragments thereof). In some embodiments, the transgene encodes a polypeptide comprising an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 12, or a biologically active fragment thereof. In some embodiments, the transgene encodes a polypeptide comprising an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 21, or a biologically active fragment thereof. In some embodiments, the transgene encodes a polypeptide comprising an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof.

[73] In certain embodiments, the nucleic acid construct may comprise one or more transgenes. In some embodiments, the transgene comprises more than one *LMNA* splice variant (*e.g.* both lamin A and lamin C), or fragments derived from more than *LMNA* splice variant. This may be accomplished using a single nucleic acid construct carrying two or more heterologous sequences, or using a single nucleic acid construct carrying a single sequence which encodes two or more *LMNA* splice variants (*e.g.* lamin A and lamin C). In some embodiments, the transgene comprises only one *LMNA* splice variant (*e.g.* lamin A or lamin C), or fragments derived from one *LMNA* splice variant. It is contemplated that two or more nucleic acid constructs each carrying one or more heterologous sequences encoding at least one *LMNA* splice variant may be used separately or together (*e.g.*, in the same or different viral vector(s)). In some embodiments, in addition to a *LMNA* gene, splice variant, or fragment thereof, the nucleic acid construct may also encode additional proteins, peptides, RNA, enzymes, or catalytic RNAs.

[74] In certain embodiments, any of the nucleic acid constructs disclosed herein comprises a nucleotide sequence encoding exons 1-12 of a wild-type *LMNA* gene (*e.g.* SEQ ID NOs: 81-93) and introns 8-11 of a wild-type *LMNA* gene (*e.g.* SEQ ID NOs: 77-80). In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding exons 1-

12 of a wild-type *LMNA* gene (e.g. SEQ ID NOs: 81-93) and introns 9 and 10 of a wild-type *LMNA* gene (e.g. SEQ ID NOs: 78 and 79). In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding exons 1-12 of a wild-type *LMNA* gene (e.g. SEQ ID NOs: 81-93) and intron 10 of a wild-type *LMNA* gene (e.g. SEQ ID NO: 79).

[75] In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that comprises, consists of, or consists essentially of, the nucleic acid sequence of any one of SEQ ID NOs: 1-10, and nucleic acid sequences that are at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any of the foregoing, and fragments of any of the foregoing. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is the sequence of any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 65% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 70% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 75% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 80% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 82% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 85% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 87% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 90% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 91%

identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 92% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 93% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 94% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 95% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 96% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 97% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 98% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 99% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof.

[76] In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is 100% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 1 that encodes the polypeptide sequence of SEQ ID NO: 12 or 21. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 6 that encodes the polypeptide sequence of SEQ ID NO: 12 or 21. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 2 that encodes the polypeptide sequence of SEQ ID NO: 13. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%,

65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 7 that encodes the polypeptide sequence of SEQ ID NO: 13. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 3 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 4 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 5 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 8 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 9 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 10 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21.

[77] In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that comprises, consists of, or consists essentially of, the nucleic acid sequence of any one of SEQ ID NOs: 3-5, and/or nucleic acid sequences that are at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any of the foregoing or fragments of any of the foregoing. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is the sequence of any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment

thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 65% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 70% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 75% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 80% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 82% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 85% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 87% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 90% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 91% identical to any one of SEQ ID NOs: 3-5, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 92% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 93% identical to any one of SEQ ID NOs: 3-5, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 94% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 95% identical to any one of SEQ ID NOs: 3-5, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 96% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide

sequence that is at least 97% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 98% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 99% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is 100% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof.

[78] In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that comprises, consists of, or consists essentially of, the amino acid sequence of any one of SEQ ID NOs: 12-21 and 24, and polypeptides that are at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any of the foregoing. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide of any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 60% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 65% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 70% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 75% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 80% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 82% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain

embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 85% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 87% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 90% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 91% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 92% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 93% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 94% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 95% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 96% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 97% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 98% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is at least 99% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof. In certain

embodiments, the nucleic acid construct comprises a nucleotide sequence encoding a polypeptide that is 100% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof.

[79] In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A that comprises, consists of, or consists essentially of, an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 12, or biologically active fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A that comprises, consists of, or consists essentially of, an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 21, or biologically active fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin C that comprises, consists of, or consists essentially of, an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 13, or biologically active fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A having an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 12 or biologically active fragments thereof, and also encoding lamin C having an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 13 or biologically active fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A having an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 21 or biologically active fragments thereof, and also encoding lamin C having an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 13 or biologically active fragments thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 12. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A that comprises, consists of, or consists

essentially of, the amino acid sequence of SEQ ID NO: 21. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin C that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 13. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A and lamin C that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 12 and/or 13. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A and lamin C that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 21 and/or 13. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A having the amino acid sequence of SEQ ID NO: 12, and also encoding lamin C having the amino acid sequence of SEQ ID NO: 13. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence encoding lamin A having the amino acid sequence of SEQ ID NO: 21, and also encoding lamin C having the amino acid sequence of SEQ ID NO: 13.

[80] In some cases, the nucleic acid construct comprises a nucleotide sequence encoding lamin A and/or lamin C, wherein the nucleotide sequence does not comprise one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, or eleven or more introns from a wild-type *LMNA* gene. In certain embodiments, the nucleic acid construct does not comprise the nucleotide sequence corresponding to introns 1-7 of a wild-type *LMNA* gene (*e.g.* SEQ ID NOs: 70-76). In certain embodiments, the nucleic acid construct does not comprise the nucleotide sequence corresponding to introns 1-8 and 11 of a wild-type *LMNA* gene (*e.g.* SEQ ID NOs: 70-77 and 80). In certain embodiments, the nucleic acid construct does not comprise the nucleotide sequence corresponding to introns 1-9 and 11 of a wild-type *LMNA* gene (*e.g.* SEQ ID NOs: 70-78 and 80).

[81] In some cases, the nucleic acid construct comprises a nucleotide sequence encoding lamin A and/or lamin C, wherein the nucleotide sequence comprises one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, or eleven or more introns (*e.g.* SEQ ID NOs: 70-80). In certain embodiments, the one or more introns correspond to the introns from a wild-type *LMNA* gene, *e.g.*, a wild-type human *LMNA* gene. In other embodiments, the one or more introns are synthetic introns. In particular embodiments, the one or more introns are positioned in the nucleic acid construct such that the nucleotide sequence is capable of encoding both lamin A

and lamin C in a splice-dependent manner. In particular embodiments, the one or more introns are positioned in the nucleic acid construct such that the pre-mRNA undergoes alternative splicing to produce mature mRNA encoding lamin A, and/or lamin C. In particular embodiments, the one or more introns are positioned in the nucleic acid construct such that the pre-mRNA undergoes alternative splicing to produce more mature mRNA encoding lamin C than mature mRNA encoding lamin A. In particular embodiments, the one or more introns are positioned in the nucleic acid construct such that the pre-mRNA undergoes alternative splicing to produce more mature mRNA encoding lamin A than mature mRNA encoding lamin C. In certain embodiments, the one or more introns are positioned in the nucleic acid construct such that the pre-mRNA undergoes alternative splicing to produce about the same levels of mature mRNA encoding lamin A and mature mRNA encoding lamin C. In certain embodiments, the nucleic acid construct comprises nucleotide sequences corresponding to introns 8-11 of a wild-type *LMNA* gene (e.g. SEQ ID NOs: 77-80). In certain embodiments, the nucleic acid construct comprises nucleotide sequences corresponding to introns 9 and 10 of a wild-type *LMNA* gene (e.g. SEQ ID NOs: 78 and 79). In certain embodiments, the nucleic acid construct comprises the nucleotide sequence corresponding to intron 10 of a wild-type *LMNA* gene (e.g. SEQ ID NO: 79).

[82] In some embodiments, the nucleic acid construct comprises at least one, but not all, of the endogenous introns of the wild-type human *LMNA* gene. In some embodiments, the nucleic acid construct comprises at least one intron corresponding to introns 8-11 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 77-80), and lacks at least one intron corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the nucleic acid comprises introns corresponding to introns 8-11 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 77-80), and lacks at least one intron corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the nucleic acid comprises introns corresponding to introns 8-11 of the human wild-type *LMNA* gene (e.g. SEQ ID NOs: 77-80), and lacks all of the introns corresponding to introns 1-7 of the human wild-type *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the nucleic acid comprises introns corresponding to introns 9-10 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 78 and 79), and lacks at least one intron corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the nucleic acid comprises introns corresponding to introns 9-10 of the

wild-type human *LMNA* gene (e.g. SEQ ID NOs: 78 and 79), and lacks all of the introns corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the nucleic acid comprises introns corresponding to introns 9-10 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 78 and 79), and lacks all of the introns corresponding to introns 1-8 and 11 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-77 and 80). In some embodiments, the nucleic acid comprises the intron corresponding to intron 10 of the wild-type human *LMNA* gene (e.g. SEQ ID NO: 79), and lacks at least one intron corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the nucleic acid comprises the intron corresponding to intron 10 of the wild-type human *LMNA* gene (e.g. SEQ ID NO: 79), and lacks all of the introns corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the nucleic acid comprises the intron corresponding to intron 10 of the wild-type human *LMNA* gene (e.g. SEQ ID NO: 79), and lacks all of the introns corresponding to introns 1-9 and 11 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-78 and 80). In some embodiments, the intron corresponding to intron 8 of the wild-type human *LMNA* gene comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 77, or a fragment thereof. In some embodiments, the intron corresponding to intron 9 of the wild-type human *LMNA* gene comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 78, or a fragment thereof. In some embodiments, the intron corresponding to intron 10 of the wild-type human *LMNA* gene comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 79 or a fragment thereof. In some embodiments, the intron corresponding to intron 11 of the wild-type human *LMNA* gene comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 80 or a fragment thereof.

[83] In some cases, the nucleic acid construct comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises intron 8 of a wild-type *LMNA* gene. In some cases, the nucleic acid construct comprises a

nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises intron 9 of a wild-type LMNA gene. In some cases, the nucleic acid construct comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises intron 10 of a wild-type LMNA gene. In some cases, the nucleic acid construct comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises intron 11 of a wild-type LMNA gene. In some cases, the nucleic acid construct comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises introns 9 and 10 of a wild-type LMNA gene. In some cases, the nucleic acid construct comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises introns 8, 9, 10, and 11 of a wild-type LMNA gene.

[84] In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that comprises, consists of, or consists essentially of, the nucleic acid sequence of any one or more of SEQ ID NOs: 77-80, and nucleic acid sequences that are at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any one or more of the foregoing. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is the sequence of any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 60% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 65% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 70% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 75% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant

and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 80% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 82% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 85% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 87% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 90% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 91% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 92% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 93% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 94% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 95% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 96% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 97% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is at least 98% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide

sequence that is at least 99% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the nucleic acid construct comprises a nucleotide sequence that is 100% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof.

[85] In some embodiments, a transgene of the disclosure comprises a variant of these sequences, wherein such variants can include missense mutations, nonsense mutations, duplications, deletions, and/or additions. In some embodiments, the variant comprises a polynucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the specific nucleic acid sequence set forth in SEQ ID NO: 3. In some embodiments, the variant comprises a polynucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the specific nucleic acid sequence set forth in SEQ ID NO: 4. In some embodiments, the variant comprises a polynucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the specific nucleic acid sequence set forth in SEQ ID NO: 5. In some embodiments, the variant comprises a polynucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the specific nucleic acid sequence set forth in SEQ ID NO: 6. In some embodiments, the variant comprises a polynucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the specific nucleic acid sequence set forth in SEQ ID NO: 7. In some embodiments, the variant comprises a polynucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, or at least 99% identical to the specific nucleic acid sequence set forth in SEQ ID NO: 8. In some embodiments, the variant comprises a polynucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the specific nucleic acid sequence set forth in SEQ ID NO: 9. In some embodiments, the variant comprises a polynucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the specific nucleic acid sequence set forth in SEQ ID NO: 10.

[86] In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 1 that encodes the polypeptide sequence of SEQ ID NO: 12 or 21. In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 6 that encodes the polypeptide sequence of SEQ ID NO: 12 or 21. In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 2 that encodes the polypeptide sequence of SEQ ID NO: 13. In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 7 that encodes the polypeptide sequence of SEQ ID NO: 13. In some embodiments, the variant comprises a nucleic acid construct comprising a

nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 3 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 4 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 5 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 8 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 9 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the variant comprises a nucleic acid construct comprising a nucleotide sequence that is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 82%, at least 85%, at least 87%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 10 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21.

[87] One of ordinary skill in the art will appreciate that nucleic acid sequences complementary to the nucleic acids, and variants of the nucleic acids are also within the scope of this disclosure. Nucleic acid sequences may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic or synthetic), cDNA, or RNA molecules. RNA molecules include mRNA molecules. Additional coding or non-coding sequences may, but need not, be present within a nucleic acid sequence of the present disclosure, and a nucleic acid sequence may, but need not, be linked to other molecules and/or support materials. In further embodiments, the nucleic acid sequences of the disclosure can be isolated, recombinant, and/or fused with a heterologous nucleotide sequence. In some embodiments, any of the nucleotides disclosed herein (*e.g.*, SEQ ID NOs: 1-10, or variants or fragments thereof) is codon-optimized (*e.g.*, codon-optimized for human expression). In some embodiments, a transgene encodes a biologically active lamin A and/or lamin C polypeptide with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid substitutions, deletions, and/or additions relative to the wild-type polypeptide (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 12, 13, or 21). In some embodiments, a transgene encodes a biologically active lamin A and/or lamin C polypeptide with 1, 2, 3, 4, or 5 amino acid deletions relative to the wild-type polypeptide (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 12, 13, or 21). In some embodiments, a transgene encodes a biologically active lamin A and/or lamin C polypeptide with 1, 2, 3, 4, or 5 amino acid substitutions relative to the wild-type polypeptide (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 12, 13, or 21). In some embodiments, a transgene encodes a biologically active lamin A and/or lamin C polypeptide with 1, 2, 3, 4, or 5 amino acid insertions relative to the wild-type polypeptide (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 12, 13, or 21).

[88] It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present disclosure (*i.e.* codon optimization). For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC are synonyms for histidine) may result in “silent” mutations which do not affect the amino

acid sequence of the protein. One skilled in the art will appreciate that these variations in one or more nucleotides (up to about 3-5% of the nucleotides) of the nucleic acids encoding a particular protein may exist among members of a given species due to natural allelic variation. Any and all such nucleotide variations and resulting amino acid polymorphisms are within the scope of this disclosure. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present disclosure. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

[89] The nucleic acids/polynucleotides of this disclosure can be obtained using chemical synthesis, recombinant methods, or PCR. Methods of chemical polynucleotide synthesis are well known in the art and need not be described in detail herein. One of skill in the art can use the sequences provided herein and a commercial DNA synthesizer to produce a desired DNA sequence. In other embodiments, nucleic acids of the disclosure also include nucleotide sequences that hybridize under highly stringent conditions to any of the nucleotide sequences set forth in any one of SEQ ID NOs: 1-10 (or variants or fragments thereof), or sequences complementary thereto. One of ordinary skill in the art will readily understand that appropriate stringency conditions which promote DNA hybridization can be varied. For example, one could perform the hybridization at 6.0 x sodium chloride/sodium citrate (SSC) at about 45 °C, followed by a wash of 2.0 x SSC at 50 °C. For example, the salt concentration in the wash step can be selected from a low stringency of about 2.0 x SSC at 50 °C to a high stringency of about 0.2 x SSC at 50 °C. In addition, the temperature in the wash step can be increased from low stringency conditions at room temperature, about 22 °C, to high stringency conditions at about 65 °C. Both temperature and salt may be varied, or temperature or salt concentration may be held constant while the other variable is changed. In one embodiment, the disclosure provides nucleic acids which hybridize under low stringency conditions of 6 x SSC at room temperature followed by a wash at 2 x SSC at room temperature.

[90] As provided herein, any of the *LMNA* transgenes or fragments thereof (*e.g.* a gene encoding lamin A and/or lamin C) disclosed herein may be used to correct or ameliorate gene

deficiencies, which may include deficiencies in which normal variant gene products of *LMNA* are expressed at less than normal levels or deficiencies in which the functional variants are not expressed. In some embodiments, the transgene sequence encodes a single *LMNA* isoform or biologically active fragment thereof. The disclosure further includes using multiple transgenes, *e.g.*, two or more transgenes encoding two or more *LMNA* isoforms or biologically active fragments thereof. In a particular embodiment, different *LMNA* isoforms (*e.g.* lamin A and/or lamin C or biologically active fragments or variants thereof) may be encoded by the same transgene by utilizing alternative splicing of a single nucleotide sequence. In certain situations, a different transgene may be used to encode different *LMNA* isoforms or biologically active fragments thereof (*e.g.* lamin A and/or lamin C or biologically active fragments or variants thereof). Alternatively, multiple different *LMNA* isoforms (*e.g.* lamin A and/or lamin C or biologically active fragments or variants thereof) may be encoded by the same transgene. In some embodiments, a single transgene includes the DNA encoding multiple *LMNA* isoforms (*e.g.* lamin A and lamin C or biologically active fragments or variants thereof) with the DNA for each protein or functional fragment thereof separated by one or more internal ribozyme entry site (IRES) or self-cleaving 2A peptides. In some embodiments, this is desirable when the size of the DNA encoding each of the subunits is small, *e.g.*, the total size of the DNA encoding the subunits and the IRES is less than five kilobases. As an alternative to an IRES, the DNA may be separated by one or more sequences encoding a 2A peptide, which self-cleaves in a post-translational event. See, *e.g.*, MX. Donnelly, et al, J. Gen. Virol, 78(Pt 1): 13-21 (Jan 1997); Furler, S., et al, Gene Ther., 8(11):864-873 (June 2001); Klump H., et al, Gene Ther., 8(10):811-817 (May 2001). This 2A peptide is significantly smaller than an IRES, making it well suited for use when space is a limiting factor. In some embodiments, the one or more self-cleaving 2A peptides are selected from the group consisting of T2A, P2A, E2A, and F2A.

2. Regulatory Elements

[91] In certain embodiments, the lamin A and/or lamin C constructs disclosed herein are part of a nucleic acid construct comprising one or more regulatory elements in addition to the lamin A and/or lamin C sequence. In exemplary embodiments, the lamin A and/or lamin C constructs disclosed herein are part of a nucleic acid construct comprising a promoter situated upstream of the lamin A and/or lamin C construct so as to be capable of driving expression of the lamin A and/or lamin C sequence in a cell.

[92] In one embodiment, a nucleic acid construct disclosed herein comprises a promoter comprising a sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any one of SEQ ID NOs: 30-69 or 100-102 (as shown below in Tables 3 and 4). In one embodiment, a nucleic acid construct disclosed herein comprises a promoter having any one of SEQ ID NOs: 30-69 or 100-102 (as shown below in Tables 3 and 4) operably linked to any one of the lamin A and/or lamin C sequences disclosed herein, e.g., a lamin A and/or lamin C sequence comprising any one of SEQ ID NOs: 1-5 (as shown below in Table 1), or a functional fragment thereof. In one embodiment, a nucleic acid construct comprises a promoter comprising a sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 102. In one embodiment, a nucleic acid construct comprises a promoter having the sequence of SEQ ID NO: 102. In another embodiment, a nucleic acid construct disclosed herein comprises a regulatory element having a combination of two or more (e.g., two or more, three or more, four or more, five or more, or 2, 3, 4, or 5) of any one of SEQ ID NOs: 30-69 or 100-102 (as shown below in Tables 3 and 4) operably linked to any one of the lamin A and/or lamin C sequences disclosed herein, e.g., a lamin A and/or lamin C sequence comprising any one of SEQ ID NOs: 1-5 (as shown below in Table 1), or a functional fragment thereof.

[93] In certain embodiments, a nucleic acid construct disclosed herein comprises a promoter having any one of SEQ ID NOs: 30-69 or 100-102 (as shown below in Tables 3 and 4) operably linked to any one of the lamin A and/or lamin C sequences disclosed herein, e.g., a lamin A and/or lamin C sequence comprising any one of SEQ ID NOs: 1-5 (as shown below in Table 1), or a functional fragment thereof. In certain embodiments, the promoter sequence produces at least 5-fold, 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 35-fold, 40-fold, 45-fold, 50-fold, 55-fold, 60-fold, 65-fold, 70-fold, or 75-fold, or at least 20-90 fold, 20-80 fold, 20-70 fold, 20-60 fold, 30-90 fold, 30-80 fold, 30-70 fold, 30-60 fold, 40-90 fold, 40-80 fold, 40-70 fold, 40-60 fold, 50-90 fold, 50-80 fold, 50-70 fold, 50-60 fold, 60-90 fold, 60-80 fold, 60-70 fold, 70-90 fold, 70-80 fold, 80-90 fold greater expression of the lamin A and/or lamin C sequence in a mammalian cell relative to the level of expression of the same lamin A and/or lamin C sequence from the CMV promoter in the same type of mammalian cell. In certain embodiments, the promoter sequence drives expression of the lamin A and/or lamin C sequence in a high percentage of cardiomyocyte cells, e.g., at least 20%, 25%, 30%,

40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater, or at least 20-90%, 20-80%, 20-70%, 30-90%, 30-80%, 30-70%, 40-90%, 40-80%, 40-70%, 50-90%, 50-80%, 50-70%, 60-90%, 60-80%, 60-70%, 70-90%, 70-80%, 80-100%, 80-95%, 80-90%, 90-100%, or 90-95% of cardiomyocytes containing the nucleic acid construct express the lamin A and/or lamin C construct. In certain embodiments, the promoter sequence drives expression of the lamin A and/or lamin C sequence in a high percentage of hepatocyte cells, e.g., at least 20%, 25%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater, or at least 20-90%, 20-80%, 20-70%, 30-90%, 30-80%, 30-70%, 40-90%, 40-80%, 40-70%, 50-90%, 50-80%, 50-70%, 60-90%, 60-80%, 60-70%, 70-90%, 70-80%, 80-100%, 80-95%, 80-90%, 90-100%, or 90-95% of hepatocytes containing the nucleic acid construct express the lamin A and/or lamin C construct.

[94] In one embodiment, a nucleic acid construct disclosed herein comprises a promoter having any one of SEQ ID NOs: 30-69 or 100-102 operably linked to a lamin A and/or lamin C sequence comprising (i) any one of SEQ ID NOs: 1-5, (ii) a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13 and/or 21.

[95] In one embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 33 operably linked to a lamin A and/or lamin C sequence comprising (i) any one of SEQ ID NOs: 1-5, (ii) a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain

embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13, and/or 21.

[96] In one embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 44 operably linked to a lamin A and/or lamin C sequence comprising (i) any one of SEQ ID NOs: 1-5, (ii) a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13, and/or 21.

[97] In one embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 35 operably linked to a lamin A and/or lamin C sequence comprising (i) any one of SEQ ID NOs: 1-5, (ii) a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13, and/or 21.

[98] In an exemplary embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 44 operably linked to a lamin A and/or lamin C sequence comprising (i) SEQ ID NO: 3, (ii) a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 3, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NO: 12, 13, and/or 21.

[99] In an exemplary embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 44 operably linked to a lamin A and/or lamin C sequence comprising (i) SEQ ID NO: 4, (ii) a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 4, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NO: 12, 13, and/or 21.

[100] In an exemplary embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 44 operably linked to a lamin A and/or lamin C sequence comprising (i) SEQ ID NO: 5, (ii) a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 5, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NO: 12, 13, and/or 21.

[101] In an exemplary embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 35 operably linked to a lamin A and/or lamin C sequence comprising (i) SEQ ID NO: 3, (ii) a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 3, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13, and/or 21.

[102] In an exemplary embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 35 operably linked to a lamin A and/or lamin C sequence

comprising (i) SEQ ID NO: 4, (ii) a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 4, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13, and/or 21.

[103] In an exemplary embodiment, a nucleic acid construct of the disclosure comprises a promoter having SEQ ID NO: 35 operably linked to a lamin A and/or lamin C sequence comprising (i) SEQ ID NO: 5, (ii) a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 5, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13, and/or 21.

[104] In one embodiment, a nucleic acid construct disclosed herein comprises a promoter selected from the group consisting of: the cytomegalovirus (CMV) promoter, the chicken β -actin (CBA) promoter, the CMV enhancer used upstream of a CBA promoter (e.g. SEQ ID NO: 61), the super core promoter (SCP) promoter, the SerpE_TTR promoter (e.g. SEQ ID NO: 63), the Proto1 promoter (e.g. SEQ ID NO: 64), the minimal CMV (minCMV) promoter, the University College London hybrid liver-specific promoter (UCL-HLP) promoter, the CMV enhancer (CMVe), the CMV early enhancer/CBA (CAG) promoter, the Myh6 promoter, the Desmin promoter, the cardiac troponin T (cTnT) promoter, the alpha-myosin heavy chain (α -MHC) promoter, the myosin light chain 2 (MLC-2) promoter, SEQ ID NO: 102, and the EF1 α short (EFS) promoter operably linked to a lamin A and/or lamin C sequence comprising (i) any one of SEQ ID NOs: 1-5, (ii) a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence

encodes a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and 21). In certain embodiments, such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13, and 21. In one embodiment, a nucleic acid construct disclosed herein comprises a promoter having any one of SEQ ID NOs: 30-58 or 100-102 operably linked to a lamin A and/or lamin C sequence comprising (i) any one of SEQ ID NOs: 1-5, (ii) a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, or (iii) a functional fragment of any of the foregoing. In certain embodiments, such lamin A and/or lamin C nucleotide sequence are sequences that encode a protein having a sequence that is at least 90%, 95%, 98%, 99% or 100% identical to the wild type lamin A and/or lamin C protein sequence (e.g., SEQ ID NOs: 12, 13, and/or 21). In certain embodiments, such lamin A and/or lamin C sequences may comprise (i) any one of SEQ ID NOs: 1-5, or (ii) a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, wherein such lamin A and/or lamin C sequence encodes a full length lamin A and/or lamin C protein, e.g., having one or more of SEQ ID NOs: 12, 13, and/or 21.

[105] In certain embodiments, a nucleic acid construct disclosed herein comprises a lamin A and/or lamin C nucleotide sequence that has been truncated so as to encode a functional fragment of a lamin A and/or lamin C protein. Exemplary truncated lamin A and/or lamin C nucleotide sequences may comprise a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, wherein such lamin A and/or lamin C nucleotide sequence encodes a functional fragment of lamin A and/or lamin C. In certain embodiments, a nucleic acid construct disclosed herein comprises a variant lamin A and/or lamin C nucleotide sequence that has been truncated so as to encode a functional fragment of a lamin A and/or lamin C protein. Exemplary truncated lamin A and/or lamin C nucleotide sequences may a sequence having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to any one of SEQ ID NOs: 1-5, wherein such truncated variant lamin A and/or lamin C nucleotide sequence encodes a functional fragment of lamin A and/or lamin C protein.

[106] In certain embodiments, the nucleic acid constructs described herein comprise another regulatory element in an addition to a promoter, such as, for example, sequences associated with transcription initiation or termination, enhancer sequences, and efficient RNA processing signals. Exemplary regulatory elements include, for example, an intron, an enhancer, UTR, stability element, WPRE sequence, a Kozak consensus sequence, posttranslational response element, or a polyadenylation (polyA) sequence, or a combination thereof. Regulatory elements can function to modulate gene expression at the transcriptional phase, post-transcriptional phase, or at the translational phase of gene expression. At the RNA level, regulation can occur at the level of translation (e.g., stability elements that stabilize mRNA for translation), RNA cleavage, RNA splicing, and/or transcriptional termination. In various embodiments, regulatory elements can recruit transcription factors to a coding region that increase gene expression selectivity in a cell type of interest, increase the rate at which RNA transcripts are produced, increase the stability of RNA produced, and/or increase the rate of protein synthesis from RNA transcripts.

[107] In one embodiment, the nucleic acid constructs described herein further comprise an enhancer sequence. Exemplary enhancer sequences include, for example, the En34 enhancer (34 bp core enhancer from the human apolipoprotein hepative control region, the EnTTR enhancer (100 bp enhancer sequence from transthyretin), the α 1-microglobulin/bikunin precursor enhancer, the ABPS enhancer (shortened version of the 100 bp distal enhancer from the α 1-microglobulin/bikunin precursor to 42 bp), or the ApoE enhancer. See e.g., WO 2018/126116 and Wu et al., *Mol Therapy* 16(2): 280-289 (2008)). In another embodiment, a suitable enhancer sequence is an intronic sequence comprising SEQ ID NO: 30 or SEQ ID NO: 31. In certain embodiments, an enhancer sequence is positioned upstream of the transgene and the promoter, or between the promoter and the transgene in the nucleic acid constructs described herein.

[108] In certain embodiments, the nucleic acid constructs described herein further comprise a polyA sequence. Suitable polyA sequences include, for example, an artificial polyA that is about 75 bp in length (PA75) (see e.g., WO 2018/126116), the bovine growth hormone polyA, SV40 early polyA signal, SV40 late polyA signal, rabbit beta globin polyA, HSV thymidine kinase polyA, protamine gene polyA, adenovirus 5 EIb polyA, growth hormone polyA, or a PBGD polyA. In certain embodiments, the polyA sequence is positioned downstream of the transgene in the nucleic acid constructs described herein.

[109] In certain embodiments, a regulatory element suitable for use in accordance with the nucleic acid molecules described herein comprises less than 900 bp, 850 bp, 800 bp, 750 bp, 700 bp, 650 bp, 600 bp, 550 bp, 500 bp, 450 bp, 400 bp, 350 bp, 300 bp, 250 bp, 225 bp, 200 bp, 175 bp, 150 bp, 145 bp, 140 bp, 135 bp, 130 bp, 125 bp, 120 bp, 115 bp, 110 bp, 105 bp, 100 bp, 95 bp, 90 bp, 85 bp, 80 bp or 75 bp, or from about 80-300 bp, 80-275 bp, 80-250 bp, 80-200 bp, 80-150 bp, 80-125 bp, 80-120 bp, 80-115 bp, 80-110 bp, 80-105 bp, 80-100 bp, 85-300 bp, 85-275 bp, 85-250 bp, 85-200 bp, 85-150 bp, 85-125 bp, 85-120 bp, 85-115 bp, 85-110 bp, 85-105 bp, 85-100 bp, 90-300 bp, 90-275 bp, 90-250 bp, 90-200 bp, 90-150 bp, 90-125 bp, 90-120 bp, 90-115 bp, 90-110 bp, 90-105 bp, 90-100 bp, 95-300 bp, 95-275 bp, 95-250 bp, 95-200 bp, 95-150 bp, 95-125 bp, 95-120 bp, 95-115 bp, 95-110 bp, 95-105 bp, 95-100 bp, 100-300 bp, 100-275 bp, 100-250 bp, 100-200 bp, 100-150 bp, 100-125 bp, 100-120 bp, 100-115 bp, 100-110 bp, or 100-105 bp. In exemplary embodiments, a regulatory element suitable for use in accordance with the nucleic acid molecules described herein comprises from about 100-120 bp, about 117 bp, or about 100 bp.

[110] In certain embodiments, a nucleic acid construct described herein comprising an lamin A and/or lamin C nucleic acid sequence and a regulatory element is suitable for packaging in an AAV vector, e.g., comprising less than ~4.7 Kb. In certain embodiments, a nucleic acid construct described herein comprising an lamin A and/or lamin C nucleic acid sequence and a regulatory element comprising from about 4,450-4,550 bp, 4,450-4,540 bp, 4,450-4,530 bp, 4,450-4,520 bp, 4,450-4,510 bp, 4,450-4,500 bp, 4,460-4,550 bp, 4,460-4,540 bp, 4,460-4,530 bp, 4,460-4,520 bp, 4,460-4,510 bp, 4,460-4,500 bp, 4,470-4,550 bp, 4,470-4,540 bp, 4,470-4,530 bp, 4,470-4,520 bp, 4,470-4,510 bp, 4,470-4,500 bp, 4,480-4,550 bp, 4,480-4,540 bp, 4,480-4,530 bp, 4,480-4,520 bp, 4,480-4,510 bp, 4,480-4,500 bp, 4,490-4,550 bp, 4,490-4,540 bp, 4,490-4,530 bp, 4,490-4,520 bp, 4,490-4,510 bp, or 4,490-4,500 bp, or comprises about 4,498 bp or about 4,515 bp. In exemplary embodiments, such nucleic acid constructs encode a full length lamin A and/or lamin C protein, e.g., an lamin A and/or lamin C protein having one or more of SEQ ID NOs: 12, 13, and/or 21.

[111] In another embodiment, the transgenes useful herein include reporter sequences, which upon expression produce a detectable signal. Such reporter sequences include, without limitation, DNA sequences encoding β -lactamase, β -galactosidase (LacZ), alkaline phosphatase, thymidine kinase, green fluorescent protein (GFP), red fluorescent protein (RFP), chloramphenicol acetyltransferase (CAT), luciferase, membrane bound proteins

including, for example, CD2, CD4, CD8, the influenza hemagglutinin protein, and others well known in the art, to which high affinity antibodies directed thereto exist or can be produced by conventional means, and fusion proteins comprising a membrane bound protein appropriately fused to an antigen tag domain from, among others, hemagglutinin or Myc. These coding sequences, when associated with regulatory elements which drive their expression, provide signals detectable by conventional means, including enzymatic, radiographic, colorimetric, fluorescence or other spectrographic assays, fluorescent activating cell sorting assays and immunological assays, including enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and immunohistochemistry. For example, where the marker sequence is the LacZ gene, the presence of the vector carrying the signal is detected by assays for beta-galactosidase activity. Where the transgene is green fluorescent protein or luciferase, the vector carrying the signal may be measured visually by color or light production in a luminometer.

D. Expression Vectors

[112] In certain embodiments, and of the lamin A and/or lamin C nucleotide sequences or expression constructs described herein may be incorporated into an expression vector.

[113] Expression vectors may be used to deliver the nucleic acid molecule to a target cell via transfection or transduction. A vector may be an integrating or non-integrating vector, referring to the ability of the vector to integrate the expression cassette or transgene into the genome of the host cell. Examples of expression vectors include, but are not limited to, (a) non-viral vectors such as nucleic acid vectors including linear oligonucleotides and circular plasmids; artificial chromosomes such as human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), and bacterial artificial chromosomes (BACs or PACs); episomal vectors; transposons (e.g., PiggyBac); and (b) viral vectors such as retroviral vectors, lentiviral vectors, adenoviral vectors, and adeno-associated viral vectors.

[114] Expression vectors may be linear oligonucleotides or circular plasmids and can be delivered to a cell via various transfection methods, including physical and chemical methods. Physical methods generally refer to methods of delivery employing a physical force to counteract the cell membrane barrier in facilitating intracellular delivery of genetic material. Examples of physical methods include the use of a needle, ballistic DNA, electroporation, sonoporation, photoporation, magnetofection, and hydroporation. Chemical methods generally refer to methods in which chemical carriers deliver a nucleic acid

molecule to a cell and may include inorganic particles, lipid-based vectors, polymer-based vectors and peptide-based vectors.

[115] In some embodiments, an expression vector is administered to a target cell using an inorganic particle. Inorganic particles may refer to nanoparticles, such as nanoparticles that are engineered for various sizes, shapes, and/or porosity to escape from the reticuloendothelial system or to protect an entrapped molecule from degradation. Inorganic nanoparticles can be prepared from metals (e.g., iron, gold, and silver), inorganic salts, or ceramics (e.g., phosphate or carbonate salts of calcium, magnesium, or silicon). The surface of these nanoparticles can be coated to facilitate DNA binding or targeted gene delivery. Magnetic nanoparticles (e.g., supermagnetic iron oxide), fullerenes (e.g., soluble carbon molecules), carbon nanotubes (e.g., cylindrical fullerenes), quantum dots and supramolecular systems may also be used.

[116] In some embodiments, an expression vector is administered to a target cell using a cationic lipid (e.g., cationic liposome). Various types of lipids have been investigated for gene delivery, such as, for example, a lipid nano emulsion (e.g., which is a dispersion of one immiscible liquid in another stabilized by emulsifying agent) or a solid lipid nanoparticle.

[117] In some embodiments, any of the expression vectors disclosed herein is administered to a target cell using a peptide based delivery vehicle. Peptide based delivery vehicles can have advantages of protecting the genetic material to be delivered, targeting specific cell receptors, disrupting endosomal membranes and delivering genetic material into a nucleus. In some embodiments, an expression vector is administered to a target cell using a polymer based delivery vehicle. Polymer based delivery vehicles may comprise natural proteins, peptides and/or polysaccharides or synthetic polymers. In one embodiment, a polymer based delivery vehicle comprises polyethylenimine (PEI). PEI can condense DNA into positively charged particles which bind to anionic cell surface residues and are brought into the cell via endocytosis. In other embodiments, a polymer based delivery vehicle may comprise poly-L-lysine (PLL), poly (DL-lactic acid) (PLA), poly (DL-lactide-co-glycoside) (PLGA), polyornithine, polyarginine, histones, protamines, dendrimers, chitosans, synthetic amino derivatives of dextran, and/or cationic acrylic polymers. In certain embodiments, polymer based delivery vehicles may comprise a mixture of polymers, such as, for example PEG and PLL.

[118] Provided herein are viral vectors comprising any of the nucleic acid constructs and/or polynucleotide sequences disclosed herein. In particular embodiments, the viral vector comprises a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof of any of the foregoing. In particular embodiments, the viral vector comprises a nucleotide sequence encoding (a) a biologically active fragment of a lamin A polypeptide; (b) a biologically active fragment of a lamin C polypeptide; (c) a biologically active fragment of a lamin A and biologically active fragment of a lamin C polypeptide; and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A or a biologically active variant and/or fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin C or a biologically active variant and/or fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A and lamin C or biologically active variants and/or fragments thereof.

[119] In certain embodiments, an expression vector may be a viral vector suitable for gene therapy. Preferred characteristics of viral gene therapy vectors or gene delivery vectors may include the ability to be reproducibly and stably propagated and purified to high titres; to mediate targeted delivery (*e.g.*, to deliver the transgene specifically to the tissue or organ of interest without widespread vector dissemination elsewhere); and to mediate gene delivery and transgene expression without inducing harmful side effects.

[120] Several types of viruses, for example the non-pathogenic parvovirus referred to as adeno-associated virus, have been engineered for the purposes of gene therapy by harnessing the viral infection pathway but avoiding the subsequent expression of viral genes that can lead to replication and toxicity. Such viral vectors can be obtained by deleting all, or some, of the coding regions from the viral genome, but leaving intact those sequences (*e.g.*, terminal repeat sequences) that may be necessary for functions such as packaging the vector genome into the virus capsid or the integration of vector nucleic acid (*e.g.*, DNA) into the host chromatin.

[121] In some cases, the viral vector comprises a transgene operably linked to one or more regulatory elements, wherein the transgene encodes lamin A, lamin C, lamin A and lamin C, or a codon-optimized variant and/or fragment thereof. In certain embodiments, the transgene comprises a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C

polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof. In certain embodiments, the transgene comprises a nucleotide sequence encoding lamin C or biologically active variants and/or fragments thereof. In certain embodiments, the transgene comprises a nucleotide sequence encoding lamin A and lamin C or biologically active variants and/or fragments thereof.

[122] In certain embodiments, the viral vector comprises a nucleotide sequence encoding exons 1-12 of a wild-type LMNA gene (e.g. SEQ ID NOs: 81-93) and introns 8-11 of a wild-type LMNA gene (e.g. SEQ ID NOs: 77-80). In certain embodiments, the viral vector comprises a nucleotide sequence encoding exons 1-12 of a wild-type LMNA gene (e.g. SEQ ID NOs: 81-93) and introns 9 and 10 of a wild-type LMNA gene (e.g. SEQ ID NOs: 78 and 79). In certain embodiments, the viral vector comprises a nucleotide sequence encoding exons 1-12 of a wild-type LMNA gene (e.g. SEQ ID NOs: 81-93) and intron 10 of a wild-type LMNA gene (e.g. SEQ ID NO: 79).

[123] In certain embodiments, the viral vector comprises a nucleotide sequence that comprises, consists of, or consists essentially of, the nucleic acid sequence of any one or more of SEQ ID NOs: 1-10, and nucleic acid sequences that are at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any of the foregoing. In certain embodiments, the viral vector comprises a nucleotide sequence that is the sequence of any one or more of SEQ ID NOs: 1-10, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 60% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 65% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 70% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 75% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 80% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 82% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a

fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 85% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 87% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 90% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 91% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 92% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 93% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 94% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 95% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 96% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 97% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 98% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 99% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof.

[124] In certain embodiments, the viral vector comprises a nucleotide sequence that is 100% identical to any one of SEQ ID NOs: 1-10, or codon-optimized variant and/or a fragment thereof.

In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 1 that encodes the polypeptide sequence of SEQ ID NO: 12

or 21. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 6 that encodes the polypeptide sequence of SEQ ID NO: 12 or 21. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 2 that encodes the polypeptide sequence of SEQ ID NO: 13. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 7 that encodes the polypeptide sequence of SEQ ID NO: 13. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 3 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 4 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 5 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 8 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 9 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21. In some embodiments, the viral vector comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 10 that encodes the polypeptide sequence of any one or more of SEQ ID NOs: 12, 13 or 21.

[125] In certain embodiments, the viral vector comprises a nucleotide sequence that comprises, consists of, or consists essentially of, the nucleic acid sequence of any one of SEQ

ID NOs: 3-5, and nucleic acid sequences that are at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any of the foregoing. In certain embodiments, the viral vector comprises a nucleotide sequence that is the sequence of any one of SEQ ID NOs: 3-5, or codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 60% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 65% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 70% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 75% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 80% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 82% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 85% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 87% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 90% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 91% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 92% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 93% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 94% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral

vector comprises a nucleotide sequence that is at least 95% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 96% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 97% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 98% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 99% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is 100% identical to any one of SEQ ID NOs: 3-5, or a codon-optimized variant and/or a fragment thereof.

[126] In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that comprises, consists of, or consists essentially of, the amino acid sequence of any one or more of SEQ ID NOs: 12-21 and 24, and polypeptides that are at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any of the foregoing. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide of any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or a fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 60% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 65% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 70% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 75% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 80% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments

thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 82% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 85% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 87% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 90% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 91% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 92% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 93% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 94% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 95% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 96% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 97% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 98% identical to any one of SEQ ID NOs: 12-21 or 24, or biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is at least 99% identical to any one of SEQ ID NOs: 12-21 or 24, or

biologically active variants and/or fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding a polypeptide that is 100% identical to any one of SEQ ID NOs: 12-21 and 24, or biologically active variants and/or fragments thereof.

[127] In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A that comprises, consists of, or consists essentially of, an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 12, or biologically active fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A that comprises, consists of, or consists essentially of, an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 21, or biologically active fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin C that comprises, consists of, or consists essentially of, an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 13, or biologically active fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A having an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 12 or biologically active fragments thereof, and also encoding lamin C having an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 13 or biologically active fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A having an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 21 or biologically active fragments thereof, and also encoding lamin C having an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 13 or biologically active fragments thereof. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 12. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 21. In certain

embodiments, the viral vector comprises a nucleotide sequence encoding lamin C that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 13. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A and lamin C that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 12 and/or 13. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A and lamin C that comprises, consists of, or consists essentially of, the amino acid sequence of SEQ ID NO: 21 and/or 13. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A having the amino acid sequence of SEQ ID NO: 12, and also encoding lamin C having the amino acid sequence of SEQ ID NO: 13. In certain embodiments, the viral vector comprises a nucleotide sequence encoding lamin A having the amino acid sequence of SEQ ID NO: 21, and also encoding lamin C having the amino acid sequence of SEQ ID NO: 13.

[128] In some cases, the viral vector comprises a nucleotide sequence encoding lamin A and/or lamin C, wherein the nucleotide sequence does not comprise one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, or eleven or more introns from a wild-type *LMNA* gene. In certain embodiments, the viral vector does not comprise the nucleotide sequence corresponding to introns 1-7 of a wild-type *LMNA* gene (*e.g.* SEQ ID NOs: 70-76). In certain embodiments, the viral vector does not comprise the nucleotide sequence corresponding to introns 1-8 and 11 of a wild-type *LMNA* gene (*e.g.* SEQ ID NOs: 70-77 and 80). In certain embodiments, the viral vector does not comprise the nucleotide sequence corresponding to introns 1-9 and 11 of a wild-type *LMNA* gene (*e.g.* SEQ ID NOs: 70-78 and 80).

[129] In some cases, the viral vector comprises a nucleotide sequence encoding lamin A and/or lamin C, wherein the nucleotide sequence comprises one or more, two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, or eleven or more introns (*e.g.* any one or combination of SEQ ID NOs: 70-80). In certain embodiments, the one or more introns correspond to the introns from a wild-type *LMNA* gene, *e.g.*, a wild-type human *LMNA* gene. In other embodiments, the one or more introns are synthetic introns. In particular embodiments, the one or more introns are positioned in the nucleotide sequence in the viral vector such that it is capable of encoding both lamin A and lamin C in a splice-dependent manner. In particular embodiments, the one or more introns are positioned in the nucleic acid construct such that the pre-mRNA undergoes alternative splicing

to produce mature mRNA encoding lamin A and/or lamin C. In particular embodiments, the one or more introns are positioned in the nucleic acid construct such that the pre-mRNA undergoes alternative splicing to produce more mature mRNA encoding lamin C than mature mRNA encoding lamin A. In particular embodiments, the one or more introns are positioned in the nucleic acid construct such that the pre-mRNA undergoes alternative splicing to produce about the same levels of mature mRNA encoding lamin A and mature mRNA encoding lamin C. In particular embodiments, the one or more introns are positioned in the nucleic acid construct such that the pre-mRNA undergoes alternative splicing to produce more mature mRNA encoding lamin A than mature mRNA encoding lamin C. In certain embodiments, the viral vector comprises nucleotide sequences corresponding to introns 8-11 of a wild-type *LMNA* gene (e.g. SEQ ID NOs: 77-80). In certain embodiments, the viral vector comprises nucleotide sequences corresponding to introns 9 and 10 of a wild-type *LMNA* gene (e.g. SEQ ID NOs: 78 and 79). In certain embodiments, the viral vector comprises the nucleotide sequence corresponding to intron 10 of a wild-type *LMNA* gene (e.g. SEQ ID NO: 79).

[130] In some embodiments, the viral vector comprises a nucleotide sequence comprising at least one, but not all, of the endogenous introns of the wild-type human *LMNA* gene. In some embodiments, the viral vector comprises a nucleotide sequence comprising at least one intron corresponding to introns 8-11 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 77-80), and lacking at least one intron corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the viral vector comprises a nucleotide sequence comprising introns corresponding to introns 8-11 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 77-80), and lacking at least one intron corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the viral vector comprises a nucleotide sequence comprising introns corresponding to introns 8-11 of the human wild-type *LMNA* gene (e.g. SEQ ID NOs: 77-80), and lacking all of the introns corresponding to introns 1-7 of the human wild-type *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the viral vector comprises a nucleotide sequence comprising introns corresponding to introns 9-10 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 78 and 79), and lacking at least one intron corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the viral vector comprises a nucleotide sequence comprising introns corresponding to introns 9-10 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 78 and 79), and lacking all of the introns corresponding to introns 1-7 of

the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the viral vector comprises a nucleotide sequence comprising introns corresponding to introns 9-10 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 78 and 79), and lacking all of the introns corresponding to introns 1-8 and 11 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-77 and 80). In some embodiments, the viral vector comprises a nucleotide sequence comprising the intron corresponding to intron 10 of the wild-type human *LMNA* gene (e.g. SEQ ID NO: 79), and lacking at least one intron corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the viral vector comprises a nucleotide sequence comprising the intron corresponding to intron 10 of the wild-type human *LMNA* gene (e.g. SEQ ID NO: 79), and lacking all of the introns corresponding to introns 1-7 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-76). In some embodiments, the viral vector comprises a nucleotide sequence comprising the intron corresponding to intron 10 of the wild-type human *LMNA* gene (e.g. SEQ ID NO: 79), and lacking all of the introns corresponding to introns 1-9 and 11 of the wild-type human *LMNA* gene (e.g. SEQ ID NOs: 70-78 and 80). In some embodiments, the intron corresponding to intron 8 of the wild-type human *LMNA* gene comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 77, or a fragment thereof. In some embodiments, the intron corresponding to intron 9 of the wild-type human *LMNA* gene comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 78, or a fragment thereof. In some embodiments, the intron corresponding to intron 10 of the wild-type human *LMNA* gene comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 79 or a fragment thereof. In some embodiments, the intron corresponding to intron 11 of the wild-type human *LMNA* gene comprises a nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 80 or a fragment thereof.

[131] In some cases, the viral vector comprises a nucleotide sequence encoding lamin A and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises intron 8 of a wild-type *LMNA* gene. In some cases, the viral vector comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or

variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises intron 9 of a wild-type LMNA gene. In some cases, the viral vector comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises intron 10 of a wild-type LMNA gene. In some cases, the viral vector comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises intron 11 of a wild-type LMNA gene. In some cases, the viral vector comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises introns 9 and 10 of a wild-type LMNA gene. In some cases, the viral vector comprises a nucleotide sequence encoding lamin A (or a biologically active fragment or variant thereof) and/or lamin C (or a biologically active fragment or variant thereof), wherein the nucleotide sequence comprises introns 8, 9, 10, and 11 of a wild-type LMNA gene.

[132] In certain embodiments, the viral vector comprises a nucleotide sequence that comprises, consists of, or consists essentially of, the nucleic acid sequence of any one or more of SEQ ID NO: 77-80, and nucleic acid sequences that are at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to any one or more of the foregoing. In certain embodiments, the viral vector comprises a nucleotide sequence that is the sequence of any one of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 60% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 65% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 70% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 75% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 80% identical to any one or more of

SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 82% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 85% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 87% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 90% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 91% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 92% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 93% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 94% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 95% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 96% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 97% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 98% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is at least 99% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof. In certain embodiments, the viral vector comprises a nucleotide sequence that is

100% identical to any one or more of SEQ ID NOs: 77-80, or a biologically active variant and/or a fragment thereof.

[133] In certain embodiments, the viral vectors described herein further comprise a polyadenylation (polyA) sequence. Suitable polyA sequences include, for example, an artificial polyA that is about 75 bp in length (PA75) (see *e.g.*, WO 2018/126116), the bovine growth hormone polyA, SV40 early polyA signal, SV40 late polyA signal, rabbit beta globin polyA, HSV thymidine kinase polyA, protamine gene polyA, adenovirus 5 EIb polyA, growth hormone polyA, or a PBGD polyA. In certain embodiments, the polyA sequence comprises or consists of SEQ ID NO: 11. In certain embodiments, the polyA sequence is positioned downstream of the transgene in the nucleic acid constructs described herein.

E. Viral Vectors

[134] In various embodiments, suitable viral vectors include retroviruses (*e.g.*, A-type, B-type, C-type, and D-type viruses), adenovirus, parvovirus (*e.g.* adeno-associated viruses or AAV), coronavirus, negative strand RNA viruses such as orthomyxovirus (*e.g.*, influenza virus), rhabdovirus (*e.g.*, rabies and vesicular stomatitis virus), paramyxovirus (*e.g.* measles and Sendai), positive strand RNA viruses such as picornavirus and alphavirus, and double-stranded DNA viruses including adenovirus, herpesvirus (*e.g.*, Herpes Simplex virus types 1 and 2, Epstein-Barr virus, cytomegalovirus), and poxvirus (*e.g.*, vaccinia, fowlpox and canarypox). Examples of retroviruses include avian leukosis-sarcoma virus, human T-lymphotrophic virus type 1 (HTLV-1), bovine leukemia virus (BLV), lentivirus, and spumavirus. Other viruses include Norwalk virus, togavirus, flavivirus, reoviruses, papovavirus, hepadnavirus, and hepatitis virus, for example. Viral vectors may be classified into two groups according to their ability to integrate into the host genome – integrating and non-integrating. Oncoretroviruses and lentiviruses can integrate into host cellular chromatin while adenoviruses, adeno-associated viruses, and herpes viruses predominantly persist in the cell nucleus as extrachromosomal episomes.

[135] In certain embodiments, a suitable viral vector is a retroviral vector. Retroviruses refer to viruses of the family Retroviridae. Examples of retroviruses include oncoretroviruses, such as murine leukemia virus (MLV), and lentiviruses, such as human immunodeficiency virus 1 (HIV-1). Retroviral genomes are single-stranded (ss) RNAs and comprise various genes that may be provided in cis or trans. For example, retroviral genome may contain cis-acting sequences such as two long terminal repeats (LTR), with elements for gene expression,

reverse transcription and integration into the host chromosomes. Other components include the packaging signal (ψ), for the specific RNA packaging into newly formed virions and the polypurine tract (PPT), the site of the initiation of the positive strand DNA synthesis during reverse transcription. In addition, the retroviral genome may comprise gag, pol and env genes. The gag gene encodes the structural proteins, the pol gene encodes the enzymes that accompany the ssRNA and carry out reverse transcription of the viral RNA to DNA, and the env gene encodes the viral envelope. Generally, the gag, pol and env are provided in trans for viral replication and packaging.

[136] In certain embodiments, a retroviral vector provided herein may be a lentiviral vector. At least five serogroups or serotypes of lentiviruses are recognized. Viruses of the different serotypes may differentially infect certain cell types and/or hosts. Lentiviruses, for example, include primate retroviruses and non-primate retroviruses. Primate retroviruses include HIV and simian immunodeficiency virus (SIV). Non-primate retroviruses include feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), caprine arthritis-encephalitis virus (CAEV), equine infectious anemia virus (EIAV) and visnavirus. Lentiviruses or lentivectors may be capable of transducing quiescent cells. As with oncoretrovirus vectors, the design of lentivectors may be based on the separation of cis- and trans-acting sequences.

[137] In certain embodiments, the disclosure provides expression vectors that have been designed for delivery by an optimized therapeutic retroviral vector. The retroviral vector can be a lentivirus comprising a left (5') LTR; sequences which aid packaging and/or nuclear import of the virus; a regulatory element (such as, for example, a cell-type selective (*e.g.*, cardiomyocyte) promoter and/or enhancer) operably linked to a sequence encoding lamin A and/or lamin C; optionally one or more additional regulatory elements (such as, for example, a polyA sequence); optionally a lentiviral reverse response element (RRE); optionally an insulator; and a right (3') retroviral LTR.

[138] In exemplary embodiments, a viral vector provided herein is an adeno-associated virus (AAV). AAV is a small, replication-defective, non-enveloped animal virus that infects humans and some other primate species. AAV is not known to cause human disease and induces a mild immune response. AAV vectors can also infect both dividing and quiescent cells without integrating into the host cell genome.

[139] The AAV genome consists of a linear single stranded DNA which is ~4.7kb in length. The genome consists of two open reading frames (ORF) flanked by inverted terminal repeat (ITR) sequences that are about 145bp in length. The ITR consists of a nucleotide sequence at the 5' end (5' ITR) and a nucleotide sequence located at the 3' end (3' ITR) that contain palindromic sequences. The ITRs function in cis by folding over to form T-shaped hairpin structures by complementary base pairing that function as primers during initiation of DNA replication for second strand synthesis. The two open reading frames encode for rep and cap genes that are involved in replication and packaging of the virion. In an exemplary embodiment, an AAV vector provided herein does not contain the rep or cap genes. Such genes may be provided in trans for producing virions as described further below.

[140] In certain embodiments, an AAV vector may include a stuffer nucleic acid. In some embodiments, the stuffer nucleic acid may encode a green fluorescent protein or antibiotic resistance gene such as kanamycin or ampicillin. In certain embodiments, the stuffer nucleic acid may be located outside of the ITR sequences (*e.g.*, as compared to the lamin A and/or lamin C transgene sequence and regulatory sequences, which are located between the 5' and 3' ITR sequences).

[141] Various serotypes of AAV exist, including AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, and AAV13. These serotypes differ in their tropism, or the types of cells they infect. AAVs may comprise the genome and capsids from multiple serotypes (*e.g.*, pseudotypes). For example, an AAV may comprise the genome of serotype 2 (*e.g.*, ITRs) packaged in the capsid from serotype 5 or serotype 9. Pseudotypes may improve transduction efficiency as well as alter tropism.

[142] In certain embodiments, the viral vectors described herein comprise at a minimum, AAV inverted terminal repeats (ITRs) and a transgene encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof. In certain embodiments, the viral vectors described herein comprise a minigene composed of, at a minimum, AAV inverted terminal repeats (ITRs) and a transgene encoding (a) a biologically active fragment of a lamin A polypeptide; (b) a biologically active fragment of a lamin C polypeptide; (c) a biologically active fragment of a lamin A and biologically active fragment of a lamin C polypeptide; or biologically active variants and/or fragments thereof. In one particular embodiment, the ITRs of AAV serotype 6 or AAV serotype 9 are used. However, ITRs from other suitable serotypes may be

selected. The viral vector is packaged into a capsid protein and delivered to a selected host cell. AAV vectors of the present disclosure may be generated from a variety of adeno-associated viruses. The tropism of the vector may be altered by packaging the recombinant genome of one serotype into capsids derived from another AAV serotype. In some embodiments, the ITRs of the rAAV virus may be based on the ITRs of any one of AAV1-12 and may be combined with an AAV capsid selected from any one of AAV1-12, AAV-DJ, AAV-DJ8, AAV-DJ9 or other modified serotypes.

[143] In some embodiments, an AAV vector or an AAV viral particle, or virion, may be used to deliver a construct comprising a regulatory element operably linked to a sequence encoding lamin A and/or lamin C into a cell, cell type, or tissue, and may be done either in vivo, ex vivo, or in vitro. In exemplary embodiments, such an AAV vector is replication-deficient. In some embodiments, an AAV virus is engineered or genetically modified so that it can replicate and generate virions only in the presence of helper factors.

[144] In certain embodiments, a viral vector can be selected to produce a virion having high infectivity without selectivity for a particular cell type, while a cardiomyocyte-selective regulatory element confers selective expression of a transgene in cardiomyocytes and not in other muscle cells, even though other muscle cells might be infected with the virus. In certain embodiments, a viral vector can be designed to produce a virion that infects many different cell types but expression of the transgene is enhanced and/or optimized in a cell type of interest (*e.g.* cardiomyocytes), and expression of the transgene is reduced and/or minimized in other non-target cell types (*e.g.*, non-cardiomyocytes). The differential expression of the transgene in different cell types can be controlled, engineered, or manipulated using different regulatory elements that are selective for one or more cell types. In some cases, one or more regulatory elements operably linked to a transgene enhances selective expression of the transgene in a target cell, cell type, or tissue, while the one or more regulatory elements suppress transgene expression in off-target cells, cell type, or tissue, or confers significantly lower, de minimis, or statistically lower gene expression in one or more off-target cells, cell types, or tissue. For gene therapy, selective expression of a transgene in a target cell type (*e.g.*, cardiomyocyte) and/or minimized expression of the transgene in a non-target cell type can be desired. Expression of the transgene in an unintended cell-type (*e.g.*, non-target cell type) may result in an adverse effect to the subject.

Expression of the transgene in an unintended cell-type can counteract the therapeutic effect of the transgene in the intended cell type.

[145] In exemplary embodiments, the disclosure provides expression vectors that have been designed for delivery by an AAV. The AAV can be any serotype, for examples, AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV-DJ, or a chimeric, hybrid, or variant AAV. The AAV can also be a self-complementary AAV (scAAV). In certain embodiments, an expression vector designed for delivery by an AAV comprises a 5' ITR and a 3' ITR. In certain embodiments, an expression vector designed for delivery by an AAV comprises a 5' ITR, a promoter, a construct comprising a regulatory element (such as, for example, a cell-type selective (*e.g.* cardiomyocyte) promoter and/or enhancer) operably linked to a sequence encoding lamin A and/or lamin C, and a 3' ITR. In certain embodiments, an expression vector designed for delivery by an AAV comprises a 5' ITR, an enhancer, a promoter, a construct comprising a regulatory element (such as, for example, a cell-type selective (*e.g.* cardiomyocyte) promoter and/or enhancer) operably linked to a sequence encoding lamin A and/or lamin C, a polyA sequence, and a 3' ITR. In exemplary embodiments, an expression vector designed for delivery by an AAV comprises a 5' ITR, a regulatory element comprising any one of SEQ ID NOs: 30-69 or 100-102 or a variant or functional fragment thereof, a sequence encoding lamin A and/or lamin C, and a 3' ITR. In one embodiment, an expression vector designed for delivery by an AAV comprises a 5' ITR, a promoter comprising any one or more of SEQ ID NOs: 31, 33, 60, or 61 or a variant or functional fragment thereof, a sequence encoding lamin A and/or lamin C, and a 3' ITR. In another embodiment, an expression vector designed for delivery by an AAV comprises a 5' ITR, a regulatory element comprising SEQ ID NO: 31 or a variant or functional fragment thereof, a sequence encoding lamin A and/or lamin C, and a 3' ITR. In another embodiment, an expression vector designed for delivery by an AAV comprises a 5' ITR, a regulatory element comprising SEQ ID NO: 33 or a variant or functional fragment thereof, a sequence encoding lamin A and/or lamin C, and a 3' ITR. In another embodiment, an expression vector designed for delivery by an AAV comprises a 5' ITR, a regulatory element comprising SEQ ID NO: 60 or a variant or functional fragment thereof, a sequence encoding lamin A and/or lamin C, and a 3' ITR. In another embodiment, an expression vector designed for delivery by an AAV comprises a 5' ITR, a regulatory element comprising SEQ ID NO: 61 or a variant or functional fragment thereof, a sequence

encoding lamin A and/or lamin C, and a 3' ITR. Exemplary AAV expression vectors are illustrated in Figures 1-5 and 11A-C.

F. Viral particle

[146] In certain embodiments, the disclosure provides viral particles comprising a viral vector comprising a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof. In certain embodiments, the disclosure provides viral particles comprising a viral vector comprising a nucleotide sequence encoding (a) a biologically active fragment of a lamin A polypeptide; (b) a biologically active fragment of a lamin C polypeptide; (c) a biologically active fragment of a lamin A and biologically active fragment of a lamin C polypeptide; or biologically active variants and/or fragments thereof. The terms “viral particle”, and “virion” are used herein interchangeably and relate to an infectious and typically replication-defective virus particle comprising the viral genome (*e.g.*, the viral expression vector) packaged within a capsid and, as the case may be *e.g.*, for retroviruses, a lipidic envelope surrounding the capsid. A “capsid” refers to the structure in which the viral genome is packaged. A capsid consists of several oligomeric structural subunits made of proteins. For example, AAV have an icosahedral capsid formed by the interaction of three capsid proteins: VP1, VP2 and VP3. In one embodiment, a virion provided herein is a recombinant AAV virion or rAAV virion obtained by packaging an AAV vector comprising a regulatory element (including for example, a cell-type (*e.g.*, cardiomyocyte) selective regulatory element) operably linked to a sequence encoding lamin A and/or lamin C as described herein in a protein shell.

[147] In certain embodiments, a recombinant AAV virion provided herein may be prepared by encapsidating an AAV genome derived from a particular AAV serotype in a viral particle formed by natural Cap proteins corresponding to an AAV of the same particular serotype. In other embodiments, an AAV viral particle provided herein comprises a viral vector comprising ITR(s) of a given AAV serotype packaged into proteins from a different serotype. See *e.g.*, Bunning H et al. J Gene Med 2008; 10: 717-733. For example, a viral vector having ITRs from a given AAV serotype may be package into: a) a viral particle constituted of capsid proteins derived from a same or different AAV serotype (*e.g.* AAV2 ITRs and AAV9 capsid proteins; AAV2 ITRs and AAV8 capsid proteins; etc.); b) a mosaic viral particle constituted of a mixture of capsid proteins from different AAV serotypes or mutants (*e.g.*

AAV2 ITRs with AAV1 and AAV9 capsid proteins); c) a chimeric viral particle constituted of capsid proteins that have been truncated by domain swapping between different AAV serotypes or variants (*e.g.* AAV2 ITRs with AAV8 capsid proteins with AAV9 domains); or d) a targeted viral particle engineered to display selective binding domains, enabling stringent interaction with target cell specific receptors (*e.g.* AAV5 ITRs with AAV9 capsid proteins genetically truncated by insertion of a peptide ligand; or AAV9 capsid proteins non-genetically modified by coupling of a peptide ligand to the capsid surface).

[148] The skilled person will appreciate that an AAV virion provided herein may comprise capsid proteins of any AAV serotype. In one embodiment, the viral particle comprises capsid proteins from an AAV serotype selected from the group consisting of an AAV1, an AAV2, an AAV5, an AAV6, an AAV8, and an AAV9, which are more suitable for delivery to myocardium (M. Hocquemiller et al., *Hum Gene Ther* 27(7): 478-496 (2016)). In some embodiments, the viral vector comprises capsid proteins from an AAV6 serotype. In some embodiments, the viral vector comprises capsid proteins from an AAV9 serotype.

[149] Numerous methods are known in the art for production of rAAV virions, including transfection, stable cell line production, and infectious hybrid virus production systems which include adenovirus-AAV hybrids, herpesvirus-AAV hybrids (Conway, J E et al., (1997) *J. Virology* 71(11):8780-8789) and baculovirus-AAV hybrids. rAAV production cultures for the production of rAAV virus particles all require; 1) suitable host cells, including, for example, human-derived cell lines such as HeLa, A549, or 293 cells, or insect-derived cell lines such as SF-9, in the case of baculovirus production systems; 2) suitable helper virus function, provided by wild-type or mutant adenovirus (such as temperature sensitive adenovirus), herpes virus, baculovirus, or a plasmid construct providing helper functions; 3) AAV rep and cap genes and gene products; 4) a transgene (*e.g.*, a sequence encoding lamin A and/or lamin C as described herein) flanked by AAV ITR sequences; and 5) suitable media and media components to support rAAV production.

[150] In various embodiments, the host cells described herein comprise the following three components: (1) a rep gene and a cap gene, (2) genes providing helper functions, and (3) a transgene (*e.g.*, a sequence encoding lamin A and/or lamin C described herein flanked by ITRs). The AAV rep gene, AAV cap gene, and genes providing helper functions can be introduced into the cell by incorporating said genes into a vector such as, for example, a plasmid, and introducing said vector into the host cell. The rep, cap and helper function

genes can be incorporated into the same plasmid or into different plasmids. In a preferred embodiment, the AAV rep and cap genes are incorporated into one plasmid and the genes providing helper functions are incorporated into another plasmid. The various plasmids for creation of a host cell for virion production (*e.g.*, comprising AAV rep and cap genes, helper functions, or a transgene) can be introduced into the cell by using any suitable method well known in the art. Examples of transfection methods include, but are not limited to, co-precipitation with calcium phosphate, DEAE-dextran, polybrene, electroporation, microinjection, liposome-mediated fusion, lipofection, retrovirus infection and biolistic transfection. In certain embodiments, the plasmids providing the rep and cap genes, the helper functions and the transgene (*e.g.*, a sequence encoding lamin A and/or lamin C disclosed herein flanked by ITRs) can be introduced into the cell simultaneously. In another embodiment, the plasmids providing the rep and cap genes and the helper functions can be introduced in the cell before or after the introduction of plasmid comprising the transgene. In an exemplary embodiment, the cells are transfected simultaneously with three plasmids (*e.g.*, a triple transfection method): (1) a plasmid comprising the transgene (*e.g.*, a sequence encoding lamin A and/or lamin C disclosed herein flanked by ITRs), (2) a plasmid comprising the AAV rep and cap genes, and (3) a plasmid comprising the genes providing the helper functions. Exemplary host cells may be 293, A549 or HeLa cells.

[151] In other embodiments, one or more of (1) the AAV rep and cap genes, (2) genes providing helper functions, and (3) the transgene, may be carried by the packaging cell, either episomally and/or integrated into the genome of the packaging cell. In one embodiment, host cells may be packaging cells in which the AAV rep and cap genes and helper functions are stably maintained in the host cell and the host cell is transiently transfected with a plasmid containing a transgene (*e.g.*, a sequence encoding lamin A and/or lamin C disclosed herein flanked by ITRs). In another embodiment, host cells are packaging cells in which the AAV rep and cap genes are stably maintained in the host cell and the host cell is transiently transfected with a plasmid containing a transgene (*e.g.*, a sequence encoding lamin A and/or lamin C disclosed herein flanked by ITRs) and a plasmid containing the helper functions. In another embodiment, host cells may be packaging cells in which the helper functions are stably maintained in the host cell and the host cell is transiently transfected with a plasmid containing a transgene (*e.g.*, a sequence encoding lamin A and/or lamin C disclosed herein flanked by ITRs) and a plasmid containing rep and cap genes. In another embodiment, host

cells may be producer cell lines that are stably transfected with rep and cap genes, helper functions and the transgene sequence (*e.g.*, a sequence encoding lamin A and/or lamin C disclosed herein flanked by ITRs). Exemplary packaging and producer cells may be derived from 293, A549 or HeLa cells.

[152] In another embodiment, the producer cell line is an insect cell line (typically Sf9 cells) that is infected with baculovirus expression vectors that provide Rep and Cap proteins. This system does not require adenovirus helper genes (Ayuso E, et al., *Curr. Gene Ther.* 2010, 10:423-436).

[153] The term “cap protein”, as used herein, refers to a polypeptide having at least one functional activity of a native AAV Cap protein (*e.g.* VP1, VP2, VP3). Examples of functional activities of cap proteins include the ability to induce formation of a capsid, facilitate accumulation of single-stranded DNA, facilitate AAV DNA packaging into capsids (*i.e.* encapsidation), bind to cellular receptors, and facilitate entry of the virion into host cells. In principle, any Cap protein can be used in the context of the present invention.

[154] Cap proteins have been reported to have effects on host tropism, cell, tissue, or organ specificity, receptor usage, infection efficiency, and immunogenicity of AAV viruses. Accordingly, an AAV cap for use in an rAAV may be selected taking into consideration, for example, the subject's species (*e.g.* human or non-human), the subject's immunological state, the subject's suitability for long or short-term treatment, or a particular therapeutic application (*e.g.* treatment of a particular disease or disorder, or delivery to particular cells, tissues, or organs). In certain embodiments, the cap protein is derived from the AAV of the group consisting of AAV1, AAV2, AAV5, AAV6, AAV8, and AAV9 serotypes. In some embodiments, the cap protein is derived from AAV6. In some embodiments, the cap protein is derived from AAV9.

[155] In some embodiments, an AAV Cap for use in the method of the invention can be generated by mutagenesis (*i.e.* by insertions, deletions, or substitutions) of one of the aforementioned AAV caps or its encoding nucleic acid. In some embodiments, the AAV cap is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% or more similar to one or more of the aforementioned AAV caps.

[156] In some embodiments, the AAV cap is chimeric, comprising domains from two, three, four, or more of the aforementioned AAV caps. In some embodiments, the AAV cap is a mosaic of VP1, VP2, and VP3 monomers originating from two or three different AAV or a

recombinant AAV. In some embodiments, a rAAV composition comprises more than one of the aforementioned caps.

[157] In some embodiments, an AAV cap for use in a rAAV virion is engineered to contain a heterologous sequence or other modification. For example, a peptide or protein sequence that confers selective targeting or immune evasion may be engineered into a cap protein. Alternatively or in addition, the cap may be chemically modified so that the surface of the rAAV is polyethylene glycolated (i.e., pegylated), which may facilitate immune evasion. The cap protein may also be mutagenized (e.g., to remove its natural receptor binding, or to mask an immunogenic epitope).

[158] The term “rep protein”, as used herein, refers to a polypeptide having at least one functional activity of a native AAV rep protein (e.g. rep 40, 52, 68, 78). Examples of functional activities of a rep protein include any activity associated with the physiological function of the protein, including facilitating replication of DNA through recognition, binding and nicking of the AAV origin of DNA replication as well as DNA helicase activity. Additional functions include modulation of transcription from AAV (or other heterologous) promoters and site-specific integration of AAV DNA into a host chromosome. In a particular embodiment, AAV rep genes may be from the serotypes AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 or AAVrh10. In some embodiments, the AAV rep genes are from AAV6. In some embodiments, the AAV rep genes are from AAV9.

[159] In some embodiments, an AAV rep protein for use in the method of the invention can be generated by mutagenesis (i.e. by insertions, deletions, or substitutions) of one of the aforementioned AAV reps or its encoding nucleic acid. In some embodiments, the AAV rep is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% or more similar to one or more of the aforementioned AAV reps.

[160] The expressions “helper functions” or “helper genes”, as used herein, refer to viral proteins upon which AAV is dependent for replication. The helper functions include those proteins required for AAV replication including, without limitation, those proteins involved in activation of AAV gene transcription, stage specific AAV mRNA splicing, AAV DNA replication, synthesis of cap expression products, and AAV capsid assembly. Viral-based accessory functions can be derived from any of the known helper viruses such as adenovirus, herpesvirus (other than herpes simplex virus type-1), and vaccinia virus. Helper functions include, without limitation, adenovirus E1, E2a, VA, and E4 or herpesvirus UL5, ULB,

UL52, and UL29, and herpesvirus polymerase. In a preferred embodiment, the proteins upon which AAV is dependent for replication are derived from adenovirus.

[161] In some embodiments, a viral protein upon which AAV is dependent for replication for use in the method of the invention can be generated by mutagenesis (i.e. by insertions, deletions, or substitutions) of one of the aforementioned viral proteins or its encoding nucleic acid. In some embodiments, the viral protein is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% or more similar to one or more of the aforementioned viral proteins.

[162] Methods for assaying the functions of cap proteins, rep proteins and viral proteins upon which AAV is dependent for replication are well known in the art.

G. Host Cell

[163] In another aspect, the invention relates to a host cell comprising a viral vector or viral particle which comprises a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof. In another embodiment, the invention relates to a host cell comprising a viral vector or viral particle which comprises a nucleotide sequence encoding (a) a biologically active fragment of a lamin A polypeptide; (b) a biologically active fragment of a lamin C polypeptide; (c) a biologically active fragment of a lamin A and a biologically active fragment of a lamin C polypeptide; or biologically active variants and/or fragments thereof. Host cells may be a bacterial cell, a yeast cell, an insect cell or a mammalian cell. In an exemplary embodiment, a host cell refers to any cell line that is susceptible to infection by a virus of interest, and amenable to culture in vitro.

[164] In certain embodiments, a host cell provided herein may be used for ex vivo gene therapy purposes. In such embodiments, the cells are transfected with a nucleic acid molecule or expression vector comprising a sequence encoding lamin A and/or lamin C and subsequently transplanted into the patient or subject. Transplanted cells can have an autologous, allogenic or heterologous origin. For clinical use, cell isolation will generally be carried out under Good Manufacturing Practices (GMP) conditions. Before transplantation, cell quality and absence of microbial or other contaminants is typically checked and preconditioning, such as with radiation and/or an immunosuppressive treatment, may be carried out. Furthermore, the host cells may be transplanted together with growth factors to stimulate cell proliferation and/or differentiation.

[165] In certain embodiments, a host cell may be used for ex vivo gene therapy into the heart or other tissue(s) of interest. Preferably, said cells are eukaryotic cells such as mammalian cells, these include, but are not limited to, humans, non-human primates such as apes; chimpanzees; monkeys, and orangutans, domesticated animals, including dogs and cats, as well as livestock such as horses, cattle, pigs, sheep, and goats, or other mammalian species including, without limitation, mice, rats, guinea pigs, rabbits, hamsters, and the like. A person skilled in the art will choose the more appropriate cells according to the patient or subject to be transplanted.

[166] In certain embodiments, a host cell provided herein may be a cell with self-renewal and pluripotency properties, such as stem cells or induced pluripotent stem cells. Stem cells are preferably mesenchymal stem cells. Mesenchymal stem cells (MSCs) are capable of differentiating into at least one of an osteoblast, a chondrocyte, an adipocyte, or a myocyte and may be isolated from any type of tissue. Generally, MSCs will be isolated from bone marrow, adipose tissue, umbilical cord, or peripheral blood. Methods for obtaining thereof are well known to a person skilled in the art. Induced pluripotent stem cells (also known as iPS cells or iPSCs) are a type of pluripotent stem cell that can be generated directly from adult cells. Yamanaka et al. induced iPS cells by transferring the Oct3/4, Sox2, Klf4 and c-Myc genes into mouse and human fibroblasts, and forcing the cells to express the genes (WO 2007/069666). Thomson et al. subsequently produced human iPS cells using Nanog and Lin28 in place of Klf4 and c-Myc (WO 2008/118820).

[167] In an exemplary embodiment, a host cell provided herein is a packaging cell. Said cells can be adherent or suspension cells. The packaging cell, and helper vector or virus or DNA construct(s) provide together in trans all the missing functions which are required for the complete replication and packaging of the viral vector.

[168] Preferably, said packaging cells are eukaryotic cells such as mammalian cells, including simian, human, dog and rodent cells. Examples of human cells are PER.C6 cells (WO01/38362), MRC-5 (ATCC CCL-171), WI-38 (ATCC CCL-75), HEK-293 cells (ATCC CRL-1573), HeLa cells (ATCC CCL2), and fetal rhesus lung cells (ATCC CL-160). Examples of non-human primate cells are Vero cells (ATCC CCL81), COS-1 cells (ATCC CRL-1650) or COS-7 cells (ATCC CRL-1651). Examples of dog cells are MDCK cells (ATCC CCL-34). Examples of rodent cells are hamster cells, such as BHK21-F, HKCC cells, or CHO cells.

[169] As an alternative to mammalian sources, cell lines for use in the invention may be derived from avian sources such as chicken, duck, goose, quail or pheasant. Examples of avian cell lines include avian embryonic stem cells (WO01/85938 and WO03/076601), immortalized duck retina cells (WO2005/042728), and avian embryonic stem cell derived cells, including chicken cells (WO2006/108846) or duck cells, such as EB66 cell line (WO2008/129058 & WO2008/142124).

[170] In another embodiment, said host cell are insect cells, such as SF9 cells (ATCC CRL-1711), Sf21 cells (IPLB-Sf21), MG1 cells (BTI-TN-MG1) or High FiveTM cells (BTI-TN-5B1-4).

[171] In certain embodiments, the host cells provided herein comprising a viral vector or viral particle which comprises a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof, may further comprise one or more additional nucleic acid constructs, such as, for example (i) a nucleic acid construct (*e.g.*, an AAV helper plasmid) that encodes rep and cap genes, but does not carry ITR sequences; and/or (ii) a nucleic acid construct (*e.g.*, a plasmid) providing the adenoviral functions necessary for AAV replication. In an exemplary embodiment, a host cell provided herein comprises: i) any of the nucleic acid constructs or a viral vectors disclosed herein (*e.g.*, any of the nucleic acid constructs or vectors disclosed herein comprising a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof; ii) a nucleic acid construct encoding AAV rep and cap genes which does not carry the ITR sequences; and iii) a nucleic acid construct comprising adenoviral helper genes (as described further below).

[172] In certain embodiments, the rep, cap, and adenoviral helper genes can be combined on a single plasmid (Blouin V et al. J Gene Med. 2004; 6(suppl): S223-S228; Grimm D. et al. Hum. Gene Ther. 2003; 7: 839-850). Thus, in another exemplary embodiment, a host cell provided herein comprises: i) a nucleic acid molecule or an expression vector comprising a sequence encoding lamin A and/or lamin C (*i.e.*, the recombinant AAV genome); and ii) a plasmid encoding AAV rep and cap genes which does not carry the ITR sequences and further comprising adenoviral helper genes.

[173] In another embodiment, a host cell provided herein comprises: a) any of the nucleic acid constructs or a viral vectors disclosed herein (*e.g.*, any of the nucleic acid constructs or

viral vectors disclosed herein comprising a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof; b) a plasmid encoding AAV rep and cap genes which does not carry the ITR sequences; and c) a plasmid comprising adenoviral helper genes E2a, E4, and VA RNAs; wherein co-transfection is performed in cells, preferably mammalian cells, that constitutively express and transcomplement the adenoviral E1 gene, like HEK-293 cells (ATCC CRL-1573).

[174] In certain embodiments, a host cell suitable for large-scale production of AAV vectors is an insect cell that can be infected with a combination of recombinant baculoviruses (Urabe et al. Hum. Gene Ther. 2002; 13: 1935-1943). For example, SF9 cells may be co-infected with three baculovirus vectors respectively expressing AAV rep, AAV cap and the AAV vector to be packaged. The recombinant baculovirus vectors will provide the viral helper gene functions required for virus replication and/or packaging.

[175] Further guidance for the construction and production of virions for gene therapy according to the invention can be found in: Viral Vectors for Gene Therapy, Methods and Protocols. Series: Methods in Molecular Biology, Vol. 737. Merten and Al-Rubeai (Eds.); 2011 Humana Press (Springer); Gene Therapy. M. Giacca. 2010 Springer-Verlag; Heilbronn R. and Weger S. Viral Vectors for Gene Transfer: Current Status of Gene Therapeutics. In: Drug Delivery, Handbook of Experimental Pharmacology 197; M. Schafer-Korting (Ed.). 2010 Springer-Verlag; pp. 143-170; Adeno-Associated Virus: Methods and Protocols. R. O. Snyder and P. Moullier (Eds). 2011 Humana Press (Springer); Bunning H. et al. Recent developments in adeno-associated virus technology. J. Gene Med. 2008; 10:717-733; and Adenovirus: Methods and Protocols. M. Chillon and A. Bosch (Eds.); Third. Edition. 2014 Humana Press (Springer).

[176] Host cells for expressing a transgene of interest (*e.g.*, a sequence encoding a lamin A and/or lamin C) may be grown under conditions adequate for assembly of the AAV virions. In certain embodiments, host cells are grown for a suitable period of time in order to promote the assembly of the AAV virions and the release of virions into the media. Generally, cells may be grown for about 24 hours, about 36 hours, about 48 hours, about 72 hours, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or up to about 10 days. After about 10 days (or sooner, depending on the culture conditions and the particular host cell used), the level of production generally decreases significantly. Generally, time of

culture is measured from the point of viral production. For example, in the case of AAV, viral production generally begins upon supplying helper virus function in an appropriate host cell as described herein. Generally, cells are harvested about 48 to about 100, preferably about 48 to about 96, preferably about 72 to about 96, preferably about 68 to about 72 hours after helper virus infection (or after viral production begins).

[177] rAAV production cultures can be grown under a variety of conditions (over a wide temperature range, for varying lengths of time, and the like) suitable to the particular host cell being utilized. rAAV production cultures include attachment-dependent cultures which can be cultured in suitable attachment-dependent vessels such as, for example, roller bottles, hollow fiber filters, microcarriers, and packed-bed or fluidized-bed bioreactors. rAAV vector production cultures may also include suspension-adapted host cells such as HeLa, 293, and SF-9 cells which can be cultured in a variety of ways including, for example, spinner flasks, stirred tank bioreactors, and disposable systems such as the Wave bag system.

[178] Suitable media known in the art may be used for the production of rAAV virions. These media include, without limitation, media produced by Hyclone Laboratories and JRH including Modified Eagle Medium (MEM), Dulbecco's Modified Eagle Medium (DMEM), each of which is incorporated herein by reference in its entirety. In certain embodiments, rAAV production culture media may be supplemented with serum or serum-derived recombinant proteins at a level of 0.5%-20% (v/v or w/v). Alternatively, rAAV vectors may be produced in serum-free conditions which may also be referred to as media with no animal-derived products.

[179] After culturing the host cells to allow AAV virion production, the resulting virions may be then be harvested and purified. In certain embodiments, the AAV virions can be obtained from (1) the host cells of the production culture by lysis of the host cells, and/or (2) the culture medium of said cells after a period of time post-transfection, preferably 72 hours. The rAAV virions may be harvested from the spent media from the production culture, provided the cells are cultured under conditions that cause release of rAAV virions into the media from intact cells (see *e.g.*, U.S. Pat. No. 6,566,118). Suitable methods of lysing cells are also known in the art and include for example multiple freeze/thaw cycles, sonication, microfluidization, and treatment with chemicals, such as detergents and/or proteases.

[180] After harvesting, the rAAV virions may be purified. The term "purified" as used herein includes a preparation of rAAV virions devoid of at least some of the other

components that may also be present where the rAAV virions naturally occur or are initially prepared from. Thus, for example, purified rAAV virions may be prepared using an isolation technique to enrich it from a source mixture, such as a culture lysate or production culture supernatant. Enrichment can be measured in a variety of ways, such as, for example, by the proportion of DNase-resistant particles (DRPs) or genome copies (gc) present in a solution, or by infectivity, or it can be measured in relation to a second, potentially interfering substance present in the source mixture, such as contaminants, including production culture contaminants or in-process contaminants, including helper virus, media components, and the like.

[181] In certain embodiments, the rAAV production culture harvest may be clarified to remove host cell debris. In some embodiments, the production culture harvest may be clarified using a variety of standard techniques, such as, centrifugation or filtration through a filter of 0.2 μm or greater pore size (*e.g.*, a cellulose acetate filter or a series of depth filters).

[182] In certain embodiments, the rAAV production culture harvest is further treated with BenzonaseTM to digest any high molecular weight DNA present in the production culture. In some embodiments, the BenzonaseTM digestion is performed under standard conditions, for example, a final concentration of 1-2.5 units/ml of BenzonaseTM at a temperature ranging from ambient to 37°C for a period of 30 minutes to several hours.

[183] In certain embodiments, the rAAV virions may be isolated or purified using one or more of the following purification steps: equilibrium centrifugation; flow-through anionic exchange filtration; tangential flow filtration (TFF) for concentrating the rAAV particles; rAAV capture by apatite chromatography; heat inactivation of helper virus; rAAV capture by hydrophobic interaction chromatography; buffer exchange by size exclusion chromatography (SEC); nanofiltration; and rAAV capture by anionic exchange chromatography, cationic exchange chromatography, or affinity chromatography. These steps may be used alone, in various combinations, or in different orders. Methods to purify rAAV particles are found, for example, in Xiao et al., (1998) *Journal of Virology* 72:2224-2232; U.S. Pat. Nos. 6,989,264 and 8,137,948; and WO 2010/148143.

[184] In certain embodiments, purified AAV virions can be dialyzed against PBS, filtered and stored at -80°C. Titers of viral genomes can be determined by quantitative PCR using linearized plasmid DNA as standard curve (see *e.g.*, Lock M, et al., *Hum. Gene Ther.* 2010; 21:1273-1285).

H. Pharmaceutical composition

[185] In certain embodiments, the disclosure provides compositions comprising any of the nucleic acid constructs, expression vectors, viral vectors, viral particles or host cells disclosed herein. In some embodiments, the disclosure provides compositions comprising a viral vector or viral particle which comprises a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof and a pharmaceutically acceptable carrier. In some embodiments, the disclosure provides compositions comprising a viral vector or viral particle which comprises a nucleotide sequence encoding (a) a biologically active fragment of a lamin A polypeptide; (b) a biologically active fragment of a lamin C polypeptide; (c) a biologically active fragment of a lamin A and a biologically active fragment of a lamin C polypeptide; or biologically active variants and/or fragments thereof and a pharmaceutically acceptable carrier. In other embodiments, the disclosure provides host cells which comprise a viral vector or viral particle comprising a nucleotide sequence encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A and lamin C polypeptide; or biologically active variants and/or fragments thereof and a pharmaceutically acceptable carrier. In particular embodiments, such compositions are suitable for gene therapy applications. Pharmaceutical compositions are preferably sterile and stable under conditions of manufacture and storage. Sterile solutions may be accomplished, for example, by filtration through sterile filtration membranes.

[186] Acceptable carriers and excipients in the pharmaceutical compositions are preferably nontoxic to recipients at the dosages and concentrations employed. Acceptable carriers and excipients may include buffers such as phosphate, citrate, HEPES, and TAE, antioxidants such as ascorbic acid and methionine, preservatives such as hexamethonium chloride, octadecyldimethylbenzyl ammonium chloride, resorcinol, and benzalkonium chloride, proteins such as human serum albumin, gelatin, dextran, and immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, histidine, and lysine, and carbohydrates such as glucose, mannose, sucrose, and sorbitol.

Pharmaceutical compositions of the disclosure can be administered parenterally in the form of an injectable formulation. Pharmaceutical compositions for injection can be formulated using a sterile solution or any pharmaceutically acceptable liquid as a vehicle.

Pharmaceutically acceptable vehicles include, but are not limited to, sterile water and physiological saline.

[187] The pharmaceutical compositions of the disclosure may be prepared in microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules and polymethylmethacrylate microcapsules. The pharmaceutical compositions of the disclosure may also be prepared in other drug delivery systems such as liposomes, albumin microspheres, microemulsions, nanoparticles, and nanocapsules. The pharmaceutical composition for gene therapy can be in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded.

[188] Pharmaceutical compositions provided herein may be formulated for parenteral administration, subcutaneous administration, intravenous administration, systemic administration, intramuscular administration, intra-arterial administration, intraparenchymal administration, intrathecal administration, intra-cisterna magna administration, intracerebroventricular administration, or intraperitoneal administration. In one embodiment, the pharmaceutical composition is formulated for intravenous administration. In one embodiment, the pharmaceutical composition is formulated for systemic administration. The pharmaceutical composition may also be formulated for, or administered via, nasal, spray, oral, aerosol, rectal, or vaginal administration. In one embodiment, a pharmaceutical composition provided herein is administered to the muscle, i.e. by intramuscular injection. The tissue target may be specific, for example the heart, or it may be a combination of several tissues, for example the heart and liver tissues. Exemplary tissue or other targets may include liver, skeletal muscle, heart muscle, adipose deposits, kidney, lung, vascular endothelium, epithelial, hematopoietic cells, CNS and/or CSF. In a particular embodiment, a pharmaceutical composition provided herein is administered to the heart, i.e. by intracardiac injection, intravenous injection or systemically. One or more of these methods may be used to administer a pharmaceutical composition of the disclosure.

[189] In certain embodiments, a pharmaceutical composition provided herein comprises an “effective amount” or a “therapeutically effective amount.” As used herein, such amounts refer to an amount effective, at dosages and for periods of time necessary to achieve the desired therapeutic result, such as increasing the level of *LMNA* expression and/or increasing ventricular output.

[190] The dosage of the pharmaceutical compositions of the disclosure depends on factors including the route of administration, the disease to be treated, and physical characteristics (*e.g.*, age, weight, general health) of the subject. Dosage may be adjusted to provide the optimum therapeutic response. Typically, a dosage may be an amount that effectively treats the disease without inducing significant toxicity. In one embodiment, an AAV vector provided herein can be administered to the patient for the treatment of a laminopathy (including for example, dilated cardiomyopathy) in an amount or dose within a range of 5×10^{11} to 1×10^{14} gc/kg (genome copies per kilogram of patient body weight (gc/kg)). In a more particular embodiment, the AAV vector is administered in an amount comprised within a range of about 5×10^{11} gc/kg to about 3×10^{13} gc/kg, or about 1×10^{12} to about 1×10^{14} gc/kg, or about 1×10^{12} to about 1×10^{13} gc/kg, or about 5×10^{11} gc/kg, 1×10^{12} gc/kg, 1.5×10^{12} gc/kg, 2.0×10^{12} gc/kg, 2.5×10^{12} gc/kg, 3×10^{12} gc/kg, 3.5×10^{12} gc/kg, 4×10^{12} gc/kg, 4.5×10^{12} gc/kg, 5×10^{12} gc/kg, 5.5×10^{12} gc/kg, 6×10^{12} gc/kg, 6.5×10^{12} gc/kg, 7×10^{12} gc/kg, 7.5×10^{12} gc/kg, 8×10^{12} gc/kg, 8.5×10^{12} gc/kg, 9×10^{12} gc/kg or 9.5×10^{12} gc/kg. The gc/kg may be determined, for example, by qPCR or digital droplet PCR (ddPCR) (see *e.g.*, M. Lock et al, Hum Gene Ther Methods. 2014 Apr; 25(2): 115-25). In another embodiment, an AAV vector provided herein can be administered to the patient for the treatment of a laminopathy (including for example, dilated cardiomyopathy) in an amount or dose within a range of 1×10^9 to 1×10^{11} iu/kg (infective units of the vector (iu)/subject's or patient's body weight (kg)). In certain embodiments, the pharmaceutical composition may be formed in a unit dose as needed. Such single dosage units may contain about 1×10^9 gc to about 1×10^{15} gc.

[191] Pharmaceutical compositions of the disclosure may be administered to a subject in need thereof, for example, one or more times (*e.g.*, 1 -10 times or more) daily, weekly, monthly, biannually, annually, or as medically necessary. In an exemplary embodiment, a single administration is sufficient. In one embodiment, the pharmaceutical composition is suitable for use in human subjects and is administered by intramuscular injection. In one embodiment, the pharmaceutical composition is suitable for use in human subjects and is administered by intracardiac injection, intravenous injection, or systemic administration. In one embodiment, the pharmaceutical composition is delivered via a peripheral vein by bolus injection. In other embodiments, the pharmaceutical composition is delivered via a peripheral vein by infusion over about 10 minutes (± 5 minutes), over about 20 minutes (± 5

minutes), over about 30 minutes (± 5 minutes), over about 60 minutes (± 5 minutes), or over about 90 minutes (± 10 minutes).

[192] In another aspect, the disclosure further provides a kit comprising a nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition as described herein in one or more containers. A kit may include instructions or packaging materials that describe how to administer a nucleic acid molecule, vector, host cell or virion contained within the kit to a patient. Containers of the kit can be of any suitable material, *e.g.*, glass, plastic, metal, etc., and of any suitable size, shape, or configuration. In certain embodiments, the kits may include one or more ampoules or syringes that contain a nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition in a suitable liquid or solution form.

I. Methods of Treatment

[193] The nuclear lamina, that underlies the inner nuclear membrane, is a meshwork of type V intermediate filament proteins consisting primarily of the A and B type lamins.

Mammalian somatic cells express four major and three minor types of lamins. The *LMNA* gene encodes A-type lamins, including two major isoforms, A and C, and two minor isoforms AΔ10 and C2. The B type lamins major isoforms B1 and B2 are encoded by *LMNB1* and *LMNB2*, respectively. *LMNB2* further encodes the minor isoform B3. In addition to providing mechanical strength to the nucleus, recent discoveries in nuclear-lamina associated human diseases have established that lamins contribute to at least three pathways: (a) gene expression and differentiation by contributing to subnuclear localization and epigenetic regulation of genes; (b) DNA damage repair and genome stability; and (c) regulation of transcription factors and signaling components controlling various differentiation pathways.

[194] Some 15 different diseases/anomalies, called laminopathies or nuclear envelopathies, are linked to mutations within lamins and lamin-binding proteins. More than 500 mutations have been reported within *LMNA*, which result in aberrant folding, instability, and misassembly of the lamin polypeptide, or they can affect the biochemical properties of protein domain surfaces, resulting in disturbed lamin A/C interactions. These mutations give rise to multiple disease phenotypes in four major disease types: striated muscle diseases, lipodystrophic syndromes, peripheral neuropathy, and accelerating aging disorders. These disease phenotypes range from cardiac and skeletal myopathies, lipodystrophies, peripheral neuropathies, to premature aging with early death.

[195] Dilated cardiomyopathy is a type of striated muscle disease characterized by dilation and impaired contraction of the left ventricle or both ventricles and impaired systolic function. The prevalence of dilated cardiomyopathy ranges from 1:2500 individuals to 1:250 individuals. Despite being a rare disease, dilated cardiomyopathy represents a serious health burden, often leading to arrhythmias (i.e. bradyarrhythmias and tachyarrhythmias), atrioventricular block, thromboembolism and sudden death at any stage of disease. As of 2014, 165 dilated cardiomyopathy associated mutations had been identified in the *LMNA* gene (Tesson F. *Cardiol J.* 2014;21(4):331-42). These mutations included missense/nonsense mutations, splicing mutations, small deletions, small insertions, small indel, gross deletions, or gross insertions. The majority of *LMNA* mutations leading to dilated cardiomyopathy are autosomal dominant missense mutations found throughout the gene that generate mutated lamin A/C proteins.

[196] In certain embodiments, the disclosure provides methods for treating laminopathies. Laminopathies appropriate for treatment include, but are not limited to, Charcot-Marie-Tooth disease, Emery-Dreifuss Muscular Dystrophy (EDMD), familial partial lipodystrophy, Hutchinson-Gilford Progeria syndrome (HGPS), limb-girdle muscular dystrophy, LMNA-related congenital muscular dystrophy, mandibuloacral dysplasia, arrhythmogenic right ventricular cardiomyopathy, familial atrial fibrillation, left ventricular noncompaction, dilated cardiomyopathy, Atypical Werner syndrome, Barraquer-Simons syndrome, Buschke-Ollendorff syndrome, Familial partial lipodystrophy of the Dunnigan type (FPLD), Greenberg dysplasia, leukodystrophy, limb-girdle muscular dystrophy type 1B, lipodystrophy with diabetes, hepatic steatosis, hypertrophic cardiomyopathy, and leukomelanodermic papules (LDHCP), Mandibuloacral dysplasia with type A lipodystrophy (MADA), Mandibuloacral dysplasia with type B lipodystrophy (MADB), Pelger-Huet anomaly (PHA), Pelizaeus-Merzbacher disease and Tight skin contracture syndrome.

[197] In some embodiments, the laminopathy may be a laminopathic lipodystrophy disorder, systemic laminopathy, laminopathic neurological disorder, or muscle laminopathy. By "laminopathic" lipodystrophy disorders and "laminopathic" neurological disorders is meant lipodystrophy and neurological disorders resulting from or associated with abnormal nuclear envelope morphology. Lipodystrophy disorders are characterized by abnormal distribution of adipose tissue, optionally associated with metabolic disorders such as diabetes and hypertriglyceridemia. Lipodystrophy patients often experience selective loss and/or

excessive accumulation of adipose tissue in certain regions of the body (*e.g.*, loss in the limbs accompanied by excessive deposit in the upper back). Examples of laminopathic lipodystrophy disorders include, for instance, familial partial lipodystrophy (Dunnigan type), acquired partial lipodystrophy, type A insulin resistance syndrome, generalized lipodystrophy syndrome, and familial partial lipodystrophy (Kobberling).

[198] Systemic laminopathies affect a variety of tissue types and include, *e.g.*, atypical Werner syndrome, progeria (*e.g.*, Hutchinson-Gilford progeria syndrome), restrictive dermopathy, and mandibuloacral dysplasia. The symptoms associated with systemic laminopathies are diverse. Atypical Werner syndrome patients prematurely exhibit features commonly associated with aging such as short stature, osteoporosis, thinning hair, atherosclerosis, and cataracts. Restrictive dermopathy, on the other hand, is commonly associated with skin and joint contracture, abnormal skull mineralization, and pulmonary defects. Laminopathic neurological disorders, or laminopathies with peripheral nerve involvement, also are suitable for treatment by the inventive method. Neurological laminopathies include, *e.g.*, Charcot-Marie-Tooth disease type 2B1, autosomal dominant leukodystrophy, and autosomal dominant spinal muscular dystrophy.

[199] A majority of laminopathies caused by lamin A/C mutations involve striated muscle. Emery-Dreifuss muscular dystrophy (EDMD), limb-girdle muscular dystrophy type 1B, congenital muscular dystrophy, multisystem dystrophy syndrome, dilated cardiomyopathy 1A, familial dilated cardiomyopathy, and dilated cardiomyopathy with conduction system defects are diagnosed as muscle laminopathies. Patients suffering from muscle laminopathies exhibit, for example, muscle weakness or wasting, hypertrophy of select muscles (*e.g.*, calf), muscle or tendon contractures, cardiomyopathy, impaired cardiac conduction, and mental retardation.

[200] In certain embodiments, the disclosure provides methods for treating a laminopathy in a subject comprising administering a therapeutically effective amount of any of the nucleic acid constructs, viral vectors, viral particles, host cells, and/or pharmaceutical compositions disclosed herein. In certain embodiments, the disclosure provides methods for expressing (a) a lamin A polypeptide or biologically active fragment thereof; (b) a lamin C or biologically active fragment thereof polypeptide; (c) a lamin A polypeptide or biologically active fragment thereof and a lamin C polypeptide or biologically active fragment thereof; or biologically active variants and/or fragments thereof in a subject comprising administering to

said subject a viral vector, viral particle, host cell, or pharmaceutical composition disclosed herein. In certain embodiments, the disclosure provides methods for increasing expression of (a) a functional lamin A polypeptide; (b) a functional lamin C polypeptide; (c) a functional lamin A polypeptide and a functional lamin C polypeptide; or biologically active variants and/or fragments thereof in a subject comprising administering a viral vector, viral particle, host cell, or pharmaceutical composition disclosed herein. In some embodiments, such subject has been diagnosed with or is at risk for a laminopathy, wherein the laminopathy is any one or more of: Charcot-Marie-Tooth disease, Emery-Dreifuss muscular dystrophy, familial partial lipodystrophy, Hutchinson-Gilford progeria syndrome, limb-girdle muscular dystrophy, *LMNA*-related congenital muscular dystrophy, mandibuloacral dysplasia, arrhythmogenic right ventricular cardiomyopathy, familial atrial fibrillation, left ventricular noncompaction, and dilated cardiomyopathy. In some cases, a nucleotide sequence encoding a polypeptide encoding (a) a lamin A polypeptide; (b) a lamin C polypeptide; (c) a lamin A polypeptide and a lamin C polypeptide; or biologically active variants and/or fragments thereof is delivered using a virus or a viral vector, such as AAV6 or AAV9. In some cases, the subject in need thereof has an insufficient gene expression or a mutation in any one or more of *LMNA*, *LMNB1*, and *LMNB2*.

[201] In some cases, treatment using a nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition described herein results in improved heart function, improved heart muscle contractions, increased expression of lamin A and/or lamin C, or in reduced mTOR activity. In certain embodiments, the disclosure provides a method for treating a subject with, or at risk of developing, dilated cardiomyopathy. Symptoms associated with dilated cardiomyopathy include shortness of breath, swelling in the legs, fatigue, weight gain, fainting, palpitations, dizziness, blood clots, chest pain, and/or sudden death. Furthermore, dilated cardiomyopathy arising from *LMNA* mutations results in hyperactivated mTOR signaling in the heart. Treatment with a nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition described herein can result in an improvement of one or more symptoms, such as a reduction in mTOR signaling. Administration of a therapy as described herein to a subject at risk of developing dilated cardiomyopathy can prevent the development of or slow the progression of one or more symptoms.

[202] In certain embodiments, treatment with a nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition described herein reduces mTOR signaling, by at least 1%, 2%, 3%, 4%, 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%, 35%, 36%, 37%, 38%, 39%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% as compared to an untreated control or as compared to the level before treatment.

[203] In certain embodiments, treatment with a nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition described herein increases lamin A and/or lamin C expression, by at least 1%, 2%, 3%, 4%, 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%, 35%, 36%, 37%, 38%, 39%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% as compared to an untreated control or as compared to the level before treatment.

[204] In certain embodiments, treatment with a nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition described herein is combined with one or more additional therapies selected from the group consisting of: beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARB), nifedipine inhibitors, diuretics, aldosterone antagonist, isosorbide dinitrate, hydralazine, digoxin, ivabradine, cardiac resynchronization therapy (CRT), implantable cardioverter defibrillators (ICD), surgery, heart transplant, and/or combinations thereof.

[205] In certain embodiments, methods and compositions of this disclosure can be used to treat a subject who has been diagnosed with a disease, for example, a laminopathy. In various embodiments, the laminopathy can be caused by a known genetic event (*e.g.*, any of the *LMNA* mutations known in the art) or may have an unknown cause. The subject can be a patient suffering from a muscle laminopathy. In some instances, the subject is a patient with dilated cardiomyopathy.

[206] In certain embodiments, methods and compositions of this disclosure can be used to treat a subject who is at risk of developing a disease. The subject can be known to be predisposed to a disease, for example, a laminopathy (*i.e.* dilated cardiomyopathy). The subject can be predisposed to a disease due to a genetic event, or due to known risk factors.

For example, a subject can carry a mutation in *LMNA* which is associated with dilated cardiomyopathy.

[207] In certain embodiments, treatments provided herein can result in a decrease or cessation of symptoms, *e.g.*, any of the laminopathy symptoms disclosed herein. For example, treatment can result in improved heart function, improved ECG readings, ERK1/2 downregulation, decreased mTOR signaling, and increased survival times. Measurements of heart function, ECG readings, ERK1/2 downregulation, mTOR signaling, increased survival times, and other relevant parameters can be performed in a specific disease model of a laminopathy. For instance, several mouse models of laminopathies (*e.g.* muscular dystrophy or dilated cardiomyopathy) have been developed. In particular, the H222P *LMNA* mouse model contains a point mutation (H222P) resulting in muscular dystrophy and dilated cardiomyopathy with conduction-system disease. While heterozygous mice (*LMNA*^{H222P/+}) do not show any phenotypes as neonates or adults, adult homozygous mutant mice (*LMNA*^{H222P/H222P}) develop muscular dystrophy and dilated cardiomyopathy with conduction-system disease similar to the clinical features of human laminopathies affecting striated muscles. *See, e.g.*, Arimura T, *et al. Human Molecular Genetics*, 2005;14(1):155–169. The *LMNA*^{flox/flox} mouse model displays more severe defects in a range of tissues, with skeletal muscles being the most impaired. *See, e.g.*, Kim Y, *Biochem Biophys Res Commun*. 2013;440(1):8–13. The *LMNA*^{flox/flox} mouse model has loxP sites flanking the second exon of *Lmna*, effectively creating a conditional *Lmna* knockout mouse. Germline Cre expression results in *Lmna* homozygous mutants with postnatal lethality at postnatal days 16–18. In some embodiments, the animal model is a H222P *LMNA* mutant mouse. In some embodiments, the animal model is an *LMNA*^{flox/flox} mutant mouse (*e.g.* Jackson laboratories stock number 026284). Such disease model systems can be used for discovery of specific nucleic acid constructs, viral vectors, viral particles, host cells, or pharmaceutical compositions to treat the laminopathy.

[208] In certain embodiments, a nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition described herein is administered to the subject intravenously or systemically. Other forms of administration that may be useful in the methods described herein include, but are not limited to, direct delivery to the desired organ (*e.g.*, the heart), orally, intravenously, intramuscularly, intrathecally, subcutaneously, sublingually, nasally, inhalation, nebulization, cutaneously, topically, systemically, intramyocardially,

transdermally, and other parental routes of administration. Routes of administration may be combined, if desired.

J. Examples

[209] The disclosure now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain embodiments and embodiments of the present disclosure, and are not intended to limit the disclosure.

Example 1: LMNA minigene construct 1 production of Lamin A and Lamin C

[210] HEK293T cells (Fujifilm) were seeded in 6-well plates at a density of 900,000 cells/well and incubated at 37 degrees Centigrade overnight. The next day, cells were transiently transfected with 3 micrograms of plasmid DNA encoding LMNA under the control of the chicken beta actin (CB) promoter (Minigene 1), or a GFP control. The CB regulatory element incorporates the chicken beta actin promoter and corresponds to SEQ ID NO: 102. Cells were transfected according to standard methods using Fugene transfection reagent (Promega). Two days post transfection, cells were trypsinized, centrifuged, and processed for protein analysis. Samples were prepared for Western blot analysis by lysing cells in Laemli 4x buffer with beta-mercaptoethanol (Biorad) and boiling for 5 minutes at 95 degrees Centigrade. Protein lysates were then separated by TGX gel and transferred to a nitrocellulose membrane. Membranes were blocked and washed using a standard western blot protocol, and blotted with a primary antibody overnight at 4 degrees Centigrade. Mouse anti-Lamin A/C (CST #4777, 1:1000) and mouse anti-GAPDH (GeneTex #GT239, 1:2000) were used as the primary antibodies. Anti-mouse IgG HRP (Invitrogen A16078, 1:5000) was used as a secondary antibody for chemiluminescence detection. Lamin C and Lamin A, were detected at 65 kDa and 72 kDa , respectively, while GAPDH was detected at 37 kDa.

[211] HEK293T cells transfected with a construct encoding only Lamin A or Lamin C showed production of each respective protein, as expected. HEK293T cells transfected with LMNA minigene construct 1 showed production of both Lamin A and Lamin C, indicating that the single construct was capable of generating both isoforms (FIG. 6). Minigenes 2 and 3 did not produce both Lamin isoforms under the tested conditions.

Example 2: Lamin A and Lamin C mRNA Expression

[212] HEK293T cells were grown and transiently transfected as described above. iPS cardiomyocytes (Fujifilm) were also transiently transfected. Cardiomyocytes were seeded at 500,000 cells/well in 6-well plates and incubated at 37 degrees Centigrade for two days. Two days post-transfection, cells were trypsinized, centrifuged, and processed for RNA-based analysis. RNA was extracted from cell pellets using the RNAeasy mini kit (Qiagen) following the manufacturer's instructions, and used to synthesize cDNA with SuperScript IV Reverse Transcriptase (Invitrogen). Quantitative PCR was performed using Lamin A/C, Lamin A or Lamin C-specific primer sets (Table 5), to evaluate expression levels of the respective genes.

[213] Cells transfected with a construct encoding only Lamin A or Lamin C showed mRNA transcription for each respective gene, as expected. HEK293T cells transfected with minigene construct 1, however, showed transcription of both Lamin A and Lamin C mRNA, indicating that the single construct was capable of transcribing both isoforms (FIG. 7).

TABLE 5: Primers used for quantitative PCR experiments

SEQ ID NO:	Gene	Primer	Sequence
94	Human Lamin A	Forward	GCTCTTCTGCCTCCAGTGTC
95		Reverse	ATGATGCTGCAGTTCTGGGG
96	Human Lamin C	Forward	CCTGGTGTGGAAGGCACAGAAC
97		Reverse	GGCTACCACTCACGTGGTGGTG
98	Human Lamin A/C	Forward	ACCAAGAAGGAGGGTGACCT
99		Reverse	AGCCTGTTCTCAGCATCCAC

Example 3: Minigene construct 1 production of Lamin A and Lamin C in heart and liver tissue

[214] Lamin A and Lamin C production was measured in vitro in HEK293T cells. Cells were grown, transiently transfected, and processed for Western blot analysis as described above. Lamin A and Lamin C production was also measured in vivo in 12 week old wild-type (FIG. 8, top) mice, and 24 week old mice heterozygous for the *LMNA* gene (*LMNA*^{+/−}) (FIG. 8, bottom). Both mouse strains were administered the AAV9 virus carrying minigene construct 1. Tissue samples were collected and snap-frozen post extraction and stored at -80 degree Centigrade until needed. They were then thawed, homogenized using bead

homogenizer in RIPA buffer containing protease inhibitor cocktail, and resuspended in Laemli 4x buffer with beta-mercaptoethanol (Biorad). Western blot analysis was performed as described above.

[215] HEK293T cells transfected with a construct encoding only Lamin A or Lamin C showed protein for each respective protein, as expected (FIG. 8, top). HEK293T cells transfected with minigene construct 1 showed production of both Lamin A and Lamin C, indicating that the single construct was capable of generating both isoforms (FIG. 8 top). Lamin A and Lamin C isoforms are both detected in wild-type and heterozygous $LMNA^{+/-}$ mice when dosed with AAV9 virus carrying the minigene construct 1 (FIG. 8, top and bottom). Endogenous LMNA levels are detectable in both wild-type and heterozygous $LMNA^{+/-}$ mice.

Example 4: Rescue of disease phenotype in $LMNA^{-/-}$ KO mice

[216] $LMNA^{-/-}$ KO animals were generated by mating $LMNA^{+/-}$ males and females. $LMNA^{+/-}$ x $LMNA^{+/-}$ litters underwent facial vein injections at p1. Facial vein injections were performed as generally described in Lampe et al. (*J Vis Exp.* 2014;(93):e52037). Mice were dosed with 10 microliters of AAV9 virus carrying minigene construct 1 (2E11 virus genomes per mouse), or PBS. Pups were left with their mother for three weeks to wean with no pup manipulation.

[217] $LMNA^{-/-}$ KO mice treated with PBS control survived less than 50 days (FIG. 9). However, mice dosed with AAV9 carrying minigene construct 1 survived more than 80 days, indicating that minigene construct 1 substantially mitigated the severe disease phenotype normally observed in $LMNA^{-/-}$ KO mice.

Example 5: In vivo expression of Lamin A and Lamin C isoforms in mice

[218] 12 week old C57BL/6 wild-type, male mice underwent a systemic administration of AAV9 carrying minigene construct 1, or PBS via tail vein of approximately 200 microliters. AAV9 preparations included AAV9 carrying minigene construct 1, using a ubiquitous promoter, AAV9 carrying a LMNA construct under the control of a heart-specific promoter (cTNT), or AAV9 carrying GFP under a ubiquitous promoter. A low dose of 4E11 vg/mouse or a high dose of 2E12 vg/mouse were used. All animals were processed and samples taken at six weeks post injection. Heart and liver tissue was harvested and stored using standard methods for later experimentation.

[219] Tissues were kept in RNAlater post extraction and stored at -80 degrees Centigrade until needed. They were then thawed and homogenized in RLT buffer using bead homogenizer. RNA was extracted using the RNAeasy mini kit (Qiagen) following the manufacturer's instructions. cDNA libraries were produced from RNA extracts using TRUseq cDNA library preparation kit (Illumina), and underwent NGS sequencing on a Nextseq 500 platform and analyzed.

[220] Mice dosed with AAV9 carrying minigene construct 1 (ubiquitous promoter) showed expression of Lamin A and Lamin C in both heart and liver (FIG. 10A). As expected, mice dosed with LMNA under the control of a heart-specific promoter (cTNT) showed expression of Lamin A and Lamin C in the heart, but not the liver (FIG. 10B). High doses of LMNA under the control of a ubiquitous promoter showed some liver toxicity in mice, and was separately confirmed by measurement of serum biomarkers (AST, ALT, ALP, bilirubin, creatine, etc.). Low dose animals were healthy.

Example 6: Expression of Lamin A and/or Lamin C in HEK293T Cells with CMV

Promoter

[221] HEK293T cells were incubated at 37 degrees Centigrade overnight. The next day, cells were transiently transfected with DNA encoding LMNA under the control of the CMV promoter, or a GFP control. Cells were transfected according to standard methods. Cells were cultured and later trypsinized, centrifuged, and processed for protein analysis.

[222] Samples were prepared for Western blot analysis by lysing cells and boiling at 95 degrees Centigrade. Protein lysates were then gel separated and transferred to a nitrocellulose membrane. Membranes were blocked and washed using a standard western blot protocol and blotted with primary antibody overnight at 4 degrees Centigrade. Mouse anti-Lamin A/C and mouse anti-GAPDH were used as the primary antibodies. Anti-mouse IgG HRP was used as a secondary antibody for chemiluminescence detection. Lamin C and A were detected at 65 kDa and 72 kDa, respectively, while GAPDH was detected at 37 kDa.

[223] HEK293T cells transfected with a construct encoding only Lamin A or only Lamin C showed protein for each respective protein (Figure 12). HEK293T cells transfected with an LMNA minigene construct having a Lamin A/C sequence (see the Lamin A/C sequence of minigene construct 1), indicating that the single construct was capable of generating both isoforms (Figure 12).

Example 7: Lamin A and Lamin C mRNA Expression

[224] HEK293T cells were grown and transiently transfected as described in Example 6.

Two days post transfection, cells were trypsinized, centrifuged, and processed for RNA-based analysis. RNA was extracted from cell pellets using the standard extraction, and used to synthesize cDNA with reverse transcriptase. Quantitative PCR was performed using Lamin A/C, Lamin A specific primer sets, to evaluate expression levels of the respective genes.

[225] Cells transfected with a construct encoding only Lamin A or only Lamin C showed mRNA transcription for each respective gene. HEK293T cells transfected with an LMNA minigene construct having a Lamin A/C sequence (see the Lamin A/C sequence of minigene construct 1), however, showed transcription of both Lamin A and Lamin C mRNA, indicating that the single construct was capable of transcribing both isoforms.

K. Sequences

TABLE 1: List of exemplary Lamin A and/or Lamin C nucleic acid sequences.

SEQ ID NO:	Nucleic Acid Sequence	Name
1	ATGGAGACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGG GCGCAGGCCAGCTCCACTCCGCTGTCGCCCACCCGCATCA CCCGGCTGCAGGAGAAGGAGGACCTGCAGGAGCTCAATG ATCGCTTGGCGGTCTACATCGACCGTGTGCGCTCGCTGGA AACGGAGAACGCAGGGCTGCGCCTTCGCATCACCGAGTCT GAAGAGGTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCC GCCTACGAGGCCGAGCTCGGGGATGCCCGCAAGACCCTTG ACTCAGTAGCCAAGGAGCGCGCCCGCCTGCAGCTGGAGCT GAGCAAAGTGCGTGAGGAGTTTAAGGAGCTGAAAGCGCG CAATACCAAGAAGGAGGGTGACCTGATAGCTGCTCAGGC TCGGCTGAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAG GCCGCACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGG AGGGCGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGC TTGAGGCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGG ATGAGATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGC AGACCATGAAGGAGGAACCTGGACTTCCAGAAGAACATCT ACAGTGAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGA CCCGACTGGTGGAGATTGACAATGGGAAGCAGCGTGAGT TTGAGAGCCGGCTGGCGGATGCGCTGCAGGAACTGCGGG CCCAGCATGAGGACCAGGTGGAGCAGTATAAGAAGGAGC TGGAGAAGACTTATTCTGCCAAGCTGGACAATGCCAGGCA GTCTGCTGAGAGGAACAGCAACCTGGTGGGGGCTGCCCA CGAGGAGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTC TCTGCCCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCA	Lamin A sequence

SEQ ID NO:	Nucleic Acid Sequence	Name
	AGGAGGCGAAGCTTCGAGACCTGGAGGACTCACTGGCCC GTGAGCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGG AGCGGGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGC AGCTGGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGC CCTGGACATGGAGATCCACGCCTACCGCAAGCTCTTGAG GGCGAGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCT CGCAGCGCAGCCGTGGCCGTGCTTCCTCTCACTCATCCCA GACACAGGGTGGGGGCGAGCGTCACCAAAAAGCGCAAAC GGAGTCCACTGAGAGCCGCAGCAGCTTCTCACAGCACGCA CGCACTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAG GAGGGCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAG GACCAGTCCATGGGCAATTGGCAGATCAAGCGCCAGAAT GGAGATGATCCCTTGCTGACTTACCGGTTCCCACCAAAGT TCACCCTGAAGGCTGGGCAGGTGGTGACGATCTGGGCTGC AGGAGCTGGGGCCACCCACAGCCCCCTACCGACCTGGTG TGGAAGGCACAGAACACCTGGGGCTGCGGGAACAGCCTG CGTACGGCTCTCATCAACTCCACTGGGGAAGAAGTGGCCA TGCGCAAGCTGGTGCGCTCAGTGACTGTGGTTGAGGACGA CGAGGATGAGGATGGAGATGACCTGCTCCATCACCACCAC GGCTCCCCTGTCAGCAGCTCGGGGGACCCCGCTGAGTACA ACCTGCGCTCGCGCACCGTGCTGTGCGGGACCTGCGGGCA GCCTGCCGACAAGGCATCTGCCAGCGGCTCAGGAGCCCA GGTGGGCGGACCCATCTCCTCTGGCTCTTCTGCCTCCAGTG TCACGGTCACTCGCAGCTACCGCAGTGTGGGGGGCAGTGG GGGTGGCAGCTTCGGGGACAATCTGGTCACCCGCTCCTAC CTCCTGGGCAACTCCAGCCCCGAACCCAGAGCCCCCAGA ACTGCAGCATCATGTAA	
2	ATGGAGACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGG GCGCAGGCCAGCTCCACTCCGCTGTGCCCCACCCGCATCA CCCGGCTGCAGGAGAAGGAGGACCTGCAGGAGCTCAATG ATCGCTTGGCGGTCTACATCGACCGTGTGCGCTCGCTGGA AACGGAGAACGCAGGGCTGCGCCTTCGCATCACCGAGTCT GAAGAGGTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCC GCCTACGAGGCCGAGCTCGGGGATGCCCGCAAGACCCTTG ACTCAGTAGCCAAGGAGCGCGCCCGCCTGCAGCTGGAGCT GAGCAAAGTGCGTGAGGAGTTTAAGGAGCTGAAAGCGCG CAATACCAAGAAGGAGGGTGACCTGATAGCTGCTCAGGC TCGGCTGAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAG GCCGCACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGG AGGGCGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGC TTGAGGCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGG ATGAGATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGC AGACCATGAAGGAGGAACCTGGACTTCCAGAAGAACATCT ACAGTGAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGA CCCGACTGGTGGAGATTGACAATGGGAAGCAGCGTGAGT	Lamin C sequence

SEQ ID NO:	Nucleic Acid Sequence	Name
	TTGAGAGCCGGCTGGCGGATGCGCTGCAGGAACTGCGGG CCCAGCATGAGGACCAGGTGGAGCAGTATAAGAAGGAGC TGGAGAAGACTTATTCTGCCAAGCTGGACAATGCCAGGCA GTCTGCTGAGAGGAACAGCAACCTGGTGGGGGCTGCCCA CGAGGAGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTC TCTGCCCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCA AGGAGGCGAAGCTTCGAGACCTGGAGGACTCACTGGCCC GTGAGCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGG AGCGGGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGC AGCTGGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGC CCTGGACATGGAGATCCACGCCTACCGCAAGCTCTTGAG GGCAGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCT CGCAGCGCAGCCGTGGCCGTGCTTCCTCTCACTCATCCCA GACACAGGGTGGGGGCAGCGTCACCAAAAAGCGCAAAC GGAGTCCACTGAGAGCCGCAGCAGCTTCTCACAGCACGCA CGCACTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAG GAGGGCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAG GACCAGTCCATGGGCAATTGGCAGATCAAGCGCCAGAAT GGAGATGATCCCTTGCTGACTTACCGGTTCCCACCAAAGT TCACCTGAAGGCTGGGCAGGTGGTGACGATCTGGGCTGC AGGAGCTGGGGCCACCCACAGCCCCCTACCGACCTGGTG TGGAAGGCACAGAACCTGGGGCTGCGGGAACAGCCTG CGTACGGCTCTCATCAACTCCACTGGGGAAGAAGTGGCCA TCGCAAGCTGGTGCGCTCAGTGAAGTGTGGTTGAGGACGA CGAGGATGAGGATGGAGATGACCTGCTCCATCACCACCAC GTGAGTGGTAGCCGCCGCTGA	
3	ATGGAGACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGG GCGCAGGCCAGCTCCACTCCGCTGTGCGCCACCCGCATCA CCCGGCTGCAGGAGAAGGAGGACCTGCAGGAGCTCAATG ATCGCTTGGCGGTCTACATCGACCGTGTGCGCTCGCTGGA AACGGAGAACGCAGGGCTGCGCCTTCGCATCACCGAGTCT GAAGAGGTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCC GCCTACGAGGCCGAGCTCGGGGATGCCCGCAAGACCCTTG ACTCAGTAGCCAAGGAGCGCGCCCGCCTGCAGCTGGAGCT GAGCAAAGTGCGTGAGGAGTTTAAGGAGCTGAAAGCGCG CAATACCAAGAAGGAGGGTGACCTGATAGCTGCTCAGGC TCGGCTGAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAG GCCGCACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGG AGGGCGAGCTGCATGATCTGCGGGGGCCAGGTGGCCAAGC TTGAGGCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGG ATGAGATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGC AGACCATGAAGGAGGAAGTGGACTTCCAGAAGAATCTCT ACAGTGAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGA CCCGACTGGTGGAGATTGACAATGGGAAGCAGCGTGAGT TTGAGAGCCGGCTGGCGGATGCGCTGCAGGAACTGCGGG	Lamin A/C sequence from minigene 1

SEQ ID NO:	Nucleic Acid Sequence	Name
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SEQ ID NO:	Nucleic Acid Sequence	Name
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4	ATGGAGACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGG GCGCAGGCCAGCTCCACTCCGCTGTGCGCCACCCGCATCA CCCGGCTGCAGGAGAAGGAGGACCTGCAGGAGCTCAATG ATCGCTTGGCGGTCTACATCGACCGTGTGCGCTCGCTGGA AACGGAGAACGCAGGGCTGCGCCTTCGCATCACCGAGTCT GAAGAGGTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCC GCCTACGAGGCCGAGCTCGGGGATGCCCGCAAGACCCTTG ACTCAGTAGCCAAGGAGCGCGCCCGCCTGCAGCTGGAGCT GAGCAAAGTGCGTGAGGAGTTTAAGGAGCTGAAAGCGCG CAATACCAAGAAGGAGGGTGACCTGATAGCTGCTCAGGC TCGGCTGAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAG GCCGCACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGG AGGGCGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGC TTGAGGCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGG ATGAGATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGC AGACCATGAAGGAGGAAGTGGACTTCCAGAAGAACATCT ACAGTGAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGA CCCGACTGGTGGAGATTGACAATGGGAAGCAGCGTGAGT TTGAGAGCCGGCTGGCGGATGCGCTGCAGGAAGTGCAGG CCCAGCATGAGGACCAGGTGGAGCAGTATAAGAAGGAGC	Lamin A/C sequence from minigene 2

SEQ ID NO:	Nucleic Acid Sequence	Name
	TGGAGAAGACTTATTCTGCCAAGCTGGACAATGCCAGGCA GTCTGCTGAGAGGAACAGCAACCTGGTGGGGGCTGCCCA CGAGGAGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTC TCTGCCCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCA AGGAGGGCGAAGCTTCGAGACCTGGAGGACTCACTGGCCC GTGAGCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGG AGCGGGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGC AGCTGGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGC CCTGGACATGGAGATCCACGCCTACCGCAAGCTCTTGAG GGCGAGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCT CGCAGCGCAGCCGTGGCCGTGCTTCCTCTCACTCATCCCA GACACAGGGTGGGGGCAGCGTCACCAAAAAGCGCAAAT GGAGTCCACTGAGAGCCGCAGCAGCTTCTCACAGCACGCA CGCACTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAG GAGGGCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAG GACCAGTCCATGGGCAATTGGCAGATCAAGCGCCAGAAT GGAGATGATCCCTTGCTGACTTACCGGTTCCCAACAAAGT TCACCCTGAAGGCTGGGCAGGTGGTGACGATCTGGGCTGC AGGAGCTGGGGCCACCCACAGCCCCCTACCGACCTGGTG TGGAAGGCACAGAACACCTGGGGCTGCGGGAACAGCCTG CGTACGGCTCTCATCAACTCCACTGGGGAAGTAAGTAGGC CTGGGCCTGGCTGCTTGCTGGACGAGGCTCCCCCTGATGG CCAACATCGGAGCCAGCTGCCCCCAACCCAAGTTTGCCAA TTCAGGGCCCCTTTCTAGAGCTCTCTGTTGCAGGCTCCAGA CTTCTCCACCCAGTAGGCAAACCAAAAAGATGCTTCCTCAA CAGCACAAGGGGTGGAAGTTAGACAGTGAGGATTGTAA AGGCAGAGCCATACTCCTACCCGGAGAGCTTGACAGTGTC CCTCTGGGGTGGAAATGAGTTCCTTAGCTCCATCACCACA GAGGACAGAGTAAGCAGCAGGCCGGACAAAGGGCAGGCC ACAAGAAAAGTTGCAGGTGGTCACTGGGGTAGACATGCT GTACAACCCTTCCCTGGCCCTGACCCTTGGACCTGGTTCCA TGTCCCCACCAGGAAGTGGCCATGCGCAAGCTGGTGCCT CAGTGAAGTGTGGTTGAGGACGACGAGGATGAGGATGGAG ATGACCTGCTCCATCACCACCACGTGAGTGGTAGCCGCCG CTGAGGCCGAGCCTGCACTGGGGCCACCCAGCCAGGCCTG GGGGCAGCCTCTCCCCAGCCTCCCCGTGCCAAAATCTTT TCATTAAAGAATGTTTTGGAACCTTACTCGCTGGCCTGGCC TTTCTTCTCTCCTCCCTATACCTTGAACAGGGAACCCAG GTGTCTGGGTGCCCTACTCTGGTAAGGAAGGGAGTGGGAA CTTTCTGATGCCATGGAATATTCCTGTGGGAGCAGTGGAC AAGGGTCTGGATTTGTCTTCTGGGAAAGGGAGGGGAGGA CAGACGTGGGGCATGCCCGCCCTGCCTCTCTCCCCATTCT TGTTGCATGCATATCCTCTCATTTCCTCATTTTCCTGCA AGAATGTTCTCTCTCATTCTGACCGCCCCCTCCACTCCAAT TAATAGTGCATGCCTGCTGCCCTACAAGCTTGCTCCCGTTC TCTCTTCTTTTCTCTTAAGCTCAGAGTAGCTAGAACAGAG	

SEQ ID NO:	Nucleic Acid Sequence	Name
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5	ATGGAGACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGG GCGCAGGCCAGCTCCACTCCGCTGTGCGCCACCCGCATCA CCCGGCTGCAGGAGAAGGAGGACCTGCAGGAGCTCAATG ATCGCTTGGCGGTCTACATCGACCGTGTGCGCTCGCTGGA AACGGAGAACGCAGGGCTGCGCCTTCGCATCACCGAGTCT GAAGAGGTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCC GCCTACGAGGCCGAGCTCGGGGATGCCCGCAAGACCCTTG ACTCAGTAGCCAAGGAGCGCGCCCGCCTGCAGCTGGAGCT GAGCAAAGTGCGTGAGGAGTTTAAGGAGCTGAAAGCGCG CAATACCAAGAAGGAGGGTGACCTGATAGCTGCTCAGGC TCGGCTGAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAG GCCGCACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGG AGGGCGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGC TTGAGGCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGG ATGAGATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGC AGACCATGAAGGAGGAACCTGGACTTCCAGAAGAACATCT ACAGTGAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGA CCCGACTGGTGGAGATTGACAATGGGAAGCAGCGTGAGT TTGAGAGCCGGCTGGCGGATGCGCTGCAGGAACTGCGGG CCCAGCATGAGGACCAGGTGGAGCAGTATAAGAAGGAGC TGGAGAAGACTTATTCTGCCAAGCTGGACAATGCCAGGCA GTCTGCTGAGAGGAACAGCAACCTGGTGGGGGCTGCCCA CGAGGAGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTC TCTGCCCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCA AGGAGGCGAAGCTTCGAGACCTGGAGGACTCACTGGCCC GTGAGCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGG AGCGGGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGC AGCTGGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGC CCTGGACATGGAGATCCACGCCTACCGCAAGCTCTTGAG GGCAGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCT CGCAGCGCAGCCGTGGCCGTGCTTCCCTCTCACTCATCCCA	Lamin A/C sequence from minigene 3

SEQ ID NO:	Nucleic Acid Sequence	Name
	GACACAGGGTGGGGGCAGCGTCACCAAAAAGCGCAAAC GGAGTCCACTGAGAGCCGCAGCAGCTTCTCACAGCACGCA CGCACTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAG GAGGGCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAG GACCAGTCCATGGGCAATTGGCAGATCAAGCGCCAGAAT GGAGATGATCCCTTGCTGACTTACCGGTTCCCACCAAAGT TCACCCTGAAGGCTGGGCAGGTGGTGACGATCTGGGCTGC AGGAGCTGGGGCCACCCACAGCCCCCTACCGACCTGGTG TGGAAGGCACAGAACACCTGGGGCTGCGGGAACAGCCTG CGTACGGCTCTCATCAACTCCACTGGGGAAGAAGTGGCCA TGCGCAAGCTGGTGCGCTCAGTGAAGTGTGGTTGAGGACGA CGAGGATGAGGATGGAGATGACCTGCTCCATCACCACCAC GTGAGTGGTAGCCGCCGCTGAGGCCGAGCCTGCACTGGG GCCACCCAGCCAGGCCTGGGGGCAGCCTCTCCCCAGCCTC CCCGTGCCAAAAATCTTTTCATTAAAGAATGTTTTGGAAC TTTACTCGCTGGCCTGGCCTTTCTTCTCTCTCCTCCCTATAC CTTGAACAGGGAACCCAGGTGTCTGGGTGCCCTACTCTGG TAAGGAAGGGAGTGGGAACCTTTCTGATGCCATGGAATATT CCTGTGGGAGCAGTGGACAAGGGTCTGGATTTGTCTTCTG GGAAAGGGAGGGGAGGACAGACGTGGGGCATGCCCGCCC TGCTCTCTCCCCATTCTTGTTCATGCATATCCTCTCATT TCCCTCATTTTTCTGCAAGAATGTTCTCTCTCATTCTGA CCGCCCCCTCCACTCCAATTAATAGTGCATGCCTGCTGCCCT ACAAGCTTGCTCCCGTTCTCTCTTCTTTTCTCTTAAGCTC AGAGTAGCTAGAACAGAGTCAGAGTCACTGCTCTGGTTCT CTGTCCCCAAGTCTTCCTGAGCCTTCTCCCCTTTTATGTCTT CCCTCTCCTCCTCCGGGCCCCCTAGCCTCCCAAACCCCCATT GCCCCGTGGCTCCTTGGGCACAGAACACACCTTCCTGCC TGGCGGCTGGGAGCCTGCAGGAGCCTGGAGCCTGGTTGG GCCTGAGTGGTCAGTCCCAGACTCGCCGTCCCGCCTGAGC CTTGTCTCCCTTCCCAGGGCTCCCACTGCAGCAGCTCGGG GGACCCCGCTGAGTACAACCTGCGCTCGCGCACCGTGCTG TGCGGGACCTGCGGGCAGCCTGCCGACAAGGCATCTGCCA GCGGCTCAGGAGCCCAGGTGGGCGGACCCATCTCCTCTGG CTCTTCTGCCTCCAGTGTACGGTCACTCGCAGCTACCGCA GTGTGGGGGGCAGTGGGGGTGGCAGCTTCGGGGACAATC TGGTCACCCGCTCCTACCTCCTGGGCAACTCCAGCCCCCG AACCCAGAGCCCCCAGAACTGCAGCATCATG	
6	GTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCTCAAGTCTCCACCCATTGA CGTCAATGGGAGTTTGTCTTGGCACCAAAATCAACGGGAC TTTCCAAAATGTCGTAACAACCTCCGCCCCATTGACGCAAA TGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCA GAGCTGGTACCGTGTGTATGCTCAGGGGCTGGGAAAGGA GGGGAGGGAGCTCCGGCTCAGGAATTCGCCACCATGGAG	Lamin A construct

SEQ ID NO:	Nucleic Acid Sequence	Name
	ACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGGGCGCAG GCCAGCTCCACTCCGCTGTCGCCCACCCGCATCACCCGGC TGCAGGAGAAGGAGGACCTGCAGGAGCTCAATGATCGCT TGGCGGTCTACATCGACCGTGTGCGCTCGCTGGAAACGGA GAACGCAGGGCTGCGCCTTCGCATCACCGAGTCTGAAGAG GTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCCGCTACG AGGCCGAGCTCGGGGATGCCCCGAAGACCCTTGACTCAGT AGCCAAGGAGCGCGCCCGCCTGCAGCTGGAGCTGAGCAA AGTGCCTGAGGAGTTTAAGGAGCTGAAAGCGCGCAATAC CAAGAAGGAGGGTGACCTGATAGCTGCTCAGGCTCGGCT GAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAGGCCGC ACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGGAGGG CGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGCTTGAG GCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGGATGAG ATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGCAGACC ATGAAGGAGGAACTGGACTTCCAGAAGAACATCTACAGT GAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGACCCGA CTGGTGGAGATTGACAATGGGAAGCAGCGTGAGTTTGAG AGCCGGCTGGCGGATGCGCTGCAGGAACTGCGGGGCCAG CATGAGGACCAGGTGGAGCAGTATAAGAAGGAGCTGGAG AAGACTTATTCTGCCAAGCTGGACAATGCCAGGCAGTCTG CTGAGAGGAACAGCAACCTGGTGGGGGCTGCCCACGAGG AGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTCTCTGC CCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCAAGGA GCGGAAGCTTCGAGACCTGGAGGACTCACTGGCCCGTGA GCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGGAGCG GGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGCAGCT GGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGCCCTG GACATGGAGATCCACGCCTACCGCAAGCTCTTGAGGGCG AGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCTCGCA GCGCAGCCGTGGCCGTGCTTCCTCTCACTCATCCAGACA CAGGGTGGGGGCAGCGTCACCAAAAAGCGCAAACCTGGAG TCCACTGAGAGCCGCAGCAGCTTCTCACAGCACGCACGCA CTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAGGAGG GCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAGGACCA GTCCATGGGCAATTGGCAGATCAAGCGCCAGAATGGAGA TGATCCCTTGCTGACTTACCGGTTCCCAACAAAGTTCACCC TGAAGGCTGGGCAGGTGGTGACGATCTGGGCTGCAGGAG CTGGGGCCACCCACAGCCCCCTACCGACCTGGTGTGGAA GGCACAGAACACCTGGGGCTGCGGGAACAGCCTGCGTAC GGCTCTCATCAACTCCACTGGGGAAGAAGTGGCCATGCGC AAGCTGGTGCGCTCAGTGAAGTGTGGTTGAGGACGACGAG GATGAGGATGGAGATGACCTGCTCCATCACCACCACGGCT CCCACTGCAGCAGCTCGGGGGACCCCGCTGAGTACAACCT GCGCTCGCGCACCGTGCTGTGCGGGACCTGCGGGCAGCCT GCCGACAAGGCATCTGCCAGCGGCTCAGGAGCCCAGGTG	

SEQ ID NO:	Nucleic Acid Sequence	Name
	GGCGGACCCATCTCCTCTGGCTCTTCTGCCTCCAGTGTCAC GGTCACTCGCAGCTACCGCAGTGTGGGGGGCAGTGGGGG TGGCAGCTTCGGGGACAATCTGGTCACCCGCTCCTACCTC CTGGGCAACTCCAGCCCCCGAAGCCAGAGCCCCCAGAACT GCAGCATCATGTAACTAGTAATAAAAGATCTTTATTTTC ATTAGATCTGTGTGTTGGTTTTTTGTGTG	
7	GTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCTCAAGTCTCCACCCCATTTGA CGTCAATGGGAGTTTGTGTTTTGGCACCAAAATCAACGGGAC TTTCCAAAATGTCTGTAACAACTCCGCCCCATTGACGCAAA TGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCA GAGCTGGTACCGTGTGTATGCTCAGGGGCTGGGAAAGGA GGGGAGGGAGCTCCGGCTCAGGAATTGCGCCACCATGGAG ACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGGGCGCAG GCCAGCTCCACTCCGCTGTCTGCCCCACCCGCATCACCCGGC TGCAGGAGAAGGAGGACCTGCAGGAGCTCAATGATCGCT TGGCGGTCTACATCGACCGTGTGCGCTCGCTGGAAACGGA GAACGCAGGGCTGCGCCTTCGCATCACCGAGTCTGAAGAG GTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCCGCCTACG AGGCCGAGCTCGGGGATGCCCCGAAGACCCTTGACTCAGT AGCCAAGGAGCGCGCCCCGCTGCAGCTGGAGCTGAGCAA AGTGCCTGAGGAGTTTAAGGAGCTGAAAGCGCGCAATAC CAAGAAGGAGGGTGACCTGATAGCTGCTCAGGCTCGGCT GAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAGGCCGC ACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGGAGGG CGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGCTTGAG GCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGGATGAG ATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGCAGACC ATGAAGGAGGAACTGGACTTCCAGAAGAACATCTACAGT GAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGACCCGA CTGGTGGAGATTGACAATGGGAAGCAGCGTGAGTTTGAG AGCCGGCTGGCGGATGCGCTGCAGGAACTGCGGGGCCAG CATGAGGACCAGGTGGAGCAGTATAAGAAGGAGCTGGAG AAGACTTATTCTGCCAAGCTGGACAATGCCAGGCAGTCTG CTGAGAGGAACAGCAACCTGGTGGGGGCTGCCACGAGG AGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTCTCTGC CCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCAAGGA GGCGAAGCTTCGAGACCTGGAGGACTCACTGGCCCGTGA GCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGGAGCG GGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGCAGCT GGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGCCCTG GACATGGAGATCCACGCCTACCGCAAGCTCTTGGAGGGCG AGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCTCGCA GCGCAGCCGTGGCCGTGCTTCCTCTCACTCATCCAGACA CAGGGTGGGGGCAGCGTCACCAAAAAGCGCAAACTGGAG	Lamin C construct

SEQ ID NO:	Nucleic Acid Sequence	Name
	TCCACTGAGAGCCGCGCAGCAGCTTCTCACAGCACGCACGCA CTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAGGAGG GCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAGGACCA GTCCATGGGCAATTGGCAGATCAAGCGCCAGAATGGAGA TGATCCCTTGCTGACTTACCGGTTCCCACCAAAGTTCACCC TGAAGGCTGGGCAGGTGGTGACGATCTGGGCTGCAGGAG CTGGGGCCACCCACAGCCCCCTACCGACCTGGTGTGGAA GGCACAGAACACCTGGGGCTGCGGGAACAGCCTGCGTAC GGCTCTCATCAACTCCACTGGGGAAGAAGTGGCCATGCGC AAGCTGGTGCGCTCAGTGACTGTGGTTGAGGACGACGAG GATGAGGATGGAGATGACCTGCTCCATCACCACCACGTGA GTGGTAGCCGCCGCTGAACTAGTAATAAAAGATCTTTATT TTCATTAGATCTGTGTGTTGGTTTTTTGTGTG	
8	GTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCOAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTGTTTGGCACCAAAATCAACGGGAC TTTCCAAAATGTCGTAACAACCTCCGCCCCATTGACGCAAA TGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCA GAGCTGGTACCGTGTGTATGCTCAGGGGCTGGGAAAGGA GGGGAGGGAGCTCCGGCTCAGGAATTCGCCACCATGGAG ACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGGGCGCAG GCCAGCTCCACTCCGCTGTGCGCCACCCGCATCACCCGGC TGCAGGAGAAGGAGGACCTGCAGGAGCTCAATGATCGCT TGGCGGTCTACATCGACCGTGTGCGCTCGCTGGAAACGGA GAACGCAGGGCTGCGCCTTCGCATCACCGAGTCTGAAGAG GTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCCGCCTACG AGGCCGAGCTCGGGGATGCCCGCAAGACCCTTGACTCAGT AGCCAAGGAGCGCGCCCGCTGCAGCTGGAGCTGAGCAA AGTGCGTGAGGAGTTTAAGGAGCTGAAAGCGCGCAATAC CAAGAAGGAGGGTGACCTGATAGCTGCTCAGGCTCGGCT GAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAGGCCGC ACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGGAGGG CGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGCTTGAG GCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGGATGAG ATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGCAGACC ATGAAGGAGGAACTGGACTTCCAGAAGAACATCTACAGT GAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGACCCGA CTGGTGGAGATTGACAATGGGAAGCAGCGTGAGTTTGAG AGCCGGCTGGCGGATGCGCTGCAGGAACTGCGGGGCCAG CATGAGGACCAGGTGGAGCAGTATAAGAAGGAGCTGGAG AAGACTTATTCTGCCAAGCTGGACAATGCCAGGCAGTCTG CTGAGAGGAACAGCAACCTGGTGGGGGCTGCCACGAGG AGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTCTCTGC CCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCAAGGA GGCGAAGCTTCGAGACCTGGAGGACTCACTGGCCCGTGA	Minigene 1 construct

SEQ ID NO:	Nucleic Acid Sequence	Name
	GCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGGAGCG GGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGCAGCT GGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGCCCTG GACATGGAGATCCACGCCTACCGCAAGCTCTTGGAGGGCG AGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCTCGCA GCGCAGCCGTGGCCGTGCTTCTCTCACTCATCCAGACA CAGGGTGGGGGCAGCGTCACCAAAAAGCGCAAACCTGGAG TCCACTGAGAGCCGCAGCAGCTTCTCACAGCACGCACGCA CTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAGGAGG GCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAGGACCA GTCCATGGGCAATTGGCAGATCAAGCGCCAGAATGGAGA TGATCCCTTGCTGACTTACCGGTTCCCACCAAAGTTCACCC TGAAGGCTGGGCAGGTGGTGACGGTGAGTGGCAGGGCGC TTGGGACTCTGGGGAGGCCTTGGGTGGCGATGGGAGCGCT GGGGTAAGTGTCTTTTCTCTCTCCAGATCTGGGCTGCAG GAGCTGGGGCCACCCACAGCCCCCTACCGACCTGGTGTG GAAGGCACAGAACACCTGGGGCTGCGGGAACAGCCTGCG TACGGCTCTCATCAACTCCACTGGGGAAGTAAGTAGGCCT GGGCCTGGCTGCTTGCTGGACGAGGCTCCCCCTGATGGCC AACATCGGAGCCAGCTGCCCCCAACCCAAGTTTGCCAATT CAGGGCCCCCTTCTAGAGCTCTCTGTTGCAGGCTCCAGAC TTCTCCACCCAGTAGGCAAACCAAAAGATGCTTCTCAAC AGCACAAGGGGTGGAAGTTAGACAGTGAGGATTGTAAA GGCAGAGCCATACTCCTACCCGGAGAGCTTGACAGTGTCC CTCTGGGGTGGAATGAGTTCCTTAGCTCCATCACACAG AGGACAGAGTAAGCAGCAGGCCGGACAAAGGGCAGGCCA CAAGAAAAGTTGCAGGTGGTCACTGGGGTAGACATGCTGT ACAACCCTTCCCTGGCCCTGACCCTTGGACCTGGTTCCATG TCCCCACCAGGAAGTGGCCATGCGCAAGCTGGTGCGCTCA GTGACTGTGGTTGAGGACGACGAGGATGAGGATGGAGAT GACCTGCTCCATCACACCACGTGAGTGGTAGCCGCCGCT GAGGCCGAGCCTGCACTGGGGCCACCCAGCCAGGCCTGG GGGCAGCCTCTCCCCAGCCTCCCCGTGCCAAAAATCTTTT CATTAAAGAATGTTTTGGAACTTTACTCGCTGGCCTGGCCT TTCTTCTCTCTCCTCCCTATACCTTGAACAGGGAACCCAGG TGTCTGGGTGCCCTACTCTGGTAAGGAAGGGAGTGGGAAC TTTCTGATGCCATGGAATATTCCTGTGGGAGCAGTGGACA AGGGTCTGGATTTGTCTTCTGGGAAAGGGAGGGGAGGAC AGACGTGGGGCATGCCCGCCCTGCCTCTCTCCCCATTCTT GTTGCATGCATATCCTCTCATTTCCCTCATTTTTCTGCAA GAATGTTCTCTCTCATTCCTGACCGCCCCTCCACTCCAATT AATAGTGCATGCCTGCTGCCCTACAAGCTTGCTCCCGTTCT CTCTTCTTTTCTCTTAAGCTCAGAGTAGCTAGAACAGAGT CAGAGTCACTGCTCTGGTTCTCTGTCCCCAAGTCTTCCTGA GCCTTCTCCCCTTTTATGTCTTCCCTCTCCTCCTCCGGGCC CTAGCCTCCCAAACCCCCATTGCCCGCTGGCTCCTTGGGC	

SEQ ID NO:	Nucleic Acid Sequence	Name
	ACAGAACCACACCTTCCTGCCTGGCGGCTGGGAGCCTGCA GGAGCCTGGAGCCTGGTTGGGCCTGAGTGGTCAGTCCCAG ACTCGCCGTCCCGCCTGAGCCTTGTCTCCCTTCCCAGGGCT CCCACTGCAGCAGCTCGGGGGACCCCGCTGAGTACAACCT GCGCTCGCGCACCGTGCTGTGCGGGACCTGCGGGCAGCCT GCCGACAAGGCATCTGCCAGCGGCTCAGGAGCCCAGGTG GGCGGACCCATCTCCTCTGGCTCTTCTGCCTCCAGTGTCAC GGTCACTCGCAGCTACCGCAGTGTGGGGGGCAGTGGGGG TGGCAGCTTCGGGGACAATCTGGTCACCCGCTCCTACCTC CTGGGCAACTCCAGCCCCCGAACCCAGGTGAGTTGTCTCT GCTTTGTCTCCAAATCCTGCAGGCGGGTCCCTGGTCATCG AGGGGTAGGACGAGGTGGCCTTGCAGGGGGGAGAGCCTG CCTTCTCTTCCGCAGCCCGGGGGAGTGGGAGCCTCCTCCC CACAGCCTGAGTCCTAGACAGCCACCTCTGCATCCTGCC CCTCTTGTCTGAGCCCCAGACTGGAGGGCAGGGGCAGGGC TGGAGTGTGAGGGATGGGGGAGATGCTACCTCCCTTCTAG GGGCCAGGGGAGGGAGGGTCTGGGTCCAGGCCCTGCTGC TCACACCTCTCTCCTCTGTTTTCTCTCTTAGAGCCCCCAGA ACTGCAGCATCATGTAACTAGTAATAAAAGATCTTTATT TTCATTAGATCTGTGTGTTGGTTTTTTGTGTG	
9	GTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCAAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTGTTTTGGCACCAAAATCAACGGGAC TTTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAA TGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCA GAGCTGGTACCGTGTGTATGCTCAGGGGCTGGGAAAGGA GGGGAGGGAGCTCCGGCTCAGGAATTCGCCACCATGGAG ACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGGGCGCAG GCCAGCTCCACTCCGCTGTGCGCCACCCGCATCACCCGGC TGCAGGAGAAGGAGGACCTGCAGGAGCTCAATGATCGCT TGGCGGTCTACATCGACCGTGTGCGCTCGCTGGAAACGGA GAACGCAGGGCTGCGCCTTCGCATCACCGAGTCTGAAGAG GTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCCGCCTACG AGGCCGAGCTCGGGGATGCCCCGAAGACCCTTGACTCAGT AGCCAAGGAGCGCGCCCGCTGCAGCTGGAGCTGAGCAA AGTGCCTGAGGAGTTTAAGGAGCTGAAAGCGCGCAATAC CAAGAAGGAGGGTGACCTGATAGCTGCTCAGGCTCGGCT GAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAGGCCGC ACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGGAGGG CGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGCTTGAG GCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGGATGAG ATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGCAGACC ATGAAGGAGGAACTGGACTTCCAGAAGAACATCTACAGT GAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGACCCGA CTGGTGGAGATTGACAATGGGAAGCAGCGTGAGTTTGAG	Minigene 2 construct

SEQ ID NO:	Nucleic Acid Sequence	Name
	AGCCGGCTGGCGGATGCGCTGCAGGAAGTGCGGGCCCAG CATGAGGACCAGGTGGAGCAGTATAAGAAGGAGCTGGAG AAGACTTATTCTGCCAAGCTGGACAATGCCAGGCAGTCTG CTGAGAGGAACAGCAACCTGGTGGGGGCTGCCCACGAGG AGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTCTCTGC CCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCAAGGA GGCGAAGCTTCGAGACCTGGAGGACTCACTGGCCCGTGA GCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGGAGCG GGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGCAGCT GGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGCCCTG GACATGGAGATCCACGCCTACCGCAAGCTCTTGGAGGGCG AGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCTCGCA GCGCAGCCGTGGCCGTGCTTCCTCTCACTCATCCAGACA CAGGGTGGGGGCAGCGTCACCAAAAAGCGCAAAGTGGAG TCCACTGAGAGCCGCAGCAGCTTCTCACAGCACGCACGCA CTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAGGAGG GCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAGGACCA GTCCATGGGCAATTGGCAGATCAAGCGCCAGAATGGAGA TGATCCCTTGCTGACTTACCGGTTCCCAACAAAGTTCACCC TGAAGGCTGGGCAGGTGGTGACGATCTGGGCTGCAGGAG CTGGGGCCACCCACAGCCCCCTACCGACCTGGTGTGGAA GGCACAGAACACCTGGGGCTGCGGGAACAGCCTGCGTAC GGCTCTCATCAACTCCACTGGGGAAGTAAGTAGGCCTGGG CCTGGCTGCTTGCTGGACGAGGCTCCCCCTGATGGCCAAC ATCGGAGCCAGCTGCCCCCAACCAAGTTTGCCAATTGAG GGCCCCTTTCTAGAGCTCTCTGTTGCAGGCTCCAGACTTCT CCACCCAGTAGGCAAACCAAAAGATGCTTCCTCAACAGCA CAAGGGGTGGAAGTTAGACAGTGAGGATTGTTAAAGGCA GAGCCATACTCCTACCCGGAGAGCTTGACAGTGTCCCTCT GGGGTGGAATGAGTTCCTTAGCTCCATCACCACAGAGGA CAGAGTAAGCAGCAGGCCGGACAAAGGGCAGGCCACAAG AAAAGTTGCAGGTGGTCACTGGGGTAGACATGCTGTACAA CCCTTCCCTGGCCCTGACCCTTGACCTGGTTCCATGTCCC CACCAGGAAGTGGCCATGCGCAAGCTGGTGCCTCAGTG ACTGTGGTTGAGGACGACGAGGATGAGGATGGAGATGAC CTGCTCCATCACCACCACGTGAGTGGTAGCCGCCGCTGAG GCCGAGCCTGCACTGGGGCCACCCAGCCAGGCCTGGGGG CAGCCTCTCCCCAGCCTCCCCGTGCCAAAAATCTTTTCATT AAAGAATGTTTTGGAACTTTACTCGCTGGCCTGGCCTTTCT TCTCTCTCCTCCCTATACCTTGAACAGGGAACCCAGGTGTC TGGGTGCCCTACTCTGGTAAGGAAGGGAGTGGGAACCTTC TGATGCCATGGAATATTCCTGTGGGAGCAGTGGACAAGGG TCTGGATTTGTCTTCTGGGAAAGGGAGGGGAGGACAGAC GTGGGGCATGCCCGCCCTGCCTCTCTCCCCATTCTTGTG CATGCATATCCTCTCATTTCCCTCATTTTCTCTGCAAGAAT GTTCTCTCTCATTCCTGACCGCCCCTCCACTCCAATTAATA	

SEQ ID NO:	Nucleic Acid Sequence	Name
	GTGCATGCCTGCTGCCCTACAAGCTTGCTCCCGTTCTCTCT TCTTTTCTCTTAAGCTCAGAGTAGCTAGAACAGAGTCAG AGTCACTGCTCTGGTTCTCTGTCCCCAAGTCTTCCTGAGCC TTCTCCCCTTTTATGTCTTCCCTCTCCTCCTCCGGGCCCTA GCCTCCCAAACCCCCATTGCCCGCTGGCTCCTTGGGCACA GAACCACACCTTCCTGCCTGGCGGCTGGGAGCCTGCAGGA GCCTGGAGCCTGGTTGGGCCTGAGTGGTCAGTCCCAGACT CGCCGTCCCGCCTGAGCCTTGTCTCCCTTCCCAGGGCTCCC ACTGCAGCAGCTCGGGGGACCCCGCTGAGTACAACCTGCG CTCGCGCACCGTGCTGTGCGGGACCTGCGGGCAGCCTGCC GACAAGGCATCTGCCAGCGGCTCAGGAGCCCAGGTGGGC GGACCCATCTCCTCTGGCTCTTCTGCCTCCAGTGTACGGT CACTCGCAGCTACCGCAGTGTGGGGGGCAGTGGGGGTGG CAGCTTCGGGGACAATCTGGTCACCCGCTCCTACCTCCTG GGCAACTCCAGCCCCCGAAGCCAGAGCCCCCAGAACTGC AGCATCATGTAACTAGTAATAAAAGATCTTTATTTTCATT AGATCTGTGTGTTGGTTTTTTGTGTG	
10	GTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCTCAAGTCTCCACCCCATTTGA CGTCAATGGGAGTTTGTCTTGGCACCAAAATCAACGGGAC TTTCCTCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAA TGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCA GAGCTGGTACCGTGTGTATGCTCAGGGGCTGGGAAAGGA GGGGAGGGAGCTCCGGCTCAGGAATTCGCCACCATGGAG ACCCCGTCCCAGCGGCGCGCCACCCGCAGCGGGGCGCAG GCCAGCTCCACTCCGCTGTGCGCCACCCGCATCACCCGGC TGCAGGAGAAGGAGGACCTGCAGGAGCTCAATGATCGCT TGGCGGTCTACATCGACCGTGTGCGCTCGCTGGAAACGGA GAACGCAGGGCTGCGCCTTCGCATCACCGAGTCTGAAGAG GTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCCGCTACG AGGCCGAGCTCGGGGATGCCCGCAAGACCCTTGACTCAGT AGCCAAGGAGCGCGCCCGCTGCAGCTGGAGCTGAGCAA AGTGCGTGAGGAGTTTAAGGAGCTGAAAGCGCGCAATAC CAAGAAGGAGGGTGACCTGATAGCTGCTCAGGCTCGGCT GAAGGACCTGGAGGCTCTGCTGAACTCCAAGGAGGCCGC ACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGGAGGG CGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAGCTTGAG GCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAGGATGAG ATGCTGCGGCGGGTGGATGCTGAGAACAGGCTGCAGACC ATGAAGGAGGAACTGGACTTCCAGAAGAACATCTACAGT GAGGAGCTGCGTGAGACCAAGCGCCGTCATGAGACCCGA CTGGTGGAGATTGACAATGGGAAGCAGCGTGAGTTTGAG AGCCGGCTGGCGGATGCGCTGCAGGAACTGCGGGGCCAG CATGAGGACCAGGTGGAGCAGTATAAGAAGGAGCTGGAG AAGACTTATTCTGCCAAGCTGGACAATGCCAGGCAGTCTG	Minigene 3 construct

SEQ ID NO:	Nucleic Acid Sequence	Name
	CTGAGAGGAACAGCAACCTGGTGGGGGCTGCCCACGAGG AGCTGCAGCAGTCGCGCATCCGCATCGACAGCCTCTCTGC CCAGCTCAGCCAGCTCCAGAAGCAGCTGGCAGCCAAGGA GGCGAAGCTTCGAGACCTGGAGGACTCACTGGCCCGTGA GCGGGACACCAGCCGGCGGCTGCTGGCGGAAAAGGAGCG GGAGATGGCCGAGATGCGGGCAAGGATGCAGCAGCAGCT GGACGAGTACCAGGAGCTTCTGGACATCAAGCTGGCCCTG GACATGGAGATCCACGCCTACCGCAAGCTCTTGGAGGGCG AGGAGGAGAGGCTACGCCTGTCCCCCAGCCCTACCTCGCA GCGCAGCCGTGGCCGTGCTTCCTCTCACTCATCCAGACA CAGGGTGGGGGCAGCGTCACCAAAAAGCGCAAAGTGGAG TCCACTGAGAGCCGCAGCAGCTTCTCACAGCACGCACGCA CTAGCGGGCGCGTGGCCGTGGAGGAGGTGGATGAGGAGG GCAAGTTTGTCCGGCTGCGCAACAAGTCCAATGAGGACCA GTCCATGGGCAATTGGCAGATCAAGCGCCAGAATGGAGA TGATCCCTTGCTGACTTACCGGTTCCCAACAAAGTTCACCC TGAAGGCTGGGCAGGTGGTGACGATCTGGGCTGCAGGAG CTGGGGCCACCCACAGCCCCCTACCGACCTGGTGTGGAA GGCACAGAACACCTGGGGCTGCGGGAACAGCCTGCGTAC GGCTCTCATCAACTCCACTGGGGAAGAAGTGGCCATGCGC AAGCTGGTGCGCTCAGTGAAGTGTGGTTGAGGACGACGAG GATGAGGATGGAGATGACCTGCTCCATCACCACCAGTGA GTGGTAGCCGCCGCTGAGGCCGAGCCTGCACTGGGGCCAC CCAGCCAGGCCTGGGGGCAGCCTCTCCCCAGCCTCCCCGT GCCAAAAATCTTTTCATTAAAGAATGTTTTGGAAGTTTACT CGCTGGCCTGGCCTTTCTTCTCTCTCCTCCCTATACCTTGA ACAGGGAACCCAGGTGTCTGGGTGCCCTACTCTGGTAAGG AAGGGAGTGGGAAGTTTCTGATGCCATGGAATATTCCTGT GGGAGCAGTGGACAAGGGTCTGGATTTGTCTTCTGGGAAA GGGAGGGGAGGACAGACGTGGGGCATGCCCCGCCCTGCCT CTCTCCCCCATTCTTGTGTCATGCATATCCTCTCATTTCCCT CATTTTTCTGCAAGAATGTTCTCTCTCATTCTGACCGCC CCTCCACTCCAATTAATAGTGCATGCCTGCTGCCCTACAA GCTTGCTCCCGTTCTCTCTTTCTTTCTCTTAAGCTCAGAGT AGCTAGAACAGAGTCAGAGTCACTGCTCTGGTTCTCTGTC CCCAAGTCTTCCTGAGCCTTCTCCCCCTTTATGTCTTCCCTC TCCTCCTCCGGGCCCCTAGCCTCCCAAACCCCCATTGCCCG CTGGCTCCTTGGGCACAGAACCACACCTTCCTGCCTGGCG GCTGGGAGCCTGCAGGAGCCTGGAGCCTGGTTGGGCCTGA GTGGTCACTCCAGACTCGCCGTCCCGCCTGAGCCTTGTC TCCCTTCCCAGGGCTCCCACTGCAGCAGCTCGGGGGACCC CGCTGAGTACAACCTGCGCTCGCGCACCGTGCTGTGCGGG ACCTGCGGGCAGCCTGCCGACAAGGCATCTGCCAGCGGCT CAGGAGCCCAGGTGGGCGGACCCATCTCCTCTGGCTCTTC TGCTTCCAGTGTACGGTCACTCGCAGCTACCGCAGTGTG GGGGGCAGTGGGGGTGGCAGCTTCGGGGACAATCTGGTC	

SEQ ID NO:	Nucleic Acid Sequence	Name
	ACCCGCTCCTACCTCCTGGGCAACTCCAGCCCCCGAACCC AGAGCCCCCAGAACTGCAGCATCATGTAACTAGTAATAA AAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTTTTTGT GTG	
11	AATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTT TTTGTGTG	Polyadeny lation signal sequence
70	GTGAGTTCGCCCAGGTGGCTGCGTGCCTGGCGGGGAGTGG AGAGGGCGGCGGGCCGGCGCCCCCTGGCCGGCCGCAGGAA GGGAGTGAGAGGGCCTGGAGGCCGATAACTTTGCCATAG TCTCCTCCCTCCCCGGAAGTCCCCCAGCGGGTGACTGGC AGTGTCAAGGGGAATTGTCAAGACAGGACAGAGAGGGAA GTGGTGGTCTCTGGGAGAGGGTCGGGGAGGATATAAGGA ATGGTGGGGGTATCAGGGACAAGTTGGGGCTGGGGCCGG CCTGAATTTCGGTCAGATTGGGATTTGCCAACTATTTGGAG CCGGGGGGAGGGGCTTGAGCAAAACAGAACTAGCCCTGC CAGCTCGAAGAACTCTGGGCACCCAGGACACATCGGAGT GGCAGAAAGGGTCCTGTTAGAACTTTGTTAGCGGGCTTGG CACTGTGCTAGCTTTGCCCAAGCTGGCTCTGAACACATGA TGCCCATAAGACATAACTCTCAAGTTGGCATCTGTCCAG CGTGTTGGAGCGAGGTCAGGAAGGCAGGGCAATCCCCCTT TTCCCTCCCAAGGGCTTGCGGGTGGCCCCCCTCAGCATG ACCTTGTCCTGGGTTCTAAGGGTTGGGAAGTTCTCCCTCAC TCTGCCACTCTGCGTGTCTGGGACCTTCCTTGGGCTCTGAC AGGCCACCAAAAGAGCTCCGGGAGATGAGAGATCGGCT CCCCCGCAGCTCCCACAGCCCTTGGCCTGCTTGGCCCAGG AATGCAAGGGAGGGAGGGAGGCAGAGGGCAGAGGCTCCC AGCTCAGGAAGTTGTGTTATGCCAGGTCTGGCCGCACTC CTCCCTTGGCCCTCTGCCTAGTGTCTTCGAGGGTTGGGGG ACTGTCCTTCCCTCCTTGGGGTGAGCCACTTTTCAATTTCCC AGCGGGGGCCAGGCAGTCTTTGCTCGGGCCCATCCTCTTAG CTGCTGACGTTTTGATCTTTGTCTTATTGAAGTGCTGGAAT ACAGTGACATTTTTGAAATCCAGCCGTTGGAAGATTCAGG CCACTCCCCTTTACCCACCCCTGCCCCACCCTACCCACC CTACTCAACTGCACCTTCTTCTTTTCTAAAAAAGCCTTTGG GAGCTTGGAAGTATAGGCCCTCTCTTCCAGCCCCATCAAA ATTTGTTTCCCTTCTTCCCTGCCTTCCCTTTCTCTATGCAGAC CCAGGCCAAGAGCACTAAGGGTGCTTGGAGATCCGTA GGGCTGTTGGCTTTGACTTCTTCTCTCTTTTATCATCTAC TCCAACTTCTGCTCTTCCCTAGAACCTTTGCTAGGTGTGG TTTTGTTGCCCAGGCTGGAGTGCAATGGCACAATCTCGGC TCACTGCAACCTCCGCCTCCAGGTTCAAGTGATTCTCCTG CCTCAGCCTCCCGAATAGCTGAGATTACAGGCATGTGCCA CCATGCCGGGCTAATTTTGTATTCTAGTAGAGATGGGGT	Intron 1 of lamin A and lamin C

SEQ ID NO:	Nucleic Acid Sequence	Name
	TTCTCCATGTTTCGTCAGGCTAGTCTTGAACCTCCCAACCTCA GGTGATCCACCCGCCTCAGCCTCCCAAAGTGCTAGGATTA CAGGCATGAGCCACCACGCTGGGCCCATCACCCCTTCTTTC TGAAGAGTCAATGGAAGTTGTGTGTAGGAAGACAGGCTT AACGGTTTTTTTTTTGAGACAGGGTCTTACTCTGTCACCCAG ACTGGAGTGAAGTGGTGCATCTTGGCTCACCACAACCTC TGCCTCCCAGGCTCAAAAGATTCTCCTGCCTCAGCCTCCTG AGTAGCTGGGATTATAAGTGTGTGCCACCACACATGGCTA TTTTTTTTTTTTTTTTTTTTTTAATTTTATAGTAGAGATGGG GTTTCACCATGTTGGCTAGGCTGGTCTCAAACCTCCTGACTT CAAATGATCCACCTGCCTCGGCCTCCCAAAGTGCTGGGAT TACAGGTGTGAGCTACCATGCCCGGCCATCAACCTTTATT TTGTTTTTTTTGAGACGGAGTCTTGCTTTGTTGCCCAGGCTG GAGTACAGTAGTGTGACCTCAGGTCCTGCAACCTCTGCC TCCCAGGTTCAAGCCATGCTCCTGCCTCAGCCTCCCAAGT AGCTGGGACTATAGGTGCCTGCCACCACGCCCGGCTACTT TTTATATTTTTTAGTAGAGACGGGGTTTCACCATGTTGGCCA GGGTGATCTCGAACTCCTGACCTCAAGTGATCTGCCTGCC TCAGCCTCCCAAAGTGTTGGGATTAGAGACGGGAGCCACT GCGCCTGGCTTCTTTTTTTCTTGAGATAGGGTTTCACTCTG TTACCCAGGCTGGAGTGCAGTGGCAAGGTCATGGCTCACT GCAGCCTCTACCTCTCTGGCTCAAGCCATCCTCCCGCCTCA GCCTCCTGAGTAGCTGGGACCACAGGCAGGCACCACCACC CACAGCTAATGTTTTTGTATTATTTTGTAGAGATGGGGTTT TGCCATGTTGCCACAGTCTTGAACCTCCTGGGTTCATTCTG CTGAAAGAGACCACACCTGTCCTTTTCTTTATTTTTATTAT ATTTTTTCAGAGACAGGGCCTTGCCCTGTTGCTCAGGCTAG AGTGCAATGGTACAATCATAACTTGCTGCAGCCTGGAAC CCTCCTGGGCTCAAGCGATCCTACCGTCTCACCTTCCGGA ATAGCTGAGACTAAGGGCAGGCACCACCACGCTTGGCTA ATTTTTTTTTTTTTTTTTTTTTTTTTGCTTTTTGTTTGTAAG ATGGAACTTGCTATGTTGCTCAGCTGGTTCCGAAGTTTTG GCCTCAAGCAATCCTCCTGCCTCGGCCTCCGGAAGCACTG GGATTACAGGCATAAGCCACCAGGCCTGACGCCAGGCCT GTCTTTTTTCTACTAGTGATATGAACAATTTAGTTAGCAAG ACAGATAGGAAGCAAGGAAGGGGAGACCCAGAGAATTTCG TTGCATTCTAACTAGTCCACTCATCTACCAAAGCCCTGTG AAGGACATTTTTAGCAGTTTTAGCAGTTTTCTGGTCAAAA CTTTGATCGAGAAACAGATTGAGTGGATTTCGATATTCTCT TGCTCACCCAGCCACGCCAGTTTGTCTCCTCTGCCTCCTAG TGCAGCTGTCCAGGCCTGGGACACCAGGCGGGTATGTGCG CATGTGGGGCAGGGCGGAGGTGGTGTGTGTACTTGTTATA TTAGCCACCTCCCTCTGTTCTCCCCCACTGATCCTGGCTG GAAAGGCTGGGCTTCCGGAAGAGAGGTGGATTTGCAC ACCTGGATCCCAAGCTGATAGAAAGTGGGGTGAAGACAA AGGGGACTCAGACTGGGGTGTCTGTCTCTTCTATGCCCA	

SEQ ID NO:	Nucleic Acid Sequence	Name
	CAGTAGGAGGAGCCAGGATTGGTTACTCCCTGCTGGGTCT GCTGTGCTCAGAGTGAGGTAGAGAAGTGGGTAGAGTAAA GAATTTGGGAGAGGAAAAAAGGCATTTTCCCAACCCCTCC CACCAAAGCCTAGAGAGAAGGTGTTGTCTGGTTTAATGTT TAATTAGAGCTCAGAGTTCAGGGCCAGATTTGGAGTTGGG ATGGAAAGTTGTTTTTAAGACCCTGTAGCAATTTTTGACCC AGCCTGGGTACCTCAACCACACTCAGGAGTTTGGGGGACC TTCTGTTGGGCTGGATTATAGGCTCCAAGAAGAAACCCCT TTCGCCAATACTCTCTCTCTCTTTCTTTTTTGAGACAGGGT CTTGTTCTGTTGCCCAGGCTGGGGTGCAGTGGCATGATCA CAGCTCACTGCAACGTCAGCCTCACAGGCTCTGGTGATTC TCCCACCTCAGCCTCCTGAGTAGCTGGGATTACAAGTGTG TGCCACCATGCCCAGCTAATTTTTTTTTTCTTTTTTTTTTT TGAGACGGAGTCTTGTTCTGTTGCCAGGCTGGAGTGCAGT GGTGCGATCTCGGCTCATTGCAACCTCCACCTCCCAGGTT CAAGCGATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGGAC TACAGGCACATGCCATCACGCCAGTTAATTTTTGTATTTT TAGTAGAGTTGGGGTTTCACCATGTTGGCCAGGATGGTCT TGATCTCTTGACCTCGTGATCCGTCCACCTTGGCCTCCCAA AGTGCTGGGATTACAGGTGTGAGCCACCGTACCCGGCCAC TAATTTTTATATATTTTGTAGAGATGGGGTTTCACCGTGTT GCCCAAGCTGGTCTCGAACTCCTAGGCTCAAGTAATCCAC CTGCCTTGGCCTTGGCCTCCCAAAGTGCTGGGATGTATAG GCATGAGCTACCGCACCTGGTACCCCTGCCCTTCTCTGT CTCTTTCTAGTCTGTAGCCCAAGGGATTTGGATACCCAAG TGCAGGCAGAATGGGAAGGTTGTAAGCACCAGGGAAGCC TGTCTGGAGTCCAGGCTTGCAGCTGGGCCCCACCCCAGGC AAGGCAGCTGGGTGGATGACTCAGATGCTGCCCCCTCCC TCCCACCCTGGTGGCTTTACAGAAGACAGCAGGAGACAG GGTGGAGACAGCAGTTGTCTTAAAGGGAGGAGTGGTGGT CTGAATGTCTACCTCTTCTGCCCCCTCCCCATTGCATCCT GGAGTCCCTTGCCTGGCTCCTTCCTGAGACCCTCTGGTGGT GTCTGGACACATAGCTCTCTCTGGACAGGTAACATGCACA AGTAATTAGAATCCAGAGTTGAGTTCAGAGTTATGGATTG GGCTGCAGGATAGTGCCAGGGTCTGTGCCTTCCCATGTGA AACTGATGGAGGAAGGCTGAGTCAGAAGTGGGGAGATCC GAGGCCCAAAAGCAGAAGCGCTACTTCCACTCCAAAAA GGCCCTGGTGCTTGACAACTTCCTGGATTGCCCACTGTTGC AGCCCCAGTGTGGACAGGCAGGGAGATGCAGGCTCCAGT TCATGTAGGCTCTGATCAAGACAAGAACAGCAAAGGCCA CAGAGGCACAGATGCTTGTCCCATGTCACACAATAAAGGG GTCAGCACTTGATCACAGGCCTTATGACTTCCAGCTGGGT GTGCTCTTACCATTAAAGCCTCACTTCTCTAGCTTGGGGGAC AGGTTGGAGGGAGGATCTAGAGGGTGAGGTAAGGTGAAG TCAGGTAGCTGAGGCTCACTTCTGCAGCCTGGAACTCTG CTCTGGGGCCAGTGACACCTTAGTGCTCTATGGCCATACT	

SEQ ID NO:	Nucleic Acid Sequence	Name
	TCGTGGCTCATGCCTGTAATCCCAGTGCTTTGGGAGGCTA AGGCAGGAGGATCACTTGAGGCCAGGAGTTTGAGACCAG TCTGGGCAACATAGCAAGACCCCTTCTGTACAAAAAAT TAGCCGGTCAACACCTGTAGTCCAGCTGCTTGGGAAGCTG AGGCGGGAGGATCACCTGAAGCCAGGAGTTTGAGGCTAT TGTGAGCTATGACTGCACTACTGCACTCTAGCCTGGGAGA GAGAAAGACCCTGTCTCTGAAAAAGAAAAAACAAAACA AAACTCTGCTGTCCTGCAGGGCCTGTTAGCATATGATCGA TAGCCTTTGCTCCAGCCTATACCTGGACCCAGGACCCCTG CCAGCCCCCTCAATCGTGAGACGGTCAGAGCTCTGGGAGGC TGGTGATTCTTGTCTTGAGACTATCTTGAGACTTGTATGG GAATTGTCCACCCGGATTGAAAGGAAGCTGTGCCTTTTGG CAGACCCATTAGGTTAATGGGGTTGGAGACCTTTGAGGAT GCATGGGGCCCTGGGCTTTATCTGAGGGTATCTCCTGGTGT ACCTCTCCAACCCTCCACCACCAAATCCATTCTTTTTTTTT TTTTTTTTTTTTTTTTTGACAGTCTCGCTCCCTGGCCCAGGCT GGAGTGCAGTGGCATGATCTTGGCTTACTGCAATCTCCAC CTCCCAGGCTCAAGTGATCCTCCCACCTCAGCCTCCCAAG AAGCTGGGACTATAGGCACGTGCCACATGCTCGGCTAATT TTTCTATTTTTAGTAGAGACCAGGTTTCACCATGTTACTCA GGCTGGTCTTGAAGTCTGGGGCTTAAGCAGTCCACCCACC TTGACCTCCCAAAGTGCTGAGAGCCACTGAGCCTAGCCCA AATCCACGTTCTGATTCAAAGGGAAAGAAGAAGGGTGCA GCTAAACCTGGGGGGTGAGAAGTACTTAAAAAGCCCAAG AGAAACAAAAGAGAGAATAATTCCTCACTAGGACCCCT ATTGCCTTCCCCTATTGGTGCCCTTGCTTGGCACTTCCCC TGGCCTCCAGGAGTCTGAGACTTACTCTTCCATGGATGTG CCCATTTGCCCCCACTTCCAGGTCCACCCCCCAGTGATTCG GTAGCTTAGTGTCTGCGCTGAAGCCCAGGACAGCTGGATG GACAACTGGTAGATCCCTTCACCTACCAACTGTGCTTTCTG CTCCCCCTCCCCCTTGCTTCCCTCCTCCCCAGCCCCCTCGCCA CCCCTAGCAGCTGCAGCAGCCAAGACCAAGTCTTCAGAGA CCCAGACACAAGGGCAGGGTTTATTCCATTCTCACCTCCT TGGGGTCCCAGTGTACTGATAGGCCGAAGTCTAATATTAT AGGAGATCTCTGGAAGATTGCAGGGTCTCTTATCCCTCAA TAAGGGGCAAGGCAAGCCGGGCGCAGTGGCTCACGCCTG TAATCCCAGCACTTTGAGAAGCCGAGGGGAACAGATCACT TCAGGTCAGGAGTTAAGAGACCAGCCTGGCCAACATGGT GAAACCCTGTCTCTACTAAAAATAAAAAATTAACCAGAA ATCGCTTGAACCCAGGAGGCAGATGTTGCAGTGAGCCGA GATCACGCCACTGCACTCCAGCCAGGGCGACAGAGCAAG ATTCCGTCTCAAAAAAATAATACTAATAATAATAATAA ATAAGGGGCAAGGTAGTCCACCAACAAAATGACAGGCAG TGTGATATAGTGGACACCCTAGCCCTCGGTGCCCTTAGTT CTGTGTGTGGCCCTTTCATAAATTGCTGTGTGACCTTGAG CAAATCGCCTCCCCTTTCTGGCTTTCCTTAGCTGTAAAAGA	

SEQ ID NO:	Nucleic Acid Sequence	Name
	AAGGGATTGGAGCGGAAAGTCTCCAGAGACCTTTTAGGTT CCAAAGTAGTACAGTGACCCACAAAGTGAGAAAACAGTC TTCTAAAATACCAAGTTATTAATAGTAAAATCAAATATAA ATAATGTGAATATAGTTAATAGCTAATGTTGTTCTCAATA GAAATGTTTCCCACAAGCTGTGGAATTAAACATACTACCA CATTTCTCTATTTCCCCGTGAAAGTTTGTTAGAAATGGTTA AATTGTGACATTACCCTCTTGGCAAATGTTTTGTTTTTCATT GCTACTAGGAAAGGGCAACTCGTTTTTCGATGCCTCTCCCT TCTGGACGGTGGAAAGGGCTGTGTCATAGAGTAGGAACG GGAGATGCGGCACAGGAATGGCTCCCATTGACCCGGGTTG GGGGCTAGGGCGAAGGCCTAGGAGAGGCAGAACTGTTAC CTTAGAGCTGGCCAGGATTAGAGAACAGTGCCTGGAACC GGGGGGAGGGGCACGGTGACCTTGGGCTGCCCACCTTCTA CCCTTCCAGCACCCATACTGGCTCCCCCAACCTGCGGCTG GGCTGGGAGGAGGTCTTGGCCCCTACCAATCCCTTAAGGA AGGGGAAAGAGTTTGGGAAGGGGAGTCCTCCCTTCACCCC TGCTTCCCCCAAGTTGTGAGAGAGGAAGCCGGAATCCTGC CTGCTGAAGCCAGGAATAATTCTGGCTGAGATCCCAGGCC CGGCAGGGGCGCTGAGTCATGGTAGAGGGCAGAGTGGAG AGTGGACAGGAGACCCTAAGCTTGTCCAGTCAGAAAAGC AGAGGCTGAGGGGTGGCCTTTTCTTGAGAACTACATTCAA GTTGCAGCAAGAAGGACAGTGGTCTGAATTTGACGGGGA CAAATGGAAGGGAGATAGGACACATGAGTTCCTTTAGGTC TGGCTCAGGGGAGCTAGACTTCATTTCAAGGGGTCTAGGT TCTGGGCAGTTGAGAAGGAGGCTATTTGGGGTCACCAAGG CTCCCCTTTCTTCCCAAAGCTCTAACACTGCCACCTTCTGC TGGCTAGGAGAGAGCTGTGTCTTCTGAGGCTAGAGCTGGA ATGCAGTGAGACCAGACTGCCTAGGTCCTCCCTCACTTCT TCTCCTGACCTTGGGGTGTGGCTCCCACTCTCTCCCAGTGT CCTCAGGGTTAATAACTATGTGCCACCAGATAGAGAGTTA AGGGGCTGCTGAATTGGCTTCTTGTGAAGGGAATCCCCTA AATGTCCCTCGTTTTTGGTCACTGGCCTCCCTCCCGCCCCCT TCAGGACATTCTACTATCTTCTTAGGCCATCCCTCCCTCCT CCAGGCACTACTTCTTTTGCTCTATCCCCAAGCCCCACCCC TGCATTTTTTGTGACAACACCGGAATGATTTCTAGAGAGAG AGGCCAGGAAGAAGGAAAGTGGCACTTGGCAGGAGACCT TGCAGGGGGGCGGCTGGTGAGGAAGCCAGCCGCCATTGT CCAGGACCCCAGTGCCCTGGCCTCCGGCCTCAGGCTTCTC CTGCCTCTGTACAATGCCACGTTGATACGCCCAGCAGCTG TGA CTCAGGCCTGGCCCCCTGCCAGGCCCAGCACTTCTAC TGGAGTTGCGTCTGAACATGTCAACAGGCTTCCTATCCCT CTCTCAGCACCAAGTTCTCCCCACTTCAGCCCCCTCCCTCTGC CTGGAATTAAAACCTGGCTTTGTCTTAGGGAAGGACAGCT GGGAGCCTAGTGGCTCTGGTAGGGGATCTGAGAGGCCTCA GACCCTAGGCATATTTGGCTGTTTGGCAGGTGTCACGCCC AAGGGAAGCGTGTGGAAGCAGAGCCATGCCTGCTGTGGG	

SEQ ID NO:	Nucleic Acid Sequence	Name
	TGCACATGCCCCGCGTGAGGGAGTCGGGGTGTTTCATCCTG GGGCACCTGTGGGCTTTTGAGGTGTATGATATTCAGAACT TCACAGGTTGGGGTTTGGGGAAGGCTCAAGGGGCTTCTAA GTCCCTGGAACAGCTGCCCCCTCAGTTCCTCTCTCTCTCT CTCTTTTTTTTTGAGATGGAGTCTCGCTCTGTTGCCAGGC TAGAATGCAGTGGCGCGATCTTGGCTCACTGCAAACCTCCG CCTCCTGGGTTCAAGTGATTCTCCTGCCTCAGCCTCCCAAG TAGCTGGGACTATAGGTGCCCGCCACCATGCCTGGCTAAT TTTTGTATTTTAGTAGAAATGGGGTTTCACCATGCTGGCC AGGATGGTCTCAAACCTCCTGACCTCGTGATCCACCCACCT TGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACTG CGCCAGCCTCAGTTCCTCTCTTTAAGGTCTCCTTTCCAGA GAGGGATAGCACCTCAAATGCCAGGGAGGGGAATTCTCC ACATCCTGCCCTTACCCGAGTTGTGGCAGACCCACAGACT AGCCAAGAAACCAAGCAGTGGTTACTTTGCCGGGTGGGG GGGAGGTAGGGGCTATCAAACCTCATGATTGGCCGCACAC AAAGGTGTGAGTATGTGTATATTTGAGGGTGGGTGGGAGT GGCACTTTCACTAGGCCTCCGTATCACTCTCTGACTGGGGT ATCTCCAGCAAGCGAGACAGAGGCAGACACGCTTCCCA GACTGTCTTACTGGGTCTCTCTGTGTTATTCTCTGCAGTGT CTGTGTGTATCGTGCCATTTTCTATGTTTTGCACCAATCTG CTGTGAGTGTCTCAGGTGACCTGGGGGCAGGTTTTTAGT GCCTGAGCCTACCCGTCTCCAGGCTTTAGTTTCCCCCTGTA AAAGTATAGGAGTTGGTTCAAGAGAAGGTTCTCTAGAAG CCTTGAGCCTGTGAACCGTCTAGTCTCCGGGTATTTGTGG GACACACAGAAAAAGCCCCACGACCCAACAGGTAGAACA CTGGCTGAAATCAGCAGGGCAGAGCTGAGACAGGCTCAA GTAGGCTGAGGGGTAGGGAGGTTTTGGGTGAATGGGAGG GAGGGACAGAGAGAAGGAGGATATATTGCAGTAGGAGGA GTTGCTGGAACAAAAGGAGGGGTGGTAGGAGTGGCTTGG GGTGGCAGCAGAAGACGCCCTGTCACATGGCGGGAAGTC AGCCTGGGCAGAGGTCTAGGTGTCCAGGAGGGGCTGGGT GTGGTGGCTCACGCCTGTAATCCCAGGACTTTGGGAGGCT GATGCAGGAGGATCACGTGAGGTCAGGAGTTCAAGACCA GCCTGGCCAACATGGCGAAACCCTATCTCTACTAAAAATG CCAAAAATTAGCTGGGTGTGGTGGCAGGCGCCTGTAATCC CAGCTACTCTGGAGGCTGAGGCACAAGAATTGCTTGAACC TGGGAGGTGGAGGTTGCAGGGAGCCGAGATCGCGCCACT CTACTCTAGCCTGGGCAACACAGTGAGACTCTGTCTCAA AATAATAATAATAGGGGCTGGGCGCGGTGGCTCATGACTG TAATCCCAGCATTTTGGGAGGTGGAGGCGGGTGGATCACC TGAGGTCAGGAGTCCGAGACCAGCCTGGCCAACATGGCA AACTCCGTCTCTACTAAAAATAGAAAAATTAGCTAGGCA TGGTGGTGCAGGCCTGTAATCCAGCTACTCGGGAGGCTGA GAAGCAGGAGAATCACTTGAACCTGGGAGGTGAAGTTG CAGTGAGATCACCTGGGCGACAGAATGAGACTCCACCTCA	

SEQ ID NO:	Nucleic Acid Sequence	Name
	AAATAATAATAATAGTAATAATAATAAATGAAAAATTTTA AAATTAAACAATTAAAAATTTTAAATTAAAAATTAAACAAA TTAGATGCCCAGGAGGATACAGGAGAGCATTGTCACCA GGCGGACTCCCTGTACCCACCCGGCCACAGGGGGCGATGT TCCTGGGAGACAGGAAATGCCCAGGGGCTGGGAGACCCT CTGCTCTTCTGCTCCCTTCCTGTGTGCTGCCTGGCAATGGG GAACTCTGAGGGCTGGTGAGCAGGGCTGCTGAGGAGTGG GTCTAAGGAGTCCCTGCAGGGCTGGGCCAGCTCCTCCACC TCCCCTTTGTCTTCCCCCTCCCACTTGTTATTTTAGCTACAG TGTCTGTCCCTCTTGCTTCTCCCCCAGATTGGGAGAGGAA ACGGAGGCCTCTCCCTCCGGGCCTAGCCTGTTGCCCCCAG CAACCGGGCCCAAACAGGCCTGTGGCCGGCCCTGGCTTCC ATATCTGGCATCAGAGTTGGGCTGAGCAGGGTGACTCAGA GGGTGGGTCAGCGCCTGGCCCGGTGCCACCTAGCCCCTT TGCTGTGCTGGTGCTTTCTTCCCCAAACAGCCCCAAGGG CCCGGGCCTGCTGCAGCTGGGGAGCCGGACTTCCTTGTC CACCAGGCACAGCTCTTCAGACCCCTGCCTTGGGTCACAT TTGCAAGTGCCAACCTCTCATTTCTACCTTATTCTTTTCTCT CTGTTCCCCTCCCCACCCCTCTCTTCCCTCTTTCTGAGATC AGATTTGCCAGTGATGGGAAGAGTTAGAAACAGGATGCC CAGCCCTTCTCGCCTCAAGAGGCCACTGGGATGCAGCCAC TCCTGTGCTTGGGGAACCTGGAGGATGCAAGGGAAAGGA CTGGCACTCTGCTGGCACAGCACCCGGCCTGGGGCAGGAC ACGGGCGAAGCCAGGGTCTCCCCTGTGAGCACTAGAGGA TTTCCCGACCCCTGCCCCGGGTATTGTGTGCCTGAGCATGA GTCACCTGAGGGGGCCAGGTTCCCAACCCTTCCAGCTCCT CTGGCCTGCCCCACCCTGTCTCCCTGCCAACCAGCACG GGGACGGCACTCAGCGTGTGCTCAGCTTTCCTGATGCCAA CCCCAGTGGAGTGGGCTGCACCACCACCCTGGGACCGAA TGCCTGGCTAGGGTCTACTTTGGTCCCTGCTAGGTCTGAG GACCCCTCCTAGGAAGGAAATGGCACTTGGGGGCGGGGG CAGGGAGGAGGGAGGAGAGACACTGGGCTCTACTGTACC CCTAGTCATCTCTTGGGGTGTGCGTGTGGCTCCCTGGCCAC AGAGCTCCCAAGGTCTGAGTCATGAGCCCATGGGTGATAG TGGCTTCTTCCCCGCAGATGGGAGCTCCCCGTGCCTAAGA AAACCACAAAGGTTCTTCCTCACTTCCCTCTCTGCTCGTGG TTTTTCTCATCTGCAGGGTGTGTCTTAGTCCTTTAATCTCCT CTCTTTGCAGTGCTAGTCAAAACCTCCACCAGGGAAAGAC AAATAACCCCTTACTGTTTTTTTTTTTTTTTTTTTTTTTTT TGAGATGGAGTCTCGCTCTGTACCCATGCTGTAGTGCAG TGGCACAATCTCGGCTCACTGCAACCTCCGCCTCCCAAGT TCAAGTGATCCTCCTACCTCAGCCTCCTCAGTAGCTGGGA CTACAGGTGCACACCACCGTACCCAGCTAAATTTTTTTTTT TTTTTTTTTGAGATAGAGTCTCACTCTGTCACCCAGGCTGGA GTACAGTGGTACAATCTCAACTCACTACAATCTCCGCCTC CCAGGCTCAAGCAATTCTCGTGTCTCAGCCTCCCAAGTTG	

SEQ ID NO:	Nucleic Acid Sequence	Name
	CTGGGACTATGGACGTGCACCACCTTGCCCGACTAATTTT TGTATTTTTGATAGAGTCAGAGTTTCACCATGTTGGCAGG CTGGTCTCGAACTCCTGGCCTCAAGTGATCCACCTGCCTTG GCCTCCCAAAGTGCTGGGATTACAGGTGTGAGCCACCACA CTCAGCCAGCCCCCTTACTTTCTTGGAGACCATATACTGT GGCTTGTGCCAAAGTGGTACAGCATGGATTTCCAGCTCCC CTATCTACTTGCTGCGGGACCCTAGATATAGCTTTCTGTGC CTATTTCTCAATTGCATAGGAATAGCACCTATCGCATAG GGTAGCTGTGAAGATGACGTGAGTTAACATAATATTTAGA GCAGTGCTTGGTACCTAATAAGCTCTATATAAGTGTTTGCT ATTATATTATTATTATCACTGCCACCACCGCTTTTGCAAGC AGCAGAAGGTGAAGAGGTTAGACTGAAGAAAAAACTTCT GTGCTCATCAGCCCATAAGCTCGCAGAGCACAGGGATCAT GCATCTATGTTTTCTCAGTCAGTGTCTGCCAGGCACTGGC AAGGAAAGGCTGTTACCAGGGGGAACTCCAGGAATTCT CCTGGCACCTAAGGAGGCTGGGGAGACAGGACTAGGGAA AAGGTGCCCTTGAGACACCTTCTGAAATCATCCCATTGCC TTCCAGCTTCTTTCAGCTCAGGCTGGCTGGTCAGGGAAAC GCTTTGTGCCATAGTGTCTGCCCTCTTCTCCTCCTGGCTT CTCCATTCTCTCTGGAACCTTGTTGGCTTAGGAAAGCAGTGA GGTGGAGGAGGAGGAACCCTAGATCAGCAGCTAGAATTG ACTGGAATGCTGCTGCTGGCTTTCGGTAATTGACACTGGG CCATTACCTTCCTCCTTTGCACCTCAGTTTCCTCATCTAT AAAAGGGAGAGGGTTGAGCTGAATCAACTCTAAGCTCCTT CTAGTTCTCTAAATTCTGAGAGCCTCCTAGTACAGCCAGC AGCAGCCATTAGCCTTCAGGGTAGAGAGGCCTCTTCTGGG AAGCCCCAGCCAGCCTGGGGGTCAGCCCAAGGAGCTCGG AATCTAAGTTGCCCCAGTTGCTTCACTTTACCAGCGGTTTT TCTTCATTTTCCCTCCTCCCCCTGCAGCTGCTTCAGCTTCG GAAAAGTTCTGAAGTCATGGAAAGTTGGGGCTGTGCTCCC AGCCAGGGGCTAGGCCGGATGGCAGCCAAAACCTGAGCT GGGTTTTGACTTTATTTTTAGCTTTTCTGACTGAGACAGAG GAGGGAATACATTCTCCGTTCTGGAAGGGGCTCTTTTTT GCAGGAGACAGACACTTACATTAAACAACCTGTTCTGAGG TGTGGCCAGAGGCCTGGACTGAGCAAGTGTGCAGGCTGG GGGAGCTTCCTCTGGCTTCTCATGTCCTTCCCCTGCCCTC TGAGTGTCACTCTATCCTCCTCCCTGCCTGGTGGGGGGAG GTGGGGGTGACTCCTTTTTTTGGACTCTCCTAAGCAGAAC CTGCCTGGGTCTCGTCCTCCAGAGCTTCTGCAAATCTAGCC TTCCCTATCCCTCTTCACAGTGAATTGCTGGGCCTCTTGA GTTTAGGACTTTTGTGGTAGAAGAAAAATGTTGGCAGGGC TGCTTTTCTCCTTTCCAGGATAGATTTTCTTCTGCCAC GCTTGGTTTTCTTTTTTCCATCTGCTGTGGTGGGCTCATG CTTAAGCACTGATGAGTTACAGATGGCAGCTGGAACCAGG TCCTCTGGATCTTCCCTCCGCTCCCTGGGTCTGCTGCTTT CTCTCACCTATATTTGTGAAGCAATTGTAACATCTAGAA	

SEQ ID NO:	Nucleic Acid Sequence	Name
	AGTTCTTGGGTTCTCTGGAGGTTTTTAAGAAAATAGGACC TTTCTATTTCTCCAGTCCACTAGCAAAAATAATCAGGGGC CCAGAAAAGGTGAGGGAGGTGGCAGAGGCAGCGCTGTTC GACTGGTTATAGCTAAAGCTTTACCCACTTTGAGGAGCAG GGAGGCTTAAAGCTGGGGCCCAGATGGACCTGGAGGCCT GGGATCCACATCTGGAACCAGATGCTGAGGCTATGGTAGA TGGGTAGGGCTCAGCCTTCTCCCAGGGCACGGATGAGGCA GGAGGGAGGGAGGCAGGGACCCCTCTGTTCAGTGCAGAT CAGGGCACCCAGACTGGGTCTTGAGAAAGGAAAGGGTCA ATATTGTGCCTGGTCATCCTTGTCTGAGGTCCCTCTGAGCT CTAACCAGACTTTCCTTCCCCACAGTCCCACATGTGTAAA AGGGACTAGGAGAGGTGACCAGTACCTTTGGGGCTCAGA TCGAGAAGTGCTAGGGACATGTGGGCCATGAGCTTAGTTG TCAGGCTCCTCAGAGGGAGGGAAGCTTGGCCAAAGGGAA GTGAGTAGAGTCCAGGGAGAAGGCTAAGTAAGGCCCTGT GTGGGAAGGGGCAGGAGACAAAGGTACCCCTGTCTCTTTG GGAAAGAATGGGAGGAGAGAGAGGGAAAAGCATTTCATAT CACGGGGTAGAGCTCTGCCCTTGGCCCCAGGCACGTTCT GAGCCCTGAGTCATGGGAAGGGTGGAGAAGCAGGAAGGG GGTTTTCAAGGACCTTGGGGAGGTGGGAGCCCAGCCCCAG AGGCAAGCAGATGCAAACCAACCTAATGCAAGGATGCCC TCTCCTGGTAATTGCAGGCATAGCAGCGCCAGCCCCCATG GCTGACCTCCTGGGAGCCTGGCACTGTCTAGGCACACAGA CTCCTTCTCTTAAATCTACTCTCCCCTCTCTTCTTTAG	
71	GTGAGGGCCACCCTGCAGGGGCCACCCATGGCCCCACCTAA CACATGTACACTCACTCTTCTACCTAGGCCCTCCCCCATGT GGTGCCTGGTCTGACCTGTCACCTGATTTTCAGAGCCATTC ACCTGTCCTAGAGTCATTTTACCCACTGAGGTCACATCTTA TCCTAATTTGGCTGCCAATGGGATCTACCACAGTGAATTT AAAATAATCCAGGAGGCGGGCATGGTGGTTCACGCCTGT AATCCCAGCACTTTAGGAGGCCGAGGTGGGCCGATCACG AGGTCAGGAGATCGAGATCATCCTGACTAACATGGTGAA ACCCCGTCTCTACTAAAAAATACAAAAAATTAGCCTGGCAT GGTGGCGGGCGCCTGTAGTCCCACTACTCGGGAGGCTGA GGCAGGAGAATGGCGTGAGCCTGCGAGGCAGAGCTTGCA GTGAGCTGAGATCATGCCACTGCACTCCAGCCTGGGCAAC AGAGTGAGACTCCGTCTCAAAAAAATAATAATAATAATA ATAAAAAATAATCCAGGCCATGTGTGGTGGCTCATGCCTGT AATCCCAGCATTTTGGGAGGCCAAGGAGGCAGGATTGCTT GAGTCCAGGAGTTTGAGACCAGCCTGGGCAACACAGACC CCATCTCTAGAAAATAAAAAATTTAAAGAAATTAGCTGGGC ATGGTGGTGTGCACCTATAGTCCCAGCTACTTGGGAGGCT GAGGCAGGAGGATGGCTTGAACCTGAGAGGTCGAGGATA CAGTGAGCTGTGATTGCACCACTGCACTTCAGCCTGGGTG ACAGAGGGAAACCCTGTCTCTACATAAATAAATACATAAA ATAAAATAATCCACAAGCCATTTCTACTTAACTTTGCAAT	Intron 2 of lamin A and lamin C

SEQ ID NO:	Nucleic Acid Sequence	Name
	GAACTGTACCTGACCCTAGATCCCTCCCAGTTTGGCCCTCC GGTATACAAGGGCCTCCTATAGGCCCTTGTGATTTCTCTG GGGAAAAGGAGGACTGGAGTTGATCATTTATTGAGGCCAT CAGAAGCGGATGGCTAATTACATATGGGACATGTGTTAAT AATGCTTTGTGTATATAGAGTGGCCTTTACTTTCAAAACAC TCTTCTCCAATTTATCATGTTAAAAGCTAGGAATTGGGCTG GGTGCAGTGGCTCACGCCTATAATCCCAGCACTTTGGGAG GCCAAGGCGGGTGGATCATTTGAGGTCAGGAGTTTGAGAC CAGTCTGACCAACATGGTTAAACTCCGTCTCTACTAAAAA TACAAAATTAGCCAGGCGTGGTGGCACACACCTGTAGTCC CAACAACACTTGTGAGGCTGAGGCAGGAAAATCATTTGA ACCCAGGATCAGAGGTTGTGGTGAAGTGAAGATTGCACCAT TGCCTCCAGCCTGGGCAACAAGAGCAAACTCTATCTCA AAAAAAATAAAAAATAGCCAGGCACGGTGGCTCATGCCT GTAATCCTAGCACTTTGGGAGGCAGAGGTGGGCAGATCAC CTGAGGTTAGGAGTTCGAGACTAGCCTGGCCAACATGGTG AAACCCCATCTCTACTACAAATACAAAAATTAGCTAGGCA TGGTGGCAGCCACCTGTAATCCCAGCTACTTGGGAGGCTG AGGCAGGAGAATCGCTTGAACCCGGGAGGTGGAGGTTGC AGTGAGCCAAGATCGGGTCACAGCACTCCAGCCTAGGCA ACAGAGCGAGACTCCATCTCAAAAAAACATAAATAAATA AAAATAAAAAATAAATAAATAAATAAAGCTAAGAATCAAA GAAGCAGTTTATTCCTAATTTACAGTCTCATCTGTTCATA GTGGGGCCAGGATTAGAGTCAGTGGCCAAGCTTCCATCCT GGGTTCTTTCCCTTCCCAGGCCCTACCATCATAGTATACCA GGGAAAGACCTGGAGAAGCCAGCAGGTTGACCACCGAAC CAAGGCTGGGCCACCTTCCTCCTGGGTCTGGTCTCCAGCC TCCCAGTTGTACCCTTCCCCAGCCCTTCCTGGATGCACTG ATCAGCCTGTGCTTCCTTGCCCTGTTTTTCTTTATAAATAG AGCCATGTTCTCCTCTCTCTCTCTCTTTTTTTTTTTTTTT TTTTGAGATGGAGTCTTACTCTGTACCCAGGCTGGAGTG CAATGGCACGATCTCAGCTCACTGCAACCTCTGTCTCCCA GGTTCAAGCAATTCTCCTGCCTCAGCCTCCCGAGTAGCTG GGATTACAGGTGCCCACCACCATGCCCAGCTACTTTTTGG ATTTTGTAGTAGAGACAGGGTTTCACCATGTTGGTCAGGCT GGTCTTGAACTCCTGACCTTAGGTGTTCTGCCCCGCTCAGC CTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACCACGCC TGGCAAGACGTGTTCTCTCTATGTTGTTGAGGCTGGTCTTG AACTCCTGGCTGCAAGAGATCTTCCTGCCTCAGCCTCCCA ATGTGCTGGGATTATAGGCATGAGCCACCACACTTAGCCC AGCCTGTGCTTTCTTAAATGAAAATCTAAGCATACGGCTG GGTGTGGTGGCTCACGCCTGTAATCCCAGCATTTTGGGAG GCCAAGGTGGGCAGATCACGAGGTCAGGAGATCGAGACT ATCCTGGCCAACATGGTGAAACCCTGTCTCTACTAAAGAT ACAAAAATTAGCTGGGTGTGGTGGCCCATGTCTGTAGTCC CAGCTACTCGGGAGACTGAGGCAGGAGAATGGCATGAAC	

SEQ ID NO:	Nucleic Acid Sequence	Name
	CTGGGAGGCAGAGCTTGCAGTGAGCTGAGATCGCGCCACT GCTCTCCAGCCTAGGTGACAGAGCGAGACTCCATCTCAAA AAAAAATAAAAAATAAAAAAAGAAAATCTAAGCGTGGT GCTCCCCTGCTCAAACATCCTCAGGTTCTTTTCATGGCAGA TAAGGGCATCTCTTCATGAGCCAGCCCCTGCCTACTGACC CAGCCACCTCTCCCATCCCTTCCCACCCCGTACTTCAGGCT TCAGCAGTACTGATCTTTCCAAAGACCCCAGAACACACAT GCCTTCATACCTCTGTGCCTGTACATGCTTGTTTCTGCCCT TGAAATCATGACAGTAGCTCTCTGTAGGCCCCGCTAGCCT GTCCCTTGGGTCTTAGCCTCTTGGAGGCCTTCCCAGAGCCC CCCAAAGTACCCAGGCATACTTTGGTTCCTTCTCTCATG TCCCCTCAGTACTTTGCACATACCTCCTTTATAGCAGTTGC TATGTTGTGCCAGAGAAGGGAGTCCTGTGGCTGGGGGGCA TATATCTTTTCTTTTGTAGACAGAGTCTAGCTGTGTCACCC AGGCTGGAGTGCAGTAGTGCGATCTCGGCTCACTGCAACC TCCACCTCCTGGATTCAAGCGATTCTTGTGCCTCAGCCTCC TGAGTAGCTGGGACTACAGGCGTGTGCCACCATCATGCCT GGCTACTTTTTTGTATTAGATATATATTTTCTCTCTTAGCA CAGTACCTACCAAGAGTGAGTGAGTAGATGTCCTGACCCC TGCAGGCATCCAAGGCCCTCCTTCCCTGGACCTGTTTCCAC ATGTGTGAAGGGGTGCACAGGCAGCAGCCACCTCTCAGC TTCTTCCAGTTCTTGTGTTCTGTGACCCCTTTTCTCATCT CTGCCTGCTTCCTCACAG	
72	GTGGGGACTGTGCTTTGCAAGCCAGAGGGCTGGGGCTGG GTGATGACAGACTTGGGCTGGGCTAGGGGGGACCAGCTG TGTGCAGAGCTCGCCTTCCTGAGTCCCTTGCCCTAGTGGA CAGGGAGTTGGGGGTGGCCAGCACTCAGCTCCCAGGTTAA AGTGGGGCTGGTAGTGGCTCATGGAGTAGGGCTGGGCAG GGAGCCCCGCCCTGGGTCTTGGCCTCCCAGGAACATAATT CTGATTTTGGTTTCTGTGTCCTTCCTCCAACCCTTCCAG	Intron 3 of lamin A and lamin C
73	GTGCTTGCTCTCGATTGGTTCCCTCACTGCCTCTGCCCTTG GCAGCCCTACCTTACCCACGCTGGGCTATGCCTTCTGGG GATCAGGCAGATGGTGGCAGGGAGCTCAGGGTGGCCCAG GACCTGGGGCTGTAGCAGTGATGCCCAACTCAGGCCTGTG CCTCCACCCCTCCCAGTCACCACAGTCCTAACCCTTTGTCC TCCCCTCCAG	Intron 4 of lamin A and lamin C
74	GTGATACCCACCTCACCCCTCTCTCCAGGGGCCTAGAGT CTGGGCCGGATGCAGGCTGGAAGCCCAGGGTTGGGGGTG GGGGTGGGGGTGGGAGGTTCTGAGGAGGAGAGGGATGA AAAGTGTCCCCACAACCACAGAGAAGGGTCGCAGGATGT GGAGTCAGATGGCCTGTGTGCTGTTTCTGTACACTCTTACC TCACCTTCACTTCTCAGGGCTTTGGTTTTCCCATTCGAAAA TGGAGGCTGTTCTTAATCTCCCTAACTCAGAGTTGCCACA GGACTCTGCAATGTGAGGTGTTAAAAGCATCAGTATTTTT CTAGTTGGCTGTGCTATTTGTGACAGGAGAAAAAGTCTAG CCTCAGAACGAGAGGTTTCAGTTAGACAAGGGGAAGGAC	Intron 5 of lamin A and lamin C

SEQ ID NO:	Nucleic Acid Sequence	Name
	TTCCCAGTTGCCAGCCAAGACTATGTTTAGAGCTTGTGAT G TTCAGAGCTGGCTCTGATGAGGGCTCTGGGGAAGCTCTG ATTGCAGATCCTGGAGAGAGTAGCCAGGTGTCTCCTACAC CGACCCACGTCCCTCCTTCCCCATACTTAGGGCCCTTGGG AGCTCACCAAACCCTCCCACCCCCCTTCAG	
75	GTGGGCTGGGGAGACGTCGGGGAGGTGCTGGCAGTGTCC TCTGGCCGGCAACTGGCCTTGACTAGACCCCCACTTGGTC TCCCTCTCCCCAG	Intron 6 of lamin A and lamin C
76	G TAGGCTCCTGCTCAGGGTCTAAGGGGATACAGCTGCATC AGGGAGAGAGTGGCAAGACAGAAGGATGGCATGTGGAGA GAGGAACATCCTTGCCCTCAGAGGGTGGACCAGGGTGAG CCTGTATATCTCCTCCACACTCTGGTTCCAGGCCTGGCTCC TGGACTCTTTGGCTGTGAGACCTTGAGCAGGTTATTTAAC CTCTCAGAGCATCAGTTTCCTCATCTGTAAAATGGGGATG AATACTGATCCCTAAGTCTTTGAGTTGTCAGGAAGATGAA AGATAAGGTATCCGTGTGCCTGGTGCTGCGTATGTGTCCA CAGATCATGGCTATTATCCCCGGGGGAAGGGCAGTGACA GGGGTGTGTGTAGATGGAAGGAGAGGCCTCAATTGCAGG CAGGCAGAGGGCTGGGCCTTTGAGCAAGATACACCCAAG AGCCTGGGTGAGCCTCCCCGACCTTCCTCTTCCCTATCTTC CCGGCAG	Intron 7 of lamin A and lamin C
77	GTGAGTGGCAGGGCGCTTGGGACTCTGGGGAGGCCTTGG GTGGCGATGGGAGCGCTGGGGTAAGTGTCTTTTCTCCTC TCCAG	Intron 8 of lamin A and lamin C
78	GTAAGTAGGCCTGGGCCTGGCTGCTTGCTGGACGAGGCTC CCCCTGATGGCCAACATCGGAGCCAGCTGCCCCCAACCCA AGTTTGCCAATTCAGGGCCCCCTTTCTAGAGCTCTCTGTTGC AGGCTCCAGACTTCTCCACCCAGTAGGCCAAACCAAAAGAT GCTTCCTCAACAGCACAAAGGGGTGGAAGTTAGACAGTGA GGATTGTTAAAGGCAGAGCCATACTCCTACCCGGAGAGCT TGACAGTGTCCCTCTGGGGTGGAAATGAGTTCCTTAGCTC CATCACCACAGAGGACAGAGTAAGCAGCAGGCCGGACAA AGGGCAGGCCACAAGAAAAGTTGCAGGTGGTCACTGGGG TAGACATGCTGTACAACCCTTCCCTGGCCCTGACCCTTGG ACCTGGTTCCATGTCCCCACCAG	Intron 9 of lamin A and lamin C
79	GTGAGTGGTAGCCGCCGCTGAGGCCGAGCCTGCACTGGG GCCACCCAGCCAGGCCTGGGGGCAGCCTCTCCCCAGCCTC CCCGTGCCAAAATCTTTTCATTAAAGAATGTTTTGGAAC TTTACTCGCTGGCCTGGCCTTTCTTCTCTCCTCCCTATAC CTTGAACAGGGAACCCAGGTGTCTGGGTGCCCTACTCTGG TAAGGAAGGGAGTGGGAACTTTCTGATGCCATGGAATATT CCTGTGGGAGCAGTGGACAAGGGTCTGGATTTGTCTTCTG GGAAAGGGAGGGGAGGACAGACGTGGGGCATGCCCGCCC TGCTCTCTCCCCATTCTTGTTGCATGCATATCCTCTCATT	Intron 10 of lamin A

SEQ ID NO:	Nucleic Acid Sequence	Name
	TCCCTCATTTTTTCCTGCAAGAATGTTCTCTCTCATTCCTGACCGCCCCCTCCACTCCAATTAATAGTGCATGCCTGCTGCCCTACAAGCTTGCTCCCGTTCTCTCTTTCTTTTCCCTCTTAAGCTCAGAGTAGCTAGAACAGAGTCAGAGTCACTGCTCTGGTTCTCTGTCCCCAAGTCTTCCTGAGCCTTCTCCCCTTTTATGTCTTCCCTCTCCTCCTCCGGGCCCCCTAGCCTCCCAAACCCCCATTGCCCGCTGGCTCCTTGGGCACAGAACCACACCTTCCTGCC TGGCGGCTGGGAGCCTGCAGGAGCCTGGAGCCTGGTTGG GCCTGAGTGGTCAGTCCCAGACTCGCCGTCCCGCCTGAGC CTTGTCTCCCTTCCCAG	
80	GTGAGTTGTCTCTGCTTTGTCTCCAAATCCTGCAGGCGGGTCCCTGGTCATCGAGGGGTAGGACGAGGTGGCCTTGCAGG GGGGAGAGCCTGCCTTCTCTTCCGCAGCCCGGGGGAGTGG GAGCCTCCTCCCCACAGCCTGAGTCCTAGACAGCCACCT CTGCATCCTGCCCCCTCTTGTCTGAGCCCCAGACTGGAGGG CAGGGGCAGGGCTGGAGTGTGAGGGATGGGGGAGATGCT ACCTCCCTTCTAGGGGCCAGGGGAGGGAGGGTCTGGGTCC AGGCCCTGCTGCTCACACCTCTCTCCTCTGTTTTCTCTCTT AG	Intron 11 of lamin A
81	ATGGAGACCCCGTCCCAGCGGCGGCCACCCGCAGCGGG GCGCAGGCCAGCTCCACTCCGCTGTGCGCCACCCGCATCA CCCGGCTGCAGGAGAAGGAGGACCTGCAGGAGCTCAATG ATCGCTTGGCGGTCTACATCGACCGTGTGCGCTCGCTGGA AACGGAGAACGCAGGGCTGCGCCTTCGCATCACCGAGTCT GAAGAGGTGGTCAGCCGCGAGGTGTCCGGCATCAAGGCC GCCTACGAGGCCGAGCTCGGGGATGCCCGCAAGACCCTTG ACTCAGTAGCCAAGGAGCGCGCCCGCCTGCAGCTGGAGCT GAGCAAAGTGCGTGAGGAGTTTAAGGAGCTGAAAGCGCG	Exon 1 of of lamin A and lamin C
82	CAATACCAAGAAGGAGGGTGACCTGATAGCTGCTCAGGC TCGGCTGAAGGACCTGGAGGCTCTGCTGA ACTCCAAGGAG GCCGCACTGAGCACTGCTCTCAGTGAGAAGCGCACGCTGG AGGGCGAGCTGCATGATCTGCGGGGCCAGGTGGCCAAG	Exon 2 of of lamin A and lamin C
83	CTTGAGGCAGCCCTAGGTGAGGCCAAGAAGCAACTTCAG GATGAGATGCTGCGGCGGGTGGATGCTGAGAACAGGCTG CAGACCATGAAGGAGGAACTGGACTTCCAGAAGAACATC TACAGTGAG	Exon 3 of lamin A and lamin C
84	GAGCTGCGTGAGACCAAGCGCCGTCATGAGACCCGACTG GTGGAGATTGACAATGGGAAGCAGCGTGAGTTTGAGAGC CGGCTGGCGGATGCGCTGCAGGAACTGCGGGCCCAGCAT GAGGACCAGGTGGAGCAGTATAAGAAGGAGCTGGAGAAG ACTTATTCTGCCAAG	Exon 4 of of lamin A and lamin C
85	CTGGACAATGCCAGGCAGTCTGCTGAGAGGAACAGCAAC CTGGTGGGGGCTGCCACGAGGAGCTGCAGCAGTCGCGC ATCCGCATCGACAGCCTCTCTGCCCAGCTCAGCCAGCTCC AGAAGCAG	Exon 5 of of lamin A and lamin C

SEQ ID NO:	Nucleic Acid Sequence	Name
86	CTGGCAGCCAAGGAGGGCGAAGCTTCGAGACCTGGAGGAC TCACTGGCCCGTGAGCGGGACACCAGCCGGCGGCTGCTGG CGGAAAAGGAGCGGGAGATGGCCGAGATGCGGGCAAGG ATGCAGCAGCAGCTGGACGAGTACCAGGAGCTTCTGGAC ATCAAGCTGGCCCTGGACATGGAGATCCACGCCTACCGCA AGCTCTTGGAGGGGCGAGGAGGAGAG	Exon 6 of of lamin A and lamin C
87	GCTACGCCTGTCCCCCAGCCCTACCTCGCAGCGCAGCCGT GGCCGTGCTTCTCTCACTCATCCAGACACAGGGTGGGG GCAGCGTCACCAAAAAGCGCAAAGTGGAGTCCACTGAGA GCCGCAGCAGCTTCTCACAGCACGCACGCACTAGCGGGCG CGTGGCCGTGGAGGAGGTGGATGAGGAGGGCAAGTTTGT CCGGCTGCGCAACAAGTCCAATGAG	Exon 7 of of lamin A and lamin C
88	GACCAGTCCATGGGCAATTGGCAGATCAAGCGCCAGAAT GGAGATGATCCCTTGCTGACTTACCGGTTCCCAACAAAGT TCACCCTGAAGGCTGGGCAGGTGGTGACG	Exon 8 of of lamin A and lamin C
89	ATCTGGGCTGCAGGAGCTGGGGCCACCCACAGCCCCCTA CCGACCTGGTGTGGAAGGCACAGAACACCTGGGGCTGCG GGAACAGCCTGCGTACGGCTCTCATCAACTCCACTGGGGA A	Exon 9 of of lamin A and lamin C
90	GAAGTGGCCATGCGCAAGCTGGTGCGCTCAGTGACTGTGG TTGAGGACGACGAGGATGAGGATGGAGATGACCTGCTCC ATCACCACCAC	Exon 10 of lamin A
91	GAAGTGGCCATGCGCAAGCTGGTGCGCTCAGTGACTGTGG TTGAGGACGACGAGGATGAGGATGGAGATGACCTGCTCC ATCACCACCACGTGAGTGGTAGCCGCCGCTGA	Exon 10 of lamin C
92	GGCTCCCACTGCAGCAGCTCGGGGGACCCCGCTGAGTACA ACCTGCGCTCGCGCACCGTGCTGTGCGGGACCTGCGGGCA GCCTGCCGACAAGGCATCTGCCAGCGGCTCAGGAGCCCA GGTGGGCGGACCCATCTCCTCTGGCTCTTCTGCCTCCAGTG TCACGGTCACTCGCAGCTACCGCAGTGTGGGGGGCAGTGG GGGTGGCAGCTTCGGGGACAATCTGGTCACCCGCTCCTAC CTCCTGGGCAACTCCAGCCCCCGAACCAG	Exon 11 of lamin A
93	AGCCCCCAGAACTGCAGCATCATGTAA	Exon 12 of lamin A

TABLE 2: List of certain amino acid sequences disclosed herein.

SEQ ID NO:	Amino Acid Sequence	Name
12	METPSQRRATRSGAQASSTPLSPTRITRLQEKEDLQELNDRL AVYIDRVRSLETENAGLRLRITESEEVVSREVSIGIKAAAYEAE GDARKTLDSVAKERARLQLELSKVREEFKELKARNTKKEGD LIAAQARLKDLEALLNSKEAALSTALSEKRTLEGELHDLRGQ VAKLEAALGEAKKQLQDEMLRRVDAENRLQTMKEELDFQK NIYSEELRETKRRHETRLVEIDNGKQREFESRLADALQELRA	Pre-lamin A sequence

SEQ ID NO:	Amino Acid Sequence	Name
	QHEDQVEQYKKELEKTYSAKLDNARQSAERNSNLVGAAHE ELQQSRIRIDSLSAQLSQLQKQLAAKEAKLRDLEDLARERD TSRLLAEKEREMAEMRARMQQQLDEYQELLDIKLALDMEI HAYRKLEEGEEERLRLSPSPTSQRSRGRASSHSSQTQGGGSV TKKRKLESTESRSSFSQHARTSGRVAVEEVDEEGKFWRLRNK SNEDQSMGNWQIKRQNGDDPLLTYRFPKFTLKAGQVVTIW AAGAGATHSPPTDLVWKAQNTWGCNSLRTALINSTGEEV AMRKLVRSVTVVEDDEDEDGDDLLHHHHGSHCSSSGDPAE YNLRSTVLCGTGCGPADKASASGSGAQVGGPISSGSSASSV TVTRSYRSVGGSGGGSFGDNLVTRSYLLGNSSPRTQSPQNC IM	
13	METPSQRRATRSGAQASSTPLSPTRITRLQEKEDLQELNDRL AVYIDRVRSLETENAGLRLRITESEEVVSREVSGIKAAEYAE LGDARKTLDSVAKERARLQLELSKVREEFKELKARNTKKEGD LIAAQARLKDLEALLNSKEAALSTALSEKRTLEGELHDLRGQ VAKLEAALGEAKKQLQDEMLRRVDAENRLQTMKEELDFQK NIYSEELRETKRRHETRLVEIDNGKQREFESRLADALQELRA QHEDQVEQYKKELEKTYSAKLDNARQSAERNSNLVGAAHE ELQQSRIRIDSLSAQLSQLQKQLAAKEAKLRDLEDLARERD TSRLLAEKEREMAEMRARMQQQLDEYQELLDIKLALDMEI HAYRKLEEGEEERLRLSPSPTSQRSRGRASSHSSQTQGGGSV TKKRKLESTESRSSFSQHARTSGRVAVEEVDEEGKFWRLRNK SNEDQSMGNWQIKRQNGDDPLLTYRFPKFTLKAGQVVTIW AAGAGATHSPPTDLVWKAQNTWGCNSLRTALINSTGEEV AMRKLVRSVTVVEDDEDEDGDDLLHHHHVSGSRR	Lamin C sequence
14	METPSQRRATRSGAQASSTPLSPTRITRLQEKEDLQELNDRL AVYIDRVRSLETENAGLRLRITESEEVVSREVSGIKAAEYAE LGDARKTLDSVAKERARLQLELSKVREEFKELKARNTKKEGD LIAAQARLKDLEALLNSKEAALSTALSEKRTLEGELHDLRGQ VAKLEAALGEAKKQLQDEMLRRVDAENRLQTMKEELDFQK NIYSEELRETKRRHETRLVEIDNGKQREFESRLADALQELRA QHEDQVEQYKKELEKTYSAKLDNARQSAERNSNLVGAAHE ELQQSRIRIDSLSAQLSQLQKQLAAKEAKLRDLEDLARERD TSRLLAEKEREMAEMRARMQQQLDEYQELLDIKLALDMEI HAYRKLEEGEEERLRLSPSPTSQRSRGRASSHSSQTQGGGSV TKKRKLESTESRSSFSQHARTSGRVAVEEVDEEGKFWRLRNK SNEDQSMGNWQIKRQNGDDPLLTY	Minigene 1 Lamin isoform A/C (exons 1-8)
15	RFPPKFTLKAGQVVTIWAAGAGATHSPPTDLVWKAQNTWGCNSLRTALINSTGE	Minigene 1 Lamin isoforms A/C (exon

SEQ ID NO:	Amino Acid Sequence	Name
		9)
16	EVAMRKLVRSVTVVEDDEDEDGDDLLHHHHVSGSRR	Minigene 1 Lamin isoform C (exon 10)
17	EVAMRKLVRSVTVVEDDEDEDGDDLLHHHH	Minigene 1 Lamin Isoform A (exon 10)
18	GSHCSSSGDPAEYNLRSRTVLCGTCGQPADKASASGSGAQV GGPISSGSSASSVTVTRSRSVGGSGGGSFGDNLVTRSYLLG NSSPRTQ	Minigene 1 Lamin A exon 11
19	SPQNCSIM	Minigene 1 Lamin A exon 12
20	METPSQRRATRSGAQASSTPLSPTRITRLQEKEDLQELNDRL AVYIDRVRSLETENAGLRLRITESEEVVSREVSGIKAAYEAE GDARKTLDSVAKERARLQLELSKVREEFKELKARNTKKEGD LIAAQARLKDLEALLNSKEAALSTALSEKRTLEGELHDLRGQ VAKLEAALGEAKKQLQDEMLRRVDAENRLQTMKEELDFQK NIYSEELRETKRRHETRLVEIDNGKQREFESRLADALQELRA QHEDQVEQYKKELEKTYSAKLDNARQSAERNNSNLVGAAHE ELQQSRIRIDSLSAQLSQLQKQLAAKEAKLRDLEDLARERD TSRLLAEKEREMAEMRARMQQQLDEYQELLDIKLALDMEI HAYRKLLLEGEEERLRLSPSPTSQRSRGRASSHSSQTQGGGSV TKKRKLESTESRSSFSQHARTSGRVAVEEVDEEGK FVRLRNK SNEDQSMGNWQIKRQNGDDPLLTYRFPKFTLKAGQVVTIW AAGAGATHSPPTDLVWKAQNTWGCGNSLTALINSTGE	Minigene 2 Lamin Isoform A/C (exons 1-9)
21	METPSQRRATRSGAQASSTPLSPTRITRLQEKEDLQELNDRL AVYIDRVRSLETENAGLRLRITESEEVVSREVSGIKAAYEAE GDARKTLDSVAKERARLQLELSKVREEFKELKARNTKKEGD LIAAQARLKDLEALLNSKEAALSTALSEKRTLEGELHDLRGQ VAKLEAALGEAKKQLQDEMLRRVDAENRLQTMKEELDFQK NIYSEELRETKRRHETRLVEIDNGKQREFESRLADALQELRA	Mature Lamin A Sequence

SEQ ID NO:	Amino Acid Sequence	Name
	QHEDQVEQYKKELEKTYSAKLDNARQSAERNSNLVGAAHE ELQQSRIRIDSLSAQLSQLQQLAAKEAKLRDLEDLARERD TSRRLLAEKEREMAEMRARMQQQLDEYQELLDIKLALDMEI HAYRKLLEGEEERLRLSPSPTSQRSRGRASSHSSQTQGGGSV TKKRKLESTESRSSFSQHARTSGRVAVEEVDEEGKFVRLRNK SNEDQSMGNWQIKRQNGDDPLLTYRFPPKFTLKAGQVVTIW AAGAGATHSPPTDLVWKAQNTWGCNSLRTALINSTGEEV AMRKLVRSTVVEDEDEDGDDLLHHHHGSHCSSSGDPAE YNLRSRTVLCGTCGQPADKASASGSGAQVGGPISSGSSASSV TVTRSYRSVGGSGGGSGFDNLVTRSY	
22	[Reserved]	
23	[Reserved]	
24	GSHCSSSGDPAEYNLRSRTVLCGTCGQPADKASASGSGAQV GGPISSGSSASSVTVTRSYRSVGGSGGGSGFDNLVTRSYLLG NSSPRTQSPQNC SIM	Minigene 2 Lamin Isoform A (exon 11- 12)
25	[Reserved]	
26	[Reserved]	
27	[Reserved]	
28	[Reserved]	
29	[Reserved]	

TABLE 3: List of exemplary regulatory element nucleic acid sequences

SEQ ID NO:	Nucleic Acid Sequence	Length
30	GTAAGGTAAGAATTGAATTTCTCAGTTGAAGGATGCTTAC ACTCTTGTC CATCTAG	56bp
31	GTGTGTATGCTCAGGGGCTGGGAAAGGAGGGGAGGGAGC TCCGGCTCAG	49bp
32	GTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTC CAAGTCTCCACCCCATTTGA CGTCAATGGGAGTTTGT TTTGGCACCAAAATCAACGGGAC TTTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAA TGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCA GAGCTGGTACCGTAAGGTAAGAATTGAATTTCTCAGTTGA AGGATGCTTACACTCTTGTC CATCTAG	266bp

SEQ ID NO:	Nucleic Acid Sequence	Length
33	GTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCTCAAGTCTCCACCCCATTGA CGTCAATGGGAGTTTGTGTTTGGCACCAAAATCAACGGGAC TTTCCAAAATGTCGTAACAACCTCCGCCCCATTGACGCAAA TGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCA GAGCTGGTACCGTGTGTATGCTCAGGGGCTGGGAAAGGA GGGGAGGGAGCTCCGGCTCAG	259bp
34	GTGATGACGTGTCCCATAAGGCCCTCGGTCTAAGGCTTC CCTATTTCTGTTTCGCCGGCGGCCATTTTGGGTGGAAGC GATAGCTGAGTGGCGGCGGCTGCTGATTGTGTTCTAG	117bp
35	GTGATGACGTGTCCCATACTTCCGGGTGAGGTGGGCCGGC TGTCTTGACCTTCTTTGCGGCTCGGCCATTTTGTCCAGTC AGTCCGGAGGCTGCGGCTGCAGAAGTACCGCCTGCG	117bp
36	GTGATGACGTGTCCCATAATTTTCATCTCGCGAGACTTGTGA GCGGCCATCTTGGTCCTGCCCTGACAGATTCTCCTATCGG GGTCACAGGGACGCTAAGATTGCTACCTGGACTTTC	117bp
37	GTGATGACGTGTCCCATGGCCTCATTGGATGAGAGGTCCC ACCTCACGGCCCGAGGCGGGGCTTCTTTGCGCTTAAAAGC CGAGCCGGGCCAATGTTCAAATGCGCAGCTCTTAGTC	117bp
38	GTGATGACGTGTCCCATCCCCCTCCACCCCCTAGCCCGC GGAGCACGCTGGGATTTGGCGCCCCCTCCTCGGTGCAAC CTATATAAGGCTCACAGTCTGCGCTCCTGGTACACGC	117bp
39	CCCCCTCCACCCCCTAGCCCGCGGAGCACGCTGGGATTT GGCGCCCCCTCCTCGGTGCAACCTATATAAGGCTCACAG TCTGCGCTCCTGGTACACGC	100bp
40	GGCCTCATTGGATGAGAGGTCCACCTCACGGCCCGAGGC GGGGCTTCTTTGCGCTTAAAAGCCGAGCCGGGCCAATGTT CAAATGCGCAGCTCTTAGTC	100bp
41	GGGTGGGGCCCGCGCGTATAAAGGGGGCGCAGGCGGGCT GGGCGTTCCACAGGCCAAGTGCCTGTGCTCGAGGGGTGC CGGCCAGGCCTGAGCGAGCGA	100bp
42	GGTGCATATTCGGATTGGCTGGAGTCGGCCATCACGCTC CAGCTACGCCACTTCCTTTTCGTGGCACTATAAAGGGTGC TGCACGGCGCTTGCATCTCT	100bp
43	ACTTCCGGGTGAGGTGGGCCGGCTGTCTTGACCTTCTTTGC GGCTCGGCCATTTTGTCCAGTCAGTCCGGAGGCTGCGGC TGCAGAAGTACCGCCTGCG	100bp
44	GCTGAGCGCGCGCGATGGGGCGGGAGGTTTGGGGTCAAG GAGCAAACCTCTGCACAAGATGGCGGCGGTAGCGGCAGTG GCGGCGCGTAGGAGGCGGTGAG	100bp
45	ATTTTCATCTCGCGAGACTTGTGAGCGGCCATCTTGGTCCT GCCCTGACAGATTCTCCTATCGGGGTCACAGGGACGCTAA GATTGCTACCTGGACTTTC	100bp
46	TGGGACCCCCGGAAGGCGGAAGTTCTAGGGCGGAAGTGG CCGAGAGGAGAGGAGAATGGCGGCGGAAGGCTGGATTTG GCGTTGGGGCTGGGGCCGGCGG	100bp

SEQ ID NO:	Nucleic Acid Sequence	Length
47	AAGGCCCTCGGTCTAAGGCTTCCCTATTTCTGGTTCGCC GGCGGCCATTTTGGGTGGAAGCGATAGCTGAGTGGCGGC GGCTGCTGATTGTGTTCTAG	100bp
48	AGTGACCCGGAAGTAGAAGTGGCCCTTGCAGGCAAGAGT GCTGGAGGGCGGCAGCGGCACCGGAGCGGTAGGAGCAG CAATTTATCCGTGTGCAGCCCC	100bp
49	GGGAGGGGCGCGCTGGGGAGCTTCGGCGCATGCGCGCTG AGGCCTGCCTGACCGACCTTCAGCAGGGCTGTGGCTACCA TGTTCTCTCGCGCGGGTGTCTG	100bp
50	ACTGCGCACGCGCGCGGTTCGCACCGATTACGCCCCCTTC CGGCGCCTAGAGCACCGCTGCCGCCATGTTGAGGGGGGG ACCGCGACCAGCTGGGCCCCCT	100bp
51	CCCTCGAGGGGCGGAGCAAAAAGTGAGGCAGCAACGCCT CCTTATCCTCGCTCCCGCTTTCAGTTCTCAATAAGGTCCGA TGTTTCGTGTATAAATGCTCG	100bp
52	CTTGGTGACCAAATTTGAAAAAAAAAAAAAACCGCGCCA ACTCATGTTGTTTTCAATCAGGTCCGCCAAGTTTGTATTTA AGGAACTGTTTCAGTTCATA	100bp
53	GGCTGAGCTATCCTATTGGCTATCGGGACAAAATTTGCTT GAGCCAATCAAAGTGCTCCGTGGACAATCGCCGTTCTGTC TATAAAAAGGTGAAGCAGCG	100bp
54	GGAAGTGCCAGACCGGAGGTGCGTCATTCACCGGCGACG CCGATACGGTTCCTCCACCGAGGCCCATGCGAAGCTTTCC ACTATGGCTTCCAGCACTGTC	100bp
55	CCCTCGAGGGGCGGAGCAAAAAGTGAGGCAGCAACGCCT CCTTATCCTCGCTCCCGCTTTCAGTTCTCAATAAGGTCCGA TGTTTCGTGTATAAATGCTCG	100bp
56	CTTGGTGACCAAATTTGAAAAAAAAAAAAAACCGCGCCA ACTCATGTTGTTTTCAATCAGGTCCGCCAAGTTTGTATTTA AGGAACTGTTTCAGTTCATA	100bp
57	GGCTGAGCTATCCTATTGGCTATCGGGACAAAATTTGCTT GAGCCAATCAAAGTGCTCCGTGGACAATCGCCGTTCTGTC TATAAAAAGGTGAAGCAGCG	100bp
58	GGAAGTGCCAGACCGGAGGTGCGTCATTCACCGGCGACG CCGATACGGTTCCTCCACCGAGGCCCATGCGAAGCTTTCC ACTATGGCTTCCAGCACTGTC	100bp
102	GCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACC GCCCAACGACCCCCGCCATTGACGTCAATAATGACGTAT GTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTC AATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGT ACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGAC GTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCAGT ACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTAC GTATTAGTCATCGCTATTACCATGGTCGAGGTGAGCCCCA CGTTCTGCTTCACTCTCCCCATCTCCCCCCCCCTCCCCACCC CCAATTTTGTATTTATTTATTTTAAATTATTTTGTGCAGCG	584bp

SEQ ID NO:	Nucleic Acid Sequence	Length
	ATGGGGGCGGGGGGGGGGGGGGGGGGGCGCGCGCCAGGCGG GGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAGGCGGA GAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAA AGTTTCCTTTTATGGCGAGGCGGCGGCGGCGGCGGCCCTA TAAAAAGCGAAGCGCGCGGCGGGCG	

TABLE 4: Additional nucleic acid sequences disclosed herein

SEQ ID NO:	Nucleic Acid Sequence	Source / Genomic Location
59	GTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGC GGTTTGACTCACGGGGATTTCCTCAAGTCTCCACCCCATTTGA CGTCAATGGGAGTTTGTGTTTGGCACCAAAATCAACGGGAC TTTCCAAAATGTCGTAACAACCTCCGCCCCATTGACGCAAA TGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCA GAGCT	CMV Promoter
60	TCGAGGTGAGCCCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAA TTATTTTGTGCAGCGATGGGGGCGGGGGGGGGGGGGGGGG CGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGC GGGGCGAGGCGGAGAGGTGCGGCGGCAGCCAATCAGAGC GGCGCGCTCCGAAAGTTTCCTTTTATGGCGAGGCGGCGGC GGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCG	CBA Promoter
61	GCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACC GCCCAACGACCCCCGCCCATTTGACGTCAATAATGACGTAT GTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTC AATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGT ACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGAC GTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCACT ACATGACCTTATGGGACTTTCTACTTGGCAGTACATCTAC GTATTAGTCATCGCTATTACCATG	CMV enhancer used upstream of CBA promoter
62	GTAATTATATAAGGGGGTGGGGGCGCGTTCGTCCTCAGTC GCGATCGAACACTCGAGCCGAGCAGACGTGCCTACGGAC C	SCP
63	GGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGT TATCGGAGGAGCAAACAGGGGCTAAGTCCACGCTAGCGT CTGTCTGCACATTTTCGTAGAGCGAGTGTTCGATACTCTA ATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATT CTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGT TTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAA GGAGGGGGGTATAAAAAGCCCCCTTACCAGGAGAAGCCGTC	SerpE_TTR
64	GTTTGCTGCTTGCAATGTTTGCCCATTTTAGGGTGGACACA	Proto1

	GGACGCTGTGGTTTCTGAGCCAGGGCTAGCGGGCGACTCA GATCCCAGCCAGTGGACTTAGCCCCCTGTTTGCTCCTCCGAT AACTGGGGTGACCTTGGTTAATATTCACCAGCAGCCTCCC CCGTTGCCCTCTGGATCCACTGCTTAAATACGGACGAGG ACAGGGCCCTGTCTCCTCAGCTTCAGGCACCACCCTGAC CTGGGACAGTGAATCGCCAC	
65	TGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGCG GTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTTGAC GTCAATGGGAGTTTGTGTTTGGCACCAAAATCAACGGGACT TTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAAT GGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAG AGCT	minCMV
66	GTTTGCTGCTTGCAATGTTTGCCCATTTTAGGGTGGACACA GGACGCTGTGGTTTCTGAGCCAGGGGGCGACTCAGATCCC AGCCAGTGGACTTAGCCCCCTGTTTGCTCCTCCGATAACTG GGGTGACCTTGGTTAATATTCACCAGCAGCCTCCCCCGTT GCCCCCTCTGGATCCACTGCTTAAATACGGACGAGGACAGG GCCCTGTCTCCTCAGCTTCAGGCACCACCCTGACCTGGG ACAGTGAATC	UCL-HLP
67	CGTTACATAACTTACGGTAAATGGCCCCGCCTGGCTGACCG CCCAACGACCCCCGCCATTGACGTCAATAATGACGTATG TTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCA ATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTA CATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACG TCAATGACGGTAAATGGCCCCGCCTGGCATTATGCCCAGTA CATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACG TATTAGTCATCGCTATTACCATG	CMVe
68	GTTACATAACTTACGGTAAATGGCCCCGCCTGGCTGACCGC CCAACGACCCCCGCCATTGACGTCAATAATGACGTATGT TCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAA TGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTAC ATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGT CAATGACGGTAAATGGCCCCGCCTGGCATTATGCCCAGTAC ATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGT ATTAGTCATCGCTATTACCATGGGTGAGGTGAGCCCCAC GTTCTGCTTCACTCTCCCCATCTCCCCCCCCCTCCCCACCCC CAATTTTGTATTTATTTATTTTAAATTATTTTGTGCAGCGA TGGGGGCGGGGGGGGGGGGGGGGGCGCGCGCCAGGCGGGGC GGGGCGGGGCGAGGGGCGGGGCGGGGCGAGGCGGAGAG GTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGT TTCTTTTATGGCGAGGCGGCGGCGGCGGCGGCCCTATAA AAAGCGAAGCGCGCGGCGGGCGGGAGTCGCTGCGTTGCC TTCGCCCCGTGCCCCGCTCCGCGCCGCCTCGCGCCGCCCG CCCCGGCTCTGACTGACCGCGTTACTCCACAGGTGAGCG GGCGGGACGGCCCTTCTCCTCCGGGCTGTAATTAGCGCTT GGTTTAAATGACGGCTCGTTTCTTTTCTGTGGCTGCGTGAAA GCCTTAAAGGGCTCCGGGAGGGCCCTTTGTGCGGGGGGG AGCGGCTCGGGGGGTGCGTGCCTGTGTGTGTGCGTGGGGA	CAG

	GCGCCGCGTGCGGGCCCGCGCTGCCCGGCGGCTGTGAGCGC TGCGGGCGCGGGCGCGGGGCTTTGTGCGCTCCGCGTGTGCG CGAGGGGAGCGCGGCCGGGGGCGGTGCCCCGCGGTGCGG GGGGGCTGCGAGGGGAACAAAGGCTGCGTGCGGGGTGTG TGCGTGGGGGGGTGAGCAGGGGGTGTGGGCGCGGGCGGTC GGGCTGTAACCCCCCCTGCACCCCCCTCCCCGAGTTGCT GAGCACGGCCCGGCTTCGGGTGCGGGGCTCCGTGCGGGG CGTGCGCGGGGCTCGCCGTGCCGGGCGGGGGGTGGCGG CAGGTGGGGGTGCCGGGCGGGGCGGGGCCGCCTCGGGCC GGGGAGGGCTCGGGGGAGGGGCGCGGCGGCCCCGGAGCG CCGGCGGCTGTCGAGGCGCGGCGAGCCGCAGCCATTGCCT TTTATGGTAATCGTGCGAGAGGGCGCAGGGACTTCCTTTG TCCCAAATCTGGCGGAGCCGAAATCTGGGAGGCGCCGCC GCACCCCCTCTAGCGGGCGCGGGCGAAGCGGTGCGGCGC CGGCAGGAAGGAAATGGGCGGGGAGGGCCTTCGTGCGTC GCCGCGCCGCGTCCCCTTCTCCATCTCCAGCCTCGGGGCT GCCGCAGGGGGACGGCTGCCTTCGGGGGGGACGGGGCAG GGCGGGGTTCGGCTTCTGGCGTGTGACCGGCGGCTCTAGA GCCTCTGCTAACCATGTTTCATGCCTTCTTCTTTTCCTACA GCTCCTGGGCAACGTGCTGGTTGTTGTGCTGTCTCATCATT TTGGCAAAGAATT	
69	GCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCAC AGTCCCCGAGAAGTTGGGGGGAGGGGTGCGCAATTGAAC CGGTGCCTAGAGAAGGTGGCGCGGGGTAACTGGGAAAG TGATGTCGTGTACTGGCTCCGCCTTTTCCCGAGGGTGGG GGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTT TTTTTCGCAACGGGTTTGCCGCCAGAACACAGG	EFS
100	GAGTGGGTAAAGTGTGAAAAATCTGCATGTGTGGCTGAAG ATGGGCACAGACACGGTCAAGTCTGTATGTGAGAGTGCTG AACTGGGGTTCTGTGTGAAAATCTGCCTGAGGCGGCAGGG AGAATCACTGCCATTGCGTGAGCAGGTTGGATGTTGGCCA CTCTATCAGGAGCATTAGGGAAGGGGTGGGGACTCCAGA CGTGTCCCCAAACCAGGGTGGCCTCAAGACCTTGGGAGAA CACTTGTCTGAAGACTTGGGGAACAGAAGGAGACCAGGC ATGGCACTTATGCAGACTGAGGCCAGGACAGAATTTCTTG ACAAAAGAAAATGAGCCATGGAGATGGACAACAGATCC CTTCCCTGGGCACCATACTGCAGCTTTTAGTCCCTAGCACT GGGGGCTCCAGTACTAACAGCAGGAAGATGCTCCCAGCCT GGGACTGTGTGAGGGAGGTCAGAATGGGAAGGAGAGGCT GGGGAACAGGGGAGGAAAGCCCATGGTTGGGAGGCGGAG GACAGGCATTTGGCCTGCAGGAGAAGGTGACCCTCACCCA TGTTTTTCAGTTCACCCTTCGGGTAAAAAATAACTGAGGTA AGGGCCATGGCAGGGTGGGAGAGGCGGTGTGAGAAGGTC CTGTCTTCCCACTATCTGCTCATCAGCCCTTTGAAGGGGAG GAATGTGCCCAAGGACTAAAAAAAGGCCGTGGAGCCAGA GAGGCTGGGGCAGCAGACCTTTCTTGGGCAAATCAGGGG GCCCTGCTGTCCTCCTGTCACCTCCAGAGCCAAAGGATCA AAGGAGGAGGAGCCAGGAGGGGAGAGAGGTGGGAGGGA	Myh6

	GGGTCCCTCCGGAAGGACTCCAAATTTAGACAGAGGGTG GGGGAAACGGGATATAAAGGAACTGGAGCTTTGAGGACA GATAGAGAGACTCCTGCGGCCAGGTAAGAGGAGGTTTG GGGT	
101	AGCAGTCTGGGCTTTCACATGACAGCATCTGGGGCTGCGG CAGAGGGTCGGGTCCGAAGCGCTGCCTTATCAGCGTCCCC AGCCCTGGGAGGTGACAGCTGGCTGGCTTGTGTCAGCCCC TCGGGCACTCACGTATCTCCATCCGACGGGTTTAAAATAG CAAAACTCTGAGGCCACACAATAGCTTGGGCTTATATGGG CTCCTGTGGGGGAAGGGGGAGCACGGAGGGGGCCGGGGC CGCTGCTGCCAAAATAGCAGCTCACAAGTGTTGCATTCT CTCTGGGCGCCGGGCACATTCTGCTGGCTCTGCCCCGCC CGGGGTGGGCGCCGGGGGACCTTAAAGCCTCTGCCCCC AAGGAGCCCTTCCCAGACAGCCGCCGGCACCCACCGCTCC GTGGGAC	cTnT

INCORPORATION BY REFERENCE

[226] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

WHAT IS CLAIMED IS:

1. A nucleic acid construct comprising a nucleotide sequence encoding a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or fragment thereof, wherein said construct comprises at least intron 8 or intron 11 of the wildtype-human *LMNA* gene.
2. The nucleic acid construct of claim 1, wherein intron 8 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 77, or a fragment thereof.
3. The nucleic acid construct of claim 1, wherein intron 11 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 80, or a fragment thereof.
4. The nucleic acid construct of any one of claims 1-3, wherein the nucleotide sequence further comprises intron 10 of the wildtype-human *LMNA* gene.
5. The nucleic acid construct of claim 4, wherein intron 10 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 79, or a fragment thereof.
6. The nucleic acid construct of any one of claims 1-5, wherein the nucleotide sequence further comprises intron 9 of the wildtype-human *LMNA* gene.
7. The nucleic acid construct of claim 6, wherein intron 9 comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the nucleotide sequence of SEQ ID NO: 78, or a fragment thereof.
8. The nucleic acid construct of any one of claims 1-7, wherein the nucleotide sequence comprises introns 8 and 11 of the wildtype-human *LMNA* gene.
9. The nucleic acid construct of any one of claims 1-8, wherein the nucleotide sequence comprises intron 8 of the wildtype-human *LMNA* gene.
10. The nucleic acid construct of any one of claims 1-8, wherein the nucleotide sequence comprises intron 11 of the wildtype-human *LMNA* gene.
11. The nucleic acid construct of any one of claims 1-10, wherein the nucleotide sequence

further comprises introns 9 and 10 of the wildtype-human *LMNA* gene.

12. The nucleic acid construct of any one of claims 1-11, wherein the nucleotide sequence comprises introns 8, 9, 10 and 11 of the wildtype-human *LMNA* gene.

13. The nucleic acid construct of any one of claims 1-12, wherein the nucleic acid construct lacks at least one intron corresponding to introns 1-7 of the wildtype human *LMNA* gene.

14. The nucleic acid construct of any one of claims 1-12, wherein the nucleic acid construct lacks introns 1-7 of the wildtype human *LMNA* gene.

15. The nucleic acid construct of any one of claims 1-14, wherein the nucleic acid construct further comprises intron 9 of the wildtype human *LMNA* gene, and lacks at least one intron corresponding to introns 1-7 of the wildtype human *LMNA* gene.

16. The nucleic acid construct of any one of claims 1-15, wherein the nucleic acid construct further comprises intron 10 of the wildtype human *LMNA* gene, and lacks at least one intron corresponding to introns 1-7 of the wildtype human *LMNA* gene.

17. The nucleic acid construct of any one of claims 1-16, wherein the nucleic acid construct comprises introns 8-11 of the wildtype human *LMNA* gene, and lacks introns 1-7 of the wildtype human *LMNA* gene.

18. The nucleic acid construct of any one of claims 1-17, wherein the regulatory element has less than or equal to 500 base pairs.

19. The nucleic acid construct of any one of claims 1-17, wherein the regulatory element has less than or equal to 900 base pairs.

20. The nucleic acid construct of any one of claims 1-17, wherein the regulatory element has less than or equal to 800 base pairs (bp), 700 bp, 600 bp, 500 bp, 400 bp, 300bp, 250bp, 200bp, 150bp, 140bp, 130bp, 120bp, 110bp, 100bp, 70bp, or 50bp.

21. The nucleic acid construct of any one of claims 1-20, wherein the regulatory element is any one of or combination of: any one of SEQ ID NOs: 30-58, SEQ ID NO: 102, CBA, CMV, SCP, SERpE_TTR, Proto1, minCMV, UCL-HLP, CMVe, Myh6, Desmin, cTnT, α -MHC, MLC-2, CAG, or EFS.

22. The nucleic acid construct of any one of claims 1-21, wherein the regulatory element is any one of or combination of SEQ ID NO: 31, SEQ ID NO: 33, CBA, or minCMV.

23. The nucleic acid construct of claim 21, wherein the regulatory element is SEQ ID NO: 33.
24. The nucleic acid construct of claim 21, wherein the regulatory element is CBA.
25. The nucleic acid construct of claim 21, wherein the regulatory element is minCMV.
26. The nucleic acid construct of any one of claims 1-25, wherein the regulatory element is cell-type selective.
27. The nucleic acid construct of any one of claims 1-26, wherein the regulatory element is selectively expressed in cardiomyocytes.
28. The nucleic acid construct of claim 27, wherein the regulatory element is any one of or combination of Myh6, Desmin, cTnT, α -MHC, or MLC-2.
29. The nucleic acid construct of claim 26, wherein the regulatory element is cTNT.
30. The nucleic acid construct of claim 29, wherein the cTNT regulatory element comprises SEQ ID NO: 101.
31. The nucleic acid construct of any one of claims 1-30, wherein the nucleic acid construct comprises a nucleotide sequence that is at least 80% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof.
32. The nucleic acid construct of any one of claims 1-30, wherein the nucleic acid construct comprises a nucleotide sequence that is at least 90% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof.
33. The nucleic acid construct of any one of claims 1-30, wherein the nucleic acid construct comprises a nucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof.
34. The nucleic acid construct of any one of claims 1-30, wherein the nucleic acid construct comprises a nucleotide sequence that is the sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof.
35. The nucleic acid construct of any one of claims 1-34, wherein the nucleotide sequence encodes a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 12, or a biologically active fragment thereof, and a lamin C polypeptide comprising an amino acid

sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof.

36. The nucleic acid construct of any one of claims 1-34, wherein the nucleotide sequence encodes a lamin A polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, or a biologically active fragment thereof, and a lamin C polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13, or a biologically active fragment thereof.

37. The nucleic acid construct of any one of claims 1-36, wherein the nucleotide sequence further comprises a polyadenylation signal.

38. A viral vector comprising the nucleic acid construct of any one of claims 1-37.

39. A viral vector comprising a nucleotide sequence encoding a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or fragment thereof, wherein said nucleotide sequence comprises at least intron 8 or intron 11 of the wildtype-human *LMNA* gene.

40. A viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type *LMNA* gene; and (b) intron 8 of a wild-type *LMNA* gene.

41. A viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type *LMNA* gene; and (b) intron 11 of a wild-type *LMNA* gene.

42. A viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type *LMNA* gene; and (b) intron 8 and intron 11 of a wild-type *LMNA* gene.

43. The viral vector of any one of claims 39-42, wherein the nucleotide sequence further encodes one or more of introns 9 and 10 of a wild-type *LMNA* gene.

44. A viral vector comprising a nucleotide sequence encoding: (a) exons 1-12 of a wild-type *LMNA* gene; and (b) introns 8-11 of a wild-type *LMNA* gene.

45. The viral vector of any one of claims 38-44, wherein the nucleotide sequence is at least 80% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof.

46. The viral vector of any one of claims 38-44, wherein the nucleotide sequence is at least

90% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof.

47. The viral vector of any one of claims 38-44, wherein the nucleotide sequence is at least 95% identical to the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof.

48. The viral vector of any one of claims 38-44, wherein the nucleotide sequence is the sequence of SEQ ID NO: 3 or SEQ ID NO: 8, or a codon-optimized variant and/or a fragment thereof.

49. The viral vector of any one of claims 38-48, wherein the nucleotide sequence encodes: a) a lamin A polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 12, and b) a lamin C polypeptide having an amino acid sequence at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13.

50. The viral vector of any one of claims 38-48, wherein the nucleotide sequence encodes: a) a lamin A polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 21, and b) a lamin C polypeptide having an amino acid sequence at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 13.

51. The viral vector of any one of claims 38-50, wherein the nucleotide sequence encodes a polypeptide having the amino acid sequence of any one or more of SEQ ID NO: 12-19, or 21.

52. The viral vector of any one of claims 38-51, wherein the nucleotide sequence does not comprise the nucleotide sequence corresponding to introns 1-7 of a wild-type *LMNA* gene.

53. The viral vector of any one of claims 38-52, wherein the nucleotide sequence is operably linked to a regulatory element.

54. The viral vector of any one of claims 38-53, wherein the nucleotide sequence is operably linked to a regulatory element having less than 500 bp.

55. The viral vector of any one of claims 38-53, wherein the nucleotide sequence is operably linked to a regulatory element having less than 900 bp.

56. The viral vector of any one of claims 38-55, wherein the nucleotide sequence is operably linked to a regulatory element having less than or equal to 800bp, 700bp, 600bp, 500bp,

400bp, 300bp, 250bp, 200bp, 150bp, 140bp, 130bp, 120bp, 110bp, 100bp, 70bp, or 50bp.

57. The viral vector of any one of claims 53-56, wherein the regulatory element is any one of or combination of any one of SEQ ID NOs: 30-58, SEQ ID NO: 102, CBA, CMV, SCP, SERpE_TTR, Proto1, minCMV, UCL-HLP, CMVe, Myh6, Desmin, cTnT, α -MHC, MLC-2, CAG, or EFS.

58. The viral vector of any one of claims 53-56, wherein the regulatory element is any one of or combination of SEQ ID NO: 31, SEQ ID NO: 33, CBA, or minCMV.

59. The viral vector of any one of claims 53-58, wherein the regulatory element is SEQ ID NO: 33.

60. The viral vector of any one of claims 53-58, wherein the regulatory element is CBA.

61. The viral vector of any one of claims 53-58, wherein the regulatory element is minCMV.

62. The viral vector of any one of claims 53-59, wherein the regulatory element is cell-type selective.

63. The viral vector of any one of claims 53-62, wherein the regulatory element is selectively expressed in neuronal cells, retinal cells, renal cells, skeletal muscle cells, adipocytes, or cardiomyocytes.

64. The viral vector of any one of claims 53-63, wherein the regulatory element is selectively expressed in cardiomyocytes.

65. The viral vector of claim 64, wherein the regulatory element is any one of or combination of Myh6, Desmin, cTnT, α -MHC, or MLC-2.

66. The viral vector of any one of claims 62-65, wherein the regulatory element is cTNT.

67. The nucleic acid construct of claim 65 or 66, wherein the cTNT regulatory element comprises SEQ ID NO: 101.

68. The viral vector of any one of claims 38-67, wherein the nucleotide sequence further comprises a polyadenylation signal.

69. The viral vector of any one of claims 38-68, wherein the viral vector is an adeno-associated virus (AAV) vector.

70. The viral vector of claim 69, wherein the AAV vector is AAV1, AAV2, AAV5, AAV6,

AAV8, AAV9, scAAV1, scAAV2, scAAV5, scAAV6, scAAV8, or scAAV9.

71. The viral vector of claim 69 or 70, wherein the nucleotide sequence further comprises a 5' AAV inverted terminal repeat (ITR) sequence and a 3' AAV ITR sequence.

72. A viral particle comprising the viral vector of any one of claims 38-71.

73. The viral particle of claim 72, wherein the viral particle comprises capsid proteins of an AAV.

74. The viral particle of any one of claims 69-73, wherein the AAV is an AAV6 or AAV9.

75. A host cell comprising the nucleic acid construct of any one of claims 1-36, the viral vector of any one of claims 38-71 or the viral particle of any one of claims 72-74.

76. A pharmaceutical composition comprising the nucleic acid construct of any one of claims 1-36, the viral vector of any one of claims 38-71, the viral particle of any one of claims 72-74, the host cell of claim 75, and one or more pharmaceutically acceptable excipients.

77. A method for treating a laminopathy in a subject comprising administering a therapeutically effective amount of the nucleic acid construct of any one of claims 1-37, the viral vector of any one of claims 38-71, the viral particle of any one of claims 72-74, the host cell of claim 75, or the pharmaceutical composition of claim 76 to a subject in need thereof.

78. A method for expressing a lamin A polypeptide and a lamin C polypeptide, or a biologically active variant and/or a fragment thereof in a subject comprising administering to said subject a therapeutically effective amount of the nucleic acid construct of any one of claims 1-36, the viral vector of any one of claims 38-71, the viral particle of any one of claims 72-74, the host cell of claim 75, or the pharmaceutical composition of claim 76.

79. A method for increasing expression of a functional lamin A polypeptide and a functional lamin C polypeptide, or a biologically active variant and/or a fragment thereof in a subject comprising administering to said subject a therapeutically effective amount of the nucleic acid construct of any one of claims 1-36, the viral vector of any one of claims 38-71, the viral particle of any one of claims 72-74, the host cell of claim 75, or the pharmaceutical composition of claim 76.

80. The method of claim 78 or 79, wherein the subject is suffering from a laminopathy.

81. The method of claim 77 or 80, wherein the laminopathy is any one or more of: Charcot-Marie-Tooth disease, Emery-Dreifuss muscular dystrophy, familial partial lipodystrophy, Hutchinson-Gilford progeria syndrome, limb-girdle muscular dystrophy, *LMNA*-related congenital muscular dystrophy, mandibuloacral dysplasia, arrhythmogenic right ventricular cardiomyopathy, familial atrial fibrillation, left ventricular noncompaction, or dilated cardiomyopathy.

82. The method of any one of claims 77-81, wherein said nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition is administered intramyocardially, intravenously, intramuscularly, intrathecally, subcutaneously, systemically, or locally into the myocardium.

83. The method of any one of claims 77-81, wherein said nucleic acid construct, viral vector, viral particle, host cell, or pharmaceutical composition is administered intravenously or systemically.



File 2

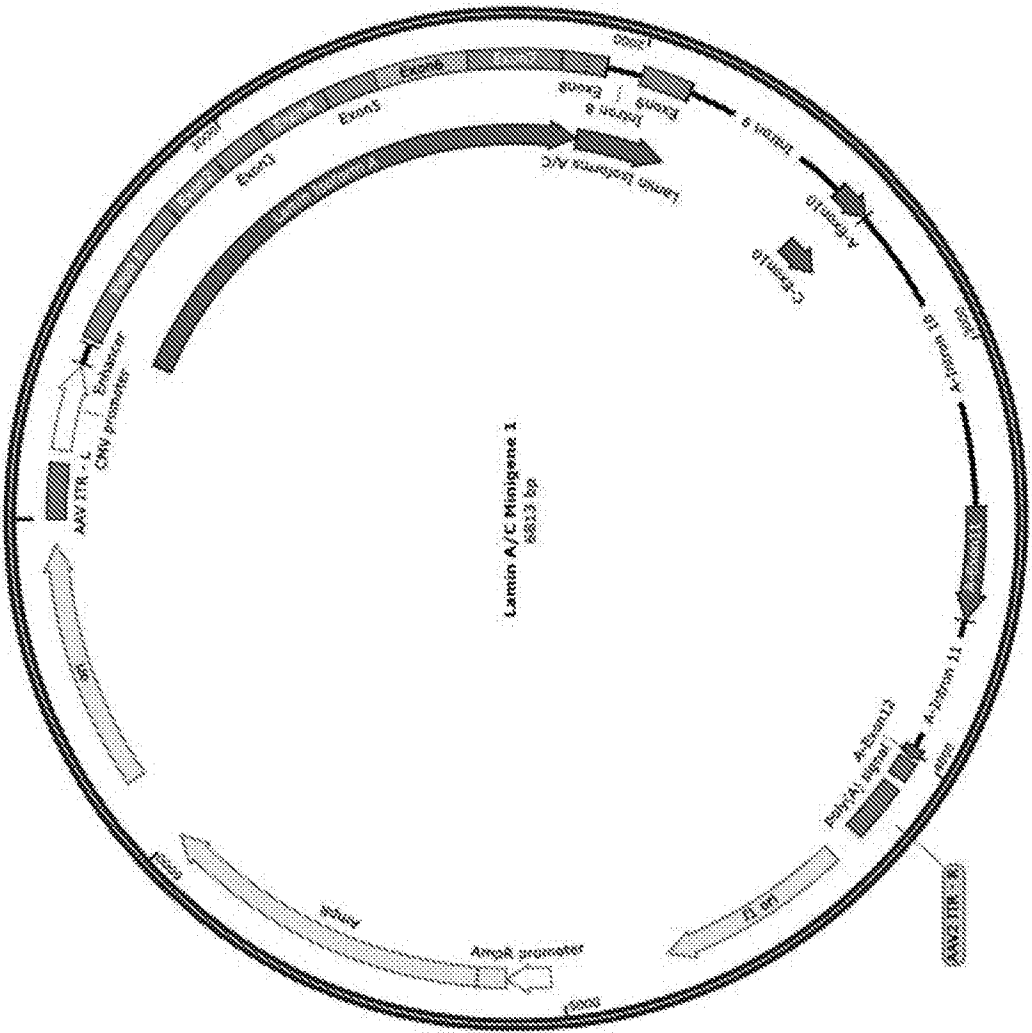
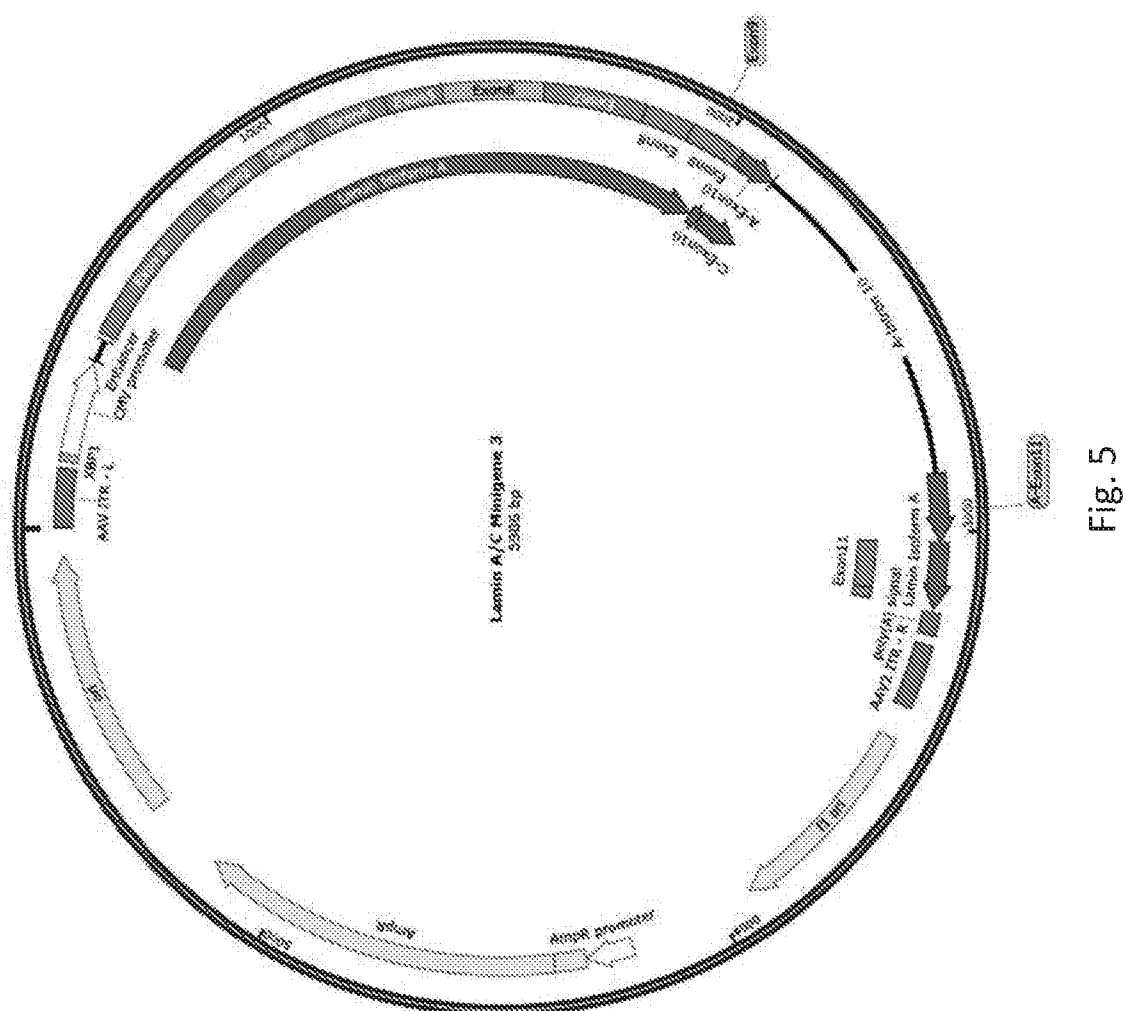


Fig. 3

4
E.O.



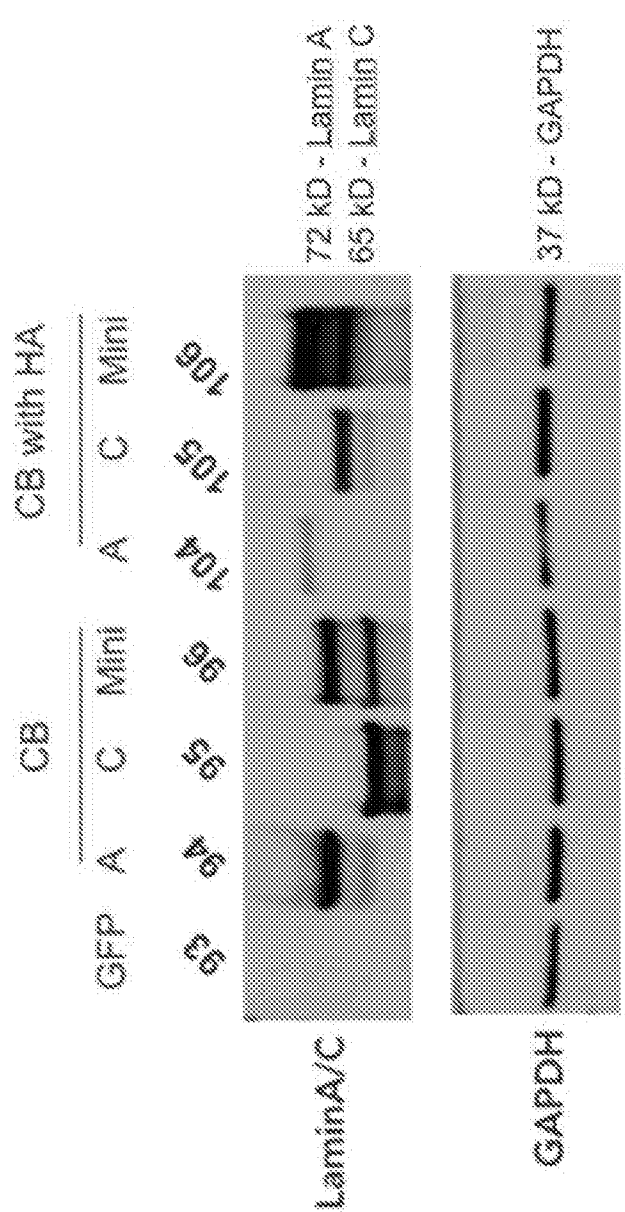


Fig. 6

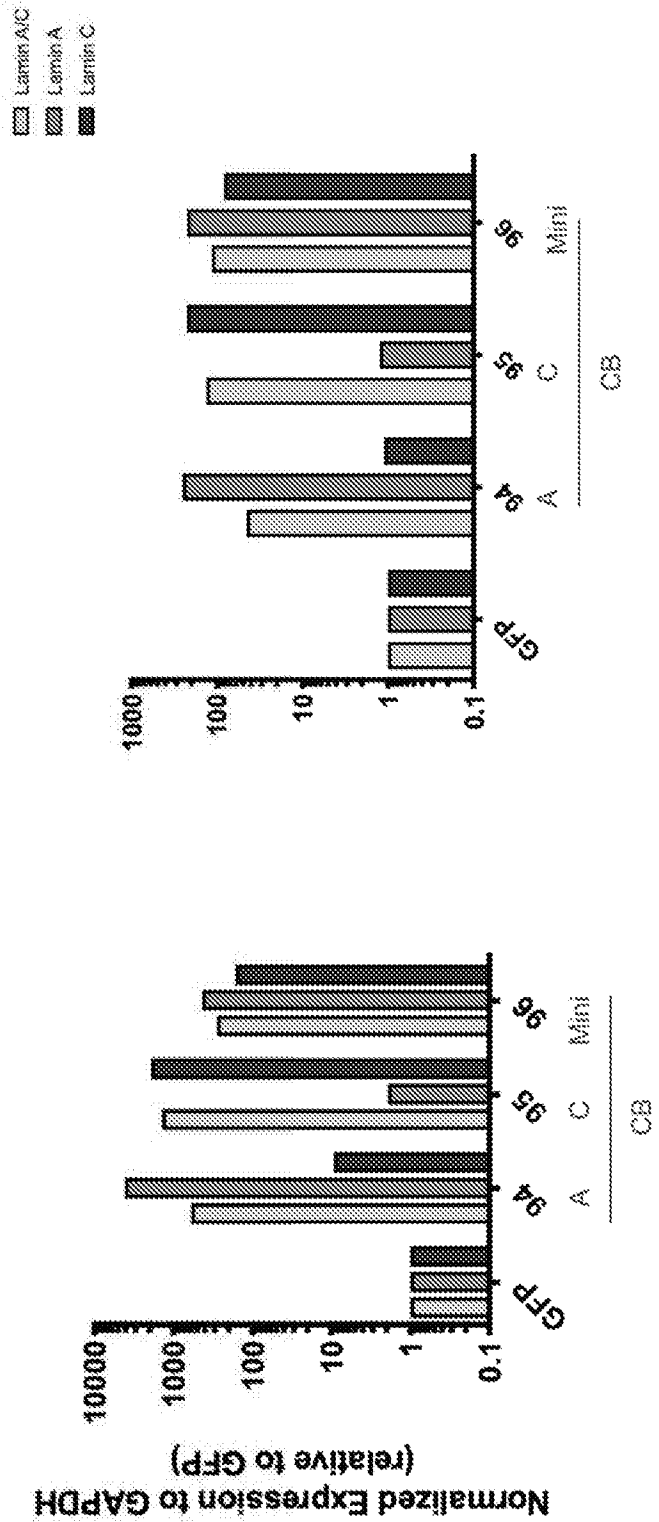


Fig. 7

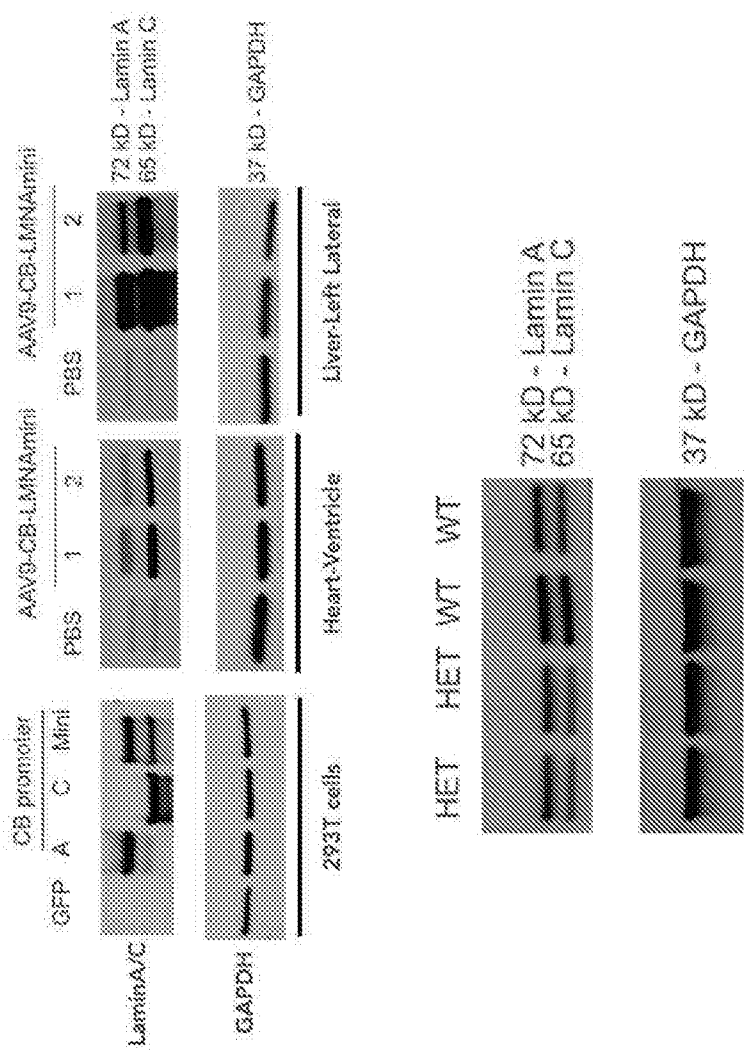


Fig. 8

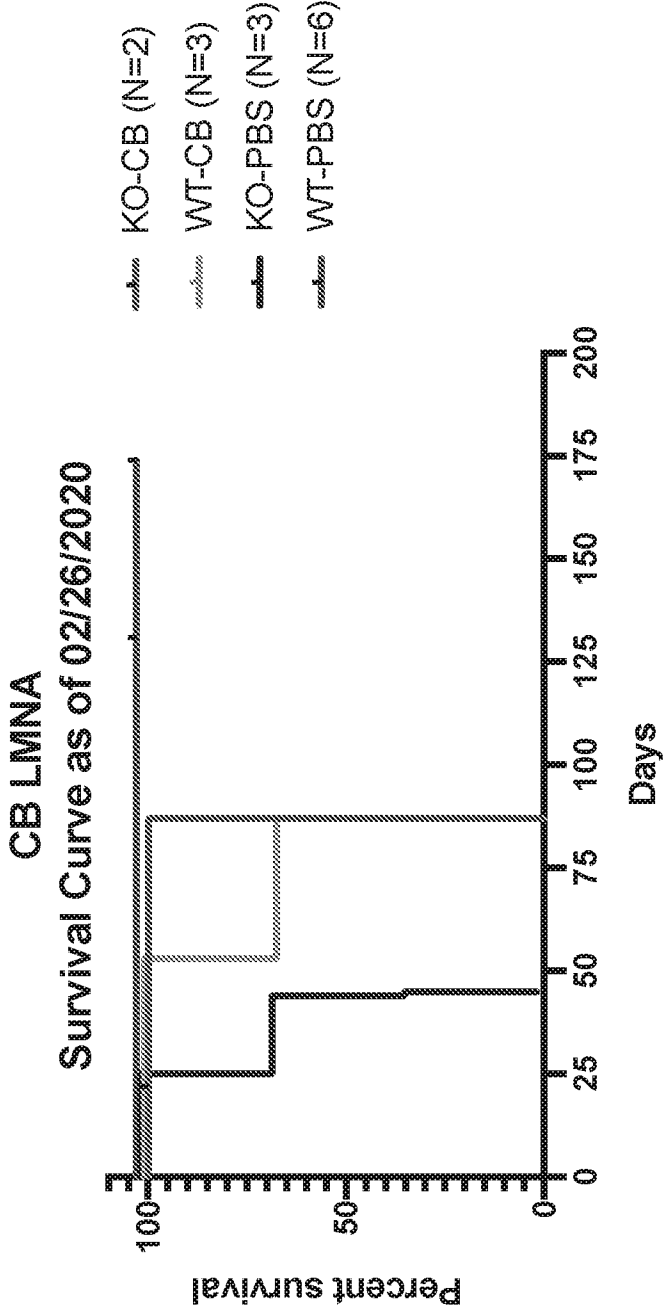


Fig. 9

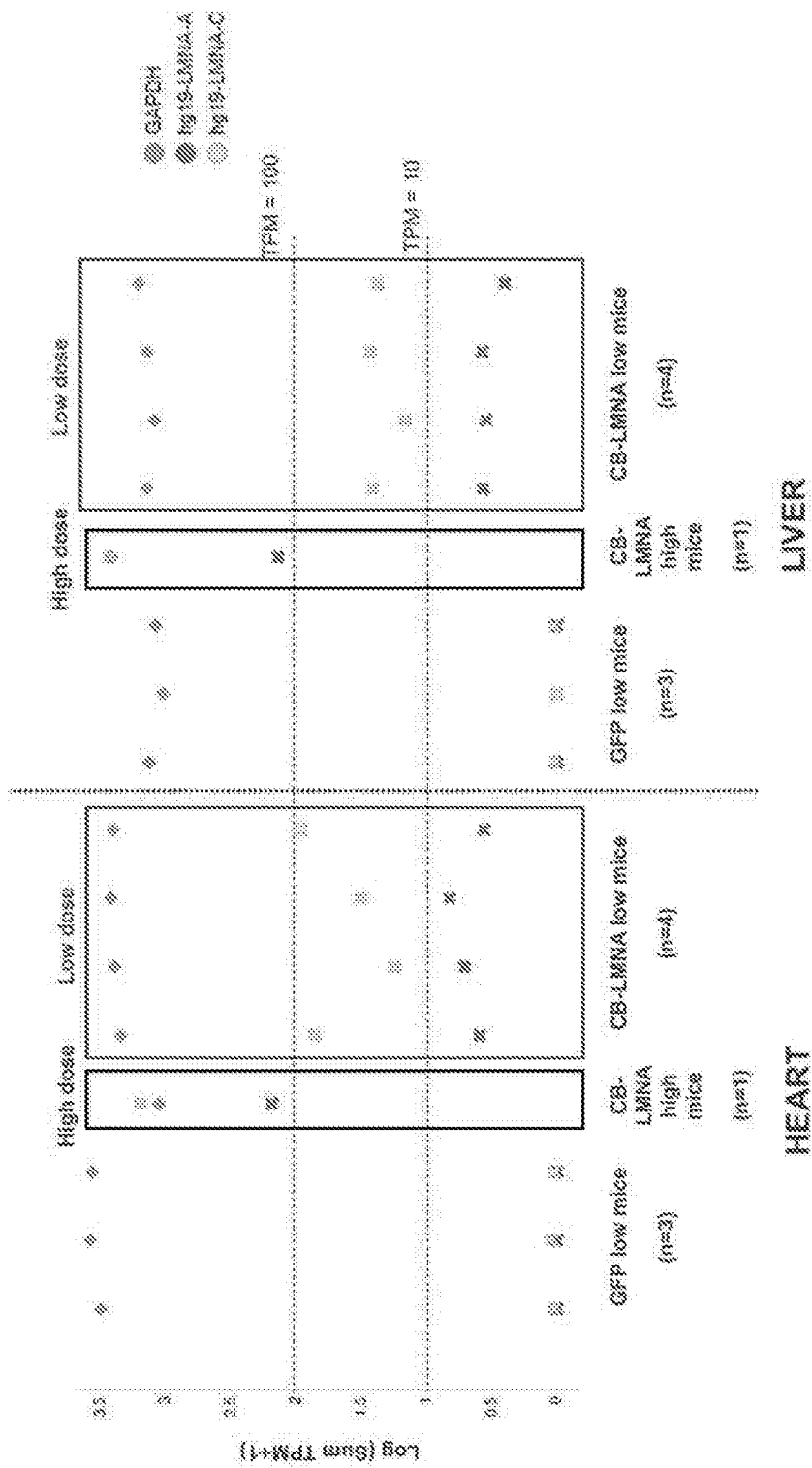


Fig. 10A

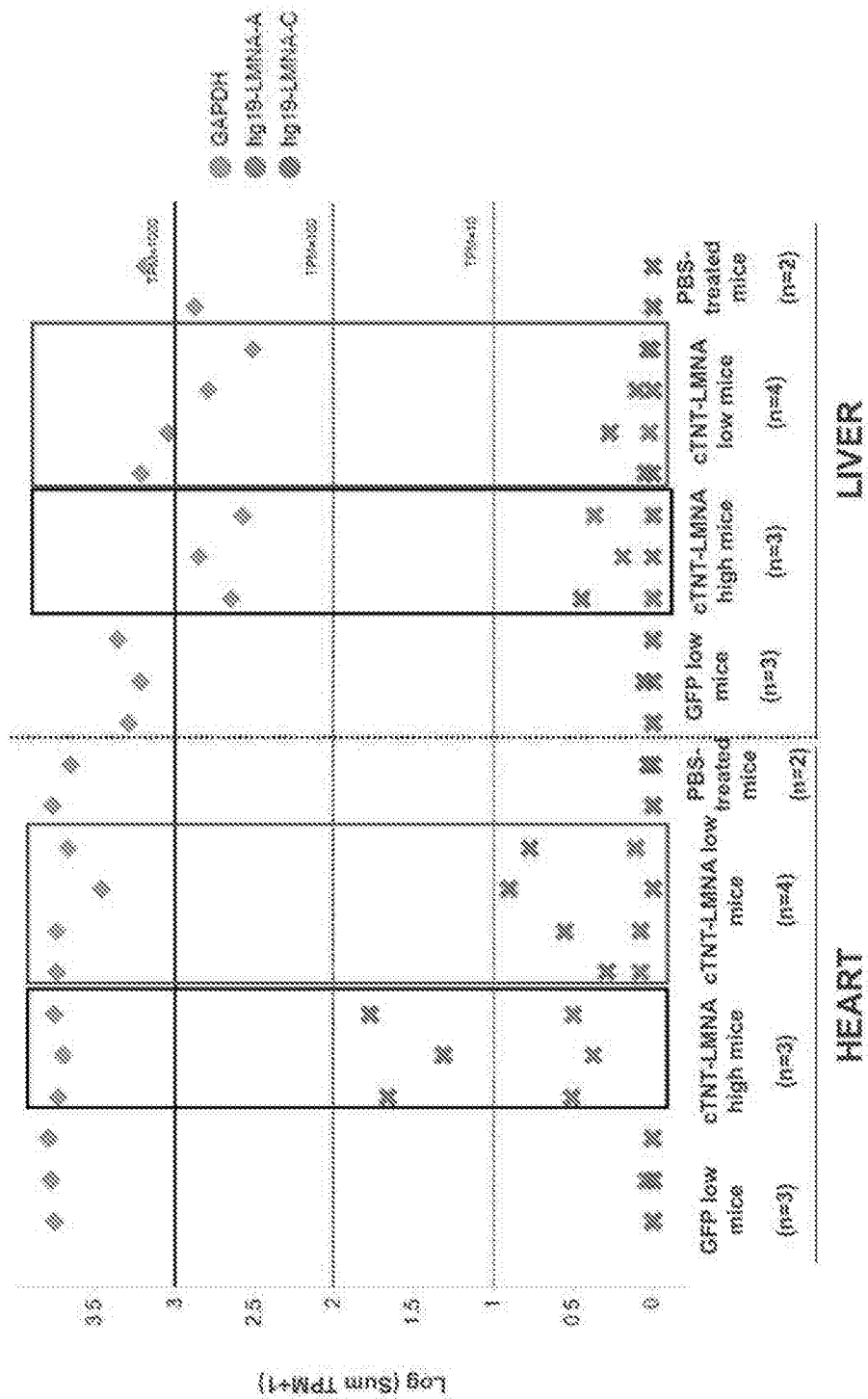


Fig. 10B

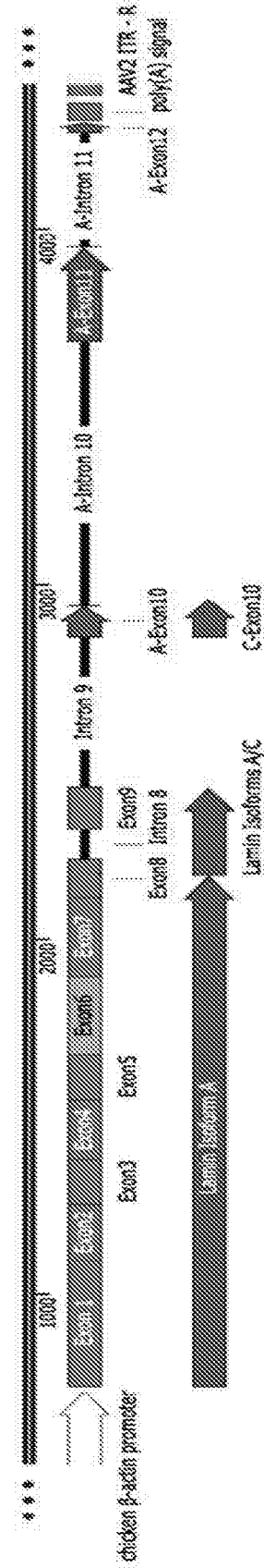


Fig 11A

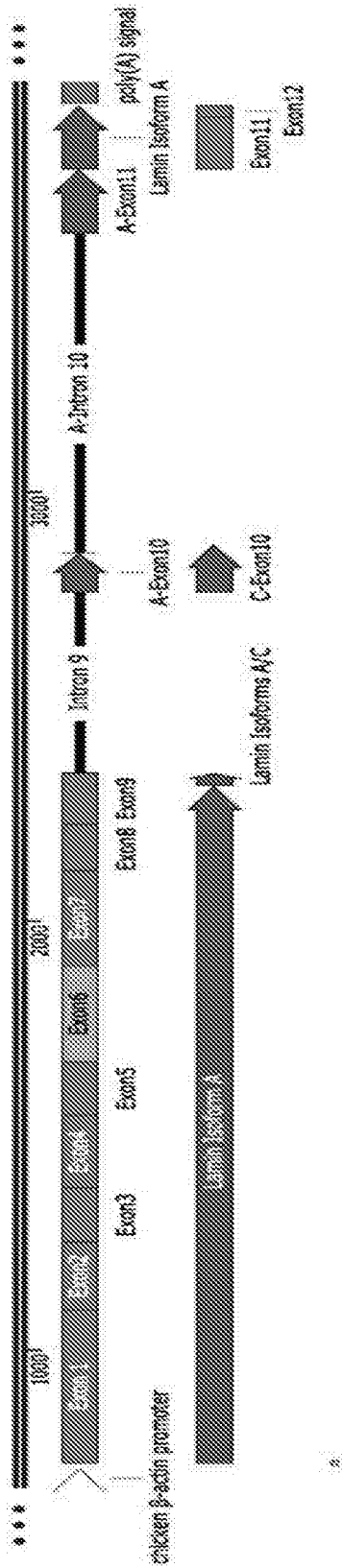


Fig 11B

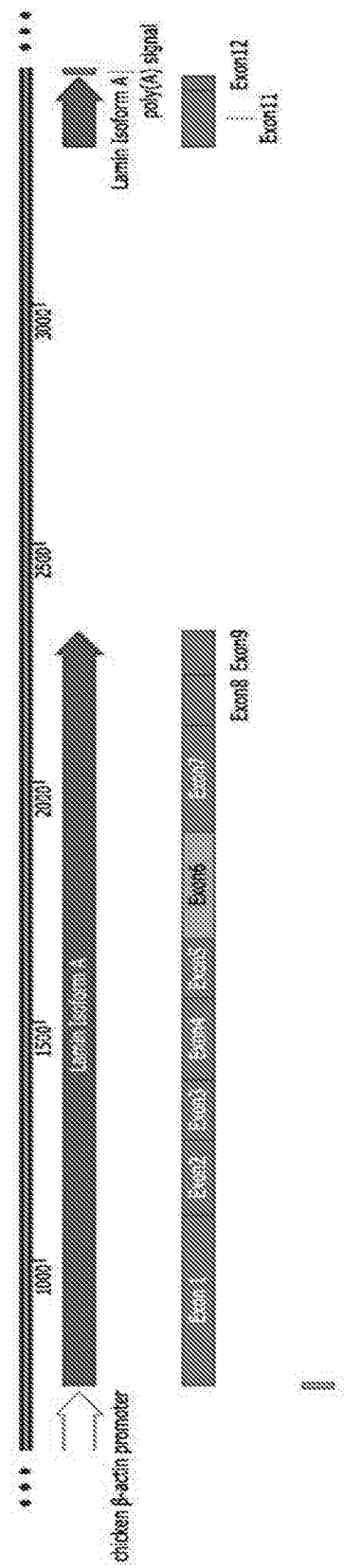


Fig 11C

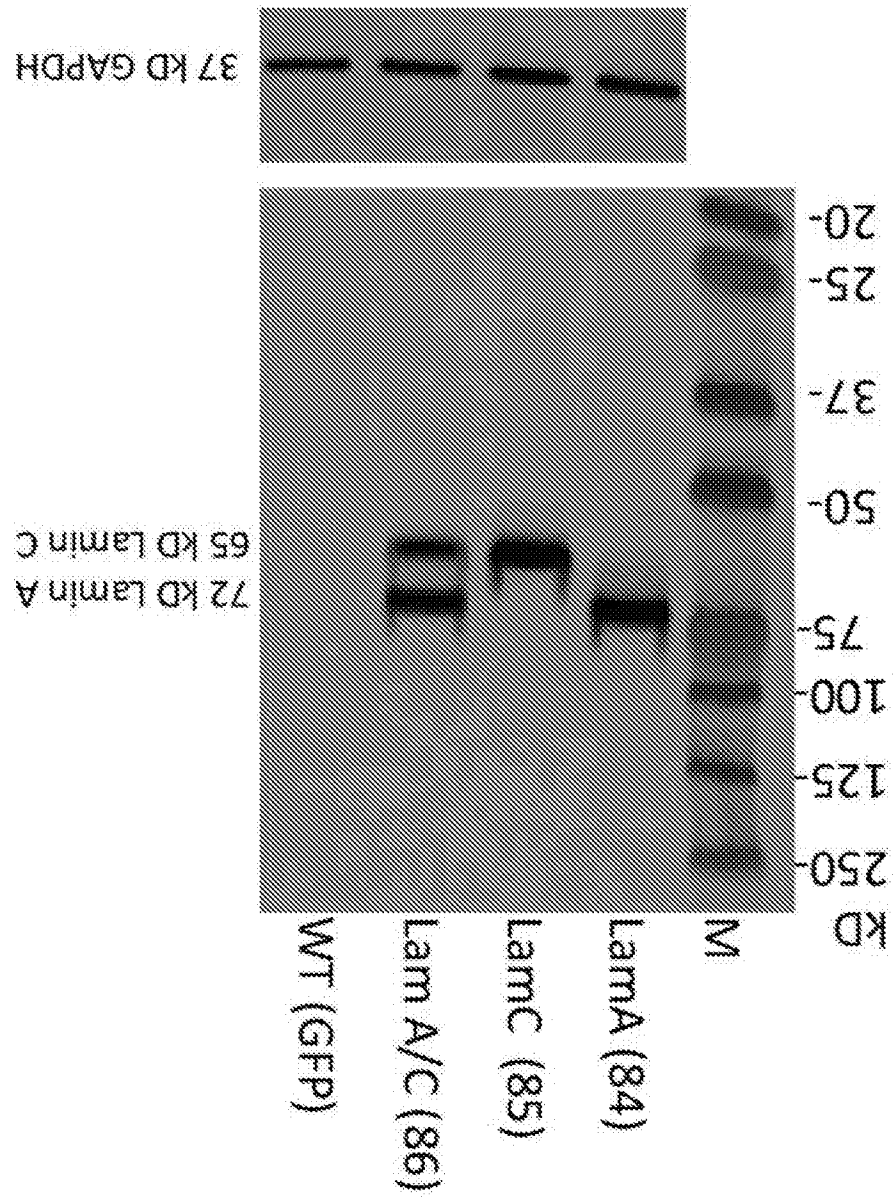


Fig 12

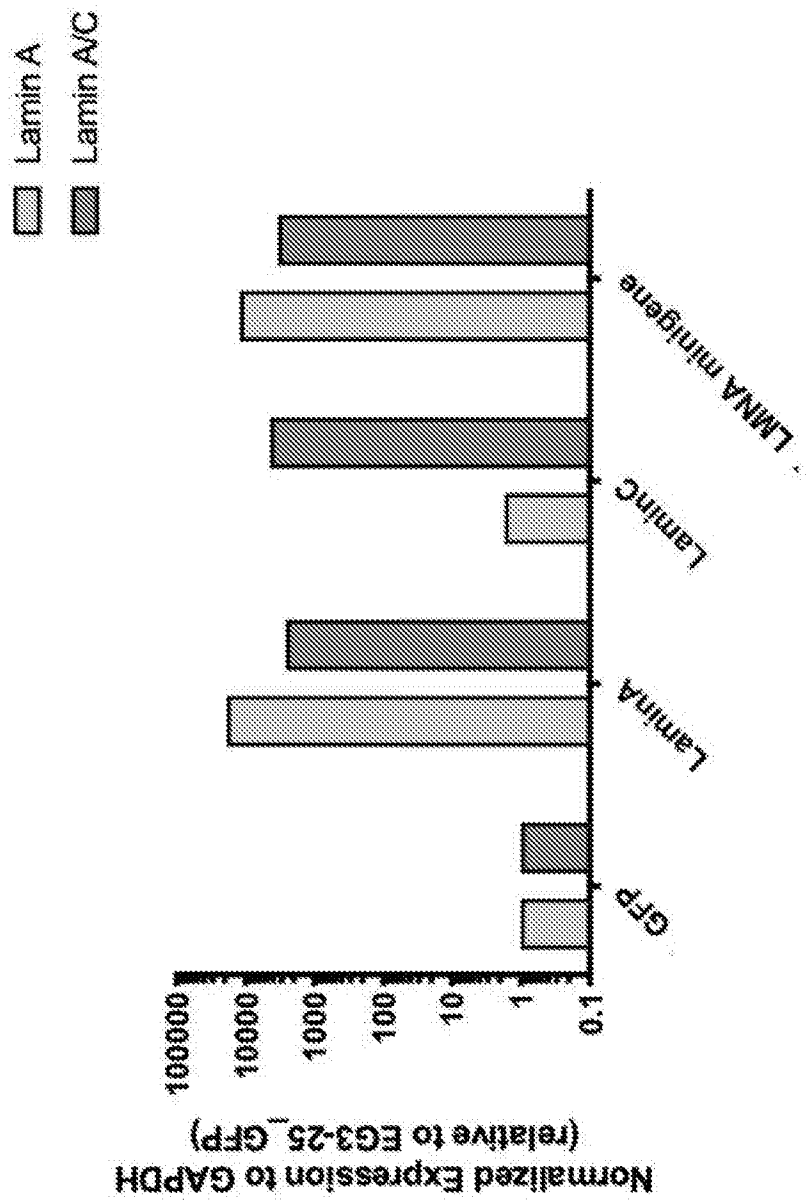


Fig 13

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☐ forming part of the international application as filed:
☐ in the form of an Annex C/ST.25 text file.
☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:
SEQ ID NOs: 3, 8, 77-80 were searched at 80% sequence identity.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2020/020520

A. CLASSIFICATION OF SUBJECT MATTER

C12N 15/86 (2006.01) A61K 48/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PATENW, CAPLus, BIOSIS, EMBASE, MEDLINE - keywords used: LMNA, lamin A, lamin C, laminopathies, intron, and like terms

IPC/CPC: C12N15/86, C12N2800/00, C12N2830/008, A61K48/00

GenomeQuest: SEQ ID NOs: 3, 8, 77-80 searched at 80% sequence identity.

Esp@cenet, PubMed: Applicant/Inventors search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"D" document cited by the applicant in the international application	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
5 June 2020Date of mailing of the international search report
05 June 2020

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/US2020/020520
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAGELIUS, H., et al., "Targeted transgenic expression of the mutation causing Hutchinson-Gilford progeria syndrome leads to proliferative and degenerative epidermal disease", Journal of Cell Science, 2008, Vol. 121, pp 969-978 Figures 1 and 2	1-77, 81-83
A	LIU, G-H., et al., "Targeted Gene Correction of Laminopathy-Associated <i>LMNA</i> Mutations in Patient-Specific iPSCs", Cell Stem Cell, 2011, Vol. 8, pp 688-694	1-83
A	LIN, F., et al., "Expression of Nuclear Lamins in Human Tissues and Cancer Cell Lines and Transcription from the Promoters of the Lamin A/C and B1 Genes", Experimental Cell Research, 1997, Vol. 236, pp 378-384	1-83
A	LIN, F., et al., "Structural Organization of the Human Gene Encoding Nuclear Lamin A and Nuclear Lamin C", The Journal of Biological Chemistry, 1993, Vol. 268, pp 16321-16326	1-83
A	WOJTANIK, K.M., "The role of <i>LMNA</i> in adipose: a novel mouse model of lipodystrophy based on the Dunnigan-type familial partial lipodystrophy mutation", Journal of Lipid Research, 2009, Vol. 50, pp 1068-1079	1-83
A	TSAL, J-Y., et al., "Cardiac Myocyte-specific Expression of LMNAD300N Activates MMP2 and Induces Severe Interstitial Fibrosis and Cardiac Systolic Dysfunction Leading to Premature Death in Mice", Circulation, 2012, Vol. 126, Conference Abstract 17773	1-83
A	US 9856473 B2 (IONIS PHARMACEUTICALS, INC.) 02 January 2018	1-83
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INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/US2020/020520	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 9856473 B2 02 January 2018 US 2014309282 A116 Oct 2014 US 9856473 B202 Jan 2018 US 2009156526 A118 Jun 2009 US 8258109 B204 Sep 2012 US 2013035370 A107 Feb 2013 US 8791088 B229 Jul 2014 WO 2007047913 A226 Apr 2007			
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2019)			