rowth and viability, SUN1 null mice are infertile and deaf. Simultaneous loss of *Sun1* and *Sun2* results in perinatal lethality, indicating a degree of redundancy during embryogenesis [K. Lei *et al*., *Proc Natl Acad Sci USA* 106: 10207-10212 (2009)].

There is a need to develop alternative methods to ameliorate the negative effects over-accumulation of Sun1 has on cells carrying *Lmna* mutations. The present disclosure aims at providing such a method.

SUMMARY

Surprisingly, the inventors have found that disruption of the LINC complex rather than removal of accumulated Sun1 protein can ameliorate diseases caused by one or more *Lmna* mutations. One way of achieving the disruption is via an expression construct/vector comprising an operably linked transgene, the expression of which generates dominant negative SUN domain protein or mutated endogenous SUN domain protein and/or dominant negative KASH domain protein or mutated endogenous KASH domain protein. The exogenous dominant negative SUN domain and KASH domain proteins act as LINC complex binding competitors, thereby uncoupling the nucleus from its linkage to the cytoskeleton. The mutated SUN domain and KASH domain proteins are endogenous Sun and Nesprin proteins that have been mutated in the SUN or KASH domain, respectively, and cannot form a LINC complex because they cannot bind to their cognate LINC complex partner. These strategies may be used to disrupt the LINC complex to treat, for example, laminopathies. The result was achieved without actively reducing the endogenous SUN1 protein levels. Results shown herein support these claims.

According to a first aspect of the disclosure, there is provided use of an nucleic acid molecule comprising an adeno-associated expression vector (AAV) in the manufacture of a medicament for treating a disease caused by a mutation to *LMNA*, wherein the AAV comprises an operably linked transgene, wherein expression of the transgene in a transfected cell results in disruption of a LInker of Nucleoskeleton and Cytoskeleton (LINC) complex in the transfected cell, and wherein the transgene comprises nucleic acid sequences for expressing the SUN domain of a SUN domain-containing protein, an N-terminal signal sequence, a signal peptidase cleavage site, and a C-terminal targeting peptide sequence preventing secretion of a peptide expressed from the transgene. In one example, there is provided an isolated nucleic acid molecule, wherein the nucleic acid molecule comprises an expression vector and a transgene, whereby the transgene is operably linked to the expression vector, wherein expression of the transgene in a transfected cell results in disruption of a LINC complex in the transfected cell.

In some examples, the expression vector is a cardiac- or cardiomyocyte-specific expression vector.

CLAIMS:

1. Use of an nucleic acid molecule comprising an adeno-associated expression vector (AAV) in the manufacture of a medicament for treating a disease caused by a mutation to *LMNA*, wherein the AAV comprises an operably linked transgene, wherein expression of the transgene in a transfected cell results in disruption of a LInker of Nucleoskeleton and Cytoskeleton (LINC) complex in the transfected cell, and wherein the transgene comprises nucleic acid sequences for expressing the SUN domain of a SUN domain-containing protein, an N-terminal signal sequence, a signal peptidase cleavage site, and a C-terminal targeting peptide sequence preventing secretion of a peptide expressed from the transgene.

2. The use according to claim 1, wherein expression of the transgene results in the disruption of the protein-protein interaction between SUN and KASH of the LINC complex.

3. The use according to claim 1 or claim 2, wherein the transgene comprises nucleic acid sequences for expressing the lumenal domain of the SUN domain-containing protein, wherein the lumenal domain comprises a coiled coil domain and a SUN domain.

4. The use according to any one of claims 1 to 3, wherein the SUN domain-containing protein is SUN1 or SUN2.

5. The use according to any one of claims 1 to 4, wherein the C-terminal targeting peptide sequence is a KDEL sequence.

6. The use according to any one of claims 1 to 5, wherein the AAV is a cardiac- or cardiomyocyte-specific expression vector.

7. The use according to any one of claims 1 to 6, wherein in the AAV vector is selected from the group consisting of: AAV9, AAV1, AAV6, AAV8, AAV2i8, and AAV9.45.

8. The use according to any one of claims 1 to 7, wherein the AAV comprises a cardiac- or cardiomyocyte-specific promoter.

9. The use according to any one of claims 1 to 8, wherein the AAV comprises a cardiac- or cardiomyocyte-specific promoter selected from the group comprising a cardiac troponin T promoter (cTnT), a α-myosin heavy chain (α-MHC) promoter and a myosin light chain (MLC2v) promoter.

10. The use according to any one of claims 1 to 9, wherein the disease is selected from the group consisting of: a cardiovascular disease, restrictive dermopathy, familial partial lipodystrophy, mandibuloacral dysplasia with type A lipodystrophy, metabolic syndrome, Charcot-Marie-Tooth disease type 2, Charcot-Marie-Tooth disease type 2B1 and diseases presented in normal font in Table 1.

11. The use according to claim 10, wherein the cardiovascular disease is selected from the group consisting of: laminopathy, cardiomyopathy, dilated cardiomyopathy (DCM), dilated cardiomyopathy 1A, dilated cardiomyopathy with conduction system defects, cardiomyopathy with advanced AV block and arrhythmia, lone atrial fibrillation; muscular

dystrophy, cardiomyopathy associated with Emery-Dreifuss muscular dystrophy (autosomal dominant), cardiomyopathy associated with Emery-Dreifuss muscular dystrophy (autosomal recessive), cardiomyopathy associated with Limb-girdle muscular dystrophy type 1B, cardiomyopathy associated with congenital muscular dystrophy; premature aging syndromes, cardiomyopathy associated with Atypical Werner syndrome, cardiomyopathy associated with Hutchinson-Gilford progeria syndrome, and diseases presented in bold font in Table 1.