

CLAIMS

WHAT IS CLAIMED IS:

1. ~~Use of a A method for treating a heart disease or disorder in an individual in need thereof, the method comprising administering a~~ composition comprising (a) a ~~gene therapy~~ viral vector comprising a nucleic acid ~~sequence that is at least 90% identical to SEQ ID NO: 2~~ encoding a plakophilin 2 (PKP2) polypeptide ~~or a fragment thereof~~ operatively linked to ~~at least one~~ a cardiac specific promoter and a 3' element; and (b) a pharmaceutically acceptable carrier or excipient ~~in the manufacture of a medicament for treating arrhythmogenic right ventricular cardiomyopathy (ARVC) or arrhythmogenic cardiomyopathy (ACM) in a mammal with ARVC or ACM.~~
- ~~2. The method of claim 1, wherein the gene therapy vector comprises a viral vector.~~
- ~~3.2. The method use of claim 21, wherein the viral vector is selected from the group consisting of an adeno-associated virus, an adenovirus, a lentivirus, a pox virus, a vaccinia virus, and a herpes virus.~~
- ~~4.3. The use method of claim 2 or claim 31, wherein the gene therapy viral vector is an adeno-associated virus.~~
- ~~4. The use method of claim 43, wherein the adeno-associated virus is selected from the group consisting of an AAV6, an AAV.rh74, an AAV8, and an AAV9.~~
- ~~5. The use of claim 4, wherein the adeno-associated virus is an AAV9.~~
- ~~6. The method of claim 5, wherein the adeno-associated virus is an AAV9 or a derivative thereof.~~
- ~~7. The method of claim 6, wherein the AAV9 has a nucleic acid sequence with at least 95% identity to SEQ ID NO: 7.~~
- ~~8. The method of any one of claims 1 to 7, wherein the gene therapy vector targets cells in the myocardium, the epicardium, or both.~~
- ~~9. The method of any one of claims 1 to 8, wherein the heart disease or disorder is arrhythmogenic right ventricular cardiomyopathy (ARVC) or arrhythmogenic cardiomyopathy (ACM).~~
- ~~10. The method of any one of claims 1 to 9, wherein the composition is administered intravenously, intracardially, pericardially, or intraarterially.~~
- ~~11. The method of any one of claims 1 to 10, wherein the promoter is a cardiac specific promoter.~~
- ~~12. The method of claim 11, wherein the cardiac specific promoter directs gene expression in the myocardium, the epicardium, or both.~~
- ~~13. The method of claim 11 or claim 12, wherein the cardiac specific promoter is a troponin promoter, or an alpha-myosin heavy chain promoter.~~
- ~~14. The method of claim 13, wherein the troponin promoter has a nucleic acid sequence having at least 95% identity to SEQ ID NO: 3.~~
- ~~15. The method of any one of claims 1 to 12, wherein the promoter is a PKP2 promoter.~~
- ~~16. The method of claim 15, wherein the PKP2 promoter has a nucleic acid sequence having at least 95% identity to SEQ ID NO: 4.~~

~~17. The method of any one of claims 1 to 10, wherein the promoter is a constitutive promoter.~~

~~18. The method of claim 17, wherein the constitutive promoter is a beta-actin promoter.~~

~~19.6.~~ The use method of ~~any one of claims 1 to 18,~~ wherein the ~~gene therapy~~viral vector further comprises a cardiac specific enhancer.

~~20. The method of any one of claims 1 to 19, wherein the gene therapy vector further comprises a 3' element.~~

~~21.7.~~ The use method of claim ~~20~~1, wherein the 3' element comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE), a bovine growth hormone polyadenylation (bGH polyA) sequence, or a combination thereof.

~~8.~~ The use method of ~~any one of claims 1 to 21,~~ wherein the nucleic acid encoding the PKP2 gene ~~has a sequence having is~~ at least 95% ~~identity~~identical to ~~SEQ ID NO: 1 or~~ SEQ ID NO: 2.

~~9.~~ The use of claim 1, wherein the nucleic acid encoding the PKP2 gene is identical to SEQ ID NO: 2.

~~22.10.~~ The use of claim 1, wherein the PKP2 gene encodes a PKP2 polypeptide having a sequence of SEQ ID NO: 8.

~~23. The method of any one of claims 1 to 22, wherein the gene therapy vector comprises a nucleic acid sequence having at least 95% identity to SEQ ID NO: 5.~~

~~24.11.~~ The use method of ~~any one of claims 1 to 23,~~ wherein the pharmaceutically acceptable carrier or excipient comprises a buffer, a polymer, a salt, or a combination thereof.

~~25.12.~~ The use method of ~~any one of claims 1 to 24,~~ wherein the medicament reverses, reduces, or prevents at least one of fibrofatty tissue replacement; myocardial atrophy; predominant right ventricular dilation; ventricular arrhythmias; sudden cardiac death; exercise-triggered cardiac events; right ventricular cardiomyopathy, dilation, or heart failure; left ventricular cardiomyopathy, dilation, or heart failure; atrial arrhythmias; syncope; palpitations; shortness of breath; or chest pain~~wherein the method reverses, reduces, or prevents at least one of fibrofatty tissue replacement, myocardial atrophy, predominant right ventricular dilation, ventricular arrhythmias, sudden cardiac death, or exercise-triggered cardiac events.~~

~~26. The method of claim 25, wherein the method reverses, reduces, or prevents fibrofatty tissue replacement in myocardium, epicardium, or both.~~

~~27.13.~~ The method use of ~~any one of claims 1 to 26,~~ wherein the ~~method~~medicament restores desmosome structure and/or function.

~~28.14.~~ The method use of ~~any one of claims 1 to 27,~~ wherein the ~~method~~medicament restores PKP2 protein and activity levels.

~~29.15.~~ The method use of ~~any one of claims 1 to 28,~~ wherein the ~~method~~medicament restores PKP2 induced gene expression.

~~30.16.~~ The method use of ~~any one of claims 1 to 29,~~ wherein the ~~method~~medicament restores expression of one or more of Ryanodine Receptor 2 (Ryr2), Ankyrin-B (Ank2), Cacna1c (CaV1.2), ~~triadin~~Triadin (Trdn), or ~~ealsequestrin~~Calsequestrin-2 (Casq2).

~~31.17.~~ The ~~method-use~~ of ~~any one of~~ claims ~~1 to 30~~, wherein the ~~individual-mammal~~ is identified as having at least one variation in a desmosome protein.

~~32.18.~~ The ~~method-use~~ of claim ~~3117~~, wherein the desmosome protein is PKP2.

~~33.19.~~ The ~~method-use~~ of claim ~~3218~~, wherein the variation comprises a deletion, an insertion, a single nucleotide variation, or a copy number variation.

~~34. A gene therapy vector comprising a plakophilin 2 gene operatively linked to at least one promoter.~~

~~35. The gene therapy vector of claim 34, wherein the gene therapy vector comprises a viral vector.~~

~~36. The gene therapy vector of claim 35, wherein the viral vector is selected from the group consisting of an adeno-associated virus, an adenovirus, a lentivirus, a pox virus, a vaccinia virus, and a herpes virus.~~

~~37. The gene therapy vector of claim 35 or claim 36, wherein the gene therapy vector is an adeno-associated virus.~~

~~38. The gene therapy vector of claim 37, wherein the adeno-associated virus is selected from the group consisting of an AAV6, an AAV8, and an AAV9.~~

~~39. The gene therapy vector of claim 38, wherein the adeno-associated virus is an AAV9 or a derivative thereof.~~

~~40. The gene therapy vector of claim 39, wherein the AAV9 has a nucleic acid sequence with at least 95% identity SEQ ID NO: 7.~~

~~41. The gene therapy vector of any one of claims 34 to 40, wherein the gene therapy vector targets cells in the myocardium, the epicardium, or both.~~

~~42. The gene therapy vector of any one of claims 34 to 41, wherein the promoter is a cardiac specific promoter.~~

~~43. The gene therapy vector of claim 42, wherein the cardiac specific promoter directs gene expression in the myocardium, the epicardium, or both.~~

~~44. The gene therapy vector of claim 42 or claim 43, wherein the cardiac specific promoter is a troponin promoter or an alpha-myosin heavy chain promoter.~~

~~45. The gene therapy vector of claim 43, wherein the troponin promoter has a nucleic acid sequence having at least 95% identity to SEQ ID NO: 3.~~

~~46. The gene therapy vector of any one of claims 34 to 45, wherein the promoter is a PKP2 promoter.~~

~~47. The gene therapy vector of claim 46, wherein the PKP2 promoter has a nucleic acid sequence having at least 95% identity to SEQ ID NO: 4.~~

~~48. The gene therapy vector of any one of claims 34 to 41, wherein the promoter is a constitutive promoter.~~

~~49. The gene therapy vector of claim 48, wherein the constitutive promoter is a beta-actin promoter.~~

~~50. The gene therapy vector of any one of claims 34 to 49, further comprising a cardiac specific enhancer.~~

~~51. The gene therapy vector of any one of claims 34 to 50, wherein the gene therapy vector further comprises a 3' element.~~

~~52. The gene therapy vector of claim 51, wherein the 3' element comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE), a bovine growth hormone polyadenylation (bGH polyA) sequence, or a combination thereof.~~

~~53. The gene therapy vector of any one of claims 34 to 52, wherein the nucleic acid encoding the PKP2 gene has a sequence having at least 95% identity to SEQ ID NO: 1 or SEQ ID NO: 2.~~

~~54. The gene therapy vector of any one of claims 34 to 53, wherein the gene therapy vector comprises a nucleic acid sequence having at least 95% identity to SEQ ID NO: 5.~~

~~55. The gene therapy vector of any one of claims 34 to 54, wherein the gene therapy vector is formulated in a pharmaceutically acceptable carrier or excipient comprising a buffer, a polymer, a salt, or a combination thereof.~~

~~56. A method for treating a heart disease or disorder in an individual in need thereof, the method comprising administering a composition comprising (a) a gene therapy vector comprising a nucleic acid encoding a plakophilin 2 (PKP2) polypeptide or a fragment thereof operatively linked to a promoter and a 3' element; and (b) a pharmaceutically acceptable carrier or excipient.~~

~~57. The method of claim 56, wherein the gene therapy vector comprises a viral vector selected from the group consisting of an adeno-associated virus, an adenovirus, a lentivirus, a pox virus, a vaccinia virus, and a herpes virus.~~

~~58. The method of claim 56, wherein the gene therapy vector is an adeno-associated virus.~~

~~59. The method of claim 58, wherein the adeno-associated virus is selected from the group consisting of an AAV6, an AAV8, and an AAV9.~~

~~60. The method of claim 59, wherein the adeno-associated virus targets cells in the myocardium, the epicardium, or both.~~

~~61. The method of claim 59, wherein the adeno-associated virus is an AAV9 having a nucleic acid sequence with at least 95% identity to SEQ ID NO: 7.~~

~~62. The method of claim 56, wherein the heart disease or disorder is arrhythmogenic right ventricular cardiomyopathy (ARVC) or arrhythmogenic cardiomyopathy (ACM).~~

~~63. The method of claim 56, wherein the promoter is a promoter that causes expression in tissues including the heart or a cardiac specific promoter.~~

~~64. The method of claim 63, wherein the cardiac specific promoter directs gene expression in the myocardium, the epicardium, or both.~~

~~65. The method of claim 63, wherein the cardiac specific promoter is a PKP2 promoter, a troponin promoter, or an alpha-myosin heavy chain promoter.~~

~~66. The method of claim 65, wherein the PKP2 promoter has a nucleic acid sequence having at least 95% identity to SEQ ID NO: 4.~~

~~67. The method of claim 65, wherein the troponin promoter has a nucleic acid sequence having at least 95% identity to SEQ ID NO: 3.~~

~~68. The method of claim 56, wherein the 3' element comprises a Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE), a bovine growth hormone polyadenylation (bGH polyA) sequence, or a combination thereof.~~

~~69. The method of claim 56, wherein the gene therapy vector further comprises a cardiac specific enhancer.~~

~~70. The method of claim 56, wherein the nucleic acid encoding the PKP2 gene has a sequence having at least 95% identity to SEQ ID NO: 1 or SEQ ID NO: 2.~~

~~71. The method of claim 56, wherein the gene therapy vector comprises a nucleic acid sequence having at least 95% identity to SEQ ID NO: 5.~~

~~72. The method of claim 56, wherein the nucleic acid has a size less than or equal to about 4.7 kb.~~

~~73. The method of claim 56, wherein the pharmaceutically acceptable carrier or excipient comprises a buffer, a polymer, a salt, or a combination thereof.~~

~~74. The method of claim 56, wherein the method reverses, reduces, or prevents at least one of fibrofatty tissue replacement; myocardial atrophy; predominant right ventricular dilation; ventricular arrhythmias; sudden cardiac death; exercise triggered cardiac events; right ventricular cardiomyopathy; dilation, or heart failure; left ventricular cardiomyopathy, dilation, or heart failure; atrial arrhythmias; syncope; palpitations; shortness of breath; or chest pain.~~

~~75. The method of claim 74, wherein the method reverses, reduces, or prevents fibrofatty tissue replacement in myocardium, epicardium, or both.~~

~~76. The method of claim 56, wherein the method restores desmosome structure and/or function.~~

~~77. The method of claim 56, wherein the method restores PKP2 mRNA expression and/or PKP2 protein and activity levels.~~

~~78. The method of claim 56, wherein the method restores expression of one or more genes having a direct or indirect effect on one or more symptoms of the heart disease.~~

~~79. The method of claim 78, wherein the gene comprises one or more of Ryanodine Receptor 2 (Ryr2), Ankyrin-B (Ank2), Caen1c (CaV1.2), triadin (Trdn), or calsequestrin 2 (Casq2).~~

~~80. The method of claim 56, wherein the individual is identified as having at least one variation in a desmosome protein.~~

~~81. The method of claim 80, wherein the desmosome protein is PKP2.~~

~~82. The method of claim 81, wherein the variation comprises a deletion, an insertion, a single nucleotide variation, or a copy number variation.~~