

CLAIMS

1. A method of treating a subject in need thereof, the method comprising administering an effective amount of a recombinant adeno-associated virus (rAAV) virion, the rAAV virion comprising an AAV capsid and an expression cassette comprising a polynucleotide encoding a DWORF polypeptide operatively linked to a promoter.
2. The method of claim 1, wherein the method treats heart failure.
3. The method of claim 1, wherein the method prevents heart failure.
4. The method of claim 1, wherein subject suffers from or is at risk for cardiomyopathy.
5. The method of claim 1, wherein the subject suffers from or is at risk for dilated cardiomyopathy.
6. The method of claim 1, wherein the subject has an inherited risk allele for heart failure.
7. The method of claim 1, wherein the heart failure is myocardial infarction.
8. The method of claim 1, wherein the heart failure is heart failure with reduced ejection fraction (HFrEF).
9. The method of claim 1, wherein the heart failure is heart failure with preserved ejection fraction (HFpEF).
10. The method of any one of claims 1 to 9, wherein subject suffers from or is at risk for from myocardial infarction.
11. The method of claim 10, wherein the myocardial infarction is chronic myocardial infarction.
12. The method of claim 10, wherein the myocardial infarction is acute myocardial infarction.

13. The method of any one of claim 1 to 12, wherein the subject has an inherited risk allele for heart failure.
14. The method of any of claims 1 to 13, wherein the method causes expression of the DWORF polypeptide in the heart of the subject.
15. The method of any one of claims 1 to 14, wherein the method causes no detectable expression of the DWORF polypeptide in the muscles of the subject except the heart.
16. The method of any one of claims 1 to 15, wherein the method causes no detectable expression of the DWORF polypeptide in the liver of the subject.
17. The method of any one of claims 1 to 16, wherein the method causes expression of the DWORF polypeptide in cardiomyocytes.
18. The method of any one of claims 1 to 17, wherein the method causes no detectable expression of the DWORF polypeptide in cardiac fibroblasts.
19. The method of any one of claim 1 to 18, wherein the method improves one or more measures of cardiac function, optionally fractional shortening and/or left ventricular internal dimension (LVID).
20. The method of claim 18, wherein the improvement in cardiac function is observed at weeks 2 through 12.
21. The method of any one of claim 1 to 20, wherein the method reduces cardiac remodeling.
22. The method of any one of claim 1 to 21, wherein the method prevents a decrease in DWORF expression in subjects suffering from myocardial infarction.
23. The method of any one of claims 1 to 22, wherein the rAAV virion is administered by intravenous or intracoronary injection.
24. The method of claim 17, wherein the method increases SERCA activity.

25. The method of any one of claims 1 to 24, wherein the rAAV virion is an rAAV virion of serotype AAV9.
26. The method of any one claims 1 to 25, wherein the AAV capsid comprises a capsid protein that shares at least 98% identity to SEQ ID NO: 14.
27. The method of any one claims 1 to 26, wherein the AAV capsid comprises a capsid protein shares at least 99% identity to SEQ ID NO: 14.
28. The method of any one claims 1 to 27, wherein the AAV capsid comprises a capsid protein comprising the polypeptide sequence of SEQ ID NO: 14.
29. The method of any one of claims 1 to 28, wherein the promoter is a cardiac troponin-T (cTnT) promoter.
30. The method of any one of claims 1 to 29, wherein the cardiac troponin-T (cTnT) promoter comprises a polynucleotide sequence that shares at least 95% identity to SEQ ID NO: 11.
31. The method of any one of claims 1 to 30, wherein the cardiac troponin-T (cTnT) promoter comprises a polynucleotide sequence that shares at least 98% identity to SEQ ID NO: 11.
32. The method of any one of claims 1 to 31, wherein the cardiac troponin-T (cTnT) promoter comprises the polynucleotide sequence of SEQ ID NO: 11.
33. The method of any one of claims 1 to 32, wherein DWORF polypeptide is human DWORF polypeptide.
34. The method of any one of claims 1 to 33, wherein DWORF polypeptide comprises a polypeptide sequence that shares at least 95% identity to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9.

35. The method of any one of claims 1 to 34, wherein DWORF polypeptide comprises a polypeptide sequence that shares at least 98% identity to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9.
36. The method of any one of claims 1 to 35, wherein DWORF polypeptide comprises the polypeptide sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9.
37. The method of any one of claims 1 to 36, wherein the expression cassette is flanked by AAV inverted terminal repeats (ITRs).
38. The method of any one of claims 1 to 37, wherein the ITRs are AAV2 ITRs.
39. The method of any one of claims 1 to 38, wherein the ITRs comprise the polynucleotide sequence of SEQ ID NO: 12 or SEQ ID NO: 13.
40. The method of any one of claims 1 to 39, wherein the subject experiences improved symptoms following administration.
41. The method of any one of claims 40, wherein the improved symptoms are one or more of enhanced contractility; reduced fatigue; reduced dyspnea; reduced edema; reduced chest pain; reduced arrhythmias; reduced blood clots; improved heart valve function; and reduced heart murmur.
42. A recombinant adeno-associated virus (rAAV) virion, the rAAV virion comprising an AAV capsid and an expression cassette comprising a polynucleotide encoding a DWORF polypeptide operatively linked to a promoter.
43. The rAAV virion of claim 42, wherein the rAAV virion is an rAAV virion of serotype AAV9.
44. The rAAV virion of claims 42 or 43, wherein the AAV capsid comprises a capsid protein that shares at least 98% identity to SEQ ID NO: 14.

45. The rAAV virion of any one of claims 42 to 44, wherein the AAV capsid comprises a capsid protein shares at least 99% identity to SEQ ID NO: 14.
46. The rAAV virion of any one of claims 42 to 45, wherein the AAV capsid comprises a capsid protein comprising the polypeptide sequence of SEQ ID NO: 14.
47. The rAAV virion of any one of claims 42 to 46, wherein the promoter is a cardiac troponin-T (cTnT) promoter.
48. The rAAV virion of any one of claims 42 to 47, wherein the cardiac troponin-T (cTnT) promoter comprises a polynucleotide sequence that shares at least 95% identity to SEQ ID NO: 11.
49. The rAAV virion of any one of claims 42 to 48, wherein the cardiac troponin-T (cTnT) promoter comprises a polynucleotide sequence that shares at least 98% identity to SEQ ID NO: 11.
50. The rAAV virion of any one of claims 42 to 49, wherein the cardiac troponin-T (cTnT) promoter comprises the polynucleotide sequence of SEQ ID NO: 11.
51. The rAAV virion of any one of claims 42 to 50, wherein DWORF polypeptide is human DWORF polypeptide.
52. The rAAV virion of any one of claims 42 to 51, wherein DWORF polypeptide comprises a polypeptide sequence that shares at least 95% identity to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9.
53. The rAAV virion of any one of claims 42 to 52, wherein DWORF polypeptide comprises a polypeptide sequence that shares at least 98% identity to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9.
54. The rAAV virion of any one of claims 42 to 53, wherein DWORF polypeptide comprises the polypeptide sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9.

55. The rAAV virion of any one of claims 42 to 54, wherein the expression cassette is flanked by AAV inverted terminal repeats (ITRs).
56. The rAAV virion of any one of claims 42 to 55, wherein the ITRs are AAV2 ITRs.
57. The rAAV virion of any one of claims 42 to 56, wherein the ITRs comprise the polynucleotide sequence of SEQ ID NO: 12 or SEQ ID NO: 13.
58. A pharmaceutical composition comprising the recombinant adeno-associated virus (rAAV) virion of any one of claims 42 to 57 and a pharmaceutically acceptable carrier.
59. A kit comprising a container housing the pharmaceutical composition of claim 58.