CLAIMS

1. A nucleic acid construct comprising:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding an endogenous KCNQ1 polypeptide within a cell and suppressing expression of said endogenous KCNQ1 polypeptide within said cell, and

(b) a second nucleotide sequence encoding a KCNQ1 polypeptide, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not suppress expression of said KCNQ1 polypeptide from said second nucleotide sequence within said cell.

2. The nucleic acid construct of claim 1, wherein:

(a) said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, or SEQ ID NO:36, and wherein said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:9; or

(b) said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:36 and said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:9.

3. A nucleic acid construct comprising:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding an endogenous KCNH2 polypeptide within a cell and suppressing expression of said endogenous KCNH2 polypeptide within said cell, and

(b) a second nucleotide sequence encoding a KCNH2 polypeptide, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not

suppress expression of said KCNH2 polypeptide from said second nucleotide sequence within said cell.

4. The nucleic acid construct of claim 3, wherein said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:27 and said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:29.

5. A nucleic acid construct for treating a congenital heart disease caused by an endogenous cardiac polypeptide containing one or more mutations causative of said congenital heart disease, wherein said construct comprises:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding said endogenous cardiac polypeptide within a cell and suppressing expression of said endogenous cardiac polypeptide within said cell, and

(b) a second nucleotide sequence encoding a replacement version of said endogenous cardiac polypeptide that lacks said one or more mutations causative of said congenital heart disease, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not suppress expression of said replacement version of said endogenous cardiac polypeptide that lacks said one or more mutations causative of said congenital heart disease from said second nucleotide sequence within said cell.

6. The nucleic acid construct of any one of claim 1 to 5, wherein said first nucleotide sequence is operably linked to a first promoter and said second nucleotide sequence is operably linked to a second promoter.

7. The nucleic acid construct of claim 6, wherein:

(a) said first and second promoters are the same; or

(b) said first and second promoters are different.

8. The nucleic acid construct of claim 7(b), wherein said first promoter is a U6 promoter and said second promoter is a cytomegalovirus immediate-early (CMV) promoter.

9. The nucleic acid construct of any one of claims 1 to 8, further comprising a nucleotide sequence encoding a reporter.

10. The nucleic acid construct of claim 9, wherein said reporter is a fluorescent polypeptide.

11. The nucleic acid construct of claim 9 or claim 10, wherein said nucleotide sequence encoding said reporter is downstream of said second nucleotide sequence encoding said cDNA, and is separated from said second nucleotide sequence by an internal ribozyme entry sequence (IRES) or P2A self-cleaving peptide sequence.

12. The nucleic acid construct of any one of claims 1 to 11, wherein said nucleic acid construct is within a viral vector.

13. The nucleic acid construct of claim 12, wherein said viral vector is an adeno-associated virus (AAV) vector.

14. The nucleic acid construct of claim 13, wherein said AAV vector is an AAV serotype 9 vector or an AAV2/9 vector.

15. The nucleic acid construct of any one of claims 1 to 14, wherein said cell is a cardiomyocyte.

16. A virus particle comprising the nucleic acid construct of any one of claims 1 to 15.

17. Use of a nucleic acid construct in the manufacture of a medicament for treating a congenital cardiac disease in a mammal, wherein said nucleic acid construct comprises:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding an endogenous KCNQ1 polypeptide within a cell of said mammal and suppressing expression of said endogenous KCNQ1 polypeptide within said cell, and

(b) a second nucleotide sequence encoding a KCNQ1 polypeptide, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not

suppress expression of said KCNQ1 polypeptide from said second nucleotide sequence within said cell.

18. The use of claim 17, wherein said congenital cardiac disease is long QT syndrome (LQTS) or short QT syndrome (SQTS), or wherein said congenital cardiac disease is LQT1.

19. The use of any one of claims 17 to 18, wherein:

(a) said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, or SEQ ID NO:36, and wherein said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:9; or

(b) said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:36 and said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:9.

20. Use of a nucleic acid construct in the manufacture of a medicament for treating a congenital cardiac disease in a mammal, wherein said nucleic acid construct comprises:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding an endogenous KCNH2 polypeptide within a cell of said mammal and suppressing expression of said endogenous KCNH2 polypeptide within said cell, and

(b) a second nucleotide sequence encoding a KCNH2 polypeptide, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not suppress expression of said KCNH2 polypeptide from said second nucleotide sequence within said cell.

21. The use of claim 20, wherein said congenital cardiac disease is LQTS or SQTS; or wherein said congenital cardiac disease is LQT2.

22. The use of any one of claims 20 to 21, wherein said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:27 and said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:29.

23. Use of a nucleic acid construct in the manufacture of a medicament for treating a congenital cardiac disease in a mammal, wherein said nucleic acid construct comprises:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding said endogenous cardiac polypeptide within a cell and suppressing expression of said endogenous cardiac polypeptide within said cell, and

(b) a second nucleotide sequence encoding a replacement version of said endogenous cardiac polypeptide that lacks said one or more mutations causative of said congenital heart disease, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not suppress expression of said replacement version of said endogenous cardiac polypeptide that lacks said one or more mutations causative of said congenital heart disease from said second nucleotide sequence within said cell.

24. The use of any one of claims 17 to 23, wherein said first nucleotide sequence is operably linked to a first promoter and said second nucleotide sequence is operably linked to a second promoter.

25. The use of claim 24, wherein:

(a) said first and second promoters are the same; or

(b) said first and second promoters are different.

26. The use of claim 25(b), wherein said first promoter is a U6 promoter and said second promoter is a CMV promoter.

27. The use of any one of claims 17 to 26, wherein said nucleic acid construct further comprises a nucleotide sequence encoding a reporter.

28. The use of claim 27, wherein said reporter is a fluorescent polypeptide.

29. The use of claim 27 or claim 28, wherein said nucleotide sequence encoding said reporter is downstream of said second nucleotide sequence encoding said cDNA, and is separated from said second nucleotide sequence by an IRES.

30. The use of any one of claims 17 to 29 wherein said nucleic acid construct is within a viral vector.

31. The use of claim 30, wherein said viral vector is an AAV vector.

32. The use of claim 31, wherein said AAV vector is an AAV serotype 9 vector or an AAV2/9 vector.

33. The use of any one of claims 17 to 32, wherein said cell is a cardiomyocyte.

34. Use of a nucleic acid construct in the manufacture of a medicament for reducing the action potential duration (APD) in cardiac cells within a mammal, wherein said nucleic acid construct comprises:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding an endogenous KCNQ1 polypeptide within cardiac cells of said mammal and suppressing expression of said endogenous KCNQ1 polypeptide within said cardiac cells, and

(b) a second nucleotide sequence encoding a KCNQ1 polypeptide, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not suppress expression of said KCNQ1 polypeptide from said second nucleotide sequence within said cell.

35. The use of claim 34, wherein:

(a) said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, or SEQ ID NO:36, and wherein said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:9; or

(b) said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:36 and said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:9.

36. Use of a nucleic acid construct in the manufacture of a medicament for reducing the APD in cardiac cells within a mammal, wherein said nucleic acid construct comprises:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding an endogenous KCNH2 polypeptide within cardiac cells of said mammal and suppressing expression of said endogenous KCNH2 polypeptide within said cardiac cells, and

(b) a second nucleotide sequence encoding a KCNH2 polypeptide, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not suppress expression of said KCNH2 polypeptide from said second nucleotide sequence within said cell.

37. The use of claim 36, wherein said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:27 and said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:29.

38. The use of any one of claims 34 to 37, wherein said first nucleotide sequence is operably linked to a first promoter and said second nucleotide sequence is operably linked to a second promoter.

39. The use of claim 38, wherein:

(a) said first and second promoters are the same; or

(b) said first and second promoters are different.

40. The use of claim 39(b), wherein said first promoter is a U6 promoter and said second promoter is a CMV promoter.

41. The use of any one of claims 34 to 40, wherein said nucleic acid construct is within a viral vector.

42. The use of claim 41, wherein said viral vector is an AAV vector.

43. The use of claim 42, wherein said AAV vector is an AAV serotype 9 vector or an AAV2/9 vector.

44. Use of a nucleic acid construct in the manufacture of a medicament for reducing one or more symptoms of LQTS in a mammal, wherein said nucleic acid construct comprises:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding an endogenous KCNQ1 polypeptide within a cell of said mammal and suppressing expression of said endogenous KCNQ1 polypeptide within said cell, and

(b) a second nucleotide sequence encoding a KCNQ1 polypeptide, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target sequence of said first nucleotide sequence, and wherein said RNAi molecule does not suppress expression of said KCNQ1 polypeptide from said second nucleotide sequence within said cell.

45. The use of claim 44, wherein said LQTS is LQT1.

46. The use of claim 44 or claim 45, wherein:

(a) said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, or SEQ ID NO:36, and wherein said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:9; or

(b) said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:36 and said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:9.

47. Use of a nucleic acid construct in the manufacture of a medicament for reducing one or more symptoms of LQTS in a mammal, wherein said nucleic acid construct comprises:

(a) a first nucleotide sequence encoding an RNAi molecule capable of hybridizing to a target sequence encoding an endogenous KCNH2 polypeptide within a cell of said mammal and suppressing expression of said endogenous KCNH2 polypeptide within said cell, and

(b) a second nucleotide sequence encoding a KCNH2 polypeptide, wherein said second nucleotide sequence comprises a target sequence identical to said target sequence of said first nucleotide sequence with the exception that said target sequence of said second nucleotide sequence comprises 1 to 13 wobble position variants as compared to said target

sequence of said first nucleotide sequence, and wherein said RNAi molecule does not suppress expression of said KCNH2 polypeptide from said second nucleotide sequence within said cell.

48. The use of claim 47, wherein said LQTS is LQT2.

49. The use of claim 47 or claim 48, wherein said first nucleotide sequence comprises the sequence set forth in SEQ ID NO:27 and said second nucleotide sequence comprises the sequence set forth in SEQ ID NO:29.

50. The use of any one of claims 44 to 49, wherein said first nucleotide sequence is operably linked to a first promoter and said second nucleotide sequence is operably linked to a second promoter.

51. The use of claim 50, wherein:

(a) said first and second promoters are the same; or

(b) said first and second promoters are different.

52. The use of claim 51(b), wherein said first promoter is a U6 promoter and said second promoter is a CMV promoter.

53. The use of any one of claims 44 to 52 wherein said nucleic acid construct is within a viral vector.

54. The use of claim 53, wherein said viral vector is an AAV vector.

55. The use of claim 54, wherein said AAV vector is an AAV serotype 9 vector or an AAV2/9 vector.

56. The use of any one of claims 44 to 55, wherein said cell is a cardiomyocyte.