

CLAIMS

What is claimed is:

- ~~1. A vector, comprising a MYOCD polynucleotide and either or both of an ASCL1 polynucleotide or a MYF6 polynucleotide; each polynucleotide operatively linked to at least one promoter.~~
- ~~2. The vector of claim 1, wherein the vector comprises a MYOCD polynucleotide and an ASCL1 polynucleotide.~~
- ~~3. The vector of claim 1 or claim 2, wherein the vector comprises a MYOCD polynucleotide and a MYF6 polynucleotide.~~
- ~~4. The vector of claim 1, wherein the vector comprises a MYOCD polynucleotide; either or both of a MEF2C polynucleotide and a TBX5 polynucleotide; and either or both of an ASCL1 polynucleotide and a MYF6 polynucleotide.~~
- ~~5. The vector of claim 4, wherein the vector comprises a MYOCD polynucleotide, an ASCL1 polynucleotide, a MEF2C polynucleotide, and a TBX5 polynucleotide.~~
- ~~6. The vector of claim 4, wherein the vector comprises a MYOCD polynucleotide, a MYF6 polynucleotide, a MEF2C polynucleotide, and a TBX5 polynucleotide.~~
- ~~7. The vector of any one of claims 1 to 6, wherein the MYOCD is an engineered myocardin.~~
- ~~8. The vector of any one of claims 1 to 7, wherein the vector comprises no reprogramming factor polynucleotide other than a MYOCD polynucleotide, an ASCL1 polynucleotide, a MYF6 polynucleotide, a MEF2C polynucleotide, or a TBX5 polynucleotide.~~
- ~~9. The vector of any one of claims 1 to 8, wherein the vector comprises no other other protein coding gene.~~
- ~~10. The vector of any one of claims 1 to 9, wherein the vector is a polycistronic vector.~~
- ~~11. The vector of any one of claims 1 to 10, wherein the vector is a viral vector.~~
- ~~12. The vector of claim 11, wherein the vector is an AAV vector.~~
- ~~13. The vector of claim 11, wherein the vector is lentiviral vector.~~
- ~~14. The vector of any one of claims 1 to 13, wherein the ASCL1 polynucleotide, if present, or the MYF6 polynucleotide, if present, and the MYOCD polynucleotide are operatively linked to the same promoter and are co-translationally expressed.~~
- ~~15. The vector of any one of claim 2 or claims 7 to 13, wherein the vector comprises a~~

~~MYOCD-2A-ASCL1 polynucleotide or an ASCL1-2A-MYOCD polynucleotide, operatively linked to a single promoter.~~

~~16. The vector of any one of claim 3 or claims 7 to 13, wherein the vector comprises a~~

~~MYOCD-2A-MYF6 polynucleotide or an ASCL1-2A-MYF6 polynucleotide, operatively linked to a single promoter.~~

~~17. The vector of any one of claims 1 to 16, wherein the MTOCD polynucleotide comprises the nucleotide sequence of human MYOCD (SEQ ID NO: 4) or a codon variant thereof.~~

~~18. The vector of any one of claims 1 to 17, wherein the MTOCD polynucleotide shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the nucleotide sequence of human MYOCD (SEQ ID NO: 4).~~

~~19. The vector of any one of claims 1 to 18, wherein the MTOCD polynucleotide encodes human MYOCD (SEQ ID NO: 3) or a functional variant thereof.~~

~~20. The vector of any one of claims 1 to 19, wherein the MTOCD polynucleotide encodes a polypeptide that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to human MYOCD (SEQ ID NO: 3).~~

~~21. The vector of any one of claims 1 to 16, wherein the MTOCD polynucleotide comprises the nucleotide sequence of MyA3 (SEQ ID NO: 72) or a codon variant thereof.~~

~~22. The vector of any one of claims 1 16 or 21, wherein the MYOGD polynucleotide shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the nucleotide sequence of MyA3 (SEQ ID NO: 72).~~

~~23. The vector of any one of claims 1 16 or 21 22, wherein the MTOCD polynucleotide encodes MyA3 (SEQ ID NO: 16) or a functional variant thereof.~~

~~24. The vector of any one of claims 1 16 or 21 23, wherein the MTOCD polynucleotide encodes a polypeptide that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to MyA3 (SEQ ID NO: 16) or a codon variant thereof.~~

~~25. The vector of any one of claims 1 to 24, wherein the ASCL1 polynucleotide comprises the nucleotide sequence of human ASCL1 (SEQ ID NO: 2) or a codon variant thereof.~~

~~26. The vector of any one of claims 1 to 25, wherein the ASCL1 polynucleotide shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the nucleotide sequence of human ASCL1 (SEQ ID NO: 2) or a codon variant thereof.~~

~~27. The vector of any one of claims 1 to 25, wherein the ASCL1 polynucleotide encodes a polypeptide that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to human ASCL1 (SEQ ID NO: 1).~~

~~28. The vector of any one of claims 1 to 25, wherein the ASCL1 polynucleotide encodes human ASCL1 (SEQ ID NO: 1).~~

~~29. The vector of any one of claims 1 to 24, wherein the MYOFD polynucleotide shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the nucleotide sequence of human MYF6 (SEQ ID NO: 56).~~

~~30. The vector of claim 11, wherein the vector comprises an expression cassette, the expression cassette comprising:~~

~~a. the MYOCD polynucleotide, wherein the MYOCD polynucleotide comprises~~

~~MyA3 (SEQ ID NO: 72) or a codon variant thereof, and/or encodes MyA3 (SEQ~~

~~ID NO: 16) or a functional variant thereof, the MTOCD polynucleotide operatively linked to a first promoter; and~~

~~b. the ASCL1 polynucleotide, wherein the ASCL1 polynucleotide comprises ASCL1 (SEQ ID NO: 2) or a codon variant thereof, and/or encodes ASCL1 (SEQ ID NO: 1) or a functional variant thereof, the ASCL1 polynucleotide operatively linked to a second promoter.~~

~~31. The vector of claim 30, wherein the first promoter shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to a CAG promoter (SEQ ID NO: 67) and/or the second promoter shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to a SCP promoter (SEQ ID NO: 68).~~

~~32. The vector of claim 11, wherein the vector comprises an expression cassette, the~~

~~expression cassette comprising a MYOCD-2A-ASCL1 polynucleotide, operatively linked to a single promoter.~~

~~33. The vector of claim 32, wherein the MYOCD-2A-ASCL1 polynucleotide comprises SEQ ID NO: 37 or a codon variant thereof.~~

~~34. The vector of claim 32 or claim 33, wherein the MYOCD-2A-ASCL1 polynucleotide shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 37.~~

~~35. The vector of claim 32, wherein the MYOCD-2A-ASCL1 polynucleotide encodes SEQ ID NO: 59 or a functional variant thereof.~~

~~36. The vector of claim 32, wherein the MYOCD-2A-ASCL1 polynucleotide encodes a~~

~~polypeptide that shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 59.~~

~~37. The vector of any one of claims 32 to 36, wherein the expression cassette comprises one or more of an SV40 intron (SEQ ID NO: 73), a short polyA signal (SEQ ID NO: 74) and a WPRE (SEQ ID NO: 75).~~

- ~~38. The vector of any one of claims 32 to 37, wherein the expression cassette is flanked by inverted terminal repeats, optionally AAV2 ITRs (SEQ ID NO: 76).~~
- ~~39. The vector of any one of claims 32 to 38, wherein the vector comprises an AAV5 capsid protein, optionally comprising SEQ ID NO: 71 or a functional variant thereof.~~
- ~~40. The vector of any one of claims 1 to 39, wherein the vector is capable of reprogramming differentiated cells into induced cardiomyocyte (iCM) cells.~~
- ~~41. The vector of claim 40, wherein at least 2.5%, at least 5%, at least 10%, at least 15%, or at least 20% of iCM cells are a-actinin positive.~~
- ~~42. The vector of claim 41, wherein at least 2%, at least 5%, or at least 8% of iCM cells are eTnT positive.~~
- ~~43. A vector system, comprising a first vector encoding a MYOCD polynucleotide and either or both of an ASCL1 polynucleotide or a MYF6 polynucleotide; and a second vector comprising a MEF2C polynucleotide and a TBX5 polynucleotide.~~
- ~~44. The vector system of claim 22, wherein the first vector comprises a MYOCD-2A ASCL1 polynucleotide or an ASCL1-2A MYOCD polynucleotide.~~
- ~~45. The vector system of claim 22, wherein the first vector comprises a MYOCD-2A MYF6 polynucleotide or an ASCL1-2A MYF6 polynucleotide.~~
- ~~46. A vector system, comprising a first vector encoding a MYOCD polynucleotide and a second vector encoding an ASCL1 polynucleotide or MYF6 polynucleotide.~~
- ~~47. The vector system of any one of claims 43 to 46, wherein the first vector and the second vector are each independently selected from a lipid nanoparticle, a transposon, an adeno-associated virus (AAV) vector, an adenovirus, a retrovirus, an integrating lentiviral vector (LVV), and a non-integrating LVV.~~
- ~~48. The vector system of any one of claims 43 to 47, wherein the ASCL1 polynucleotide shares at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the nucleotide sequence of human ASCL1 (SEQ ID NO: 2).~~
- ~~49. The vector system of any one of claims 43 to 48, wherein the MYOCD polynucleotide encodes human MYOCD (SEQ ID NO: 3) or a functional variant thereof or MyA3 (SEQ ID NO: 16) or a functional variant thereof.~~
- ~~50. A method of inducing a cardiomyocyte phenotype in differentiated cells, comprising contacting the differentiated cells with the vector of any one of claims 1 to 42 or the vector system of any one of claims 43 to 49.~~
- ~~51. The method of claim 50, wherein the differentiated cells are cardiac fibroblast cells.~~
- ~~52. The method of claim 50 or claim 51, wherein the differentiated cells are in vitro cells during the contacting step.~~

53. The method of any one of claims 50 to 52, wherein the differentiated cells are in vivo cells in a subject suffering from or at risk for a heart condition.

54. A method of treating a heart condition in a subject suffering from or at risk for the heart condition, comprising contacting the differentiated cells in vitro with the vector of any one of claims 1 to 42 or the vector system of any one of claims 43 to 49 to generate iCM cells, and administering the iCM cells to the subject.

55. The method of claims 54, wherein the heart condition is dilated cardiomyopathy.

56. A method of treating a heart condition in a subject suffering from or at risk for a heart condition, comprising administering the the vector of any one of claims 1 to 42 or the vector system of any one of claims 43 to 49 to the subject.

57. The method of claim 56, wherein the heart condition is a myocardial infarction.

58. The method of claim 56, wherein the heart condition is an acute myocardial infarction.

59. The method of claim 56, wherein the heart condition is a heart failure.

60. The method of claim 56, wherein the heart condition is a chronic ischemic heart failure.

61. A kit comprising the vector any one of claims 1 to 42 or the vector system of any one of claims 43 to 49, and instructions for use in treating a heart condition.

62. A method of converting a differentiated non-cardiomyocyte cell into a cardiomyocyte, comprising comprising contacting the differentiated cells with the vector any one of claims 1 to 42 or the vector system of any one of claims 43 to 49.

63. The method of claim 62, wherein the differentiated non-cardiomyocyte cell is a differentiated non-cardiomyocyte cell.

64. The method of claim 62 or claim 63, wherein the differentiated non-cardiomyocyte cell is a human differentiated non-cardiomyocyte cell.

65. The method of any one of claims 62 to 64, wherein the differentiated non-cardiomyocyte cell is an in vivo differentiated non-cardiomyocyte cell.

66. The method of any one of claims 62 to 64, wherein the differentiated non-cardiomyocyte cell is an in vitro differentiated non-cardiomyocyte cell.

67. The method of any one of claims 61 to 66, wherein the differentiated non-cardiomyocyte cell is a cardiac cell.

68. An isolated polynucleotide, comprising an engineered MYOCD polynucleotide encoding an engineered myocardin protein having a length of at most 850 amino acids, wherein the engineered myocardin protein comprises an SRF interaction domain, an SAP domain, and a TAD domain.

~~69. The polynucleotide of claim 68, wherein the engineered myocardin protein comprises an Mef2c interaction domain.~~

~~70. The polynucleotide of claim 69, wherein:~~

~~a. the Mef2c interaction domain shares at least 85% identity to SEQ ID NO: 17,~~

~~b. the SRF domain shares at least 85% identity to SEQ ID NO: 18,~~

~~c. the SAP domain shares at least 85% identity to SEQ ID NO: 19, and~~

~~d. the TAD domain shares at least 85% identity to SEQ ID NO: 11.~~

~~71. The polynucleotide of claim 68 or 70, wherein the engineered myocardin protein comprises an LZ domain.~~

~~72. The polynucleotide of claim 71, wherein the LZ domain shares at least 85% identity to SEQ ID NO: 20.~~

~~73. The polynucleotide of any of claims 68 to 72, wherein the engineered myocardin protein comprises:~~

~~a. a first polypeptide that shares at least 85% identity to residues 5-413 of human myocardin (SEQ ID NO: 10), and~~

~~b. second polypeptide that shares at least 85% identity to residues 764-986 of human myocardin (SEQ ID NO: 11),~~

~~wherein the first polypeptide and the second polypeptide are linked by a linker comprising a peptide bond or a polypeptide linker of 1-50 amino acid residues.~~

~~74. The polynucleotide of any of claims 68 to 72, wherein the engineered myocardin protein comprises:~~

~~a. a first polypeptide that shares at least 85% identity to residues 5-438 of human myocardin (SEQ ID NO: 12), and~~

~~b. second polypeptide that shares at least 85% identity to residues 764-938 of human myocardin (SEQ ID NO: 11),~~

~~wherein the first polypeptide and the second polypeptide are linked by a linker comprising a peptide bond or a polypeptide linker of 1-50 amino acid residues.~~

~~75. The polynucleotide of any of claims 68 to 72, wherein the engineered myocardin protein comprises:~~

~~a. a first polypeptide that shares at least 85% identity to residues 5-559 of human myocardin (SEQ ID NO: 13), and~~

b. second polypeptide that shares at least 85% identity to residues 764-938 of human myocardin (SEQ ID NO: 11);

wherein the first polypeptide and the second polypeptide are linked by a linker comprising a peptide bond or a polypeptide linker of 1-50 amino acid residues.

76. The polynucleotide of any of claims 73 to 75, wherein the linker consists of a peptide bond.

77. The polynucleotide of any of claims 73 to 75, wherein the linker is a polypeptide selected from G, GG, GGG, GSS, GGS, GGS GGS (SEQ ID NO: 30), GSS GGS (SEQ ID NO: 31), GGS GGS (SEQ ID NO: 32), GGS GGS GGS (SEQ ID NO: 33), GGS GGS GGS GGS (SEQ ID NO: 34).

78. The polynucleotide of claim 76, wherein the engineered myocardin protein comprises a sequence selected from SEQ ID NOs: 14-16.

79. An isolated polynucleotide, comprising an engineered MYOCD polynucleotide encoding an engineered myocardin protein, wherein the engineered myocardin protein comprises a deletion of at least 50 amino acids in the region corresponding to amino acids 414-764 of the native myocardin (SEQ ID NO: 3).

80. The polynucleotide of claim 79, wherein the engineered myocardin protein comprises a deletion of amino acids from about 414 to about 763 of the native myocardin (SEQ ID NO: 3).

81. The polynucleotide of claim 80, wherein the engineered myocardin protein comprises a sequence at least 85% identical to SEQ ID NO: 14.

82. The polynucleotide of claim 81, wherein the engineered myocardin protein consists of sequence identical to SEQ ID NO: 14.

83. The polynucleotide of claim 79, wherein the engineered myocardin protein comprises a deletion of amino acids from about 439 to about 763 of the native myocardin (SEQ ID NO: 3).

84. The polynucleotide of claim 83, wherein the engineered myocardin protein comprises a sequence at least 85% identical to SEQ ID NO: 15.

85. The polynucleotide of claim 74, wherein the engineered myocardin protein consists of sequence identical to SEQ ID NO: 15.

86. The polynucleotide of claim 79, wherein the engineered myocardin protein comprises a deletion of amino acids from about 560 to about 763 of the native myocardin (SEQ ID NO: 3).

87. The polynucleotide of claim 86, wherein the engineered myocardin protein comprises a sequence at least 85% identical to SEQ ID NO: 16.

88. The polynucleotide of claim 87, wherein the engineered myocardin protein consists of sequence identical to SEQ ID NO: 16.

89. The polynucleotide of any of claims 68 to 88, wherein the engineered myocardin protein is a functional engineered myocardin protein.

90. The polynucleotide of claim 89, wherein the functional engineered myocardin protein is expressed at at least 10% of the level of native MYOCD in the same expression system.

91. The polynucleotide of claim 89 or 90, wherein the functional engineered myocardin protein is capable of inducing increased expression of at least one marker of cardiomyocyte phenotype either (a) when expressed in human cardiac fibroblasts with MEF2C and TBX5 or TBX5 in the presence of a TGF β inhibitor, optionally SB431542, and a Wnt inhibitor, optionally XAV939, or (b) when expressed in human cardiac fibroblasts with ASCL1.

92. The polynucleotide of any of claim 68 to 91, wherein the polynucleotide is operatively linked to a promoter.

93. The polynucleotide of any of claim 68 to 92, wherein the polynucleotide comprises a MEF2C polynucleotide and a TBX5 polynucleotide.

94. The polynucleotide of any of claim 68 to 93, wherein the polynucleotide comprises an TBX5 polynucleotide.

95. The polynucleotide of any of claim 68 to 93, wherein the polynucleotide comprises an ASCL1 polynucleotide.

96. The polynucleotide of any of claim 68 to 95, wherein the polynucleotide is flanked by inverted terminal repeats (ITRs) or the polynucleotide is flanked by long terminal repeats (LTRs).

97. A recombinant virus comprising the polynucleotide of any of claims 68 to 96.

98. The recombinant virus of claim 97, wherein the recombinant virus is a recombinant adeno-associated virus (rAAV).

99. The recombinant virus of claim 97, wherein the recombinant virus is a lentivirus.

100. A population of cells comprising the polynucleotide of any of claim 68 to 96.

101. The population of cells of claim 100, wherein the percentage of cells in the population that exhibit calcium transients (CaT) in an in vitro CaT assay is at least 2 fold greater than the percentage of cells in a control population of cells not comprising the polynucleotide in the same in vitro CaT assay.

102. An induced cardiomyocyte (iCM), wherein the iCM comprises the polynucleotide of any of claims 68 to 96.

103. A pharmaceutical composition comprising the polynucleotide of any of claims 68 to 96 and a non-viral delivery system.

~~104. A pharmaceutical composition comprising the recombinant virus of any of claims 97 to 99.~~

~~105. A method of generating an induced cardiomyocyte (iCM), comprising contacting a mammalian fibroblast with the polynucleotide of any of claims 68 to 96, the recombinant virus of any of claims 97 to 99, or the pharmaceutical composition of claim 103 or claim 104.~~

~~106. A method of treating a heart condition in a subject, comprising administering the pharmaceutical composition of claim 105 to the subject.~~

~~107. The method of claim 106, wherein the recombinant virus is administered via intracardiac catheterization.~~

~~108. The method of claim 106, wherein the recombinant virus is administered via intracardiac injection.~~

~~109. A recombinant adeno-associated virus (rAAV), comprising an expression cassette, wherein the expression cassette comprises in 5' to 3' order a 5' inverted terminal repeat (ITR), a CAG promoter, an SV40 intron, a polynucleotide encoding one or more proteins, a short polyadenylation signal, and a 3' ITR, and wherein the polynucleotide encoding one or more proteins comprises in 5' to 3' order a polynucleotide encoding MyA3, a polynucleotide encoding a P2A linker, and a polynucleotide encoding ASCL1.~~

~~110. The rAAV of claim 109, wherein the expression cassette comprises a WPRE.~~

~~111. The rAAV of claim 109 or 110, wherein the MyA3 comprises SEQ ID NO: 16.~~

~~112. The rAAV of any of claims 109 to 111, wherein the 2A linker comprises ATNF SLLKQ AGD VEENPGP (SEQ ID NO: 23).~~

~~113. The rAAV of any of claims 109 to 111, wherein the ASCL1 comprises SEQ ID NO: 1.~~

~~114. The rAAV of claim 113, wherein the rAAV comprises a polynucleotide at least 95% identical to SEQ ID NO: 35 (MyA3A AAV).~~

~~115. A pharmaceutical composition comprises the rAAV of any of claims 109 to 114.~~

~~116. A method of treating a heart condition in a subject, comprising administering the pharmaceutical composition of claim 115 to the subject.~~

1. A vector, comprising a myocardin (MYOCD) polynucleotide encoding a MYOCD polypeptide and an Achaete-scute homolog 1 (ASCL1) polynucleotide encoding an ASCL1 polypeptide; wherein each polynucleotide is operatively linked to at least one promoter.

2. The vector of claim 1, wherein the vector further comprises a MEF2C polynucleotide encoding an MEF2C polypeptide and/or a TBX5 polynucleotide encoding a TBX5 polypeptide.

3. The vector of claim 1 or claim 2, wherein the MYOCD polynucleotide comprises an internal deletion, and encodes a functional MYOCD polypeptide comprising an internal deletion.
4. The vector of any one of claims 1 to 3, wherein the vector is a viral vector.
5. The vector of claim 4, wherein the vector is an AAV vector.
6. The vector of claim 5, wherein the AAV vector comprises an AAV5 capsid.
7. The vector of claim 4, wherein the vector is lentiviral vector.
8. The vector of any one of claims 1 to 7, wherein the ASCL1 polynucleotide and the MYOCD polynucleotide are operatively linked to the same promoter and are co-translationally expressed.
9. The vector of claim 8, wherein the MYOCD polynucleotide and ASCL1 polynucleotide are linked via a 2A sequence to form a MYOCD-2A-ASCL1 polynucleotide.
10. The vector of claim 8, wherein the MYOCD polynucleotide and ASCL1 polynucleotide are linked via a 2A sequence to form an ASCL1-2A-MYOCD polynucleotide.
11. The vector of any one of claims 1 to 7, wherein the MYOCD polynucleotide is operatively linked to a first promoter, and the ASCL1 polynucleotide is operatively linked to a second promoter.
12. The vector of any one of claims 1 to 11, wherein the MYOCD polynucleotide encodes a MYOCD polypeptide that shares at least 95% identity to SEQ ID NO: 16.
13. The vector of claim 12, wherein the MYOCD polynucleotide encodes a MYOCD polypeptide having the amino acid sequence of SEQ ID NO: 16.
14. The vector of any one of claims 1 to 13, wherein the ASCL1 polynucleotide encodes an ASCL1 polypeptide that shares at least 95% identity SEQ ID NO: 1.
15. The vector of claim 14, wherein the ASCL1 polynucleotide encodes an ASCL1 polypeptide having the amino acid sequence of SEQ ID NO: 1.

16. The vector of claim 9 , wherein the MYOCD-2A-ASCL1 polynucleotide encodes a polypeptide that shares at least 95% identity with SEQ ID NO: 59.

17. The vector of claim 16, wherein the MYOCD-2A-ASCL1 polynucleotide encodes a polypeptide having the amino acid sequence of SEQ ID NO: 59.

18. The vector of any one of claims 1-17, which comprises an expression cassette comprising the MYOCD polynucleotide and the ASCL1 polynucleotide, wherein the expression cassette is flanked by two AAV inverted terminal repeats (ITRs).

19. A vector system, comprising:

- a) a first vector encoding a MYOCD polynucleotide and a MEF6 polynucleotide, and a second vector comprising an ASCL1 polynucleotide;
- b) a first vector comprising a MYOCD polynucleotide and a TBX5 polynucleotide, and a second vector comprising an ASCL1 polynucleotide;
- c) a first vector comprising a MYOCD polynucleotide and a second vector comprising an ASCL1 polynucleotide and a MEF6 polynucleotide;
- d) a first vector comprising a MYOCD polynucleotide and a second vector comprising an ASCL1 polynucleotide and a TBX5 polynucleotide; or
- e) a first vector of any one of claims 1 to 15, and a second vector comprising a MEF6 polynucleotide and/or a TBX5 polynucleotide;
wherein in any a), b), c), d) and e), the MYOCD polynucleotide comprises an internal deletion, and encodes a functional MYOCD polypeptide comprising an internal deletion.

20. A vector system comprising a first vector comprising a MYOCD polynucleotide and a second vector comprising an ASCL1 polynucleotide, when used for:

- (a) inducing a cardiomyocyte (iCM) phenotype in differentiated cells;
- (b) treating a heart condition in a subject suffering from or at risk for the heart condition, wherein the vector system is brought into contact with differentiated cells in vitro to generate iCM cells, and the iCM cells are administered to the subject; or
- (c) treating a heart condition in a subject suffering from or at risk for a heart condition, wherein the vector system is administered to the subject.

21. A pharmaceutical composition comprising the vector or vector system of any one of claims 1 to 20.

22. A method of inducing a cardiomyocyte phenotype in differentiated cells, comprising contacting the differentiated cells with the vector or the vector system of any one of claims 1-20 or the pharmaceutical composition of claim 21.

23. The method of claim 22, wherein the differentiated cells are cardiac fibroblast cells.

24. The method of claim 22 or claim 23, wherein the differentiated cells are in vitro cells during the contacting step.

25. An induced cardiomyocyte (iCM) when produced by the method of any one of claims 22 to 24.

26. A recombinant adeno-associated virus (rAAV), comprising an expression cassette, wherein the expression cassette comprises in 5' to 3' order a 5' inverted terminal repeat (ITR), a CAG promoter, an SV40 intron, a polynucleotide encoding one or more proteins, a short polyadenylation signal, and a 3' ITR, and wherein the polynucleotide encoding one or more proteins comprises in a MYOCD polynucleotide encoding a MYOCD polypeptide, a polynucleotide encoding a P2A linker, and an ASCL1 polynucleotide encoding an ASCL1 polypeptide.

27. The rAAV of claim 26, wherein the MYOCD polypeptide shares at least 95% sequence identity to SEQ ID NO:16, and the ASCL1 polypeptide shares at least 95% sequence identity to SEQ ID NO:1.

28. Use of

- a) the vector or vector system of any one of claims 1 to 20;
- b) the pharmaceutical composition of claim 21;
- c) the rAAV of claim 26 or claim 27; or
- d) iCM generated by contacting differentiated cells in vitro with the vector of any one of claims 1 to 20, the pharmaceutical composition of claim 21 or the rAAV of claim 26 or claim 27; or the iCM of claim 25.

in the manufacture of a medicament for treating a heart condition in a subject suffering from or at risk for the heart condition.

29. The use of claim 28, wherein the heart condition is selected from the group consisting of chronic myocardial infarction, acute myocardial infarction (AMI), heart failure and chronic ischemic heart failure.

30. The use of claim 28 or claim 29, wherein the medicament treats one or more symptoms, wherein the one or more symptoms comprises a decrease in ejection fraction of the heart of the subject.

31. The use of any one of claims 28 to 30, wherein the medicament is to be administered by intramyocardial injection.