

CLAIMS

What is claimed is:

1. A recombinant circular RNA comprising a protein-coding sequence, wherein the protein-coding sequence encodes at least one reprogramming factor, wherein the at least one reprogramming factor is Oct3/4, Klf4, Sox2, Nanog, Lin28, c-Myc, or L-Myc, or a fragment or variant thereof.
2. The recombinant circular RNA of claim 1, wherein the at least one reprogramming factor is a human or a humanized reprogramming factor.
3. The recombinant circular RNA of claim 1 or 2, wherein the at least one reprogramming factor is Oct3/4, and wherein the Oct3/4 has the sequence of SEQ ID NO: 1, or a sequence at least 90% or at least 95% identical thereto.
4. The recombinant circular RNA of claim 3, wherein the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 33, or a sequence at least 90% or at least 95% identical thereto.
5. The recombinant circular RNA of claim 1 or 2, wherein the at least one reprogramming factor is Klf4, and wherein the Klf4 has the sequence of SEQ ID NO: 2 or 3, or a sequence at least 90% or at least 95% identical thereto.
6. The recombinant circular RNA of claim 4, wherein the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 37, or a sequence at least 90% or at least 95% identical thereto.
7. The recombinant circular RNA of claim 1 or 2, wherein the at least one reprogramming factor is Sox2, and wherein Sox2 has the sequence of SEQ ID NO: 4, or a sequence at least 90% or at least 95% identical thereto.

8. The recombinant circular RNA of claim 7, wherein the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 34, or a sequence at least 90% or at least 95% identical thereto.
9. The recombinant circular RNA of claim 1 or 2, wherein the at least one reprogramming factor is Nanog, and wherein the Nanog has the sequence of SEQ ID NO: 5 or 6, or a sequence at least 90% or at least 95% identical thereto.
10. The recombinant circular RNA of claim 9, wherein the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 36, or a sequence at least 90% or at least 95% identical thereto.
11. The recombinant circular RNA of claim 1 or 2, wherein the at least one reprogramming factor is Lin28, and wherein the Lin28 has the sequence of SEQ ID NO: 7, or a sequence at least 90% or at least 95% identical thereto.
12. The recombinant circular RNA of claim 11, wherein the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 35, or a sequence at least 90% or at least 95% identical thereto.
13. The recombinant circular RNA of claim 1 or 2, wherein the at least one reprogramming factor is c-Myc, and wherein the c-Myc has the sequence of SEQ ID NO: 8 or 9, or a sequence at least 90% or at least 95% identical thereto.
14. The recombinant circular RNA of claim 13, wherein the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 38, or a sequence at least 90% or at least 95% identical thereto.
15. The recombinant circular RNA of claim 1 or 2, wherein the at least one reprogramming factor is L-Myc, and wherein the L-Myc has the sequence of any one of SEQ ID NO: 10-12, or a sequence at least 90% or at least 95% identical thereto.
16. The recombinant circular RNA of any one of claims 1-15, wherein the circular RNA is substantially non-immunogenic.

17. The recombinant circular RNA of claim 16, wherein the circular RNA comprises one or more M-6-methyladenosine (m⁶A) residues.
18. The recombinant circular RNA of any one of claim 1-17, wherein the circular RNA comprises from about 200 nucleotides to about 5,000 nucleotides.
19. The recombinant circular RNA of any one of claims 1-18, wherein the circular RNA comprises an internal ribosome entry site (IRES) operably linked to the protein-coding sequence.
20. A complex comprising a recombinant circular RNA of any one of claims 1-19, and a lipid nanoparticle (LNP).
21. The complex of claim 20, wherein the LNP comprises a cationic lipid.
22. The complex of claim 20 or 21, wherein the recombinant circular RNA and the LNP are conjugated.
23. The complex of claim 22, wherein the recombinant circular RNA and the LNP are covalently conjugated.
24. The complex of claim 22, wherein the recombinant circular RNA and the LNP are non-covalently conjugated.
25. A vector comprising a nucleic acid encoding the recombinant circular RNA of any one of claims 1-19.
26. The vector of claim 25, wherein the vector is a non-viral vector.
27. The vector of claim 26, wherein the non-viral vector is a plasmid.
28. The vector of claim 25, wherein the vector is a viral vector.

29. The vector of claim 28, wherein the viral vector is a retroviral vector, a herpesvirus vector, an adenovirus vector, an adeno-associated virus (AAV) vector, a baculoviral vector, an alphavirus vector, a picornavirus vector, a vaccinia virus vector, or a lentiviral vector.
30. A composition comprising the recombinant circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, or the vector of any one of claims 25-29.
31. The composition of claim 30, wherein the composition comprises a carrier and/or a vehicle.
32. A composition comprising two or more of the recombinant circular RNAs of any one of claims 1-19, wherein the composition comprises a combination of recombinant circular RNAs encoding the reprogramming factors selected from those in Table 2.
33. A composition comprising two or more recombinant circular RNAs, wherein the composition comprises a combination of recombinant circular RNAs encoding the reprogramming factors selected from:
- (i) Oct3/4, Klf4, Sox2, and c-Myc;
 - (ii) Oct3/4, Klf4, Sox2, and L-Myc;
 - (iii) Oct3/4, Klf4, and Sox2;
 - (iv) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc; or
 - (iv) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc.
34. A kit comprising the recombinant circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33.
35. A cell comprising the recombinant circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33.
36. The cell of claim 35, wherein the cell is a eukaryotic cell.

37. The cell of claim 36, wherein the cell is a mammalian cell.
38. The cell of claim 37, wherein the cell is a human cell.
39. The cell of any one of claims 35-38, wherein the cell is a CD34+ cell.
40. A method of expressing a protein in a cell, the method comprising contacting the cell with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the protein is expressed.
41. The method of claim 40, wherein the method comprises contacting the cell with an additional circular RNA, wherein the additional circular RNA is circBIRC6, circCORO1C, or circMAN1A2.
42. The method of claim 41, wherein the additional circular RNA is circBIRC6, and wherein the circBIRC6 has a sequence of SEQ ID NO: 13, or a sequence at least 90% or at least 95% identical thereto.
43. The method of claim 41, wherein the additional circular RNA is circCORO1C, and wherein the circCORO1C has a sequence of SEQ ID NO: 14, or a sequence at least 90% or at least 95% identical thereto.
44. The method of claim 41, wherein the additional circular RNA is circMAN1A2, and wherein the circMAN1A2 has a sequence of SEQ ID NO: 15, or a sequence at least 90% or at least 95% identical thereto.
45. The method of any one of claims 40-44, wherein the method comprises contacting the cell with a circular RNA encoding B18R.
46. The method of claim 45, wherein the B18R has a sequence of SEQ ID NO: 16, or a sequence at least 90% or at least 95% identical thereto.

47. A method of producing an induced pluripotent stem cell (iPSC), the method comprising contacting a somatic cell with at least one of the recombinant circular RNAs of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, and/or the composition of any one of claims 30-33, and maintaining the cell under conditions under which a reprogrammed iPSC is obtained.

48. The method of claim 47, wherein the method comprises contacting the cell with at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, or at least 9 circular RNAs.

49. The method of claim 47 or 48, wherein the method comprises contacting the cell with a first circular RNAs encoding Oct4, a second circular RNA encoding Sox2, a third circular RNA encoding Klf4, a fourth circular RNA encoding C-Myc or L-Myc, and a fifth circular RNA encoding Lin28.

50. The method of claim 47 or 48, wherein the method comprises contacting the cell with a first circular RNAs encoding Oct4, a second circular RNA encoding Sox2, a third circular RNA encoding Klf4, a fourth circular RNA encoding C-Myc or L-Myc, a fifth circular RNA encoding Lin28, and a sixth circular RNA encoding Nanog.

51. The method of claim 47, comprising contacting the somatic cell with at least one non-circular RNA nucleic acids encoding one or more reprogramming factors.

52. The method of claim 51, wherein the one non-circular RNA nucleic acids are selected from an mRNA or a plasmid.

53. The method of any one of claims 47-52, wherein the method comprises contacting the cell with at least one additional circular RNA, wherein the at least one additional circular RNA is circBIRC6, circCORO1C, or circMAN1A2.

54. The method of claim 53, wherein the at least one additional circular RNA is BIRC6, and wherein BIRC6 has a sequence of SEQ ID NO: 13, or a sequence at least 90% or at least 95% identical thereto.

55. The method of claim 53, wherein the at least one additional circular RNA is CORO1C, and wherein CORO1C has a sequence of SEQ ID NO: 14, or a sequence at least 90% or at least 95% identical thereto.
56. The method of claim 53, wherein the at least one additional circular RNA is MAN1A2, and wherein MAN1A2 has a sequence of SEQ ID NO: 15, or a sequence at least 90% or at least 95% identical thereto.
57. The method of any one of claims 47-56, wherein the method comprises contacting the cell with a circular RNA encoding B18R.
58. The method of claim 57, wherein the B18R has a sequence of SEQ ID NO: 16, or a sequence at least 90% or at least 95% identical thereto.
59. The method of any one of claims 47-58, wherein the cell is a fibroblast, a peripheral blood-derived cell, an endothelial progenitor cell, a cord-blood derived cell, a keratinocyte, a melanocyte, an adipose-tissue derived cell, or a urine-derived cell.
60. The method of any one of claims 47-58, wherein the cell is a CD34+ cell.
61. The method of any one of claims 47-60, wherein the cell is an adherent cell.
62. The method of any one of claims 47-60, wherein the cell is in suspension.
63. A method of producing an induced pluripotent stem cell (iPSC), the method comprising contacting a CD34+ in suspension cell with at least one of the recombinant circular RNAs of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, and/or the composition of any one of claims 30-33, and maintaining the cell under conditions under which a reprogrammed iPSC is obtained.
64. The method of any one of claims 47-63, wherein the method results in one or more of:

- (i) an increase in the number of reprogrammed iPSC present at the end of culture compared to a method of producing an iPSC with one or more linear RNAs;
- (ii) an increase in the rate of reprogrammed iPSC maturation compared to a method of producing an iPSC with one or more linear RNAs; and/or
- (iii) a decrease in cell toxicity at one or more timepoints during reprogramming compared to a method of producing an iPSC with one or more linear RNAs.

65. The method of any one of claims 47-63, wherein the method results in each of:

- (i) an increase in the number of reprogrammed iPSC present at the end of culture compared to a method of producing an iPSC with one or more linear RNAs;
- (ii) an increase in the rate of reprogrammed iPSC maturation compared to a method of producing an iPSC with one or more linear RNAs; and
- (iii) a decrease in cell toxicity at one or more timepoints during reprogramming compared to a method of producing an iPSC with one or more linear RNAs.

66. The method of any one of claims 47-65, comprising contacting the cell one or more times with at least one of the recombinant circular RNAs of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, and/or the composition of any one of claims 30-33.

67. The method of claim 66, comprising contacting the cell two, three, four, or more times.

68. The method of claim 66, comprising contacting the cell less than four times.

69. The method of claim 66, comprising contacting the cell between 2 and 4 times.

70. An iPSC produced using the method of any one of claims 47-69.

71. A differentiated cell derived from the iPSC of claim 70.

72. The differentiated cell of claim 71, wherein the differentiated cell is a muscle cell, a neuron, a cardiomyocyte, a hepatocyte, an islet cell, a keratinocyte, a T-cell, or a NK-cell.

73. A method of directly converting a cell from a first cell type to a second cell type, the method comprising contacting the cell with the recombinant circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, and/or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the cell is converted to the second cell type.

74. The method of claim 73, wherein the first cell type is a somatic cell and the second cell type is a somatic cell.

75. The method of claim 73, wherein the second cell type is a muscle cell, a neuron, a cardiomyocyte, a hepatocyte, an islet, a keratinocyte, a T-cell, or a NK-cell.

76. The method of claim 74 or 75, wherein the first cell type is a fibroblast.

77. The method of claim 76, wherein the cell is contacted with a plurality of recombinant circular RNAs, wherein the plurality of circular RNAs comprise circular RNAs encoding any one of the combinations of transdifferentiation factors listed in Column B of Table 6.

78. The method of any one of claims 73-77, wherein the cell does not enter an intermediate pluripotent state.

79. The method of any one of claims 73-78, wherein the cell is converted directly from the first cell type to the second cell type, without becoming a progenitor cell.

80. The method of any one of claims 78 to 79, wherein the first type of cell is a fibroblast, the second type of cell is a muscle cell, and the recombinant circular RNA encodes myoD.

81. A cell produced by the method of any one of claims 73 to 80.

82. A method for reprogramming and editing the genome of a cell, the method comprising:

contacting the cell with:

- (i) a recombinant circular RNA comprising a protein-coding sequence, wherein the protein-coding sequence encodes at least one reprogramming factor, and
- (ii) an enzyme capable of editing the DNA or RNA of the cell, or a nucleic acid encoding the same.

83. The method of claim 82, wherein the recombinant circular RNA is the recombinant circular RNA of any one of claims 1-19.

84. The method of claim 82 or 83, wherein the enzyme is a TALEN, a NgAgo, a SGN, or a RGN, or a modified or truncated variant thereof.

85. The method of any one of claims 82-84, wherein the enzyme is a Cas9 nuclease, a Cas12(a) nuclease (Cpf1), a Cas12b nuclease, a Cas12c nuclease, a TrpB-like nuclease, a Cas13a nuclease (C2c2), a Cas13b nuclease, a Cas 14 nuclease or a modified or truncated variant thereof.

86. The method of claim 85, wherein the enzyme is a Cas9 nuclease, and the Cas9 nuclease is isolated or derived from *S. pyogenes* or *S. aureus*.

87. The method of claim 82 or 83, wherein the enzyme is an ADAR.

88. The method of any one of claims 82-84, wherein the enzyme is a RNA-guided nuclease.

89. The method of claim 88, wherein the RNA-guided nuclease is selected from any one of APG05083.1, APG07433.1, APG07513.1, APG08290.1, APG05459.1, APG04583.1, and APG1688.1, APG05733.1, APG06207.1, APG01647.1, APG08032.1, APG05712.1, APG01658.1, APG06498.1, APG09106.1, APG09882.1, APG02675.1, APG01405.1, APG06250.1, APG06877.1, APG09053.1, APG04293.1, APG01308.1, APG06646.1, APG09748, APG07433.1, APG00969, APG03128, APG09748, APG00771, APG02789, APG09106, APG02312, APG07386, APG09980, APG05840, APG05241, APG07280, APG09866, and APG00868.

90. The method of any one of claims 82-89, wherein the method further comprises contacting the cell with a guide RNA, or a nucleic acid encoding the same.
91. The method of any one of claims 82-90, wherein the cell is contacted with the recombinant circular RNA before it is contacted with the enzyme or the nucleic acid encoding the same.
92. The method of any one of claims 82-90, wherein the cell is contacted with the recombinant circular RNA after it is contacted with the enzyme or the nucleic acid encoding the same.
93. The method of any one of claims 82-90, wherein the cell is contacted with the recombinant circular RNA at approximately the same time that it is contacted with the enzyme or the nucleic acid encoding the same.
94. A cell generated by the method of any one of claims 82-93.
95. A method for transdifferentiating and editing the genome of a cell, the method comprising:
contacting the cell with:
(i) a recombinant circular RNA comprising a protein-coding sequence, wherein the protein-coding sequence encodes at least one transdifferentiation factor, and
(ii) an enzyme capable of editing the DNA or RNA of the cell, or a nucleic acid encoding the same.
96. The method of claim 95, wherein the at least one transdifferentiation factor is any one of MyoD, C/EBP α , C/EBP β , Pdx1, Ngn3, Mafa, Pdx1, Hnf4 α , Foxa1, Foxa2, Foxa3, Ascl1 (also known as Mash1), Brn2, Myt1l, miR-124, Brn2, Myt1l, Ascl1, Nurr1, Lmx1a, Ascl1, Brn2, Myt1l, Lmx1a, FoxA2, Oct4, Sox2, Klf4 and c-Myc, Tbx5, Mef2c, Gata-4, or Mesp1.
97. The method of claim 95, wherein the at least one transdifferentiation factor is any one of the transdifferentiation factors listed in Table 6.

98. The method of claim 95, comprising two or more transdifferentiation factors selected from those listed in Table 6.
99. The method of claim any one of claims 95-98, wherein the enzyme is a TALEN, a NgAgo, a SGN, or a RGN, or a modified or truncated variant thereof.
100. The method of any one of claims 95-98, wherein the enzyme is a Cas9 nuclease, a Cas12(a) nuclease (Cpf1), a Cas12b nuclease, a Cas12c nuclease, a TrpB-like nuclease, a Cas13a nuclease (C2c2), a Cas13b nuclease, a Cas 14 nuclease or a modified or truncated variant thereof.
101. The method of claim 100, wherein the nuclease is a Cas9 nuclease, and the Cas9 nuclease is isolated or derived from *S. pyogenes* or *S. aureus*.
102. The method of any one of claims 95-98, wherein the enzyme is an ADAR.
103. The method of any one of claims 95-98, wherein the enzyme is a RNA-guided nuclease.
104. The method of claim 103, wherein the RNA-guided nuclease is selected from any one of APG05083.1, APG07433.1, APG07513.1, APG08290.1, APG05459.1, APG04583.1, and APG1688.1, APG05733.1, APG06207.1, APG01647.1, APG08032.1, APG05712.1, APG01658.1, APG06498.1, APG09106.1, APG09882.1, APG02675.1, APG01405.1, APG06250.1, APG06877.1, APG09053.1, APG04293.1, APG01308.1, APG06646.1, APG09748, APG07433.1, APG00969, APG03128, APG09748, APG00771, APG02789, APG09106, APG02312, APG07386, APG09980, APG05840, APG05241, APG07280, APG09866, and APG00868.
105. The method of any one of claims 95-104, wherein the method further comprises contacting the cell with a guide RNA, or a nucleic acid encoding the same.
106. The method of any one of claims 95-105, wherein the cell is contacted with the recombinant circular RNA before it is contacted with the enzyme or the nucleic acid encoding the same.

107. The method of any one of claims 95-105, wherein the cell is contacted with the recombinant circular RNA after it is contacted with the enzyme or the nucleic acid encoding the same.

108. The method of any one of claims 95-105, wherein the cell is contacted with the recombinant circular RNA at approximately the same time that it is contacted with the enzyme or the nucleic acid encoding the same.

109. A cell generated by the method of any one of claims 95-108.

110. A method for reprogramming a cell, the method comprising contacting a cell with one or more of:

- (i) a circular RNA encoding a reprogramming factor;
- (ii) a circular RNA that does not encode any protein or miRNA;
- (iii) a circular or linear RNA encoding a miRNA; and/or
- (iv) a circular or linear RNA encoding a viral protein.

111. A method for reprogramming a cell, the method comprising contacting a cell with each of:

- (i) a circular RNA encoding a reprogramming factor;
- (ii) a circular RNA that does not encode any protein or miRNA;
- (iii) a circular or linear RNA encoding a miRNA; and
- (iv) a circular or linear RNA encoding a viral protein.

112. A method for reprogramming a cell, the method comprising contacting a cell with each of:

- (i) a circular RNA encoding a reprogramming factor;
- (ii) a circular or linear RNA encoding a miRNA; and
- (iii) a circular or linear RNA encoding a viral protein.

113. A method for reprogramming a cell, the method comprising contacting a cell with each of:

- (i) a circular RNA encoding a reprogramming factor; and

(ii) a circular or linear RNA encoding a miRNA.

114. The method of any one of claims 110 – 113, wherein any one of the circular RNA or linear RNAs are conjugated to a lipid nanoparticle.

115. The method of any one of claims 110-113, wherein the reprogramming factor is any one of the reprogramming factors listed in Table 1, Table 2, or Table 3.

116. The method of any one of claims 110-115, wherein the circular RNA is the recombinant circular RNA of any one of claims 1-19.

117. The method of claim 111, wherein the circular RNA that does not encode any protein or miRNA is circBIRC6, circCORO1c, or circMAN1A2.

118. The method of any one of claims 111-113, wherein the miRNA is miR302d, miR302a, miR302c, miR302b, or miR367.

119. The method of any one of claims 111-113, the miRNA is miR146a, miR485, miR182, nc886, miR-155, miR526a, or miR132.

120. The method of any one of claims 111-112, wherein the viral protein is B18R, E3, or K3.

121. The method of any one of claims 111-112, wherein the viral protein is any one of the viral proteins listed in Table 4.

122. The method of any one of claims 111-112, wherein the viral protein is B18R, E3, and K3.

123. A cell generated by the method of any one of claims 111-122.

124. A composition comprising an isolated somatic cell that comprising one or more exogenous circular RNAs encoding a reprogramming factor.

125. The composition of claim 124, wherein the somatic cell comprises one or more exogenous circular RNAs encoding a reprogramming factor selected from the reprogramming factors listed in Table 1, Table 2, or Table 3.

126. The composition of claim 124, wherein the somatic cell comprises one or more exogenous circular RNAs, wherein the one or more exogenous circular RNAs each encode a reprogramming factor selected from Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc.

127. The composition of claim 124, wherein the somatic cell comprises six exogenous circular RNAs, wherein each circular RNA encodes one of Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc.

128. The composition of claim 124, wherein the somatic cell comprises one or more exogenous circular RNAs, wherein the one or more endogenous circular RNAs each encode a reprogramming factor selected from Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc.

129. The composition of claim 124, wherein the somatic cell comprises six exogenous circular RNAs, wherein each circular RNA encodes one of Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc.

130. The composition of claim 124, wherein the somatic cell comprises four exogenous circular RNAs, wherein each circular RNA encodes one of Oct3/4, Klf4, Sox2, and c-Myc.

131. The composition of claim 124, wherein the somatic cell comprises four exogenous circular RNAs, wherein each circular RNA encodes one of Oct3/4, Klf4, Sox2, and L-Myc.

132. The composition of claim 124, wherein the somatic cell comprises four exogenous circular RNAs, wherein each circular RNA encodes one of Oct3/4, Klf4, and Sox2.

133. The composition of any one of claims 124-132, wherein the cell comprises at least one, at least two, or all three exogenous viral proteins selected from B18R, E3, and K3.

134. The composition of any one of claims 124-133, wherein the cell comprises an exogenous miRNA.

135. The composition of any one of claim 124-133, wherein the cell comprises a circular RNA encoding an exogenous miRNA

136. The composition of claim 134 or 135, wherein the miRNA is selected from miR302a, miR302b, miR302c, miR302d and miR367.

137. A composition comprising a transdifferentiated cell, wherein the transdifferentiated cell comprises one or more exogenous circular RNAs encoding a transdifferentiation factor.

138. The composition of claim 137, wherein the transdifferentiation factor is any one of the transdifferentiation factors or combinations of transdifferentiation factors listed in Table 6.

139. The composition of claim 137 or 138, wherein the transdifferentiated cell is any one of the second cell types listed in Table 6.

140. The composition of claim 137 or 138, wherein the transdifferentiated cell is derived from a first cell type that is any one of the first cell types listed in Table 6.

141. A method of reprogramming a cell which produces reduced cell death as compared to a method using linear RNA, the method comprising contacting a cell with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the protein is expressed.

142. The method of claim 141, wherein the method comprises contacting the cell with a plurality of circular RNAs, wherein each circular RNA encodes one of the following reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc; or
- (vii) Oct3/4, Klf4, and Sox2.

143. A method of reducing time from reprogramming to picking, the method comprising contacting a cell with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the protein is expressed, wherein the time is reduced relative to a reprogramming method using linear RNA.

144. The method of claim 143, wherein the method comprises contacting the cell with a plurality of circular RNAs, wherein each circular RNA encodes one of the following reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc; or
- (vii) Oct3/4, Klf4, and Sox2.

145. A method of reducing the number of transfections induce to effect reprogramming of a cell, the method comprising contacting a cell with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining

the cell under conditions under which the protein is expressed, relative to a method using linear RNA.

146. The method of claim 145, wherein the method comprises contacting the cell with a plurality of circular RNAs, wherein each circular RNA encodes one of the following reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc; or
- (vii) Oct3/4, Klf4, and Sox2.

147. A method of increasing duration of protein expression in a cell, the method comprising contacting a cell with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the protein is expressed, and wherein the duration of protein expression is increased relative to transfection of the cell with a linear RNA encoding the same protein.

148. The method of claim 147, wherein the method comprises contacting the cell with a plurality of circular RNAs, wherein each circular RNA encodes one of the following reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc; or
- (vii) Oct3/4, Klf4, and Sox2.

149. A method of improving cellular reprogramming efficiency, the method comprising contacting a cell with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the protein is expressed, and wherein the efficacy of cellular reprogramming is increased relative to a cellular reprogramming method in which linear RNA is used.

150. The method of claim 149, wherein the method comprises contacting the cell with a plurality of circular RNAs, wherein each circular RNA encodes one of the following reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc, or
- (vii) Oct3/4, Klf4, and Sox2.

151. A method of increasing the number of reprogrammed cell colonies formed after reprogramming, the method comprising contacting a cell with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the protein is expressed, wherein the number of reprogrammed cell colonies formed after reprogramming is increased relative to a cellular reprogramming method in which linear RNA is used.

152. The method of claim 151, wherein the method comprises contacting the cell with a plurality of circular RNAs, wherein each circular RNA encodes one of the following reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;

- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc; or
- (vii) Oct3/4, Klf4, and Sox2.

153. A method of reprogramming cells in suspension, the method comprising contacting a cell in suspension with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the protein is expressed.

154. The method of claim 153, wherein the method comprises contacting the cell in suspension with a plurality of circular RNAs, wherein each circular RNA encodes one of the following reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc; or
- (vii) Oct3/4, Klf4, and Sox2.

155. The method of claim 153 or 154, wherein the cell expresses CD34.

156. A method of improving morphological maturation of reprogrammed colonies, the method comprising contacting a cell in suspension with the circular RNA of any one of claims 1-19, the complex of any one of claims 20-24, the vector of any one of claims 25-29, or the composition of any one of claims 30-33, and maintaining the cell under conditions under which the protein is expressed, wherein the morphological maturation is improved relative to a cellular reprogramming method in which linear RNA is used.

157. The method of claim 156, wherein the method comprises contacting the cell in suspension with a plurality of circular RNAs, wherein each circular RNA encodes one of the following reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc; or
- (vii) Oct3/4, Klf4, and Sox2.

158. A suspension culture comprising one or more CD34-expressing cells, wherein the CD34-expressing cells comprise one or more exogenous circRNAs encoding a reprogramming factor.

159. The suspension culture of claim 158, wherein the reprogramming factor is selected from Oct3/4, Klf4, Sox2, Nanog, Lin28, c-Myc, and L-Myc.

160. The suspension culture of claim 158, wherein the CD34-expressing cells each comprise a plurality of circRNAs encoding one of the following combinations of reprogramming factors:

- (i) Oct3/4, Klf4, Sox2, Nanog, Lin28, and c-Myc;
- (ii) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (iii) Oct3/4, Klf4, Sox2, Nanog, Lin28, and L-Myc;
- (iv) Oct3/4, Klf4, Sox2, Nanog, and Lin28;
- (v) Oct3/4, Klf4, Sox2, and c-Myc;
- (vi) Oct3/4, Klf4, Sox2, and L-Myc; or
- (vii) Oct3/4, Klf4, and Sox2.

161. A kit comprising:

- (i) a vessel comprising a circular RNA encoding OCT4 and a buffer;
- (ii) a vessel comprising a circular RNA encoding SOX2 and a buffer;
- (iii) a vessel comprising a circRNA encoding KLF4 and a buffer; and
- (iv) packaging and instructions therefor.

162. The kit of claim 161, wherein the kit comprises:

a vessel comprising a circular RNA encoding c-MYC or L-MYC and a buffer;

a vessel comprising a cirRNA encoding LIN28 and a buffer;
a vessel comprising a cirRNA encoding NANOG and a buffer;
or a combination thereof.

163. A method for inducing a mesenchymal-to-epithelial transition (MET) of a somatic cell to an iPSC comprising contacting the somatic cell with one or more circular RNA encoding a reprogramming factor.

164. A method for inducing a mesenchymal-to-epithelial transition (MET) of a somatic cell to an iPSC comprising contacting the somatic cell with one or more circular RNA encoding a reprogramming factor.

165. A method for transdifferentiating a cell, the method comprising contacting the cell with a recombinant circular RNA comprising a protein-coding sequence, wherein the protein-coding sequence encodes at least one transdifferentiation factor.

166. The method of claim 165, wherein the at least one transdifferentiation factor is any one of MyoD, C/EBP α , C/EBP β , Pdx1, Ngn3, Mafa, Pdx1, Hnf4 α , Foxa1, Foxa2, Foxa3, Ascl1 (also known as Mash1), Brn2, Myt1l, miR-124, Brn2, Myt1l, Ascl1, Nurr1, Lmx1a, Ascl1, Brn2, Myt1l, Lmx1a, FoxA2, Oct4, Sox2, Klf4 and c-Myc, Tbx5, Mef2c, Gata-4, or Mesp1.

167. The method of claim 165, wherein the at least one transdifferentiation factor is any one of the transdifferentiation factors listed in Table 6.

168. The method of claim 167, wherein the cell is contacted with circular RNAs encoding the combination of transdifferentiation factors listed in any one of the combinations shown in Column B of Table 6.

169. A method for differentiating an iPSC, the method comprising contacting the iPSC with a circular RNA encoding one or more of the following differentiation factors: RORA, HLF, MYB, KLF4, ERG, SOX4, LUC, HOXA9, HOXA10, or HOXA5.

170. The method of claim 169, wherein the iPSC is differentiated to a T-cell.

171. A cell generated by the method of any one of claims 165-170.

CLAIMS

What is claimed is:

1. A method of producing an induced pluripotent stem cell (iPSC), the method comprising contacting a somatic cell with a circular RNA comprising a protein-coding sequence, wherein the protein-coding sequence encodes at least one reprogramming factor, wherein the at least one reprogramming factor is Oct3/4, Klf4, Sox2, Nanog, Lin28, c-Myc, or L-Myc, or a fragment or variant thereof, and maintaining the somatic cell under conditions under which a reprogrammed iPSC is obtained.
2. The method of claim 1, wherein the at least one reprogramming factor is a human or a humanized reprogramming factor.
3. The method of claim 1 or 2, wherein:
 - (a) the at least one reprogramming factor is Oct3/4, and wherein the Oct3/4 has the sequence of SEQ ID NO: 1, or a sequence at least 90% or at least 95% identical thereto;
 - (b) the at least one reprogramming factor is Klf4, and wherein the Klf4 has the sequence of SEQ ID NO: 2 or 3, or a sequence at least 90% or at least 95% identical thereto;
 - (c) the at least one reprogramming factor is Sox2, and wherein Sox2 has the sequence of SEQ ID NO: 4, or a sequence at least 90% or at least 95% identical thereto;
 - (d) the at least one reprogramming factor is Nanog, and wherein the Nanog has the sequence of SEQ ID NO: 5 or 6, or a sequence at least 90% or at least 95% identical thereto;
 - (e) the at least one reprogramming factor is Lin28, and wherein the Lin28 has the sequence of SEQ ID NO: 7, or a sequence at least 90% or at least 95% identical thereto;
 - (f) the at least one reprogramming factor is c-Myc, and wherein the c-Myc has the sequence of SEQ ID NO: 8 or 9, or a sequence at least 90% or at least 95% identical thereto; and/or

(g) the at least one reprogramming factor is L-Myc, and wherein the L-Myc has the sequence of any one of SEQ ID NO: 10-12, or a sequence at least 90% or at least 95% identical thereto.

4. The method of claim 3, wherein

(a) the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 33, or a sequence at least 90% or at least 95% identical thereto;

(b) the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 37, or a sequence at least 90% or at least 95% identical thereto;

(c) the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 34, or a sequence at least 90% or at least 95% identical thereto;

(d) the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 36, or a sequence at least 90% or at least 95% identical thereto;

(e) the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 35, or a sequence at least 90% or at least 95% identical thereto; and/or

(f) the recombinant circular RNA comprises a nucleic acid sequence of SEQ ID NO: 38, or a sequence at least 90% or at least 95% identical thereto.

5. The method of any one of claims 1-4, wherein the circular RNA is substantially non-immunogenic, optionally wherein the circular RNA comprises one or more M-6-methyladenosine (m⁶A) residues.

6. The method of claim 5, wherein the circular RNA comprises from about 200 nucleotides to about 5,000 nucleotides, optionally wherein the circular RNA comprises an internal ribosome entry site (IRES) operably linked to the protein-coding sequence.

7. The method of any one of claims 1-6, wherein the circular RNA is complexed with a lipid nanoparticle (LNP), wherein optionally the LNP comprises a cationic lipid.

8. The method of claim 7, wherein the recombinant circular RNA and the LNP are conjugated.

9. The method of claim 8, wherein the recombinant circular RNA and the LNP are covalently conjugated or are non-covalently conjugated.
10. The method of any one of claims 1-9, wherein the method comprises contacting the somatic cell with at least 2, at least 3, at least 4, at least 5, at least 6 circular RNAs encoding Oct4, Sox2, Klf4, C-Myc, L-Myc, Lin28, or Nanog, optionally wherein a first circular RNA encodes Oct4, a second circular RNA encodes Sox2, a third circular RNA encodes Klf4, a fourth circular RNA encodes C-Myc or L-Myc, and a fifth circular RNA encodes Lin28.
11. The method of any one of claims 1-9, wherein the method comprises contacting the somatic cell with at least 2, at least 3, at least 4, at least 5, at least 6 circular RNAs encoding Oct4, Sox2, Klf4, C-Myc, L-Myc, Lin28, or Nanog, optionally wherein a first circular RNA encodes Oct4, a second circular RNA encodes Sox2, a third circular RNA encodes Klf4, a fourth circular RNA encodes C-Myc or L-Myc, a fifth circular RNA encodes Lin28, and a sixth circular RNA encodes Nanog.
12. The method of any one of claims 1-11, wherein the somatic cell is a fibroblast, a peripheral blood-derived cell, an endothelial progenitor cell, a cord-blood derived cell, a keratinocyte, a melanocyte, an adipose-tissue derived cell, or a urine-derived cell.
13. The method of any one of claims 1-12, wherein the somatic cell is a CD34+ cell.
14. The method of any one of claims 1-13, wherein the somatic cell is an adherent cell or is in suspension.
15. The method of any one of claims 1-12, wherein the somatic cell is a CD34+ cell in suspension.

16. The method of any one of claims 1-15, comprising contacting the somatic cell one or more times with at least one of the recombinant circular RNAs, optionally wherein the somatic cell is contacted two, three, or four times.
17. The method of any one of claims 1-16, wherein the method results in one or more of:
 - (i) an increase in the number of reprogrammed iPSC present at the end of culture compared to a method of producing an iPSC with one or more linear RNAs;
 - (ii) an increase in the rate of reprogrammed iPSC maturation compared to a method of producing an iPSC with one or more linear RNAs; and/or
 - (iii) a decrease in cell toxicity at one or more timepoints during reprogramming compared to a method of producing an iPSC with one or more linear RNAs.
18. An iPSC produced using the method of any one of claims 1-17.
19. A differentiated cell derived from the iPSC of claim 18.
20. The differentiated cell of claim 19, wherein the differentiated cell is a muscle cell, a neuron, a cardiomyocyte, a hepatocyte, an islet cell, a keratinocyte, a T-cell, or a NK-cell.