

CLAIMS

What is claimed is:

1. A method of inducing immune tolerance to an agent in an individual, the method comprising administering an effective amount of an EV to the individual in conjunction with administering the agent to the individual, wherein EV comprises a lipid bilayer comprising one or more immunosuppressive molecules.
2. The method of claim 1, wherein the one or more immunosuppressive molecules comprise one or more immune checkpoint proteins.
3. The method of claim 1 or 2, wherein the one or more immunosuppressive molecules comprise one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA or HVEM.
4. The method of claim 1 or 2, wherein the one or more immunosuppressive molecules targets CD40 or CD40L.
5. The method of claim 4, wherein the immunosuppressive molecule is an antibody that binds CD40 or CD40L.
6. The method of any one of claims 1-5, wherein the lipid bilayer comprises two or more, three or more, or four or more different immunosuppressive molecules; or comprises two or more, three or more, or four or more different checkpoint proteins.
7. The method of any one of claims 1-6, wherein the lipid bilayer comprises CTLA4 and PD-L1; CTLA4 and PD-L2; CTLA4 and VISTA; PD-L1 and PD-L2; PD-L1 and VISTA; PD-L2 and VISTA; CTLA4 and PD-L1 and PD-L2; CTLA4 and PD-L1 and VISTA; CTLA4 and PD-L2 and VISTA; PD-L1 and PD-L2 and VISTA; or CTLA4 and PD-L1 and PD-L1 and VISTA.
8. The method of any one of claims 1-7, wherein one or more of the immunosuppressive molecules comprises a transmembrane domain.

9. The method of claim 8, wherein the transmembrane domain is a PDGFR transmembrane domain, an EGFR transmembrane domain or a murine CTLA4 transmembrane domain.
10. The method of any one of claims 1-9, wherein the lipid bilayer further comprises a targeting molecule.
11. The method of claim 10, wherein the targeting molecule confers cell- or tissue-specificity to the EV.
12. The method of claim 10 or 11, wherein the targeting molecule confers specificity of the method to the liver, spleen, and/or thymus.
13. The method of claim 10 or 11, wherein the targeting molecule targets MHC class I or MHC class II mismatches between donor tissue and the individual.
14. The method of any one of claims 10-13, wherein the targeting molecule is an antibody.
15. The method of any one of claims 10-14, wherein the one or more targeting molecules comprises a transmembrane domain.
16. The method of any one of claims 1-15, wherein the EV is produced from a producer cell engineered to express the one or more immunosuppressive molecules.
17. The method of any one of claims 1-16, wherein the EV is produced from a producer cell engineered to express the one or more immunosuppressive molecules.
18. The method of any one of claims 1-17, wherein the EV is produced from a producer cell engineered to express one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA, HVEM, an anti-CD40 antibody or an anti-CD40L antibody.
19. The method of claim 18, wherein the producer cell is a human embryonic kidney 293 (HEK 293) cell, HeLa cell, or a Per.C6 cell.

20. The method of any one of claims 1-19, wherein the EV is produced from a producer cell which contains no additional heterologous molecules other than the one or more immunosuppressive molecules and targeting molecules.
21. The method of any one of claims 1-20, wherein the EV contains no additional molecules heterologous to the cell from which it was derived other than the one or more immunosuppressive molecules and targeting molecules.
22. The method of any one of claims 1-21, wherein the EV is administered to the individual before, at the same time, or after administration of the agent.
23. The method of any one of claims 1-22, wherein the EV is administered to the individual at the same time as administration of the agent.
24. The method of any one of claims 1-23, wherein the EV and the agent are in different formulations.
25. The method of any one of claims 1-24, wherein the EV and the agent are in the same formulation.
26. The method of claim 25, wherein the agent associates with the EV.
27. The method of claim 25 or 26, wherein the agent associates with the exterior surface of the EV.
28. The method of any one of claims 25-27, wherein the stimulation of immune tolerance facilitates repeat administration of the agent to the individual.
29. The method of claim 28, wherein the repeat administration comprises more than about 2 administrations, 3 administrations, 4 administrations, 5 administrations, 6 administrations, 7 administrations, 8 administrations, 9 administrations, or 10 administrations of the agent.
30. The method of any one of claims 1-29, wherein the agent is a therapeutic agent.
31. The method of any one of claims 1-30, wherein the agent is a polypeptide, a nucleic

acid, a polypeptide-nucleic acid complex, a viral vector, a liposome, a cell, or transplanted cells or tissue.

32. The method of claim 31, wherein the agent is a therapeutic polypeptide.

33. The method of claim 32, wherein the therapeutic polypeptide is an enzyme, a hormone, an antibody, an antibody fragment, a clotting factor, a growth factor, a receptor, or a functional derivative thereof.

34. The method of claim 32 or 33, wherein the therapeutic polypeptide is Factor VIII, Factor IX, myotubularin, survival motor neuron protein (SMN), retinoid isomerohydrolase (RPE65), NADH-ubiquinone oxidoreductase chain 4, Choroideremia protein (CHM), huntingtin, alpha-galactosidase A, acid beta-glucosidase, alpha-glucosidase, ornithine transcarbamylase, argininosuccinate synthetase, β -globin, γ -globin, phenylalanine hydroxylase, adrenoleukodystrophy protein (ALD), dystrophin, a truncated dystrophin, Niemann Pick C protein (NPC-1), an anti-VEGF agent, or a functional variant thereof.

35. The method of claim 31, wherein the agent is a nucleic acid encoding a therapeutic polypeptide or a therapeutic nucleic acid.

36. The method of claim 35, wherein the nucleic acid encodes Factor VIII, Factor IX, myotubularin, survival motor neuron protein (SMN), retinoid isomerohydrolase (RPE65), NADH-ubiquinone oxidoreductase chain 4, Choroideremia protein (CHM), huntingtin, alpha-galactosidase A, acid beta-glucosidase, alpha-glucosidase, ornithine transcarbamylase, argininosuccinate synthetase, β -globin, γ -globin, phenylalanine hydroxylase, or adrenoleukodystrophy protein (ALD).

37. The method of claim 35, wherein the therapeutic nucleic acid is a siRNA, miRNA, shRNA, antisense RNA, RNAzyme, or DNAzyme.

38. The method of claim 37, wherein the nucleic acid encodes one or more gene editing products.

39. The method of claim 31, wherein the polypeptide-nucleic acid complex is a gene editing complex.

40. The method of claim 31, wherein the agent is a viral vector or a capsid protein thereof.
41. The method of claim 40, wherein the viral vector is an adeno-associated viral (AAV) vector, a lentiviral vector, an adenoviral vector, a herpes simplex viral vector or a baculovirus vector.
42. The method of claim 31, wherein the agent is a cell used in cell therapy.
43. The method of claim 42, wherein the cell is a stem cell, an induced pluripotent cell (iPS), or a differentiated cell.
44. The method of claim 42 or 43, wherein the cell is a pluripotent cell or a multipotent cell.
45. The method of claim 43 or 44, wherein the cell is an embryonic stem cell or an adult stem cell.
46. The method of claim 45, wherein the cell is a hematopoietic stem cell, a liver stem cell, a muscle stem cell, a cardiomyocyte stem cell, a neural stem cell, a bone stem cell, a mesenchymal stem cell, or an adipose stem cell.
47. The method of claim 42 or 43, wherein the cell is a blood cell, a hepatocyte, a myocyte, a cardiomyocyte, a pancreatic cell, an islet cell, an ocular cell, a neural cell, an astrocyte, an oligodendrocyte, an inner ear hair cell, a chondrocyte, or an osteoblast.
48. The method of any one of claims 42-47, wherein the cell is allogeneic to the individual.
49. The method of any one claims 1-48, wherein the individual is a human.
50. A method of treating a disease or disorder in an individual, the method comprising administering an effective amount of an EV to the individual, wherein EV comprises a lipid bilayer comprising one or more immunosuppressive molecules.
51. The method of claim 50, wherein the disease or disorder is an autoimmune disease or

disorder.

52. The method of claim 50, wherein the EV is administered in conjunction with a tissue transplant or cell engraftment.

53. A method of treating a disease or disorder in an individual, the method comprising administering an effective amount of an EV to the individual in conjunction with administering an agent to the individual, wherein EV comprises a lipid bilayer comprising one or more immunosuppressive molecules, and wherein the agent treats the disease or disorder.

54. The method of any one of claims 50-53, wherein the one or more immunosuppressive molecules comprise one or more immune checkpoint proteins.

55. The method of any one of claims 50-54, wherein the one or more immunosuppressive molecules comprise one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA or HVEM.

56. The method of any one of claims 50-54, wherein the one or more immunosuppressive molecules targets CD40 or CD40L.

57. The method of claim 56, wherein the immunosuppressive molecule is an antibody that binds CD40 or CD40L.

58. The method of any one of claims 50-57, wherein the lipid bilayer comprises two or more, three or more, or four or more different immunosuppressive molecules; or comprises two or more, three or more, or four or more different checkpoint proteins.

59. The method of any one of claims 50-58, wherein the lipid bilayer comprises CTLA4 and PD-L1; CTLA and PD-L2; CTLA-4 and VISTA; PD-L1 and PD-L2; PD-L1 and VISTA; PD-L2 and VISTA; CTLA4 and PD-L1 and PD-L2; CTLA4 and PD-L1 and VISTA; CTLA4 and PD-L2 and VISTA; PD-L1 and PD-L2 and VISTA; or CTLA4 and PD-L1 and PD-L1 and VISTA.

60. The method of any one of claims 50-59, wherein one or more of the

immunosuppressive molecules comprises a transmembrane domain.

61. The method of claim 60, wherein the transmembrane domain is a PDGFR transmembrane domain, an EGFR transmembrane domain or a murine CTLA4 transmembrane domain.

62. The method of any one of claims 50-61, wherein the lipid bilayer further comprises a targeting molecule.

63. The method of claim 62, wherein the targeting molecule confers cell- or tissue-specificity to the EV.

64. The method of claim 62 or 63, wherein the targeting molecule confers specificity of the method to the liver, spleen, and/or thymus.

65. The method of claim 62 or 63, wherein the targeting molecule targets MHC class I or MHC class II mismatches between donor tissue and the individual.

66. The method of any one of claims 62-65, wherein the targeting molecule is an antibody.

67. The method of any one of claims 62-66, wherein the one or more targeting molecules comprises a transmembrane domain.

68. The method of any one of claims 50-67, wherein the EV is produced from a producer cell engineered to express the one or more immunosuppressive molecules.

69. The method of any one of claims 50-68, wherein the EV is produced from a producer cell engineered to express the one or more immunosuppressive molecules.

70. The method of any one of claims 50-69, wherein the EV is produced from a producer cell engineered to express one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA, HVEM, an anti-CD40 antibody or an anti-CD40L antibody.

71. The method of any one of claims 50-70, wherein the producer cell is a human embryonic kidney 293 (HEK 293) cell, HeLa cell, or a Per.C6 cell.
72. The method of any one of claims 50-71, wherein the EV is produced from a producer cell which contains no additional heterologous molecules other than the one or more immunosuppressive molecules and targeting molecules.
73. The method of any one of claims 50-72, wherein the EV contains no additional molecules heterologous to the cell from which it was derived other than the one or more immunosuppressive molecules and targeting molecules.
74. The method of claim 50 or 73, wherein the EV is administered to the individual before, at the same time, or after administration of the agent.
75. The method of any one of claims 52-74, wherein the EV is administered to the individual at the same time as administration of the agent.
76. The method of any one of claims 52-75, wherein the EV and the agent are in different formulations.
77. The method of any one of claims 52-75, wherein the EV and the agent are in the same formulation.
78. The method of claim 77, wherein the agent associates with the EV.
79. The method of claim 77 or 78, wherein the agent associates with the exterior surface of the EV.
80. The method of any one of claims 52-79, wherein the stimulation of immune tolerance facilitates repeat administration of the agent to the individual.
81. The method of claim 80, wherein the repeat administration comprises more than about 2 administrations, 3 administrations, 4 administrations, 5 administrations, 6 administrations, 7 administrations, 8 administrations, 9 administrations, or 10 administrations of the agent.

82. The method of any one of claims 52-81, wherein the agent is a therapeutic agent.
83. The method of any one of claims 52-82, wherein the agent is a polypeptide, a nucleic acid, a polypeptide-nucleic acid complex, a viral vector, a liposome, or transplanted cells or tissue.
84. The method of claim 83, wherein the agent is a therapeutic polypeptide.
85. The method of claim 84, wherein the therapeutic polypeptide is an enzyme, a hormone, an antibody, an antibody fragment, a clotting factor, a growth factor, a receptor, or a functional derivative thereof.
86. The method of claim 84 or 85, wherein the therapeutic polypeptide is Factor VIII, Factor IX, myotubularin, survival motor neuron protein (SMN), retinoid isomerohydrolase (RPE65), NADH-ubiquinone oxidoreductase chain 4, Choroideremia protein (CHM), huntingtin, alpha-galactosidase A, acid beta-glucosidase, alpha-glucosidase, ornithine transcarbamylase, argininosuccinate synthetase, β -globin, γ -globin, phenylalanine hydroxylase, or adrenoleukodystrophy protein (ALD).
87. The method of claim 83, wherein the agent is a nucleic acid encoding a therapeutic polypeptide or a therapeutic nucleic acid.
88. The method of claim 87, wherein the nucleic acid encodes Factor VIII, Factor IX, myotubularin, survival motor neuron protein (SMN), retinoid isomerohydrolase (RPE65), NADH-ubiquinone oxidoreductase chain 4, Choroideremia protein (CHM), huntingtin, alpha-galactosidase A, acid beta-glucosidase, alpha-glucosidase, ornithine transcarbamylase, argininosuccinate synthetase, β -globin, γ -globin, phenylalanine hydroxylase, or adrenoleukodystrophy protein (ALD).
89. The method of claim 88, wherein the therapeutic nucleic acid is a siRNA, miRNA, shRNA, antisense RNA, RNAzyme, or DNAzyme.
90. The method of claim 83, wherein the nucleic acid encodes one or more gene editing products.

91. The method of claim 90, wherein the polypeptide-nucleic acid complex is a gene editing complex.
92. The method of claim 83, wherein the agent is a viral vector or a capsid protein thereof.
93. The method of claim 92, wherein the viral vector is an adeno-associated viral (AAV) vector, a lentiviral vector, an adenoviral vector, a herpes simplex viral vector or a baculovirus.
94. The method of claim 83, wherein the agent is a cell used in cell therapy.
95. The method of claim 94, wherein the cell is a stem cell, an induced pluripotent cell (iPS), or a differentiated cell.
96. The method of claim 94 or 95, wherein the cell is a pluripotent cell or a multipotent cell.
97. The method of claim 95 or 96, wherein the cell is an embryonic stem cell or an adult stem cell.
98. The method of claim 97, wherein the cell is a hematopoietic stem cell, a liver stem cell, a muscle stem cell, a cardiomyocyte stem cell, a neural stem cell, a bone stem cell, a mesenchymal stem cell, or an adipose stem cell.
99. The method of claim 94 or 95, wherein the cell is a blood cell, a hepatocyte, a myocyte, a cardiomyocyte, a pancreatic cell, an islet cell, an ocular cell, a neural cell, an astrocyte, an oligodendrocyte, an inner ear hair cell, a chondrocyte, or an osteoblast.
100. The method of any one of claims 94-99, wherein the cell is allogeneic to the individual.
101. The method of any one claims 50-100, wherein the individual is a human.
102. A composition comprising an extracellular vesicle (EV) and one or more pharmaceutically acceptable excipients for inducing immune tolerance to an agent in an

individual, wherein EV comprises a lipid bilayer comprising one or more immunosuppressive molecules, and a therapeutic agent.

103. The composition of claim 102, wherein the agent is a polypeptide, a nucleic acid, a polypeptide-nucleic acid complex, a viral vector, a liposome, a cell, or transplanted cells or tissue.

104. The composition of claim 102 or 103, wherein the agent associates with the EV.

105. The composition of any one of claims 102-104, wherein the agent associates with the exterior surface of the EV.

106. The composition of any one of claims 102-105, wherein the one or more immunosuppressive molecules comprise one or more immune checkpoint proteins.

107. The composition of any one of claims 102-106, wherein the one or more immunosuppressive molecules comprise one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA, or HVEM.

108. The composition of any one of claims 102-107, wherein the one or more immunosuppressive molecules targets CD40 or CD40L.

109. The composition of claim 108, wherein the immunosuppressive molecule is an antibody that binds CD40 or CD40L.

110. The composition of any one of claims 102-109, wherein the lipid bilayer comprises two or more, three or more, or four or more different immunosuppressive molecules; or comprises two or more, three or more, or four or more different checkpoint proteins.

111. The composition of any one of claims 102-110, wherein the lipid bilayer comprises CTLA4 and PD-L1; CTLA and PD-L2; CTLA-4 and VISTA; PD-L1 and PD-L2; PD-L1 and VISTA; PD-L2 and VISTA; CTLA4 and PD-L1 and PD-L2; CTLA4 and PD-L1 and VISTA; CTLA4 and PD-L2 and VISTA; PD-L1 and PD-L2 and VISTA; or CTLA4 and PD-L1 and PD-L1 and VISTA.

112. The composition of any one of claims 102-111, wherein one or more of the immunosuppressive molecules comprises a transmembrane domain.
113. The composition of claim 112, wherein the transmembrane domain is a PDGFR transmembrane domain, an EGFR transmembrane domain or a murine CTLA4 transmembrane domain.
114. The composition of any one of claims 102-113, wherein the lipid bilayer further comprises a targeting molecule.
115. The composition of claim 114, wherein the targeting molecule confers cell- or tissue-specificity to the EV.
116. The composition of claim 114 or 115, wherein the targeting molecule confers specificity of the EV to the liver, spleen, and/or thymus.
117. The composition of any one of claims 114-116, wherein the targeting molecule targets MHC class I or MHC class II mismatches between donor tissue and the individual.
118. The composition of any one of claims 114-117, wherein the targeting molecule is an antibody.
119. The composition of any one of claims 114-118, wherein the one or more targeting molecules comprises a transmembrane domain.
120. The composition of any one of claims 102-119, wherein the EV is produced from a producer cell engineered to express the one or more immunosuppressive molecules.
121. The composition of any one of claims 102-120, wherein the EV is produced from a producer cell engineered to express the one or more immunosuppressive molecules.
122. The composition of any one of claims 102-121, wherein the EV is produced from a producer cell engineered to express one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA, HVEM, an anti-CD40 antibody or an anti-CD40L antibody.

123. The composition of any one of claims 102-122, wherein the producer cell is a human embryonic kidney 293 (HEK 293) cell, HeLa cell, or a Per.C6 cell.

124. The composition of any one of claims 102-123, wherein the EV is produced from a producer cell which contains no additional heterologous molecules other than the one or more immunosuppressive molecules and targeting molecules.

125. The composition of any one of claims 102-124, wherein the EV contains no additional molecules heterologous to the cell from which it was derived other than the one or more immunosuppressive molecules and targeting molecules.

126. A method of producing the composition of any of claims 102-125, the method comprising

- a) culturing EV producer cells *in vitro* under conditions to generate EVs, wherein the EV producer cells comprise nucleic acids encoding one or more one or more membrane-bound immunosuppressive molecules,
- b) collecting the EVs, and
- c) formulating the EVs with the agent.

127. The method of claim 126, wherein the EV producer cells comprise exogenous nucleic acids encoding the membrane-bound immunosuppressive molecules.

128. The method of claim 126 or 127, wherein the membrane-bound immunosuppressive molecules comprise one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA or HVEM.

129. The method of claim 126 or 127, wherein the one or more immunosuppressive molecules targets CD40 or CD40L.

130. The method of claim 129, wherein the immunosuppressive molecule is an antibody that binds CD40 or CD40L.

131. The method of any one of claims 126-130, wherein one or more of the immunosuppressive molecules comprises a transmembrane domain.

132. The method of claim 131, wherein the transmembrane domain is a PDGFR transmembrane domain, an EGFR transmembrane domain or a murine CTLA4 transmembrane domain.
133. The method of any one of claims 126-132, wherein the lipid bilayer further comprises a targeting molecule.
134. The method of claim 133, wherein the targeting molecule confers cell- or tissue-specificity to the EV.
135. The method of claim 133 or 134, wherein the targeting molecule confers specificity of the EV to the liver, spleen, and/or thymus.
136. The method of claim 133 or 134, wherein the targeting molecule targets MHC class I or MHC class II mismatches between donor tissue and the individual.
137. The method of any one of claims 133-136, wherein the targeting molecule is an antibody.
138. The method of any one of claims 133-137, wherein the one or more targeting molecules comprises a transmembrane domain.
139. The method of any one of claims 126-138, wherein the EV is produced from a producer cell engineered to express the one or more immunosuppressive molecules.
140. The method of any one of claims 126-139, wherein the EV is produced from a producer cell engineered to express one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA or HVEM.
141. The method of claim 140, wherein the producer cell is a human embryonic kidney 293 (HEK 293) cell, HeLa cell, or a Per.C6 cell.
142. The method of any one of claims 126-141, wherein the EV is produced from a producer cell which contains no additional heterologous molecules other than the one or more immunosuppressive molecules and targeting molecules.

143. The method of any one of claims 126-142, wherein the EV contains no additional molecules heterologous to the cell from which it was derived other than the one or more immunosuppressive molecules and targeting molecules.
144. A producer cell for producing an immunosuppressive EV, wherein EV comprises a lipid bilayer comprising one or more immunosuppressive molecules, wherein the one or more immunosuppressive molecules are membrane-bound.
145. The producer cell of claim 144, wherein the producer cell is engineered to express the one or more immunosuppressive molecules.
146. The producer cell of claim 144 or 145, wherein the producer cell is engineered to express one or more of CTLA4, B7-1, B7-2, PD-1, PD-L1, PD-L2, CD28, VISTA, TIM-3, GAL9, TIGIT, CD155, LAG3, VISTA, BTLA or HVEM.
147. The producer cell of claim 144 or 145, wherein the one or more immunosuppressive molecules targets CD40 or CD40L.
148. The producer cell of claim 147, wherein the immunosuppressive molecule is an antibody that binds CD40 or CD40L.
149. The producer cell of any one of claims 144-148, wherein one or more of the immunosuppressive molecules comprises a transmembrane domain.
150. The producer cell of claim 149, wherein the transmembrane domain is a PDGFR transmembrane domain, an EGFR transmembrane domain or a murine CTLA4 transmembrane domain.
151. The producer cell of any one of claims 144-150, wherein the lipid bilayer further comprises a targeting molecule.
152. The producer cell of claim 151, wherein the targeting molecule confers cell- or tissue-specificity to the EV.
153. The producer cell of claim 151 or 152, wherein the targeting molecule confers

specificity of the EV to the liver, spleen, and/or thymus.

154. The producer cell of claim 152 or 153, wherein the targeting molecule targets MHC class I or MHC class II mismatches between donor tissue and the individual.

155. The producer cell of any one of claims 151-154, wherein the targeting molecule is an antibody.

156. The producer cell of any one of claims 151-155, wherein the one or more targeting molecules comprises a transmembrane domain.

157. The producer cell of any one of claims 151-156, wherein the cell comprises nucleic acid encoding the one or more immunosuppressive molecule and/or the one or more targeting molecule.

158. The producer cell of claim 157, wherein the nucleic acid encoding the one or more immunosuppressive molecule and/or the one or more targeting molecule is stably integrated into the genome of the cell.

159. The producer cell of any one of claims 144-158, wherein the producer cell is a mammalian cell.

160. The producer cell of any one of claims 144-159, wherein the producer cell is a human cell.

161. The producer cell of any one of claims 144-160, wherein the producer cell is a human embryonic kidney 293 (HEK 293) cell, HeLa cell, or a Per.C6 cell.

162. The producer cell of any one of claims 144-161, wherein the producer cell contains no additional heterologous molecules other than the one or more immunosuppressive molecules and targeting molecules.