CLAIMS

~~1. A virus that produces from its genome a non-replicating retrovirus, wherein the virus is an oncolytic virus.~~

~~2. The virus of claim 1, wherein the non-replicating retrovirus comprises a transgene that codes for a non-retroviral protein.~~

~~3. A virus that produces from its genome a non-replicating retrovirus, wherein the virus is an oncolytic virus, wherein the non-replicating retrovirus comprises a transgene that codes for a non-retroviral protein, and wherein the non-replicating retrovirus is capable of expressing the non-retroviral protein in cells that are infected by the oncolytic virus and in cells that are not infected by the oncolytic virus, in a tumor microenvironment.~~

~~4. An oncolytic virus that produces from its genome a non-replicating retrovirus, wherein the non-replicating retrovirus comprises a transgene that codes for a non-lentiviral protein, and wherein the non-replicating retrovirus is capable of infecting and transducing both dividing and non-dividing cells in a target population of mammalian cells.~~

~~5. A virus comprising a transgene that codes for a non-retroviral protein, wherein the transgene is within an exogenous nucleic acid construct that further comprises a gene that codes for a protein of a non-replicating retrovirus, and wherein the virus is oncolytic.~~

~~6.~~**1.** A virus comprising a retroviral envelope construct, a retroviral packaging ~~packing~~ construct, and a retroviral transfer construct, wherein at least one of the envelope construct, the packaging construct, or the transfer construct comprises a transgene that codes for a non-retroviral protein, and wherein the virus is an oncolytic virus.

~~7.~~**2.** The virus of claim ~~6~~1, wherein the envelope construct, the packaging ~~packing~~ construct, and the transfer construct are inserted at different locations within the genome of the oncolytic virus.

~~8.~~3. The virus of claim ~~6~~ 1 or ~~7~~2, wherein the envelope construct comprises a gene that codes for a retroviral envelope protein and the packaging construct comprises a gene that codes for a retroviral structural protein.

~~**9.** The virus of claim 8, wherein the gene that codes for the retroviral envelope protein is under the control of a first early viral promoter and the gene that codes for the retroviral structural protein is under the control of a second early viral promoter.~~

~~10.~~4. The virus of claim ~~8~~3, wherein the gene that codes for the retroviral envelope protein is under the control of a first early viral promoter, a first early/late viral promoter or a first late viral promoter; and the gene that codes for a retroviral structural protein is under the control of a second early viral promoter, a second early/late viral promoter, or a second late viral promoter.

~~**11.** The virus of any one of claims 6-10, wherein the envelope construct further comprises a termination sequence at its 5'-terminal region.~~

~~**12.** The virus of any one of claims 6-11, wherein the packaging construct further comprises a termination sequence at its 3'-terminal region.~~

~~**13.** The virus of any one of claims 6-12, wherein the transfer construct comprises a 3'-long terminal repeat region.~~

~~**14.** The virus of any one of claims 6-13, wherein the transfer construct comprises a hybrid 5'-long terminal repeat region.~~

~~**15.** The virus of claim 14, wherein the hybrid 5'-long terminal repeat region comprises a third early viral promoter and a HIV-1 protein 5'-long terminal repeat region.~~

~~**16.** The virus of claim 14, wherein the hybrid 5'-long terminal repeat region comprises a HIV-1 protein 5'-long terminal repeat region and a viral promoter, wherein the viral promoter is a third early viral promoter, a third early/late viral promoter, or a third late viral promoter.~~

~~**17.** The virus of any one of claims 6-16, wherein the transfer construct further comprises a gene that codes for a self-cleaving RNA ribozyme.~~

~~**18.** The virus of claim 17, wherein the gene that codes for the self-cleaving RNA ribozyme is positioned downstream to the 3' long terminal repeat region of the transfer construct.~~

~~**19.** The virus of claim 18, wherein the self-cleaving ribozyme comprises a delta virus ribozyme or a hammerhead ribozyme.~~

~~**20.** The virus of any one of claims 9-19, wherein the packaging construct comprises a 5' long terminal repeat region and wherein the second early viral promoter is fused to the 5' long terminal repeat region.~~

~~**21.** The virus of any one of claims 6-20, wherein the envelope construct comprises a termination sequence at its 5' terminal region.~~

~~**22.** The virus of any one of claims 6-21, wherein the packaging construct comprises a termination sequence at its 3' terminal region.~~

~~**23.** The virus of any one of claims 6-22, wherein the transfer construct comprises a termination sequence at its 3' terminal region.~~

~~**24.** The virus of any one of claims 11-23, wherein the termination sequence comprises a nucleotide sequence as set forth in SEQ ID No. 7.~~

~~**25.** The virus of any one of claims 8-24, wherein the retroviral structural protein comprises a mature gag-pol protein.~~

~~**26.** The virus of claim 25, wherein the mature gag-pol protein comprises p55, p41, and p24.~~

~~**27.** The virus of any one of claims 8-26, wherein the retroviral envelope protein comprises a VSV-G protein.~~

~~**28.**~~**5.** The virus of any one of claims 1~~-3 and 5-27~~ to 4, comprising an exogenous

nucleic acid sequence that codes for a nucleic acid polymerase.

~~29.~~**6.** The virus of claim ~~28~~5, wherein the nucleic acid polymerase is selected from the group consisting of: T7 RNA polymerase, T3 RNA polymerase and SP6 RNA polymerase, a RNA polymerase variant, and a DNA polymerase mutant.

~~30.~~**7.** The virus of any one of claims ~~1-3 and 5-27~~1 to 6, comprising an exogenous nucleic acid sequence that codes for a bacteriophage polymerase.

~~31.~~**8.** The virus of claim ~~30~~7, wherein the bacteriophage is selected from the group consisting of a T3 bacteriophage, a T7 bacteriophage and an SP6 bacteriophage.

~~32.~~**9.** The virus of claim ~~31~~8, wherein a T3 bacteriophage polymerase is expressed with a T3 bacteriophage promoter, a T7 bacteriophage polymerase is expressed with a T7 bacteriophage promoter, and an SP6 bacteriophage polymerase is expressed with an SP6 bacteriophage promoter.

~~**33.** The oncolytic virus of claim 4, comprising an exogenous nucleic acid sequence that codes for a bacteriophage polymerase.~~

~~**34.** The oncolytic virus of claim 33, wherein the nucleic acid polymerase is selected from the group consisting of: T7 RNA polymerase, T3 RNA polymerase and SP6 RNA polymerase, a RNA polymerase variant, and a DNA polymerase mutant.~~

~~**35.** The oncolytic virus of claim 4, comprising an exogenous nucleic acid sequence that codes for a bacteriophage polymerase.~~

~~**36.** The oncolytic virus of claim 35, wherein the bacteriophage is selected from the group consisting of a T3 bacteriophage, a T7 bacteriophage and an SP6 bacteriophage.~~

~~**37.** The oncolytic virus of claim 36, wherein a T3 bacteriophage polymerase is expressed with a T3 bacteriophage promoter, a T7 bacteriophage polymerase is expressed with a T7 bacteriophage promoter, and an SP6 bacteriophage polymerase is expressed with an SP6 bacteriophage promoter.~~

38. A virus comprising: (i) a retroviral envelope construct inserted at a first location within the genome of the virus; and (ii) a retroviral packaging construct inserted at a second location within the genome of the virus, wherein the first location and the second location are not contiguous, wherein the envelope construct comprises a nucleic acid that codes for a retroviral envelope protein, wherein the packaging construct comprises a nucleic acid that codes for a retroviral structural protein, and wherein the virus is an oncolytic virus.

39. The virus of claim 38, further comprising (iii) a transfer construct inserted at a third location within the genome of the oncolytic virus.

40. The virus of claim 39, wherein the transfer construct comprises a transgene that codes for a non-retroviral protein.

41. The virus of claim 39 or 40, wherein the transfer construct is inserted near the 3' end of the genome of the oncolytic virus.

42. The virus of any one of claims 38-41, wherein the gene that codes for the retroviral envelope protein is under the control of a first early viral promoter and the gene that codes for the retroviral structural protein is under the control of a second early viral promoter.

43. The virus of any one of claims 38-41, wherein the gene that codes for the retroviral envelope protein is under the control of a first early viral promoter, a first early/late viral promoter or a first late viral promoter; and the gene that codes for a retroviral structural protein is under the control of a second early viral promoter, a second early/late viral promoter, or a second late viral promoter.

44. The virus of any one of claims 38-42, wherein the transfer construct comprises a hybrid 5' long terminal repeat region.

45. The virus of claim 44, wherein the hybrid 5'-long terminal repeat region comprises a third early viral promoter and a HIV-1 protein 5'-long terminal repeat region.

46. The virus of claim 44, wherein the hybrid 5'-long terminal repeat region comprises a HIV-1 protein 5'-long terminal repeat region and a viral promoter, wherein the viral promoter is a third early viral promoter, a third early/late viral promoter, or a third late viral promoter.

47. The virus of any one of claims 39-46, wherein the transfer construct further comprises a gene that codes for a self-cleaving RNA ribozyme.

48. The virus of claim 47, wherein the gene that codes for the self-cleaving RNA ribozyme is positioned downstream to the 3'-long terminal repeat region of the transfer construct.

49. The virus of claim 48, wherein the self-cleaving ribozyme comprises a delta virus ribozyme or a hammerhead ribozyme.

50. The virus of any one of claims 42-49, wherein the packaging construct comprises a 5'-long terminal repeat region and wherein the second early viral promoter is fused to the 5'-long terminal repeat region.

51. The virus of any one of claims 38-50, wherein the nucleic acid that codes for the retroviral envelope protein comprises a nucleotide sequence as set forth in SEQ ID No. 1, or a nucleotide sequence that is at least about 70% to at least about 99% identical to the sequence set forth as SEQ ID No. 1.

52. The virus of any one of claims 38-51, wherein the nucleic acid that codes for the retroviral structural protein comprises a nucleotide sequence as set forth in SEQ ID No. 2, or a nucleotide sequence that is at least about 70% to at least about 99% identical to the sequence set forth as SEQ ID No. 2.

53. The virus of any one of claims 38-52, wherein the transfer construct comprises a 3'-long terminal repeat region.

54. The virus of any one of claims 38-53, wherein the envelope construct comprises a termination sequence at its 5'-terminal region.

55. The virus of any one of claims 38-54, wherein the packaging construct comprises a termination sequence at its 3'-terminal region.

56. The virus of any one of claims 39-55, wherein the transfer construct comprises a termination sequence at its 3'-terminal region.

57. The virus of any one of claims 53-56, wherein the termination sequence comprises nucleotide sequence as set forth in SEQ ID No. 5.

58. The virus of any one of claims 38-57, wherein the first location and the second location are separated by at least about 10,000 bases.

59. The virus of any one of claims 39-58, wherein the first location and the third location are separated by at least about 10,000 bases.

60. The virus of any one of claims 39-59, wherein the second location and the third location are separated by at least about 10,000 bases.

61. The virus of any one of claims 38-60, wherein the structural protein comprises a mature gag-pol protein.

62. The virus of claim 61, wherein the mature gag-pol protein comprises p55, p41, and p24.

63. The virus of any one of claims 38-62, wherein the envelope protein comprises a VSV-G protein.

64. The virus of any one of claims 1-63, wherein the oncolytic virus is tumor selective in replication.

65. The virus of claim 64, wherein the non-replicating retrovirus is produced selectively within a tumor microenvironment.

66. The virus of any one of claims 1-65, wherein the oncolytic virus in an oncolytic vaccinia virus.

~~67. The virus of claim 66, comprising the first, the second, and the third early viral promoters, wherein the first early viral promoter is a first vaccinia virus early promoter, the second early viral promoter is a second vaccinia virus early promoter, and the third early viral promoter is a third vaccinia virus early promoter.~~

~~68. The virus of claim 67, wherein the first vaccinia virus early promoter comprises a sequence as set forth in SEQ ID No. 9.~~

~~69. The virus of claim 67 or 68, wherein the second vaccinia virus early promoter comprises a sequence as set forth in SEQ ID No. 10.~~

~~70. The virus of any one of claims 67-69, wherein the third vaccinia virus early promoter comprises a sequence set forth as SEQ ID No. 11.~~

~~71. The virus of any one of claims 6-37 and 39-70, wherein the transfer construct comprises a human PGK promoter (SEQ ID No. 12).~~

~~72. The virus of claim any one of claims 66-71, wherein the envelope construct is inserted between genes vacwr032 and vacwr033 of the oncolytic vaccinia virus.~~

~~73. The virus of any one of claims 66-72, wherein the packaging construct is inserted between genes vacwr093 and vacwr095 of the oncolytic vaccinia virus.~~

~~74. The virus of any one of claims 6-73, wherein the genome of the oncolytic vaccinia virus comprises a deletion of the vacwr094 gene, and wherein the packaging construct is inserted into the location of the vacwr094 gene.~~

~~75. The virus of any one of claims 66-74, wherein the transfer construct is inserted between genes vacwr205 and vacwr206 of the oncolytic vaccinia virus.~~

~~76.~~**10.** The virus of any one of claims 1~~-75~~ to 7, wherein the non-retroviral protein comprises a therapeutic protein or a diagnostic protein.

~~77.~~**11.** The virus of claim ~~76~~8, wherein the non-retroviral protein comprises the therapeutic protein, and wherein the therapeutic protein comprises an immune checkpoint modulator, an antibody or portion thereof, a Fc fusion protein, an

anticoagulant, a blood factor, a bone morphogenetic protein, an immunosuppressive agent, an immunostimulatory agent, an enzyme, a growth factor, a hormone, an interferon, an interleukin, a thrombolytic, an anti-angiogenic, a chemotherapeutic, an antibiotic, an antifungal, an antiviral, and any combination thereof.

~~78.~~**12.** The virus of any one of claims ~~1-77~~1 to 9, wherein the retroviral envelope construct, the retroviral packaging construct, and the retroviral transfer construct are from~~retrovirus is~~ an Alpharetrovirus, a Betaretrovirus, a Deltaretrovirus, an Epsilonretrovirus, a Gamma retrovirus, ~~or~~ a Lentivirus, or any combination thereof.

~~79.~~**13.** The virus of claim ~~78~~12, wherein the retroviral envelope construct, the retroviral packaging construct, and the retroviral transfer construct are from~~retrovirus is~~ the lentivirus.

~~80.~~**14.** The virus of claim ~~79~~13, wherein the lentivirus is an HIV.

~~81.~~**15.** The virus of claim ~~78~~12, wherein the retroviral envelope construct, the retroviral packaging construct, and the retroviral transfer construct are from ~~retrovirus is~~ the Gamma retrovirus.

~~82.~~**16.** The virus of claim ~~81~~15, wherein the Gamma retrovirus is a Moloney murine leukemia virus.

~~**83.** The virus of any one of claims 78-80, comprising an exogenous nucleic acid sequence that codes for a nucleic acid polymerase.~~

~~**84.** The virus of claim 83, wherein the nucleic acid polymerase is selected from the group consisting of: T7 RNA polymerase, T3 RNA polymerase and SP6 RNA polymerase, a RNA polymerase variant, and a DNA polymerase mutant.~~

~~**85.** The virus of any one of claims 78-80, comprising an exogenous nucleic acid sequence that codes for a bacteriophage polymerase.~~

~~**86.** The virus of claim 85, wherein the bacteriophage is selected from the group~~

~~consisting of a T3 bacteriophage, a T7 bacteriophage and an SP6 bacteriophage.~~

~~**87.** The virus of claim 86, wherein a T3 bacteriophage polymerase is expressed with a T3 bacteriophage promoter, a T7 bacteriophage polymerase is expressed with a T7 bacteriophage promoter, and an SP6 bacteriophage polymerase is expressed with an SP6 bacteriophage promoter.~~

~~**88.** A method of treating cancer, the method comprising: administering to a subject an oncolytic virus according to any one of claims 1-87, wherein the non-replicating retrovirus generated from the oncolytic virus is selectively targeted to a tumor tissue.~~

~~**89.** The method of claim 88, wherein the tumor tissue comprises a malignant neoplastic tissue.~~

~~**90.** An engineered producer virus that generates a non-replicating retrovirus from its genome, wherein the engineered producer virus comprises at least one of the following modifications:~~

~~i. mutation or deletion of at least one viral gene;~~

~~ii. insertion of at least one exogenous nucleic acid;~~

~~iii. altered tropism; or~~

~~iv. any combinations thereof.~~

~~**91.** The engineered producer virus of claim 90, wherein the non-replicating retrovirus comprises a transgene that codes for a non-retroviral protein.~~

~~**92.**__**17.**__ The ~~engineered producer~~ virus of __any one of__ claim__s__ ~~90~~ __1 to 15__~~or 91~~, wherein the ~~producer~~ virus __comprises a mutation or deletion of at least one viral gene__ ~~is a vaccinia virus and the at least one viral gene is~~ selected from the group consisting of: B5R, A52R (VACWR178), F13L, A36R, A34R, A33R, B8R, B18R, SPI-1, SPI-2, B15R, VGF, E3L, K3L, A41L, K7R, N1L, C12L, TK, and any combinations thereof.

~~**93.** The engineered producer virus of any one of claims 90-92, wherein the at least one exogenous nucleic acid codes for a protein selected from the group consisting of:~~

~~CXCR4, CCR2, PH-20, HMGB1, PIAS3, IL15, IL15-Rα, LIGHT, ITAC, fractalkine, CCL5, a metabolic modulating protein, a cytokine, a fusion protein comprising any combinations of the above, and a functional domain or fragment or variant thereof, or any combinations thereof.~~

~~94.~~ ~~The engineered producer virus of claim 93, wherein the at least one exogenous nucleic acid codes for the PIAS3.~~

~~95.~~ ~~The engineered producer virus of any one of claims 90-94, wherein the producer virus comprises a retroviral envelope construct, a retroviral packaging construct and a retroviral transfer construct, wherein the envelope construct, the packing construct, and the transfer construct are inserted at different locations within the genome of the producer virus.~~

~~96.~~ ~~The engineered producer virus of claim 95, wherein the envelope construct comprises a gene that codes for a retroviral envelope protein and the packaging construct comprises a gene that codes for a retroviral structural protein.~~

~~97.~~ ~~The engineered producer virus of claim 96, wherein the gene that codes for the retroviral envelope protein is under the control of a first early viral promoter and the gene that codes for the retroviral structural protein is under the control of a second early viral promoter.~~

~~98.~~ ~~The engineered producer virus of any one of claims 95-97, wherein the envelope construct further comprises a termination sequence at its 5'-terminal region.~~

~~99.~~ ~~The engineered producer virus of any one of claims 95-98, wherein the packaging construct further comprises a termination sequence at its 3'-terminal region.~~

~~100.~~ ~~The engineered producer virus of any one of claims 95-99, wherein the transfer construct comprises a termination sequence.~~

~~101.~~ ~~The engineered producer virus of any one of claims 95-100, wherein the~~

transfer construct comprises a hybrid 5'-long terminal repeat region.

102. The engineered producer virus of claim 101, wherein the hybrid 5'-long terminal repeat region comprises a third early viral promoter and a HIV-1 protein 5'-long terminal repeat region.

103. The engineered producer virus of any one of claims 95-102, wherein the packaging construct comprises a 5'-long terminal repeat region and wherein the second early viral promoter is fused to the 5'-long terminal repeat region.

104. The engineered producer virus of any one of claims 95-103, wherein the envelope construct comprises a termination sequence at its 5'-terminal region.

105. The engineered producer virus of any one of claims 95-104, wherein the packaging construct comprises a termination sequence at its 3'-terminal region.

106. The engineered producer virus of any one of claims 95-105, wherein the transfer construct comprises a termination sequence.

107. The engineered producer virus of any one of claims 104-106, wherein the termination sequence comprises a nucleotide sequence as set forth in SEQ ID No. 7.

108. The engineered producer virus of any one of claims 96-107, wherein the retroviral structural protein comprises a mature gag-pol protein.

109. The engineered producer virus of claim 108, wherein the mature gag-pol protein comprises p55, p41, and p24.

110. The engineered producer virus of any one of claims 96-109, wherein the retroviral envelope protein comprises a VSV-G protein.

111. The engineered producer virus of any one of claims 95-110, wherein the producer virus in an oncolytic vaccinia virus.

112. The engineered producer virus of claim 111, wherein the envelope construct

comprises a first early vaccinia promoter, the packaging construct comprises a second early vaccinia promoter, and the transfer construct comprises a third early vaccinia promoter.

113. The engineered producer virus of claim 112, wherein the first vaccinia virus early promoter comprises a sequence as set forth in SEQ ID No. 9.

114. The engineered producer virus of claim 112 or 113, wherein the second vaccinia virus early promoter comprises a sequence as set forth in SEQ ID No. 10.

115. The engineered producer virus of any one of claims 112-114, wherein the third vaccinia virus early promoter comprises a sequence set forth as SEQ ID No. 11.

116. The engineered producer virus of any one of claims 95-115, wherein the transfer construct comprises a human PGK promoter (SEQ ID No. 12).

117. The engineered producer virus of claim any one of claims 95-116, wherein the envelope construct is inserted between genes vacwr032 and vacwr033 of the oncolytic vaccinia virus.

118. The engineered producer virus of any one of claims 95-116, wherein the packaging construct is inserted between genes vacwr093 and vacwr095 of the oncolytic vaccinia virus.

119. The engineered producer virus of any one of claims 95-118, wherein the genome of the oncolytic vaccinia virus comprises a deletion of the vacwr094 gene, and wherein the packaging construct is inserted into the location of the vacwr094 gene.

120. The engineered producer virus of any one of claims 95-119, wherein the transfer construct is inserted between genes vacwr205 and vacwr206 of the oncolytic vaccinia virus.

121. The engineered producer virus of any one of claims 90-120, wherein the non-

retroviral protein comprises a therapeutic protein or a diagnostic protein.

122. The engineered producer virus of claim 121, comprising the transgene that codes for the non-retroviral protein, wherein the non-retroviral protein comprises the therapeutic protein, and wherein the therapeutic protein comprises an immune checkpoint modulator, an antibody or portion thereof, a Fc fusion protein, an anticoagulant, a blood factor, a bone morphogenetic protein, an immunosuppressive agent, an immunostimulatory agent, an enzyme, a growth factor, a hormone, an interferon, an interleukin, a thrombolytic, an anti-angiogenic, a chemotherapeutic, an antibiotic, an antifungal, an antiviral, and any combination thereof.

123. The engineered producer virus of any one of claims 90-122, wherein the retrovirus is an Alpharetrovirus, a Betaretrovirus, a Deltaretrovirus, an Epsilonretrovirus, a Gamma retrovirus, or a Lentivirus.

124. The engineered producer virus of claim 123, wherein the retrovirus is a lentivirus.

125. The engineered producer virus of claim 124, wherein the lentivirus is an HIV.

126. The engineered producer virus of claim 123, wherein the retrovirus is the Gamma retrovirus.

127. The engineered producer virus of claim 126, wherein the Gamma retrovirus is a Moloney murine leukemia virus (MMLV).

128. A method of treating cancer, the method comprising: administering to a subject an engineered producer virus according to any one of claims 90-127, wherein the non-replicating retrovirus generated from the engineered producer virus is selectively targeted to a tumor tissue.

129. The method of claim 128, wherein the tumor tissue comprises a malignant neoplastic tissue.

~~**130.** A process for generating an oncolytic virus that produces a non-replicating retrovirus, the process comprising: growing a population of the oncolytic virus in mammalian cells, followed by adding and selecting for, sequentially, a retroviral envelope construct, a retroviral packaging construct, and a retroviral transfer construct, wherein at least one of the envelope construct, the packaging construct, or the transfer construct comprises a transgene that codes for a non-retroviral protein.~~

~~**131.** The process of claim 130, wherein the retrovirus is an Alpharetrovirus, a Betaretrovirus, a Deltaretrovirus, an Epsilonretrovirus, a Gamma retrovirus, or a Lentivirus.~~

~~**132.** The process of claim 131, wherein the retrovirus is the lentivirus.~~

~~**133.** The process of claim 132, wherein the lentivirus is an HIV.~~

~~**134.** The process of claim 131, wherein the retrovirus is the Gamma retrovirus.~~

~~**135.** The process of claim 134, wherein the Gamma retrovirus is a Moloney murine leukemia virus.~~

18. The virus of any one of claims 1 to 17, wherein the oncolytic virus is a measles virus, a poliovirus, a poxvirus, a vaccinia virus, an adenovirus, an adeno-associated virus, a herpes simplex virus, a vesicular stomatitis virus, a reovirus, a Newcastle disease virus, a senecavirus, a lentivirus, a mengovirus, or a myxomavirus.

19. The virus of claim 18, wherein the oncolytic virus is the vaccinia virus.

20. Use of the virus of any one of claims 1 to 19 in the manufacture of a medicament for the treatment of cancer.

21. A virus of any one of claims 1 to 19 for use in therapy.