CLAIMS

1. An invention not claimed in any divisional application~~A lipid nanoparticle (LNP) comprising a recombinant DNA molecule comprising a polynucleotide sequence encoding a replication-competent viral genome, wherein the polynucleotide sequence is operably linked to a promoter sequence capable of binding a mammalian RNA polymerase II (Pol II) and is flanked by a 3' junctional cleavage sequence and a 5' junctional cleavage sequence, wherein the 3' and 5' junctional cleavage sequence are of different types, and wherein the polynucleotide encoding the replication-competent viral genome is non-viral in origin~~.

~~2. The LNP of claim 1, wherein the 3' junctional cleavage sequence is a ribozyme sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, an artificial miR (AmiR) target sequence, a guide RNA (gRNA) target sequence, a pri-miR sequence, and an aptazyme sequence.~~

~~3. The LNP of claim 2, wherein the 3' junctional cleavage sequence is a ribozyme sequence and the 5' junctional cleavage sequence is an artificial miR (AmiR) target sequence.~~

~~4. The LNP of claim 1, wherein the 3' junctional cleavage sequence is a microRNA (miR) target sequence and the 5' junctional cleavage sequence is selected from a ribozyme sequence, an artificial miR (AmiR) target sequence, a guide RNA (gRNA) target sequence, a pri-miR sequence, and an aptazyme sequence.~~

~~5. The LNP of claim 1, wherein the 3' junctional cleavage sequence is an artificial miR (AmiR) target sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, a ribozyme sequence, a guide RNA (gRNA) target sequence, a pri-miR sequence, and an aptazyme sequence.~~

~~6. The LNP of claim 1, wherein the 3' junctional cleavage sequence is a guide RNA (gRNA) target sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, an artificial miR (AmiR) target sequence, a ribozyme sequence, a pri-miR sequence, and an aptazyme sequence.~~

~~7. The LNP of claim 1, wherein the 3' junctional cleavage sequence is a pri-miR sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, an~~

~~artificial miR (AmiR) target sequence, a guide RNA (gRNA) target sequence, a ribozyme sequence, and an aptazyme sequence.~~

~~8. The LNP of claim 1, wherein the 3' junctional cleavage sequence is an aptazyme sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, an artificial miR (AmiR) target sequence, a guide RNA (gRNA) target sequence, a pri-miR sequence, and a ribozyme sequence.~~

~~9. The LNP of any one of claims 1-8, wherein the replication-competent viral genome is a single-stranded RNA (ssRNA) virus.~~

~~10. The LNP of claim 9, wherein the single-stranded RNA (ssRNA) virus is a positive sense ((+)-sense) or a negative-sense ((-)-sense) ssRNA virus.~~

~~11. The LNP of claim 10, wherein the replication-competent viral genome is a (+)-sense ssRNA virus and the (+)-sense ssRNA virus is a Picornavirus.~~

~~12. The LNP of claim 11, wherein the Picornavirus is a Seneca Valley Virus (SVV) or a Coxsackievirus.~~

~~13. The LNP of any one of claims 1 – 12, wherein contacting the LNP with a cell results in production of viral particles by the cell, and wherein the viral particles are infectious and lytic.~~

~~14. The LNP of any one of claims 1 – 13, wherein the recombinant DNA molecule further comprises a polynucleotide sequence encoding an exogenous payload protein.~~

~~15. The LNP of any one of claims 1 – 13, wherein the LNP further comprises a second polynucleotide sequence encoding an exogenous payload protein.~~

~~16. The LNP of claim 14 or 15, wherein the exogenous payload protein is a fluorescent protein, an enzymatic protein, a cytokine, a chemokine, a ligand for a cell-surface receptor, or an antigen-binding molecule capable of binding to a cell surface receptor.~~

~~17. The LNP of claim 16, wherein the cytokine is selected from IL-18, IL-36γ, LIGHT, and IL-2.~~

~~18. The LNP of claim 16, wherein the ligand for a cell-surface receptor is Flt3 ligand.~~

~~19. The LNP of claim 16, wherein the chemokine is selected from CCL21, CCL5, CXCL10, and CCL4.~~

~~20. The LNP of claim 16, wherein the antigen-binding molecule is capable of binding to and inhibiting an immune checkpoint receptor.~~

~~21. The LNP of claim 20, wherein the immune checkpoint receptor is PD1.~~

~~22. The LNP of claim 16, wherein the antigen-binding molecule is capable of binding to a tumor associated antigen selected from DLL3, EpCam, and CEA.~~

~~23. The LNP of any one of claims 16-22, wherein the antigen binding molecule is a bispecific T cell engager molecule comprising a first domain specific for a tumor antigen and a second domain specific for a T cell surface molecule.~~

~~24. The LNP of claim 23, wherein the T cell surface molecule is CD3.~~

~~25. The LNP of any one of claims 1 – 22, wherein a micro RNA (miRNA) target sequence (miR-TS) cassette is inserted into the nucleic acid sequence encoding the replication-competent viral genome, wherein the miR-TS cassette comprises one or more miRNA target sequences, and wherein expression of one or more of the corresponding miRNAs in a cell inhibits replication of the replication-competent viral genome in the cell.~~

~~26. The LNP of claim 25, wherein the one or more miRNAs are selected from miR-124, miR-1, miR-143, miR-128, miR-219, miR-219a, miR-122, miR-204, miR-217, miR-137, and miR-126.~~

~~27. The LNP of claim 26, wherein the miR-TS cassette comprises one or more copies of a miR-124 target sequence, one or more copies of a miR-1 target sequence, and one or more copies of a miR-143 target sequence.~~

~~28. The LNP of claim 26, wherein the miR-TS cassette comprises one or more copies of a miR-128 target sequence, one or more copies of a miR-219a target sequence, and one or more copies of a miR-122 target sequence.~~

~~29. The LNP of claim 26, wherein the miR-TS cassette comprises one or more copies of a miR-128 target sequence, one or more copies of a miR-204 target sequence, and one or more copies of a miR-219 target sequence.~~

~~30. The LNP of claim 26, wherein the miR-TS cassette comprises one or more copies of a miR-217 target sequence, one or more copies of a miR-137 target sequence, and one or more copies of a miR-126 target sequence.~~

~~31. The LNP of any one of claims 1—30, wherein the recombinant DNA molecule is a plasmid comprising the polynucleotide sequence encoding a replication-competent viral genome.~~

~~32. The LNP of any one of claims 1—31, wherein the LNP comprises a cationic lipid, a cholesterol, and a neutral lipid.~~

~~33. The LNP of claim 32, wherein the cationic lipid is 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), and wherein the neutral lipid is 1,2-Dilauroyl-sn-glycero-3-phosphoethanolamine (DLPE) or 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE).~~

~~34. The LNP of claim 32 or 33, further comprising a phospholipid-polymer conjugate, wherein the phospholipid-polymer conjugate is 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol) (DSPE-PEG) or 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)] (DSPE-PEG-amine).~~

~~35. The LNP of claim 32, wherein the cationic lipid is D-Lin-MC3-DMA (MC3)and wherein the neutral lipid is 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC).~~

~~36. The LNP of claim 34, wherein further comprising a phospholipid-polymer conjugate of 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol (DMG-PEG).~~

~~37. The LNP of any one of claims 1—36, wherein hyaluronan is conjugated to the surface of the LNP.~~

~~38. The LNP of any one of claims 1—36, wherein an RGD peptide is conjugated to the surface of the LNP.~~

~~39. A therapeutic composition comprising a plurality of lipid nanoparticles according to any one of claims 1 – 37, wherein the plurality of LNPs have an average size of about 50 nm to about 500 nm.~~

~~40. The therapeutic composition of claim 39, wherein the plurality of LNPs have an average size of about 50 nm to about 200 nm, about 100 nm to about 200 nm, about 150 nm to about 200 nm, about 50 nm to about 150 nm, about 100 nm to about 150 nm, about 200 nm to about 500 nm, about 300 nm to about 500 nm, about 350 nm to about 500 nm, about 400 nm to about 500 nm, about 425 nm to about 500 nm, about 450 nm to about 500 nm, or about 475 nm to about 500 nm.~~

~~41. The therapeutic composition of claim 39 or 40, wherein the plurality of LNPs have an average zeta potential of less than about -20 mV, less than about -30 mV, less than about 35 mV, or less than about -40 mV.~~

~~42. The therapeutic composition of claim 41, wherein the plurality of LNPs have an average zeta potential of between about -50 mV to about -20 mV, about -40 mV to about -20 mV, or about -30 mV to about -20 mV.~~

~~43. The therapeutic composition of claim 41 or 42, wherein the plurality of LNPs have an average zeta potential of about -30 mV, about -31 mV, about -32 mV, about -33 mV, about -34 mV, about -35 mV, about -36 mV, about -37 mV, about -38 mV, about -39 mV, or about -40 mV.~~

~~44. The therapeutic composition of any one of claims 39 – 43, wherein administering the therapeutic composition to a subject delivers the recombinant DNA polynucleotide to a target cell of the subject, and wherein the recombinant DNA polynucleotide produces an infectious virus capable of lysing the target cell of the subject.~~

~~45. The therapeutic composition of claim 44, wherein the composition is delivered intravenously or intratumorally.~~

~~46. The therapeutic composition of claim 44, wherein the target cell is a cancerous cell.~~

~~47. A method of inhibiting the growth of a cancerous tumor in a subject in need thereof comprising administering a therapeutic composition according to any one of claims 39 – 46 to the subject in need thereof, wherein administration of the composition inhibits the growth of the tumor.~~

48. The method of claim 47, wherein the administration is intratumoral or intravenous.

49. The method of claim 47 or 48, wherein the cancer is a lung cancer or a liver cancer.

50. A recombinant DNA molecule comprising a polynucleotide sequence encoding a replication competent viral genome, wherein the polynucleotide sequence is operably linked to promoter sequence capable of binding a mammalian RNA polymerase II (Pol II) and is flanked by a 3' junctional cleavage sequence and a 5' junctional cleavage sequence, wherein the 3' and 5' junctional cleavage sequence are of different types, and wherein the polynucleotide encoding the replication competent viral genome is non-viral in origin.

51. The recombinant DNA molecule of claim 50, wherein the 3' junctional cleavage sequence is a ribozyme sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, an artificial miR (AmiR) target sequence, a guide RNA (gRNA) target sequence, a pri-miR sequence, and an aptazyme sequence.

52. The recombinant DNA molecule of claim 51, wherein the 3' junctional cleavage sequence is a ribozyme sequence and the 5' junctional cleavage sequence is an artificial miR (AmiR) target sequence.

53. The recombinant DNA molecule of claim 50, wherein the 3' junctional cleavage sequence is a microRNA (miR) target sequence and the 5' junctional cleavage sequence is selected from a ribozyme sequence, an artificial miR (AmiR) target sequence, a guide RNA (gRNA) target sequence, a pri-miR sequence, and an aptazyme sequence.

54. The recombinant DNA molecule of claim 50, wherein the 3' junctional cleavage sequence is an artificial miR (AmiR) target sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, a ribozyme sequence, a guide RNA (gRNA) target sequence, a pri-miR sequence, and an aptazyme sequence.

55. The recombinant DNA molecule of claim 50, wherein the 3' junctional cleavage sequence is a guide RNA (gRNA) target sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, an artificial miR (AmiR) target sequence, a ribozyme sequence, a pri-miR sequence, and an aptazyme sequence.

~~56. The recombinant DNA molecule of claim 50, wherein the 3' junctional cleavage sequence is a pri-miR sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, an artificial miR (AmiR) target sequence, a guide RNA (gRNA) target sequence, a ribozyme sequence, and an aptazyme sequence.~~

~~57. The recombinant DNA molecule of claim 50, wherein the 3' junctional cleavage sequence is an aptazyme sequence and the 5' junctional cleavage sequence is selected from a microRNA (miR) target sequence, an artificial miR (AmiR) target sequence, a guide RNA (gRNA) target sequence, a pri-miR sequence, and a ribozyme sequence..~~

~~58. The recombinant DNA molecule of any one of claims 50-57, wherein the encoded virus is a single-stranded RNA (ssRNA) virus~~

~~59. The recombinant DNA molecule of claim 58, wherein the ssRNA virus is a positive sense ((+) sense) or a negative sense ((-) sense) ssRNA virus.~~

~~60. The recombinant DNA molecule of claim 59, wherein the (+) sense ssRNA virus is a Picornavirus.~~

~~61. The recombinant DNA molecule of claim 60, wherein the Picornavirus is a Seneca Valley Virus (SVV) or a Coxsackievirus.~~

~~62. The recombinant DNA molecule of any one of claims 50 – 61, wherein the recombinant DNA molecule is capable of producing an infectious, lytic virus when introduced into a cell by a non-viral delivery vehicle.~~

~~63. The recombinant DNA molecule of any one of claims 50 – 62, wherein the recombinant DNA molecule further comprises a polynucleotide sequence encoding an exogenous payload protein.~~

~~64. The recombinant DNA molecule of claim 63, wherein the exogenous payload protein is a fluorescent protein, an enzymatic protein, a cytokine, a chemokine, a ligand for a cell surface receptor, or an antigen binding molecule capable of binding to a cell surface receptor.~~

~~65. The recombinant DNA molecule of claim 64, wherein the cytokine is IL-18, IL-36γ, LIGHT, and IL-2.~~

~~66. The recombinant DNA molecule of claim 64, wherein the ligand for a cell-surface receptor is Flt3 ligand.~~

~~67. The recombinant DNA molecule of claim 64, wherein the chemokine is selected from CCL21, CCL5, CXCL10, and CCL4.~~

~~68. The recombinant DNA molecule of claim 64, wherein the antigen-binding molecule is capable of binding to and inhibiting an immune checkpoint receptor.~~

~~69. The recombinant DNA molecule of claim 68, wherein the immune checkpoint receptor is PD1.~~

~~70. The recombinant DNA molecule of claim 64, wherein the antigen-binding molecule is capable of binding to a tumor associated antigen selected from DLL3, EpCam, and CEA.~~

~~71. The recombinant DNA molecule of claim 64 or claim 70, wherein the antigen binding molecule is a bispecific T cell engager molecule comprising a first domain specific for a tumor antigen and a second domain specific for a T cell surface molecule.~~

~~72. The recombinant DNA molecule of claim 71, wherein the T cell surface molecule is CD3.~~

~~73. The recombinant DNA molecule of any one of claims 50 – 72, wherein a micro RNA (miRNA) target sequence (miR-TS) cassette is inserted into the nucleic acid sequence encoding the replication competent viral genome, wherein the miR-TS cassette comprises one or more miRNA target sequences, and wherein expression of one or more of the corresponding miRNAs in a cell inhibits replication of the encoded virus in the cell.~~

~~74. The recombinant DNA molecule of claim 73, wherein the one or more miRNAs are selected from miR-124, miR-1, miR-143, miR-128, miR-219, miR-219a, miR-122, miR-204, miR-217, miR-137, and miR-126.~~

~~75. The recombinant DNA molecule of claim 73, wherein the miR-TS cassette comprises one or more copies of a miR-124 target sequence, one or more copies of a miR-1 target sequence, and one or more copies of a miR-143 target sequence.~~

~~76. The recombinant DNA molecule of claim 73, wherein the miR-TS cassette comprises one or more copies of a miR-128 target sequence, one or more copies of a miR-219a target sequence, and one or more copies of a miR-122 target sequence.~~

~~77. The recombinant DNA molecule of claim 73, wherein the miR-TS cassette comprises one or more copies of a miR-128 target sequence, one or more copies of a miR-204 target sequence, and one or more copies of a miR-219 target sequence.~~

~~78. The recombinant DNA molecule of claim 73, wherein the miR-TS cassette comprises one or more copies of a miR-217 target sequence, one or more copies of a miR-137 target sequence, and one or more copies of a miR-126 target sequence.~~

~~79. The recombinant DNA molecule of any one of claims 50 – 78, wherein the recombinant DNA molecule is a plasmid or a NanoV comprising the polynucleotide sequence encoding a replication-competent viral genome.~~