

What is claimed is:

CLAIMS

1. A synthetic oncolytic virus, comprising:
 - (i) a lipid nanoparticle comprising N1,N3,N5-tris(3-
5 (didodecylamino)propyl)benzene-1,3,5-tricarboxamide (TT3); and
 - (ii) a self-amplifying replicon RNA comprising a sequence that encodes an interleukin (IL)-12 molecule;
and
wherein the IL-12 molecule is expressed by the self-amplifying replicon RNA.
- 10 2. The synthetic oncolytic virus of claim 1, wherein the lipid nanoparticle further comprises 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE).
3. The synthetic oncolytic virus of claim 2, wherein the lipid nanoparticle further
15 comprises cholesterol.
4. The synthetic oncolytic virus of claims 2 or 3, wherein the lipid nanoparticle further comprises C14-PEG2000.
- 20 5. The synthetic oncolytic virus of any one of claims 1-4, wherein the self-amplifying replicon RNA is derived from an alphavirus, or a hepatitis C virus.
6. The synthetic oncolytic virus of claim 5, wherein the alphavirus is Venezuela Equine Encephalitis virus, Semliki Forest virus, or Sindbis virus.
- 25 7. The synthetic oncolytic virus of any one of claims 1-6, wherein the sequence that encodes the IL-12 molecule is located in a subgenomic region of the self-amplifying replicon RNA.
- 30 8. The synthetic oncolytic virus of any one of claims 1-7, wherein the self-amplifying replicon RNA comprises a nucleotide sequence that has at least 90% sequence identity to the sequence set forth in SEQ ID NO: 1.
9. The synthetic oncolytic virus of claim 8, wherein the self-amplifying replicon RNA
35 comprises a point mutation of G3936C and/or A4758G of SEQ ID NO: 1.

10. The synthetic oncolytic virus of any one of claims 1-9, wherein the IL-12 molecule is selected from the group consisting of IL-12, an IL-12 subunit, or a mutant IL-12 molecule that retains the immunomodulatory function.
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11. The synthetic oncolytic virus of claim 10, wherein the IL-12 molecule comprises IL-12 α and/or IL-12 β subunits.
12. The synthetic oncolytic virus of any one of claims 1-11, wherein the lipid nanoparticle
- 10 has a diameter of 100-120 nm and/or has a zeta potential of 3-6 mv.
13. The synthetic oncolytic virus of any one of claims 1-12, wherein the lipid nanoparticle is capable of triggering immunogenic cell death.
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14. A pharmaceutical composition, comprising:
the synthetic oncolytic virus of any one of claims 1-13 and a pharmaceutically acceptable carrier.
15. The pharmaceutical composition of claim 14, wherein the pharmaceutical
- 20 composition is formulated for intratumoral injection.
16. Use of the synthetic oncolytic virus of any one of claims 1-13 or the pharmaceutical composition of claim 14 or 15 in the manufacture of a medicament for treating cancer in a subject in need thereof.
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17. The use of claim 16, wherein the subject is a human patient having or suspected of having a cancer.
18. The use of claim 17, wherein the human patient has melanoma, breast cancer, colon
- 30 cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, prostate cancer, vulval cancer,

thyroid cancer, hepatic carcinoma, gastric cancer, squamous cell head and neck cancer, renal-cell cancer, urothelial carcinoma, or Hodgkin's lymphoma.

19. The use of any one of claims 16-18, wherein the synthetic oncolytic virus or the
5 pharmaceutical composition is to be administered to the subject in a single dose.

20. The use of any one of claims 16-19, wherein the synthetic oncolytic virus or the
pharmaceutical composition is to be administered to the subject by intratumoral injection,
intramuscular injection, subcutaneous injection, or intravenous injection.

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