

CLAIMS

We claim:

1. Use of a composition comprising a dendritic cell-targeting lentiviral vector particle wherein the particle comprises a lentiviral vector genome comprising a polynucleotide sequence encoding IL-12, in the manufacture of a medicament for the treatment of cancer, wherein the composition is to be administered intratumorally.
2. The use according to claim 1 wherein the IL-12 is a single chain IL-12 (scIL-12).
3. The use according to claim 2 wherein the scIL-12 comprises p35-L-p40.
4. The use according to claim 2 wherein the scIL-12 comprises p40-L-p35.
5. The use according to claim 1 wherein the lentiviral vector particle comprises a modified alphavirus E2 glycoprotein which selectively binds to dendritic cells expressing DC-SIGN.
6. The use according to claim 1 wherein the lentiviral vector particle comprises an envelope comprising a Sindbis virus E2 glycoprotein of SEQ ID NO: 1 in which 160X is absent or is an amino acid other than glutamic acid, or a variant of SEQ ID NO: 1 thereof having at least 80% identity to SEQ ID NO: 1 and in which 160X is absent or is an amino acid other than glutamic acid, capable of infecting dendritic cells; wherein E2 is not part of a fusion protein with Sindbis virus E3.
7. The use according to claim 1 wherein an adjuvant is to be administered intratumorally in combination with the lentiviral vector particle.
8. The use according to claim 7 wherein the adjuvant is an aqueous or oil in water emulsion formulation of glucopyranosyl lipid A (GLA).

9. The use according to claim 1 wherein the composition comprising the lentiviral vector particle further comprises an aqueous formulation of glucopyranosyl lipid A (GLA).
10. The use according to claim 1 wherein the lentiviral vector particle is to be administered in a single dose.
11. The use according to claim 1 wherein the lentiviral vector particle produces a level of IL-12 between 0.1 µg and 1 µg/1E10 vector genomes produced during the first 48 hours as measured in an in vitro transduction assay.
12. The use according to claim 1 wherein a regulatory T cell depletion agent is to be administered in combination with the lentiviral vector particle.
13. The use according to claim 12 wherein the regulatory T cell depletion agent is to be administered systemically, and the regulatory T cell depletion agent is cyclophosphamide or an anti-CD25 antibody.
14. The use according to claim 13 wherein the cyclophosphamide or anti-CD25 antibody is to be administered systemically prior to the composition comprising the lentiviral vector, which is to be injected intratumorally.
15. The use according to claim 1 wherein a second lentiviral vector particle encoding a tumor antigen is to be administered in combination with the lentiviral vector particle.
16. Use of: (a) a first composition comprising a dendritic cell-targeting lentiviral vector particle comprising a lentiviral vector genome comprising a sequence encoding IL-12; and (b) a second composition comprising a second lentiviral vector particle encoding a tumor antigen; in the manufacture of a medicament for treating cancer in a subject, wherein the first composition is

to be administered intratumorally and the second composition is to be administered by a different route.

17. The use of claim 16 wherein the second composition is to be administered intradermally, subcutaneously or intramuscularly.

18. The use of claim 16 wherein the first composition and the second composition are to be administered concurrently.

19. The use of claim 16 wherein the first composition and the second composition are to be administered sequentially.

20. A lentiviral vector particle comprising:

- a. an envelope comprising a Sindbis virus E2 glycoprotein of SEQ ID NO: 1 in which 160X is absent or is an amino acid other than glutamic acid, or a variant of SEQ ID NO: 1 thereof having at least 80% identity to SEQ ID NO: 1 and in which 160X is absent or is an amino acid other than glutamic acid, capable of infecting dendritic cells; wherein E2 is not part of a fusion protein with Sindbis virus E3; and
- b. a lentiviral vector genome comprising a polynucleotide sequence encoding IL-12.

21. The lentiviral vector particle of claim 20 wherein the IL-12 is a single chain IL-12 (scIL-12).

22. The lentiviral vector particle of claim 21 wherein the scIL-12 comprises p35-L-p40.

23. The lentiviral vector particle of claim 21 wherein the scIL-12 comprises p40-L-p35.

24. The lentiviral vector particle of claim 20 wherein the lentiviral vector genome further comprises a sequence encoding an antigen.

25. The lentiviral vector particle of claim 24 wherein the antigen is a tumor associated antigen, a viral antigen, a bacterial antigen or a fungal antigen.

26. The lentiviral vector particle of claim 25 wherein the tumor associated antigen is selected from the group consisting of prostatic acid phosphatase, prostate specific antigen, NKX3.1, prostate specific membrane antigen, PRAME; BAGE; RAGE, NY-ESO-1, SAGE, HAGE, GAGE, Plu-1, HASH -1, HasH-2, Cripto, Criptin, MART-1/Melan-A, gp100, gp75, mda-7, tyrosinase, tyrosinase-related protein, p53, Ras, c-Myc, A-Raf, B-Raf, and C-Raf, MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A6, MAGE-A10, MAGE-A12, MART-1, BAGE, DAM-6, -10, GAGE-1, GAGE -2, GAGE -8, GAGE-3, GAGE -4, GAGE -5, GAGE -6, GAGE -7B, NA88-A, MART-1, MC1R, Gp100, PSM, TRP-1, TRP-2, ART-4, CAMEL, CEA, Cyp-B, hTERT, hTRT, iCE, MUC1, MUC2, PRAME, P15, RU1, RU2, SART-1, SART-3, Wilms' tumor antigen (WT1), AFP, β -catenin/m, Caspase-8/m, CEA, CDK-4/m, ELF2M, GnT-V, G250, HSP70-2M, HST-2, KIAA0205, MUM-1, MUM-2, MUM-3, Myosin/m, SART-2, TRP-2/INT2, 707-AP, Annexin II, CDC27/m, TPI/mbcr-abl, BCR-ABL, interferon regulatory factor 4 (IRF4), ETV6/AML, LDLR/FUT, Pml/RAR, Tumor-associated calcium signal transducer 1 (TACSTD1) TACSTD2, Epidermal Growth Factor receptor (EGFR and EGFRvIII), platelet derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), integrin-linked kinase (ILK), STAT3, STAT5, STAT6, HIF-1, HIF-2, Nuclear Factor-Kappa B (NF- κ B), Notch1-4, c-Met, mammalian targets of rapamycin (mTOR), WNT, PMSA, PR-3, MDM2, Mesothelin, renal cell carcinoma – 5T4, SM22-alpha, carbonic anhydrases I (CAI) and IX (CAIX) (also known as G250), STEAD, TEL/AML1, GD2, proteinase3, hTERT, sarcoma translocation breakpoints, EphA2, ML-IAP, EpCAM, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, ALK, androgen receptor, cyclin B1, polysialic acid, MYCN, RhoC, GD3, fucosyl GM1, mesothelium, PSCA, sLe, PLAC1, GM3, BORIS, Tn, GLobH, NY-BR-1, RGs5, SART3, STn, PAX5, OY-TES1, sperm protein 17, LCK, HMWMAA, AKAP-4, SSX2, XAGE 1, B7H3, legumain, TIE2, Page4, MAD-CT-1, FAP, MAD-CT-2, and fos related antigen 1.

27. Use of a composition comprising the lentiviral vector particle of claim 20 in the manufacture of a medicament for treating cancer in a subject.

28. The use of claim 27 wherein a composition comprising a second lentiviral vector encoding a tumor antigen is to be administered in combination with the lentiviral vector particle of claim 20.
29. The use of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are to be administered concurrently.
30. The use of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are to be administered sequentially at different times.
31. The use of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are to be administered by different routes.
32. The use of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are to be administered at different sites.
33. The use of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are to be administered at different sites, by the same route.
34. The use of claim 27 wherein the lentiviral vector particle is to be administered intratumorally.
35. The use of claim 28 wherein the lentiviral vector particle of claim 20 is to be administered intratumorally and the second lentiviral vector is to be administered concurrently at a different site and by a different route.
36. Use of a composition comprising the lentiviral vector particle of claim 24 in the manufacture of a medicament for treating cancer in a subject.

37. The use of claim 27 wherein a TLR4 agonist is to be administered intratumorally in combination with the lentiviral vector particle of claim 20.
38. The use of claim 37 wherein the TLR4 agonist is an aqueous or oil in water emulsion formulation of glucopyranosyl lipid A (GLA).
39. The use of claim 34 wherein the composition comprising the lentiviral vector particle further comprises an aqueous formulation of glucopyranosyl lipid A (GLA).
40. The use of claim 34 wherein the lentiviral vector particle is to be administered in a single dose.
41. The use of claim 34 wherein the lentiviral vector particle produces a low-level of IL-12, and wherein the low-level of IL-12 is between 0.1 μg and 1 $\mu\text{g}/1\text{E}10$ vector genomes produced during the first 48 hours as measured in an in vitro transduction assay.
42. The use of claim 36 wherein the lentiviral vector particle is to be administered intratumorally.
43. The lentiviral vector particle according to any one of claims 20-26 for use in a method of treatment of a human or animal subject.
44. A composition comprising the lentiviral vector particle according to claim 20 and a second lentiviral vector particle encoding a tumor antigen.
45. A therapeutic or prophylactic vaccine comprising the lentiviral vector particles of claim 24 and a pharmaceutically acceptable excipient.