

CLAIMS

We claim:

1. 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, for use in the treatment of cancer wherein the composition is administered intratumorally.
2. The composition for use according to claim 1 wherein the IL-12 is a single chain IL-12 (scIL-12).
3. The composition for use according to claim 2 wherein the scIL-12 comprises p35-L-p40.
4. The composition for use according to claim 2 wherein the scIL-12 comprises p40-L-p35.
5. The composition for 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 composition for 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 composition for use according to claim 1 wherein the treatment further comprises administering an adjuvant intratumorally.
8. The composition for use according to claim 7 wherein the adjuvant is an aqueous or oil in water emulsion formulation of glucopyranosyl lipid A (GLA).

9. The composition for use according to claim 7 wherein the composition comprising the lentiviral vector particle further comprises an aqueous formulation of glucopyranosyl lipid A (GLA).

10. The composition for use according to claim 1 wherein the lentiviral
5 vector particle is administered in a single dose.

11. The composition for use according to claim 1 wherein the lentiviral vector particle produces a level of IL-12 between about 0.1 µg and 1 µg/1E10 vector genomes produced during the first 48 hours as measured in an in vitro transduction assay.

10 12. The composition for use according to claim 1 wherein the treatment further comprises regulatory T cell depletion.

13. The composition for use according to claim 12 wherein the regulatory T cell depletion comprises systemic administration of cyclophosphamide or an anti-CD25 antibody.

15 14. The composition for use according to claim 13 wherein the systemic administration of cyclophosphamide or an anti-CD25 antibody is prior to the intratumoral injection of the composition comprising the lentiviral vector.

15. The composition for use according to claim 1 wherein the treatment further comprises administering a second lentiviral vector particle encoding a tumor
20 antigen.

16. A product comprising: (a) a first composition 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; for use in a method of treating cancer in a
25 subject wherein the first composition is administered intratumorally and the second composition is administered by a different route.

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

18. The product of claim 16 wherein the first composition and the second composition are administered concurrently.

19. The product of claim 16 wherein the first composition and the second composition are administered sequentially.

5 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;
10 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).

15 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.

20 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,

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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, hTERT, iCE, MUC1, MUC2,
 PRAME, P15, RU1, RU2, SART-1, SART-3, Wilms' tumor antigen (WT1), AFP, β -
 5 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
 10 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,
 15 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, mesothelian, PSCA, sLe, PLAC1, GM3, BORIS, Tn,
 GLoboH, 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,
 20 MAD-CT-2, and fos related antigen 1.

27. A method of treating cancer in a subject, comprising administering
 to the subject an effective amount of a composition comprising the lentiviral vector particle
 of claim 20.

28. The method of claim 27 further comprising administering to the
 25 subject an effective amount of a composition comprising a second lentiviral vector
 encoding a tumor antigen.

29. The method of claim 28 wherein the lentiviral vector particle of
 claim 20 and the second lentiviral vector are administered concurrently.

30. The method of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are administered sequentially at different times.

31. The method of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are administered by different routes.

5 32. The method of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are administered at different sites.

33. The method of claim 28 wherein the lentiviral vector particle of claim 20 and the second lentiviral vector are administered at different sites, by the same route.

10 34. The method of claim 27 wherein the lentiviral vector particle is administered intratumorally.

35. The method of claim 28 wherein the lentiviral vector particle of claim 20 is administered intratumorally and the second lentiviral vector is administered concurrently at a different site and by a different route.

15 36. A method of treating cancer in a subject, comprising administering to the subject an effective amount of a composition comprising the lentiviral vector particle of claim 24.

37. The method of claim 27 wherein the method further comprises administering intratumorally a TLR4 agonist.

20 38. The method of claim 37 wherein the TLR4 agonist is an aqueous or oil in water emulsion formulation of glucopyranosyl lipid A (GLA).

39. The method of claim 34 wherein the composition comprising the lentiviral vector particle further comprises an aqueous formulation of glucopyranosyl lipid A (GLA).

25 40. The method of claim 34 wherein the lentiviral vector particle is administered in a single dose.

41. The method of claim 34 wherein the lentiviral vector particle produces a low-level of IL-12.

42. The method of claim 41 wherein the low-level of IL-12 is between about 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.

43. The method of claim 36 wherein the lentiviral vector particle is
5 administered intratumorally.

44. 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.

45. A composition comprising the lentiviral vector particle according to claim 20 and a second lentiviral vector particle encoding a tumor antigen.

10 46. A therapeutic or prophylactic vaccine comprising the lentiviral vector particles of claim 24 and a pharmaceutically acceptable excipient.