

Claims

1. A method for reducing tumor size and/or increasing survival in a subject having a cancerous tumor, the method comprising intratumorally administering to the subject a recombinant modified Vaccinia Ankara (MVA) comprising a first nucleic acid
5 encoding a tumor-associated antigen (TAA) and a second nucleic acid encoding 4-1BBL, wherein the intratumoral administration of the recombinant MVA enhances an inflammatory response in the cancerous tumor, increases tumor reduction, and/or increases overall survival of the subject as compared to a non-intratumoral injection of a recombinant MVA virus comprising a first and second nucleic acid encoding a TAA and a 4-1BBL
10 antigen.
2. A method for reducing tumor size and/or increasing survival in a subject having a cancerous tumor, the method comprising intravenously administering to the subject a recombinant modified Vaccinia Ankara (MVA) comprising a first nucleic acid encoding a tumor-associated antigen (TAA) and a second nucleic acid encoding 4-1BBL,
15 wherein the intravenous administration of the recombinant MVA enhances Natural Killer (NK) cell response and enhances CD8 T cell responses specific to the TAA as compared to a non-intravenous injection of a recombinant MVA virus comprising a first and second nucleic acid encoding a TAA and a 4-1BBL antigen.
3. A method for reducing tumor size and/or increasing survival in a subject
20 having a cancerous tumor, the method comprising administering to the subject a recombinant modified Vaccinia Ankara (MVA) comprising a first nucleic acid encoding a tumor-associated antigen (TAA) and a second nucleic acid encoding 4-1BBL, wherein the administration of the recombinant MVA increases tumor reduction and/or increases overall survival of the subject as compared to administration of a recombinant MVA and 4-1BBL
25 antigen by themselves.
4. A method of inducing an enhanced inflammatory response in a cancerous tumor of a subject, the method comprising intratumorally administering to the subject a recombinant modified Vaccinia Ankara (MVA) comprising a first nucleic acid encoding a first heterologous tumor-associated antigen (TAA) and a second nucleic acid encoding a 4-

1BBL antigen, wherein the intratumoral administration of the recombinant MVA generates an enhanced inflammatory response in the tumor as compared to an inflammatory response generated by a non-intratumoral injection of a recombinant MVA virus comprising a first and second nucleic acid encoding a heterologous tumor-associated antigen and a 4-1BBL antigen.

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5. A method of reducing tumor size and/or increasing survival in a subject having a cancerous tumor, the method comprising administering to the subject a recombinant modified Vaccinia Ankara (MVA) comprising a first nucleic acid encoding an endogenous retroviral (ERV) protein and a second nucleic acid encoding 4-1BBL, wherein the administration of the recombinant MVA increases tumor reduction and/or increases overall survival of the subject as compared to administration of a recombinant MVA and 4-1BBL antigen by themselves.

6. A method for reducing tumor size and/or increasing survival in a subject having a cancerous tumor, the method comprising administering to the subject a recombinant modified Vaccinia Ankara (MVA) comprising a first nucleic acid encoding a tumor-associated antigen (TAA), a second nucleic acid encoding 4-1BBL, and a third nucleic acid encoding CD40L, wherein the administration of the recombinant MVA increases tumor reduction and/or increases overall survival of the subject as compared to administration of a recombinant MVA, 4-1BBL antigen, and CD40L antigen by themselves.

7. A method of inducing an enhanced inflammatory response in a cancerous tumor of a subject, the method comprising intratumorally administering to the subject a recombinant modified Vaccinia Ankara (MVA) comprising a first nucleic acid encoding a first heterologous tumor-associated antigen (TAA), a second nucleic acid encoding a 4-1BBL antigen, and a third nucleic acid encoding a CD40L antigen, wherein the intratumoral administration of the recombinant MVA generates an enhanced inflammatory response in the tumor as compared to an inflammatory response generated by a non-intratumoral injection of a recombinant MVA virus comprising a first nucleic acid

encoding a heterologous tumor-associated antigen, a second nucleic acid encoding a 4-1BBL antigen, and a third nucleic acid encoding a CD40L antigen.

8. A recombinant modified Vaccinia virus Ankara (MVA) comprising:

- (a) a first nucleic acid encoding a tumor-associated antigen (TAA);
- 5 (b) a second nucleic acid encoding a 4-1BB ligand (4-1BBL); and
- (c) at least one further nucleic acid encoding a TAA.

9. The recombinant MVA according to claim 8, further comprising:

- (d) a nucleic acid encoding a CD40 ligand (CD40L).

10. The recombinant MVA according to claim 8 or 9, comprising two, three, four, five, six, or more nucleic acids each encoding a different TAA.

11. The recombinant MVA according to any of claims 8 to 10, wherein the TAA is selected from the group consisting of an endogenous retroviral (ERV) protein, an endogenous retroviral (ERV) peptide, carcinoembryonic antigen (CEA), mucin 1 cell surface associated (MUC-1), prostatic acid phosphatase (PAP), prostate specific antigen (PSA), human epidermal growth factor receptor 2 (HER-2), survivin, tyrosine related protein 1 (TRP1), tyrosine related protein 2 (TRP2), Brachyury, p15, AH1A5, folate receptor alpha (FOLR1), preferentially expressed antigen of melanoma (PRAME), and MEL; and combinations thereof.

12. The recombinant MVA according to claim 11, wherein the ERV protein is from the human endogenous retroviral K (HERV-K) family, preferably is selected from a HERV-K envelope (HERV-K-env) protein and a HERV-K gag protein.

13. The recombinant MVA according to claim 12, wherein the ERV peptide is from the human endogenous retroviral K (HERV-K) family, preferably is selected from a pseudogene of a HERV-K envelope protein (HERV-K-env/MEL).

25 14. A recombinant modified Vaccinia virus Ankara (MVA) comprising:

- (i) a nucleic acid encoding HERV-K-env/MEL;
- (ii) a nucleic acid encoding HERV-K gag;

- (iii) a nucleic acid encoding FOLR1 and PRAME, preferably expressed as a fusion protein; and
 - (iv) a nucleic acid encoding 4-1BBL.
15. The recombinant MVA according to claim 14 further comprising:
- 5 (v) a nucleic acid encoding CD40L.
16. The recombinant MVA according to any of claims 8 to 15, wherein the recombinant MVA is derived from MVA-BN.
17. A pharmaceutical preparation or composition comprising a recombinant MVA according to any of claims 8 to 16.
- 10 18. The pharmaceutical preparation or composition according to claim 17 which is adapted to intratumoral and/or intravenous administration, preferably intratumoral administration.
19. A recombinant MVA according to any of claims 8 to 16 for use as a medicament or a vaccine.
- 15 20. A recombinant MVA according to any of claims 8 to 16 for use in the treatment of cancer, preferably melanoma, breast cancer, colon cancer, or ovarian cancer.
21. A recombinant MVA according to any of claims 8 to 16 for use in enhancing an inflammatory response in a cancerous tumor, reducing the size of a cancerous tumor, retarding or arresting the growth of a cancerous tumor and/or increasing the overall
- 20 survival of a subject, preferably a human.
22. The recombinant MVA for use according to any of claims 19 to 21, wherein the recombinant MVA is administered intratumorally and/or intravenously, preferably intratumorally.
23. The recombinant MVA for use according to any of claims 19 to 22, wherein
- 25 the recombinant MVA is used in combination with a TAA specific antibody.

24. The recombinant MVA for use according to any of claims 19 to 22, wherein the recombinant MVA is used in combination with either an immune checkpoint molecule antagonist or agonist.

25. The method according to any of claims 1 to 7, wherein the recombinant
5 MVA is according to any of claims 8 to 16.