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 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 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, 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 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 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.

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.~~

1~~8~~. A recombinant modified Vaccinia virus Ankara (MVA) comprising:

(a) a first nucleic acid encoding an endogenous retroviral (ERV) protein ~~a tumor-associated antigen (TAA)~~;

(b) a second nucleic acid encoding a 4-1BB ligand (4-1BBL); and

(c) at least one further nucleic acid encoding a TAA.

2~~9~~. The recombinant MVA according to claim 1~~8~~, further comprising:

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

3~~10~~. The recombinant MVA according to claim 1~~8 or 9~~, comprising two, three, four, five, six, or more nucleic acids each encoding a different TAA.

4~~11~~. The recombinant MVA according to any of claims 1 to 3~~8 to 10~~, wherein the TAA is selected from the group consisting of ~~an~~ another 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 1 (TRP2), Brachyury, p15, AH1A5, folate receptor alpha (FOLR1), preferentially expressed antigen of melanoma (PRAME), and MEL; and combinations thereof.

5~~12~~. The recombinant MVA according to claim 4~~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.

6~~13~~. The recombinant MVA according to claim 5~~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).

7~~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.

8~~15~~. The recombinant MVA according to claim 7~~14~~ further comprising:

(v) a nucleic acid encoding CD40L.

9~~16~~. The recombinant MVA according to any of claims 1 to 3, 7, or 8~~ to 15~~, wherein the recombinant MVA is derived from MVA-BN.

10~~17~~. A pharmaceutical preparation or composition comprising a recombinant MVA according to ~~any of claims 8 to 16~~claim 9.

11~~18~~. The pharmaceutical preparation or composition according to claim 10~~17~~ which is adapted to intratumoral and/or intravenous administration, preferably intratumoral administration.

12~~19~~. A recombinant MVA according to any of claims 1 to 3, 7 or 8~~ to 16~~ for use as a medicament or a vaccine for use in the treatment of cancer.

13~~20~~. A recombinant MVA according to any of claims 1 to 3, 7 or 8 ~~to 16~~ for use in the treatment of cancer, preferably melanoma, breast cancer, colon cancer, or ovarian cancer.

14~~21~~. A recombinant MVA according to any of claims 1 to 3, 7 or 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 survival of a subject, preferably a human.

15~~22~~. The recombinant MVA for use according to ~~any of claims 19 to 21~~claim 12, wherein the recombinant MVA is administered intratumorally and/or intravenously, preferably intratumorally.

16~~23~~. The recombinant MVA for use according to ~~any of claims 19 to 22~~claim 12, wherein the recombinant MVA is used in combination with a TAA specific antibody.

17~~24~~. The recombinant MVA for use according to ~~any of claims 19 to 22~~claim 12, 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 MVA is according to any of claims 8 to 16.~~