

What is claimed is:

1. A composition comprising a recombinant modified vaccinia Ankara (MVA) virus selected from the group consisting of (i) MVA harboring a human Fms-like tyrosine kinase 3 ligand (hFlt3L) (MVA-hFlt3L); and (ii) MVA Δ E3L harboring hFlt3L (MVA Δ E3L-hFlt3L) in an amount effective, upon delivery to tumor cells of a subject afflicted with a malignant solid tumor, to treat the tumor.
2. The composition of claim 1 wherein the treatment of the tumor is manifest by one or more of the following: induction, in the subject, of an immune response against the tumor or enhancement or promotion in the subject of an ongoing immune response against the tumor, reduction of the size of the tumor, eradication of the tumor, inhibition of growth of the tumor, inhibition of metastasis of the tumor, and reduction or eradication of metastatic tumor.
3. The composition of claim 1 wherein the induction, enhancement or promotion of the immune response comprises one or more of the following:
 - proliferation and activation of CD8⁺ cytotoxic T cells;
 - proliferation and activation of CD4⁺ effector T cells; ;
 - increase of the ratio of CD8⁺/Treg and of Tconv/Treg;
 - recruitment of CD45⁺ cells and CD8⁺ T cells in the injected and distant tumors;
 - reduction of tumor-associated macrophages (TAM) in the injected and distant tumors;
 - influx of Ly6C^{hi}CD11b⁺ inflammatory monocytes and Ly6C^{hi}CD11b⁻ myeloid cells into the injected and distant tumors; activation and mobilization of cross-presenting CD103⁺ dendritic cells in the injected and distant tumors via the production of type IFN and proinflammatory cytokines; and
 - generation of anti-tumor CD8⁺ T cells and cross-protection against heterologous tumor(s)
4. The composition of claim 1 wherein the recombinant MVA is not harboring nucleic acid encoding or expressing a tumor antigen.
5. The composition of claim 1 or 2 further comprising one or more pharmaceutically acceptable excipients.
6. The composition of claim 3 wherein the one or more excipients is selected from the group consisting of solvents, dispersion media, coatings, antibacterial and

antifungal agents, isotonic agents, absorption delaying agents and combinations of two or more of the foregoing.

7. The composition of claim 1-4 wherein the recombinant MVA comprises MVA Δ E3L-hFlt3L.
- 5 8. The composition of any one of claims 1-4 and 7 the composition further comprising a second amount of a replication competent recombinant attenuated vaccinia virus with deletion of thymidine kinase encoding and expressing human Flt3L, wherein the second amount contributes to augmenting the induced or enhanced or promoted immune response.
- 10 9. The composition of any one of claims 1-4, 7 and 8 the composition further comprising a third amount of inactivated MVA wherein the third amount contributes to augmenting the induced or enhanced or promoted immune response.
- 15 10. A method for treating a subject afflicted with a malignant solid tumor, the method comprising delivering to the cells of the tumor a recombinant MVA virus selected from the group of MVA-hFlt3L and MVA Δ E3L-hFlt3L and combinations thereof and thereby treating the tumor.
- 20 11. The method of claim 10 wherein the amount of said virus is effective to bring about one or more of the following: induce the immune system of the subject to mount an immune response against the tumor or enhance or promote an ongoing immune response by the immune system against the tumor; reduce the size of the tumor; eradicate the tumor; inhibit growth of the tumor; inhibit metastasis of the tumor; and reduce or eradicate metastatic tumor.
- 25 12. The method of claim 11 wherein the immune response against the tumor accomplishes one or more of the following:
 - proliferation and activation of CD8⁺ cytotoxic T cells;
 - proliferation and activation of CD4⁺ effector T cells; ;
 - increase of the ratio of CD8⁺/Treg and of Tconv/Treg;
 - recruitment of CD45⁺ cells and CD8⁺ T cells in the injected and distant tumors;
 - 30 reduction of tumor-associated macrophages (TAM) in the injected and distant tumors;
 - influx of Ly6C^{hi}CD11b⁺ inflammatory monocytes and Ly6C^{hi}CD11b⁻ myeloid cells into the injected and distant tumors;

- activation and mobilization of cross-presenting CD103⁺ dendritic cells in the injected and distant tumors via the production of type IFN and proinflammatory cytokines; and
generation of anti-tumor CD8⁺ T cells and cross-protection against heterologous tumor(s)
- 5
13. The method of any one of claims 10-12 wherein said MVA or MVAΔE3L is not harboring nucleic acid encoding or expressing a tumor antigen.
14. The method of claim 13 wherein the recombinant MVA is delivered by intratumoral or intravenous injection or a simultaneous or sequential combination
- 10 of intratumoral and intravenous injection.
15. The method of claim 13 wherein the tumor is melanoma or colon carcinoma.
16. The method of one or more of claims 13 wherein delivery of the recombinant MVA is continued for several weeks, months or years or indefinitely, as long as benefits persist or a maximum tolerated dose is reached.
- 15 17. The method of claim 13 wherein delivery of the recombinant MVA is by intratumoral injection.
18. The method of claim 13 wherein the subject is a human.
19. The method of one or more of claims 13-18 wherein the recombinant MVA is delivered at a dosage per administration within the range of about 10⁶ - 10¹⁰
- 20 plaque-forming units (pfu), preferably within the range of about 10⁷ to about 10⁹ plaque-forming units (pfu).
20. The method of any one of the preceding claims wherein the amount delivered is sufficient to infect all tumor cells.
21. The method of one or more of claims 13-19 wherein the delivery is repeated with a
- 25 frequency within the range from once per month to two times per week.
22. The method of claim 13-19 wherein the delivery is repeated once weekly.
23. The method of claim 13-19 wherein the melanoma is metastatic melanoma.
24. The method of any one or more of claims 13 -19 wherein the recombinant MVA is MVAΔE3L-hFlt3L.
- 30 25. A method for treating a solid malignant tumor in a subject comprising delivering to a tumor of the subject an amount of recombinant modified vaccinia virus Ankara (MVA) selected from the group consisting of MVA-hFlt3L, MVAΔE3L-hFlt3L or a combination of both, effective to bring about at least one of the following immunologic effects: proliferation and activation of CD8⁺ cytotoxic T cells;

- proliferation and activation of CD8⁺ cytotoxic T cells;
 proliferation and activation of CD4⁺ effector T cells; ;
 increase of the ratio of CD8⁺/Treg and of Tconv/Treg;
 recruitment of CD45⁺ cells and CD8⁺ T cells in the injected and distant
 5 tumors;
 reduction of tumor-associated macrophages (TAM) in the injected and distant
 tumors;
 influx of Ly6C^{hi}CD11b⁺ inflammatory monocytes and Ly6C^{hi}CD11b⁻ myeloid
 cells into the injected and distant tumors;
 10 activation and mobilization of cross-presenting CD103⁺ dendritic cells in the
 injected and distant tumors via the production of type IFN and
 proinflammatory cytokines; and
 generation of anti-tumor CD8⁺ T cells and cross-protection against
 heterologous tumor(s)
- 15 26. A method for treating a solid malignant tumor in a subject comprising delivering to
 tumor cells of the subject MVA-hFlt3L or MVAΔE3L-hFlt3L or a combination
 thereof in an amount effective to induce the immune system of the subject to mount
 an immune response against the tumor or to enhance or promote an ongoing
 immune response of said subject against the tumor, so as to accomplish one or
 20 more of the following: reduce the size of the tumor, eradicate the tumor, inhibit
 growth of the tumor, inhibit metastatic growth of the tumor, induce apoptosis of
 tumor cells or prolong survival of the subject.
- 25 27. A method for treating a malignant tumor in a subject, the method comprising
 delivering to tumor cells of the subject a virus selected from the group consisting of
 MVA-hFlt3L , MVAΔE3L-hFlt3L and a combination thereof in an amount
 effective to induce the immune system of the subject to mount an immune response
 against the tumor or to enhance or promote an ongoing immune response of said
 subject against the tumor and conjointly administering to the subject a second
 amount of an immune checkpoint blocking agent or an immune checkpoint agonist
 30 effective to block immune suppressive mechanisms within the tumor.
28. The method of claim 27 wherein the administration of the checkpoint inhibitor or
 checkpoint agonist is by parenteral route.
29. The method of claim 27 wherein the delivery is by intratumoral injection and the
 administration is by intravenous route.

30. The method of claim 27 wherein both the delivery and the administration are by intravenous route.
31. The method of claim 27 wherein both the delivery and the administration are by intratumoral injection.
- 5 32. The method of claim 27 wherein the immune checkpoint blocking agent is selected from the group consisting of PD-1 inhibitors, PD-L1 inhibitors, CTLA4 inhibitors, inhibitory antibodies against LAG-3 (lymphocyte activation gene 3), TIM3 (T cell Immunoglobulin and Mucin-3), B7-H3, and TIGIT (T-cell immunoreceptor with Ig and ITIM domains); CD80, CD86, PDL2, B7-H4, II and DLBCL inhibitors, 10 BTLA, or any combination thereof; and the immune checkpoint agonist is selected from the group consisting of anti-ICOS antibody anti-OX40 antibody agonist antibody against 4-1BB (CD 137) and against GITR.
33. The method of claim 27 wherein the tumor is primary or metastatic melanoma or primary or metastatic colon carcinoma.
- 15 34. The method of claim 27 wherein the virus is delivered and the immune checkpoint blocking agent is administered each according to its own administration schedule of spaced apart intervals.
35. The method of claim 27 wherein a first dose of the virus is delivered first and after a lapse of time a first dose of the immune checkpoint blocking agent is 20 administered.
36. The method of claim 27 wherein the delivery and administration occur in parallel during the same overall period of time.
37. The method of claim 27 wherein one or both of the virus and the immune checkpoint blocking agent are respectively delivered and administered during a 25 period of time of several weeks, months or years, or indefinitely as long as benefits persist and a maximum tolerated dose is not reached.
38. The method of claim 27 wherein the virus and the immune checkpoint blocking agent are administered simultaneously. The method of claim 61 wherein the virus and the immune checkpoint blocking agent are administered in the same 30 composition.
39. The method of claim 27 wherein the recombinant MVA and the immune checkpoint blocking agent are delivered intratumorally.
40. The method of claim 27 wherein the recombinant MVA and the immune checkpoint blocking agent are administered sequentially.

41. The method of claim 13 or 25 further comprising administering to the subject a replication competent recombinant attenuated vaccinia virus with deletion of thymidine kinase encoding and expressing human Flt3L, or inactivated MVA, or both, respectively in a second and third amount, said second amount or third amount or both contributing to augmenting the induced or enhanced or promoted immune response.
42. A kit comprising:
- 1) A first component comprising a composition according to any one of claims 1-7;
 - 2) a second component comprising one or both of a replication competent recombinant attenuated vaccinia virus with deletion of thymidine kinase encoding and expressing GM-CSF or human Flt3L, and inactivated MVA, respectively in a second and third amount, said second amount or third amount or both second and third amount contributing to augmenting the induced or enhanced or promoted immune response in said subject.
43. A method for treating a malignant tumor in a subject, wherein the subject has been previously treated or dosed with, a virus selected from the group consisting of MVA-hFlt3L, MVAΔE3L-hFlt3L and a combination thereof in an amount effective to induce the immune system of the subject to mount an immune response against the tumor, the method comprising delivering to the subject tumor cells of the subject an amount of an immune checkpoint blocking agent effective to block immune suppressive mechanisms within the tumor elicited by tumor cells, stromal cells, or tumor infiltrating immune cells.
44. A method for treating a malignant tumor in a subject, wherein the subject has been previously treated or dosed with an amount of an immune checkpoint blocking agent effective to block immune suppressive mechanisms within the tumor elicited by tumor cells, stromal cells, or tumor infiltrating immune cells, the method comprising delivering to tumor cells of the subject in an amount effective to induce the immune system of the subject to mount an immune response against the tumor.
45. The method of claim 43 or 44, wherein the immune checkpoint blocking agent comprises CTLA-4, CD80, CD86, PD-1, PDL1, PDL2, LAG3, B7-H3, B7-H4, TIM3, ICOS, II DLBCL inhibitors, BTLA, or any combination thereof.
46. The method of claim 43, 44 or 45, wherein the immune checkpoint blocking agent comprises ipilimumab, nivolumab, pembrolizumab, pidilizumab, AMP-224,

MPDL3280A, BMS-936559, MEDI4736, MSB 00107180, or any combination thereof.

- 5 47. A recombinant modified vaccinia Ankara virus with deletion of vaccinia virulence factor E3 (MVA Δ E3L) modified to express human Fms-like tyrosine kinase 3 ligand (hFlt3L) isolated, suitable for use as an immunotherapeutic agent against a malignant solid tumor.