

WHAT IS CLAIMED IS:

1. An oncolytic virus comprising a nucleic acid molecule that encodes a modulator of an interferon regulatory factor (IRF).
2. The oncolytic virus of claim 1, wherein the IRF is IRF1, IRF3, IRF7, or a
5 combination thereof.
3. The oncolytic virus of claim 1 or 2, wherein the IRF is IRF1.
4. The oncolytic virus of any one of claims 1-3, wherein the modulator inhibits the activity of the IRF.
5. The oncolytic virus of any one of claims 1-4, wherein the modulator inhibits the
10 activity of IRF1.
6. The oncolytic virus of any one of claims 1-5, wherein the modulator reduces IRF-mediated gene expression.
7. The oncolytic virus of any one of claims 1-6, wherein the modulator reduces the expression of *CD274* gene.
- 15 8. The oncolytic virus of any one of claims 1-7, wherein the modulator is IRF2.
9. The oncolytic virus of claim 8, wherein the IRF2 is a human IRF2 or a mouse IRF2.
10. The oncolytic virus of any one of claims 1-9, wherein the nucleic acid molecule is an exogenous nucleic acid molecule.
- 20 11. The oncolytic virus of any one of claims 1-10, wherein the nucleic acid molecule is integrated into the genome of the oncolytic virus.
12. The oncolytic virus of any one of claims 1-11, wherein the oncolytic virus is an oncolytic vaccinia virus.
13. The oncolytic virus of any one of claim 12, wherein the oncolytic vaccinia virus
25 lacks the expression of a functional thymidine kinase (TK).
14. A method of treating a subject having cancer, comprising administering to the subject an oncolytic virus of any one of claims 1-13.
15. The method of claim 14, wherein the subject is a human subject.

16. The method of claim 14 or 15, further comprising administering an immunomodulatory agent to the subject.
17. The method of claim 16, wherein the immunomodulatory agent is selected from the group consisting of immune checkpoint inhibitors, T cells, dendritic cells, therapeutic
5 antibodies, cancer vaccines, cytokines, Bacillus Calmette-Guérin (BCG), and any combinations thereof.
18. The method of claim 17, wherein the immunomodulatory agent is an immune checkpoint inhibitor.
19. The method of claim 17 or 18, wherein the immune checkpoint inhibitor is
10 selected from the group consisting of anti-PD1 antibodies, anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-BTLA antibodies, anti-TIM3 antibodies, anti-LAG-3 antibodies, and any combinations thereof.
20. The method of any one of claims 17-19, wherein the immune checkpoint inhibitor is an anti-PD-L1 antibody or an anti-CTLA-4 antibody.
- 15 21. The method of any one of claims 14-20, wherein the cancer is a solid tumor.
22. The method of any one of claims 14-21, wherein the cancer is selected from the group consisting of adenocarcinomas, osteosarcomas, cervical carcinomas, melanomas, hepatocellular carcinomas, breast cancers, lung cancers, prostate cancers, ovarian cancers, leukemias, lymphomas, renal carcinomas, pancreatic cancers, gastric cancers,
20 colon cancers, duodenal cancers, glioblastoma multiforme, astrocytomas, sarcomas, and combinations thereof.
23. The method of any one of claims 14-22, wherein the cancer is melanoma or renal carcinoma.
24. A method for improving a subject's responsiveness to an immunomodulatory
25 agent, comprising administering to the subject an oncolytic virus of any one of claims 1-13, wherein the subject has cancer.
25. The method of claim 24, wherein the subject is a human subject.
26. The method of claim 24 or 25, wherein the subject was previously treated with the immunomodulatory agent.

27. The method of any one of claims 24-26, wherein the subject has developed a resistance to the immunomodulatory agent.
28. The method of any one of claims 24-27, further comprising administering the immunomodulatory agent to the subject.
- 5 29. The method of any one of claims 24-28, wherein the immunomodulatory agent is selected from the group consisting of immune checkpoint inhibitors, T cells, dendritic cells, therapeutic antibodies, cancer vaccines, cytokines, Bacillus Calmette-Guérin (BCG), and any combinations thereof.
- 10 30. The method of claim 29, wherein the immunomodulatory agent is an immune checkpoint inhibitor.
31. The method of claim 29 or 30, wherein the immune checkpoint inhibitor is selected from the group consisting of anti-PD1 antibodies, anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-BTLA antibodies, anti-TIM3 antibodies, anti-LAG-3 antibodies, and any combinations thereof.
- 15 32. The method of any one of claims 29-31, wherein the immune checkpoint inhibitor is an anti-PD-L1 antibody or an anti-CTLA-4 antibody.
33. The method of any one of claims 24-32, wherein the cancer is a solid tumor.
34. The method of any one of claims 24-33, wherein the cancer is selected from the group consisting of adenocarcinomas, osteosarcomas, cervical carcinomas, melanomas, 20 hepatocellular carcinomas, breast cancers, lung cancers, prostate cancers, ovarian cancers, leukemias, lymphomas, renal carcinomas, pancreatic cancers, gastric cancers, colon cancers, duodenal cancers, glioblastoma multiforme, astrocytomas, sarcomas, and combinations thereof.
35. The method of any one of claims 24-34, wherein the cancer is melanoma or renal 25 carcinoma.
36. A pharmaceutical composition comprising an oncolytic virus of any one of claims 1-13.
37. The pharmaceutical composition of claim 36, further comprising an immunomodulatory agent.

38. The pharmaceutical composition of claim 37, wherein the immunomodulatory agent is selected from the group consisting of immune checkpoint inhibitors, T cells, dendritic cells, therapeutic antibodies, cancer vaccines, cytokines, Bacillus Calmette-Guérin (BCG), and any combinations thereof.
- 5 39. The pharmaceutical composition of claim 38, wherein the immunomodulatory agent is an immune checkpoint inhibitor.
40. The pharmaceutical composition of claim 38 or 39, wherein the immune checkpoint inhibitor is selected from the group consisting of anti-PD1 antibodies, anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-BTLA antibodies, anti-TIM3 antibodies,
10 anti-LAG-3 antibodies, and any combinations thereof.
41. The pharmaceutical composition of any one of claims 38-40, wherein the immune checkpoint inhibitor is an anti-PD-L1 antibody or an anti-CTLA-4 antibody.
42. The pharmaceutical composition of any one of claims 36-41, further comprising a pharmaceutically acceptable carrier.
- 15 43. The pharmaceutical composition of any one of claims 36-42, which is for treating a subject having cancer or improving a subject's responsiveness to an immunomodulatory agent.
44. A kit comprising the oncolytic virus of any one of claims 1-13, or the pharmaceutical composition of any one of claims 36-43.
- 20 45. The kit of claim 44, further comprising an immunomodulatory agent.
46. The kit of claim 45, wherein the immunomodulatory agent is an immune checkpoint inhibitor.
47. The kit of claim 46, wherein the immune checkpoint inhibitor is selected from the group consisting of anti-PD1 antibodies, anti-PD-L1 antibodies, anti-CTLA-4 antibodies,
25 anti-BTLA antibodies, anti-TIM3 antibodies, anti-LAG-3 antibodies, and any combinations thereof.
48. The kit of claim 46 or 47, wherein the immune checkpoint inhibitor is an anti-PD-L1 antibody or an anti-CTLA-4 antibody.

49. The kit of any one of claims 44-48, wherein the kit further comprises instructions for treating a subject having cancer or improving a subject's responsiveness to an immunomodulatory agent.