CLAIMS

We claim:

1. An engineered myxoma virus (MYXV) comprising a transgene encoding one or more immunomodulatory proteins.

2. The engineered MYXV of claim 1, wherein the one or more immunomodulatory proteins is Stimulator of interferon genes (STING), interleukin-12 (IL-12), Fusion-associated small transmembrane (FAST), an immune checkpoint inhibitor, a tumor necrosis factor (TNF) protein, or a combination thereof.

3. The engineered MYXV of claim 2, wherein the IL-12 is an IL-12A.

4. The engineered MYXV of claim 2, wherein the IL-12 is an IL-12B.

5. The engineered MYXV of claim 2, wherein the immune checkpoint inhibitor is a PD-L1 binding molecule.

6. The engineered MYXV of claim 5, wherein the PD-L1 binding molecule is an anti-PD-L1 antibody or an antigen-binding fragment thereof.

7. The engineered MYXV of any one of claims 1-6, wherein the one or more immunomodulatory proteins is capable of stimulating a toll like receptor (TLR), activating Nuclear factor-κB **(**NF-κB), or activating an interferon regulatory factor (IRF).

8. The engineered MYXV of any one of claims 1-7, wherein the engineered MYXV comprises a modification at or adjacent to one or more genes selected from the group consisting of M001R, M002R, M003.1R, M003.2R, M004.1R, M004R, M005R, M006R, M007R, M008.1R, M008R, M009L, M013, M036L, M063L, M11L, M128L, M131R, M135R, M136R, M141R, M148R, M151R, M152R, M153R, M154L, M156R, M-T2, M-T4, M-T5, M-T7, and SOD.

9. The engineered MYXV of any one of claims 1-8, wherein the engineered MYXV comprises a modification at or adjacent to M011L, M063, M135R, M136R, M-T2, M-T4, M-T5, M-T7 or SOD.

10. The engineered MYXV of claim 8 or claim 9, wherein the modification comprises a deletion or an insertion.

11. The engineered MYXV of any one of claims 8-10, wherein the transgene replaces a portion of M011L, M063, M135R, M136R, M-T2, M-T4, M-T5, M-T7, or SOD.

12. The engineered MYXV of any one of claims 8-11, wherein the transgene is located between the M135R and M136R genes of the genome of the MYXV.

13. The engineered MYXV of any one of claims 8-12, wherein the transgene replaces a portion of M135R.

14. The engineered MYXV of any one of claims 8-13, wherein the engineered MYXV is an M135R knockout.

15. The engineered MYXV of any one of claims 8-11, wherein engineered MYXV is a SOD knockout.

16. The engineered MYXV of any one of claims 1-15, further comprising a reporter gene.

17. The engineered MYXV of claim 15, wherein the reporter gene encodes a fluorescent protein, a luminescent substrate or an enzyme.

18. The engineered MYXV of any one of claims 1-17, wherein the engineered MYXV increases autophagy in infected cells by at least 5% compared to a MYXV that lacks the transgene as determined by an LC3-I to LC3-II conversion assay.

19. The engineered MYXV of any one of claims 1-18, wherein the engineered MYXV increases killing of infected cancer cells by at least 5% compared to a MYXV that lacks the transgene as determined by an *in vitro* flow cytometric assay.

20. The engineered MYXV of any one of claims 1-19, wherein the engineered MYXV increases killing of uninfected cancer cells by at least 5% compared to a MYXV that lacks the transgene as determined by an *in vitro* flow cytometric assay.

~~21. A pharmaceutical composition comprising the engineered MYXV of any one of claims 1-20, and a pharmaceutically acceptable excipient.~~

~~22. The pharmaceutical composition of claim 21, wherein the pharmaceutical composition is formulated for systemic administration.~~

~~23. The pharmaceutical composition of claim 21, wherein the pharmaceutical composition is formulated for local administration.~~

~~24. The pharmaceutical composition of any one of the claims 21-23, wherein the pharmaceutical composition is formulated for parenteral administration.~~

~~25. A composition comprising a plurality of cells that is exposed ex vivo to the engineered MYXV of any one of claims 1-20, wherein the plurality of cells comprises a peripheral blood mononuclear cell (PBMC), a bone marrow (BM) cell, or a combination thereof.~~

~~26. The composition of claim 25, wherein the plurality of cells is derived from a single subject.~~

~~27. A method of inhibiting or treating a cancer in a subject in need thereof, comprising administering to the subject the engineered MYXV of any one of claims 1-20 or the pharmaceutical composition of any one of claims 21-24.~~

~~28. A method of inhibiting or treating a cancer in a subject in need thereof, comprising administering to the subject the composition of any one of claims 25-26.~~

~~29. The method of claim 28, wherein the engineered MYXV is adsorbed ex vivo onto the surface of at least a portion of the plurality of cells.~~

~~30. The method of claim 29, wherein the engineered MYXV is adsorbed by exposing the plurality of cells to the engineered MYXV under a condition that permits binding of the engineered MYXV to a surface of the plurality of cells.~~

~~31. The method of claim 28, wherein the engineered MYXV is infected to at least a portion of the plurality of cells.~~

~~32. The method of any one of the claims 28-31, wherein the cancer is a solid tumor.~~

~~33. The method of any one of the claims 28-31, wherein the cancer has metastasized to a second location in the subject.~~

~~34. The method of claim 33, wherein the second location comprises a lung, a brain, a liver and/or a lymph node of the subject.~~

~~35. The method of any one of the claims 27-34, wherein the cancer comprises osteosarcoma, triple negative breast cancer, or melanoma.~~

~~36. The method of any one of the claims 27-35, further comprising administering to the subject an additional therapeutic agent.~~

~~37. The method of claim 36, wherein the additional therapeutic agent is administered to the subject prior to administering the composition.~~

~~38. The method of claim 36 or claim 37, wherein the additional therapeutic agent is administered to the subject after administering the composition.~~

~~39. The method of any one of claims 36-38, wherein the additional therapeutic agent is co-administered to the subject with the composition.~~

~~40. The method of any one of the claims 27-39, wherein the subject is a human.~~

~~41. The method of claim 40, further comprising selecting the subject that has or is suspected of having a cancer.~~

~~42. The method of any one of the claims 27-41, wherein the engineered MYXV is capable of infecting cells that have a deficient innate anti-viral response.~~

~~43. The method of claim 42, wherein cells that have a deficient innate anti-viral response comprise cancer cells.~~

~~44. The method of any one of claims 29-43, wherein the plurality of cells is obtained or derived from the subject's tissue.~~

~~45. The method of any one of claims 29-43, wherein the plurality of cells are from a donor that is allogeneic to the subject.~~

~~46. The method of any one of claims 29-43, wherein the plurality of cells is obtained or derived from a donor's tissue that is HLA-matched, HLA-mismatched, haploidentical, or a combination thereof relative to the subject.~~

~~47. A kit comprising the engineered MYXV of any one of claims 1-20, the pharmaceutical composition of any one of claims 21-24, or the composition of any one of claims 25-46.~~