CLAIMS

1. A recombinant herpes virus genome comprising one or more polynucleotides encoding an immunomodulatory polypeptide.

~~2. The recombinant herpes virus genome of claim 1, wherein the recombinant herpes virus genome is replication competent.~~

~~3. The recombinant herpes virus genome of claim 1, wherein the recombinant herpes virus genome is replication defective.~~

~~4. The recombinant herpes virus genome of any one of claims 1-3, wherein the recombinant herpes virus genome is selected from the group consisting of a recombinant herpes simplex virus genome, a recombinant varicella zoster virus genome, a recombinant human cytomegalovirus genome, a recombinant herpesvirus 6A genome, a recombinant herpesvirus 6B genome, a recombinant herpesvirus 7 genome, a recombinant Epstein-Barr virus genome, a recombinant Kaposi's sarcoma-associated herpesvirus genome, and any derivatives thereof.~~

~~5~~2. The recombinant herpes virus genome of claim 1 ~~any one of claims 1-4~~, wherein the recombinant herpes virus genome is a recombinant herpes simplex virus genome, optionally wherein the recombinant herpes simplex virus genome is a recombinant herpes simplex virus type 1 (HSV-1) genome, a recombinant herpes simplex virus type 2 (HSV-2) genome, or any derivatives thereof.

~~6. The recombinant herpes virus genome of claim 5, wherein the recombinant herpes simplex virus genome is a recombinant herpes simplex virus type 1 (HSV-1) genome, a recombinant herpes simplex virus type 2 (HSV-2) genome, or any derivatives thereof.~~

~~7. The recombinant herpes virus genome of claim 5 or claim 6, wherein the recombinant herpes simplex virus genome is a recombinant herpes simplex virus type 1 (HSV-1) genome.~~

~~8. The recombinant herpes virus genome of any one of claims 4-7, wherein the recombinant herpes simplex virus genome has been engineered to reduce or eliminate expression of one or more toxic herpes simplex virus genes.~~

~~9. The recombinant herpes virus genome of any one of claims 4-8, wherein the recombinant herpes simplex virus genome comprises an inactivating mutation.~~

~~10. The recombinant herpes virus genome of claim 9, wherein the inactivating mutation is in a herpes simplex virus gene.~~

~~11. The recombinant herpes virus genome of claim 10, wherein the inactivating mutation is a deletion of the coding sequence of the herpes simplex virus gene.~~

~~12~~3. The recombinant herpes virus genome of ~~claim 10 or~~ claim ~~11~~2, wherein the recombinant herpes simplex virus genome comprises an inactivating mutation in ~~the~~ a herpes simplex virus gene ~~is~~ selected from the group consisting of Infected Cell Protein (ICP) 0, ICP4, ICP22, ICP27, ICP47, thymidine kinase (tk), Long Unique Region (UL) 41, and UL55.

~~13~~4. The recombinant herpes virus genome of claim ~~12~~3, wherein the recombinant herpes simplex virus genome comprises an inactivating mutation in one or both copies of the ICP4 gene.

~~14~~5. The recombinant herpes virus genome of claim ~~12~~ 3 or claim ~~13~~4, wherein the recombinant herpes simplex virus genome comprises an inactivating mutation in the ICP22 gene.

~~15. The recombinant herpes virus genome of any one of claims 12-14, wherein the recombinant herpes simplex virus genome comprises an inactivating mutation in the UL41 gene.~~

~~16. The recombinant herpes virus genome of any one of claims 12-15, wherein the recombinant herpes simplex virus genome comprises an inactivating mutation in one or both copies of the ICP0 gene.~~

~~17. The recombinant herpes virus genome of any one of claims 12-16, wherein the recombinant herpes simplex virus genome comprises an inactivating mutation in the ICP27 gene.~~

~~18. The recombinant herpes virus genome of any one of claims 12-17, wherein the recombinant herpes simplex virus genome comprises an inactivating mutation in the UL55 gene.~~

~~19. The recombinant herpes virus genome of any one of claims 12-18, wherein the recombinant herpes simplex virus genome does not comprise an inactivating mutation in the ICP47 gene.~~

~~20~~6. The recombinant herpes virus genome of any one of claims 3-5~~-12-19~~, wherein the recombinant herpes simplex virus does not comprise an inactivating mutation in one or both copies of the ICP34.5 gene.

~~21~~7. The recombinant herpes virus genome of any one of claims 2-6~~-4-20~~, wherein the recombinant herpes simplex virus genome comprises the one or more polynucleotides encoding the immunomodulatory polypeptide within one or both of the ICP4 viral gene loci.

~~22~~8. The recombinant herpes virus genome of any one of claims 2-7~~-4-21~~, wherein the recombinant herpes simplex virus genome comprises the one or more polynucleotides encoding the immunomodulatory polypeptide within the ICP22 viral gene locus.

~~23. The recombinant herpes virus genome of any one of claims 4-22, wherein the recombinant herpes simplex virus genome comprises the one or more polynucleotides encoding the immunomodulatory polypeptide within the UL41 viral gene locus.~~

~~24. The recombinant herpes virus genome of any one of claims 4-23, wherein the recombinant herpes simplex virus genome comprises the one or more polynucleotides encoding the immunomodulatory polypeptide within one or both of the ICP0 viral gene loci.~~

~~25. The recombinant herpes virus genome of any one of claims 4-24, wherein the recombinant herpes simplex virus genome comprises the one or more polynucleotides encoding the immunomodulatory polypeptide within the ICP27 viral gene locus.~~

~~26. The recombinant herpes virus genome of any one of claims 4-25, wherein the recombinant herpes simplex virus genome comprises the one or more polynucleotides encoding the immunomodulatory polypeptide within the UL55 viral gene locus.~~

~~27~~9. The recombinant herpes virus genome of any one of claims 1-~~26~~8, wherein the immunomodulatory polypeptide is a human immunomodulatory polypeptide.

~~28~~10. The recombinant herpes virus genome of any one of claims 1-~~27~~9, wherein the immunomodulatory polypeptide is a cytokine or chemokine, optionally wherein the cytokine is a pro-inflammatory cytokine, optionally wherein the chemokine is a pro-inflammatory chemokine.

~~29. The recombinant herpes virus genome of claim 28, wherein the cytokine is a pro-inflammatory cytokine.~~

~~30~~11. The recombinant herpes virus genome of claim 10 ~~28 or claim 29~~, wherein the cytokine is selected from the group consisting of Interleukin (IL)-1, IL-2, IL-7, IL-12, IL-13, IL-15, IL-17, IL-18, IL-28, IL-32, IL-33, IL-34, Tumor Necrosis Factor alpha (TNFα), Interferon gamma (IFNγ), Granulocyte Colony-Stimulating Factor (G-CSF), and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF).

~~31. The recombinant herpes virus genome of claim 28 or claim 29, wherein the cytokine is IL-2.~~

~~32~~12. The recombinant herpes virus genome of claim ~~31~~11, wherein the IL-2 comprises a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 3.

~~33. The recombinant herpes virus genome of claim 28 or claim 29, wherein the cytokine is IL-12.~~

~~34~~13. The recombinant herpes virus genome of claim ~~33~~11, wherein the IL-12 comprises a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least

93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 6, and 85.

~~35~~14. The recombinant herpes virus genome of claim 10 ~~28 or claim 29~~, wherein the cytokine is not Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF).

~~36. The recombinant herpes virus genome of claim 28, wherein the chemokine is a pro-inflammatory chemokine.~~

~~37~~15. The recombinant herpes virus genome of claim 10 ~~28 or claim 34~~, wherein the chemokine is selected from the group consisting of Chemokine (C-X-C motif) Ligand 1 (CXCL1), CXCL2, CXCL8, CXCL9, CXCL11, CXCL16, C-C Motif Chemokine Ligand 2 (CCL2), CCL3, CCL4, CCL5, and CCL11.

~~38~~16. The recombinant herpes virus genome of any one of claims 1-~~37~~15, wherein the immunomodulatory polypeptide comprises a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-30.

~~39. The recombinant herpes virus genome of any one of claims 1-37, wherein the immunomodulatory polypeptide comprises a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-19.~~

~~40. The recombinant herpes virus genome of any one of claims 1-37, wherein the immunomodulatory polypeptide comprises a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 20-30.~~

~~41. The recombinant herpes virus genome of any one of claims 1-40, wherein the recombinant herpes virus genome has reduced cytotoxicity when introduced into a target cell as compared to a corresponding wild-type herpes virus genome.~~

~~42. The recombinant herpes virus genome of claim 41, wherein the target cell is a human cell.~~

~~43. The recombinant herpes virus genome of claim 41 or claim 42, wherein the target cell is a cell of the respiratory tract.~~

~~44. The recombinant herpes virus genome of any one of claims 41-43, wherein the target cell is an airway epithelial cell.~~

~~45~~17. A herpes virus comprising the recombinant herpes virus genome of any one of claims 1-~~44~~16.

~~46~~18. The herpes virus of claim ~~45~~17, wherein the herpes virus is replication competent.

~~47~~19. The herpes virus of claim ~~45~~17, wherein the herpes virus is replication defective.

~~48~~20. The herpes virus of any one of claims 17-19 ~~45-47~~, wherein the herpes virus is not oncolytic.

~~49. The herpes virus of any one of claims 45-48, wherein the herpes virus has reduced cytotoxicity as compared to a corresponding wild-type herpes virus.~~

~~50. The herpes virus of any one of claims 45-49, wherein the herpes virus is selected from the group consisting of a herpes simplex virus, a varicella zoster virus, a human cytomegalovirus, a herpesvirus 6A, a herpesvirus 6B, a herpesvirus 7, an Epstein-Barr virus, and a Kaposi's sarcoma-associated herpesvirus.~~

~~51~~21. The herpes virus of any one of claims 17-20 ~~45-50~~, wherein the herpes virus is a herpes simplex virus, optionally wherein the herpes simplex virus is a herpes simplex virus type 1 (HSV-1), a herpes simplex virus type 2 (HSV-2), or any derivatives thereof.

~~52. The herpes virus of claim 50 or claim 51, wherein the herpes simplex virus is a herpes simplex virus type 1 (HSV-1), a herpes simplex virus type 2 (HSV-2), or any derivatives thereof.~~

~~53. The herpes virus of any one of claims 50-52, wherein the herpes simplex virus is a herpes simplex virus type 1 (HSV-1).~~

~~54. The herpes virus of any one of claims 50-53, wherein the herpes simplex virus is not oncolytic.~~

~~55~~22. A pharmaceutical composition comprising the recombinant herpes virus genome of any one of claims 1-~~44~~16 or the herpes virus of any one of claims 17-21~~-45-54~~ and a pharmaceutically acceptable excipient.

~~56~~23. The pharmaceutical composition of claim ~~55~~22, wherein the pharmaceutical composition is suitable for topical, transdermal, subcutaneous, intradermal, oral, intranasal, intratracheal, sublingual, buccal, rectal, vaginal, inhaled, intravenous, intraarterial, intramuscular, intracardiac, intraosseous, intraperitoneal, transmucosal, intravitreal, subretinal, intraarticular, peri-articular, intratumoral, intrathecal, intraventricular, local, or epicutaneous administration.

~~57. The pharmaceutical composition of claim 55 or claim 56, wherein the pharmaceutical composition is suitable for oral, intranasal, intratracheal, or inhaled administration.~~

~~58. The pharmaceutical composition of any one of claims 55-57, wherein the pharmaceutical composition is suitable for intranasal or inhaled administration.~~

~~59. The pharmaceutical composition of any one of claims 55-58, wherein the pharmaceutical composition is suitable for inhaled administration.~~

~~60~~24. The pharmaceutical composition of claim 22 or claim 23~~ any one of claims 55-59~~, wherein the pharmaceutical composition is suitable for use in a dry powder inhaler, a pressurized metered dose inhaler, a soft mist inhaler, a nebulizer, an electrohydrodynamic

aerosol device, or any combinations thereof, optionally wherein the nebulizer is a vibrating mesh nebulizer.

~~61. The pharmaceutical composition of any one of claims 55-60, wherein the pharmaceutical composition is suitable for use in a nebulizer.~~

~~62. The pharmaceutical composition of claim 61, wherein the nebulizer is a vibrating mesh nebulizer.~~

~~63. The herpes virus of any one of claims 45-54 or the pharmaceutical composition of any one of claims 55-62 for use as a medicament.~~

~~64. The herpes virus of any one of claims 45-54 or the pharmaceutical composition of any one of claims 55-62 for use in a therapy.~~

~~65~~25. Use of the herpes virus of any one of claims ~~45-54~~17-21 or the pharmaceutical composition of any one of claims 22-24~~ 55-62~~ in the manufacture of a medicament for treating cancer in a subject in need thereof.

~~66~~26. The use of claim ~~65~~25, wherein the cancer is selected from the group consisting of acute myeloid leukemia, acute lymphoblastic leukemia, adrenocortical carcinoma, bladder urothelial cancer, brain stem glioma, brain lower grade glioma, brain tumor, breast cancer, bronchial tumors, Burkitt lymphoma, cancer of unknown primary site, carcinoid tumor, carcinoma of unknown primary site, central nervous system atypical teratoid/rhabdoid tumor, central nervous system embryonal tumors, cervical squamous cell carcinoma, endocervical adenocarcinoma cancer, childhood cancers, cholangiocarcinoma, chordoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, endocrine pancreas islet cell tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal cell tumor, gastrointestinal stromal tumor, gestational trophoblastic tumor, glioblastoma multiforme glioma, hairy cell leukemia, head and neck cancer, heart cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular

melanoma, islet cell tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, lip cancer, liver cancer, Lymphoid Neoplasm Diffuse Large B-cell Lymphoma, malignant fibrous histiocytoma bone cancer, medulloblastoma, medulloepithelioma, melanoma, Merkel cell carcinoma, Merkel cell skin carcinoma, mesothelioma, metastatic squamous neck cancer with occult primary, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myeloproliferative neoplasms, nasal cavity cancer, nasopharyngeal cancer, neuroblastoma, Non-Hodgkin lymphoma, nonmelanoma skin cancer, non-small cell lung cancer, oral cancer, oral cavity cancer, oropharyngeal cancer, osteosarcoma, other brain and spinal cord tumors, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, pharyngeal cancer, pheochromocytoma and paraganglioma, pineal parenchymal tumors of intermediate differentiation, pineoblastoma, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, primary hepatocellular liver cancer, prostate cancer such as prostate adenocarcinoma, rectal cancer, renal cancer, renal cell cancer, renal cell cancer, respiratory tract cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Sezary syndrome, skin cutaneous melanoma, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer testicular germ cell tumors, throat cancer, thymic carcinoma, thymoma, thyroid cancer, transitional cell cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, ureter cancer, urethral cancer, uterine cancer, uterine cancer, uveal melanoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms' tumor.

~~67. A method of expressing, enhancing, increasing, augmenting, and/or supplementing the levels of an immunomodulatory polypeptide in one or more cells of a subject, the method comprising administering to the subject an effective amount of the herpes virus of any one of claims 45-54 or the pharmaceutical composition of any one of claims 55-62.~~

~~68. The method of claim 67, wherein the one or more cells are one or more cells of the respiratory tract, airway epithelial, and/or lung.~~

~~69~~27. ~~A method of~~Use of the herpes virus of any once of claims 17-21 or the pharmaceutical composition of any one of claims 22-24 in the manufacture of a medicament for providing prophylactic, palliative, or therapeutic relief of one or more signs or symptoms of cancer in a subject in need thereof~~, the method comprising administering to the subject an effective amount of the herpes virus of any one of claims 45-54 or the pharmaceutical composition of any one of claims 55-62~~.

~~70. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of the herpes virus of any one of claims 45-54 or the pharmaceutical composition of any one of claims 55-62.~~

~~71~~28. The ~~method~~ use of claim 27~~ 69 or claim 70~~, wherein the cancer is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, a neuroendocrine tumor, mesothelioma, schwannoma, meningioma, adenocarcinoma, melanoma, leukemia, and lymphoid malignancy, optionally wherein the cancer is selected from the group consisting of a solid tumor, a hematologic cancer, bladder cancer, brain cancer, breast cancer, colon cancer, gastric cancer, glioma, head cancer, leukemia, liver cancer, lung cancer, lymphoma, myeloma, neck cancer, ovarian cancer, melanoma, pancreatic cancer, renal cancer, salivary cancer, stomach cancer, thymic epithelial cancer, and thyroid cancer, optionally wherein the cancer is small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, or squamous carcinoma of the lung, optionally wherein the cancer is non-small cell lung cancer, optionally wherein the cancer is osteosarcoma.

~~72. The method of any one of claims 69-71, wherein the cancer is selected from the group consisting of a solid tumor, a hematologic cancer, bladder cancer, brain cancer, breast cancer, colon cancer, gastric cancer, glioma, head cancer, leukemia, liver cancer, lung cancer, lymphoma, myeloma, neck cancer, ovarian cancer, melanoma, pancreatic cancer, renal cancer, salivary cancer, stomach cancer, thymic epithelial cancer, and thyroid cancer.~~

~~73. The method of any one of claims 69-72, wherein the cancer is small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, or squamous carcinoma of the lung.~~

~~74. The method of any one of claims 69-73, wherein the cancer is non-small cell lung cancer.~~

~~75. The method of any one of claims 69-72, wherein the cancer is osteosarcoma.~~

~~76~~29. The ~~method~~ use of any one of claims 25-28 ~~67-75~~, wherein the subject is a human.

~~77. The method of any one of claims 67-76, wherein the herpes virus or pharmaceutical composition is administered topically, transdermally, subcutaneously, epicutaneously, intradermally, orally, sublingually, buccally, rectally, vaginally, intravenously, intraarterially, intramuscularly, intraosseously, intracardially, intraperitoneally, transmucosally, intravitreally, subretinally, intraarticularly, peri-articularly, intratumorally, locally, or via inhalation to the subject.~~

~~78. The method of any one of claims 67-77, wherein the herpes virus or pharmaceutical composition is administered orally, intranasally, intratracheally, or via inhalation to the subject.~~

~~79. The method of any one of claims 67-78, wherein the herpes virus or pharmaceutical composition is administered intranasally or via inhalation to the subject.~~

~~80. The method of any one of claims 67-79, wherein the herpes virus or pharmaceutical composition is administered via inhalation to the subject.~~

~~81. The method of any one of claims 67-80, wherein the herpes virus or pharmaceutical composition is administered using a dry powder inhaler, a pressurized metered dose inhaler, a soft mist inhaler, a nebulizer, or an electrohydrodynamic aerosol device.~~

~~82. The method of any one of claims 67-81, wherein the herpes virus or pharmaceutical composition is administered using a nebulizer.~~

~~83. The method of claim 82, wherein the nebulizer is a vibrating mesh nebulizer.~~