

CLAIMS

We Claim:

1. A method of treating cancer, comprising administering to a subject
a therapeutically effective amount of an oncolytic virus, and
a nucleocytoplasmic transport inhibitor.
2. The method of claim 1, wherein the oncolytic virus is derived from the
Poxviridae family.
3. The method of any one of claims 1 or 2, wherein the oncolytic virus is derived from
Chordopoxvirinae subfamily or *Entomopoxvirinae* subfamily.
4. The method of any one of claims 1 to 3, wherein the oncolytic virus is derived from a
virus genus of *Orthopoxvirus*, *Cervidpoxvirus*, *Parapoxvirus*, *Avipoxvirus*,
Capripoxvirus, *Leporipoxvirus*, *Suipoxvirus*, *Molluscipoxvirus*, *Yatapoxvirus*,
Alphaentomopoxvirus, *Betaentomopoxvirus*, or *Gammaentomopoxvirus*.
5. The method of any one of claims 1 to 4, wherein the oncolytic virus is derived from
genus *Leporipoxvirus*.
6. The method of any one of claims 1 to 5, wherein the oncolytic virus is a *myxoma virus*
(MYXV).
7. The method of any one of claims 1 to 4, wherein the oncolytic virus is derived from
genus *Orthopoxvirus*.
8. The method of any one of claims 1 to 7, wherein the virus is genetically modified.
9. The method of any one of claims 1 to 8, wherein the nucleocytoplasmic transport
inhibitor is selected from the group consisting of Leptomycin A, Leptomycin B,
Ratjadone A, Ratjadone B, Ratjadone C, Ratjadone D, Anguinomycin A, Goniothalamine,
piperlongumine, plumbagin, curcumin, valtrate, acetoxychavicol acetate, prenylcoumarin
osthol, KOS 2464, PKF050-638, CBS9106, and Selinexor.
10. The method of any one of claims 1 to 9, wherein the nucleocytoplasmic transport
inhibitor is Leptomycin B.
11. The method of any one of claims 1 to 9, wherein the nucleocytoplasmic transport
inhibitor is Selinexor.
12. The method of any one of claims 1 to 11, wherein the cancer is a solid tumor.
13. The method of claim 12, wherein the solid tumor is a sarcoma or a carcinoma.
14. The method of claim 12, wherein the solid tumor is fibrosarcoma, myxosarcoma,
liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma,
endotheliosarcoma, lymphangiosarcoma, lymphoendotheliosarcoma, synovium,

mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, meningioma, melanoma, neuroblastoma, or retinoblastoma.

15. The method of claim 12, wherein the solid tumor is colorectal adenocarcinoma, pancreatic cancer, or melanoma.
16. The method of any one of claims 1 to 15, wherein the oncolytic virus and the nucleocytoplasmic transport inhibitor are administered simultaneously.
17. The method of any one of claims 1 to 15, wherein the oncolytic virus and the nucleocytoplasmic transport inhibitor are administered sequentially.
18. The method of claim 17, wherein the oncolytic virus is administered before administering the nucleocytoplasmic transport inhibitor.
19. The method of claim 17, wherein the oncolytic virus is administered after administering the nucleocytoplasmic transport inhibitor.
20. The method of any one of claims 1 to 19, wherein the method comprises administering the oncolytic virus and the nucleocytoplasmic transport inhibitor for a period of at least 1 day, at least 2 days, at least 3 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 1 month, at least 3 months, at least 6 months, or at least 1 year.
21. The method of any one of claims 1 to 20, wherein the method comprises administering the oncolytic virus, the nucleocytoplasmic transport inhibitor, or both to the subject twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once a month, or once every two months.
22. The method of any one of claims 1 to 21, wherein the oncolytic virus is administered locally to a cancer tissue to be treated.
23. The method of claim 22, wherein the oncolytic virus is administered by intratumoral injection.
24. The method of claim 22 or 23, wherein a multiplicity of infection (MOI) of the oncolytic virus for the tissue is from about 0.01 to about 10.

25. The method of any one of claims 22-24, wherein a multiplicity of infection (MOI) of the oncolytic virus for the tissue is from about 0.05 to about 5.
26. The method of any one of claims 22-25, wherein a concentration of the nucleocytoplasmic transport inhibitor at the tissue is from about 0.0001 μM to about 100 μM .
27. The method of any one of claims 22-26, wherein a concentration of the nucleocytoplasmic transport inhibitor at the tissue is from about 0.01 μM to about 1 μM .
28. A method of killing a cancer cell comprising: contacting the cancer cell with an oncolytic virus and a nucleocytoplasmic transport inhibitor, thereby killing the cancer cell.
29. A method of enhancing susceptibility of a cancer cell to infection by an oncolytic virus, comprising contacting the cancer cell to an oncolytic virus and a nucleocytoplasmic transport inhibitor.
30. A method of inducing a cancer cell to be susceptible to infection by an oncolytic virus, comprising contacting the cancer cell to the oncolytic virus and a nucleocytoplasmic transport inhibitor.
31. A method of converting a nonpermissive cancer cell to a permissive cancer cell comprising contacting the nonpermissive cancer cell with an oncolytic virus and a nucleocytoplasmic transport inhibitor.
32. A method of increasing proliferation of an oncolytic virus in a cancer cell that is not susceptible to infection by the oncolytic virus comprising contacting the cancer cell to an oncolytic virus and a nucleocytoplasmic transport inhibitor.
33. The method of any one of claims 28-32, wherein said oncolytic virus is a virus from the *Poxviridae* family.
34. The method of any one of claims 28-33, wherein said oncolytic virus is a virus from *Chordopoxvirinae* subfamily or *Entomopoxvirinae* subfamily.
35. The method of any one of claims 28-34, wherein said oncolytic virus is from a virus genus that is *Orthopoxvirus*, *Cervidpoxvirus*, *Parapoxvirus*, *Avipoxvirus*, *Capripoxvirus*, *Leporipoxvirus*, *Suipoxvirus*, *Molluscipoxvirus*, *Yatapoxvirus*, *Alphaentomopoxvirus*, *Betaentomopoxvirus*, or *Gammaentomopoxvirus*.
36. The method of any one of claims 28-35, wherein said oncolytic virus is from genus *Leporipoxvirus*.
37. The method of any one of claims 28-36, wherein said oncolytic virus is a *myxoma virus* (MYXV).
38. The method of any one of claims 28-35, wherein said oncolytic virus is from genus *Orthopoxvirus*.

39. The method of any one of claims 28-36, wherein said virus is genetically modified.
40. The method of any one of claims 28-39, wherein said nucleocytoplasmic transport inhibitor is selected from the group consisting of Leptomycin A, Leptomycin B, Ratjadone A, Ratjadone B, Ratjadone C, Ratjadone D, Anguinomycin A, Goniiothalamine, piperlongumine, plumbagin, curcumin, valtrate, acetoxychavicol acetate, prenylcoumarin osthol, KOS 2464, PKF050-638, CBS9106, and Selinexor.
41. The method of any one of claims 28-40, wherein said nucleocytoplasmic transport inhibitor is Leptomycin B.
42. The method of any one of claims 28-40, wherein said nucleocytoplasmic transport inhibitor is Selinexor.
43. The method of any one of claims 28-42, wherein the cancer cell is colorectal cancer cell, pancreatic cancer cell, melanoma cancer cell.
44. The method of any one of claims 28-43, wherein the cancer cell is a human cancer cell.
45. The method of any one of claims 28-44, wherein the cancer cell is contacted to an oncolytic virus and a nucleocytoplasmic transport inhibitor *in vivo*.
46. The method of any one of claims 28-44, wherein the cancer cell is contacted to an oncolytic virus and a nucleocytoplasmic transport inhibitor *ex vivo*.
47. The method of any one of claims 28-46, wherein the method comprises contacting the cancer cell with the oncolytic virus and the nucleocytoplasmic transport inhibitor simultaneously.
48. The method of any one of claims 28-46, wherein the method comprises contacting the cancer cell with the oncolytic virus and the nucleocytoplasmic transport inhibitor sequentially.
49. The method of claim 48, wherein the cancer cell is contacted with the oncolytic virus before being contacted with the nucleocytoplasmic transport inhibitor.
50. The method of claim 48, wherein the cancer cell is contacted with the nucleocytoplasmic transport inhibitor before being contacted with the oncolytic virus.
51. The method of any one of claims 28-50, wherein the cancer cell is contacted with the oncolytic virus at a MOI of from about 0.01 to about 10.
52. The method of any one of claims 28-51, wherein the cancer cell is contacted with the oncolytic virus at a MOI of from about 0.05 to about 5.
53. The method of any one of claims 28-52, wherein the method comprises incubating the cancer cell in a media comprising the nucleocytoplasmic transport inhibitor at a concentration of from about 0.0001 μM to about 100 μM .

54. The method of any one of claims 28-53, wherein the method comprises incubating the cancer cell in a media comprising the nucleocytoplasmic transport inhibitor at a concentration of from about 0.01 μ M to about 1 μ M.
55. The method of any one of claims 28-54, wherein the method comprises contacting the cancer cell with a media comprising the nucleocytoplasmic transport inhibitor at a concentration of from about 0.0001 μ M to about 100 μ M.
56. The method of any one of claims 28-55, wherein the method comprises contacting the cancer cell with a media comprising the nucleocytoplasmic transport inhibitor at a concentration of from about 0.01 μ M to about 1 μ M.
57. The method of any one of claims 28-56, further comprising contacting the oncolytic virus to an autologous or heterologous cell *ex vivo*.
58. The method of claim 57, wherein the autologous or heterologous cell is a bone marrow cell or a macrophage cell.
59. The method of claim 57-58, further comprising injecting the autologous or heterologous cell to the subject.
60. A pharmaceutical composition comprising:
 - a. an oncolytic virus, and
 - b. a nucleocytoplasmic transport inhibitor.
61. The pharmaceutical composition of claim 60, further comprising a pharmaceutically acceptable excipient or carrier.
62. The pharmaceutical composition of any one of claims 60-61, wherein the oncolytic virus is derived from the *Poxviridae* family.
63. The pharmaceutical composition of any one of claims 60-62, wherein the oncolytic virus is derived from *Chordopoxvirinae* subfamily or *Entomopoxvirinae* subfamily.
64. The pharmaceutical composition of any one of claims 60-63, wherein the oncolytic virus is derived from a virus genus of *Orthopoxvirus*, *Cervidpoxvirus*, *Parapoxvirus*, *Avipoxvirus*, *Capripoxvirus*, *Leporipoxvirus*, *Suipoxvirus*, *Molluscipoxvirus*, *Yatapoxvirus*, *Alphaentomopoxvirus*, *Betaentomopoxvirus*, or *Gammaentomopoxvirus*.
65. The pharmaceutical composition of any one of claims 60-64, wherein the oncolytic virus is derived from genus *Leporipoxvirus*.
66. The pharmaceutical composition of any one of claims 60-65, wherein the oncolytic virus is a *myxoma virus* (MYXV).
67. The pharmaceutical composition of any one of claims 60-64, wherein the oncolytic virus is derived from genus *Orthopoxvirus*.

68. The pharmaceutical composition of any one of claims 60-67, wherein the virus is genetically modified.
69. The pharmaceutical composition of any one of claims 60-68, wherein the nucleocytoplasmic transport inhibitor is selected from the group consisting of Leptomycin A, Leptomycin B, Ratjadone A, Ratjadone B, Ratjadone C, Ratjadone D, Anguinomycin A, Goniothalamine, piperlongumine, plumbagin, curcumin, valtrate, acetoxychavicol acetate, prenylcoumarin osthol, KOS 2464, PKF050-638, CBS9106, and Selinexor.
70. The pharmaceutical composition of any one of claims 60-69, wherein the nucleocytoplasmic transport inhibitor is Leptomycin B.
71. The pharmaceutical composition of any one of claims 60-70, wherein the nucleocytoplasmic transport inhibitor is Selinexor.
72. The pharmaceutical composition of any one of claims 60-71, wherein the pharmaceutical composition is in a unit dosage form suitable for intratumoral or parenteral administration.
73. The pharmaceutical composition of claim 72, wherein the unit dosage comprises from about 1×10^3 plaque-forming units (PFU) to about 1×10^{10} PFU of the oncolytic virus per mL.
74. The pharmaceutical composition of claim 72, wherein the unit dosage comprises from about 1×10^5 PFU to about 1×10^{10} PFU of the oncolytic virus per mL.
75. The pharmaceutical composition of any one of claims 60-74, wherein a weight ratio between the oncolytic virus and the nucleocytoplasmic transport inhibitor is from about 1×10^9 to about 1×10^{-9} .