CLAIMS

1. A modified oncolytic virus comprising:

an exogenous nucleic acid encoding a fusion protein comprising a metabolic modulating protein or a functional fragment or a variant thereof, wherein the exogenous nucleic acid encoding for the fusion protein comprises:

a region encoding for IL-2 polypeptide ~~a polypeptide comprising IL-2~~ or a functional fragment thereof, and

a region encoding for leptin polypeptide ~~a polypeptide comprising~~ leptin or a functional fragment thereof;

an exogenous nucleic acid encoding a chemokine receptor or a functional fragment or a variant thereof, wherein the chemokine receptor is CCR2; and

a genetic modification in a viral genome of the modified oncolytic virus.

2. The modified oncolytic virus of claim 1, wherein the exogenous nucleic acid encoding the chemokine receptor comprises a codon optimized variant of the human coding sequence of the chemokine receptor.

3. The modified oncolytic virus of claim ~~1~~2, wherein the fusion protein further comprises a cytokine or a functional fragment or a variant thereof.

4. The modified oncolytic virus of ~~any one of claims 1-~~claim 3, wherein the genetic modification is a mutation or a deletion of an A52R gene.

5. The modified oncolytic virus of claim 4, wherein the deletion is a complete or a partial deletion.

6. The modified oncolytic virus of ~~any one of claims 1-~~claim 5, wherein the oncolytic virus further comprises a deletion of thymidine kinase gene.

7. The modified oncolytic virus of ~~any one of claims 1-6~~ claim 1, wherein the oncolytic virus comprises measles virus, poliovirus, poxvirus, vaccinia virus, adenovirus, adeno-associated virus, herpes simplex virus, vesicular stomatitis virus, reovirus, Newcastle disease virus, Seneca virus, lentivirus, mengovirus, or myxoma virus.

8. The modified oncolytic virus of claim 7, wherein the oncolytic virus is a pox virus.

9. The modified oncolytic virus of claim 8, wherein the pox virus is a vaccina virus.

10. The modified oncolytic virus of claim 9, wherein the vaccinia virus is a Western Reserve strain Vaccinia virus, a Copenhagen strain, an IHD strain, a Wyeth strain, a NYCBOH strain, a Tian Tan strain, a Lister strain, an Ankara strain, a USSR strain, an ACAM2000 strain, a Paris strain, a Bern strain, a Temple of Heaven strain, a Dairen strain, an EM-63 strain, an Evans strain, a King strain, a Patwadangar strain, or a Tash Kent strain.

11. The modified oncolytic virus of claim ~~10~~1, wherein the exogenous nucleic acid encoding the fusion protein is cloned into a locus of thymidine kinase gene.

12. The modified oncolytic virus of ~~any one of claims 1-11~~claim 1, wherein the exogenous nucleic acid encoding the chemokine receptor is cloned into a locus of an A52R gene.

13. The modified oncolytic virus of ~~any one of claims 1-12~~claim 1, wherein the ~~polypeptide~~ region encoding ~~IL-2~~ for leptin ~~or a functional fragment thereof~~ comprises a sequence that is at least about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% homologous to the sequence of SEQ ID NO: 4.

14. The modified oncolytic virus of ~~any one of claims 1-12~~claim 1, wherein ~~polypeptide~~ region encoding ~~leptin~~ for IL-2 ~~or a functional fragment thereof~~ comprises a sequence that is at least about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% homologous to the sequence of SEQ ID NO: 5.

15. The modified oncolytic virus of ~~any one of claims 1-14~~claim 1, wherein the exogenous nucleic acid encoding the fusion protein ~~comprising a metabolic modulating protein or a functional fragment or a variant thereof~~ comprises a sequence that is at least about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% homologous to the sequence of SEQ ID NO: 1.

16. The modified oncolytic virus of ~~any one of claims 1-15~~claim 1, wherein the exogenous nucleic acid encoding the chemokine receptor or a functional fragment or a variant thereof

comprises a sequence that is at least about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% homologous to the sequence of SEQ ID NO: 2 or SEQ ID NO: 3.

17. The modified oncolytic virus of ~~any one of claims 1-16~~claim 1, further comprising an exogenous nucleic acid encoding a hyaluronidase.

18. The modified oncolytic virus of claim 17, wherein the hyaluronidase is PH-20 or HysA.

19. A modified oncolytic virus comprising:

an exogenous nucleic acid encoding a leptin-interleukin (IL)-2 fusion protein;

an exogenous nucleic acid encoding CCR2, and

a deletion of A52R gene.

20. The modified oncolytic virus of claim 19, wherein the oncolytic virus comprises measles virus, poliovirus, poxvirus, vaccinia virus, adenovirus, adeno-associated virus, herpes simplex virus, vesicular stomatitis virus, reovirus, Newcastle disease virus, Seneca virus, lentivirus, mengovirus, or myxoma virus.

21. The modified oncolytic virus of claim 20, wherein the oncolytic virus is a pox virus.

22. The modified oncolytic virus of claim 21, wherein the pox virus is a vaccina virus.

23. The modified oncolytic virus of claim 22, wherein the vaccinia virus is a Western Reserve strain Vaccinia virus, a Copenhagen strain, an IHD strain, a Wyeth strain, a NYCBOH strain, a Tian Tan strain, a Lister strain, an Ankara strain, a USSR strain, an ACAM2000 strain, a Paris strain, a Bern strain, a Temple of Heaven strain, a Dairen strain, an EM-63 strain, an Evans strain, a King strain, a Patwadangar strain, or a Tash Kent strain.

24. The modified oncolytic virus of ~~any one of claims 19 to 23~~claim 19, wherein the oncolytic virus further comprises a deletion of a thymidine kinase gene.

25. The modified oncolytic virus of claim 24, wherein the exogenous nucleic acid encoding the leptin-interleukin (IL)-2 fusion protein is cloned into the locus of the thymidine kinase gene.

26. The modified oncolytic virus of ~~any one of claims 19-25~~claim 19, wherein the nucleic acid encoding CCR2 is cloned into a locus of an A52R gene.

27. The modified oncolytic virus of ~~any one of claims 1-26~~claim 1 or claim 19, further comprising a mutation or a deletion of a viral gene selected from the group consisting of: A1, A2, VH1, A33, I7, K7R, B8R, C12L, B15R, B14R, K1L, N1L, M2L, A49R, A46R, E3L, C4, C16, and a functional domain or a fragment or a variant thereof, or any combinations thereof.

28. The modified oncolytic virus of claim 27, further comprising an exogenous nucleic acid coding for at least one of: HMGB1, PIAS3, LIGHT, fractalkine, ITAC, IL15, IL15Ralpha, CCL5, a functional domain or a fragment or a variant thereof, or any combinations thereof.

29. A pharmaceutical composition comprising ~~a~~ the modified oncolytic virus ~~according to any one~~ of ~~claims 1-28~~claim 1 or claim 19.

30. The pharmaceutical composition of claim 29, further comprising at least one of: a solubilizing agent, an excipient, or a pharmaceutically acceptable carrier.

31. The pharmaceutical composition of claim 30, wherein the excipient comprises one or more of a buffering agent, a stabilizer, an antioxidant, a binder, a diluent, a dispersing agent, a rate controlling agent, a lubricant, a glidant, a disintegrant, a plasticizer, a preservative, or any combinations thereof.

32. The pharmaceutical composition of claim 30, wherein the excipient comprises di-sodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, myo-inositol, sorbitol, or any combinations thereof.

33. The pharmaceutical composition of ~~any one of claims 29-32~~claim 29, that does not comprise a preservative.

34. The pharmaceutical composition of ~~any one of claims 29-32~~claim 29, further comprising one or more of a preservative, a diluent, and a carrier.

35. The pharmaceutical composition of ~~any one of claims 29-34~~claim 29, further comprising an additional active ingredient or a salt thereof.

36. The pharmaceutical composition of ~~any one of claims 30-35~~claim 30, wherein the solubilizing agent is sterile water.

37. The pharmaceutical composition of ~~any one of claims 29-36~~claim 29, further comprising an additional active ingredient, wherein the additional active ingredient is an anti-cancer agent or a further oncolytic virus.

~~38. A kit comprising the modified oncolytic virus of any one of claims 1 to 28.~~

~~39. A kit comprising the pharmaceutical composition of claims 29-37.~~

~~40. The kit of claim 38 or 39 further comprising at least one of: an anti-cancer agent or an additional oncolytic virus.~~

~~41.~~38. Use of the modified oncolytic virus according to claim 1 or the pharmaceutical composition as defined in claim 29 in the manufacture of a medicament for ~~A method of~~ enhancing therapeutic effect of a modified oncolytic virus upon systemic delivery of the modified oncolytic virus to a subject, relative to ~~a systemic administration of~~ a reference virus comprising a TK mutation but not the exogenous nucleic acid encoding the fusion protein or the exogenous nucleic acid encoding the chemokine receptor that is to be administered by systemic administration, and wherein ~~comprising a systemic administration of~~ the modified oncolytic virus according to ~~any one of claims 1-28~~claim 1, or the pharmaceutical composition as defined in ~~any one of claims 29-37~~claim 29 is to be administered by systemic administration.

~~42.~~39. Use of ~~A method of treatment comprising administering to a subject~~ the oncolytic virus according to ~~any one of claims 1-28~~claim 1, or the pharmaceutical composition of ~~any one of claims 29-37~~claim 29 in the manufacture of a medicament for enhancing systemic immune response in a subject, wherein the oncolytic virus or the pharmaceutical composition that is to be administered results in an enhanced systemic immune response ~~administering results in an enhanced systemic immune response~~ in the subject, relative to

~~administering to the subject~~ a reference oncolytic virus that comprises a deletion of a thymine kinase gene (TK-) and does not comprise the exogenous nucleic acid encoding a fusion protein comprising a metabolic modulating protein or functional fragment or variant thereof or the exogenous nucleic acid encoding the chemokine receptor or functional fragment or variant thereof that is to be administered to the subject.

~~43.~~40. The use~~method~~ of claim ~~42~~39, wherein the oncolytic virus or the pharmaceutical composition is to be administered~~administering is a~~ by systemic administration.

~~44.~~41. The use~~method~~ of ~~any one of claims 41-43~~claim 38, wherein the systemic administration comprises at least one of: intratumoral, intravenous, parenteral, intradermal, intramuscular, transdermal, rectal, intraurethral, intravaginal, intranasal, intrathecal, intraperitoneal. intradental, subcutaneous, percutaneous, intratracheal, intraarterial, intravesical, inhalation, oral or any combinations thereof.

~~45.~~42. The use~~method~~ of claim 41~~44~~, wherein the administration is intratumoral.

~~46.~~43. The use~~method~~ of claim 41~~44~~, wherein the administration is intravenous.

~~47.~~44. The use~~method~~ of ~~any one of claims 41-46~~claim 38, wherein the subject has a cancer.

45. The modified oncolytic virus according to claim 1 or the pharmaceutical composition of claim 29 for use in therapy.

~~48. A method of treating a cancer in a subject, said method comprising administering to said subject a therapeutically effective amount of the modified oncolytic virus of any one of claims 1-28.~~

~~49. The method of claim 47 or 48, wherein the cancer is at least one of: a melanoma, a hepatocellular carcinoma, a breast cancer, a lung cancer, a Non-small lung cancer, a peritoneal cancer, a prostate cancer, a bladder cancer, an ovarian cancer, a leukemia, a lymphoma, a renal cell carcinoma, a pancreatic cancer, an epithelial carcinoma, a gastric/GE junction adenocarcinoma, a cervical cancer, a colon carcinoma, a colorectal cancer, a duodenal cancer, a pancreatic adenocarcinoma, an adenoid cystic, a sarcoma, a mesothelioma, a glioblastoma multiforme, a astrocytoma, a multiple myeloma, a prostate~~

carcinoma, a hepatocellular carcinoma, a cholangiocarcinoma, a pancreatic adenocarcinoma, a head and neck squamous cell carcinoma, a cervical squamous-cell carcinoma, an osteosarcoma, an epithelial ovarian carcinoma, an acute lymphoblastic lymphoma, a myeloproliferative neoplasm, or any combinations thereof.

50. The method of any one of claims 41-49, wherein the modified oncolytic virus, or the pharmaceutical composition is administered at a dosage that comprises about 10^6 PFU/mL to about 10^{10} PFU/mL of the oncolytic virus.

51. The method of any one of claims 41-49, wherein the modified oncolytic virus, or the pharmaceutical composition is administered at a dosage that comprises about 5 x 10^9 PFU/mL of the oncolytic virus.

52. The method of any one of claims 41-51, wherein the modified oncolytic virus, or the pharmaceutical composition is administered, independently, in an initial dose for a first period of time, an intermediate dose for a second period of time, and a high dose for a third period of time.

53. The method of claim 52, comprising administration of the initial, the intermediate, and the high dose, independently, wherein the initial dose is lower than the intermediate dose and the intermediate dose is lower than the high dose.

54. The method of claim 52 or 53, wherein the first, second, and third periods of time are each from about 1 week to about 3 weeks.

55. The method of any one of claims 41-54, wherein the modified oncolytic virus, and the pharmaceutical composition independently comprises a liquid dosage form that is administered at a volume of about 1 mL to about 5 mL, about 5 mL to 10 mL, about 15 mL to about 20 mL, about 25 mL to about 30 mL, about 30 mL to about 50 mL, about 50 mL to about 100 mL, about 100 mL to 150 mL, about 150 mL to about 200 mL, about 200 mL to about 250 mL, about 250 mL to about 300 mL, about 300 mL to about 350 mL, about 350 mL to about 400 mL, about 400 mL to about 450 mL, about 450 mL to 500 mL, about 500 mL to 750 mL, or about 750 mL to 1000 mL.

~~56. The method of any one of claims 41-55, wherein the modified oncolytic virus or the pharmaceutical composition is administered in a liquid dosage form, a solid dosage form, an inhalable dosage form, an intranasal dosage form, a liposomal formulation, a dosage form comprising nanoparticles, a dosage form comprising microparticles, a polymeric dosage form, or any combinations thereof.~~

~~57. The method of any one of claims 41-56, wherein the modified oncolytic virus or the pharmaceutical composition is administered for a duration of about 1 week, about 2 week, about 3 weeks, about 4 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10, weeks, or about 12 weeks.~~

~~58. The method of any one of claims 41-57, wherein the modified oncolytic virus, or the pharmaceutical composition is administered once daily, twice daily, once every week, once every two weeks, or once every three weeks.~~

~~59. The method of any one of claims 41-58, wherein the modified oncolytic virus, or the pharmaceutical composition is administered intravenously, intraperitoneally, or by an intratumoral injection.~~

~~60. The method of any one of claims 41-59, wherein the modified oncolytic virus or the pharmaceutical composition is administered as a bolus injection or a slow infusion.~~

~~61. The method of any one of claims 41-60, wherein the administration of the modified oncolytic virus or the pharmaceutical composition results in a first peak viral load after about 1 hour to about 3 days and a second peak viral load after about 3 days to about 10 days from administration of a first dose.~~

~~62. The method of any one of claims 41-61, comprising administration of a further therapy, wherein the further therapy is administered for a duration of about 1 week, about 2 week, about 3 weeks, about 4 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10, weeks, or about 12 weeks.~~

~~63. The method of claim 62, wherein the further therapy is administered once daily, once every week, once every two weeks, or once every three weeks.~~

64. The method of claim 62 or 63, wherein the further therapy is administered in a liquid dosage form, a solid dosage form, an inhalable dosage form, an intranasal dosage form, a liposomal formulation, a dosage form comprising nanoparticles, a dosage form comprising microparticles, a polymeric dosage form, or any combinations thereof.

65. The method of any one of claims 62-64, wherein the further therapy is administered for a duration of about 1 week, about 2 week, about 3 weeks, about 4 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10, weeks, or about 12 weeks.

66. The method of any one of claims 62-65, wherein the further therapy is administered once daily, once every week, once every two weeks, or once every three weeks.

67. The method of any one of claims 62-66, wherein the further therapy is administered in a liquid dosage form, a solid dosage form, an inhalable dosage form, an intranasal dosage form, a liposomal formulation, a dosage form comprising nanoparticles, a dosage form comprising microparticles, a polymeric dosage form, or any combinations thereof.

68. The method of any one of claims 62-67, wherein the further therapy is administered orally, intravenously, by an intratumoral injection, or by radiation.

69. The method of any one of claims 41-68, wherein the subject is human.

70. The method of any one of claims 41-69, wherein prior to administration of the modified oncolytic virus or the pharmaceutical composition the subject has been diagnosed with a cancer.

71. The method of any one of claims 41-70, wherein prior to administration of the modified oncolytic virus or the pharmaceutical composition or the further therapy the subject has been diagnosed with a cancer.

72. The method of any one of claims 62-71, wherein the further therapy comprises chemotherapy, radiation, oncolytic viral therapy with an additional virus, treatment with immunomodulatory proteins, a CAR T cellular therapy, an anti-cancer agent, or any combinations thereof.

~~73. The method of claim 72, wherein the further therapy comprises administration of an immunomodulatory agent comprising anti-CD33 antibody and variable region thereof, an anti-CD11b antibody and variable region thereof, a COX2 inhibitor, a cytokine, a chemokine, an anti-CTLA4 antibody or an antigen binding fragment thereof, an anti-PD-1 antibody or an antigen binding fragment thereof, an anti-PD-L1 antibody or an antigen binding fragment thereof, or a TLR agonist.~~

~~74. The method of claim 73, comprising administration of the further therapy, wherein the further therapy comprises administration of the anti-cancer agent, wherein the anti-cancer agent is a chemotherapeutic agent.~~