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 or a functional fragment thereof, and

a region encoding for leptin polypeptide 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 2, wherein the fusion protein further comprises a cytokine or a functional fragment or a variant thereof.

4. The modified oncolytic virus of 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 claim 5, wherein the oncolytic virus further comprises a deletion of thymidine kinase gene.

7. The modified oncolytic virus of 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 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 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 claim 1, wherein the region encoding for leptin 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 claim 1, wherein region encoding for IL-2 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 claim 1, wherein the exogenous nucleic acid encoding the fusion protein 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 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 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 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 claim 19, wherein the nucleic acid encoding CCR2 is cloned into a locus of an A52R gene.

27. The modified oncolytic virus of 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 the modified oncolytic virus of 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 claim 29, that does not comprise a preservative.

34. The pharmaceutical composition of claim 29, further comprising one or more of a preservative, a diluent, and a carrier.

35. The pharmaceutical composition of claim 29, further comprising an additional active ingredient or a salt thereof.

36. The pharmaceutical composition of claim 30, wherein the solubilizing agent is sterile water.

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

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 enhancing therapeutic effect of a modified oncolytic virus upon systemic delivery of the modified oncolytic virus to a subject, relative to 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 the modified oncolytic virus according to claim 1, or the pharmaceutical composition as defined in claim 29 is to be administered by systemic administration.

39. Use of the oncolytic virus according to claim 1, or the pharmaceutical composition of 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 in the subject, relative to 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.

40. The use of claim 39, wherein the oncolytic virus or the pharmaceutical composition is to be administered by systemic administration.

41. The use of 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.

42. The use of claim 41, wherein the administration is intratumoral.

43. The use of claim 41, wherein the administration is intravenous.

44. The use of 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.