CLAIMS

1. An isolated human interleukin 2 (IL-2) variant comprising at least one amino acid substitution as compared to wild-type human IL-2 having the amino acid sequence as shown in SEQ ID NO: 1, wherein the IL-2 variant comprises one or more substitutions at amino acid positions selected from the group consisting of:

a) K35,

b) both R38 and L40,

c) both T41 and K43,

d) both K43 and Y45,

e) both E62 and K64, and

f) both L72 and Q74.

2. An isolated fusion protein, comprising: a) an IL-2 variant of claim 1; and b) an Fc region of a human antibody, wherein the IL-2 variant is covalently linked to the Fc region.

3. An isolated nucleic acid encoding an IL-2 variant of claim 1.

4. A host cell comprising an isolated nucleic acid of claim 1.

5. A pharmaceutical composition, comprising an IL-2 variant of claim 1.

6. A method for treating cancer in a subject, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of claim 5.

7. A recombinant oncolytic virus (OV), which comprises a nucleotide sequence encoding an IL-2 variant of claim 1.

8. The OV of claim 7, wherein the IL-2 variant comprises one or more substitutions at amino acid positions selected from the group consisting of:

a) K35, wherein the K35 substitution is K35N,

b) both R38 and L40, wherein the R38 substitution is R38N and the L40 substitution is L40S or L40T,

c) both T41 and K43, wherein the T41 substitution is T41N and the K43 substitution is K43S or K43T,

d) both K43 and Y45, wherein the K43 substitution is K43N and the Y45 substitution is Y45S or Y45T,

e) both E62 and K64, wherein the E62 substitution is E62N and the K64 substitution is K64S or K64T, and

f) both L72 and Q74, wherein the L72 substitution is L72N and the Q74 substitution is Q74S or Q74T.

9. The OV according to claim 7, wherein the IL-2 variant comprises a substitution in position K35, and wherein the IL-2 variant further comprises substitutions at positions selected from the group consisting of:

a) both R38 and L40, wherein the R38 substitution is R38N and the L40 substitution is L40S or L40T,

b) both T41 and K43, wherein the T41 substitution is T41N and the K43 substitution is K43S or K43T,

c) both K43 and Y45, wherein the K43 substitution is K43N and the Y45 substitution is Y45S or Y45T,

d) both E62 and K64, wherein the E62 substitution is E62N and the K64 substitution is K64S or K64T,

e) both L72 and Q74, wherein the L72 substitution is L72N and the Q74 substitution is Q74S or Q74T, and

f) E62, wherein the E62 substitution is E62N, E62A, E62K, or, E62R.

10. The OV according to claim 7, wherein the IL-2 variant comprises substitutions at positions R38 and L40, and wherein the IL-2 variant further comprises substitutions at positions selected from the group consisting of:

a) both T41 and K43, wherein the T41 substitution is T41N and the K43 substitution is K43S or K43T,

b) both K43 and Y45, wherein the K43 substitution is K43N and the Y45 substitution is Y45S or Y45T,

c) both E62 and K64, wherein the E62 substitution is E62N and the K64 substitution is K64S or K64T,

d) both L72 and Q74, wherein the L72 substitution is L72N and the Q74 substitution is Q74S or Q74T, and

e) E62, wherein the E62 substitution is E62N, E62A, E62K, or, E62R.

11. The OV according to claim 7, wherein the IL-2 variant comprises substitutions at positions T41 and K43, and wherein the IL-2 variant further comprises substitutions at positions selected from the group consisting of:

a) both E62 and K64, wherein the E62 substitution is E62N and the K64 substitution is K64S or K64T,

b) both L72 and Q74, wherein the L72 substitution is L72N and the Q74 substitution is Q74S or Q74T, and

c) E62, wherein the E62 substitution is E62N, E62A, E62K, or, E62R.

12. The OV according to claim 7, wherein the IL-2 variant comprises substitutions at positions K43 and Y45, and wherein the IL-2 variant further comprises substitutions at positions selected from the group consisting of:

a) both E62 and K64, wherein the E62 substitution is E62N and the K64 substitution is K64S or K64T,

b) both L72 and Q74, wherein the L72 substitution is L72N and the Q74 substitution is Q74S or Q74T, and

c) E62, wherein the E62 substitution is E62N, E62A, E62K, or, E62R.

13. The OV according to claim 7, wherein the IL-2 variant comprises substitutions at positions E62 and K64, and wherein the IL-2 variant further comprises substitutions at positions L72 and Q74, wherein the L72 substitution is L72N and the Q74 substitution is Q74S or Q74T.

14. The OV according to claim 7, wherein the IL-2 variant comprises substitutions at positions R38, L40, K43, and Y45.

15. The OV according to claim 7, wherein the IL-2 variant comprises the amino acid substitutions R38N, L40T, K43N, and Y45T.

16. The OV according to claim 7, wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO:29 or SEQ ID NO:31.

17. The OV according to claim 7, wherein the IL-2 variant comprises substitutions at amino acid positions K43, Y45, L72, and Q74.

18. The OV according to claim 7, wherein the IL-2 variant comprises the amino acid substitutions K43N, Y45T, L72N, and Q74T.

19. The OV according to claim 7, wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO:33 or SEQ ID NO:35.

20. The OV of any one of claims 7-19, wherein the IL-2v polypeptide-encoding nucleotide sequence is operably linked to a regulatable promoter.

21. The OV of claim 15, wherein the regulatable promoter is regulated by tetracycline or a tetracycline analog or derivative.

22. The OV of any one of claims 7-21, which further comprises a nucleotide sequence encoding heterologous thymidine kinase (TK) polypeptide.

23. The OV of claims 22, wherein heterologous TK polypeptide is capable of catalyzing phosphorylation of deoxyguanosine.

24. The OV of claims 22 or 23, wherein the heterologous TK polypeptide is a variant herpes simplex virus (HSV) TK polypeptide.

25. The OV of claim 24, wherein the variant HSV TK polypeptide comprises an amino acid sequence having at least 80% amino acid sequence identity to wild-type HSV TK, and comprises a substitution of one or more of L159, I160, F161, A168, and L169, based on the amino acid numbering of wild-type HSV TK amino acid sequence of SEQ ID NO: 1.

26. The OV of claim 25, wherein the variant HSV TK polypeptide comprises an A168H substitution.

27. The OV of claim 25, wherein the variant HSV TK polypeptide comprises an L159I substitution, an I160L substitution, an F161A substitution, an A168Y substitution, and an L169F substitution.

28. The OV of claim 25, wherein the variant HSV TK polypeptide comprises an L159I substitution, an I160F substitution, an F161L substitution, an A168F substitution, and an L169M substitution.

29. The OV of claim 25, wherein the variant HSV TK polypeptide comprises the amino acid sequence of SEQ ID NO: 26, 27, or 28.

30. The OV of any one of claims 7-29, wherein the virus comprises an A34R gene comprising a K151E substitution.

31. The OV of any one of claims 7-30, wherein the virus comprises a modification that renders the vaccinia thymidine kinase deficient.

32. The OV of claim 31, wherein the modification that renders the vaccinia thymidine kinase deficient is deletion of all or portion of the J2R gene.

33. The OV of any one of claims 7-27, wherein the virus is a vaccinia virus.

34. The OV of claim 33, wherein the vaccinia virus is a Copenhagen strain.

35. The OV of claim 33, wherein the vaccinia virus is a Western Reserve (WR) strain.

36. A recombinant oncolytic vaccinia virus (OV), comprising, in its genome: (1) a nucleotide sequence encoding a variant interleukin-2 (IL-2v) polypeptide comprising amino acid sequence of SEQ ID NO:29; (2) a nucleotide sequence encoding a heterologous thymidine kinase (TK) polypeptide comprising the amino acid sequence of SEQ ID NO: 28; and (3) a K151E substitution in the A34R gene,

wherein the virus is a Copenhagen strain vaccinia virus and is vaccinia thymidine kinase deficient.

37. A composition comprising: a) the OV of any one of claims 7-36; and b) a pharmaceutically acceptable carrier.

~~38. A method of treating cancer in an individual having a cancer, the method comprising administering to the individual an effective amount of the OV any one of claims 7-36, or the composition of claim 37.~~

~~39. The method of claim 38, wherein the cancer is brain cancer, head and neck cancer, esophageal cancer, skin cancer, lung cancer, thymic cancer, stomach cancer, colon cancer, liver cancer, ovarian cancer, uterine cancer, bladder cancer, testicular cancer, rectal cancer, breast cancer, or pancreatic cancer.~~

~~40. The method of claim 37, wherein the cancer is a colorectal adenocarcinoma, a non-small cell lung carcinoma, or a triple-negative breast cancer.~~

~~41. The method of any one of claims 38-40, wherein the cancer is recurrent.~~

~~42. The method of any one of claims 38-41, wherein the cancer is a primary tumor.~~

~~43. The method of any one of claims 38-41, wherein the cancer is metastatic.~~

~~44. The method of any one of claims 38-43, further comprising administering to the individual a second cancer therapy.~~

~~45. The method of claim 44, wherein the second cancer therapy is selected from chemotherapy, biological therapy, radiotherapy, immunotherapy, hormone therapy, anti-vascular therapy, cryotherapy, toxin therapy, oncolytic virus therapy, a cell therapy, and surgery.~~

~~46. The method of claim 44, wherein the second cancer therapy comprises an anti-PD1 antibody or an anti-PD-L1 antibody.~~

~~47. The method of any one of claims 37-46, wherein the individual is immunocompromised.~~

~~48. The method of any one of claims 37-47, wherein said administering of the OV or the composition is intratumoral, peritumoral. intra-arterial, intrabladder, intrathecal, or intravenous.~~

~~49. A method of treating cancer in an individual, comprising administering to the individual: a) an effective amount of a recombinant oncolytic virus of any one~~

~~of claims 22-29; and b) a synthetic analog of 2'-deoxy-guanosine in an amount that is effective to reduce an adverse side effect of the oncolytic virus.~~

~~50. The method of claim 49, wherein the synthetic analog of 2'-deoxy-guanosine is selected from the group consisting of acyclovir, famciclovir, ganciclovir, valaciclovir, and valganciclovir.~~