

CLAIMS

1. An engineered fusogenic oncolytic virus wherein the oncolytic virus expresses one or more exogenous membrane bound immune cell targeting ligands comprising an uncleaved signal anchor.
2. The engineered oncolytic virus of claim 1, wherein the fusogenic oncolytic virus is a modified or engineered parainfluenza virus type 5.
3. The engineered oncolytic virus of claim 1, wherein the fusogenic oncolytic virus comprises a gene which codes for a peptide that allows a hyperfusogenic property that allows tumor cells to fuse.
4. The engineered oncolytic virus of claim 1, wherein the uncleaved signal anchor is a neuraminidase transmembrane segment.
5. The engineered oncolytic virus of claim 1, wherein the one or more exogenous membrane bound immune cell targeting ligands comprises an engineered immunoglobulin Fc domain; wherein the immunoglobulin Fc domain is modified to have an inverted orientation with the amino terminal end facing intracellularly.
6. The engineered oncolytic virus of claim 5, wherein the immunoglobulin Fc domain comprises an IgG1 Fc domain.
7. The engineered oncolytic virus of claim 5, wherein the IgG1 Fc domain further comprises modifications to increase FcR binding or ADCC.
8. The engineered oncolytic virus of claim 1, wherein the one or more exogenous membrane bound immune cell targeting ligand comprises a protein agonist of the NK cell receptor NKG2D.
9. The engineered oncolytic virus of claim 1, wherein the one or more exogenous membrane bound immune cell targeting ligand comprises a protein epitope region that is reactive to anti-CD19.

10. The engineered oncolytic virus of claim 1, wherein the one or more exogenous membrane bound immune cell targeting ligands is CD19 or CD20.
11. The engineered oncolytic virus of claim 1, wherein the oncolytic virus is engineered to express one or more of IL-12, IL-21, or IL-15.
12. A pharmaceutical composition comprising the engineered oncolytic virus of claim 1, and a pharmaceutically acceptable carrier.
13. Use of an engineered fusogenic oncolytic virus for the preparation of a medicament for treating cancer; wherein the oncolytic virus expresses one or more exogenous membrane bound immune cell targeting ligands comprising an uncleaved signal anchor.
14. The use of claim 13, wherein the one or more membrane bound immune cell targeting ligands comprises an engineered immunoglobulin Fc domain; and wherein the immunoglobulin Fc domain is modified to have an inverted orientation with the amino terminal end facing intracellularly.
15. The use of claim 13, wherein the one or more membrane bound immune cell targeting ligands comprises a protein agonists of the NK cell receptor NKG2D.
16. The use of claim 13, wherein immune cells, antibodies that target one or more of the one or more exogenous membrane bound immune cell targeting ligands, or CAR T cells that are designed to target one or more of the one or more exogenous membrane bound immune cell targeting ligands are adoptively transferred.
17. The use of claim 16, wherein the adoptively transferred immune cells are natural killer (NK) cells.
18. The use of claim 17, wherein the NK cells are stimulated and expanded with one or more NK cell stimulating agents.
19. The use of claim 18, wherein the one or more NK cell stimulating agent is a cytokine, growth factor, synthetic ligand, NK cell stimulating particle, NK cell stimulating exosome, or NK cell stimulating feeder cell.

20. The use of claim 19, wherein the one or more NK stimulating agent is an NK cell stimulating particle, NK cell stimulating exosome, or NK cell stimulating feeder cell; and wherein the one or more agents comprise IL-21, 4-1BBL or a fragment thereof.
21. The use of claim 19, wherein the one or more NK cell stimulating agents comprise at least one cytokine selected from the group consisting of IL-2, IL-12, IL-18, IL-15 or a combination thereof.
22. The use of claim 17, wherein the NK cells are engineered to express CD19 targeting anti-CD19 chimeric antigen receptors or CD20 targeting anti-CD20 chimeric antigen receptors.
23. The use of claim 16, wherein the immune cells are engineered CD19 targeting anti-CD19 CAR-T cells or CD20 targeting anti-CD20 CAR-T cells.
24. The use of claim 16, wherein the immune cells are antibodies specific for one or more of the exogenous membrane bound immune cell targeting ligands.
25. The use of claim 13, wherein the cancer is selected from the group consisting of leukemia, lymphoma, myeloma, melanoma, colorectal cancer, breast cancer, ovarian cancer, renal cell cancer, malignant melanoma, malignant glioma, neuroblastoma, non small cell lung carcinoma renal cell carcinoma, merkel cell carcinoma, skin cancer, brain cancer, pancreatic adenocarcinoma, malignant mesothelioma, lung adenocarcinoma, lung small cell carcinoma, lung squamous cell carcinoma, anaplastic thyroid cancer or head and neck squamous cell carcinoma.
26. The use of claim 17, wherein the NK cells are genetically modified.
27. A fusion protein comprising an uncleaved signal anchor domain comprising: a cytoplasmic tail region, a transmembrane region and an extracellular stalk region; and an immune cell targeting ligand comprising an N-terminus fused to a C-terminus of the extracellular stalk region; wherein the fusion protein allows tumor cells to fuse.
28. The fusion protein of claim 27, wherein the immune cell targeting ligand is capable of binding an immune cell selected from the group consisting of an NK cell, a B cell, a T cell, and a CAR-T cell.

29. The fusion protein of claim 27, wherein the immune cell targeting ligand comprises an immunoglobulin Fc domain comprising an amino acid modification wherein the N-terminus of the Fc domain fuses to the C-terminus of the extracellular stalk domain.
30. The fusion protein of claim 27, wherein the immune cell targeting ligand comprises an immunoglobulin Fc domain selected from the group consisting of IgG1, IgG2, IgG3, and IgG4.
31. The fusion protein of claim 30, wherein the Fc domain further comprises at least one amino acid modification selected from the group consisting of: 256A/K290A/S298A/E333A/K334A or L235V/F243L/R292P/Y300L/P396L.
32. The fusion protein of claim 27, wherein the uncleaved signal anchor domain comprises a signal anchor domain selected from the signal anchor domain of neuraminidase, parainfluenza virus hemagglutinin-neuraminidase, transferrin receptor, MHC class II invariant chain, P glycoprotein, asialoglycoprotein receptor, and a neutral endopeptidase.
33. The fusion protein of claim 27, wherein the uncleaved signal anchor domain comprises a neuraminidase signal anchor domain.
34. The fusion protein of claim 27, wherein the targeting ligand is selected from the group consisting of an immunoglobulin Fc domain, an NK2GD ligand, and an anti-ligand domain.
35. The fusion protein of claim 27, wherein the targeting ligand is an NK2GD ligand selected from RAET1, RAET1E, RAET1G, RAET1H, RAET1L, RAET1N, MICA, and MICB.
36. The fusion protein of claim 27, wherein the targeting ligand is an anti-ligand domain selected from CD19 and CD20.
37. The fusion protein of claim 27, comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 1.
38. A polynucleotide sequence encoding the fusion protein of claim 37.
39. A host virus comprising a modified viral genome comprising the polynucleotide of claim 38.
40. The host virus of claim 39, wherein the host virus is an oncolytic virus.

41. The host virus of claim 39, wherein the host virus is selected from a parainfluenza virus type 5, a CPI parainfluenza, a wild-type parainfluenza, a CPI-WT parainfluenza chimeric virus having a viral backbone encoding P/V from CPI and WT parainfluenza, an Adenovirus, an Adeno-associated virus, a Herpesvirus, a Poxvirus, a Reovirus, a Picornavirus, a Togavirus, a Coronavirus, a Flavivirus, a Filovirus, a Arenavirus, a Bunyavirus, a Paramyxovirus, a Rhabdovirus, a Pneumovirus, a Orthomyxovirus, a Delta virus, a Retrovirus, a Hepadnavirus, a Orthohepevirus, a Human Papillomavirus, a Polyomavirus, the HSV-1 oncolytic virus HSV1716, Talimogene laherparepvec, the adenovirus oncolytic virus H101, the poliovirus oncolytic virus PVSRIPO, the Reovirus oncolytic virus reoslyn, the seneca valley virus SVV-001, the coxsackie virus oncolytic virus Coxsackievirus A21, the enterovirus oncolytic virus Riga virus, and the vaccinia virus oncolytic viruses GL-ONC1 or JX-594.

42. The host virus of claim 39, wherein the host virus is a cell fusogenic oncolytic virus.

43. Use of a modified oncolytic virus comprising the polynucleotide of claim 38 for the preparation of a medicament for cancer immunotherapy; wherein an immune cell is targeted to a cancer cell and the cancer cell is contacted with the modified oncolytic virus.

44. Use of a modified oncolytic virus comprising the polypeptide of claim 38 for the preparation of a medicament for cancer immunotherapy, wherein the oncolytic virus is modified by inserting the polynucleotide into the viral genome; and wherein an immune cell is targeted to a cancer cell, and the cancer cell is contacted with the modified oncolytic virus.