CLAIMS

1. An engineered oncolytic virus for delivering an exogenous membrane-bound Natural Killer (NK) cell targeting ligand to a target cell, wherein the engineered oncolytic virus comprises a polynucleotide sequence encoding a fusion protein comprising an uncleaved signal anchor domain operably linked to the exogenous membrane-bound NK cell targeting ligand, and wherein the exogenous membrane-bound NK cell targeting ligand comprises an engineered immunoglobulin Fc domain modified to have an inverted orientation with the amino terminal end of the engineered immunoglobulin Fc domain facing the exterior (outside) surface of the cell membrane when the fusion protein is expressed on the cell membrane of the target cell.

2. The engineered oncolytic virus of claim 1, wherein the engineered oncolytic virus is a fusogenic virus comprising a modified or engineered parainfluenza virus type 5.

3. The engineered oncolytic virus of claim 1, wherein the uncleaved signal anchor comprises: a cytoplasmic tail region, a transmembrane region, and an extracellular stalk region.

4. The engineered oncolytic virus of claim 3, wherein the uncleaved signal anchor domain is a neuraminidase signal anchor domain.

5. The engineered oncolytic virus of claim 4, wherein the N-terminus of the engineered immunoglobulin Fc domain is fused to the neuraminidase signal anchor domain by a peptide linker of 2-20 amino acids in length.

6. The engineered oncolytic virus of claim 5, wherein the peptide linker is a restriction site linker.

7. The engineered oncolytic virus of claim 5, wherein the immunoglobulin Fc domain comprises an IgG1 Fc domain modified to increase FcR binding or antibody dependent cell mediated cytotoxicity (ADCC).

8. The engineered oncolytic virus of claim 1, wherein the immunoglobulin Fc domain further comprises at least one amino acid modification selected from: T256A, K290A, S298A, E333A, K334A, L235V, F243L, R292P, Y300L, or P396L.

9. 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.

10. A pharmaceutical composition comprising the engineered oncolytic virus of claim 1, and a pharmaceutically acceptable carrier.

11. Use of an engineered oncolytic virus for the preparation of a medicament for treating cancer,wherein the engineered oncolytic virus comprises a polynucleotide sequence encoding a fusion protein comprising an uncleaved signal anchor domain operably linked to an exogenous membrane bound Natural Killer (NK) cell targeting ligand, and wherein the exogenous membrane-bound NK cell targeting ligand comprises an engineered immunoglobulin Fc domain modified to have an inverted orientation with the amino terminal end of the engineered immunoglobulin Fc domain facing the exterior (outside) surface of the cell membrane when the fusion protein is expressed on the cell membrane of a target cell.

12. The use of claim 11, wherein the uncleaved signal anchor domain comprises a cytoplasmic tail region, a transmembrane region, and an extracellular stalk region.

13. The use of claim 11, wherein the NK cells are stimulated and expanded with one or more NK cell stimulating agents.

14. The use of claim 13, wherein the one or more NK cell stimulating agents is a cytokine, a growth factor, a synthetic ligand, a NK cell stimulating particle, an NK cell stimulating exosome, or an NK cell stimulating feeder cell.

15. The use of claim 14, wherein the one or more NK stimulating agents 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.

16. The use of claim 14, 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.

17. The use of claim 11, wherein the NK cells are engineered to express CD19 targeting anti-CD19 chimeric antigen receptors or CD20 targeting anti-CD20 chimeric antigen receptors.

18. The use of claim 11, 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.

19. A fusion protein comprising an uncleaved signal anchor domain comprising: a cytoplasmic tail region, a transmembrane region and an extracellular stalk region; and a membrane-boundNatural Killer (NK) cell targeting ligand comprising an N-terminus fused to a C-terminus of the extracellular stalk region, wherein the NK cell targeting ligand comprises an engineered immunoglobulin Fc domain modified to have an inverted orientation with the amino terminal end of the engineered immunoglobulin Fc domain facing the exterior (outside) surface of the cell membrane when the fusion protein is expressed on the cell membrane of a target cell.

20. The fusion protein of claim 19, wherein the engineered Fc domain is selected from the group consisting of an IgG1, IgG2, IgG3, and IgG4 FC domain.

21. The fusion protein of claim 20, wherein the engineered Fc domain further comprises at least one amino acid modification selected from the group consisting of: T256A, K290A, S298A, E333A, K334A, L235V, F243L, R292P, Y300L, or P396L.

22. The fusion protein of claim 19, 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.

23. The fusion protein of claim 22, wherein the uncleaved signal anchor domain comprises a neuraminidase signal anchor domain.

24. The fusion protein of claim 19, comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 1.

25. A polynucleotide sequence encoding the fusion protein of claim 24.

26. An oncolytic host virus comprising a modified viral genome comprising the polynucleotide of claim 25.

27. The oncolytic host virus of claim 26, 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 a Papilomavirus, a Polyomavirus, the HSV-1 oncolytic virus HSV1716, Talimogene laherparepvec, the adenovirus oncolytic virus H101, the poliovirus oncolytic virus PVSRIPO, the Reovirus oncolytic vbiurs reosylin, 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.

28. The oncolytic host virus of claim 26, wherein the host virus is a cell fusogenic oncolytic virus.

29. Use of an engineered oncolytic virus comprising the polynucleotide of claim 25 for use in the preparation of a medicament for cancer immunotherapy.

30. The use of claim 29, wherein the oncolytic virus is modified by inserting the polynucleotide of claim 25 into its viral genome.