

## CLAIMS

1. An engineered ~~fusogenic~~ oncolytic virus ~~wherein the oncolytic virus expresses one or more for delivering an~~ exogenous membrane-bound ~~immune~~Natural Killer (NK) cell targeting ~~ligands~~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 ~~fusogenic~~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 fusogenic oncolytic virus comprises a gene which codes for a peptide that allows a hyperfusogenic property that allows tumor cells to fuse.~~
- 4.3. The engineered oncolytic virus of claim 1, wherein the uncleaved signal anchor ~~is a neuraminidase~~ comprises: a cytoplasmic tail region, a transmembrane segmentregion, and an extracellular stalk region.
4. The engineered oncolytic virus of claim 4.3, wherein the uncleaved signal anchor domain is a neuraminidase signal anchor domain.
5. The~~one or more exogenous membrane-bound immune-cell targeting ligands comprises an~~ engineered oncolytic virus of claim 4, wherein the N-terminus of the engineered immunoglobulin Fc domain; ~~wherein the immunoglobulin Fc domain is modified is fused to have an inverted orientation with the the neuraminidase signal anchor domain by a peptide linker of 2-20 amino terminal end facing intracellularly~~ acids in length.
6. The engineered oncolytic virus of claim 5, wherein the peptide linker is a restriction site linker.

~~6-7.~~ 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).

~~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.

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 ~~one or more exogenous membrane bound immune cell targeting ligand~~ comprises a protein epitope region that is reactive to anti-CD19.

~~10-8.~~ The engineered oncolytic virus of claim 1, wherein the ~~one or more exogenous membrane bound immune cell targeting ligands~~ is CD19 or CD20.

~~11-9.~~ 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.

~~12-10.~~ 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~~ engineered oncolytic virus ~~expresses one or more comprises a polynucleotide sequence encoding a fusion protein comprising an uncleaved signal anchor domain operably linked to an~~ exogenous membrane bound ~~immune~~ Natural Killer (NK) cell targeting ~~ligands comprising an uncleaved signal anchor.~~

~~14.~~ The use of claim 13, ~~ligand, and~~ wherein the ~~one or more~~ exogenous membrane ~~bound immune~~ NK cell targeting ~~ligand~~ ligand comprises an engineered immunoglobulin Fc domain; ~~and wherein the immunoglobulin Fc domain is~~ modified to have an inverted orientation with the amino terminal end of the engineered immunoglobulin Fc domain facing ~~intracellularly.~~

~~15.11.~~ 11. The use of claim 13, wherein the one or more exterior (outside) surface of the cell membrane bound immune cell targeting ligands comprises a protein agonists of the NK when the fusion protein is expressed on the cell receptor NKG2D membrane of a target cell.

~~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.

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.

~~17.~~ The use of claim 16, wherein the adoptively transferred immune cells are natural killer (NK) cells.

~~18.13.~~ 13. The use of claim ~~17~~11, wherein the NK cells are stimulated and expanded with one or more NK cell stimulating agents.

~~19.14.~~ The use of claim ~~18~~13, wherein the one or more NK cell stimulating ~~agent~~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.

~~20.15.~~ 15. The use of claim ~~19~~14, wherein the one or more NK stimulating ~~agent~~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.

~~21.16.~~ 16. The use of claim ~~19~~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.

~~22.17.~~ 17. The use of claim ~~17~~11, 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.~~

~~25-18. The use of claim 13~~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.

~~26. The use of claim 17, wherein the NK cells are genetically modified.~~

~~27-19. A fusion protein comprising an uncleaved signal anchor domain comprising: a cytoplasmic tail region, a transmembrane region and an extracellular stalk region; and an immunea membrane-boundNatural Killer (NK) 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, 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.~~

~~28-20. The fusion protein of claim 2719, wherein the immune cell targeting ligand is capable of binding an immune cellengineered Fc domain is~~ selected from the group consisting of an NK cell, a B cell, a T cell, and a CAR-T cell.IgG1, IgG2, IgG3, and IgG4 FC domain.

~~29. The fusion protein of claim 2720, 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.~~

~~31-21. The fusion protein of claim 30, wherein theengineered~~ Fc domain further comprises at least one amino acid modification selected from the group consisting of: 256A/T256A, K290A/\_ S298A/\_ E333A/\_ K334A-or\_ L235V/\_ F243L/\_ R292P/\_ Y300L/\_ or P396L.

~~32-22.~~ The fusion protein of claim ~~2719~~, 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 ~~2722~~, wherein the uncleaved signal anchor domain comprises a neuraminidase signal anchor domain.

~~33.—~~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.

~~34.—~~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.

~~35.—~~The fusion protein of claim ~~27~~, wherein the targeting ligand is an anti-ligand domain selected from CD19 and CD20.

~~36-24.~~ The fusion protein of claim ~~2719~~, comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 1.

~~37-25.~~ A polynucleotide sequence encoding the fusion protein of claim ~~3724~~.

~~38-26.~~ An oncolytic host virus comprising a modified viral genome comprising the polynucleotide of claim ~~3825~~.

~~39.—~~The oncolytic host virus of claim ~~39~~, wherein the host virus is an oncolytic virus.

~~40-27.~~ The host virus of claim ~~3926~~, 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 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 reosyn, the seneca valley virus SVV-001, the coxsackie virus oncolytic virus Cocksackievirus A21, the enterovirus oncolytic virus Riga virus, and the vaccinia virus oncolytic viruses GL-ONC1 or JX-594.

41-28. The oncolytic host virus of claim 3926, wherein the host virus is a cell fusogenic oncolytic virus.

42-29. Use of a modified an engineered oncolytic virus comprising the polynucleotide of claim 3825 for use in 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.~~

43-30. ~~Use of a modified oncolytic virus comprising the polypeptide~~ The use of claim 38 ~~for the preparation of a medicament for cancer immunotherapy~~29, wherein the oncolytic virus is modified by inserting the polynucleotide of claim 25 into ~~the~~its viral genome; ~~and wherein an immune cell is targeted to a cancer cell, and the cancer cell is contacted with the modified oncolytic virus.~~