

WHAT IS CLAIMED IS:

1. A population of nucleated cells comprising a plurality of natural killer (NK) cells, wherein the population comprises at least 1.0×10^6 nucleated cells, wherein at least about 70% of the NK cells in the population are viable and express Receptor Linker IL-15, wherein:
 - at least about 85% of cells in the population are CD56+;
 - no more than about 0.5% of the cells in the population are CD3+;
 - no more than about 10% of the cells in the population are CD19+;
 - no more than about 10% of the cells in the population are CD14+;
 - no more than about 20% of the cells in the population are LAG3+;
 - at least about 10% of the cells in the population are CD122+, and
 - no more than about 20% of the cells in the population are NKG2A+.
2. The population of nucleated cells of claim 1, wherein the Receptor Linker IL-15 is SEQ ID NO: 25 or SEQ ID NO: 28.
3. The population of nucleated cells of any one of claims 1-2, wherein at least about 75% of the NK cells that express Receptor Linker IL-15, and optionally, wherein said 75% of the NK cells also do not express CISH.
4. A population of nucleated cells comprising a plurality of NK cells, wherein the population comprises at least 1.0×10^6 nucleated cells, wherein at least about 70% of the NK cells in the population are viable and express anti-CD38 chimeric antigen receptor (CAR), wherein:
 - at least about 85% of cells in the population are CD56+;
 - no more than about 0.5% of the cells in the population are CD3+;
 - no more than about 10% of the cells in the population are CD19+;
 - no more than about 10% of the cells in the population are CD14+; and
 - no more than about 15% of the cells in the population are CD38+;and wherein said CAR comprises an anti-CD38 scFv.
5. The population of nucleated cells of claim 4, wherein the CAR comprises:
 - (i) a hinge domain selected from CD28 and CD8, optionally
 - (ii) a transmembrane domain selected from CD28, CD8, and NKG2D, optionally

(iii) a co-stimulatory domain selected from CD28, 4-1BB, 2B4, CD3zetaR, OX40, Lsk, ICOS, DAP10, and Fc fragment of IgE receptor Ig, optionally

(iv) an activation domain is selected from CD3 ζ , FcR- γ , and Fc-epsilon-R, and optionally

5 (v) a signal peptide.

6. The population of nucleated cells of any one of claims 4 or 5, wherein the CAR is selected from SEQ ID NO: 31 and SEQ ID NO: 32.

7. The population of nucleated cells of any one of claims 1-4, wherein the cells that express Receptor Linker IL-15 or anti CD38 CAR, further comprise a mutant chemokine receptor, and optionally wherein the mutant chemokine receptor is SEQ ID NO: 69.

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8. A method of *ex vivo* producing genetically modified natural killer (NK) cells of any one of claims 1-7, the method comprising:

(a) downregulating expression of a gene of interest in a population of NK cells so as to obtain a population of NK cells having been genetically modified to down-regulate a gene of interest;

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(b) expanding said population of NK cells having been genetically modified to down-regulate a gene of interest so as to obtain an *ex vivo* expanded population of NK cells; and

(c) upregulating expression of at least one membrane bound protein in said *ex vivo* expanded population of NK cells, thereby producing the genetically modified NK cells.

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9. A method of *ex vivo* producing natural killer (NK) cells expressing at least one membrane bound protein of any one of claims 1-7, the method comprising:

(a) expanding a population of NK cells by a method comprising:

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(i) culturing said population of NK cells under conditions allowing for cell proliferation, wherein said conditions comprise providing an effective amount of nutrients, serum, IL-15 and nicotinamide; and

(ii) supplementing said population of NK cells with an effective amount of fresh nutrients, serum, IL-15 and nicotinamide 5-10 days following step (i) to produce expanded NK cells;

so as to obtain an *ex vivo* expanded population of NK cells, and

(b) upregulating expression of at least one membrane bound protein in said *ex vivo* expanded population of NK cells, thereby producing the NK cells expressing the at least one membrane bound protein.

5 10. The method of claim 8 or 9, wherein said population of NK cells is derived from cord blood, peripheral blood, bone marrow, CD34⁺ cells or iPSCs, optionally wherein said population of NK cells is deprived of CD3⁺ cells, and optionally wherein said population of NK cells comprises CD3⁻CD56⁺ cells.

11. The method of any one of claims 8 or 10, wherein said downregulating is effected by a
10 gene editing system wherein said NK cells are in a culture and wherein said downregulating is affected 24-72 hours from initiation of said culture.

12. The method of any one of claims 8 or 10-11, wherein said gene of interest comprises a gene whose product effects proliferation and/or survival of said NK cells, and, optionally, wherein said gene of interest is selected from the group consisting of CISH, TGFβ receptor and
15 CD38.

13. The method of any one of claims 8 or 10-12, wherein said expanding said population of NK cells is affected under conditions allowing for cell proliferation, wherein:

(i) said conditions comprise an effective amount of nutrients, serum, growth factors and nicotinamide, and/or

20 (ii) said growth factors comprise at least one growth factor selected from the group consisting of IL-15, IL-2, IL-7, IL-12, IL-21, SCF and FLT3, and/or

(iii) wherein said effective amount of said nicotinamide comprises an amount between 1.0 mM to 10 mM, and/or

(iv) wherein said expanding said population of NK cells is affected in the presence
25 of feeder cells or a feeder layer, and/or

(v) wherein said expanding said population of NK cells is affected in the presence of a CD3 agonist, and optionally, wherein said CD3 agonist is OKT3, and/or

(vi) wherein said expanding said population of NK cells is affected in the presence of feeder cells or a feeder layer and wherein said feeder cells comprise irradiated cells and/or wherein said feeder cells comprise T cells or PBMCs.

14. The method of any one of claims 8-13, wherein said expanding said population of NK
5 cells is affected for 14-16 days.

15. The method of any one of claims 12-14, wherein said upregulating expression of said
at least one membrane bound protein is affected on day 12-14 from initiation of culture, and,
optionally, wherein said upregulating expression of said at least one membrane bound protein
is affected by mRNA electroporation and, optionally, wherein said at least one membrane
10 bound protein is transiently expressed.

16. An isolated population of NK cells of any one of claims 1-7 obtainable according to the
method of any one of claims 8-15.

17. A pharmaceutical composition comprising the isolated population of NK cells of claim
16 and a pharmaceutically active carrier.

15 18. A therapeutically effective amount of the isolated population of NK cells of claim 17
for use in the treatment of a disease in a subject in need thereof.

19. The isolated population of NK cells of claim 18, wherein the disease is selected from
the group consisting of a malignant disease, a viral disease, a bacterial disease, a fungal disease,
a protozoa disease, and a parasite disease, and optionally

20 (i) wherein said malignant disease is a solid tumor or tumor metastasis,

(ii) wherein said malignant disease is selected from the group consisting of a breast
cancer, an ovarian cancer, a bladder cancer, a pancreatic cancer, a stomach cancer, a lung
cancer, a melanoma, a sarcoma, a neuroblastoma, a colon cancer, a colorectal cancer, an
esophageal cancer, a synovial cell cancer, a uterus cancer, a glioma and a cervical cancer,

25 (iii) wherein said malignant disease is a hematological malignancy, and wherein said
hematological malignancy comprises a leukemia, a lymphoma or multiple myeloma.