

VI. CLAIMS

What is claimed is:

1. A method of treating a cancer in a subject comprising administering to the subject an NK
5 cell that has been modified to comprise a knockout of the CD38 gene.
2. The method of treating a cancer of claim 1, wherein the cancer comprises multiple
myeloma, acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL), or
Blastic plasmacytoid dendritic cell neoplasm (BPDCN).
3. The method of treating a cancer of claim 1 or 2, further comprising administering to the
10 subject an anti-cancer agent comprising a small molecule, antibody, peptide, protein, or siRNA
that targets CD38.
4. The method of treating a cancer of claim 3, wherein the anti-cancer agent comprises
Daratumumab, isatuximab, TAK-079, or MOR202.
5. The method of treating a cancer of claim 3 or 4, further comprising administering to the
15 subject an angiogenesis inhibitor and a steroid.
6. The method of treating a cancer of claim 5, wherein the angiogenesis inhibitor comprises
Pomalidomide, Lenalidomide, or Apremilast.
7. The method of treating a cancer of claim 5, wherein the steroid comprises a
glucocorticoid.
- 20 8. The method of treating a cancer of claim 7, wherein the glucocorticoid comprises
dexamethasone, betamethasone, prednisolone, methylprednisolone, triamcinolone, or
fludrocortisone acetate.
9. A method of adoptively transferring an engineered NK cells to a subject in need thereof
said method comprising
25 a) obtaining a target NK cell to be modified;
b) obtaining gRNA specific for the target DNA sequence;
c) introducing via electroporation into the target NK cell, a RNP complex comprising a
class 2 CRISPR/Cas endonuclease (Cas9) complexed with a corresponding CRISPR/Cas
guide RNA that hybridizes to a target sequence within the genomic DNA of the target
30 NK cell creating an engineered NK cell; and
d) transferring the engineered NK cell into the subject.
10. The method of claim 9, wherein the subject has a cancer.

11. The method of claim 9, wherein the NK cell is a primary NK cell that has been modified ex vivo and after modification transferred to the subject.
12. The method of claim 9, wherein the NK cell is an autologous NK cell.
13. The method of claim 9, wherein the NK cell is from an allogeneic donor source.
- 5 14. The method of claim 9, wherein the NK cell is expanded with irradiated mbIL-21 expressing feeder cells prior to administration to the subject.
15. The method of claim 9, wherein the NK cell is expanded in the subject following transfer of the NK cells to the subject via the administration of IL-21 or irradiated mbIL-21 expressing feeder cells.
- 10 16. The method of claim 9, wherein the RNP complex targets the CD38 gene.
17. A genetically modified NK cell comprising a knockout of the gene encoding clustering of differentiation 38 (CD38) made by the method of any of claims 9-16.
18. A method of treating a cancer in a subject comprising administering to the subject the genetically modified NK cell of claim 17.
- 15 19. The method of claim 18, further comprising administering to the subject an anti-cancer agent comprising a small molecule, antibody, peptide, protein, or siRNA that targets CD38.
20. The method of treating a cancer of claim 19, wherein the anti-cancer agent comprises an anti-CD38 antibody.
21. The method of treating a cancer of claim 20, wherein the anti-CD38 antibody comprises
20 Daratumumab, isatuximab, TAK-079, or MOR202.
22. The method of treating a cancer of any of claims 18-21, wherein the cancer comprises multiple myeloma, acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL), or Blastic plasmacytoid dendritic cell neoplasm (BPDCN).
23. A method of reducing NK cell fratricide in a subject receiving anti-CD38
25 immunotherapy comprising administering to the subject the genetically modified NK cell of claim 17.