CLAIMS

What is claimed is:

1. An engineered feeder cell that has been modified to express soluble or membrane bound TGF-β.

2. The engineered feeder cell of claim 1, wherein TGF-β is expressed by an inducible or constitutive promoter.

3. The engineered feeder cell of claim 1 or 2, wherein the feeder cell comprises a leukemia K562 cell.

4. The engineered feeder cell of claim 1 or 2, wherein the feeder cell comprises a NK cell.

5. The engineered feeder cell of any of claims 1-3, further comprising at least one additional NK cell effector agent on its cell surface, wherein the at least one additional NK cell effector agent is a cytokine, an adhesion molecule, or an NK cell activating agent.

6. The engineered feeder cell of claim 5, wherein the at least one additional NK cell effector agent is selected from 4-1BBL, IL-2, IL-12, IL-15, IL-18, IL-21, MICA, LFA-1, 2B4, CCR7, OX40L, UBLP2, BCM1/SLAMF2, NKG2D agonists, CD155, CD112, Jagged1, Jagged2, Delta-1, Pref-1, DNER, Jedi, SOM-11, wingless, CCN3, MAGP2, MAGP1, TSP2, YB-1, EGFL7, CCR7, DAP12, and DAP10, Notch ligands, NKp46 agonists, NKp44 agonists, NKp30 agonists, other NCR agonists, and CD16 agonists.

7. The engineered feeder cell of claim 5, wherein the at least one additional NK cell effector agent comprises IL-21, 4-1BBL, IL-15, IL-21 and 4-1BBL, IL-21 and IL-15, or IL-15 and 4-1BBL.

8. The engineered feeder cell of any of claims 1-7, wherein the feeder cells comprise PBMCs, RPMI8866, HFWT, K562 cells, EBV-LCL, NK cells transfected with membrane bound IL-21, NK cells transfected with membrane bound 4-1BBL, NK cells transfected with membrane bound IL-15 and 4-1BBL , or NK cells transfected with membrane bound IL-21 and 4-1BBL.

9. A plasma membrane particle or exosome derived from the engineered feeder cell of any of claims 1-8.

10. A method of generating TGF-β resistant NK cells, comprising incubating NK

cells in the presence of the engineered feeder cells of any of claims 1-8 or the exosome or plasma membrane particle of claim 9.

11. A method of generating TGF-β resistant NK cells, comprising incubating NK cells in the presence of feeder cells that have been engineered to express TGF-β or incubating NK cells in the presence of plasma membrane particles or exosomes derived from said feeder cells.

12. The method of generating TGF-β resistant NK cells of claim 11, wherein the feeder cells comprise PBMCs, RPMI8866, HFWT, K562 cells, EBV-LCL, NK cells transfected with membrane bound IL-21, NK cells transfected with membrane bound 4-1BBL, NK cells transfected with membrane bound IL-15 and 4-1BBL , or NK cells transfected with membrane bound IL-21 and 4-1BBL.

13. The method of generating TGF-β resistant NK cells of claim 11 or 12, wherein the feeder cells, further comprising comprises at least one additional NK cell effector agent on its cell surface, wherein the at least one additional NK cell effector agent is a cytokine, an adhesion molecule, or an NK cell activating agent.

14. The method of generating TGF-β resistant NK cells of claim 13, wherein the at least one additional NK cell effector agent is selected from 4-1BBL, IL-2, IL-12, IL-15, IL-18, IL-21, MICA, LFA-1, 2B4, CCR7, OX40L, UBLP2, BCM1/SLAMF2, NKG2D agonists, CD155, CD112, Jagged1, Jagged2, Delta-1, Pref-1, DNER, Jedi, SOM-11, wingless, CCN3, MAGP2, MAGP1, TSP2, YB-1, EGFL7, CCR7, DAP12, and DAP10, Notch ligands, NKp46 agonists, NKp44 agonists, NKp30 agonists, other NCR agonists, and CD16 agonists.

15. The method of generating TGF-β resistant NK cells of claim 14, wherein the at least one additional NK cell effector agent comprises IL-21, 4-1BBL, IL-15, IL-21 and 4-1BBL, IL-21 and IL-15, or IL-15 and 4-1BBL.

16. The method of generating TGF-β resistant NK cells of any of claims 11-15, wherein the NK cells comprise memory-like NK cells such as NKG2C^{+}, CD56^{bright} NK cells, CD56^{dim} NK cells, peripheral NK cells, and NK T cells, tumor infiltrating NK cells.

17. The method of generating TGF-β resistant NK cells of any of claims 11-16, wherein the NK cells are obtained from a donor subject.

18. The method of generating TGF-β resistant NK cells of any of claims 11-16,

wherein the NK cells are obtained from autologous donor, allogeneic donor, or syngeneic donor.

19. The method of generating TGF-β resistant NK cells of any of claims 11-18, wherein the NK cells are incubated in the presence of the engineered feeder cells, plasma membrane particles, or exosomes for at least 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 45, or 60 days.

20. A TGF-β resistant NK cell made by the method of any of claims 10-19.

21. ~~A method of treating~~Use of a TGF-β resistant NK cell of claim 20 in the manufacture of a medicament for the treatment of a cancer in a subject ~~comprising administering to the subject the TGF-β resistant NK cell of claim 20~~.

22. Use of a TGF-β resistant NK cell~~A~~ in the manufacture of a medicament for the treatment of ~~method of treating~~ a cancer in a subject, wherein the ~~with a~~ TGF-β resistant NK cell is obtained by a method comprising obtaining an NK cell; culturing the cell in the presence of feeder cells engineered to express TGF-β thereby creating a TGF-β resistant NK cell or in the presence of ~~of~~ plasma membrane particles or exosomes derived from said feeder cells~~; and administering to the subject the TGF-β resistant NK cell~~.

23. The ~~method of treating a cancer~~use of claim 22, wherein the NK cells are memory-like NK cells such as NKG2C^{+}, CD56^{bright} NK cells, CD56^{dim} NK cells, peripheral NK cells, and NK T cells, tumor infiltrating NK cells.

24. The ~~method of treating a cancer~~use of claim 22 or 23, wherein the NK cells are obtained from a donor subject.

25. The ~~method of treating a cancer~~use of any of claims 22-24, wherein the NK cells are obtained from autologous donor, allogeneic donor, or syngeneic donor.

26. The ~~method of treating a cancer~~use of any of claims 22-25, ~~wherein the~~ wherein the feeder cells comprise PBMCs, RPMI8866, HFWT, K562 cells, EBV-LCL, NK cells transfected with membrane bound IL-21, NK cells transfected with membrane bound 4-1BBL, NK cells transfected with membrane bound IL-15 and 4-1BBL , or NK cells transfected with membrane bound IL-21 and 4-1BBL.

27. The ~~method of treating a cancer~~use of any of claims 22-26, wherein the feeder cells further comprise at least one additional NK cell effector agent on its cell surface,

wherein the at least one additional NK cell effector agent is a cytokine, an adhesion molecule, or an NK cell activating agent.

28. The ~~method of treating a cancer~~use of claim 27, wherein the at least one additional NK cell effector agent is selected from 4-1BBL, IL-2, IL-12, IL-15, IL-18, IL-21, MICA, LFA-1, 2B4, CCR7, OX40L, UBLP2, BCM1/SLAMF2, NKG2D agonists, CD155, CD112, Jagged1, Jagged2, Delta-1, Pref-1, DNER, Jedi, SOM-11, wingless, CCN3, MAGP2, MAGP1, TSP2, YB-1, EGFL7, CCR7, DAP12, and DAP10, Notch ligands, NKp46 agonists, NKp44 agonists, NKp30 agonists, other NCR agonists, and CD16 agonists.

29. The ~~method of treating a solid tumor~~use of claim ~~of claim~~ 28, wherein the cancer is a solid tumor and wherein the at least one additional NK cell effector agent comprises IL-21, 4-1BBL, IL-15, IL-21 and 4-1BBL, IL-21 and IL-15, or IL-15 and 4-1BBL.

30. The ~~method of treating a cancer~~use of any of claims 22-29, wherein the NK cells are incubated in the presence of the engineered feeder cells, plasma membrane particles, or exosomes for at least 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 45, or 60 days.