

CLAIMS

1. An NK cell expanding composition comprising
 - a) a feeder cell comprising a membrane bound inverted Fc domain bound to an external surface of the feeder cell,
 - b) an engineered plasma membrane (PM) particle comprising a membrane bound inverted Fc domain bound to an external surface of the engineered PM particle, or
 - c) an engineered exosome comprising a membrane bound inverted Fc domain bound to an external surface of the engineered exosome,wherein the inverted Fc domain is part of a fusion protein comprising a transmembrane domain linked to the amino terminus of Fc domain, the amino terminus of the Fc domain facing the external surface of the feeder cell, engineered PM particle, or engineered exosome, and
wherein the NK cell expanding composition further comprises at least one NK cell effector agent.
2. The NK cell expanding composition of claim 1, comprising the engineered PM particle or engineered exosome substantially free of feeder cells.
3. The NK cell expanding composition of claim 2, wherein the at least one NK cell effector agent of the engineered PM particle comprises IL-21 or IL-15.
4. The NK cell expanding composition of claim 3, wherein the IL-21 is membrane bound.
5. The NK cell expanding composition of claim 1, wherein the at least one NK cell effector agent is IL-21 or IL-15.
6. The NK cell expanding composition of claim 5, further comprising a second NK cell effector agent, wherein the second NK cell effector agent is 41 BBL.
7. The NK cell expanding composition of claim 6, further comprising at least one additional NK cell effector agent, wherein the at least one additional NK cell effector agent is a cytokine, an adhesion molecule, or an NK cell activating agent; wherein the at least one additional NK cell effector agent is selected from IL-15, IL-2, IL-12, IL-18, IL- 21 , MICA, UBLP, 2sB4, LFA-1, a Notch ligand, a ligand for NKp46, or BCM1/SLAMF2, a TLR ligand, and a NKG2D ligand.
8. An NK cell composition comprising an in vitro NK cell population in contact with the NK cell expanding composition of claim 1.
9. An expanded population of NK cells exposed in vitro to an NK cell expanding composition of claim 1, wherein the composition comprises feeder cells, or wherein the composition comprises at least one engineered plasma membrane (PM) particle that is free of feeder cells, wherein the feeder cells or engineered PM particle comprise an Fc domain bound to an external surface thereof.

10. The expanded population of NK cells of claim 9, wherein the NK cells have increased cytotoxicity compared to non-expanded NK cells.
11. A composition comprising a therapeutically effective amount of the expanded population of NK cells of claim 9 or 10, and a pharmaceutically acceptable carrier.
12. The expanded population of NK cells of claim 9 or 10 or the composition of claim 11 for use in treating, ameliorating, reducing, and/or inhibiting a cancer or metastasis or an infectious disease in a subject, wherein an effective amount of the expanded population of NK cells or the composition is to be administered to the subject in need thereof.
13. The expanded population of NK cells or the composition for use of claim 12, wherein the cancer is selected from the group consisting of a tumor, a hematologic cancer, a lymphoma, a leukemia, acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia, acute lymphoblastic leukemia, myelofibrosis, multiple myeloma, a colorectal cancer, a colon cancer, lung cancer, a head and neck cancer, ovarian cancer, pancreatic cancer, liver cancer, skin cancer, prostate cancer, kidney cancer, intraperitoneal cancer, and breast cancer.
14. The expanded population of NK cells of claim 9 or 10 or the composition of claim 11 for use in inhibiting, reducing, and/or preventing cancer or metastasis recurrence before or after stem cell transplant, wherein an effective amount of the expanded population of NK cells or the composition is to be administered to a subject in need thereof.
15. The expanded population of NK cells or the composition for use according to any one of claims 12-14, wherein at least one cancer therapeutic agent is to be further administered to the subject in combination with the effective amount of the composition or expanded NK cell population.
16. The expanded population of NK cells of claim 9 or 10 or the composition of claim 11 for use in preventing, inhibiting, reducing, or mitigating acute or chronic graft-vs-host disease (GvHD), wherein an effective amount of the expanded population of NK cells or the composition is to be administered to a subject in need thereof.
17. The expanded population of NK cells of claim 9 or 10 or the composition of claim 11 for use in preventing, inhibiting, reducing, or mitigating viral reactivation, wherein an effective amount of the expanded population of NK cells or the composition is to be administered to a subject in need thereof.
18. The expanded population of NK cells of claim 9 or 10 or the composition of claim 11 for use in preventing, inhibiting, reducing, or mitigating opportunistic infections, wherein an effective amount of the expanded populations of NK cells or the composition is to be administered to a subject in need thereof.
19. The expanded population of NK cells of claim 9 or 10, wherein the expanded NK cells exhibit increased secretion of anti-tumor cytokines compared with non-expanded NK cells or exhibit increased expression of NKG2D, NKp46 and CD16 compared with non-expanded NK cells.

20. A method of increasing NK cell cytotoxicity, comprising exposing an initial population of NK cells in vitro to an NK cell expanding composition, the NK cell expanding composition comprising

at least one feeder cell or engineered plasma membrane (PM) particle comprising at least two NK cell effector agents, wherein one of the at least two NK cell effector agents is IL-21, and

an inverted Fc domain bound to an external surface of the feeder cell or engineered PM particle.

21. The method of claim 20, wherein the NK cell expanding composition comprises at least one feeder cell having a membrane bound Fc domain.

22. The method of claim 20, wherein the NK cell expanding composition comprises at least an engineered particle selected from a PM particle having a membrane bound Fc domain and an exosome having a membrane bound Fc domain.

23. The method of claim 20, further comprising obtaining a population of expanded NK cells having increased cytotoxicity compared to the initial population of NK cells.