

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 ~~athe~~ 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 ~~engineered PM particle further comprises~~ 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 ~~1, further comprising at least one NK cell effector agent.~~
3, wherein the IL-21 is membrane bound.
5. The NK cell expanding composition of claim ~~3 or 4~~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 1, wherein the engineered PM particle comprises a plasma membrane vesicle or an exosome purified from NK cell feeder cells transfected or transduced with a fusion protein comprising a transmembrane domain linked to an Fc domain, and at least one NK cell effector agent.~~

~~87.~~ 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, ~~ligands~~a ligand for NKp46, or BCM1/SLAMF2, a TLR ~~ligands~~ligand, and a NKG2D ~~ligands~~ligand.

~~98.~~ An NK cell composition comprising an in vitro NK cell population in contact with the NK cell expanding composition of claim 1.

~~109.~~ An expanded population of NK cells exposed in vitro to an NK cell expanding composition, of claim 1, wherein the composition ~~comprising~~comprises feeder cells, or ~~comprising~~wherein the composition comprises g at least one engineered plasma membrane (PM) particle ~~and being that is~~ free of feeder cells, wherein the feeder cells or engineered PM particle comprise an Fc domain bound to an external surface thereof.

~~110.~~ The expanded population of NK cells of claim ~~109~~, wherein the NK cells have increased cytotoxicity compared to non-expanded NK cells.

~~1211.~~ A composition comprising a ~~therapeutic dose of NK cells comprising~~therapeutically effective amount of the expanded population of NK cells of claim ~~109~~ or ~~1110~~, and a pharmaceutically acceptable carrier.

~~13.~~ ~~A12.~~ The expanded population of NK cells of claim 9 or 10 or the composition of claim 11 for use in ~~method of~~ treating, ameliorating, reducing, and/or inhibiting a cancer or metastasis or an infectious disease in a subject, wherein ~~comprising administering to the subject~~

~~in need thereof~~ an effective amount of the expanded population of NK cells ~~of claim 10 or 11 or the composition of claim 12~~ is to be administered to the subject in need thereof.

~~1413.~~ The expanded population of NK cells or the composition for use~~method~~ of claim ~~1312~~, 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.

~~15.~~ ~~A14.~~ The expanded population of NK cells of claim 9 or 10 or the composition of claim 11 for use in ~~method of~~ inhibiting, reducing, and/or preventing cancer or metastasis recurrence before or after stem cell transplant, wherein ~~comprising administering to a subject in need thereof~~ an effective amount of the expanded population of NK cells ~~of claim 10 or 11 or the composition of claim 12~~ is to be administered to a subject in need thereof.

~~1615.~~ The expanded population of NK cells or the composition for use~~method~~ according to any one of claims ~~13-1512-14~~, wherein ~~further comprising administering to the subject~~ 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.

~~17.~~ ~~A method of modulating T cell repertoire during or after stem cell transplant~~~~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 ~~comprising administering to a subject in need thereof~~ an effective amount of the expanded population of NK cells ~~of claim 10 or 11 or the composition of claim 12~~ is to be administered to a subject in need thereof.

~~18.~~ ~~A method of preventing, inhibiting, reducing, or mitigating acute or chronic graft vs host disease comprising administering to a subject in need thereof an effective amount of the~~~~17.~~
The expanded population of NK cells of claim 9 or 10 or ~~11 or~~ the composition of claim ~~12.~~

~~19.~~ ~~A11 for use method of~~ preventing, inhibiting, reducing, or mitigating viral reactivation, ~~wherein comprising administering to a subject in need thereof~~ an effective amount of the expanded population of NK cells ~~of claim 10 or 11~~ or the composition ~~of claim 12 is to be administered to a subject in need thereof.~~

~~20.~~ ~~A18.~~ The expanded population of NK cells of claim 9 or 10 or the composition of claim 11 for use in ~~method of~~ preventing, inhibiting, reducing, or mitigating opportunistic infections, ~~wherein comprising administering to a subject in need thereof~~ an effective amount of the expanded populations of NK cells ~~of claim 10 or 11~~ or the composition ~~of claim 12 is to be administered to a subject in need thereof.~~

~~2419.~~ The expanded population of NK cells of claim ~~109~~ or ~~110~~, 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.

~~2220.~~ 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 Fc domain bound to an external surface of the feeder cell or engineered particle.~~

~~23~~an inverted Fc domain bound to an external surface of the feeder cell or engineered PM particle.

~~21.~~ The method of claim ~~2220~~, wherein the NK cell expanding composition comprises at least one feeder cell having a membrane bound Fc domain.

~~2422.~~ The method of claim ~~2220~~, 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.

~~2523.~~ The method of claim ~~2220~~, further comprising obtaining a population of expanded NK cells having increased cytotoxicity compared to the initial population of NK cells.