COMPOSITIONS AND METHODS FOR IMMUNOTHERAPY

CROSS-REFERENCE

[0001] This application claims priority to C.N. Patent Application No. 201811501797.8, filed December 07, 2018; PCT Application No. PCT/CN2019/073252, filed January 25, 2019; C.N. Patent Application No. 201910297171.8, filed April 12, 2019; and PCT Application No. PCT/CN2019/097996, filed July 26, 2019, each of which is entirely incorporated herein by reference.

BACKGROUND

[0002] Adoptive T cell therapy, as an example of immunotherapy, involves the isolation and ex vivo expansion of tumor specific T cells to achieve greater number of T cells than what could be obtained by vaccination alone. The tumor specific T cells are then infused into patients with cancer to provide their immune systems the ability to overwhelm remaining tumor via T cells which can attack and kill the cancer. While there are many forms of adoptive T cell therapy for cancer, they by and large suffer from various deficiencies. Amongst them are cellular exhaustion, long preparation time, and ineffective compositions of engineered cells.

SUMMARY

[0003] In view of the foregoing, there exists a considerable need for alternative compositions and methods to carry out immunotherapy. The compositions and methods of the present disclosure address this need, and provide additional advantages as well. In particular, the various aspects of the disclosure provide systems for immune cell regulation.

[0003a] In one aspect, provided herein is a population of cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) or an engineered T cell receptor (TCR), wherein said CAR or said engineered TCR comprises a ligand binding domain specific for a ligand,

wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and

wherein said population is further characterized in that:

(i) central memory T cells (TCM) in said population are at least 1-fold more abundant than effector memory T cells (TEM) in said population; and/or

(ii) at least 15% of said population of cells are stem memory T cells (TSCM)~~use of a population of immune cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell~~

~~therapy for administration, wherein said population of immune cells comprising said engineered immune cells is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and wherein said population is further characterized in that: central memory T cells (TCM) in said population are more abundant than effector memory T cells (TEM)~~.

~~**[0003b]** In one aspect, provided herein is a use of a population of immune cells comprising engineered immune cells expressing chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cells is to be~~

~~infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex-vivo expansion for 1 or more weeks, and wherein at least 15% of the population are stem memory T cells (TSCM)~~

[0003b] In one aspect, provided herein is a use of the population as described herein, in the manufacture of a medicament for the treatment of cancer.

~~**[0003c]** In one aspect, provided herein is a method of producing a population of engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR), comprising: (a) activating a population of cells comprising immune cells with an activation moiety; and concurrently; and (b) introducing a polynucleotide encoding for at least said CAR and/or said TCR, thereby producing a population of engineered immune cells expressing said CAR and/or said TCR, wherein said CAR comprises (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain;~~

~~wherein (a) and (b) are performed for no more than 24 hours.~~

~~**[0003d]**In one aspect, provided herein is a point-of-care facility comprising a cell infusion equipment configured to: infuse a population of immune cells that comprises engineered immune cells that have not been subject to ex-vivo expansion for 1 or more weeks, wherein said population of immune cells is further characterized in that: cell memory T cells (TCM) in said population are more abundant than effector memory T cells (TEM); or wherein at least 15% of said population are stem memory T cells (TSCM).~~

~~**[0003e]** In one aspect, provided herein is a population of cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or a T cell receptor (TCR), wherein said population is further characterized in that: (i) central memory T cells (TCM) in said population are more abundant than effector memory T cells (TEM); and/or (ii) at least 15% of said population of cells are stem memory T cells (TSCM), and wherein said CAR comprises (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain.~~

~~**[0003f]** In one aspect, provided herein is a use of a population of no more than about $1x10^6$ engineered immune cells expressing chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the medicament is to be infused to the subject, wherein the engineered immune cells have not been subject to ex-vivo expansion for 1 or more weeks.~~

~~**[0003g]** In one aspect, provided herein is a use of a population of immune cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cells is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex-vivo expansion for 1 or more weeks, and wherein said population is further~~

~~characterized in that a greater proliferation is observed in said population as compared to the proliferation of a comparable population that undergoes ex vivo expansion for 1 or more weeks.~~

~~**[0003h]** In one aspect, provided herein is a use of a population of immune cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cells is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and wherein said population is further characterized in that a greater cytotoxicity is observed in said population as compared to the cytotoxicity of a comparable population that undergoes ex vivo expansion for 1 or more weeks.~~

~~**[0003i]** In one aspect, provided herein is a use of a population of immune cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cell is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and wherein said population is further characterized in that a greater bone marrow migration is observed of said population as compared to the bone marrow migration of a comparable population that undergoes ex vivo expansion for 1 or more weeks.~~

[0004] In an example, the present disclosure provides a method of administering a cell therapy comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR), comprising: infusing a population of immune cells comprising the engineered immune cells into a subject in need thereof, wherein the engineered immune cells have not been subject to ex vivo expansion for no more than 2 weeks or 1 week, and wherein the population is further characterized in that: central memory T cells (TCM) in the population are more abundant than effector memory T cells (TEM). In some examples, the engineered immune cells have been subject to ex vivo expansion less than 13, 12, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 days. In some examples, the engineered immune cells have been subject to ex vivo expansion less than 6, 5, 4, 3, 2, or 1 days. In some examples, the engineered immune cells have been subject to ex vivo expansion less than 5 days. In some examples, the engineered immune cells have been subject to ex vivo expansion less than 72, 48, 36, 32, or 24 hours. In some examples, the TCM are $CD45RO^{+}CD62L^{+}$. In some examples, the TEM are CD45RO+CD62L-. In some examples, a population is further characterized in that it is less abundant in PD1 and LAG3. In some examples, reduced exhaustion of cells in a population is

the cytotoxicity of a comparable population that undergoes ex vivo expansion for no more than 2 weeks or 1 week. In an example, the cytotoxicity is at least 0.1 fold, 0.2 fold, 0.3 fold, 0.4 fold, 0.5 fold, 0.6 fold, 0.7 fold, 0.8 fold, 0.9 fold, 1.0 fold, 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold or 10 fold higher in the population as compared to the comparable population that undergoes an ex vivo expansion for no more than 2 weeks or 1 week when the population and the comparable population contact a target.

[0029] Provided herein is a method of administering a cell therapy comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR), comprising: infusing a population of immune cells comprising the engineered immune cells into a subject in need thereof, wherein the engineered immune cells have not been subject to ex vivo expansion for no more than 2 weeks or 1 week, and wherein the population is further characterized in that a greater bone marrow migration is observed of the population as compared to the bone marrow migration of a comparable population that undergoes ex vivo expansion for no more than 2 weeks or 1 week. In some examples, the bone marrow migration is at least 1 fold higher in the population as compared to the comparable population that undergoes ex vivo expansion for no more than 2 weeks or 1 week when the population and the comparable population contact a target. In an example, the population is further characterized in that: central memory T cells (TCM) in the population are more abundant than effector memory T cells (TEM). In an example, TCM are CD45RO+CD62L+. In an example, TEM are CD45RO+CD62L-. In an example, engineered immune cells have been subject to ex vivo expansion less than 5 days. In an example, the engineered immune cells have been subject to ex vivo expansion less than 4 days. In an example, the engineered immune cells have been subject to ex vivo expansion less than 72 hours. In an example, the engineered immune cells have been subject to ex vivo expansion less than 48 hours. In an example, the engineered immune cells have been subject to ex vivo expansion less than 24 hours. In an example, the target is a cancer cell, a ligand of the TCR or the CAR, or a chemokine. In some examples, the chemokine is stromal cell-derived factor-1 (SDF-1), and wherein the SDF-1 is expressed in bone marrow of the subject. In some cases, the population has a greater percentage of CXCR4 positive cells as compared to the comparable population that undergoes the ex vivo expansion for no more than 2 weeks or 1 week. In an example, the population has a greater median percentage of CXCR4 positive cells that is at least 10% greater as compared to the median percentage of CXCR4 positive cells expressed by the comparable population that undergoes the ex vivo expansion for no more than 2 weeks or 1 week. In an example, the population has a greater density of CXCR4 on a

cell surface of the CXCR4 positive cells as compared to the density of CXCR4 on the cell surface of the comparable population that undergoes an ex vivo expansion for no more than 2 weeks or 1 week. In an example, the density is measured by evaluating a mean fluorescence intensity (MFI) of CXCR4 on the cell surface of the CXCR4 positive cells. In an example, the cytotoxicity is measured in an in vivo assay. In some cases, a reduced cancer burden is observed in the subject administered the population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex vivo expansion for no more than 2 weeks or 1 week. In an example, the cancer burden is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% in the subject treated with the population as compared to the comparable subject administered a comparable population that undergoes an ex vivo expansion for no more than 2 weeks or 1 week. In an example, the cancer burden is reduced by at least 0.5 fold, 1 fold, 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, or 10 fold in the subject treated with the population as compared to the comparable subject administered a comparable population that undergoes an ex vivo expansion for no more than 2 weeks or 1 week. In an example, complete remission (CR) is observed in the subject administered the population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex vivo expansion for no more than 2 weeks or 1 week. In some examples, a partial response (PR) is observed in the subject administered the population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex vivo expansion for no more than 2 weeks or 1 week. In an example, the population comprises at most $1x10^4$ cells per kg/body weight of engineered immune cells. In an example, the population comprises from about $1x10^4$ cells per kg/body weight of engineered immune cells to at most about $1x10^5$ cells per kg/body weight of engineered immune cells. In some cases, the engineered immune cells are T cells, NK cells, and/or NKT cells. In some cases, the TCR comprises (i) a ligand binding domain specific for a ligand and (ii) a transmembrane domain. In an example, the CAR comprises: (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain. In an example, the ligand of the TCR or CAR is VEGFR-2, CD19, CD20, CD30, CD22, CD25, CD28, CD30, CD33, CD52, CD56, CD80, CD86, CD81, CD123, cd171, CD276, B7H4, BCMA, CD133, EGFR, GPC3, PMSA, CD3, CEACAM6, c-Met, EGFRvIII, ErbB2, ErbB3, HER3, ErbB4 / HER-4, EphA2, IGF1R, GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, CD44V6, CEA, CA125, CD151, CTLA-4, GITR, BTLA, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2, HVEM, MAGE-A, mesothelin, NY-ESO-1, RANK, RORl, TNFRSF4, CD40, CD137,

TWEAK-R, LTPR, LIFRP, LRP5, MUC1, TCRα, TCRβ, TLR7, TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, CD79, Notch-1-4, and/or Claudin18.2. In an example, the transmembrane domain is from CD8α, CD4, CD28, CD45, PD-1 and/or CD152. In an example, the intracellular signaling domain is from CD3ζ, CD28, CD54 (ICAM), CD134 (OX40), CD137 (4-1BB), GITR, CD152 (CTLA4), CD273 (PD-L2), CD274 (PD-L1), DAP10 and/or CD278 (ICOS). In some cases, the CAR comprises at least 2 intracellular signaling domains. In some cases, the CAR comprises at least 3 intracellular signaling domains. In some cases, the CAR further comprises a hinge. A hinge can be from CD28, IgG1 and/or CD8α. In an example, the engineered immune cells are from peripheral blood, cord blood, bone marrow, and/or induced pluripotent stem cells. In some cases, the engineered immune cells are from peripheral blood, and the peripheral blood cells are T cells.

INCORPORATION BY REFERENCE

[0030] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0032] **Figure 1** shows multiplicity of infection (MOI) vs. percent CAR-positive ratio in F-CART cells.

[0033] **Figure 2** shows a comparison between percent CAR-positive expression of conventional-CART (C-CART) and fast-CART (F-CART) generated cells.

[0034] **Figure 3** shows a phenotypic analysis using flow cytometry of control (starting material) and F-CART cells.

[0035] **Figure 4A** shows a linear graphical representation of cell proliferation of anti-CD19 F-CART vs. anti-CD19 C-CART cells. **Figure 4B** shows fold proliferation of anti-CD19 F-CART vs. anti-CD19 C-CART cells.

[0036] **Figure 5** depicts *in vitro* killing efficacy over 50 hours of anti-CD19 F-CART vs. anti-CD19 C-CART cells.

CLAIMS

WHAT IS CLAIMED IS:

1. A population of cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) or an engineered T cell receptor (TCR), wherein said CAR or said engineered TCR comprises a ligand binding domain specific for a ligand,

wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and

wherein said population is further characterized in that:

(i) central memory T cells (TCM) in said population are at least 1-fold more abundant than effector memory T cells (TEM) in said population; and/or

(ii) at least 15% of said population of cells are stem memory T cells (TSCM).

42. The population of claim 1, wherein said population is characterized to exhibit (i) and/or (ii) after binding of the ligand to the ligand binding domain.

~~1. Use of a population of immune cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cells is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and wherein said population is further characterized in that: central memory T cells (TCM) in said population are more abundant than effector memory T cells (TEM).~~

~~2. The use of claim 1, wherein said engineered immune cells have been subject to ex vivo expansion less than 6 days.~~

~~3. The use of any one of claims 1-2, wherein said engineered immune cells have been subject to ex vivo expansion less than 5 days.~~

43. The population of any one of the preceding claims~~use of any one of claims 1-3~~, wherein said engineered immune cells have been subject to ex vivo expansion less than 72 hours.

54. The population of any one of the preceding claims~~use of any one of claims 1-4~~, wherein said engineered immune cells have been subject to ex vivo expansion less than 48 hours.

65. The population of any one of the preceding claims~~use of any one of claims 1-5~~,

wherein said engineered immune cells have been subject to ex vivo expansion less than 24 hours.

~~7~~6. The population of any one of the preceding claims~~use of any one of claims 1-6~~, wherein said TCM are CD45RO+CD62L+.

~~8~~7. The population of any one of the preceding claims~~use of any one of claims 1-7~~, wherein said TEM are CD45RO+CD62L-.

~~9~~8. The population of any one of the preceding claims~~use of any one of claims 1-8~~, wherein said population is further characterized in that reduced exhaustion of cells in said population is observed as compared to the exhaustion of cells in a ~~comparable~~ control population that undergoes an ex vivo expansion for 1 or more weeks.

~~10~~9. The ~~use~~ population of claim ~~9~~8, wherein said reduced exhaustion of said population is characterized in that said population comprises less cells expressing PD1 and LAG3.

~~11~~10. The population of any one of the preceding claims~~use of any one of claims 1-10~~, wherein said engineered immune cells are T cells~~, NK cells, and/or NKT cells~~.

~~12. The use of any one of claims 1-11, wherein said TCR comprises (i) a ligand binding domain specific for a ligand and (ii) a transmembrane domain.~~

~~13~~11. The population of any one of the preceding claims~~use of any one of claims 1-12~~, wherein said CAR further comprises~~: (i) a ligand binding domain specific for a ligand, (ii)~~ a transmembrane domain, and ~~(iii)~~ an intracellular signaling domain.

~~14~~12. The population of any one of the preceding claims~~use of any one of claims 12-13~~, wherein said ligand ~~of said TCR or CAR~~ is VEGFR-2, CD19, CD20, CD30, CD22, CD25, CD28, CD30, CD33, CD52, CD56, CD80, CD86, CD81, CD123, cd171, CD276, B7H4, BCMA, CD133, EGFR, GPC3, PMSA, CD3, CEACAM6, c-Met, EGFRvIII, ErbB2, ErbB3, HER3, ErbB4 / HER-4, EphA2, IGF1R, GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, CD44V6, CEA, CA125, CD151, CTLA-4, GITR, BTLA, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2, HVEM, MAGE-A, mesothelin, NY-ESO-1, RANK, RORl, TNFRSF4, CD40, CD137, TWEAK-R, LTPR, LIFRP, LRP5, MUC1, TCRα, TCRβ, TLR7, TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, CD79, Notch-1-4, and/or Claudin18.2.

~~15~~13. The population of claim 11 or 12~~use of any one of claims 13-14~~, wherein said transmembrane domain is from CD8α, CD4, CD28, CD45, PD-1 and/or CD152.

~~16~~14. The population of any one of claims 11-13~~use of any one of claims 13-15~~, wherein

said intracellular signaling domain is from CD3ζ, CD28, CD54 (ICAM), CD134 (OX40), CD137 (4-1BB), GITR, CD152 (CTLA4), CD273 (PD-L2), CD274 (PD-L1), DAP10 and/or CD278 (ICOS).

~~17~~15. The population of any one of claims 11-14~~use of any one of claims 13-16~~, wherein said CAR comprises at least 2 intracellular signaling domains.

~~18~~16. The population of any one of claims 11-15~~use of any one of claims 13-17~~, wherein said CAR comprises at least 3 intracellular signaling domains.

~~19~~17. The population of any one of the preceding claims~~use of any one of claims 13-18~~, wherein said CAR further comprises a hinge.

~~20~~18. The population of claim 17~~use of claim 19~~, wherein said hinge is from CD28, IgG1 and/or CD8α.

~~21~~19. The population of any one of the preceding claims~~use of any one of claims 13-20~~, wherein said CAR further comprises a signal peptide, and wherein said signal peptide is derived from IgG1, GM-CSF and/or CD8α.

~~22~~20. The population of any one of the preceding claims~~use of any one of claims 1-21~~, wherein said engineered immune cells are from peripheral blood, cord blood, bone marrow, and/or induced pluripotent stem cells.

~~23~~21. The population of claim 20~~use of claim 22~~, wherein said engineered immune cells are from peripheral blood, and wherein said peripheral blood cells are T cells.

~~24. The use of any one of claims 1-23, wherein a greater memory and/or stemness is observed in said population as compared to a comparable population that undergoes an ex vivo expansion for 1 or more weeks.~~

~~25~~22. The population of any one of the preceding claims~~use of claim 24~~, ~~wherein there are~~comprising at least 2 fold more TCM as compared to TEM.

~~26~~23. The population of any one of the preceding claims~~use of claim 24~~, ~~wherein there are~~comprising at least 4 fold more TCM as compared to TEM.

~~27. The use of any one of claims 1-26, wherein said infusion is intravenous.~~

~~28. The use of any one of claims 1-27, wherein said administration comprises infusion of from about 1 x10^4/kg body weight of engineered immune cells.~~

~~29. The use of any one of claims 1-28, wherein said administration comprises infusion of from about 3 x10^5/kg body weight of engineered immune cells.~~

~~30. The use of any one of claims 1-29, wherein at least 10% of said immune cells express said CAR and/or said TCR.~~

~~31. The use of any one of claims 1-29, wherein at least 40% of said immune cells express said CAR and/or said TCR.~~

~~32. The use of any one of claims 1-31, wherein a secondary agent is to be further administered to said subject in need thereof.~~

~~33. The use of claim 32, wherein said secondary agent is a therapeutically effective amount of an immunostimulant, immunosuppressive, anti-fungal, antibiotic, anti-angiogentic, chemotherapeutic, radioactive, and/or an antiviral.~~

~~34. The use of claim 33, wherein said immunostimulant is IL-2.~~

~~35. The use of any one of claims 1 to 34, wherein peripheral blood is to be further obtained from said subject in need thereof after said administration.~~

~~36. The use of claim 35, wherein said engineered immune cells in said subject are quantified from said peripheral blood.~~

~~37. The use of claim 35, wherein a level of a growth factor in said subject is quantified.~~

~~38. The use of claim 37, wherein said growth factor is selected from the group consisting of IL-10, IL-6, tumor necrosis factor α (TNF-α), IL-1β, IL-2, IL-4, IL-8, IL-12, and/or IFN-γ.~~

~~39. The use of any one of claims 1-38, comprising repeating said infusion.~~

~~40~~24. The population of claim 3~~use of any one of claims 1-39~~, wherein said population of immune cells is allogeneic to said subject in need thereof.

~~41~~25. The population of claim 3~~use of any one of claims 1-39~~, wherein said population of immune cells is autologous to said subject in need thereof.

~~42. The use of any one of claims 1-41, wherein said subject has cancer.~~

~~43. The use of claim 42, wherein said cancer is hematological.~~

~~44. The use of claim 43, wherein said hematological cancer is leukemia, myeloma, lymphoma, and/or a combination thereof.~~

~~45. The use of any one of claims 42-44, wherein said leukemia is chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia (B-ALL), T-cell acute lymphoblastic leukemia (T-ALL), and/or acute lymphoblastic leukemia (ALL).~~

~~46. The use of any one of claims 43-44, wherein said lymphoma is mantle cell lymphoma (MCL), Hodgkin's lymphoma, T-cell lymphoma, and/or non-Hodgkin's lymphoma.~~

~~47. The use of claim 42, wherein said cancer is solid.~~

~~48. The use of claim 47, wherein said solid cancer is selected from the group comprising: nephroblastoma, Ewing's sarcoma, neuroendocrine tumor, glioblastoma, neuroblastoma,~~

~~melanoma, skin cancer, breast cancer, colon cancer, rectal cancer, prostate cancer, liver cancer, kidney cancer, pancreatic cancer, lung cancer, biliary tract cancer, cervical cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, medullary thyroid carcinoma, ovarian cancer, glioma, or bladder cancer.~~

~~49. The use of any one of claims 1-48, wherein said subject in need thereof has a BCR-ABL mutation, and wherein said mutation is in a BCR-ABL kinase domain.~~

~~50. The use of claim 49, wherein said subject in need thereof has a T315I and/or V299L mutation in said BCR-ABL kinase domain.~~

~~51. The use of any one of claims 1-50, wherein said subject shows resistance to a tyrosine kinase inhibitor.~~

~~52. The use of any one of claims 1-51, wherein said subject has a tumor or is susceptible of having a tumor after chemotherapy.~~

~~53. The use of any one of claims 1-52, wherein said subject was pre-treated with chemotherapy prior to said administration.~~

~~54. The use of claim 53, wherein said chemotherapy comprises an administration of fludarabine, cyclophosphamide and/or cytarabine.~~

~~55. The use of any one of claims 1-54, wherein said subject has minimal residual disease (MRD), and wherein said MRD is acute lymphoblastic leukemia.~~

~~56~~26. The population of any one of the preceding claims~~use of any one of claims 1-55~~, wherein said population is further characterized in that a greater proliferation, cytotoxicity, and/or bone marrow migration is observed in said population as compared to the proliferation, cytotoxicity, and/or bone marrow migration of a ~~comparable~~ control population that undergoes an ex vivo expansion for 1 or more weeks.

~~57~~27. The population of claim 26~~use of claim 56~~, wherein said cytotoxicity is at least 0.1~~, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2.0, 2.5, or 3.0~~ fold higher in said population as compared to a ~~comparable~~ control population that undergoes an ex vivo expansion for 1 or more weeks when said population and ~~comparable~~ control population contact a target.

~~58~~28. The population of claim 26~~use of claim 56~~, wherein said proliferation is at least 1 fold higher in said population as compared to a ~~comparable~~ control population that undergoes an ex vivo expansion for 1 or more weeks when said population and ~~comparable~~ control population contact a target.

~~59~~29. The population of claim 26~~use of claim 56~~, wherein said bone marrow migration is at

least 0.1 fold~~, 0.2 fold, 0.3 fold, 0.4 fold, 0.5 fold, 0.6 fold, 0.7 fold, 0.8 fold, 0.9 fold, 1 fold, 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold or 10 fold~~ higher in said population as compared to a ~~comparable~~ control population that undergoes an ex vivo expansion for 1 or more weeks when said population and ~~comparable~~ control population contact a target.

~~60. The use of claim 59, wherein said target is a cancer cell, a ligand of said TCR or said CAR, or a chemokine.~~

~~61. The use of claim 60, wherein said chemokine is stromal cell-derived factor-1 (SDF-1), and wherein said SDF-1 is expressed in bone marrow of said subject.~~

~~62~~30. The population of any one of the preceding claims~~use of any one of claims 56-61~~, wherein said population has a greater percentage of CXCR4 positive cells as compared to a ~~comparable~~ control population that undergoes an ex vivo expansion for 1 or more weeks.

~~63~~31. The population of claim 30~~use of claim 62~~, wherein said population has a greater median percentage of CXCR4 positive cells that is at least 10% greater as compared to the median percentage of CXCR4 positive cells expressed by ~~a~~ the ~~comparable~~ control population that undergoes ~~an~~ the ex vivo expansion for 1 or more weeks.

~~64~~32. The population of claim 31~~use of claim 63~~, wherein said population has a greater density of CXCR4 on a cell surface of said CXCR4 positive cells as compared to the density of CXCR4 on the cell surface of ~~a~~ the ~~comparable~~ control population that undergoes ~~an~~ the ex vivo expansion for 1 or more weeks.

~~65. The use of claim 64, wherein said density is measured by evaluating a mean fluorescence intensity (MFI) of CXCR4 on said cell surface of said CXCR4 positive cells.~~

~~66. The use of claim 56, wherein said cytotoxicity is measured in an in vivo assay.~~

~~67. The use of claim 66, wherein a reduced cancer burden is observed in said subject when said subject is administered said population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex vivo expansion for 1 or more weeks.~~

~~68. The use of claim 67, wherein said cancer burden is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% in said subject treated with said population as compared to said comparable subject administered a comparable population that undergoes an ex vivo expansion for 1 or more weeks.~~

~~69. Use of a population of immune cells comprising engineered immune cells expressing chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the~~

manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cells is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex-vivo expansion for 1 or more weeks, and wherein at least 15% of the population are stem memory T cells (TSCM).

70. The use of claim 69, wherein at least 20% of the population are TSCM.

71. The use of any one of claims 69-70, wherein at least 25% of the population are TSCM.

72. The use of any one of claims 69-71, wherein at least 30% of the population are TSCM.

73. The use of any one of claims 69-72, wherein at least 50% of the population are TSCM.

74. The use of any one of claims 69-73, wherein said TSCM are CD45RO-CD62L+.

75. The use of any one of claims 69-74, wherein said engineered immune cells have been subject to ex-vivo expansion less than 5 days.

76. The use of any one of claims 69-75, wherein said engineered immune cells have been subject to ex-vivo expansion less than 72 hours.

77. The use of any one of claims 69-76, wherein said engineered immune cells have been subject to ex-vivo expansion less than 48 hours.

78. The use of any one of claims 69-77, wherein said engineered immune cells have been subject to ex-vivo expansion less than 24 hours.

79. The use of any one of claims 69-78, wherein said TCR comprises (i) a ligand binding domain specific for a ligand and (ii) a transmembrane domain.

80. The use of any one of claims 69-79, wherein said CAR comprises: (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain.

81. The use of any one of claims 79-80, wherein said ligand of said TCR or CAR is VEGFR-2, CD19, CD20, CD30, CD22, CD25, CD28, CD30, CD33, CD52, CD56, CD80, CD86, CD81, CD123, cd171, CD276, B7H4, BCMA, CD133, EGFR, GPC3, PMSA, CD3, CEACAM6, c-Met, EGFRvIII, ErbB2, ErbB3, HER3, ErbB4 / HER-4, EphA2, IGF1R, GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, CD44V6, CEA, CA125, CD151, CTLA-4, GITR, BTLA, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2, HVEM, MAGE-A, mesothelin, NY-ESO-1, RANK, RORl, TNFRSF4, CD40, CD137, TWEAK-R, LTPR, LIFRP, LRP5, MUC1, TCRα, TCRβ, TLR7,

~~TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, CD79, Notch-1-4, and/or Claudin18.2.~~

~~82. The use of any one of claims 80-81, wherein said transmembrane domain is from CD8α, CD4, CD28, CD45, PD-1 and/or CD152.~~

~~83. The use of any one of claims 80-82, wherein said intracellular signaling domain is from CD3ζ, CD28, CD54 (ICAM), CD134 (OX40), CD137 (4-1BB), GITR, CD152 (CTLA4), CD273 (PD-L2), CD274 (PD-L1), DAP10 and/or CD278 (ICOS).~~

~~84. The use of any one of claims 80-83, wherein said CAR comprises at least two intracellular signaling domains.~~

~~85. The use of any one of claims 80-84, wherein said CAR comprises at least 3 intracellular signaling domains.~~

~~86. The use of any one of claims 80-85, wherein said CAR further comprises a hinge.~~

~~87. The use of claim 19, wherein said hinge is from CD28, IgG1 and/or CD8α.~~

~~88. The use of any one of claims 80-87, wherein said CAR further comprises a signal peptide, and wherein said signal peptide is derived from IgG1, GM-CSF and/or CD8α.~~

~~89. The use of any one of claims 69-88, wherein said engineered immune cells are from peripheral blood, cord blood, bone marrow, and/or induced pluripotent stem cells.~~

~~90. The use of claim 89, wherein said engineered immune cells are from peripheral blood, and wherein said peripheral blood cells are T cells, NK cells, and/or NKT cells.~~

~~91. The use of any one of claims 69-90, wherein said infusion is intravenous.~~

~~92. The use of any one of claims 69-91, wherein said administration comprises infusion of from about 1 x10^4/kg body weight of engineered immune cells.~~

~~93. The use of any one of claims 69-92, wherein said administration comprises infusion of from about 3 x10^5/kg body weight of engineered immune cells.~~

~~94. The use of any one of claims 69-93, wherein at least 10% of said immune cells express said CAR and/or said TCR.~~

~~95. The use of any one of claims 69-94, wherein at least 40% of said immune cells express said CAR and/or said TCR.~~

~~96. The use of any one of claims 69-95, wherein a secondary agent is to be further administered to said subject in need thereof.~~

~~97. The use of claim 96, wherein said secondary agent is a therapeutically effective amount of an immunostimulant, immunosuppressive, anti-fungal, antibiotic, anti-angiogentic, chemotherapeutic, radioactive, and/or an antiviral.~~

~~98. The use of claim 97, wherein said immunostimulant is IL-2.~~

99. The use of any one of claims 69 to 98, wherein peripheral blood is to be further obtained from said subject in need thereof after said infusion.

100. The use of claim 99, wherein said engineered immune cells from said peripheral blood are quantified.

101. The use of claim 100, wherein a level of a cytokine is quantified.

102. The use of claim 101, wherein said cytokine is IL-10, IL-6, tumor necrosis factor α (TNF-α), IL-1β, IL-2, IL-4, IL-8, IL-12, and/or IFN-γ.

103. The use of any one of claims 69-102, comprising repeating said infusion.

104. The use of any one of claims 69-103, wherein said population is further characterized in that reduced exhaustion of cells in said population is observed as compared to the exhaustion of cells in a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.

105. The use of claim 104, wherein said reduced exhaustion of said population is characterized in that said population comprises less cells expressing PD1 and LAG3.

106. The use of any one of claims 69-105, wherein said population is further characterized in that a greater proliferation, cytotoxicity, and/or bone marrow migration is observed in said population as compared to the proliferation, cytotoxicity, and/or bone marrow migration of a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.

107. The use of claim 106, wherein said cytotoxicity is at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2.0, 2.5, or 3.0 fold higher in said population as compared to a comparable population that undergoes an ex-vivo expansion for 1 or more weeks when said population and comparable population contact a target.

108. The use of claim 106, wherein said proliferation is at least 0.5 fold, 1 fold, 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 50 fold, 100 fold, 500 fold, 1000 fold, 5000 fold, or 10000 fold higher in said population as compared to a comparable population that undergoes an ex-vivo expansion for 1 or more weeks when said population and comparable population contact a target.

109. The use of claim 106, wherein said bone marrow migration is at least 0.1 fold, 0.2 fold, 0.3 fold, 0.4 fold, 0.5 fold, 0.6 fold, 0.7 fold, 0.8 fold, 0.9 fold, 1 fold, 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold or 10 fold higher in said population as compared to a comparable population that undergoes an ex-vivo expansion for 1 or more weeks when said population and comparable population contact a target.

~~110. The use of claim 109, wherein said target is a cancer cell or a chemokine.~~

~~111. The use of claim 110, wherein said chemokine is stromal cell-derived factor-1 (SDF-1), and wherein said SDF-1 is expressed in bone marrow of said subject.~~

~~112. The use of any one of claims 109-111, wherein said population has a greater percentage of CXCR4 positive cells as compared to a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~113. The use of claim 112, wherein said population has a greater median percentage of CXCR4 positive cells that is at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90% or 100% greater as compared to the median percentage of CXCR4 positive cells expressed by a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~114. The use of claim 113, wherein said population has a greater density of CXCR4 on a cell surface of said CXCR4 positive cells as compared to the density of CXCR4 on the cell surface of a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~115. The use of claim 114, wherein said density is measured by evaluating a mean fluorescence intensity (MFI) of CXCR4 on said cell surface of said CXCR4 positive cells.~~

~~116. The use of claim 106, wherein said cytotoxicity is measured in an in-vivo assay.~~

~~117. The use of claim 116, wherein a reduced cancer burden is observed in said subject when said subject is administered said population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~118. The use of claim 117, wherein said cancer burden is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% in said subject treated with said population as compared to said comparable subject administered a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~119~~33. The population of claim 1, wherein the population is prepared by subjecting a source of immune cells to the steps of:~~A method of producing a population of engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR), comprising:~~

(a) ~~activating a population of cells comprising immune cells with~~activation by an activation moiety; and ~~concurrently; and~~

(b) ~~introducing~~ introduction of a polynucleotide encoding for at least said CAR and/or

said TCR, ~~thereby producing a population of engineered immune cells expressing said CAR and/or said TCR, wherein said CAR comprises (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain~~;

wherein the step of (a) and (b) are carried out concurrently~~performed for no more than 24 hours~~.

~~120. The method of claim 119, wherein said activation moiety binds: a CD3/T cell receptor complex and/or provides costimulation.~~

~~121~~34. The population of claim 33~~method of claim 120~~, wherein said activation moiety comprises ~~is any one of~~ anti-CD3 antibody and/or anti-CD28 antibody.

~~122~~35. The population of claim 34~~method of any one of claims 119-121~~, wherein said activation moiety is conjugated to a solid phase.

~~123. The method of any one of claims 122, wherein said solid phase is at least one of a bead, plate, and/or matrix.~~

~~124~~36. The population of claim 35~~method of claim 123~~, wherein said solid phase is a bead.

~~125~~37. The population of claim 33~~method of any one of claims 119-124~~, wherein said ~~introducing comprising transducing~~ introduction comprises transduction of said population of cells with a viral vector and/or a transposon vector.

~~126. The method of claim 125, wherein said viral vector is a retroviral vector, a lentiviral vector and/or an adeno-associated viral vector.~~

~~127. The method of claim 125, wherein said transposon vector is a sleeping beauty vector and/or a PiggyBac vector.~~

~~128. The method of anyone of claims 119-127, wherein step (a) and (b) are performed within 72 hours.~~

~~129. The method of anyone of claims 119-127, wherein step (a) and (b) are performed within 48 hours.~~

~~130~~38. The population of claim 33~~method of anyone of claims 119-127~~, wherein the steps of (a) and (b) are performed within ~~24~~ 5 hours.

~~131~~39. The population of claim 33~~method of anyone of claims 119-127~~, wherein the steps of (a) and (b) are performed within 3 hours.

~~132~~40. The population of claim 33~~method of anyone of claims 119-127~~, wherein the steps of (a) and (b) are performed within 1 hour.

41. The population of claim 33, wherein the population is to be administered to a subject

in need thereof without further ex vivo expansion following the steps of (a) and (b).

~~133. The method of anyone of claims 119-127, wherein step (a) and (b) are performed at the same time.~~

~~134. The method of any one of claims 125-133, wherein said transducing comprises adding an infective agent.~~

~~135. The method of claim 135, wherein said infective agent is polybrene.~~

~~136. The method of any one of claims 119-135, wherein said population of cells is seeded at a density from about 10^4/mL to about 10^8/mL.~~

~~137. The method of any one of claims 125-136, wherein said viral vector is plated at a mean of infectivity (MOI) from about 0.1 to about 10.~~

~~138. The method of any one of claims 119-137, further comprising stimulating said population of cells with a cytokine.~~

~~139. The method of claim 138, wherein said cytokine is IL2, IL7, IL15 and/or IL21.~~

~~140. The method of any one of claims 119-139, wherein said TCR comprises (i) a ligand binding domain specific for a ligand and (ii) a transmembrane domain.~~

~~141. The method of any one of claims 119-140, wherein said CAR comprises: (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain.~~

~~142. The method of any one of claims 140-141, wherein said ligand of said TCR or CAR is VEGFR-2, CD19, CD20, CD30, CD22, CD25, CD28, CD30, CD33, CD52, CD56, CD80, CD86, CD81, CD123, cd171, CD276, B7H4, BCMA, CD133, EGFR, GPC3, PMSA, CD3, CEACAM6, c-Met, EGFRvIII, ErbB2, ErbB3, HER3, ErbB4 / HER-4, EphA2, IGF1R, GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, CD44V6, CEA, CA125, CD151, CTLA-4, GITR, BTLA, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2, HVEM, MAGE-A, mesothelin, NY-ESO-1, RANK, RORl, TNFRSF4, CD40, CD137, TWEAK-R, LTPR, LIFRP, LRP5, MUC1, TCRα, TCRβ,, TLR7, TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, CD79, Notch-1-4, and/or Claudin18.2.~~

~~143. The method of any one of claims 140-142, wherein said transmembrane domain is from CD8α, CD4, CD28, CD45, PD-1 and/or CD152.~~

~~144. The method of any one of claims 140-143, wherein said intracellular signaling domain is from CD3ζ, CD28, CD54 (ICAM), CD134 (OX40), CD137 (4-1BB), GITR, CD152 (CTLA4), CD273 (PD-L2), CD274 (PD-L1), DAP10 and/or CD278 (ICOS).~~

~~145. The method of any one of claims 141-144, wherein said CAR comprises at least two~~

~~intracellular signaling domains.~~

~~146. The method of any one of claims 141-145, wherein said CAR comprises at least 3 intracellular signaling domains.~~

~~147. The method of any one of claims 141-146, wherein said CAR further comprises a hinge.~~

~~148. The method of claim 147, wherein said hinge is from CD28, IgG1 and/or CD8α.~~

~~149. The method of any one of claims 119-148, wherein said method further comprises enriching for said immune cells prior to said engineering.~~

~~150. The method of claim 149, wherein said enriching comprises collecting a monocyte fraction.~~

~~151. The method of claim 149, wherein said enriching comprises sorting said immune cells from a monocytes fraction.~~

~~152. The method of claim 149, wherein said enriching comprises sorting said immune cells based on expression of one or more markers.~~

~~153. The method of claim 152, wherein said one or more markers comprise CD3, CD28, CD4, and/or CD8.~~

~~154. The method of any one of claims 151-153, wherein said immune cells are sorted using an anti-CD3 antibody or antigen binding fragment thereof, and/or an anti-CD28 antibody or an antigen binding fragment thereof.~~

~~155. The method of claim 151-153, wherein said immune cells are sorted using a bead conjugated with said anti-CD3 or antigen binding fragment thereof, and/or an a bead conjugated with said anti-CD28 antibody or an antigen binding fragment thereof.~~

~~156. The method of any one of claims 119-155, wherein said population of engineered immune cells is characterized in that cell memory T cells (TCM) in said population are more abundant than effector memory T cells (TEM).~~

~~157. The method of any one of claims 119-156, wherein at least 15% of said population are stem memory T cells (TSCM).~~

~~158. The method of any one of claims 119-156, wherein at least 20% of said population are stem memory T cells (TSCM).~~

~~159. The method of any one of claims 119-156, wherein at least 25% of said population are stem memory T cells (TSCM).~~

~~160. The method of any one of claims 119-156, wherein at least 30% of said population are stem memory T cells (TSCM).~~

~~161. The method of any one of claims 119-156, wherein at least 50% of said population are stem memory T cells (TSCM).~~

~~162. The method of any one of claims 119-161, wherein said population of engineered immune cells is to be infused to a subject in need thereof within 72 hours from completion of (a) and (b).~~

~~163. The method of any one of claims 119-162, wherein said population is further characterized in that reduced exhaustion of cells in said population is observed as compared to the exhaustion of cells in a comparable population that undergoes a comparable method where (a) and (b) are not performed concurrently.~~

~~164. The method of claim 163, wherein said reduced exhaustion of said population is characterized in that said population comprises less cells expressing PD1 and LAG3.~~

~~165. The method of any one of claims 119-164, wherein said population is further characterized in that a greater proliferation, cytotoxicity, and/or bone marrow migration is observed in said population as compared to the proliferation, cytotoxicity, and/or bone marrow migration of a comparable population that undergoes a comparable method where (a) and (b) are not performed concurrently.~~

~~166. The method of claim 165, wherein said cytotoxicity is at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2.0, 2.5, or 3.0 fold higher in said population as compared to a comparable population wherein (a) and (b) are performed for more than 24 hours when said population and comparable population contact a target.~~

~~167. The method of claim 165, wherein said proliferation is at least 0.5 fold, 1 fold, 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 50 fold, 100 fold, 500 fold, 1000 fold, 5000 fold, or 10000 fold higher in said population as compared to a comparable population wherein (a) and (b) are performed for more than 24 hours when said population and comparable population contact a target.~~

~~168. The method of claim 165, wherein said bone marrow migration is at least 0.1 fold, 0.2 fold, 0.3 fold, 0.4 fold, 0.5 fold, 0.6 fold, 0.7 fold, 0.8 fold, 0.9 fold, 1 fold, 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold or 10 fold higher in said population as compared to a comparable population wherein (a) and (b) are performed for more than 24 hours when said population and comparable population contact a target.~~

~~169. The method of claim 168, wherein said target is a cancer cell or a chemokine.~~

~~170. The method of claim 169, wherein said chemokine is stromal cell-derived factor-1~~

~~(SDF-1), and wherein said SDF-1 is expressed in bone marrow of said subject.~~

~~171. The method of any one of claims 168-170, wherein said population has a greater percentage of CXCR4 positive cells as compared to a comparable population wherein (a) and (b) are performed for more than 24 hours.~~

~~172. The method of claim 171, wherein said population has a greater median percentage of CXCR4 positive cells that is at least 10% greater as compared to the median percentage of CXCR4 positive cells expressed by a comparable population wherein (a) and (b) are performed for more than 24 hours.~~

~~173. The method of claim 172, wherein said population has a greater density of CXCR4 on a cell surface of said CXCR4 positive cells as compared to the density of CXCR4 on the cell surface of a comparable population wherein (a) and (b) are performed for more than 24 hours.~~

~~174. The method of claim 173, wherein said density is measured by evaluating a mean fluorescence intensity (MFI) of CXCR4 on said cell surface of said CXCR4 positive cells.~~

~~175. The method of claim 165, wherein said cytotoxicity is measured in an in vivo assay.~~

~~176. The method of claim 175, wherein a reduced cancer burden is observed in said subject when said subject is administered said population as compared to the cancer burden observed in a comparable subject administered a comparable population wherein (a) and (b) are performed for more than 24 hours.~~

~~177. The method of claim 176, wherein said cancer burden is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% in said subject treated with said population as compared to said comparable subject administered a comparable population wherein (a) and (b) are performed for more than 24 hours.~~

~~178. A point-of-care facility comprising a cell infusion equipment configured to: infuse a population of immune cells that comprises engineered immune cells that have not been subject to ex-vivo expansion for 1 or more weeks, wherein said population of immune cells is further characterized in that: cell memory T cells (TCM) in said population are more abundant than effector memory T cells (TEM); or wherein at least 15% of said population are stem memory T cells (TSCM).~~

~~179. The point-of-care facility of claim 178, wherein at least 20% of said population are stem memory T cells (TSCM).~~

~~180. The point-of-care facility of claim 178, wherein at least 25% of said population are stem memory T cells (TSCM).~~

~~181. The point-of-care facility of claim 178, wherein at least 30% of said population are~~

stem memory T cells (TSCM).

182. The point-of-care facility of any one of claims 178-181, wherein at least 50% of said population are stem memory T cells (TSCM).

183. The point-of-care facility of any one of claims 178-181, wherein there are 2-fold more TCM as compared to TEM.

184. The point-of-care facility of any one of claims 178-181, wherein there are 4-fold more TCM as compared to TEM.

185. The point-of-care facility of any one of claims 178-184, wherein said engineered immune cells have been subject to ex-vivo expansion less than 5 days.

186. The point-of-care facility of any one of claims 178-185, wherein said engineered immune cells have been subject to ex-vivo expansion less than 72 hours.

187. The point-of-care facility of any one of claims 145-186, wherein said engineered immune cells have been subject to ex-vivo expansion less than 48 hours.

188. The point-of-care facility of any one of claims 178-187, wherein said engineered immune cells have been subject to ex-vivo expansion less than 24 hours.

189. The point-of-care facility of any one of claims 178-188, wherein said immune cells are T cells, NK cells, and/or NKT cells.

190. A point-of-care facility comprising a cell processing equipment configured to:

(a) receive a population of cells comprising immune cells from a subject; and

(b) activate said population of immune cells with an activation moiety, and concurrently, introduce a polynucleotide encoding for at least a chimeric antigen receptor (CAR) to said immune cells, wherein said CAR comprises (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain; and

(c) infuse said population of immune cells of (b) into said subject within 2 weeks or less from the time of performing (b).

191. The point-of-care facility of claim 190, wherein step (c) is performed within 1 week or less from the time of performing (b).

192. The point-of-care facility of any one of claims 190-191, wherein said immune cells are T cells, NK cells, and/or NKT cells.

193. The point-of-care facility of any one of claims 190-192, wherein said ligand of said CAR is VEGFR-2, CD19, CD20, CD30, CD22, CD25, CD28, CD30, CD33, CD52, CD56, CD80, CD86, CD81, CD123, cd171, CD276, B7H4, BCMA, CD133, EGFR, GPC3, PMSA, CD3, CEACAM6, c-Met, EGFRvIII, ErbB2, ErbB3, HER3, ErbB4 / HER-4, EphA2, IGF1R,

~~GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, CD44V6, CEA, CA125, CD151, CTLA-4, GITR, BTLA, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2, HVEM, MAGE-A, mesothelin, NY-ESO-1, RANK, RORl, TNFRSF4, CD40, CD137, TWEAK-R, LTPR, LIFRP, LRP5, MUC1, TCRα, TCRβ,, TLR7, TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, CD79, Notch-1-4, and/or Claudin18.2.~~

~~194. The point-of-care facility of any one of claims 190-193, wherein said transmembrane domain is from CD8α, CD4, CD28, CD45, PD-1 and/or CD152.~~

~~195. The point-of-care facility of any one of claims 190-194, wherein said intracellular signaling domain is from CD3ζ, CD28, CD54 (ICAM), CD134 (OX40), CD137 (4-1BB), GITR, CD152 (CTLA4), CD273 (PD-L2), CD274 (PD-L1), DAP10 and/or CD278 (ICOS).~~

~~196. The point-of-care facility of any one of claims 190-195, wherein said CAR comprises at least two intracellular signaling domains.~~

~~197. The point-of-care facility of any one of claims 190-196, wherein said CAR comprises at least 3 intracellular signaling domains.~~

~~198. The point-of-care facility of any one of claims 190-197, wherein said CAR further comprises a hinge.~~

~~199. The point-of-care facility of claim 198, wherein said hinge is from CD28, IgG1 and/or CD8α.~~

~~200. The point-of-care facility of any one of claims 190-199, wherein said CAR further comprises a signal peptide, and wherein said signal peptide is derived from IgG1, GM-CSF and/or CD8α.~~

~~201. The point-of-care facility of any one of claim 190-200, wherein said immune cells are T cells, NK cells, and/or NKT cells.~~

~~202. The point-of-care facility of any one of claims 190-201, wherein said activation moiety binds: a CD3/T cell receptor complex and/or provides costimulation.~~

~~203. The point-of-care facility of claim 202, wherein said activation moiety is any one of anti-CD3 and/or anti-CD28.~~

~~204. The point-of-care facility of any one of claims 190-203, wherein a viral vector and/or a transposon vector comprises said polynucleotide.~~

~~205. The point-of-care facility of claim 204, wherein said viral vector is a retroviral vector, a lentiviral vector and/or an adeno-associated viral vector.~~

~~206. The point-of-care facility of any one of claims 190-205, wherein step (a) and (b) are performed within 72 hours.~~

207. The point-of-care facility of anyone of claims 190-205, wherein step (a) and (b) are performed within 48 hours.

208. The point-of-care facility of anyone of claims 190-205, wherein step (a) and (b) are performed within 24 hours.

209. The point-of-care facility of anyone of claims 190-205, wherein step (a) and (b) are performed within 1 hour.

210. The point-of-care facility of any one of claims 190-209, wherein said population is further characterized in that reduced exhaustion of cells in said population is observed, and wherein said reduced exhaustion is characterized in that said population comprises less cells expressing PD1 and LAG3.

211. A population of cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or a T cell receptor (TCR), wherein said population is further characterized in that:

(i) central memory T cells (TCM) in said population are more abundant than effector memory T cells (TEM); and/or

(ii) at least 15% of said population of cells are stem memory T cells (TSCM), and wherein said CAR comprises (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain.

212. The population of claim 211, wherein at least 20% of the population are TSCM.

213. The population of any one of claims 211-212, wherein at least 25% of the population are TSCM.

214. The population of any one of claims 211-213, wherein at least 30% of the population are TSCM.

215. The population of any one of claims 211-214, wherein at least 50% of the population are TSCM.

216. The population of any one of claims 211-215, wherein there are 2 fold more TCM as compared to TEM.

217. The population of any one of claims 211-216, wherein there are 4 fold more TCM as compared to TEM.

218. The population of any one of claims 211-217, wherein said immune cells are T cells, NK cells, and/or NKT cells.

219. The population of any one of claims 211-218, wherein said ligand of said CAR is VEGFR-2, CD19, CD20, CD30, CD22, CD25, CD28, CD30, CD33, CD52, CD56, CD80,

~~CD86, CD81, CD123, cd171, CD276, B7H4, BCMA, CD133, EGFR, GPC3, PMSA, CD3, CEACAM6, c-Met, EGFRvIII, ErbB2, ErbB3, HER3, ErbB4 / HER-4, EphA2, IGF1R, GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, CD44V6, CEA, CA125, CD151, CTLA-4, GITR, BTLA, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2, HVEM, MAGE-A, mesothelin, NY-ESO-1, RANK, RORl, TNFRSF4, CD40, CD137, TWEAK-R, LTPR, LIFRP, LRP5, MUC1, TCRα, TCRβ,, TLR7, TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, CD79, Notch-1-4, and/or Claudin18.2.~~

~~220. The population of any one of claims 211-219, wherein said transmembrane domain is from CD8α, CD4, CD28, CD45, PD-1 and/or CD152.~~

~~221. The population of any one of claims 211-220, wherein said intracellular signaling domain is from CD3ζ, CD28, CD54 (ICAM), CD134 (OX40), CD137 (4-1BB), GITR, CD152 (CTLA4), CD273 (PD-L2), CD274 (PD-L1), DAP10 and/or CD278 (ICOS).~~

~~222. The population of any one of claims 211-221, wherein said CAR comprises at least two intracellular signaling domains.~~

~~223. The population of any one of claims 211-221, wherein said CAR comprises at least 3 intracellular signaling domains.~~

~~224. The population of any one of claims 211-223, wherein said CAR further comprises a hinge.~~

~~225. The population of claim 224, wherein said hinge is from CD28, IgG1 and/or CD8α.~~

~~226. The population of any one of claims 211-225, wherein said CAR further comprises a signal peptide, and wherein said signal peptide is derived from IgG1, GM-CSF and/or CD8α.~~

~~227. The population of any one of claims 211-226, wherein said immune cells are T cells, NK cells, and/or NKT cells.~~

~~228. The population of any one of claims 211-227, wherein said population is cryopreserved or wherein said population is freshly sourced.~~

~~229. The population of any one of claims 211-228, wherein said population is further characterized in that reduced exhaustion of cells in said population is observed, and wherein said reduced exhaustion is characterized in that said population comprises less cells expressing PD1 and LAG3.~~

~~230. Use of a population of no more than about $1x10^6$ engineered immune cells expressing chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the medicament is to be infused to the subject, wherein the engineered immune cells have not~~

~~been subject to ex-vivo expansion for 1 or more weeks.~~

~~231. The use of claim 230, wherein the population of engineered immune cells exhibits a comparable level of anti-tumor activity in vivo as compared to a population of 10 times more engineered immune cells expressing the same chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) but have been subject to ex-vivo expansion for 1 or more weeks.~~

~~232. The use of any one of claims 230-231, wherein the population of engineered immune cells have been concurrently activated and transduced with a construct expressing said CAR and/or TCR.~~

~~233. The use of any one of claims 230-232, wherein the population of engineered immune cells have not been subject to ex-vivo expansion for one week.~~

~~234. The use of any one of claims 230-232, wherein the population of engineered immune cells have not been subject to ex-vivo expansion for 72 hours.~~

~~235. The use of any one of claims 230-234, wherein the population of no more than about $1x10^6$ engineered immune cells have been prepared from peripheral blood mononuclear cells (PMBC) via a process of concurrent activation and transduction with a construct expressing said CAR and/or TCR.~~

~~236. The use of any one of claims 230-235, wherein said infusion takes places within 1 week from concurrent activation and transduction with a construct expressing said CAR and/or TCR.~~

~~237. The use of claim 236, wherein said concurrent activation comprises performing activation and transduction within 72 hours.~~

~~238. The use of claim 236, wherein said concurrent activation comprises performing activation and transduction within 48 hours.~~

~~239. The use of claim 236, wherein said concurrent activation comprises performing activation and transduction within 24 hours.~~

~~240. The use of claim 236, wherein said concurrent activation comprises performing activation and transduction within 3 hours.~~

~~241. The use of claim 236, wherein said concurrent activation comprises performing activation and transduction within 1 hour.~~

~~242. The use of claim 236, wherein said concurrent activation comprises performing activation and transduction at the same time.~~

~~243. The use of any one of claims 230-242, wherein at least 15% of said population are~~

stem memory T cells (TSCM).

244. The use of any one of claims 230-243, wherein at least 20% of said population are stem memory T cells (TSCM).

245. The use of any one of claims 230-244, wherein at least 25% of said population are stem memory T cells (TSCM).

246. The use of any one of claims 230-245, wherein at least 30% of said population are stem memory T cells (TSCM).

247. The use of any one of claims 230-246, wherein at least 50% of said population are stem memory T cells (TSCM).

248. The use of any one of claims 230-247, wherein said population is further characterized in that reduced exhaustion of cells in said population is observed as compared to the exhaustion of cells in a comparable population that undergoes an ex vivo expansion for 1 or more weeks.

249. The use of claim 248, wherein said reduced exhaustion of said population is characterized in that said population comprises less cells expressing PD1 and LAG3.

250. The use of any one of claims 230-249, wherein said infusion is no more than about 10^5 engineered immune cells.

251. The use of any one of claims 230-249, wherein said infusion is no more than about 10^4 engineered immune cells.

252. The use of any one of claims 230-249, wherein said infusion is no more than about 10^3 engineered immune cells.

253. The use of any one of claims 230-252, wherein said engineered immune cells are T cells, NK cells, and/or NKT cells.

254. The use of any one of claims 230-253, wherein said TCR comprises (i) a ligand binding domain specific for a ligand and (ii) a transmembrane domain.

255. The use of any one of claims 230-254, wherein said CAR comprises: (i) a ligand binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain.

256. The use of any one of claims 254-255, wherein said ligand of said TCR or CAR is VEGFR-2, CD19, CD20, CD30, CD22, CD25, CD28, CD30, CD33, CD52, CD56, CD80, CD86, CD81, CD123, cd171, CD276, B7H4, BCMA, CD133, EGFR, GPC3, PMSA, CD3, CEACAM6, c-Met, EGFRvIII, ErbB2, ErbB3, HER3, ErbB4 / HER-4, EphA2, IGF1R, GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, CD44V6, CEA, CA125,

CD151, CTLA-4, GITR, BTLA, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2，HVEM, MAGE-A, mesothelin, NY-ESO-1, RANK, RORl, TNFRSF4, CD40, CD137, TWEAK-R, LTPR, LIFRP, LRP5, MUC1, TCRα, TCRβ,, TLR7, TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, CD79, Notch-1-4, and/or Claudin18.2.

257. The use of any one of claims 254-255, wherein said transmembrane domain is from CD8α, CD4, CD28, CD45, PD-1 and/or CD152.

258. The use of any one of claims 255-257, wherein said intracellular signaling domain is from CD3ζ, CD28, CD54 (ICAM), CD134 (OX40), CD137 (4-1BB), GITR, CD152 (CTLA4), CD273 (PD-L2), CD274 (PD-L1), DAP10 and/or CD278 (ICOS).

259. The use of any one of claims 255-258, wherein said CAR comprises at least 2 intracellular signaling domains.

260. The use of any one of claims 255-258, wherein said CAR comprises at least 3 intracellular signaling domains.

261. The use of any one of claims 255-260, wherein said CAR further comprises a hinge.

262. The use of claim 261, wherein said hinge is from CD28, IgG1 and/or CD8α.

263. The use of any one of claims 255-262, wherein said CAR further comprises a signal peptide, and wherein said signal peptide is derived from IgG1, GM-CSF and/or CD8α.

264. The use of any one of claims 230-263, wherein said engineered immune cells are from peripheral blood, cord blood, bone marrow, and/or induced pluripotent stem cells.

265. The use of claim 264, wherein said engineered immune cells are from peripheral blood, and wherein said peripheral blood cells are T cells.

266. The use of any one of claims 230 to 265, wherein peripheral blood is further obtained from said subject in need thereof after said administration.

267. The use of claim 266, wherein said engineered immune cells in said subject are quantified from said peripheral blood.

268. The use of claim 267, wherein a level of a growth factor in said subject is quantified.

269. The use of claim 268, wherein said growth factor selected from the group consisting of IL-10, IL-6, tumor necrosis factor α (TNF-α), IL-1β, IL-2, IL-4, IL-8, IL-12, and/or IFN-γ.

270. The use of any one of claims 230 to 269, comprising repeating said infusion.

271. The use of any one of claims 230 to 270, wherein said population of immune cells is allogeneic to said subject in need thereof.

272. The use of any one of claims 230 to 270, wherein said population of immune cells is autologous to said subject in need thereof.

~~273. The use of any one of claims 230 to 272, wherein said subject has cancer.~~

~~274. The use of claim 273, wherein said cancer is hematological.~~

~~275. The use of claim 274, wherein said hematological cancer is leukemia, myeloma, lymphoma, and/or a combination thereof~~

~~276. The use of claim 275, wherein said leukemia is chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia (B-ALL), T-cell acute lymphoblastic leukemia (T-ALL), and/or acute lymphoblastic leukemia (ALL).~~

~~277. The use of claim 275, wherein said lymphoma is mantle cell lymphoma (MCL), Hodgkin's lymphoma, T-cell lymphoma, and/or non-Hodgkin's lymphoma.~~

~~278. The use of claim 273, wherein said cancer is solid.~~

~~279. The use of claim 278, wherein said solid cancer is selected from the group comprising: nephroblastoma, Ewing's sarcoma, neuroendocrine tumor, glioblastoma, neuroblastoma, melanoma, skin cancer, breast cancer, colon cancer, rectal cancer, prostate cancer, liver cancer, kidney cancer, pancreatic cancer, lung cancer, biliary tract cancer, cervical cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, medullary thyroid carcinoma, ovarian cancer, glioma, or bladder cancer.~~

~~280. The use of any one of claims 230 to 279, wherein said subject was pre-treated with chemotherapy prior to said administration.~~

~~281. The use of claim 280, wherein said chemotherapy comprises an administration of fludarabine, cyclophosphamide and/or cytarabine.~~

~~282. The use of any one of claims 230-281, wherein said population is further characterized in that a greater proliferation, cytotoxicity, and/or bone marrow migration is observed in said population as compared to the proliferation, cytotoxicity, and/or bone marrow migration of a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~283. The use of claim 282, wherein said cytotoxicity is at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2.0, 2.5, or 3.0 fold higher in said population as compared to a comparable population that undergoes an ex-vivo expansion for 1 or more weeks when said population and comparable population contact a target.~~

~~284. The use of claim 282, wherein said proliferation is at least 0.5 fold, 1 fold, 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 50 fold, 100 fold, 500 fold, 1000 fold, 5000 fold, or 10000 fold higher in said population as compared to a comparable population that undergoes an ex-vivo expansion for 1 or more weeks when said population~~

and comparable population contact a target.

285. The use of claim 282, wherein said bone marrow migration is at least 0.1 fold, 0.2 fold, 0.3 fold, 0.4 fold, 0.5 fold, 0.6 fold, 0.7 fold, 0.8 fold, 0.9 fold, 1 fold, 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold or 10 fold higher in said population as compared to a comparable population that undergoes an ex vivo expansion for 1 or more weeks when said population and comparable population contact a target.

286. The use of claim 285, wherein said target is a cancer cell or a chemokine.

287. The use of claim 286, wherein said chemokine is stromal cell-derived factor-1 (SDF-1), and wherein said SDF-1 is expressed in bone marrow of said subject.

288. The use of any one of claims 285-287, wherein said population has a greater percentage of CXCR4 positive cells as compared to a comparable population that undergoes an ex vivo expansion for 1 or more weeks.

289. The use of claim 288, wherein said population has a greater median percentage of CXCR4 positive cells that is at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90% or 100% greater as compared to the median percentage of CXCR4 positive cells expressed by a comparable population that undergoes an ex vivo expansion for 1 or more weeks.

290. The use of claim 289, wherein said population has a greater density of CXCR4 on a cell surface of said CXCR4 positive cells as compared to the density of CXCR4 on the cell surface of a comparable population that undergoes an ex vivo expansion for 1 or more weeks.

291. The use of claim 290, wherein said density is measured by evaluating a mean fluorescence intensity (MFI) of CXCR4 on said cell surface of said CXCR4 positive cells.

292. The use of claim 282, wherein said cytotoxicity is measured in an in vivo assay.

293. The use of claim 292, wherein a reduced cancer burden is observed in said subject when said subject is administered said population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex vivo expansion for 1 or more weeks.

294. The use of claim 293, wherein said cancer burden is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% in said subject treated with said population as compared to said comparable subject administered a comparable population that undergoes an ex vivo expansion for 1 or more weeks.

295. Use of a population of immune cells comprising engineered immune cells expressing

~~a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cells is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and wherein said population is further characterized in that a greater proliferation is observed in said population as compared to the proliferation of a comparable population that undergoes ex vivo expansion for 1 or more weeks.~~

~~296. The use of claim 295, wherein said proliferation is at least 0.5 fold, 1 fold, 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 50 fold, 100 fold, 500 fold, 1000 fold, 5000 fold, or 10000 fold higher in said population as compared to said comparable population that undergoes an ex vivo expansion for 1 or more weeks when said population and said comparable population contact a target.~~

~~297. Use of a population of immune cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cells is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and wherein said population is further characterized in that a greater cytotoxicity is observed in said population as compared to the cytotoxicity of a comparable population that undergoes ex vivo expansion for 1 or more weeks.~~

~~298. The use of claim 296, wherein said cytotoxicity is at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2.0, 2.5, or 3.0 fold higher in said population as compared to said comparable population that undergoes an ex vivo expansion for 1 or more weeks when said population and said comparable population contact a target.~~

~~299. Use of a population of immune cells comprising engineered immune cells expressing a chimeric antigen receptor (CAR) and/or an engineered T cell receptor (TCR) in the manufacture of a cell therapy for administration, wherein said population of immune cells comprising said engineered immune cell is to be infused into a subject in need thereof, wherein said engineered immune cells have not been subject to ex vivo expansion for 1 or more weeks, and wherein said population is further characterized in that a greater bone marrow migration is observed of said population as compared to the bone marrow migration of a comparable population that undergoes ex vivo expansion for 1 or more weeks.~~

~~300. The use of claim 299, wherein said bone marrow migration is at least 0.1 fold, 0.2~~

fold, 0.3 fold, 0.4 fold, 0.5 fold, 0.6 fold, 0.7 fold, 0.8 fold, 0.9 fold, 1 fold, 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold or 10 fold higher in said population as compared to said comparable population that undergoes ex vivo expansion for 1 or more weeks when said population and said comparable population contact a target.

301. The use of any one of claims 295-300, wherein said population is further characterized in that: central memory T cells (TCM) in said population are more abundant than effector memory T cells (TEM).

302. The use of claim 301, wherein said TCM are CD45RO+CD62L+.

303. The use of any one of claims 301-302, wherein said TEM are CD45RO+CD62L-.

304. The use of any one of claims 295-303, wherein said engineered immune cells have been subject to ex vivo expansion less than 5 days.

305. The use of any one of claims 295-304, wherein said engineered immune cells have been subject to ex vivo expansion less than 5 days.

306. The use of any one of claims 295-305, wherein said engineered immune cells have been subject to ex vivo expansion less than 72 hours.

307. The use of any one of claims 295-306, wherein said engineered immune cells have been subject to ex vivo expansion less than 48 hours.

308. The use of any one of claims 295-307, wherein said engineered immune cells have been subject to ex vivo expansion less than 24 hours.

309. The use of any one of claims 296-300, wherein said target is a cancer cell, a ligand of said TCR or said CAR, or a chemokine.

310. The use of claim 309, wherein said chemokine is stromal cell-derived factor-1 (SDF-1), and wherein said SDF-1 is expressed in bone marrow of said subject.

311. The use of any one of claims 299-310, wherein said population has a greater percentage of CXCR4 positive cells as compared to said comparable population that undergoes said ex vivo expansion for 1 or more weeks.

312. The use of claim 311, wherein said population has a greater median percentage of CXCR4 positive cells that is at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90% or 100% greater as compared to the median percentage of CXCR4 positive cells expressed by said comparable population that undergoes said ex vivo expansion for 1 or more weeks.

313. The use of claim 312, wherein said population has a greater density of CXCR4 on a

~~cell surface of said CXCR4 positive cells as compared to the density of CXCR4 on the cell surface of said comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~314. The use of claim 313, wherein said density is measured by evaluating a mean fluorescence intensity (MFI) of CXCR4 on said cell surface of said CXCR4 positive cells.~~

~~315. The use of any one of claims 297-314, wherein said cytotoxicity is measured in an in vivo assay.~~

~~316. The use of claim 315, wherein a reduced cancer burden is observed in said subject administered said population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~317. The use of claim 316, wherein said cancer burden is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% in said subject treated with said population as compared to said comparable subject administered a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~318. The use of claim 316, wherein complete remission (CR) is observed in said subject administered said population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~319. The use of claim 316, wherein a partial response (PR) is observed in said subject administered said population as compared to the cancer burden observed in a comparable subject administered a comparable population that undergoes an ex-vivo expansion for 1 or more weeks.~~

~~320. The use of any one of claims 295-319, wherein said population comprises at most $1x10^4$ cells per kg/body weight of engineered immune cells.~~

~~321. The use of any one of claims 295-319, wherein said population comprises from about $1x10^4$ cells per kg/body weight to at most about $1x10^5$ cells per kg/body weight of engineered immune cells.~~

~~322. The use of any one of claims 295-321, wherein said engineered immune cells are T cells, NK cells, and/or NKT cells.~~

~~323. The use of any one of claims 295-322, wherein said TCR comprises (i) a ligand binding domain specific for a ligand and (ii) a transmembrane domain.~~

~~324. The use of any one of claims 295-323, wherein said CAR comprises: (i) a ligand~~

~~binding domain specific for a ligand, (ii) a transmembrane domain, and (iii) an intracellular signaling domain.~~

~~325. The use of any one of claims 295-324, wherein said ligand of said TCR or CAR is VEGFR-2, CD19, CD20, CD30, CD22, CD25, CD28, CD30, CD33, CD52, CD56, CD80, CD86, CD81, CD123, cd171, CD276, B7H4, BCMA, CD133, EGFR, GPC3, PMSA, CD3, CEACAM6, c-Met, EGFRvIII, ErbB2, ErbB3, HER3, ErbB4 / HER-4, EphA2, IGF1R, GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, CD44V6, CEA, CA125, CD151, CTLA-4, GITR, BTLA, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2, HVEM, MAGE-A, mesothelin, NY-ESO-1, RANK, RORl, TNFRSF4, CD40, CD137, TWEAK-R, LTPR, LIFRP, LRP5, MUC1, TCRα, TCRβ, TLR7, TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, CD79, Notch-1-4, and/or Claudin18.2.~~

~~326. The use of any one of claims 324-325, wherein said transmembrane domain is from CD8α, CD4, CD28, CD45, PD-1 and/or CD152.~~

~~327. The use of any one of claims 324-326, wherein said intracellular signaling domain is from CD3ζ, CD28, CD54 (ICAM), CD134 (OX40), CD137 (4-1BB), GITR, CD152 (CTLA4), CD273 (PD-L2), CD274 (PD-L1), DAP10 and/or CD278 (ICOS).~~

~~328. The use of any one of claims 324-327, wherein said CAR comprises at least 2 intracellular signaling domains.~~

~~329. The use of any one of claims 324-327, wherein said CAR comprises at least 3 intracellular signaling domains.~~

~~330. The use of any one of claims 324-329, wherein said CAR further comprises a hinge.~~

~~331. The use of claim 330, wherein said hinge is from CD28, IgG1 and/or CD8α.~~

~~332. The use of any one of claims 324-331, wherein said engineered immune cells are from peripheral blood, cord blood, bone marrow, and/or induced pluripotent stem cells.~~

~~333. The use of claim 332, wherein said engineered immune cells are from peripheral blood, and wherein said peripheral blood cells are T cells.~~

42. Use of the population of any one of the preceding claims, in the manufacture of a medicament for the treatment of cancer.

43. The use of claim 42, wherein said medicament is to be administered to a subject in need thereof.

44. The use of claim 43, wherein said medicament is to be intravenously administered to the subject.

45. The use of claim 42, wherein said cancer is hematological.

46. The useof claim 45, wherein said hematological cancer is leukemia, myeloma, and/or lymphoma.

47. The use of claim 46, wherein said leukemia is chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), B cell acute lymphoblastic leukemia (B-ALL), T-cell acute lymphoblastic leukemia (T-ALL), and/or acute lymphoblastic leukemia (ALL).

48. The use of claim 42, wherein said cancer is a solid cancer.

49. The use of claim 48, wherein said solid cancer is selected from the group comprising: nephroblastoma, Ewing's sarcoma, neuroendocrine tumor, glioblastoma, neuroblastoma, melanoma, skin cancer, breast cancer, colon cancer, rectal cancer, prostate cancer, liver cancer, kidney cancer, pancreatic cancer, lung cancer, biliary tract cancer, cervical cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, medullary thyroid carcinoma, ovarian cancer, glioma, or bladder cancer.