

SUMMARY OF THE INVENTION

[0004a] In one aspect, provided herein is a cell or a population thereof, wherein the cell comprises a polynucleotide encoding the chimeric fusion receptor (CFR) as described herein, wherein the cell is an eukaryotic cell, an animal cell, a human cell, an immune cell, a feeder cell, an induced pluripotent stem cell (iPSC), a clonal iPSC, or an derivative iPSC-derived effector cell.

[0004b] In another aspect, provided herein is a composition comprising the cell or population thereof as described herein, and one or more therapeutic agents for use in therapy.

[0004c] In another aspect, provided herein is use of a composition comprising the cell or population thereof as described herein, and one or more therapeutic agents in the manufacture of a medicament for treating a subject suitable for adoptive cell therapy, wherein the subject has an autoimmune disorder, a hematological malignancy, a solid tumor, cancer, or a viral infection.

[0004d] In another aspect, provided herein is a method of manufacturing a derivative effector cell comprising the CFR as described herein, wherein the method comprises differentiating a genetically engineered iPSC, wherein the iPSC comprises a polynucleotide encoding the CFR, and optionally one or more edits resulting in:

- (i) CD38 knockout;
 - (ii) HLA-I deficiency, and optionally HLA-II deficiency;
 - (iii) introduction of HLA-G or non-cleavable HLA-G, or knockout of one or both of CD58 and CD54;
 - (iv) a CD16 or a variant thereof;
 - (v) a CAR having a targeting specificity;
 - (vi) a partial or full peptide of a cell surface expressed exogenous cytokine and/or a receptor thereof;
 - (vii) at least one of the genotypes listed in Table 1;
 - (viii) deletion or disruption of at least one of B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD25, CD69, CD44, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT; or
 - (ix) introduction of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, A_{2A}R, antigen-specific TCR, Fc receptor, an antibody or functional variant or fragment thereof, a checkpoint inhibitor, an engager, and surface triggering receptor for coupling with an agonist.
- [0004e]** In another aspect, provided herein is a composition comprising cells comprising the CFR as described herein and an agonist specific to the CFR for use in therapy, wherein the composition is to be administered to a subject in need thereof.

[0005] There is a need for functionally improved effector cells that address issues ranging from response rate, cell exhaustion, loss of transfused cells (survival and/or persistence), tumor escape through target loss or lineage switch, tumor targeting precision, off-target toxicity, off-tumor effect, to efficacy against solid tumors, i.e., tumor microenvironment and related immune suppression, recruiting, trafficking and infiltration.

[0006] It is an object of the present invention to provide methods and compositions to generate derivative non-pluripotent cells differentiated from a single cell derived iPSC (induced pluripotent stem cell) clonal line, which iPSC comprises one or several genetic modifications in its genome. Said one or several genetic modifications include DNA insertion, deletion, and substitution, and which modifications are retained and remain functional in subsequently derived cells after differentiation, expansion, passaging and/or transplantation.

[0007] In some embodiments, the iPSC-derived non-pluripotent cells of the present application include, but are not limited to, CD34 cells, hemogenic endothelium cells, HSCs (hematopoietic stem and progenitor cells), hematopoietic multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells, NKT cells, NK cells, B cells, and immune effector cells having one or more functional features that are not present in a primary NK, T, and/or NKT cell. The iPSC-derived non-pluripotent cells according to some embodiments of the present application comprise one or several genetic modifications in their genome through differentiation from an iPSC comprising the same genetic modifications. In some embodiments, the engineered clonal iPSC differentiation strategy for obtaining genetically engineered derivative cells requires that the developmental potential of the iPSC in differentiation is not adversely impacted by the engineered modality in the iPSC, and also that the engineered modality functions as intended in the derivative cell. Further, this strategy overcomes the present barrier in engineering primary lymphocytes, such as T cells or NK cells obtained from peripheral blood, as such cells are difficult to engineer, with engineering of such cells often lacking reproducibility and uniformity, resulting in cells exhibiting poor cell persistence with high cell death and low cell expansion. Moreover, this strategy avoids production of a heterogenous effector cell population otherwise obtained using primary cell sources which are heterogenous to start with.

[0008] Some aspects of the present invention provide genome-engineered iPSCs obtained using a method comprising (I), (II) or (III), reflecting a strategy of genomic engineering subsequently to, simultaneously with, and prior to the reprogramming process, respectively:

[0009] (I): genetically engineering iPSCs by one or both of (i) and (ii), in any order: (i) introducing into iPSCs one or more construct(s) to allow targeted integration at selected site(s);