specificity and the second tumor antigen specificity are different. In various embodiments of the method, the stop of introducing to the CAR-T cell a polynucleotide further comprises: differentiating a genetically engineered iPSC to a T cell, wherein the iPSC comprises: (a) the polynucleotide encoding a transgenic TCRα chain (tgTCRα); (b) the polynucleotide encoding a transgenic TCRβ chain (tgTCRβ); and (c) a polynucleotide encoding the CAR having the first tumor antigen specificity, thereby obtaining the CAR-T cell having expression of the TCR^{exo}. In various embodiments of the method, the method further comprises genomically engineering a clonal iPSC to knock in: (a) the polynucleotide encoding the transgenic TCRα chain (tgTCRα); (b) the polynucleotide encoding the transgenic TCRβ chain (tgTCRβ); and (c) the polynucleotide encoding the CAR having the first tumor antigen specificity, thereby obtaining an engineered iPSC for T cell differentiation.

[00036] Various objects and advantages of the compositions and methods as provided herein will become apparent from the following description taken in conjunction with the accompanying drawings wherein are set forth, by way of illustration and example, certain embodiments of this invention.

[00036a] In another aspect, provided herein is use of the composition as described herein in the manufacture of a medicament for the treatment of an autoimmune disorder, a hematological malignancy, a solid tumor, cancer, or a viral infection.

[00036b] In another aspect, provided herein is a method of manufacturing a derivative cell as described herein, wherein the derivative cell is a derivative effector cell, the method comprising: differentiating a genetically engineered iPSC, wherein the iPSC comprises: (a) a polynucleotide encoding a transgenic TCRα chain (tgTCRα); (b) a polynucleotide encoding a transgenic TCRβ chain (tgTCRβ); and optionally, (c) a polynucleotide encoding a chimeric antigen receptor (CAR) or an engager targeting a second tumor antigen; and optionally wherein the iPSC further comprises one or more of: (i) CD38 knockout; (ii) HLA-I deficiency and/or HLA-II deficiency; (iii) introduced 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 chimeric fusion receptor (CFR); (vi) a signaling complex comprising 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, CIITA, TAP1, TAP2, Tapasin, NLRC5, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD25, CD69, CD44, CD56, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, and TIGIT; or (ix) introduction or upregulation of at least one of HLA-E, 4-1BBL, CD3, CD4, CD8, CD16, CD47, CD113, CD131, CD137, CD80, PDL1, A2AR, Fc receptor, an antibody or functional variant or fragment thereof, a checkpoint inhibitor, and surface triggering receptor for coupling with an agonist.

[00036c] In another aspect, provided herein is use of the composition as described herein in the manufacture of a medicament for the treatment of an autoimmune disorder, a hematological malignancy, a solid tumor, cancer, or a viral infection.

[00037d] In another aspect, provided herein is the composition as described herein for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

[00037] FIGS. 1A and 1B show ectopic expression of MR1-TCR in iPSC-derived effector cells. FIG. 1A shows transduction of an MR1-TCR construct into iPSC reprogrammed from T cells (TiPSC) or from fibroblasts (FiPSC) and subsequent differentiation thereof into T lineage effector cells (TiP-iT or FiP-iT, respectively). FIG. 1B shows that the presence of endogenous TCRβ in TiPSC can lead to TCR mispairing in derivative T lineage effector cells (TiP-iT) that have endogenous TCR knockout through TRAC disruption.

[00038] FIG. 2 shows that expression of TCRαβ can stabilize surface expression of CD3 molecules.

[00039] FIG. 3 shows that MR1 TCR-expressing effector cells can specifically kill A549 tumor cells, which can be inhibited by an MR1 blocking antibody.

[00040] FIGS. 4A and 4B show that both FiPSC- (FIG. 4A) and TiPSC- (FIG. 4B) derived MR1-TCR$^+$ iT cells demonstrate MR1-dependent cytokine release and degranulation responses.

[00041] FIGS. 5A and 5B show the purity of FiP-iT cells expressing MR1-TCR within the input population (FIG. 5A), and that MR1 TCR$^+$ FiP-iT demonstrated cytotoxicity in an MR1-dependent manner with A549 cells (FIG. 5B), and that MR1-mediated TCR signaling blocked by an antibody can be restored by the addition of BiTE.