

provides a method of producing a clonal master engineered iPSC line using CRISPR mediated editing of a clonal iPSC, wherein the editing comprises a knock-in of a polynucleotide encoding a cytokine signaling complex and optionally a CAR to the clonal iPSC, wherein the cytokine signaling complex comprises an IL7 receptor fusion (IL7RF), thereby producing the clonal master engineered iPSC line. In some embodiments of the method of producing a clonal master engineered iPSC line, (a) the editing of the clonal iPSC further comprises knocking out TCR, or (b) the CAR is inserted at one of the gene loci comprising: B2M, TAP1, TAP2, Tapasin, NLRC5, CIITA, RFXANK, RFX5, RFXAP, TCR, NKG2A, NKG2D, CD38, CD25, CD69, CD44, CD58, CD54, CD56, CD71, CIS, CBL-B, SOCS2, PD1, CTLA4, LAG3, TIM3, or TIGIT; and wherein the insertion knocks out expression of the gene in the locus.

[00033] In yet another aspect, the invention provides a method of treating a disease or a condition comprising administering to a subject in need thereof the composition as described herein. In some embodiments, the subject does not need cytokine support during treatment. In some embodiments, the cells of the composition express an antibody or functional variant or fragment thereof, or an engager. In some embodiments, the cells of the composition are iPSC-derived effector cells further comprising one or more of: (i) a CD38 knockout; (ii) TCR^{neg}; (iii) an exogenous CD16 or a variant thereof; (iv) HLA-I and/or HLA-II deficiency; (v) introduced expression of HLA-G or non-cleavable HLA-G, or knockout of one or both of CD58 and CD54; (vi) introduced expression of a CFR; and/or (vii) a partial or full peptide of a cell surface expressed exogenous cytokine or a receptor thereof. In some embodiments, administration of the cells of the composition results in one or more of: (i) increased cytotoxicity; (ii) improved persistency and/or survival; (iii) enhanced ability in migrating, and/or activating or recruiting bystander immune cells, to tumor sites; (iv) improved tumor penetration; (v) enhanced ability to reduce tumor immunosuppression; (vi) improved ability in rescuing tumor antigen escape; (vii) controlled apoptosis; (viii) enhanced or acquired ADCC; and (ix) ability to avoid fratricide, in comparison to their counterpart primary cells in the absence of cytokine support.

[00034] 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.

[00034a] In another aspect, provided herein is a cell or a population thereof, wherein (a) the cell comprises a polynucleotide encoding a recombinant cytokine signaling complex, and optionally a chimeric antigen receptor (CAR); (b) the cell is an induced pluripotent cell (iPSC), an eukaryotic cell, an animal cell, a human cell, an immune cell, a feeder cell, or a derivative cell

differentiated from the iPSC; and (c) the cytokine signaling complex comprises (i) a full or partial cytokine and (ii) a full or partial IL7 receptor, IL2 receptor, IL4 receptor, IL9 receptor, IL21 receptor, or γ C receptor.

[00034b] In another aspect, provided herein is a composition comprising a derivative effector cell differentiated from the iPSC as described herein, and one or more therapeutic agents.

[00034c] 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.

[00034d] In another aspect, provided herein is the composition as described herein for use in therapy.