CLAIMS

What is claimed is:

1. A cell or a population thereof, wherein

(i) the cell is (a) an immune cell; (b) an induced pluripotent cell (iPSC); or (c) a derivative effector cell obtained from differentiating the iPSC; and

(ii) the cell comprises a construct comprising at least one of:

(a) a polynucleotide encoding an allo-immune defense receptor (ADR); and

(b) a polynucleotide encoding IL2, IL18, or a IL7RF;

(iii) the construct is inserted into a T cell receptor (TCR) locus, thereby knocking out the TCR; and

(iv) the construct is expressed under control of an endogenous TCR promoter.

2. The cell or population thereof of claim 1, further comprising a construct at a first integration site (site 1), wherein:

(i) the site 1 construct comprises two or more of:

(a) a polynucleotide encoding a TGFβ signaling redirector receptor (TGFβ-SRR) comprising a partial or full peptide of the extracellular domain (ECD) of transforming growth factor beta receptor (TGFβR);

(b) a polynucleotide encoding a C-X-C motif chemokine receptor or a variant thereof; and

(c) a polynucleotide encoding an exogenous CD16 or a variant thereof; and

(ii) the site 1 construct comprises an exogenous promoter that regulates expression of the polynucleotides in the site 1 construct.

3. The cell or population thereof of claim 2, further comprising a construct at a second integration site (site 2), wherein:

(i) the site 2 construct comprises a polynucleotide encoding a first chimeric antigen receptor (CAR1);

(ii) the site 2 construct optionally further comprises one or more of:

(a) a polynucleotide encoding a second chimeric antigen receptor (CAR2) that is different from CAR1 in antigen specificity;

(b) a polynucleotide encoding a T cell enhancer (TCE); and

(c) a polynucleotide encoding a cytokine;

(iii) the site 2 differs from the site 1; and

(iv) the site 2 construct comprises an exogenous promoter that regulates expression of the polynucleotides in the site 2 construct.

4. The cell or population thereof of claim 2, wherein (i) the site 1 comprises one of CD38, CD54, CD56, CD58, TIM3, ASB2, TIGIT, H11 or PH12; and (ii) integration of the site 1 construct at any of CD38, CD54, CD56, CD58, TIM3, ASB2, or TIGIT knocks out an endogenous gene at the site 1.

5. The cell or population thereof of claim 3, wherein (i) the site 2 comprises one of CD38, CD54, CD56, CD58, TIM3, ASB2, TIGIT, H11 or PH12; and (ii) integration of the site 2 construct at any of CD38, CD54, CD56, CD58, TIM3, ASB2, or TIGIT knocks out an endogenous gene at the site 2.

6. The cell or population thereof of claim 1, wherein the ADR is specific to 41BB.

7. The cell or population thereof of claim 1, wherein the ADR comprises a 41BB-specific ligand operably linked to a signaling domain promoting effector cell activation, and wherein:

(i) the ADR comprises an amino acid sequence of at least 75%, 80%, 85%, 90%, 95% or 99% identity to SEQ ID NOs: 66 - 69; or

(ii) the signaling domain comprises an amino acid sequence of at least 75%, 80%, 85%, 90%, 95% or 99% identity to SEQ ID NO: 60.

8. The cell or population thereof of claim 2, wherein

(i) the TGFβ-SRR further comprises a partial or full peptide of the intracellular domain (ICD) of a cytokine receptor comprising an IL2R, IL12R, IL18R, IL21R, or any combination thereof;

(ii) the C-X-C motif chemokine receptor comprises CXCR2 or CXCR3;

or

(iii) the integration site PH12 is a safe harbor locus having a coordinate of chr17:44210001-44271500 in human reference genome assembly hg38.

9. The cell or population thereof of claim 8, wherein

(i) the cytokine receptor is IL2Rβ, thereby forming a TGFβR2-IL2Rβ redirector receptor, and the intracellular domain (ICD) of IL2Rβ comprises an amino acid sequence represented by SEQ ID NO: 4; or

(ii) the cytokine receptor is IL12Rβ, thereby forming a TGFβR2-IL12Rβ redirector receptor, and the intracellular domain (ICD) of IL12Rβ comprises an amino acid sequence represented by SEQ ID NO: 5 or SEQ ID NO: 6; or

(iii) the cytokine receptor is IL18Rβ, thereby forming a TGFβR2-IL18Rβ redirector receptor, and the intracellular domain (ICD) of IL18Rβ comprises an amino acid sequence represented by SEQ ID NO: 7; or

(iv) the cytokine receptor is IL21Rβ, thereby forming a TGFβR2-IL21Rβ redirector receptor, and the intracellular domain (ICD) of IL21Rβ comprises an amino acid sequence represented by SEQ ID NO: 8.

10. The cell or population thereof of claim 3, wherein the first CAR and the second CAR are specific to different antigens, and wherein:

(i) the antigen comprises ADGRE2, B7H3, carbonic anhydrase IX (CAIX), CCR1, CCR4, carcinoembryonic antigen (CEA), CD3, CD5, CD7, CD8, CD10, CD20, CD22, CD30, CD33, CD34, CD38, CD41, CD44, CD44V6, CD49f, CD56, CD70, CD74, CD79b, CD99, CD123, CD133, CD138, CDS, CLEC12A, an antigen of a cytomegalovirus (CMV) infected cell, epithelial glycoprotein-2 (EGP-2), epithelial glycoprotein-40 (EGP-40), epithelial cell adhesion molecule (EpCAM), EGFRvIII, receptor tyrosine-protein kinases erb- B2,3,4, EGFIR, EGFR-VIII, ERBB folate-binding protein (FBP), fetal acetylcholine receptor (AChR), folate receptor-α, Ganglioside G2 (GD2), Ganglioside G3 (GD3), GPRC5D, human Epidermal Growth Factor Receptor 2 (HER2), human telomerase reverse transcriptase (hTERT), ICAM-1, Integrin B7, Interleukin-13 receptor subunit alpha-2 (IL-13Rα2), κ-light chain, kinase insert domain receptor

(KDR), KLK2, Lewis A (CA19.9), Lewis Y (LeY), L1 cell adhesion molecule (L1-CAM), LILRB2, melanoma antigen family A 1 (MAGE-A1), MICA/B, Mucin 1 (Muc-1), Mucin 16 (Muc-16), Mesothelin (MSLN), NKCSI, NKG2D ligands, c-Met, cancer-testis antigen NY-ESO-1, oncofetal antigen (h5T4), PRAME, prostate stem cell antigen (PSCA), PRAME prostate-specific membrane antigen (PSMA), tumor-associated glycoprotein 72 (TAG-72), TIM-3, TRBCI, TRBC2, vascular endothelial growth factor R2 (VEGF-R2), Wilms tumor protein (WT-1), and a pathogen antigen; or

(ii) the antigen comprises B7H3, BCMA, CD19, CD20, CD22, CD38, CD52, CD79b, CD123, EGFR, EGP2/EpCAM, GD2, GPRC5D, HER2, KLK2, MICA/B, MSLN, VEGF-R2, PSMA and PDL1.

11. The cell or population thereof of claim 3, wherein the TCE is TCF1 or CD27.

12. The cell or population thereof of claim 3, wherein the site 1 is CD38, and wherein the site 2 is one of CD58, TIM3, ASB2, TIGIT, or PH12.

13. A cell or a population thereof, wherein:

(i) the cell is (a) an immune cell; (b) an induced pluripotent cell (iPSC); or (c) a derivative effector cell obtained from differentiating the iPSC; and

(ii) comprising a construct at an integration site, wherein the construct comprises a polynucleotide encoding a first chimeric antigen receptor (CAR1), and wherein the construct further comprises one or more of:

(a) a polynucleotide encoding a second chimeric antigen receptor (CAR2) that is different from CAR1 in antigen specificity;

(b) a polynucleotide encoding a T cell enhancer (TCE);

(c) a polynucleotide encoding a cytokine;

(iii) the integration site comprises one of CD38, CD54, CD56, CD58, TIM3, ASB2, TIGIT, H11 and PH12;

(iv) the construct comprises an exogenous promoter that regulates expression of the polynucleotides in the construct; and

(v) integration of the construct at any of CD38, CD54, CD56, CD58, TIM3, ASB2, or TIGIT knocks out an endogenous gene at the integration site.

14. The cell or population thereof of claim 13, wherein the first CAR and the second CAR are specific to different antigens, wherein

the antigen comprises B7H3, BCMA, CD19, CD20, CD22, CD38, CD52, CD79b, CD123, EGFR, EGP2/EpCAM, GD2, GPRC5D, HER2, KLK2, MICA/B, MSLN, VEGF-R2, PSMA and PDL1.

15. The cell or population thereof of claim 13, wherein the TCE is TCF1 or CD27.

16. A cell or population thereof, wherein:

(i) the cell is (a) an immune cell; (b) an induced pluripotent cell (iPSC); or (c) a derivative effector cell obtained from differentiating the iPSC; and

(ii) comprising an insertion at an integration site PH12, wherein the integration site PH12 is a safe harbor locus having a coordinate of chr17:44210001-44271500 in human reference genome assembly hg38.

17. The cell or population thereof of claim 16, wherein the insertion comprises a construct comprising polynucleotides encoding one or more CARs, a cytokine, a T cell enhancer, a TGFβ-SRR, a C-X-C motif chemokine receptor or a variant thereof, an exogenous CD16 or a variant thereof, or any combination thereof.

18. The cell or population thereof of claim 1, wherein the cell comprises:

(i) CD38 targeted insertion of polynucleotides encoding TGFβ-SRR, hnCD16, and CXCR2;

(ii) TRAC targeted insertion of the polynucleotides encoding ADR and IL2;

(iii) CD58 targeted insertion of a polynucleotide encoding at least one CAR; and

(iv) knock-out of CD38, TRAC and CD58.

19. A composition comprising (i) the cell or population thereof of any one of claims 1-18; and (ii) one or more therapeutic agents.

20. The composition of claim 19, wherein the one or more therapeutic agents comprise a peptide, a cytokine, a checkpoint inhibitor, a mitogen, a growth factor, a small RNA, a dsRNA (double stranded RNA), mononuclear blood cells, feeder cells, feeder cell components or replacement factors thereof, a vector comprising one or more polynucleic acids of interest, an antibody, an engager, a chemotherapeutic agent or a radioactive moiety, or an immunomodulatory drug (IMiD).

21. A master cell bank (MCB) comprising the iPSC of any one of claims 1-18.

22. Use of the composition of claim 19 or 20 in the manufacture of a medicament for treating an autoimmune disorder, a hematological malignancy, a solid tumor, cancer, or a virus infection in a subject in need of an adoptive cell therapy.

23. The composition of claim 19 or 20 for use in therapy.