CLAIMS

WHAT IS CLAIMED IS:

1. A modified immune cell comprising:

(a) an insertion and/or deletion in one or more gene loci each encoding an endogenous immune protein selected from the group consisting of CD3δ, CD3ε, CD3γ, B2M, CIITA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, and invariant chain (Ii Chain), wherein the insertion and/or deletion is capable of downregulating gene expression of the one or more endogenous immune genes; and

(b) an exogenous nucleic acid encoding a chimeric antigen receptor (CAR), an engineered T cell receptor (TCR), a Killer cell immunoglobulin-like receptor (KIR), an antigen-binding polypeptide, a cell surface receptor ligand, or a tumor antigen; and optionally

(c) further comprising a dominant negative receptor, a switch receptor, a chemokine, a chemokine receptor, a cytokine, a cytokine receptor, IL-7, IL-7R, IL-15, IL-15R, IL-21, IL-18, CCL21, CCL19, or a combination thereof.

2. The modified immune cell of claim 1, wherein the insertion and/or deletion is capable of downregulating the gene expression of:

(a) a T cell receptor subunit selected from CD3δ, CD3ε, and/or CD3γ;

(b) a HLA class I molecule selected from B2M, TAP1, TAP2, TAPBP, and/or NLRC5; and

(c) a HLA class II molecule selected from HLA-DM, RFX5, RFXANK, RFXAP, and/or invariant chain (Ii Chain).

3. The modified immune cell of claim 2, wherein:

(a) the insertion and/or deletion is capable of downregulating:

(i) the gene expression of CD3δ, and

(ii) the gene expression of a HLA molecule selected from the group consisting of B2M, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, invariant chain (Ii Chain), and a combination thereof; or

(b) the insertion and/or deletion is capable of downregulating:

(i) the gene expression of CD3ε, and

(ii) the gene expression of a HLA molecule selected from the group consisting

of B2M, TAP1, TAP2, TAPBP, NLRC5, CIITA, HLA-DM, RFX5, RFXANK, RFXAP, invariant chain (Ii Chain), and a combination thereof; or

(c) the insertion and/or deletion is capable of downregulating:

(i) the gene expression of CD3γ, and

(ii) the gene expression of a HLA molecule selected from the group consisting of B2M, TAP1, TAP2, TAPBP, NLRC5, CIITA, HLA-DM, RFX5, RFXANK, RFXAP, invariant chain (Ii Chain), and a combination thereof.

4. The modified immune cell of any one of claims 1-3, wherein the insertion and/or deletion is capable of downregulating the gene expression of:

(I) any one of the following:

(a) CD3ε, B2M, and CIITA;

(b) CD3ε, B2M, and RFX5;

(c) CD3ε, B2M, and RFXAP;

(d) CD3ε, B2M, and RFXANK;

(e) CD3ε, B2M, and HLA-DM;

(f) CD3ε, B2M, and Ii chain;

(g) CD3ε, TAP1, and CIITA;

(h) CD3ε, TAP1, and RFX5;

(i) CD3ε, TAP1, and RFXAP;

(j) CD3ε, TAP1, and RFXANK;

(k) CD3ε, TAP1, and HLA-DM;

(l) CD3ε, TAP1, and Ii chain;

(m) CD3ε, TAP2, and CIITA;

(n) CD3ε, TAP2, and RFX5;

(o) CD3ε, TAP2, and RFXAP;

(p) CD3ε, TAP2, and RFXANK;

(q) CD3ε, TAP2, and HLA-DM;

(r) CD3ε, TAP2, and Ii chain;

(s) CD3ε, NLRC5, and CIITA;

(t) CD3ε, NLRC5, and RFX5;

(u) CD3ε, NLRC5, and RFXAP;

(v) CD3ε, NLRC5, and RFXANK;

(w) CD3ε, NLRC5, and HLA-DM;

(x) CD3ε, NLRC5, and Ii chain;

(y) CD3ε, TAPBP, and CIITA;

(z) CD3ε, TAPBP, and RFX5;

(aa) CD3ε, TAPBP, and RFXAP;

(bb) CD3ε, TAPBP, and RFXANK;

(cc) CD3ε, TAPBP, and HLA-DM; or

(dd) CD3ε, TAPBP, and Ii chain; or

(II) any one of the following:

(a) CD3δ, B2M, and CIITA;

(b) CD3δ, B2M, and RFX5;

(c) CD3δ, B2M, and RFXAP;

(d) CD3δ, B2M, and RFXANK;

(e) CD3δ, B2M, and HLA-DM;

(f) CD3δ, B2M, and Ii chain;

(g) CD3δ, TAP1, and CIITA;

(h) CD3δ, TAP1, and RFX5;

(i) CD3δ, TAP1, and RFXAP;

(j) CD3δ, TAP1, and RFXANK;

(k) CD3δ, TAP1, and HLA-DM;

(l) CD3δ, TAP1, and Ii chain;

(m) CD3δ, TAP2, and CIITA;

(n) CD3δ, TAP2, and RFX5;

(o) CD3δ, TAP2, and RFXAP;

(p) CD3δ, TAP2, and RFXANK;

(q) CD3δ, TAP2, and HLA-DM;

(r) CD3δ, TAP2, and Ii chain;

(s) CD3δ, NLRC5, and CIITA;

(t) CD3δ, NLRC5, and RFX5;

(u) CD3δ, NLRC5, and RFXAP;

(v) CD3δ, NLRC5, and RFXANK;

(w) CD3δ, NLRC5, and HLA-DM;

(x) CD3δ, NLRC5, and Ii chain;

(y) CD3δ, TAPBP, and CIITA;

(z) CD3δ, TAPBP, and RFX5;

(aa) CD3δ, TAPBP, and RFXAP;

(bb) CD3δ, TAPBP, and RFXANK;

(cc) CD3δ, TAPBP, and HLA-DM; or

(dd) CD3δ, TAPBP, and Ii chain; or

(III) any one of the following:

(a) CD3γ, B2M, and CIITA;

(b) CD3γ, B2M, and RFX5;

(c) CD3γ, B2M, and RFXAP;

(d) CD3γ, B2M, and RFXANK;

(e) CD3γ, B2M, and HLA-DM;

(f) CD3γ, B2M, and Ii chain;

(g) CD3γ, TAP1, and CIITA;

(h) CD3γ, TAP1, and RFX5;

(i) CD3γ, TAP1, and RFXAP;

(j) CD3γ, TAP1, and RFXANK;

(k) CD3γ, TAP1, and HLA-DM;

(l) CD3γ, TAP1, and Ii chain;

(m) CD3γ, TAP2, and CIITA;

(n) CD3γ, TAP2, and RFX5;

(o) CD3γ, TAP2, and RFXAP;

(p) CD3γ, TAP2, and RFXANK;

(q) CD3γ, TAP2, and HLA-DM;

(r) CD3γ, TAP2, and Ii chain;

(s) CD3γ, NLRC5, and CIITA;

(t) CD3γ, NLRC5, and RFX5;

(u) CD3γ, NLRC5, and RFXAP;

(v) CD3γ, NLRC5, and RFXANK;

(w) CD3γ, NLRC5, and HLA-DM;

(x) CD3γ, NLRC5, and Ii chain;

(y) CD3γ, TAPBP, and CIITA;

(z) CD3γ, TAPBP, and RFX5;

(aa) CD3γ, TAPBP, and RFXAP;

(bb) CD3γ, TAPBP, and RFXANK;

(cc) CD3γ, TAPBP, and HLA-DM; or

(dd) CD3γ, TAPBP, and Ii chain.

5. The modified immune cell of any one claims 1-4, wherein:

(a) the modified immune cell is selected from the group consisting of a T cell, a natural killer cell (NK cell), a natural killer T cell, a lymphoid progenitor cell, a hematopoietic stem cell, a stem cell, a macrophage, and a dendritic cell; and/or

(b) the modified immune cell is a CD4+ T cell or a CD8+ T cell; and/or

(c) the modified immune cell is an allogeneic T cell or autologous human T cell.

6. The modified immune cell of any one claims 1-5, wherein the insertion and/or deletion is the result of gene editing selected from the group consisting of:

(a) a CRISPR-associated (Cas) (CRISPR-CAs) endonuclease system and a guide RNA;

(b) a TALEN gene editing system, a zinc finger nuclease (ZFN) gene editing system, a meganuclease gene editing system, or a mega-TALEN gene editing system; and

(c) a gene silencing system selected from antisense RNA, antigomer RNA, RNAi, siRNA, or shRNA.

7. The modified immune cell of claim 6, wherein :

(a) the Cas endonuclease comprises Cas3, Cas4, Cas8a, Cas8b, Cas9, Cas10, Cas10d, Cas12a, Cas12b, Cas12d, Cas12e, Cas12f, Cas12g, Cas12h, Cas12i, Cas13, Cas14, CasX, Cse1, Csy1, Csn2, Cpf1, C2c1, Csm2, Cmr5, Fok1, *S. pyogenes* Cas9, *Staphylococcus aureus* Cas9, MAD7, or any combination thereof ; or

(b) the CRISPR-Cas system comprises an pAd5/F35-CRISPR vector; or

(c) the guide RNA comprises a guide sequence that is complementary with a sequence within the one or more gene loci each encoding the immune protein selected from the group consisting of CD3δ, CD3ε, CD3γ, B2M, CIITA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, and invariant chain (Ii Chain).

8. The modified immune cell of claim 7, wherein:

(a) the guide RNA is complementary with a sequence within: (1) one or more exons of CD3δ, CD3ε, or CD3γ, or (2) exon 1 of CD3δ, CD3ε, or CD3γ; or

(b) the sequence is within the CD3δ gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 53; or

(c) the sequence is within the CD3ε gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 52; or

(d) the sequence is within the CD3γ gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 54; or

(e) the sequence is within the B2M gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 55; or

(f) the sequence is within the CIITA gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 61; or

(g) the sequence is within the TAP1 gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 56; or

(h) the sequence is within the TAP2 gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 57; or

(i) the sequence is within the TAPBP gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 58, SEQ ID NO: 59, or a combination thereof; or

(j) the sequence is within the NLRC5 gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 60; or

(k) the sequence is within the HLA-DM gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 62; or

(l) the sequence is within the RFX5 gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 63, SEQ ID NO: 64, or a combination thereof; or

(m) the sequence is within the RFXANK gene locus and the guide RNA comprises a

nucleic acid sequence encoded by SEQ ID NO: 65; or

(n) the sequence is within the RFXAP gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 66; or

(o) the sequence is within the Ii Chain gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 67, SEQ ID NO: 68, or a combination.

9. The modified immune cell of any one of claims 1-8, wherein:

(a) the immune cell exerts a reduced immune response in a subject when the modified immune cell is administered to the subject, as compared to the immune response exerted by an unmodified immune cell administered to the same subject;

(b) the immune cell exerts a reduced immune response in a subject when the modified immune cell is administered to the subject, as compared to the immune response exerted by an immune cell comprising an insertion and/or deletion capable of downregulating the gene expression of TRAC, B2M, and CIITA, and optionally wherein the immune response is a graft-versus-host disease (GvHD) response, and further optionally wherein the reduced GvHD response is elicited against an HLA-I mismatched cell or against an HLA-II mismatched cell.

10. The modified immune cell of claim 9, wherein:

(a) the GvHD response is reduced by about 10% or more, about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 95% or more; or

(b) the GvHD response is reduced by about 1-fold or more, about 2-fold or more, about 3-fold or more, about 4-fold or more, about 5-fold or more, about 6-fold or more, about 7-fold or more, about 8-fold or more, about 9-fold or more, about 10-fold or more, about 20-fold or more, about 30-fold or more, about 50-fold or more, about 100-fold or more, about 150-fold or more, or about 200-fold or more; and/or

(c) the reduced GvHD response by the modified immune cell is compared to an equivalent immune cell without the deletion and/or insertion in one or more gene loci, or an immune cell comprising the deletion and/or insertion in TRAC, B2M, and CIITA.

11. The modified cells of any one of claims 1-10, wherein the exogenous nucleic acid encodes a chimeric antigen receptor (CAR), and wherein the CAR comprises an antigen binding

domain, a hinge domain, a transmembrane domain, a costimulatory signaling domain, and an intracellular signaling domain.

12. The modified immune cell of claim 11, wherein:

(a) the antigen-binding domain comprises a full length antibody or an antigen-binding fragment thereof, a Fab, a $F(ab)_2$, a monospecific Fab_2, a bispecific Fab_2, a trispecific Fab_2, a single-chain variable fragment (scFv), a diabody, a triabody, a minibody, a V-NAR, or a VhH; and/or

(b) the transmembrane domain is selected from an artificial hydrophobic sequence, a transmembrane domain of a type I transmembrane protein, an alpha, beta, or zeta chain of a T cell receptor, CD28, CD3 epsilon, CD45, CD4, CD2, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, OX40 (CD134), 4-1BB (CD137), ICOS (CD278), CD154, CD357 (GITR), Toll-like receptor 1 (TLR1), TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, and a transmembrane domain derived from a killer immunoglobulin-like receptor (KIR); and/or

(c) the costimulatory domain comprises one or more of a costimulatory domain of a protein selected from the group consisting of proteins in the TNFR superfamily, CD28, 4-1BB (CD137), OX40 (CD134), PD-1, CD7, LIGHT, CD83L, DAP10, DAP12, CD27, CD2, CD5, ICAM-1, LFA-1, Lck, TNFR-I, TNFR-II, Fas, CD30, CD40, ICOS (CD278), NKG2C, B7-H3 (CD276), and an intracellular domain derived from a killer immunoglobulin-like receptor (KIR), or a variant thereof; and/or

(d) the intracellular signaling domain comprises an intracellular domain selected from the group consisting of cytoplasmic signaling domains of a human CD2, CD3 zeta chain (CD3ζ), FcγRIII, FcsRI, a cytoplasmic tail of an Fc receptor, an immunoreceptor tyrosine-based activation motif (ITAM) bearing cytoplasmic receptor, TCR zeta, FcR gamma, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d, or a variant thereof; and/or

(e) the antigen binding domain targets a tumor antigen is:

(i) associated with a hematologic malignancy;

(ii) associated with a solid tumor; and/or

(iii) selected from the group consisting of ROR1, mesothelin, c-Met, PSMA, PSCA, Folate receptor alpha, Folate receptor beta, EGFR, EGFRvIII, GPC2, GPC2, Mucin 1(MUC1), Tn antigen ((Tn Ag) or (GalNAca-Ser/Thr)), TnMUC1, GDNF family receptor alpha-4 (GFRa4), fibroblast activation protein (FAP), and Interleukin-13 receptor subunit alpha-2 (IL-

13Ra2 or CD213A2); and/or

(f) the intracellular signaling domain comprises a human CD3 zeta chain (CD3ζ); and/or

(g) the CAR comprises:

(i) a PSMA antigen binding domain, a CD2 costimulatory domain, and a CD3 zeta intracellular signaling domain;

(ii) a mesothelin antigen binding domain, a 4-1BB costimulatory domain, and a CD3 zeta signaling domain; or

. (iii) a TnMUC1 antigen binding domain, a CD2 costimulatory domain, and a CD3 zeta signaling domain.

13. The modified immune cell of any one of claims 1-12, wherein:

(a) the switch receptor comprises an extracellular domain of a signaling protein associated with a negative signal, a transmembrane domain, and an intracellular domain of a signaling protein associated with a positive signal; and/or

(b) the dominant negative receptor comprises:

(i) a truncated variant of a wild-type protein associated with a negative signal;

(ii) a variant of a wild-type protein associated with a negative signal comprising an extracellular domain, a transmembrane domain, and substantially lacking an intracellular signaling domain; or

(iii) an extracellular domain of a signaling protein associated with a negative signal, and a transmembrane domain.

14. The modified immune cell of claim 13, wherein:

(a) the protein associated with the negative signal is selected from the group consisting of CTLA4, PD-1, TGFβRII, BTLA, VSIG3, VSIG8, and TIM-3; and/or

(b) the protein associated with the positive signal is selected from the group consisting of CD28, 4-1BB, IL12Rβ1, IL12Rβ2, CD2, ICOS, and CD27; and/or

(c) the switch receptor is selected from the group consisting of PD-1-CD28, PD-1^{A132L}-CD28, PD-1-CD27, PD-1^{A132L}-CD27, PD-1-4-1BB, PD-1^{A132L}-4-1BB, PD-1-ICOS, PD-1^{A132L}-ICOS, PD-1-IL12Rβ1, PD-1^{A132L}-IL12Rβ1, PD-1-IL12Rβ2, PD-1^{A132L}-IL12Rβ2, VSIG3-CD28, VSIG8-CD28, VSIG3-CD27, VSIG8-CD27, VSIG3-4-1BB, VSIG8-4-1BB, VSIG3-

ICOS, VSIG8-ICOS, VSIG3-IL12Rβ1, VSIG8-IL12Rβ1, VSIG3-IL12Rβ2, VSIG8-IL12Rβ2, TGFβRII-CD27, TGFβRII-CD28, TGFβRII-4-1BB, TGFβRII-ICOS, TGFβRII-IL12Rβ1, and TGFβRII-IL12Rβ2; and/or

(d) the dominant negative receptor is PD1, VSIG3, VISG8, or TGFβR dominant negative receptor; and/or

(e) the transmembrane domain is:

(i) selected from a transmembrane domain of a protein selected from the group consisting of CTLA4, PD-1, VSIG3, VSIG8, TGFβRII, BTLA, TIM-3, CD28, 4-1BB, IL12Rβ1, IL12Rβ2, CD2, ICOS, and CD27; or

(ii) selected from the transmembrane of the protein associated with a negative signal or the transmembrane domain of the protein associated with the negative signal.

15. An isolated modified T cell, comprising at least one functionally impaired polypeptide selected from the group consisting of CD3δ, CD3ε, CD3γ, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, and invariant chain (Ii Chain);

wherein the modified T cell comprising the functionally impaired polypeptide exhibits at least one of:

(i) reduced T cell receptor expression as compared to an unmodified T cell;

(ii) reduced expression of the impaired polypeptide;

(iii) complete absence of the T cell receptor complex surface expression; and

(iv) reduced or insufficient T cell receptor cross-linking.

16. The isolated modified T cell of claim 15, wherein:

(a) the modified T cell exerts a reduced immune response in a subject when the modified T cell is administered to the subject, as compared to the immune response exerted by an unmodified T cell administered to the same subject; and/or

(b) the modified T cell comprises two or more functionally impaired polypeptides, and wherein the second impaired polypeptide is T-cell receptor alpha chain (TRAC); and/or

(c) the modified T cell comprises:

(i) three or more functionally impaired polypeptides selected from TRAC, CD3δ, CD3ε, CD3γ, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii chain;

(ii) two functionally impaired polypeptides selected from CD3α, CD3δ, CD3ε,

CD3γ, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii chain;

(iii) three functionally impaired polypeptides selected from CD3α, CD3δ, CD3ε, CD3γ, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii chain;

(iv) a functionally impaired polypeptide selected from the group consisting of CD3δ, CD3ε, and CD3γ, and at least one functionally impaired polypeptide selected from TRAC, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii Chain; or

(v) a functionally impaired polypeptide selected from the group consisting of CD3δ, CD3ε, and CD3γ, and a functionally impaired polypeptide selected from TRAC, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii Chain; and/or

(d) the modified T cell comprises:

(i) functionally impaired CD3δ and at least one functionally impaired polypeptide selected from TRAC, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii chain;

(ii) functionally impaired CD3ε and at least one functionally impaired polypeptide selected from TRAC, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii chain; or

(iii) functionally impaired CD3γ and at least one functionally impaired polypeptide selected from TRAC, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii chain; and/or

(e) the modified T cell comprises two or more functionally impaired polypeptides selected from TRAC, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, or Ii chain; and/or

(f) the modified T cell:

(i) has a reduced expression of TRAC, CD3δ, CD3ε, CD3γ, B2M, C2TA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, Ii chain, or any combination thereof, or

(ii) does not express , CD3δ, CD3ε, CD3γ, TRAC, B2M, C2TA, TAP1,

TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, Ii chain, or any combination thereof; and/or

(g) the modified T cell further comprises a functionally impaired polypeptide selected from TRAC, B2M, and C2TA; and/or

(h) the modified T cell has a reduced expression of TRAC, B2M, or C2TA or does not express TRAC, B2M, or C2TA; and/or

(i) modification of CD3δ, CD3ε, and/or CD3γ leads to an impaired TCR/CD3 complex function; and/or

(j) CD3δ, CD3ε, or CD3γ is modified by targeting one or more exons of CD3δ, CD3ε, or CD3γ, optionally exon 1 of CD3δ, CD3ε, or CD3γ.

17. A method for generating a modified immune cell comprising:

(a) introducing into the immune cell one or more nucleic acids capable of downregulating gene expression of one or more endogenous immune genes encoding an endogenous immune protein selected from the group consisting of CD3δ, CD3ε, CD3γ, B2M, CIITA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, and invariant chain (Ii Chain);

(b) introducing into the immune cell an exogenous nucleic acid encoding a chimeric antigen receptor (CAR), an engineered T cell receptor (TCR), a Killer cell immunoglobulin-like receptor (KIR), an antigen-binding polypeptide, a cell surface receptor ligand, or a tumor antigen; and

(c) expanding the modified immune cell to generate a population of T cells; and optionally

(d) further comprising introducing into the immune cell an exogenous nucleic acid encoding a dominant negative receptor, a switch receptor, or a combination thereof.

18. The method of claim 17, wherein:

(a) wherein the one or more nucleic acids are capable of downregulating the gene expression of:

(i) a T cell receptor subunit selected from CD3δ, CD3ε, or CD3γ;

(ii) a HLA class I molecule selected from B2M, TAP1, TAP2, TAPBP, or NLRC5; and

(iii) a HLA class II molecule selected from HLA-DM, RFX5, RFXANK,

RFXAP, or invariant chain (Ii Chain); and/or

(b) wherein the one or more nucleic acids are capable of downregulating the gene expression of CD3δ, and the gene expression of a HLA molecule selected from the group consisting of B2M, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, invariant chain (Ii Chain), and a combination thereof; and/or

(c) wherein the one or more nucleic acids are capable of downregulating the gene expression of CD3ε, and a HLA molecule selected from the group consisting of B2M, TAP1, TAP2, TAPBP, NLRC5, CIITA, HLA-DM, RFX5, RFXANK, RFXAP, invariant chain (Ii Chain), and a combination thereof; and/or

(d) wherein the one or more nucleic acids are capable of downregulating the gene expression of CD3γ, and a HLA molecule selected from the group consisting of B2M, TAP1, TAP2, TAPBP, NLRC5, CIITA, HLA-DM, RFX5, RFXANK, RFXAP, invariant chain (Ii Chain), and a combination thereof.

19. The method of claim 17 or 18, wherein the one or more nucleic acids are capable of downregulating the gene expression of:

(I) any one of the following:

(a) CD3ε, B2M, and CIITA;

(b) CD3ε, B2M, and RFX5;

(c) CD3ε, B2M, and RFXAP;

(d) CD3ε, B2M, and RFXANK;

(e) CD3ε, B2M, and HLA-DM;

(f) CD3ε, B2M, and Ii chain;

(g) CD3ε, TAP1, and CIITA;

(h) CD3ε, TAP1, and RFX5;

(i) CD3ε, TAP1, and RFXAP;

(j) CD3ε, TAP1, and RFXANK;

(k) CD3ε, TAP1, and HLA-DM;

(l) CD3ε, TAP1, and Ii chain;

(m) CD3ε, TAP2, and CIITA;

(n) CD3ε, TAP2, and RFX5;

(o) CD3ε, TAP2, and RFXAP;

(p) CD3ε, TAP2, and RFXANK;

(q) CD3ε, TAP2, and HLA-DM;

(r) CD3ε, TAP2, and Ii chain;

(s) CD3ε, NLRC5, and CIITA;

(t) CD3ε, NLRC5, and RFX5;

(u) CD3ε, NLRC5, and RFXAP;

(v) CD3ε, NLRC5, and RFXANK;

(w) CD3ε, NLRC5, and HLA-DM;

(x) CD3ε, NLRC5, and Ii chain;

(y) CD3ε, TAPBP, and CIITA;

(z) CD3ε, TAPBP, and RFX5;

(aa) CD3ε, TAPBP, and RFXAP;

(bb) CD3ε, TAPBP, and RFXANK;

(cc) CD3ε, TAPBP, and HLA-DM; or

(dd) CD3ε, TAPBP, and Ii chain; or

(II) any one of the following:

(a) CD3δ, B2M, and CIITA;

(b) CD3δ, B2M, and RFX5;

(c) CD3δ, B2M, and RFXAP;

(d) CD3δ, B2M, and RFXANK;

(e) CD3δ, B2M, and HLA-DM;

(f) CD3δ, B2M, and Ii chain;

(g) CD3δ, TAP1, and CIITA;

(h) CD3δ, TAP1, and RFX5;

(i) CD3δ, TAP1, and RFXAP;

(j) CD3δ, TAP1, and RFXANK;

(k) CD3δ, TAP1, and HLA-DM;

(l) CD3δ, TAP1, and Ii chain;

(m) CD3δ, TAP2, and CIITA;

(n) CD3δ, TAP2, and RFX5;

(o) CD3δ, TAP2, and RFXAP;

(p) CD3δ, TAP2, and RFXANK;

(q) CD3δ, TAP2, and HLA-DM;

(r) CD3δ, TAP2, and Ii chain;

(s) CD3δ, NLRC5, and CIITA;

(t) CD3δ, NLRC5, and RFX5;

(u) CD3δ, NLRC5, and RFXAP;

(v) CD3δ, NLRC5, and RFXANK;

(w) CD3δ, NLRC5, and HLA-DM;

(x) CD3δ, NLRC5, and Ii chain;

(y) CD3δ, TAPBP, and CIITA;

(z) CD3δ, TAPBP, and RFX5;

(aa) CD3δ, TAPBP, and RFXAP;

(bb) CD3δ, TAPBP, and RFXANK;

(cc) CD3δ, TAPBP, and HLA-DM; or

(dd) CD3δ, TAPBP, and Ii chain; or

(III) any one of the following:

(a) CD3γ, B2M, and CIITA;

(b) CD3γ, B2M, and RFX5;

(c) CD3γ, B2M, and RFXAP;

(d) CD3γ, B2M, and RFXANK;

(e) CD3γ, B2M, and HLA-DM;

(f) CD3γ, B2M, and Ii chain;

(g) CD3γ, TAP1, and CIITA;

(h) CD3γ, TAP1, and RFX5;

(i) CD3γ, TAP1, and RFXAP;

(j) CD3γ, TAP1, and RFXANK;

(k) CD3γ, TAP1, and HLA-DM;

(l) CD3γ, TAP1, and Ii chain;

(m) CD3γ, TAP2, and CIITA;

(n) CD3γ, TAP2, and RFX5;

(o) CD3γ, TAP2, and RFXAP;

(p) CD3γ, TAP2, and RFXANK;

(q) CD3γ, TAP2, and HLA-DM;

(r) CD3γ, TAP2, and Ii chain;

(s) CD3γ, NLRC5, and CIITA;

(t) CD3γ, NLRC5, and RFX5;

(u) CD3γ, NLRC5, and RFXAP;

(v) CD3γ, NLRC5, and RFXANK;

(w) CD3γ, NLRC5, and HLA-DM;

(x) CD3γ, NLRC5, and Ii chain;

(y) CD3γ, TAPBP, and CIITA;

(z) CD3γ, TAPBP, and RFX5;

(aa) CD3γ, TAPBP, and RFXAP;

(bb) CD3γ, TAPBP, and RFXANK;

(cc) CD3γ, TAPBP, and HLA-DM; or

(dd) CD3γ, TAPBP, and Ii chain.

20. The method of any one claims 17-19, wherein:

(a) the immune cell is selected from the group consisting of a T cell, a natural killer cell (NK cell), a natural killer T cell, a lymphoid progenitor cell, a hematopoietic stem cell, a stem cell, a macrophage, and a dendritic cell; and/or

(b) the immune cell is a CD4+ T cell or a CD8+ T cell; and/or

(c) the immune cell is an allogeneic T cell or autologous T cell.

21. The method of any one of claims 17-20, wherein:

(a) the nucleic acids are introduced into the immune cell by viral transduction, wherein the viral transduction comprises contacting the immune cell with a viral vector comprising the one or more nucleic acids; and/or

(b) the nucleic acids are introduced into the immune cell by viral transduction, wherein the viral transduction comprises contacting the immune cell with a viral vector comprising the one or more nucleic acids, and further wherein the viral vector is selected from the group consisting of a retroviral vector, sendai viral vectors, adenoviral vectors, adeno-

associated virus vectors, and lentiviral vectors; and/or

(c) each of the one or more nucleic acids capable of downregulating expression comprises a gene editing system selected from the group consisting of:

(i) a CRISPR-associated (Cas) (CRISPR-CAs) endonuclease system and a guide RNA;

(ii) a TALEN gene editing system, a zinc finger nuclease (ZFN) gene editing system, a meganuclease gene editing system, or a mega-TALEN gene editing system; and

(iii) a gene silencing system selected from antisense RNA, antigomer RNA, RNAi, siRNA, or shRNA.

22. The method of claim 21, wherein :

(a) the Cas endonuclease comprises Cas3, Cas4, Cas8a, Cas8b, Cas9, Cas10, Cas10d, Cas12a, Cas12b, Cas12d, Cas12e, Cas12f, Cas12g, Cas12h, Cas12i, Cas13, Cas14, CasX, Cse1, Csy1, Csn2, Cpf1, C2c1, Csm2, Cmr5, Fok1, *S. pyogenes* Cas9, *Staphylococcus aureus* Cas9, MAD7, or any combination thereof ; and/or

(b) the CRISPR-Cas system comprises an pAd5/F35-CRISPR vector; and/or

(c) the guide RNA comprises a guide sequence that is complementary with a sequence within the one or more gene loci each encoding the immune protein selected from the group consisting of CD3δ, CD3ε, CD3γ, B2M, CIITA, TAP1, TAP2, TAPBP, NLRC5, HLA-DM, RFX5, RFXANK, RFXAP, and invariant chain (Ii Chain); and/or

(d) the guide RNA is complementary with a sequence within: (1) one or more exons of CD3δ, CD3ε, or CD3γ, or (2) exon 1 of CD3δ, CD3ε, or CD3γ; and/or

(e) the sequence is within the CD3δ gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 53;

(f) the sequence is within the CD3ε gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 52;

(g) the sequence is within the CD3γ gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 54;

(h) the sequence is within the B2M gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 55;

(i) the sequence is within the CIITA gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 61;

(j) the sequence is within the TAP1 gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 56;

(k) the sequence is within the TAP2 gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 57;

(l) the sequence is within the TAPBP gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 58, SEQ ID NO: 59, or a combination thereof;

(m) the sequence is within the NLRC5 gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 60;

(n) the sequence is within the HLA-DM gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 62;

(o) the sequence is within the RFX5 gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 63, SEQ ID NO: 64, or a combination thereof;

(p) the sequence is within the RFXANK gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 65;

(q) the sequence is within the RFXAP gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 66 or

(r) the sequence is within the Ii Chain gene locus and the guide RNA comprises a nucleic acid sequence encoded by SEQ ID NO: 67, SEQ ID NO: 68, or a combination thereof.

23. The method of any one of claims 17-22, wherein:

(a) the immune cell exerts a reduced immune response in a subject when the immune cell is administered to the subject, as compared to the immune response exerted by an unmodified immune cell administered to the same subject; and/or

(b) the immune cell exerts a reduced immune response in a subject when the immune cell is administered to the subject, as compared to the immune response exerted by an immune cell comprising one or more nucleic acids capable of downregulating the gene expression of TRAC, B2M, and CIITA; and/or

(c) the immune cell exerts a reduced immune response in a subject when the immune cell is administered to the subject, wherein the immune response is a graft-versus-host disease (GvHD) response; and/or

(d) the immune cell exerts a reduced immune response in a subject when the immune cell is administered to the subject, wherein the immune response is a graft-versus-host disease

(GvHD) response, and further wherein the reduced GvHD response is elicited against an HLA-I mismatched cell or against an HLA-II mismatched cell; and/or

(e) the immune cell exerts a reduced immune response in a subject when the immune cell is administered to the subject, wherein the immune response is a graft-versus-host disease (GvHD) response, wherein the GvHD response is:

(i) reduced by about 10% or more, about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 95% or more; or

(ii) reduced by about 1-fold or more, about 2-fold or more, about 3-fold or more, about 4-fold or more, about 5-fold or more, about 6-fold or more, about 7-fold or more, about 8-fold or more, about 9-fold or more, about 10-fold or more, about 20-fold or more, about 30-fold or more, about 50-fold or more, about 100-fold or more, about 150-fold or more, or about 200-fold or more; and/or

(f) the immune cell exerts a reduced immune response in a subject when the immune cell is administered to the subject, wherein the immune response is a graft-versus-host disease (GvHD) response, and further wherein the reduced GvHD response by the modified immune cell is compared to an equivalent immune cell without the deletion and/or insertion in one or more gene loci, or an immune cell comprising the deletion and/or insertion in TRAC, B2M, and CIITA.

24. The method of any one of claims 17-23, wherein:

(a) the exogenous nucleic acid encodes a chimeric antigen receptor (CAR), and wherein the CAR comprises an antigen binding domain, a hinge domain, a transmembrane domain, a costimulatory signaling domain, and an intracellular signaling domain; and/or

(b) the exogenous nucleic acid encodes a chimeric antigen receptor (CAR), and wherein the CAR comprises an antigen binding domain, a hinge domain, a transmembrane domain, a costimulatory signaling domain, and an intracellular signaling domain, and further wherein the antigen binding domain targets a tumor antigen:

(i) associated with a hematologic malignancy;

(ii) associated with a solid tumor; and/or

(iii) selected from the group consisting of ROR1, mesothelin, c-Met, PSMA, PSCA, Folate receptor alpha, Folate receptor beta, EGFR, EGFRvIII, GPC2, GPC2, Mucin

1(MUC1), Tn antigen ((Tn Ag) or (GalNAca-Ser/Thr)), TnMUC1, GDNF family receptor alpha-4 (GFRa4), fibroblast activation protein (FAP), and Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); and/or

(c) the exogenous nucleic acid encodes a chimeric antigen receptor (CAR), and wherein the CAR comprises an antigen binding domain, a hinge domain, a transmembrane domain, a costimulatory signaling domain, and an intracellular signaling domain, and further wherein the CAR comprises:

(i) a PSMA antigen binding domain, a CD2 costimulatory domain, and a CD3 zeta intracellular signaling domain;

(ii) a mesothelin antigen binding domain, a 4-1BB costimulatory domain, and a CD3 zeta signaling domain; or

(iii) a TnMUC1 antigen binding domain, a CD2 costimulatory domain, and a CD3 zeta signaling domain; and/or

(d) the switch receptor comprises:

(i) an extracellular domain of a signaling protein associated with a negative signal selected from the group consisting of CTLA4, PD-1, VISG3, VSIG8, TGFβRII, BTLA, and TIM-3,

(ii) a transmembrane domain, and

(iii) an intracellular domain of a signaling protein associated with a positive signal selected from the group consisting of CD28, 4-1BB, IL12Rβ1, IL12Rβ2, CD2, ICOS, and CD27; and/or

(e) the dominant negative receptor comprises:

(i) a truncated variant of a wild-type protein associated with a negative signal,

(ii) a variant of a wild-type protein associated with a negative signal comprising an extracellular domain, a transmembrane domain, and substantially lacking an intracellular signaling domain; or

(iii) an extracellular domain of a signaling protein associated with a negative signal, and a transmembrane domain; and/or

(f) the switch receptor is selected from the group consisting of PD-1-CD28, PD-1^{A132L}-CD28, PD-1-CD27, PD-1^{A132L}-CD27, PD-1-4-1BB, PD-1^{A132L}-4-1BB, PD-1-ICOS, PD-1^{A132L}-ICOS, PD-1-IL12Rβ1, PD-1^{A132L}-IL12Rβ1, PD-1-IL12Rβ2, PD-1^{A132L}-IL12Rβ2, VSIG3-

CD28, VSIG8-CD28, VSIG3-CD27, VSIG8-CD27, VSIG3-4-1BB, VSIG8-4-1BB, VSIG3-ICOS, VSIG8-ICOS, VSIG3-IL12Rβ1, VSIG8-IL12Rβ1, VSIG3-IL12Rβ2, VSIG8-IL12Rβ2, TGFβRII-CD27, TGFβRII-CD28, TGFβRII-4-1BB, TGFβRII-ICOS, TGFβRII-IL12Rβ1, and TGFβRII-IL12Rβ2; and/or

(g) the dominant negative receptor is PD1, VSIG3, VSIG8, or TGFβR dominant negative receptor; and/or

(h) the transmembrane domain is:

(i) selected from a transmembrane domain of a protein selected from the group consisting of CTLA4, PD-1, BTLA, TGFβRII, BTLA, TIM-3, CD28, 4-1BB, IL12Rβ1, IL12Rβ2, CD2, ICOS, and CD27; or

(ii) selected from the transmembrane of the protein associated with a negative signal or the transmembrane domain of the protein associated with the negative signal.

25. The method of any one of claims 17-24:

(a) wherein expanding the modified immune cell comprises culturing the T cell with a factor selected from the group consisting of flt3-L, IL- 1, IL-3, IL-2, IL-7, IL-15, IL-18, IL-21, TGFbeta, IL-10, and c-kit ligand; and/or

(b) further comprising introducing a polypeptide and/or a nucleic acid encoding Klf4, Oct3/4 and Sox2 in the immune cell to induce pluripotency of the immune cell; and/or

(c) wherein the immune cell is obtained from a blood sample, a whole blood sample, a peripheral blood mononuclear cell (PBMC) sample, or an apheresis sample; and/or

(d) wherein the immune cell is obtained from an apheresis sample and further wherein the apheresis sample is a cryopreserved sample; and/or

(e) wherein the immune cell is obtained from an apheresis sample and further wherein the apheresis sample is a fresh sample; and/or

(f) wherein the immune cell is obtained from a human subject.

26. A population of modified immune cells obtained from the method of any one of claims 17-25.

27. A composition comprising the modified immune cell or modified T cell of any one of claims 1-16, or the population of modified immune cells of claim 26, and a pharmaceutically acceptable carrier or excipient.

28. Use of the composition of claim 27 in the manufacture of a medicament for treating a disease or condition associated with enhanced immunity in a subject in need thereof.

29. The use of claim 28, wherein:

(a) the condition is a cancer; and/or

(b) the condition is a cancer and further wherein the cancer is selected from the group consisting of breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer, and any combination thereof; and/or

(c) the condition is a cancer and the cancer is a solid tumor, or a hematologic malignancy.

30. Use of the modified immune cells or modified T cells of any one of claims 1-16, the population of modified immune cells of claim 26, or the composition of claim 27 in the manufacture of a medicament for treating a cancer.

31. The use of claim 30, wherein the cancer is a solid tumor, or a hematologic malignancy.

32. Use of a pharmaceutical composition comprising the modified immune cell or modified T cell of any one of claims 1-16, the population of modified immune cells of claim 26, or the composition of claim 27 in the manufacture of a medicament for stimulating a T cell-mediated immune response to a target cell or tissue in a subject.

33. A kit comprising the modified immune cells of any one of claims 1-16, the population of modified T cells of claim 26, or the composition of claim 27, optionally comprising an instruction for use.