What is claimed is:

1. A genetically engineered mammalian cell comprising a heterologous sequence at an integration site in an exon or an intron of a *FOXP3* locus in the genome, wherein

the heterologous sequence comprises

(i) a nucleotide sequence comprising contiguously all the *FOXP3* exon sequences downstream of the integration site,

(ii) a transgene, wherein the transgene is under the transcriptional control of the endogenous *FOXP3* promoter in the *FOXP3* locus; and

when the promoter is activated, the cell expresses both FOXP3 protein and a product of the transgene from the locus as separate polypeptide products, wherein a full-length *FOXP3* mRNA is transcribed, under the transcriptional control of the endogenous *FOXP3* promoter, from the endogenous *FOXP3* exon sequences upstream of the integration site and the nucleotide sequence of (i).

2. A method of making a genetically engineered mammalian cell by inserting a heterologous sequence at an integration site in an exon or intron of a *FOXP3* locus in the genome of the cell, comprising:

contacting a mammalian cell with a nucleic acid construct comprising (i) the heterologous sequence and (ii) a first homologous region (HR) and a second HR flanking the heterologous sequence, wherein

the heterologous sequence comprises

(i) a nucleotide sequence comprising contiguously all the *FOXP3* exon sequences downstream of the integration site, and

(ii) a transgene, wherein the transgene is under the transcriptional control of a the endogenous *FOXP3* promoter in the *FOXP3* locus;

the first and second HRs are homologous to a first genomic region (GR) and a second GR flanking the integration site; and

culturing the cell under conditions that allow integration of the heterologous sequence between the first and second GRs in the *FOXP3* locus

wherein the integrated heterologous sequence allows the *FOXP3* locus to express both *FOXP3* and a product of the transgene from the locus as separate polypeptide products, and

wherein a full-length *FOXP3* mRNA is transcribed, under the transcriptional control of the endogenous *FOXP3* promoter, from the endogenous *FOXP3* exon sequences upstream of the integration site and the nucleotide sequence of (i).

3. The method of claim 2, wherein the integration is facilitated by a zinc finger nuclease or nickase (ZFN), a transcription activator-like effector domain nuclease or nickase (TALEN), a meganuclease, an integrase, a recombinase, a transposase, or a CRISPR/Cas system.

4. The method of claim 2 or 3, wherein the nucleic acid construct is a lentiviral construct, an adenoviral construct, an adeno-associated viral construct, a plasmid, a DNA construct, or an RNA construct.

5. The cell or method of any one of the preceding claims, wherein the heterologous sequence comprises an internal ribosome entry site (IRES) immediately upstream of the transgene, or a coding sequence for a self-cleaving peptide immediately upstream of and in-frame with the transgene.

6. The cell or method of claim 5, wherein the self-cleaving peptide is a 2A peptide, optionally selected from the group consisting of a P2A peptide, an E2A peptide, an F2A peptide, and a T2A peptide.

7. The cell or method of claim 6, wherein the heterologous sequence is inserted into a *FOXP3* intron upstream of one or more *FOXP3* exons, wherein

the heterologous sequence comprises a splice acceptor upstream of the nucleotide sequence to allow expression of the full-length *FOXP3* mRNA transcript from the locus.

8. The cell or method of claim 7, wherein the *FOXP3* intron is intron 4, 9, or 10.

9. The cell or method of any one of claims 1-8, wherein the transgene product is a chimeric antigen receptor (CAR) or a T-cell receptor (TCR).

10. The cell or method of claim 9, wherein the CAR or TCR is specific for (i) an autoantigen, (ii) a B cell antigen optionally selected from CD19 and CD20, or (iii) an allogeneic HLA class I molecule, wherein the class I molecule is optionally HLA-A2.

11. The cell or method of any one of claims 1-8, wherein the transgene product is a cytokine, a chemokine, a growth factor, or a signaling factor; or an AAV capsid protein selected from VP1, VP2, or VP3.

12. The cell or method of any one of the preceding claims, wherein the cell is a lymphoid cell, a lymphoid progenitor cell, a mesenchymal stem cell, a hematopoietic stem cell, an induced pluripotent stem cell, or an embryonic stem cell.

13. The cell or method of claim 12, wherein the cell is a regulatory T (Treg) cell.

14. The cell or method of any one of the preceding claims, wherein the cell comprises a null mutation in a gene selected from

a T cell receptor alpha or beta chain gene,

a Class II major histocompatibility complex transactivator (CIITA) gene,

an HLA Class I or II gene,

a transporter associated with antigen processing,

a minor histocompatibility antigen gene, and

a β2 microglobulin (B2M) gene.

15. The cell or method of any one of the preceding claims, wherein the cell is a human cell.

16. The cell or method of any one of the preceding claims, wherein the cell comprises a suicide gene optionally selected from an HSV-TK gene, a cytosine deaminase gene, a nitroreductase gene, a cytochrome P450 gene, or a caspase-9 gene.

17. Use of the Treg of claim 13 in the manufacture of a medicament in treating a patient in need of immunosuppression, wherein the transgene encodes a chimeric antigen receptor, a T-cell receptor, a cytokine, a chemokine, a growth factor, a signaling factor, a B cell antigen, an allogeneic HLA class I molecule, or an AAV capsid protein selected from VP1, VP2, or VP3.

18. The Treg of claim 13 for use in treating a patient in need of immunosuppression, wherein the transgene encodes a chimeric antigen receptor, a T-cell receptor, a cytokine, a chemokine, a growth factor, a signaling factor, a B cell antigen, an allogeneic HLA class I molecule, or an AAV capsid protein selected from VP1, VP2, or VP3.

19. The cell for use of claim 17 or 18, wherein the patient has an autoimmune disease.

20. The use or cell for use of claim 17 or 18, wherein the patient has received or will receive tissue transplantation.

21. The cell for use of claim 17 or 18, wherein the patient is a human.