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 ~~in~~ 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 ~~a~~ *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) ~~a~~ the heterologous sequence and (ii) a first homologous region (HR) and a second HR flanking the heterologous sequence ~~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~~, respectively, in a *FOXP3* locus in the mammalian cell~~; 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 ~~(i)~~ an internal ribosome entry site (IRES) immediately upstream of the transgene, or ~~(ii)~~ 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 ~~(i) a nucleotide sequence coding for the one or more *FOXP3* exons, and (ii)~~ a splice acceptor upstream of the nucleotide sequence to allow expression of ~~a~~ the full-length *FOXP3* mRNA transcript from the locus~~, and~~

~~the nucleotide sequence is (a) immediately upstream of the IRES, or (b) immediately upstream of and in-frame with the coding sequence for the self-cleaving peptide~~.

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. A method of treating a patient in need of immunosuppression, comprising administering to the patient a cell of any one of claims 1 and 5-16.~~

~~18~~17. Use of the Treg of claim 13~~cell of any one of claims 1 and 5-16~~ 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.

~~19~~18. ~~A~~ The Treg of claim 13~~cell of any one of claims 1 and 5-16~~ 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.

~~20~~19. The ~~method, use,~~ or cell for use of ~~any one of~~ claim~~s~~ 17~~-19~~ or 18, wherein the patient has an autoimmune disease.

~~21~~20. The ~~method, use,~~ or cell for use of ~~any one of~~ claim~~s~~ 17~~-19~~ or 18, wherein the patient has received or will receive tissue transplantation.

~~22~~21. The ~~method, use,~~ or cell for use of ~~any one of~~ claim~~s~~ 17~~-21~~ or 18, wherein the patient is a human.