What Is Claimed Is:

1. A population of genetically engineered cells, comprising a first exogenous nucleic acid, which comprises from 5' to 3':

a first nucleotide sequence encoding a signal peptide;

a second nucleotide sequence, which encodes one or more self-cleaving peptides, optionally wherein the self-cleaving peptide is a 2A peptide; and

a third nucleotide sequence encoding a polypeptide, which is free of an N-terminal signal peptide;

wherein the genetically engineered cells express the polypeptide at a lower level as compared to a population of counterpart genetically engineered cells comprising a nucleic acid encoding a counterpart polypeptide having an N-terminus signal peptide.

2. The population of genetically engineered cells of claim 1, wherein the polypeptide encoded by the third nucleotide is a blood factor, an antibody, a chimeric antigen receptor (CAR), a cytoplasmic signaling domain of an immune cell receptor, a hormone, an immune modulating polypeptide, or a combination thereof.

3. The population of genetically engineered cells of claim 2, wherein the polypeptide encoded by the third nucleotide sequence is an immune modulating polypeptide set forth in any one of (a)-(e) below:

(a) a cytokine selected from the group consisting of IL-2, IL-7, IL-9, IL-10, IL-15, IL-12, IL-17, IL-18, IL-21,IL-23, IL-24, IL-27, IL-33, and CCL19;

(b) an inhibitor of a checkpoint molecule selected from the group consisting of PD1, PDL1, LAG3, TIGIT, TIM3, and CTLA4, optionally wherein the checkpoint inhibitor is an anti-PD1/PDL1 antibody, an anti-LAG3 antibody, an anti-TIGIT antibody, an anti-TIM3 antibody, or an anti-CTLA4 antibody;

(c) an immune enhancer selected from the group consisting of 41BBL, anti-CD3 antibody, an anti-FcR antibody, an anti-41BB antibody, an anti-OX40 antibody, an anti-CD28 antibody, and an anti-CD40 antibody;

(d) a cytokine antagonist selected from the group consisting of an anti-IL6 antibody, an anti-GM-CSF antibody, an anti-IFN-γ antibody, an anti-TNF antibody, an anti-IL-1 antibody, and IL-1RA; and

(e) a cytoplasmic signaling domain of an immune cell receptor, which optionally is

selected from the group consisting of CD3, DAP12, FcR, CD79, CNAIP, CD28, 4-1BB, CTLA-4, PD1, TIGIT, LAG3, TIM3 and a cytokine receptor; or

wherein the polypeptide encoded by the third nucleotide sequence is a hormone, optionally wherein the hormone is an insulin or a growth hormone.

4. The population of genetically engineered cells of any one of claims 1-3, wherein the one or more self-cleaving peptides are selected from the group consisting of P2A, T2A, E2A, F2A, and a combination thereof, optionally wherein the one or more 2A self-cleaving peptides comprise a combination of P2A and T2A.

5. The population of genetically engineered cells of any one of claims 1-4, wherein the first nucleotide sequence encoding the signal peptide is directly linked to the second nucleotide sequence encoding the one or more self-cleaving peptides.

6. The population of genetically engineered cells of any one of claims 1-5, wherein the genetically engineered cells further express one or more proteins of interest, which optionally are different from the polypeptide encoded by the third nucleotide sequence.

7. The population of genetically engineered cells of claim 6, wherein the one or more proteins of interest comprise a blood factor, a chimeric antigen receptor (CAR), an immune modulating polypeptide, an antibody, a cytokine, a hormone, a cell surface marker, or a combination thereof,

optionally wherein the CAR comprises an extracellular domain, a hinge and a transmembrane domain, and optionally one or more signaling domains;

optionally wherein the cell surface marker is CD20, a truncated epidermal growth factor receptor (EGFR), or receptor tyrosine kinase–like orphan receptor 1 (ROR1); and

optionally the immune modulating polypeptide is a cytokine antagonist, which preferably is an antibody that binds IL-6, IL-1, GM-CSF, TNF, IFN-γ, or a combination thereof.

8. The population of genetically engineered cells of claim 6 or claim 7, wherein the first exogenous nucleic acid comprises a fourth nucleotide sequence encoding the one or more proteins of interest.

9. The population of genetically engineered cells of claim 8, wherein the fourth nucleotide sequence is located between the first nucleotide sequence encoding the signal peptide and the second nucleotide sequence encoding the one or more self-cleaving peptides; or

wherein the fourth nucleotide sequence is located 5' to the first nucleotide sequence encoding the signal peptide, and/or 3' to the third nucleotide sequence encoding the one or more proteins of interest.

10. The population of genetically engineered cells of any one of claims 7-9, wherein the fourth nucleotide sequence comprises a self-cleaving peptide coding sequence, a promoter sequence, a protease cleavage site coding sequence, an mRNA splicing site, or an internal ribosomal entry sequence.

11. The population of genetically engineered cells of any one of claims 1-10, wherein the population of genetically engineered cells further comprises one or more additional exogenous nucleic acids, which encode the one or more proteins of interest.

12. The population of genetically engineered cells of any one of claims 1-11, wherein the genetically engineered cells comprise immune cells, islet cells, tumor cells, or stem cells.

13. The population of genetically engineered cells of claim 12, which comprises immune cells, wherein the immune cells comprise T-cells, tumor infiltrating lymphocytes, NK cells, dendritic cells, macrophages, B cells, neutrophils, eosinophils, basophils, mast cells, myeloid- derived suppressor cells, or a combination thereof

14. The population of genetically engineered cells of any one of claims 1-13, wherein the polypeptide encoded by the third nucleotide sequence is fused to an immunoglobulin Fc domain or an albumin domain.

15. The population of genetically engineered cells of any one of claims 6-14, wherein any one of the proteins of interest encoded by the fourth nucleotide sequence or encoded by the additional exogenous nucleic acid(s) are fused to an immunoglobulin Fc domain or an albumin domain.

16. A nucleic acid, comprising from 5' to 3':

a first nucleotide sequence encoding a signal peptide;

a second nucleotide sequence, which encodes one or more self-cleaving peptides, wherein optionally the self-cleaving peptide is a 2A peptide; and

a third nucleotide sequence encoding a polypeptide, which is free of an N-terminal signal peptide,

wherein when the nucleic acid is expressed in a cell, the cell expresses the polypeptide at a lower level as compared to a counterpart cell comprising a nucleic acid encoding a counterpart polypeptide that has an N-terminus signal peptide.

17. The nucleic acid of claim 16, which is set forth in any one of claims 2-11, 14, and 15; or

wherein the nucleic acid does not encode another signal peptide between the second and third nucleotide sequences.

18. The nucleic acid of claim 16 or 17, which is a vector and/or an RNA, optionally wherein the vector is an expression vector; or wherein the nucleic acid is a vector, which is a plasmid, retroviral vector, lentiviral vector, adenoviral vector, or adeno-associated viral vector.

19. A pharmaceutical composition comprising the population of genetically engineered cells of any one of claims 1-15 and/or the nucleic acids of any one of claims 16-18 and a pharmaceutically acceptable carrier.

20. The population of genetically engineered cells of any one of claims 1-15 and/or the nucleic acids of any one of claims 16-18, or the pharmaceutical composition of claim 19 for use in treating a disease in a subject.

21. The population of genetically engineered cells, the nucleic acid or the pharmaceutical composition for use of claim 20, wherein the disease is an autoimmune

disorder, cancer, an infectious disease, an immune disorder, a fibrosis disease, or a senescence disease, optionally wherein the senescence disease is liver fibrosis, atherosclerosis, or natural aging.

22. A method for preparing genetically engineered cells, the method comprising:

delivering the nucleic acid of any one of claims 16-18 to a population of cells to produce genetically engineered cells carrying the nucleic acid.