CLAIMS

1. A nucleic acid encoding a synthetic pathway activator (SPA) peptide comprising a chimeric polypeptide comprising:

a. an extracellular domain comprising a CD34 epitope or a CD34 ectodomain;
b. a lipid anchor or a transmembrane domain;
c. an intracellular signaling domain, wherein the intracellular signaling domain comprises a type I cytokine receptor superfamily box2 peptide motif comprising VSVVEIEANDKKP (SEQ ID NO: 107), and a tyrosine phosphorylation motif comprising YXPQ; and
d. a multimerization region.

2. The nucleic acid of claim 1, wherein the intracellular signaling domain comprises a sequence at least about 80%, 85%, 90%, 95%, or 99% identity to a sequence as set forth in SEQ ID NO: 60, wherein the intracellular signaling domain comprises a type I cytokine receptor superfamily box2 peptide motif comprising VSVVEIEANDKKP (SEQ ID NO: 107), and a tyrosine phosphorylation motif comprising YXPQ.

3. The nucleic acid of claim 1 or 2, wherein the intracellular signaling domain comprises the sequence as set forth in SEQ ID NO: 60.

4. The nucleic acid of any one of claims 1-3, wherein the transmembrane domain comprises a sequence at least 90% or 95% identical to the sequence as set forth in SEQ ID NO: 61 or wherein the transmembrane domain comprises the sequence as set forth in SEQ ID NO: 61.

5. The nucleic acid any one of claims 1-4, wherein

a. the multimerization region comprises at least an unpaired cysteine residue; and/or
b. the multimerization region results in constitutive activity of the intracellular signaling domain.

6. The nucleic acid of any one of claims 1-5, wherein the CD34 epitope comprises a sequence as set forth in SEQ ID NO: 238.

7. The nucleic acid of any one of claims 1-6, wherein the extracellular domain comprises a CD34 epitope, the multimerization region comprises a multimerization region comprising an unpaired cysteine residue, the lipid anchor or transmembrane domain comprises a gp130

transmembrane domain, and the intracellular signaling domain comprises a gp130 intracellular signaling domain.

8. The nucleic acid of any one of claims 1-7, wherein the SPA peptide comprises a sequence with at least 90% or 95% sequence identity to a sequence as set forth in SEQ ID NOs: 81, 1-58, 63-80, or 82-104.

9. The nucleic acid of any one of claims 1-8, further comprising an inducible promoter or a constitutive promoter operably linked to the nucleic acid encoding the SPA, optionally wherein the inducible promoter is an HNF1α promoter and/or wherein the constitutive promoter is an EF1α promoter.

10. A vector comprising the nucleic acid of any one of claims 1-9.

11. A synthetic pathway activator (SPA) peptide comprising a chimeric polypeptide comprising:

a. an extracellular domain comprising a CD34 epitope or a CD34 ectodomain;
b. a lipid anchor or a transmembrane domain;
c. an intracellular signaling domain, wherein the intracellular signaling domain comprises a type I cytokine receptor superfamily box2 peptide motif comprising VSVVEIEANDKKP (SEQ ID NO: 107), and a tyrosine phosphorylation motif comprising YXPQ; and
d. a multimerization region.

12. The SPA peptide of claim 11, wherein the intracellular signaling domain comprises a sequence at least about 80%, 85%, 90%, 95%, or 99% identity to a sequence as set forth in SEQ ID NO: 60, wherein the intracellular signaling domain comprises a type I cytokine receptor superfamily box2 peptide motif comprising VSVVEIEANDKKP (SEQ ID NO: 107), and a tyrosine phosphorylation motif comprising YXPQ.

13. The SPA peptide of claim 11 or 12, wherein the intracellular signaling domain comprises the sequence as set forth in SEQ ID NO: 60.

14. The SPA peptide of any one of claims 11-13, wherein the transmembrane domain comprises a sequence at least 90% or 95% identical to the sequence as set forth in SEQ ID NO: 61 or wherein the transmembrane domain comprises the sequence as set forth in SEQ ID NO: 61.

15. The SPA peptide of any one of claims 11-14, wherein

a. the multimerization region comprises at least an unpaired cysteine residue; and/or

b. the multimerization region results in constitutive activity of the intracellular signaling domain.

16. The SPA peptide of any one of claims 11-15, wherein the CD34 epitope comprises a sequence as set forth in SEQ ID NO: 238.

17. The SPA peptide of any one of claims 11-16, wherein the extracellular domain comprises a CD34 epitope, the multimerization region comprises a multimerization region comprising an unpaired cysteine residue, the lipid anchor or transmembrane domain comprises a gp130 transmembrane domain, and the intracellular signaling domain comprises a gp130 intracellular signaling domain.

18. The SPA peptide of any one of claims 11-17, comprising a sequence with at least 90% or 95% sequence identity to a sequence as set forth in SEQ ID NOs: 81, 1-58, 63-80, or 82-104.

19. A multimer comprising the SPA peptide of any one of claims 11-18.

20. A system comprising:

a. optionally, a nucleic acid encoding a first chimeric polypeptide comprising a priming receptor;

b. a nucleic acid encoding a second chimeric polypeptide, optionally comprising a chimeric antigen receptor (CAR); and

c. the nucleic acid of any one of claims 1-9.

21. A cell or population of cells comprising the nucleic acid of any one of claims 1-9.

22. A cell or population of cells comprising the SPA peptide of any one of claims 11-18.

23. The cell or population of cells of claim 21 or 22, wherein the cell is an immune cell, a human immune cell, a primary human immune cell a natural killer (NK) cell, a T cell, a CD8+ T cell, a CD4+ T cell, a primary T cell, a primary human T cell or a T cell progenitor cell.

24. A pharmaceutical composition comprising the cell or population of cells of any one of claims 21-23, and a pharmaceutically acceptable excipient.

25. A pharmaceutical composition comprising the nucleic acid of any one of claims 1-9, and a pharmaceutically acceptable excipient.

26. A method of engineering a cell, comprising contacting the cell with a nucleic acid, wherein the nucleic acid encodes a synthetic pathway activator (SPA) peptide comprising a chimeric polypeptide comprising:

a. an extracellular domain comprising a CD34 epitope or a CD34 ectodomain;
b. a lipid anchor or a transmembrane domain;
c. an intracellular signaling domain, wherein the intracellular signaling domain comprises a type I cytokine receptor superfamily box2 peptide motif comprising VSVVEIEANDKKP (SEQ ID NO: 107), and a tyrosine phosphorylation motif comprising YXPQ; and
d. a multimerization region.

27. Use of the cell or population of cells of claim 21 or 22 in the manufacture of a medicament for treating a disease in a subject or inhibiting a target cell in a subject, wherein the cell or population of cells is to be administered to the subject.

28. A method of modulating a target cell comprising contacting the target cell with a cell or population of cells, wherein the contacting modulates the target cell, and wherein the cell or population of cells comprises nucleic acid encoding a synthetic pathway activator (SPA) peptide comprising a chimeric polypeptide comprising:

a. an extracellular domain comprising a CD34 epitope or a CD34 ectodomain;
b. a lipid anchor or a transmembrane domain;
c. an intracellular signaling domain, wherein the intracellular signaling domain comprises a type I cytokine receptor superfamily box2 peptide motif comprising VSVVEIEANDKKP (SEQ ID NO: 107), and a tyrosine phosphorylation motif comprising YXPQ; and
d. a multimerization region.

29. A method of modulating the activity of a cell or an immune cell comprising:

a. obtaining a cell or an immune cell comprising the nucleic acid of any one of claims 1-9; and
b. contacting the cell or immune cell with a target cell, wherein the synthetic pathway activator modulates the activity of the cell or immune cell.

30. A method of making a nucleotide sequence, comprising obtaining the nucleic acid of any one of claims 1-9; and synthesizing the nucleotide sequence, optionally wherein the synthesizing occurs via replication in a cell.

31. The cell or population of cells of claim 21 or 22, for use in therapy.