SUMMARY

[0007] In one aspect, provided herein are synthetic pathway activator (SPA) peptides comprising a chimeric polypeptide comprising:

i. optionally, an extracellular domain;

ii. a lipid anchor or a transmembrane domain;

iii. an intracellular signaling domain; and

iv. a multimerization region.

[0007a] In one aspect, provided herein is 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.

[0007b] In another aspect, provided herein is a vector comprising the nucleic acid as described herein.

[0007c] In another aspect, provided herein is 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.

[0007d] In another aspect, provided herein is a multimer comprising the SPA peptide as described herein.

[0007e] In another aspect, provided herein is 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 as described herein.

[0007f] In yet another aspect, provided herein is 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.

[0007g] In yet another aspect, provided herein is a use of the cell or population of cells as described herein 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.

[0007h] In yet another aspect, provided herein is 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.

[0007i] In yet another aspect, provided herein is 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 as described herein; 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.

[0007j] In yet another aspect, provided herein is a method of making a nucleotide sequence, comprising obtaining the nucleic acid as described herein; and synthesizing the nucleotide sequence, optionally wherein the synthesizing occurs via replication in a cell.

[0007k] In yet another aspect, provided herein is the cell or population of cells as described herein, for use in therapy.

[0008] In some embodiments, multimerization of the chimeric polypeptide via the multimerization region results in constitutive activity of the intracellular signaling domain.

[0009] In some embodiments, the multimerization region comprises at least one of an unpaired cysteine residue, a leucine zipper, a BCR domain, and a VASP domain.

[0010] In some embodiments, the multimerization region comprises at least an unpaired cysteine residue.

[0011] In some embodiments, the multimerization region comprises at least an unpaired cysteine residue and a leucine zipper.

[0012] In some embodiments, the multimerization region is intracellular when expressed by a cell.

[0013] In some embodiments, the multimerization region is extracellular when expressed by a cell.

[0014] In some embodiments, the intracellular signaling domain induces phosphorylation of STAT1, STAT3, or STAT5.

[0015] In some embodiments, the intracellular signaling domain comprises a type I cytokine receptor superfamily box1 (IWPNVDP (SEQ ID NO: 106)) or box2 (VSVVEIEANDKKP (SEQ ID NO: 107)) peptide motif.

[0016] In some embodiments, the intracellular signaling domain comprises a tyrosine phosphorylation motif comprising YXXQ or YXPQ.

[0017] In some embodiments, the intracellular signaling domain comprises a polypeptide sequence from an interleukin receptor.

[0018] In some embodiments, the interleukin receptor comprises a gp130 intracellular signaling domain.

[0019] In some embodiments, the intracellular signaling domain comprises a polypeptide sequence comprising amino acids 642 to 918 of gp130 (SEQ ID NO: 59).