WHAT IS CLAIMED IS:

1. A fusion protein comprising:

(a) an essential polypeptide;

(b) a degron; and

(c) optionally; a linker.

2. The fusion protein of claim 1, wherein the degron is C-terminal to the essential polypeptide.

3. The fusion protein of any one of claims 1 to 2, wherein the degron is an inducible degron, optionally the degron is a drug-inducible degron, optionally the drug is an immunomodulatory drug (IMiD).

4. The fusion protein of any one of claims 1 to 3, wherein the degron comprises or consists of the amino acid sequence RPFQCNQCGASFTQKGNLLRHIKLH (SEQ ID NO:3),FNVLMVHKRSHTGERPLQCEICGFTCRQKGNLLRHIKLHTGEKPFKCHLCNYACQRRDAL (SEQ ID NO:4), FNVLMVHKRSHTGERP (SEQ ID NO:5), FNVLMVHRRSHTGERP (SEQ ID NO:6), TGEKPFKCHLCNYACQRRDAL (SEQ ID NO:7), TGERPFRCHLCNYACQRRDAL (SEQ ID NO:8), FQCNQCGASFT (SEQ ID NO:9), FQCPICGLVIK (SEQ ID NO:10), LQCEICGFTCR (SEQ ID NO:11), LQCEICGYQCR (SEQ ID NO:12), or LQCEVCGFQCR (SEQ ID NO:13).

5. The fusion protein of any one of claims 1 to 4, wherein the degron is a superdegron.

6. The fusion protein of any one of claims 1 to 5, which comprises a linker sequence between the essential polypeptide and the degron.

7. The fusion protein of any one of claims 1 to 6, comprising two or more degrons, optionally wherein the degrons are in tandem.

8. The fusion protein of any one of claims 1 to 7, wherein the essential polypeptide is a STEL polypeptide, optionally wherein the STEL polypeptide is GAPDH.

9. A targeting construct comprising:

(a) a first homology arm corresponding to a 5′ target sequence comprising a first region of homology to an essential gene encoding an essential polypeptide in a target genomic locus;

(b) a nucleotide sequence encoding a degron (“degron coding sequence”);

(c) a second homology arm corresponding to a 3′ target sequence comprising second region of homology to the essential gene in the target genomic locus.

wherein the targeting construct is configured such that upon its recombination with the target genomic locus, the essential gene is modified such to encode a fusion protein comprising the essential polypeptide and the degron, optionally wherein the fusion protein has one or more features as defined in any one of claims 1 to 8.

10. The targeting construct of claims 9, wherein the first homology arm and second homology arm are each 500 to 1,500 nucleotides in length and/or wherein the length difference between the first and second homology arms, if any, is less than 75 nucleotides.

11. The targeting construct of claim 9 or claim 10, wherein the targeting construct further comprises a transgene between the degron coding sequence and the second homology arm, optionally the transgene is linked to the nucleotide sequence encoding the fusion protein (“fusion protein coding sequence”).

12. The targeting construct of any one of claims 9 to 11, which is a vector, optionally wherein the vector is a DNA vector or an RNA vector.

13. A system comprising:

(a) the targeting construct of any one of claims 9 to 12;

(b) a CRISPR-associated endonuclease (“Cas polypeptide”) or a nucleic acid encoding a Cas polypeptide; and

(c) a guide RNA (“gRNA”) comprising a scaffold for binding the Cas polypeptide and a spacer sequence corresponding to the essential gene, or a nucleic acid encoding the gRNA.

14. The system of claim 13, wherein the guide RNA is a single guide RNA (“sgRNA”).

15. The system of claim 13 or claim 14, which is in the form of a ribonucleoprotein particle (“RNP”).

16. A method of producing a gene-edited target cell, comprising:

(a) introducing the system of any one of claims 13 to 15 into a target cell; and

(b) culturing the target cell under conditions in which gene editing occurs, thereby producing gene-edited target cell.

17. The method of claim 16, wherein the target cell is a stem cell or a cell differentiated from a stem cell, optionally the cell is (a) a human embryonic stem cell, (b) an induced pluripotent stem cell (“iPSC”) or (c) a cell differentiated from (a) or (b).

18. The method of claim 17, wherein the target cell is:

(a) a human immune cell, optionally selected from a T cell, a T cell expressing a chimeric antigen receptor (CAR) or recombinant TCR, a regulatory T cell, a myeloid cell, a dendritic cell, and a macrophage (e.g., an immunosuppressive macrophage);

(b) a cell in the human nervous system, optionally selected from dopaminergic neuron, a microglial cell, an oligodendrocyte, an astrocyte, a cortical neuron, a spinal or oculomotor neuron, an enteric neuron, a Placode-derived cell, a Schwann cell, and a trigeminal or sensory neuron;

(c) a cell in the human cardiovascular system, optionally selected from a cardiomyocyte, an endothelial cell, and a nodal cell;

(d) a cell in the human metabolic system, optionally selected from a hepatocyte, a cholangiocyte, and a pancreatic beta cell,

(e) a cell in the human ocular system, optionally selected from a retinal pigment epithelial cell, a photoreceptor cone cell, a photoreceptor rod cell, a bipolar cell, or a ganglion cell, or

(f) a progenitor or precursor of any one of the aforementioned cells.

19. A gene-edited target cell obtained or obtainable by the method of any one of claims 16 to 18.

20. A gene-edited target cell comprising an essential gene that encodes a fusion protein comprising:

(a) a degron;

(b) an essential polypeptide encoded by an essential gene as defined in claim 9.

21. A recombinant cell engineered to express the fusion protein of any one of claims 1 to 8, optionally wherein the recombinant cell is a gene-edited target cell according to any one of claim 19 or claim 20.

22. The recombinant cell of claim 21, which is further engineered to express a transgene from a locus other than the essential gene.

23. The recombinant cell of claim 21, which comprises an expression vector comprising a nucleotide sequence encoding the fusion protein of any one of claims 1 to 8.

24. A pharmaceutical composition comprising the gene-edited target cell of claim 19 or claim 20, the recombinant cell of any one of claims 21 to 23 and a pharmaceutically acceptable excipient.

25. Use of the gene-edited target cell claim 19 or claim 20 or the recombinant cell of any one of claims 21 to 23, for the manufacture of a medicament for treating a patient in need thereof, optionally wherein the gene-edited target cell or the recombinant cell is (a) autologous to the patient or (b) allogeneic to the patient.

26. The gene-edited target cell of claim 19 or claim 20, the recombinant cell of any one of claims 21 to 23, or the pharmaceutical composition of claim 24, for use in treating a patient in need thereof, optionally wherein the gene-edited target cell or the recombinant cell is, or the pharmaceutical comprises cells that are: (a) autologous to the patient or (b) allogeneic to the patient.

27. The use of claim 25, an inducer of the degron is to be administered to the subject.

28. The use of claim 25 or claim 27, wherein the degron is a drug-inducible degron, optionally the drug is an immunomodulatory drug (IMiD).

29. Use of an inducer of the degron in the manufacture of a medicament for reducing engineered cells in, or eliminating engineered cells from, a subject who previously received cell therapy with a gene-edited target cell of claim 19 or claim 20, the recombinant cell of any one of claims 21 to 23, or the pharmaceutical composition of claim 24.