CLAIMS

What is claimed:

1. A human hypo-immunogenic pluripotent (HIP) cell that (a) does not express β-2 microglobulin (B2M) protein, (b) does not express CIITA protein, (c) expresses CD47 at a higher level than in a parental pluripotent cell, and (d) expresses a suicide gene that is activated by a trigger that causes the HIP cell to die, wherein the HIP cell further retains differentiation potential into a differentiated cell selected from the group consisting of an endothelial cell, smooth muscle cell, cardiomyocyte, islet cell, neuronal cell, or a retinal pigment epithelium (RPE) cell.

2. The HIP cell of claim 1, wherein the HIP cell shows increased expression of CD47 protein as a result of a modification to an endogenous CD47 gene locus.

3. The HIP cell of claim 1, wherein the increased expression of CD47 protein results from a CD47 transgene.

4. The HIP cell of any one of claims 1-3, wherein the CD47 protein has at least a 90% sequence identity to SEQ ID NO: 3.

5. The HIP cell of any one of claims 1-4, wherein the HIP cell does not express CIITA protein because a gene encoding the CIITA protein is knocked out.

6. The HIP cell of claim 5, wherein the CIITA protein has at least 90% sequence identity to SEQ ID NO: 2.

7. The HIP cell of any one of claims 1-6, wherein the HIP cell does not express B2M protein because a gene encoding the B2M protein is knocked out.

8. The HIP cell of claim 7, wherein the B2M protein has at least 90% sequence identity to SEQ ID NO: 1.

9. The HIP cell of any one of claims 1-8, wherein the suicide gene is a herpes simplex virus thymidine kinase gene (HSV-tk) and the trigger is ganciclovir.

10. The HIP cell of claim 9, wherein the HSV-tk gene encodes a protein comprising the sequence of SEQ ID NO: 4.

11. The HIP cell of any one of claims 1-8, wherein the suicide gene is an *Escherichia coli* cytosine deaminase gene (EC-CD) and the trigger is 5-fluorocytosine (5-FC).

12. The HIP cell of claim 11, wherein the EC-CD gene encodes a protein comprising the sequence of SEQ ID NO: 5.

13. The HIP cell of any one of claims 1-8, wherein the suicide gene encodes an inducible Caspase protein and the trigger is a chemical inducer of dimerization (CID).

14. The HIP cell of claim 13, wherein the inducible Caspase protein comprises the sequence of SEQ ID NO: 6 and the CID is AP1903.

15. A differentiated cell derived from the HIP cell of any one of claims 1-14, wherein said differentiated cell is suitable for therapeutic administration to an allogeneic recipient once every 2 weeks or longer.

16. The differentiated cell of claim 15, wherein said differentiated cell is suitable for therapeutic administration to an allogeneic recipient once every 4 weeks or longer.

17. The differentiated cell of claim 15, wherein said differentiated cell is suitable for therapeutic administration to an allogeneic recipient once every 6 weeks or longer.

18. A hypoimmunogenic cell comprising:

i. one or more genetic alterations that reduce expression of a functional Major Histocompatibility Antigen Class I (HLA-I) complex as compared to a parental cell, and/or one or more genetic alterations that reduce expression of a functional Major Histocompatibility Antigen Class II (HLA-II) complex as compared to the parental cell;

ii. one or more genetic alterations that increases a function of a CD47 protein as compared to a parental cell; and

iii. a safety switch,

wherein the cell is an endothelial cell, a smooth muscle cell, a cardiomyocyte, an islet cell, a neuronal cell, or a retinal pigment epithelium (RPE) cell.

19. The hypoimmunogenic cell of claim 18, wherein the cell is an islet cell.

20. The hypoimmunogenic cell of claim 18, wherein the cell is a neuronal cell.

21. The hypoimmunogenic cell of any one of claims 18-20, wherein the safety switch comprises a suicide gene that is:

i. a herpes simplex virus thymidine kinase gene (HSV-tk),

ii. an *Escherichia coli* cytosine deaminase gene (EC-CD), or

iii. an inducible Caspase protein.

22. The hypoimmunogenic cell of claim 21, wherein the suicide gene is HSV-tk.

23. The hypoimmunogenic cell of claim 21, wherein the suicide gene is EC-CD.

24. The hypoimmunogenic cell of claim 21, wherein the suicide gene is inducible Caspase protein.

25. The hypoimmunogenic cell of any one of claims 18-24, wherein the hypoimmunogenic cell is less susceptible than the parental cell to rejection when transplanted into a subject.

26. The hypoimmunogenic cell of any one of claims 18-25, wherein the hypoimmunogenic cell is less susceptible than the parental cell to macrophage phagocytosis, Natural Killer (NK) cell response, or both.

27. The hypoimmunogenic cell of any one of claims 18-26, wherein the hypoimmunogenic cell is derived from a pluripotent cell.

28. The hypoimmunogenic cell of claim 27, wherein the pluripotent cell is an induced pluripotent stem cell (iPSC), an embryonic stem cell, a fetal stem cell, an amniotic stem cell or a somatic stem cell.

29. The hypoimmunogenic cell of any one of claims 18-28, wherein the one or more genetic alterations that reduce expression of a functional HLA-I complex comprise one or more genetic alterations that reduce expression from one or more HLA-I genes.

30. The hypoimmunogenic cell of any one of claims 18-29, wherein the one or more genetic alterations that reduce expression of a functional HLA-I complex comprise one or more genetic alterations that knock-out expression from one or more HLA-I genes.

31. The hypoimmunogenic cell of claim 29 or 30, wherein the one or more genetic alterations that reduce expression of a functional HLA-I complex are present on both alleles of the one or more HLA-I genes.

32. The hypoimmunogenic cell of any one of claims 29-31, wherein the one or more HLA-I genes comprise a ß-2 microglobulin (B2M) gene, a HLA-A gene, a HLA-B gene, a HLA-C gene, or a combination thereof.

33. The hypoimmunogenic cell of any one of claims 29-32, wherein the one or more HLA-I genes comprise a B2M gene.

34. The hypoimmunogenic cell of any one of claims 18-33, wherein the one or more genetic alterations that reduce expression of a functional HLA-II complex comprise one or more genetic alterations that reduce expression from one or more HLA-II genes.

35. The hypoimmunogenic cell of any one of claims 18-34, wherein the one or more genetic alterations that reduce expression of a functional HLA-II complex comprise one or more genetic alterations that knock-out expression from one or more HLA-II genes.

36. The hypoimmunogenic cell of claim 34 or 35, wherein one or more genetic alterations that reduce expression of a functional HLA-II complex are present on both alleles of the one or more HLA-II genes.

37. The hypoimmunogenic cell of any one of claims 34-36, wherein the one or more HLA-II genes comprise a CIITA gene, a HLA-DP gene, a HLA-DR gene, a HLA-DQ gene, or a combination thereof.

38. The hypoimmunogenic cell of any one of claims 34-37, wherein the one or more HLA-II genes comprise a CIITA gene.

39. The hypoimmunogenic cell of any one of claims 18-38, wherein expression from one or more HLA-I genes comprises surface expression of one or more proteins encoded by the one or more HLA-I genes.

40. The hypoimmunogenic cell of any one of claims 18-39, wherein expression from one or more HLA-II genes comprises surface expression of one or more proteins encoded by the one or more HLA-II genes.

41. The hypoimmunogenic cell of any one of claims 18-40, wherein the one or more genetic alterations that increases expression of CD47 protein comprise a modification to an endogenous CD47 gene locus or expression of a CD47 transgene.

42. The hypoimmunogenic cell of claim 41, wherein the modification to an endogenous CD47 gene locus comprises exchanging an endogenous promoter for a constitutive promoter or an inducible promoter.

43. The hypoimmunogenic cell of any one of claims 18-41, wherein the genetic alteration that increases expression of CD47 protein comprises a CD47 transgene under the control of an inducible or constitutive promoter.

44. The hypoimmunogenic cell of any one of claims 18-43, wherein one or more of the genetic alterations are introduced to the cell using a zinc finger nuclease (ZFN), transcription activator-like effector nucleases (TALEN), clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9, a retroviral vector, a lentiviral vector, an adenovirus vector, an Sendai viral vector, or a combination thereof.

45. The hypoimmunogenic cell of any one of claims 18-44, wherein the hypoimmunogenic cell is human.

46. The hypoimmunogenic cell of any one of claims 18-45, wherein said hypoimmunogenic cell is suitable for therapeutic administration to an allogeneic recipient once every 2 weeks or longer.

47. The hypoimmunogenic cell of any one of claims 18-45, wherein said hypoimmunogenic

cell is suitable for therapeutic administration to an allogeneic recipient once every 4 weeks or longer.

48. The hypoimmunogenic cell of any one of claims 18-45, wherein said hypoimmunogenic cell is suitable for therapeutic administration to an allogeneic recipient once every 6 weeks or longer.