CLAIMS

1. A universal donor cell comprising a nucleotide sequence encoding HLA class I histocompatibility antigen, alpha chain E (HLA-E)~~a first tolerogenic factor~~ inserted within or near a gene encoding thioredoxin interacting protein (TXNIP)~~a survival factor~~, wherein the universal donor cell expresses HLA-E ~~the tolerogenic factor~~ and has disrupted expression of TXNIP~~the survival factor~~, and the universal donor cell has increased immune evasion and/or cell survival compared to a control cell.

2. The universal donor cell of claim 1, wherein the control cell is a wild type cell or a cell that does not comprise the inserted nucleotide sequence.

3. The universal donor cell of claims 1 or 2, wherein the disrupted expression of ~~the survival factor~~TXNIP comprises reduced or eliminated expression of TXNIP.

~~4. The universal donor cell of any one of claims 1 to 3, wherein the first tolerogenic factor is PD-L1, HLA-E, HLA-G, CTLA-4, or CD47.~~

~~5. The universal donor cell of any one of claims 1 to 4, wherein the survival factor is TXNIP, ZNF143, FOXO1, JNK, or MANF.~~

~~6. The universal donor cell of any one of claims 1 to 5, wherein the first tolerogenic factor is HLA-E and the survival factor is TXNIP.~~

~~7.~~4. The universal donor cell of any one of claims ~~5 or 6~~1 to 3, wherein the nucleotide sequence encoding HLA-E comprises sequence encoding a HLA-E trimer comprising a B2M signal peptide fused to an HLA-G presentation peptide fused to a B2M membrane protein fused to HLA-E without its signal peptide.

~~8.~~5. The universal donor cell of claim ~~7~~4, wherein the sequence encoding the HLA-E trimer consists essentially of SEQ ID NO: 55.

~~9.~~6. The universal donor cell of any one of claims 1 to ~~8~~5, wherein the nucleotide sequence encoding ~~the first tolerogenic factor~~HLA-E is operably linked to an exogenous promoter.

~~10.~~7. The universal donor cell of claim ~~9~~6, wherein the exogenous promoter is a CMV, EF1α, PGK, CAG, or UBC promoter.

~~11.~~8. The universal donor cell of any one of claims 1 to ~~10~~7, further comprising a nucleotide sequence encoding ~~a~~ programmed death ligand 1 (~~second tolerogenic factor~~PD-L1) inserted within or near a gene encoding beta-2 microglobulin (B2M)~~a MHC-I or MHC-II human leukocyte antigen or a component or a transcriptional regulator of a MHC-I or MHC-II complex~~, wherein the universal donor cell expresses ~~the tolerogenic factor~~PD-L1 and has disrupted expression of ~~the MHC-I or MHC-II human leukocyte antigen or the component or the transcriptional regulator of the MHC-I or MHC-II complex~~B2M.

~~12.~~9. The universal donor cell of claim ~~11~~8, wherein the disrupted expression of ~~the MHC-I or MHC-II human leukocyte antigen or the component or the transcriptional regulator of the MHC-I or MHC-II complex~~B2M comprises reduced or eliminated expression.

~~13. The universal donor cell of claims 11 or 12, wherein the second tolerogenic factor is PD-L1, HLA-E, HLA-G, CTLA-4, or CD47.~~

~~14. The universal donor cell of any one of claims 11 to 13, wherein the MHC-I or MHC-II human leukocyte antigen or the component or the transcriptional regulator of the MHC-I or MHC-II complex is HLA-A, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, B2M, NLRC5, CIITA, RFX5, RFXAP, or RFXANK.~~

~~15. The universal donor cell of any one of claims 11 to 14, wherein the second tolerogenic factor is PD-L1 and the MHC-I or MHC-II human leukocyte antigen or the component or the transcriptional regulator of the MHC-I or MHC-II complex is B2M.~~

~~16.~~10. The universal donor cell of claim ~~15~~8 or 9, wherein the nucleotide sequence encoding PD-L1 consists essentially of SEQ ID NO: 11.

~~17.~~11. The universal donor cell of any one of claims ~~11 to 16~~8 to 10, wherein the nucleotide sequence encoding ~~the second tolerogenic factor~~PD-L1 is operably linked to an exogenous promoter.

~~18.~~12. The universal donor cell of claim ~~17~~11, wherein the exogenous promoter is a CMV, EF1α, PGK, CAG, or UBC promoter.

~~19. The universal donor cell of any one of claims 11 to 18, wherein the first tolerogenic factor is HLA-E, the survival factor is TXNIP, the second tolerogenic factor is PD-L1, and the MHC-I or MHC-II human leukocyte antigen or the component or the transcriptional regulator of the MHC-I or MHC-II complex is B2M.~~

~~20.~~13. The universal donor cell of any one of claims 1 to ~~19~~12, wherein the cell is a stem cell, optionally~~.~~

~~21. The universal donor cell of claim 20~~, wherein the stem cell is an embryonic stem cell, an adult stem cell, an induced pluripotent stem cell, or a hematopoietic stem cell.

~~22. The~~ The universal donor cell of any one of claims 1 to ~~19~~13, wherein the cell is a differentiated cell or a somatic cell and/or~~.~~

~~23.~~14. ~~The universal donor cell of any one of claims 1 to 19, wherein~~ the cell is capable of being differentiated into lineage-restricted progenitor cells or fully differentiated somatic cells.

~~24. The~~ The universal donor cell of claim ~~23~~14, wherein the lineage-restricted progenitor cells are pancreatic endoderm progenitors, pancreatic endocrine progenitors, mesenchymal progenitor cells, muscle progenitor cells, blast cells, hematopoietic progenitor cells, or neural progenitor cells and/or ~~.~~

~~25.~~15. ~~The universal donor cell of claim 23, wherein~~ the fully differentiated somatic cells are pancreatic beta cells, epithelial cells, endodermal cells, macrophages, hepatocytes, adipocytes, kidney cells, blood cells, cardiomyocytes, or immune system cells.

~~26. A plurality of universal donor cells according to any one of claims 1 to 25.~~

~~27. A population of lineage-restricted progenitor cells or fully differentiated somatic cells derived from the plurality of universal donor cells of claim 26.~~

~~28. The population of cells of claim 27, wherein the lineage-restricted progenitor cells are pancreatic endoderm progenitors, pancreatic endocrine progenitors, mesenchymal progenitor cells, muscle progenitor cells, blast cells, hematopoietic progenitor cells, or neural progenitor cells, and the fully differentiated somatic cells are pancreatic beta cells, epithelial cells, endodermal cells, macrophages, hepatocytes, adipocytes, kidney cells, blood cells, cardiomyocytes, or immune system cells.~~

29. A plurality of universal donor cells according to claims 6 or 19.

30. A population of lineage-restricted progenitor cells or fully-differentiated somatic cells derived from the plurality of universal donor cells of claim 29.

31. The population of cells of claim 30, wherein the lineage-restricted progenitor cells are definitive endoderm cells, primitive gut tube cells, posterior foregut cells, pancreatic endoderm progenitors, pancreatic endocrine progenitors, immature beta cells, or maturing beta cells, and the fully differentiated somatic cells are pancreatic beta cells.

32. The plurality of cells of claim 26 or 29, wherein at least about 50%, at least about 70%, or at least about 90% of the cells express the first tolerogenic factor, the second tolerogenic factor, or the first and second tolerogenic factors.

33. The population of cells of any one of claims 27, 28, 30, or 31, wherein at least about 50%, at least about 70%, or at least about 90% of the cells express the first tolerogenic factor, the second tolerogenic factor, or the first and second tolerogenic factors.

34. A composition comprising the plurality of cells of claim 26 or the population of cells of claims 27 or 28.

35. The composition of claim 34 for use in treating a subject in need thereof.

36. The composition of claim 35, wherein the subject has, is suspected of having, or is at risk for a disease.

37. The composition of claim 36, wherein the disease is a genetically inheritable disease.

38. A composition comprising the plurality of cells of claim 29 or the population of cells of claims 30 or 31.

39. The composition of claim 38 for treating diabetes in a subject in need thereof.

40. The composition or claim 39, wherein the subject has type I diabetes or type II diabetes.

41. The composition of any one of claim 35 to 40, wherein the subject is human.

42. A method of obtaining cells for administration to a subject in need thereof, the method comprising:

(a) obtaining or having obtained the plurality of universal donor cells of any one of claims 26, 29, or 32, and

(b) maintaining the plurality of universal donor cells for a time and under conditions sufficient for the cells to differentiate into lineage-restricted progenitor cells or fully differentiated somatic cells.

43. A method for treating of a subject in need thereof, the method comprising:

(a) obtaining or having obtained the plurality of universal donor cells of any one of claims 26, 29, or 32 following differentiation into lineage-restricted progenitor cells or fully differentiated somatic cells; and

(b) administering the lineage-restricted progenitor cells or fully differentiated somatic cells to the subject.

44. The method of claim 43, wherein administering comprises implanting a device comprising the lineage-restricted progenitor cells or fully differentiated somatic cells into the subject.

45. The method of any one of claims 42 to 44, wherein the lineage-restricted progenitor cells are pancreatic endoderm progenitors, pancreatic endocrine progenitors, mesenchymal progenitor cells, muscle progenitor cells, blast cells, hematopoietic progenitor cells, or neural progenitor cells, and the fully differentiated somatic cells are pancreatic beta cells, epithelial cells, endodermal cells, macrophages, hepatocytes, adipocytes, kidney cells, blood cells, cardiomyocytes, or immune system cells.

46. The method of any one of claims 42 to 45, wherein the subject has, is suspected of having, or is at risk for a disease.

47. The method of claim 46, wherein the disease is a genetically inheritable disease.

48. The method of any one of claims 42 to 47, wherein the subject is human.

49. A method for treating diabetes in a subject in need thereof, the method comprising:

(a) obtaining or having obtained the plurality of universal donor cells of claims 29 or 32 following differentiation into pancreatic endoderm cells, pancreatic endocrine cells, immature beta cells, maturing beta cell, or pancreatic beta cells; and

(b) administering the pancreatic endoderm cells, pancreatic endocrine cells, immature beta cells, maturing beta cells, or pancreatic beta cells to the subject.

50. The method of claim 49, wherein administering comprises implanting a device comprising the pancreatic endoderm cells, pancreatic endocrine cells, immature beta cells,

maturing beta cell, or pancreatic beta cells into the subject.

51. The method of claims 49 or 50, wherein the subject has type I diabetes or type II diabetes.

52. The method of any one of claim 49 to 51, wherein the subject is human.