CLAIMS

What is claimed:

~~1. A modified pluripotent cell or a cell derived therefrom, wherein the cell is ABO blood group type 0 and Rhesus factor negative (Rh-), wherein the cell has (a) a reduced or eliminated ABO blood group antigen selected from the group consisting of Al, A2, and B; and/or (b) has a reduced or eliminated Rh protein antigen expression selected from the group consisting of Rh C antigen, Rh E antigen, Kell K antigen (KEL), Duffy (FY) Fya antigen, Duffy Fy3 antigen, Kidd (JK) Jkb antigen, MNS antigen U, and MNS antigen S.~~

~~2. A modified pluripotent cell or a cell derived therefrom, comprising: (a) a modification that reduces or eliminates antigenicity of one or more ABO blood group antigens selected from the group consisting of Al, A2, and B rendering the cell ABO blood group type 0; and/or (b) a modification that reduces or eliminates antigenicity of one or more Rh antigens selected from the group consisting of Rh C antigen, Rh E antigen, Kell K antigen (KEL), Duffy (FY) Fya antigen, Duffy Fy3 antigen, Kidd (JK) Jkb antigen, MNS antigen U, and MNS antigen S rendering the cell Rh-.~~

~~3. The modified pluripotent cell of claim 1 or claim 2, wherein the cell is a hypoimmunogenic pluripotent (HIP) cell comprising:~~
~~a. an endogenous Major Histocompatibility Antigen Class I (HLA-1) function that is reduced when compared to an unmodified pluripotent cell;~~
~~b. an endogenous Major Histocompatibility Antigen Class II (HLA-II) function that is reduced when compared to an unmodified pluripotent cell; and~~
~~c. an increased CD47 function that reduces susceptibility to NK cell killing.~~

~~4. A modified pluripotent cell or a cell derived thereform, wherein the cell comprises modulated expression of one or more of HLA-I human leukocyte antigens, HLA-II human leukocyte antigens, CD47, CCR5, CXCR4, NLRC5, CIITA, B2M, HLA-A, HLA-B, HLA-C, HLA-E, HLA-G, PD-L1, CTLA-4-Ig, CD47, Cl-inhibitor, IL-35, RFX-5, RFXAP, RFXANK, NFY-A, NFY-B, NFY-C, IRF-1, OX40, GITR, 4-1BB, CD28, B7-1, B7-2, ICOS, CD27,~~

~~HVEM, SLAM, CD226, PD1, CTL4, LAG3, TIGIT, TIM3, CD160, BTLA, CD244, CD30, TLT, VISTA, B7-H3, PD-L2, LFA-1, CD2, CD58, ICAM-3, TCRA, TCRB, FOXP3, HELIOS, ST2, PCSK9, APOC3, CD200, FASLG, CLC21, MFGE8, SERPIN B9, TGF8, CD73, CD39, LAG3, IL1R2, ACKR2, TNFRSF22, TNFRSF23, TNFRS10, DAD1 , and/or IFNγR1 d39 relative to a wild-type stem cell, wherein the cell is ABO blood group type 0 or Rhesus factor negative (Rh ).~~

~~5. A modified pluripotent cell or a cell derived therefrom, wherein the cell is an 0- hypoimmunogenic pluripotent (HIPO-) cell comprising:~~
~~a. an endogenous Major Histocompatibility Antigen Class I (HLA-I) function that is reduced when compared to an unmodified pluripotent cell;~~
~~b. an endogenous Major Histocompatibility Antigen Class II (HLA-II) function that is reduced when compared to an unmodified pluripotent cell;~~
~~c. an increased CD47 function that reduces susceptibility to NK cell killing;~~
~~d. an ABO blood group type 0 (0); and~~
~~e. optionally, a Rhesus factor negative (Rh-) blood type.~~

~~6. The modified pluripotent cell or cell derived therefrom of any one of claims 1-5, wherein the cell is selected from 0- induced pluripotent stem cells (iPSC0 ), 0- embryonic stem cells (ESC0-), 0- endothelial cells, 0- cardiomyocytes, 0- hepatocytes, 0- dopaminergic neurons, 0- pancreatic islet cells, 0- retinal pigment endothelium cells, and other 0- cell types used for transplantation and medical therapies, including 0- chimeric antigen receptor (0- CAR) cells.~~

~~7. The modified pluripotent cell or cell derived therefrom of claim 6, wherein the 0- CAR cell is an 0- chimeric antigen receptor T (0- CAR-T) cell.~~

~~8. The modified pluripotent cell or cell derived therefrom of any one of claims 1-7, wherein said ABO blood group type 0 results from a reduced ABO blood group protein expression.~~

~~9. The modified pluripotent cell or cell derived therefrom of claim 8, wherein said ABO blood group type 0 results from a disruption in human Exon 7 of the ABO gene.~~

~~10. The modified pluripotent cell or cell derived therefrom any one of claims 1-7, wherein said ABO blood group type 0 results from an enzymatic modification of an ABO gene product on a surface of said cell.~~

~~11. The modified pluripotent cell or cell derived therefrom of claim 10, wherein said enzymatic modification removes a carbohydrate from said ABO gene product.~~

~~12. The modified pluripotent cell or cell derived therefrom of claim 10, wherein said enzymatic modification removes a carbohydrate from an ABO Al antigen, A2 antigen, and/or B antigen.~~

~~13. The modified pluripotent cell or cell derived therefrom of any one of claims 1-12, wherein said Rh- results from a reduced Rh protein expression.~~

~~14. The modified pluripotent cell or cell derived therefrom of claim 13, wherein said Rhresults from a disruption in an Rh C antigen, an Rh E antigen, a Kell K antigen (KEL), a Duffy (FY) Fya antigen, a Duffy Fy3 antigen, a Kidd (JK) Jkb antigen, or a Kidd SLC14A1 gene.~~

~~15. The modified pluripotent cell or cell derived therefrom of any one of claims 1-7, wherein said ABO blood group type is endogenously type 0.~~

~~16. The modified pluripotent cell or cell derived therefrom of any one of claims 1-7, wherein said Rh- blood type is endogenously type Rh- .~~

~~17. The modified pluripotent cell or cell derived therefrom of any one of claims 3-16, wherein~~

~~said HLA-I function is reduced by a reduction in expression of a 11-2 microglobulin protein.~~

~~18. The modified pluripotent cell or cell derived therefrom of of claim 17, wherein a gene encoding said 11-2 microglobulin protein is knocked out.~~

~~19. The modified pluripotent cell or cell derived therefrom of any one of claims 3-16, wherein said HLA-I function is reduced by a reduction in expression of an HLA-A protein.~~

~~20. The modified pluripotent cell or cell derived therefrom of claim 19, wherein a gene encoding said HLA-A protein is knocked out.~~

~~21. The modified pluripotent cell or cell derived therefrom of any one of claims 3-16, wherein said HLA-I function is reduced by a reduction in expression of an HLA-B.~~

~~22. The modified pluripotent cell or cell derived therefrom of claim 21, wherein a gene encoding said HLA-B protein is knocked out.~~

~~23. The modified pluripotent cell or cell derived therefrom of any one of claims 3-16, wherein said HLA-I function is reduced by a reduction in expression of an HLA-C protein.~~

~~24. The modified pluripotent cell or cell derived therefrom of claim 23, wherein a gene encoding said HLA-C protein is knocked out.~~

~~25. The modified pluripotent cell or cell derived therefrom of any one of claims 3-24, wherein said HIPO- cell does not comprise an HLA-I function.~~

~~26. The modified pluripotent cell or cell derived therefrom of any one of claims 3-25, wherein said HLA-II function is reduced by a reduction in expression of a CIITA protein.~~

~~27. The modified pluripotent cell or cell derived therefrom of claim 26, wherein a gene encoding said CIITA protein is knocked out.~~

~~28. The modified pluripotent cell or cell derived therefrom of any one of claims 3-25, wherein said HLA-II function is reduced by a reduction in expression of an HLA-DP protein.~~

~~29. The modified pluripotent cell or cell derived therefrom of claim 28, wherein a gene encoding said HLA-DP protein is knocked out.~~

~~30. The modified pluripotent cell or cell derived therefrom of any one of claims 3-25, wherein said HLA-II function is reduced by a reduction in expression of an HLA-DR protein.~~

~~31. The modified pluripotent cell or cell derived therefrom of claim 30, wherein a gene encoding said HLA-DR protein is knocked out.~~

~~32. The modified pluripotent cell or cell derived therefrom of any one of claims 3-25, wherein said HLA-II function is reduced by a reduction in expression of an HLA-DQ protein.~~

~~33. The modified pluripotent cell or cell derived therefrom of claim 32, wherein a gene encoding said HLA-DQ protein is knocked out.~~

~~34. The modified pluripotent cell or cell derived therefrom of any one of claims 3-33, wherein said hypoimmunogenic pluripotent cell does not comprise an HLA-II function.~~

~~35. The modified pluripotent cell or cell derived therefrom of any one of claims 3-34, wherein said reduced susceptibility to NK cell killing is caused by an increased expression of a CD47 protein.~~

~~36. The modified pluripotent cell or cell derived therefrom of claim 35, wherein said increased CD47 protein expression results from a modification to an endogenous CD47~~

~~gene locus.~~

~~37. The modified pluripotent cell or cell derived therefrom of claim 35, wherein said increased CD47 protein expression results from a CD47 transgene.~~

~~38. The modified pluripotent cell or cell derived therefrom of any one of claims 35-37, wherein said CD47 protein has at least a 90% sequence identity to SEQ ID NO:3.~~

~~39. The modified pluripotent cell or cell derived therefrom of claim 38, wherein said CD47 protein has the sequence of SEQ ID NO:3.~~

~~40. The modified pluripotent cell or cell derived therefrom of any one of claims 3-39, further comprising a suicide gene that is activated by a trigger that causes said hypoimmunogenic pluripotent cell to die.~~

~~41. The modified pluripotent cell or cell derived therefrom of claim 40, wherein said suicide gene is a herpes simplex virus thymidine kinase gene (HSV-tk) and said trigger is ganciclovir.~~

~~42. The modified pluripotent cell or cell derived therefrom of claim 41, wherein said HSV-tk gene encodes a protein comprising at least a 90% sequence identity to SEQ ID NO:4.~~

~~43. The modified pluripotent cell or cell derived therefrom of claim 42, wherein said HSV-tk gene encodes a protein comprising the sequence of SEQ ID NO:4.~~

~~44. The modified pluripotent cell or cell derived therefrom of claim 40, wherein said suicide gene is an Escherichia coli cytosine deaminase gene (EC-CD) and said trigger is 5-fluorocytosine (5-FC).~~

~~45. The modified pluripotent cell or cell derived therefrom of claim 44, wherein said EC-CD~~

~~gene encodes a protein comprising at least a 90% sequence identity to SEQ ID NO:5.~~

~~46. The modified pluripotent cell or cell derived therefrom of claim 45, wherein said EC-CD gene encodes a protein comprising the sequence of SEQ ID NO:5.~~

~~47. The modified pluripotent cell or cell derived therefrom of claim 40, wherein said suicide gene encodes an inducible Caspase protein and said trigger is a chemical inducer of dimerization (CID).~~

~~48. The modified pluripotent cell or cell derived therefrom of claim 47, wherein said gene encodes an inducible Caspase protein comprising at least a 90% sequence identity to SEQ ID NO:6.~~

~~49. The modified pluripotent cell or cell derived therefrom of claim 48, wherein said gene encodes an inducible Caspase protein comprising the sequence of SEQ ID NO:6.~~

~~50. The modified pluripotent cell or cell derived therefrom of any one of claims 47-49, wherein said CID is AP1903.~~

~~51. A cell derived from the modified pluripotent cell cell of any one of claims 3-50, wherein said cell is selected from the group consisting of an 0- chimeric antigen receptor (0-CAR) cell, an endothelial cell, a dopaminergic neuron, a cardiac cell, a pancreatic islet cell, and a retinal pigment endothelium cell.~~

~~52. The cell of claim 51, wherein said 0- CAR cell is an 0- CAR-T cell.~~

~~53. The modified pluripotent cell or cell derived therefrom of any one of claims 1-51, wherein the modified pluripotent cell or cell derived therefrom is a cardiomyocyte or cardiomyocyte progenitor cell.~~

~~54. The modified pluripotent cell or cell derived therefrom of any one of claims 1-53 further comprising a reduced or eliminated expression of a CCR5 gene or a CXCR4 gene.~~

~~55. The modified pluripotent cell or cell derived therefrom of any one of claims 1-54 further comprising a reduce or eliminated expression of an NLRC5 gene.~~

~~56. The modified pluripotent cell or cell derived therefrom of any one of claims 1-55 further comprising a modified expression of at least one of gene selected from the group consisting of HLA-A, HLA-B, HLA-C, HLA-E, HLA-G, PD-L1, CTLA-4-Ig, CD47, Clinhibitor, and IL-35.~~

~~57. The modified pluripotent cell or cell derived therefrom of any one of claims 1-56 further comprising a modified expression of at least one gene selected from RFX-5, RFXAP, RFXANK, NFY-A, NFY-B, NFY-C, and IRF-1.~~

~~58. The modified pluripotent cell or cell derived therefrom of any one of claims 1-57 further comprising a modified expression of at least one gene selected from the group consisting of OX40, GITR, 4-1BB, CD28, B7-1, B7-2, ICOS, CD27, HVEM, SLAM, CD226, PD1, CTL4, LAG3, TIGIT, TIM3, CD160, BTLA, CD244, CD30, TLT, VISTA, B7-H3, PD-L2, LFA-1, CD2, CD58, ICAM-3, TCRA, TCRB, FOXP3, HELIOS, ST2, PCSK9, CCR5, and APOC3.~~

~~59. The modified pluripotent cell or cell derived therefrom of any one of claims 1-58 further comprising at least one transgene selected from the group consisting of PDL-1, HLA-G, CD47, CD200, FASLG, CLC21, MFGE8, and SERPIN B9, or at least one transgene encoding an agonist of PDL-1, HLA-G, CD47, CD200, FASLG, CLC21, MFGE8, or SERPIN 9.~~

~~60. The modified pluripotent cell or cell derived therefrom of any one of claims 1-59 further comprising at least one transgene selected from the group consisting of TGF8, CD73,~~

~~CD39, LAG3, IL1R2, ACKR2, TNFRSF22, TNFRSF23, TNFRS10, DAD1 , and IFNyR1 d39, or at least one transgene encoding an agonist of TGF8, CD73, CD39, LAG3, IL1R2, ACKR2, TNFRSF22, TNFRSF23, TNFRS10, DAD1 , or IFNyR1 d39.~~

~~61. A method of transplanting a cell, comprising admininstering one or more cells derived from the modified pluripotent cell of any one of claims 1-60 into a subject in need thereof, wherein said subject is a human, cow, pig, chicken, turkey, horse, sheep, goat, donkey, mule, duck, goose, buffalo, camel, yak, llama, alpaca, mouse, rat, dog, cat, hamster, guinea pig.~~

~~62. The method of claim 61, wherein said cell derived from the modified pluripotent cell is selected from the group consisting of an 0- CAR cell, an 0- endothelial cell, an 0- dopaminergic neuron, an 0- cardiac cell, an 0- pancreatic islet cell, and an 0- retinal pigment endothelium cell.~~

~~63. A method of treating a disease in a patient in need of transplanted cells, comprising administering to the patient a cell derived from the modified pluripotent cell of any one of claims 1-60.~~

~~64. The method of claim 63, wherein said cell derived from the modified pluripotent cell is selected from the group consisting of an 0- CAR cell, an 0- endothelial cell, an 0- dopaminergic neuron, an 0- cardiac cell, an 0- pancreatic islet cell, and an 0- retinal pigment endothelium cell.~~

~~65. The method of claim 63, wherein said disease is selected from the group consisting of Type I Diabetes, a cardiac disease, a neurological disease, a cancer, an ocular disease, and a vascular disease.~~

~~66. A method for generating a modified pluripotent cell that is ABO blood type 0 and Rh factor negative (Rh-) from a pluripotent cell that is not 0-, comprising:~~

~~a. eliminating or reducing the expression of any ABO blood group antigens Al, A2,~~

and/or B to provide an ABO blood type 0; and/or

b. eliminating or reducing expression of the Rhesus factor (Rh) blood group antigen to provide a blood type Rh negative (-).

67. A method for generating a hypoimmunogenic pluripotent ABO group 0 Rh factor negative (HIPO-) cell from an 0- pluripotent cell comprising:

a. eliminating the Major Histocompatibility Antigen Class I (HLA-I) function when compared to an unmodified pluripotent cell;

b. eliminating the Major Histocompatibility Antigen Class II (HLA-I) function when compared to an unmodified pluripotent cell; and

c. increasing the expression of CD47 as compared to an unmodified pluripotent cell.

68. The method of claim 66 or 67, wherein said puripotent cell is of human, cow, pig, chicken, turkey, horse, sheep, goat, donkey, mule, duck, goose, buffalo, camel, yak, llama, alpaca, mouse, rat, dog, cat, hamster, or guinea pig origin.

69. The method of any one of claims 66-68, wherein said ABO blood group type 0 results from eliminating an ABO blood group protein expression.

70. The method of any one of claims 66-69, wherein the cell is endogenously type 0.

71. The method of any one of claims 66-69, wherein the pluripotent cell is human and wherein the ABO blood group type 0 results from disrupting a human Exon 7 of the ABO gene.

72. The method of claim 71, wherein disrupting the human Exon 7 of the ABO gene is accomplished by a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 reaction that disrupts both alleles of the Exon 7.

73. The method of any one of claims 66-69, wherein said ABO blood group type 0 results

~~from enzymaticly modifying an ABO gene product on a surface of the pluripotent cell.~~

~~74. The method of claim 73, wherein said enzymatic modification removes a carbohydrate from said ABO gene product.~~

~~75. The method of claim 74, wherein said enzymatic modification removes a carbohydrate from an ABO Al antigen, A2 antigen, and/or B antigen.~~

~~76. The method of any one of claims 66-69, wherein the cell is endogenously type Rh-.~~

~~77. The method of any one of claims 66-69, comprising eliminating an Rh protein expression.~~

~~78. The method of claim 77, wherein said type Rh- results from disrupting a gene encoding Rh C antigen, Rh E antigen, Kell K antigen (KEL), Duffy (FY) Fya antigen, Duffy Fy3 antigen, Kidd (JK) Jkb antigen, or Kidd SLC14A1 gene.~~

~~79. The method of claim 78, wherein said disruption results from a CRISPR/Cas9 reaction that disrupts both alleles of said gene.~~

~~80. The method of any one of claims 67-79, wherein said increased CD47 expression results from introducing at least one copy of a human CD47 gene under the control of a promoter into said parent cell.~~

~~81. The method of claim 80, wherein said promoter is a constitutive promoter.~~

~~82. The method of any one of claims 67-81, comprising disrupting both alleles of said B2M gene (e.g., using a CRISPR/Cas9 reaction).~~

~~83. The method of any one of claims 67-82, wherein said HLA-I function is reduced by~~

~~reducing expression of a I3-2 microglobulin protein.~~

~~84. The method of claim 83, wherein expression of the I3-2 microglobulin protein is reduced by knocking out a gene encoding said 11-2 microglobulin protein.~~

~~85. The method of claim 84, wherein said I3-2 microglobulin protein has at least a 90% sequence identity to SEQ ID NO:1.~~

~~86. The method of claim 85, wherein said I3-2 microglobulin protein has the sequence of SEQ ID NO:1.~~

~~87. The method of any one of claims 67-81, wherein said HLA-I function is reduced by reducing expression of an HLA-A protein.~~

~~88. The method of claim 87, wherein expression of said HLA-A protein is reduced by knocking out a gene encoding said HLA-A protein.~~

~~89. The method of any one of claims 67-81, wherein said HLA-I function is reduced by reducing expression of an HLA-B protein.~~

~~90. The method of claim 89, wherein expression of said HLA-B protein is reduced by knocking out a gene encoding said HLA-B protein.~~

~~91. The method of any one of claims 67-81, wherein said HLA-I function is reduced by reducing expression of an HLA-C protein.~~

~~92. The method of claim 91, wherein expression of said HLA-C protein is reduced by knocking out a gene encoding said HLA-C protein.~~

~~93. The method of any one of claims 67-92, wherein said hypoimmunogenic pluripotent cell~~

~~does not comprise an HLA-I function.~~

~~94. The method of any one of claims 67-93, wherein said HLA-II function is reduced by reducing expression of a CIITA protein.~~

~~95. The method of claim 94, wherein expression of said CIITA protein is reduced by knocking out a gene encoding said CIITA protein.~~

~~96. The method of claim 95, wherein said CIITA protein has at least a 90% sequence identity to SEQ ID NO:2.~~

~~97. The method of claim 96, wherein said CIITA protein has the sequence of SEQ ID NO:2.~~

~~98. The method of any one of claims 67-97, comprising reducing expression of a CIITA protein by a CRISPR reaction that disrupts both alleles of a CIITA gene.~~

~~99. The method of any one of claims 67-98, wherein said HLA-II function is reduced by reducing expression of an HLA-DP protein.~~

~~100. The method of claim 99, wherein expression of said HLA-DP protein is reduced by knocking out a gene encoding said HLA-DP protein.~~

~~101. The method of any one of claims 67-98, wherein said HLA-II function is reduced by reducing expression of an HLA-DR protein.~~

~~102. The method of claim 101, wherein expression of said HLA-DR protein is reduced by knocking out a gene encoding said HLA-DR protein.~~

~~103. The method of any one of claims 67-98, wherein said HLA-II function is reduced by reducing expression of an HLA-DQ protein.~~

~~104. The method of claim 103, wherein expression of said HLA-DQ protein is reduced by knocking out a gene encoding said HLA-DQ protein.~~

~~105. The method of any one of claims 67-104, wherein said hypoimmunogenic pluripotent cell does not comprise an HLA-II function.~~

~~106. The method of any one of claims 67-105, wherein said increased expression of CD47 results from expression of a transgene that encodes a CD47 protein.~~

~~107. The method of claim 106, wherein said CD47 protein has at least a 90% sequence identity to SEQ ID NO:3.~~

~~108. The method of claim 107, wherein said CD47 protein has the sequence of SEQ ID NO:3.~~

~~109. The method of any one of claims 67-108, further comprising expressing a suicide gene that is activated by a trigger that causes said hypoimmunogenic pluripotent cell to die.~~

~~110. The method of claim 109, wherein said suicide gene is a herpes simplex virus thymidine kinase gene (HSV-tk) and said trigger is ganciclovir.~~

~~111. The method of claim 110, wherein said HSV-tk gene encodes a protein comprising at least a 90% sequence identity to SEQ ID NO:4.~~

~~112. The method of claim 111, wherein said HSV-tk gene encodes a protein comprising the sequence of SEQ ID NO:4.~~

~~113. The method of claim 109, wherein said suicide gene is an Escherichia coli cytosine deaminase gene (EC-CD) and said trigger is 5-fluorocytosine (5-FC).~~

~~114. The method of claim 113, wherein said EC-CD gene encodes a protein comprising at least a 90% sequence identity to SEQ ID NO:5.~~

~~115. The method of claim 114, wherein said EC-CD gene encodes a protein comprising the sequence of SEQ ID NO:5.~~

~~116. The method of claim 109, wherein said suicide gene encodes an inducible Caspase protein and said trigger is a specific chemical inducer of dimerization (CID).~~

~~117. The method of claim 116, wherein said gene encodes an inducible Caspase protein comprising at least a 90% sequence identity to SEQ ID NO:6.~~

~~118. The method of claim 117, wherein said gene encodes an inducible Caspase protein comprising the sequence of SEQ ID NO:6.~~

~~119. The method of any one of claims 116-118, wherein said CID is AP1903.~~

~~120. A method of transplanting a hypoimmunogenic pluripotent (HIP) cell or cell derived therefrom into a subject in need thereof comprising: determining an ABO blood group type of the HIP cell or cell derived therefrom, determining an ABO blood group type of the subject, and transplanting the HIP cell or cell derived therefrom only if the ABO blood group type of the HIP cell or cell derived therefrom matches the ABO blood group type of the subject.~~

~~121. The method of claim 120, further comprising: determining a Rhesus (Rh) factor type of the HIP cell or cell derived therefrom, determining an Rh factor type of the subject, and transplanting the HIP cell or cell derived therefrom only if the Rh blood type of the HIP cell or cell derived therefrom matches the Rh blood type of the subject.~~

~~122. The method of claim 120 or 121, wherein the HIP cell or cell derived therefrom~~

~~comprises~~

~~a. an endogenous Major Histocompatibility Antigen Class I (HLA-I) function that is reduced when compared to an unmodified pluripotent cell;~~

~~b. an endogenous Major Histocompatibility Antigen Class II (HLA-II) function that is reduced when compared to an unmodified pluripotent cell; and~~

~~c. an increased CD47 function that reduces susceptibility to NK cell killing.~~

~~123. The method of any one of claims 119-120, wherein the cell derived from the HIP cell is a cardiomyocyte or cardiomyocyte progenitor.~~

1. A modified hypoimmunogenic cell, comprising:

(a) one or more genetic alterations that result in:

(i) a hypoimmunogenic cell that is ABO blood group-compatible with a recipient;

(ii) a hypoimmunogenic cell that is Rhesus factor (Rh)-compatible with the recipient; or

(iii) both (a)(i) and (a)(ii); and

(b) one or more genetic alterations that result in reduced or eliminated cell surface expression of a Major Histocompatibility Antigen Class I (HLA-I) complex, reduced or eliminated cell surface expression of a Major Histocompatibility Antigen Class II (HLA-II) complex, and/or increased cell surface expression of CD47 as compared to an unmodified or wild-type cell.

2. The modified hypoimmunogenic cell of claim 1, wherein the one or more genetic alterations that result in the hypoimmunogenic cell that is ABO blood group-compatible with a recipient comprise one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more ABO blood group antigens.

3. The modified hypoimmunogenic cell of claim 2, wherein the one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more ABO blood group antigens comprise one or more genetic alterations in one or more genes encoding an ABO blood group antigen.

4. The modified hypoimmunogenic cell of claim 3, wherein the one or more genetic alterations in the one or more genes encoding an ABO blood group antigen comprise one or more indels.

5. The modified hypoimmunogenic cell of claim 3, wherein the one or more genetic alterations in the one or more genes encoding an ABO blood group antigen comprise one or more knock-outs of the one or more genes encoding an ABO blood group antigen.

6. The modified hypoimmunogenic cell of any one of claims 2-5, wherein the one or more ABO blood group antigens comprise ABO blood group antigen A1 (antigen A1), ABO blood group antigen A2 (antigen A2), ABO blood group antigen B (antigen B), or a combination thereof.

7. The modified hypoimmunogenic cell of any one of claims 2-6, wherein the one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more ABO blood group antigens comprise a knock-out of Exon 7 of an ABO gene.

8. The modified hypoimmunogenic cell of any one of claims 1-7, wherein the one or more genetic alterations that result in the hypoimmunogenic cell that is Rh-compatible with a recipient comprise one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more Rh antigens.

9. The modified hypoimmunogenic cell of claim 8, wherein the one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more Rh antigens comprise one or more genetic alterations in one or more genes encoding an Rh antigen.

10. The modified hypoimmunogenic cell of claim 9, wherein the one or more genetic alterations in the one or more genes encoding an Rh antigen comprise one or more indels.

11. The modified hypoimmunogenic cell of claim 9, wherein the one or more genetic alterations in the one or more genes encoding an Rh antigen comprise one or more knock-outs of the one or more genes encoding an Rh antigen.

12. The modified hypoimmunogenic cell of any one of claims 8-11, wherein the one or more Rh antigens comprise Rh C antigen, Rh E antigen, Kell K antigen (KEL), Duffy (FY) Fya antigen, Duffy

Fy3 antigen, Kidd (JK) Jkb antigen, MNS antigen U, MNS antigen S, SLC14A1, or a combination thereof.

13. The modified hypoimmunogenic cell of any one of claims 1-12, further comprising an increased cell surface expression of PD-L1, HLA-G, CD200, FASLG, CLC21, MFGE8, SERPIN 9, HLA-E, CTLA-4-Ig, CI-inhibitor, IL-35, or a combination thereof when compared to an unmodified or wild-type cell.

14. The modified hypoimmunogenic cell of claim 13, wherein the increased cell surface expression of PD-L1, HLA-G, CD200, FASLG, CLC21, MFGE8, SERPIN 9, HLA-E, CTLA-4-Ig, CI-inhibitor, IL-35, or a combination thereof results from the expression of one or more transgenes.

15. The modified hypoimmunogenic cell of any one of claims 1-14, wherein the hypoimmunogenic cell comprises one or more genetic alterations that result in:

(i) increased cell surface expression of CD47 as compared to an unmodified or wild-type cell, and

(ii) reduced or eliminated cell surface expression of a Major Histocompatibility Antigen Class I (HLA-I) complex and/or reduced or eliminated cell surface expression of a Major Histocompatibility Antigen Class II (HLA-II) complex.

16. The modified hypoimmunogenic cell of any one of claims 1-15, wherein one or more genetic alterations that result in increased cell surface expression of CD47 comprise one or more genetic alterations at an endogenous gene locus of CD47.

17. The modified hypoimmunogenic cell of any one of claims 1-16, wherein one or more genetic alterations that result in increased cell surface expression of CD47 comprise introducing a CD47 transgene.

18. The modified hypoimmunogenic cell of any one of claims 1-17, wherein the one or more genetic alterations that result in reduced or eliminated cell surface expression of an HLA-I complex comprise one or more genetic alterations in one or more HLA-I genes.

19. The modified hypoimmunogenic cell of claim 18, wherein the one or more genetic alterations in the one or more HLA-I genes comprise one or more indels.

20. The modified hypoimmunogenic cell of claim 18, wherein the one or more genetic alterations in the one or more HLA-I genes comprise one or more knock-outs of the one or more HLA-I genes.

21. The modified hypoimmunogenic cell of any one of claims 18-20, wherein the one or more HLA-I genes comprise an HLA-A gene, an HLA-B gene, an HLA-C gene, or a combination thereof.

22. The modified hypoimmunogenic cell of any one of claims 1-21, wherein the one or more genetic alterations that result in reduced or eliminated cell surface expression of the HLA-I complex comprise one or more genetic alterations in one or more HLA-I associated genes.

23. The modified hypoimmunogenic cell of claim 22, wherein the one or more genetic alterations in one or more HLA-I associated genes comprise one or more indels in the one or more HLA-I associated genes.

24. The modified hypoimmunogenic cell of claim 22, wherein the one or more genetic alterations in one or more HLA-I associated genes comprise one or more knock-outs of the one or more HLA-I associated genes.

25. The modified hypoimmunogenic cell of any one of claims 22-24, wherein the one or more HLA-I associated genes comprise a β-2 microglobulin (B2M) gene.

26. The modified hypoimmunogenic cell of any one of claims 1-25, wherein the one or more genetic alterations that result in reduced or eliminated cell surface expression of an HLA-II complex comprise one or more genetic alterations in one or more HLA-II genes.

27. The modified hypoimmunogenic cell of claim 26, wherein the one or more genetic alterations in one or more HLA-II genes comprise one or more indels.

28. The modified hypoimmunogenic cell of claim 26, wherein the one or more genetic alterations in one or more HLA-II genes comprise one or more knock-outs of the one or more HLA-II genes.

29. The modified hypoimmunogenic cell of any one of claims 26-28, wherein the one or more HLA-II genes comprise HLA-DP, HLA-DM, HLA-DOB, HLA-DQ, HLA-DR, or a combination thereof.

30. The modified hypoimmunogenic cell of any one of claims 1-29, wherein the one or more genetic alterations that result in reduced or eliminated cell surface expression of an HLA-II complex comprise one or more genetic alterations in one or more HLA-II associated genes.

31. The modified hypoimmunogenic cell of claim 30, wherein the one or more genetic alterations in one or more HLA-II associated genes comprise one or more indels.

32. The modified hypoimmunogenic cell of claim 30, wherein the one or more genetic alterations in one or more HLA-II associated genes comprise one or more knock-outs of the one or more HLA-II associated genes.

33. The modified hypoimmunogenic cell of any one of claims 30-32, wherein the one or more HLA-II associated genes comprise a Class II Major Histocompatibility Complex Transactivator (CIITA) gene.

34. The modified hypoimmunogenic cell of any one of claims 1-33, comprising:

one or more genetic alterations that result in reduced or eliminated cell surface expression of an HLA-I complex as compared to an unmodified or wild-type cell,

one or more genetic alterations that result in reduced or eliminated cell surface expression of an HLA-II complex as compared to an unmodified or wild-type cell, and

increased cell surface expression of CD47 as compared to an unmodified or wild-type cell.

35. The modified hypoimmunogenic cell of claim 34, wherein the modified hypoimmunogenic cell expresses a CD47 transgene.

36. The modified hypoimmunogenic cell of any one of claims 1-35, further comprising one or more genetic alterations that result in reduced or eliminated expression of CCR5, CXCR4, or both.

37. The modified hypoimmunogenic cell of any one of claims 1-36, comprising one or more genetic alterations that result in reduced or eliminated expression of an NLRC5 gene.

38. The modified hypoimmunogenic cell of any one of claims 1-37, comprising one or more genetic alterations that result in modified expression of HLA-A, HLA-B, HLA-C, HLA-E, HLA-G, PD-L1, CTLA-4-Ig, CI-inhibitor, IL-35, or a combination thereof.

39. The modified hypoimmunogenic cell of any one of claims 1-38, comprising one or more genetic alterations that result in modified expression of RFX-5, RFXAP, RFXANK, NFY-A, NFY-B, NFY-C, IRF-1, or a combination thereof.

40. The modified hypoimmunogenic cell of any one of claims 1-39, further comprising one or more genetic alterations that result in modified expression of OX40, GITR, 4-1BB, CD28, B7-1, B7-2, ICOS, CD27, HVEM, SLAM, CD226, PD1, CTLA-4, LAG3, TIGIT, TIM3, CD160, BTLA, CD244, CD30, TLT, VISTA, B7-H3, PD-L2, LFA-1, CD2, CD58, ICAM-3, TCRA, TCRB, FOXP3, HELIOS, ST2, PCSK9, CCR5, APOC3, or a combination thereof.

41. The modified hypoimmunogenic cell of any one of claims 1-40, further comprising one or more transgenes encoding PD-L1, HLA-G, CD200, FASLG, CLC21, MFGE8, SERPIN B9, or a combination thereof.

42. The modified hypoimmunogenic cell of any one of claims 1-41, further comprising one or more transgenes encoding a biologic that acts as an agonist of PD-L1, HLA-G, CD47, CD200, FASLG, CLC21, MFGE8, and/or SERPIN 9.

43. The modified hypoimmunogenic cell of any one of claims 1-42, further comprising one or more transgenes encoding TGFβ, CD73, CD39, LAG3, IL1R2, ACKR2, TNFRSF22, TNFRSF23, TNFRS10, DAD1, and/or IFNγR1 d39.

44. The modified hypoimmunogenic cell of any one of claims 1-43, further comprising one or more transgenes encoding a biologic that acts as an agonist of TGFβ, CD73, CD39, LAG3, IL1R2, ACKR2, TNFRSF22, TNFRSF23, TNFRS10, DAD1, and/or IFNγR1 d39.

45. The modified hypoimmunogenic cell of any one of claims 1-44, further comprising a safety switch.

46. The modified hypoimmunogenic cell of 45, wherein the safety switch is a suicide gene.

47. The modified hypoimmunogenic cell of claim 46, wherein the suicide gene is a herpes simplex virus thymidine kinase gene (HSV-tk), an Escherichia coli cytosine deaminase gene (EC-CD), or an inducible Caspase gene.

48. The modified hypoimmunogenic cell of any one of claims 1-47, wherein the modified hypoimmunogenic cell is a pluripotent cell or a cell derived therefrom.

49. The modified hypoimmunogenic cell of any one of claims 1-48, wherein the modified hypoimmunogenic cell is (i) ABO blood type O (O), (ii) Rhesus factor negative (Rh-), or (iii) O and Rh- (O-).

50. The modified hypoimmunogenic cell of any one of claims 1-49, wherein the modified hypoimmunogenic cell is an O- induced pluripotent stem cell (iPSCO-), an O- embryonic stem cell (ESCO-), an O- endothelial cell, an O- cardiomyocyte, an O- hepatocyte, an O- dopaminergic neuron, an O- pancreatic islet cell, an O- retinal pigment endothelium cell, or an O- chimeric antigen receptor (O- CAR) cell.

51. The modified hypoimmunogenic cell of claim 50, wherein the O- CAR cell is an O- chimeric antigen receptor T (O- CAR-T) cell.

52. The modified hypoimmunogenic cell of any one of claims 1-51, wherein the hypoimmunogenic cell comprises a modification of an ABO antigen on the cell surface of the hypoimmunogenic cell, wherein the modification resulted from an enzymatic conversion of the ABO antigen.

53. The modified hypoimmunogenic cell of claim 52, wherein the enzymatic conversion removed a carbohydrate from the ABO antigen.

54. The modified hypoimmunogenic cell of claim 52 or 53, wherein the enzymatic conversion removed a carbohydrate from an ABO A1 antigen, A2 antigen, B antigen, or a combination thereof.

55. The modified hypoimmunogenic cell of any one of claims 1-54, comprising:

a modification of an ABO antigen on the cell surface of the hypoimmunogenic cell, wherein the modification resulted from an enzymatic conversion of the ABO antigen; and

one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more Rh antigens as compared to an unmodified or wild-type cell, thereby rendering the cell Rh-.

56. A modified hypoimmunogenic cell, comprising one or more genetic alterations that result in:

(a) reduced or eliminated cell surface expression of one or more ABO blood group antigens as compared to an unmodified or wild-type cell, thereby rendering the cell ABO blood group type O;

(b) reduced or eliminated cell surface expression of one or more Rh antigens as compared to an unmodified or wild-type cell, thereby rendering the cell Rh-;

(c) reduced or eliminated expression of a β-2 microglobulin (B2M) gene as compared to an unmodified or wild-type cell;

(d) reduced or eliminated expression of a Class II Major Histocompatibility Complex Transactivator (CIITA) gene as compared to an unmodified or wild-type cell; and

(e) increased cell surface expression of CD47 as compared to an unmodified or wild-type cell.

57. A method for generating the modified hypoimmunogenic cell, comprising introducing:

(a) one or more genetic alterations that result in:

(i) a hypoimmunogenic cell that is ABO blood group-compatible with a recipient;

(ii) a hypoimmunogenic cell that is Rhesus factor (Rh)-compatible with the recipient; or

(iii) both (a)(i) and (a)(ii); and

(b) one or more genetic alterations that result in reduced or eliminated cell surface expression of a Major Histocompatibility Antigen Class I (HLA-I) complex, reduced or eliminated cell surface expression of a Major Histocompatibility Antigen Class II (HLA-II) complex, and/or increased cell surface expression of CD47 as compared to an unmodified or wild-type cell.

58. The method of claim 57, wherein introducing one or more genetic alterations that result in the hypoimmunogenic cell that is ABO blood group-compatible with a recipient comprise one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more ABO blood group antigens

59. The method of claim 58, wherein introducing the one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more ABO blood group antigens comprises introducing one or more genetic alterations in one or more genes encoding an ABO blood group antigen.

60. The method of claim 58 or 59, wherein introducing the one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more ABO blood group antigens comprises introducing one or more indels in the one or more genes encoding an ABO blood group antigen.

61. The method of claim 58 or 59, wherein introducing the one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more ABO blood group antigens comprises knocking out the one or more genes encoding an ABO blood group antigen.

62. The method of any one of claims 58-61, wherein the one or more ABO blood group antigens comprise ABO blood group antigen A1 (antigen A1), ABO blood group antigen A2 (antigen A2), ABO blood group antigen B (antigen B), or a combination thereof.

63. The method of any one of claims 58-62, wherein introducing the one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more ABO blood group antigens comprises knocking out Exon 7 of an ABO gene.

64. The method of any one of claims 57-63, wherein introducing the one or more genetic alterations that result in the hypoimmunogenic cell that is Rh-compatible with a recipient comprises one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more Rh antigens.

65. The method of claim 64, wherein introducing the one or more genetic alterations that result in the hypoimmunogenic cell that is Rh-compatible with a recipient comprises introducing

one or more genetic alterations in one or more genes encoding an Rh antigen.

66. The method of claim 64 or 65, wherein introducing the one or more genetic alterations that result in the hypoimmunogenic cell that is Rh-compatible with a recipient comprises introducing one or more indels in the one or more genes encoding an Rh antigen.

67. The method of claim 64 or 65, wherein introducing the one or more genetic alterations that result in the hypoimmunogenic cell that is Rh-compatible with a recipient comprises knocking out one or more genes encoding an Rh antigen.

68. The method of any one of claims 64-67, wherein the one or more Rh antigens comprise Rh C antigen, Rh E antigen, Kell K antigen (KEL), Duffy (FY) Fya antigen, Duffy Fy3 antigen, Kidd (JK) Jkb antigen, MNS antigen U, MNS antigen S, SLC14A1, or a combination thereof.

69. The method of any one of claims 57-68, wherein the modified hypoimmunogenic cell comprises an increased cell surface expression of PD-L1, HLA-G, CD200, FASLG, CLC21, MFGE8, SERPIN 9, HLA-E, CTLA-4-Ig, CI-inhibitor, IL-35, or a combination thereof when compared to an unmodified or wild-type cell.

70. The method of any one of claims 57-69, wherein the increased cell surface expression of PD-L1, HLA-G, CD200, FASLG, CLC21, MFGE8, SERPIN 9, HLA-E, CTLA-4-Ig, CI-inhibitor, IL-35, or a combination thereof results from the expression of one or more transgenes.

71. The modified hypoimmunogenic cell of any one of claims 57-70, wherein the hypoimmunogenic cell comprises one or more genetic alterations that result in:

(i) increased cell surface expression of CD47 as compared to an unmodified or wild-type cell, and

(ii) reduced or eliminated cell surface expression of a Major Histocompatibility Antigen Class I (HLA-I) complex and/or reduced or eliminated cell surface expression of a Major Histocompatibility Antigen Class II (HLA-II) complex.

72. The method of any one of claims 57-71, wherein one or more genetic alterations that result in increased cell surface expression of CD47 comprise one or more genetic alterations at an endogenous CD47 gene locus.

73. The method of any one of claims 57-72, wherein one or more genetic alterations that result in increased cell surface expression of CD47 comprise a CD47 transgene.

74. The method of any one of claims 57-73, wherein introducing the one or more genetic alterations that result in reduced or eliminated cell surface expression of the HLA-I complex comprises introducing one or more genetic alterations in the one or more HLA-I gene genes.

75. The method of claim 74, wherein introducing the one or more genetic alterations in one or more HLA-I genes comprises introducing one or more indels in the one or more HLA-I genes.

76. The method of claim 74, wherein introducing the one or more genetic alterations in the one or more HLA-I genes comprises knocking out one or more HLA-I genes.

77. The method of any one of claims 74-76, wherein the one or more HLA-I genes comprise an HLA-A gene, an HLA-B gene, an HLA-C gene, or a combination thereof.

78. The method of any one of claims 57-77, wherein introducing the one or more genetic alterations that result in reduced or eliminated cell surface expression of the HLA-I complex comprises introducing one or more genetic alterations in one or more HLA-I associated genes.

79. The method of claim 78, wherein introducing the one or more genetic alterations in one or more HLA-I associated genes comprises introducing one or more indels in the one or more HLA-I associated genes.

80. The method of claim 78, wherein introducing the one or more genetic alterations in one or more HLA-I associated genes comprises knocking out the one or more HLA-I associated genes.

81. The method of any one of claims 78-80, wherein the one or more HLA-I associated genes comprise a β-2 microglobulin (B2M) gene.

82. The method of any one of claims 57-81, wherein introducing the one or more genetic alterations that result in reduced or eliminated cell surface expression of an HLA-II complex comprises introducing one or more genetic alterations in one or more HLA-II genes.

83. The method of claim 82, wherein introducing the one or more genetic alterations in one or more HLA-II genes comprises introducing one or more indels in the one or more HLA-II genes.

84. The method of claim 82, wherein introducing the one or more genetic alterations in one or more HLA-II genes comprises knocking out the one or more HLA-II genes.

85. The method of any one of claims 82-84, wherein the one or more HLA-II genes comprise HLA-DP, HLA-DM, HLA-DOB, HLA-DQ, HLA-DR, or a combination thereof.

86. The method of any one of claims 57-85, wherein introducing the one or more genetic alterations that result in reduced or eliminated cell surface expression of an HLA-II complex comprises introducing one or more genetic alterations in one or more HLA-II associated genes.

87. The method of claim 86, wherein introducing the one or more genetic alterations in one or more HLA-II associated genes comprises introducing one or more indels in the one or more HLA-II associated genes.

88. The method of claim 86, wherein introducing the one or more genetic alterations in one or more HLA-II associated genes comprises knocking out the one or more HLA-II associated genes.

89. The method of any one of claims 86-88, wherein the one or more HLA-II associated genes comprise a Class II Major Histocompatibility Complex Transactivator (CIITA) gene.

90. The method of any one of claims 57-89, comprising introducing one or more genetic alterations that result in:

reduced or eliminated cell surface expression of an HLA-I complex as compared to an unmodified or wild-type cell,

reduced or eliminated cell surface expression of an HLA-II complex as compared to an unmodified or wild-type cell, and

increased cell surface expression of CD47 as compared to an unmodified or wild-type cell.

91. The method of claim 90, wherein the modified hypoimmunogenic cell expresses a CD47 transgene.

92. The method of any one of claims 57-91, further comprising introducing one or more genetic alterations that result in reduced or eliminated expression of CCR5, CXCR4, or both.

93. The method of any one of claims 57-92, comprising introducing one or more genetic alterations that result in reduced or eliminated expression of an NLRC5 gene.

94. The method of any one of claims 57-93, comprising introducing one or more genetic alterations that result in modified expression of HLA-A, HLA-B, HLA-C, HLA-E, HLA-G, PD-L1, CTLA-4-Ig, CD47, CI-inhibitor, IL-35, or a combination thereof.

95. The method of any one of claims 57-94, comprising introducing one or more genetic alterations that result in modified expression of RFX-5, RFXAP, RFXANK, NFY-A, NFY-B, NFY-C, IRF-1, or a combination thereof.

96. The method of any one of claims 57-95, comprising introducing one or more genetic alterations that result in modified expression of OX40, GITR, 4-1BB, CD28, B7-1, B7-2, ICOS, CD27, HVEM, SLAM, CD226, PD1, CTLA-4, LAG3, TIGIT, TIM3, CD160, BTLA, CD244, CD30, TLT, VISTA, B7-H3, PD-L2, LFA-1, CD2, CD58, ICAM-3, TCRA, TCRB, FOXP3, HELIOS, ST2, PCSK9, CCR5, APOC3, or a combination thereof.

97. The method of any one of claims 57-96, comprising introducing one or more transgenes encoding PDL-1, HLA-G, CD47, CD200, FASLG, CLC21, MFGE8, SERPIN B9, or a combination thereof.

98. The method of any one of claims 57-97, further comprising introducing one or more transgenes encoding a biologic that acts as an agonist of PDL-1, HLA-G, CD47, CD200, FASLG, CLC21, MFGE8, and/or SERPIN 9.

99. The method of any one of claims 57-98, further comprising introducing one or more transgenes encoding TGFβ, CD73, CD39, LAG3, IL1R2, ACKR2, TNFRSF22, TNFRSF23, TNFRS10, DAD1, and/or IFNγR1 d39.

100. The method of any one of claims 57-99, further comprising introducing one or more transgenes encoding a biologic that acts as an agonist of TGFβ, CD73, CD39, LAG3, IL1R2, ACKR2,

TNFRSF22, TNFRSF23, TNFRS10, DAD1, and/or IFNγR1 d39.

101. The method of any one of claims 57-100, further comprising introducing a safety switch.

102. The method of claim 101, wherein the safety switch is a suicide gene.

103. The method of claim 102, wherein the suicide gene is a herpes simplex virus thymidine kinase gene (HSV-tk), an Escherichia coli cytosine deaminase gene (EC-CD), or an inducible Caspase gene.

104. The method of any one of claims 57-103, wherein the modified hypoimmunogenic cell is a pluripotent cell or a cell derived therefrom.

105. The method of any one of claims 57-104, wherein the modified hypoimmunogenic cell is O, Rh-, or O-.

106. The method of any one of claims 57-105, wherein the modified hypoimmunogenic cell is an O- induced pluripotent stem cell (iPSCO-), an O- embryonic stem cell (ESCO-), an O- endothelial cell, an O- cardiomyocyte, an O- hepatocyte, an O- dopaminergic neuron, an O- pancreatic islet cell, an O- retinal pigment endothelium cell, or an O- chimeric antigen receptor (O- CAR) cell.

107. The method of claim 106, wherein the O- CAR cell is an O- chimeric antigen receptor T (O- CAR-T) cell.

108. The method of any one of claims 57-107, comprising enzymatically converting an ABO antigen on the cell surface.

109. The method of claim 108, wherein the enzymatic conversion removed a carbohydrate from the ABO antigen.

110. The method of claim 108 or 109, wherein the enzymatic conversion removed a carbohydrate from an ABO A1 antigen, A2 antigen, B antigen, or a combination thereof.

111. The method of any one of claims 57-110, comprising:

a modification of an ABO antigen on the cell surface of the hypoimmunogenic cell, wherein the modification resulted from an enzymatic conversion of the ABO antigen; and

one or more genetic alterations that result in reduced or eliminated cell surface expression of one or more Rh antigens as compared to an unmodified or wild-type cell, thereby rendering the cell Rh-.

112. The method of any one of claims 57-111, wherein the one or more genetic modifications are introduced using a nuclease.

113. The method of claim 112, wherein the nuclease is a zinc finger nuclease, a TALEN, or a Cas.

114. A method of generating a modified hypoimmunogenic cell, comprising introducing one or more genetic alterations that result in:

(a) reduced or eliminated cell surface expression of one or more ABO blood group antigens as compared to an unmodified or wild-type cell, thereby rendering the cell ABO blood group type O;

(b) reduced or eliminated cell surface expression of one or more Rh antigens as compared to an unmodified or wild-type cell, thereby rendering the cell Rh-;

(c) reduced or eliminated expression of a β-2 microglobulin (B2M) gene as compared to an unmodified or wild-type cell;

(d) reduced or eliminated expression of a Class II Major Histocompatibility Complex Transactivator (CIITA) gene as compared to an unmodified or wild-type cell; and

(e) increased cell surface expression of CD47 as compared to an unmodified or wild-type cell.