Claims

What is claimed:

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.