

WHAT IS CLAIMED IS:

1. A method for treating a disorder in a patient comprising administering to the patient a therapeutically effective amount of a population of hypoimmunogenic cells comprising exogenous CD47 polypeptides and reduced expression of MHC class I and/or class II human leukocyte antigens, wherein an initial population of such hypoimmunogenic cells had previously been administered to the patient.
2. The method of claim 1, wherein the hypoimmunogenic cells comprise reduced expression of MHC class I and class II human leukocyte antigens.
3. The method of claim 1 or 2, wherein the hypoimmunogenic cells express the exogenous CD47 polypeptides and reduced expression levels of B2M and/or CIITA.
4. The method of any one of claims 1–3, wherein the hypoimmunogenic cells express the exogenous CD47 polypeptides and reduced expression levels of B2M and CIITA.
5. The method of any one of claims 1–4, wherein the hypoimmunogenic cells are differentiated cells derived from pluripotent stem cells.
6. The method of claim 5, wherein the pluripotent stem cells comprise induced pluripotent stem cells.
7. The method of claim 5 or 6, wherein the differentiated cells are selected from the group consisting of cardiac cells, neural cells, endothelial cells, pancreatic islet cells, retinal pigmented epithelium cells, hepatocytes, thyroid cells, and T cells.
8. The method of any one of claims 1–4, wherein the hypoimmunogenic cells comprise cells derived from primary T cells.
9. The method of claim 8, wherein the cells derived from primary T cells are derived from a pool of T cells comprising primary T cells from one or more, optionally two or more, three or more, four or more, five or more, ten or more, twenty or more, fifty or more, or one hundred or more, subjects different from the patient.
10. The method of claim 8 or 9, wherein the cells derived from primary T cells comprise a chimeric antigen receptor.
11. The method of claim 10, wherein the chimeric antigen receptor (CAR) is selected from the group consisting of:

- (a) a first generation CAR comprising an antigen binding domain, a transmembrane domain, and a signaling domain;
- (b) a second generation CAR comprising an antigen binding domain, a transmembrane domain, and at least two signaling domains;
- (c) a third generation CAR comprising an antigen binding domain, a transmembrane domain, and at least three signaling domains; and
- (d) a fourth generation CAR comprising an antigen binding domain, a transmembrane domain, three or four signaling domains, and a domain which upon successful signaling of the CAR induces expression of a cytokine gene.

12. The method of claim 11, wherein the antigen binding domain is selected from the group consisting of

- (a) an antigen binding domain targets an antigen characteristic of a neoplastic cell;
- (b) an antigen binding domain that targets an antigen characteristic of a T cell;
- (c) an antigen binding domain targets an antigen characteristic of an autoimmune or inflammatory disorder;
- (d) an antigen binding domain that targets an antigen characteristic of senescent cells;
- (e) an antigen binding domain that targets an antigen characteristic of an infectious disease; and
- (f) an antigen binding domain that binds to a cell surface antigen of a cell.

13. The method of claim 10 or 11, wherein the antigen binding domain is selected from the group consisting of an antibody, an antigen-binding portion thereof, an scFv, and a Fab.

14. The method of any one of claims 11–13, wherein the antigen binding domain binds to CD19, CD20, CD22, or BCMA.

15. The method of any one of claims 11–14, wherein the transmembrane domain comprises one selected from the group consisting of a transmembrane region of TCR α , TCR β , TCR ζ , CD3 ϵ , CD3 γ , CD3 δ , CD3 ζ , CD4, CD5, CD8 α , CD8 β , CD9, CD16, CD28, CD45, CD22, CD33, CD34, CD37, CD40, CD40L/CD154, CD45, CD64, CD80, CD86, OX40/CD134, 4-1BB/CD137, CD154, Fc ϵ RI γ , VEGFR2, FAS, FGFR2B, and functional variant thereof.

16. The method of any one of claims 11–15, wherein the signaling domain(s) comprises a costimulatory domain(s).

17. The method of claim 16, wherein the costimulatory domains comprise two costimulatory domains that are not the same.
18. The method of claim 16 or 17, wherein the costimulatory domain(s) enhances cytokine production, CAR T cell proliferation, and/or CAR T cell persistence during T cell activation.
19. The method of any one of claims 11–18, wherein the cytokine gene is an endogenous or exogenous cytokine gene to the hypoinmunogenic cells.
20. The method of claim 19, wherein the cytokine gene encodes a pro-inflammatory cytokine.
21. The method of claim 20, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1, IL-2, IL-9, IL-12, IL-18, TNF, IFN-gamma, and a functional fragment thereof.
22. The method of any one of claims 11–21, wherein the domain which upon successful signaling of the CAR induces expression of the cytokine gene comprises a transcription factor or functional domain or fragment thereof.
23. The method of any one of claims 10–22, wherein the CAR comprises a CD3 zeta domain or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof.
24. The method of any one of claims 10–23, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; and (ii) a CD28 domain, or a 4-1BB domain, or functional variant thereof.
25. The method of any one of claims 10–24, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; and (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof.
26. The method of any one of claims 10–25, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof; and (iv) a cytokine or costimulatory ligand transgene.

27. The method of any one of claims 10–24, wherein the CAR comprises a (i) an anti-CD19 scFv; (ii) a CD8 α hinge and transmembrane domain or functional variant thereof; (iii) a 4-1BB costimulatory domain or functional variant thereof; and (iv) a CD3 ζ signaling domain or functional variant thereof.

28. The method of any one of claims 8–27, wherein the cells derived from primary T cells comprise reduced expression of an endogenous T cell receptor.

29. The method of any one of claims 8–28, wherein the cells derived from primary T cells comprise reduced expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and/or programmed cell death (PD1).

30. The method of any one of claims 1–29, wherein the population of the hypoinmunogenic cells is administered at least 3 days or more after the initial administration, optionally at least 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months, 54 months, or 60 months or more.

31. The method of any one of claims 1–30, wherein the population of the hypoinmunogenic cells is administered at least 3 days to at least 7 days or more after the initial administration.

32. The method of any one of claims 1–30, wherein the population of the hypoinmunogenic cells is administered least 1 month or more after the initial administration.

33. The method of any one of claims 1–30, wherein the population of the hypoinmunogenic cells is administered at least 2 months or more after the initial administration.

34. The method of any one of claims 1–33, wherein upon the initial and/or subsequent administrations, the population of hypoinmunogenic cells elicits a reduced level of immune activation or no immune activation in the patient.

35. The method of any one of claims 1–34, wherein upon the initial and/or subsequent administrations, the population of hypoinmunogenic cells elicits a reduced level of systemic TH1 activation or no systemic TH1 activation in the patient.

36. The method of any one of claims 1–35, wherein upon the initial and/or subsequent administrations, the population of hypoimmunogenic cells elicits a reduced level of immune activation of peripheral blood mononuclear cells (PBMCs) or no immune activation of PBMCs in the patient.

37. The method of any one of claims 1–36, wherein upon the initial and/or subsequent administrations, the population of hypoimmunogenic cells elicits a reduced level of donor-specific IgG antibodies or no donor specific IgG antibodies against the hypoimmunogenic cells in the patient.

38. The method of any one of claims 1–37, wherein upon the initial and/or subsequent administrations, the population of hypoimmunogenic cells elicits a reduced level of IgM and IgG antibody production or no IgM and IgG antibody production against the hypoimmunogenic cells in the patient.

39. The method of any one of claims 1–38, wherein upon administration, the population of hypoimmunogenic cells elicits a reduced level of cytotoxic T cell killing or no cytotoxic T cell killing of the hypoimmunogenic cells of the hypoimmunogenic cells in the patient.

40. The method of any one of claims 1–39, wherein the population of hypoimmunogenic cells of the initial administration are no longer present in the patient at the subsequent administration.

41. The method of any one of claims 1–40, wherein the patient is not administered an immunosuppressive agent at least 3 days or more before or after the initial administration of the population of hypoimmunogenic cells.

42. The method of any one of claims 1–41, wherein the patient is not administered an immunosuppressive agent at least 3 days or more before or after the initial subsequent administration of the population of hypoimmunogenic cells.

43. The method of any one of claims 1–42, wherein the hypoimmunogenic cell is selected from the group consisting of a pluripotent stem cell, an induced pluripotent stem cell, a T cell differentiated from an induced pluripotent stem cell, a primary T cell, and a cell derived from a primary T cell, and the hypoimmunogenic cell is a B2M^{indel/indel}, CIITA^{indel/indel} cell comprising the exogenous CD47 polypeptides and optionally a CAR.

44. A method for treating a disorder in a patient comprising administering to the patient therapeutically effective amounts of a population of hypoimmunogenic cells in a dosing regimen comprising a first administration, a recovery period and a second administration, wherein the hypoimmunogenic cells comprise exogenous CD47 polypeptides and reduced expression of MHC class I and/or class II human leukocyte antigens.

45. The method of claim 44, wherein the hypoimmunogenic cells further comprise reduced expression of MHC class I and II human leukocyte antigens.

46. The method of claim 44 or 45, wherein the hypoimmunogenic cells express the exogenous CD47 polypeptide and reduced expression levels of B2M and/or CIITA.

47. The method of any one of claims 44–46, wherein the hypoimmunogenic cells express the exogenous CD47 polypeptide and reduced expression levels of B2M and CIITA.

48. The method of any one of claims 44–47, wherein the hypoimmunogenic cells are differentiated cells derived from pluripotent stem cells.

49. The method of claim 48, wherein the pluripotent stem cells comprise induced pluripotent stem cells.

50. The method of claim 48 or 49, wherein the differentiated cells are selected from the group consisting of cardiac cells, neural cells, endothelial cells, pancreatic islet cells, retinal pigmented epithelium cells, hepatocytes, thyroid cells, and T cells.

51. The method of any one of claims 44–47, wherein the hypoimmunogenic cells comprise cells derived from primary T cells.

52. The method of claim 51, wherein the cells derived from primary T cells are derived from a pool of T cells comprising primary T cells from one or more subjects different from the patient.

53. The method of claim 51 or 52, wherein the cells derived from primary T cells comprise a chimeric antigen receptor.

54. The method of claim 53, wherein the chimeric antigen receptor (CAR) is selected from the group consisting of:

(a) a first generation CAR comprising an antigen binding domain, a transmembrane domain, and a signaling domain;

(b) a second generation CAR comprising an antigen binding domain, a transmembrane domain, and at least two signaling domains;

(c) a third generation CAR comprising an antigen binding domain, a transmembrane domain, and at least three signaling domains; and

(d) a fourth generation CAR comprising an antigen binding domain, a transmembrane domain, three or four signaling domains, and a domain which upon successful signaling of the CAR induces expression of a cytokine gene.

55. The method of claim 54, wherein the antigen binding domain is selected from the group consisting of

- (a) an antigen binding domain targets an antigen characteristic of a neoplastic cell;
- (b) an antigen binding domain that targets an antigen characteristic of a T cell,
- (c) an antigen binding domain targets an antigen characteristic of an autoimmune or inflammatory disorder;
- (d) an antigen binding domain that targets an antigen characteristic of senescent cells;
- (e) an antigen binding domain that targets an antigen characteristic of an infectious disease; and
- (f) an antigen binding domain that binds to a cell surface antigen of a cell.

56. The method of claim 54 or 55, wherein the antigen binding domain is selected from the group consisting of an antibody, an antigen-binding portion thereof, an scFv, and a Fab.

57. The method of any one of claims 54–56, wherein the antigen binding domain binds to CD19, CD20, CD22, or BCMA.

58. The method of any one of claims 54–57, wherein the transmembrane domain comprises one selected from the group consisting of a transmembrane region of TCR α , TCR β , TCR ζ , CD3 ϵ , CD3 γ , CD3 δ , CD3 ζ , CD4, CD5, CD8 α , CD8 β , CD9, CD16, CD28, CD45, CD22, CD33, CD34, CD37, CD40, CD40L/CD154, CD45, CD64, CD80, CD86, OX40/CD134, 4-1BB/CD137, CD154, Fc ϵ RI γ , VEGFR2, FAS, FGFR2B, and functional variant thereof.

59. The method of any one of claims 54–58, wherein the signaling domain(s) comprises a costimulatory domain(s).

60. The method of claim 59, wherein the costimulatory domains comprise two costimulatory domains that are not the same.

61. The method of claim 59 or 60, wherein the costimulatory domain(s) enhances cytokine production, CAR T cell proliferation, and/or CAR T cell persistence during T cell activation.

62. The method of any one of claims 54–61, wherein the cytokine gene is an endogenous or exogenous cytokine gene to the hypoinmunogenic cells.

63. The method of claim 62, wherein the cytokine gene encodes a pro-inflammatory cytokine.

64. The method of claim 63, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1, IL-2, IL-9, IL-12, IL-18, TNF, IFN-gamma, and a functional fragment thereof.

65. The method of any one of claims 54–64, wherein the domain which upon successful signaling of the CAR induces expression of the cytokine gene comprises a transcription factor or functional domain or fragment thereof.

66. The method of any one of claims 53–65, wherein the CAR comprises a CD3 zeta domain or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof.

67. The method of any one of claims 53–66, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; and (ii) a CD28 domain, or a 4-1BB domain, or functional variant thereof.

68. The method of any one of claims 53–67, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; and (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof.

69. The method of any one of claims 53–68, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof; and (iv) a cytokine or costimulatory ligand transgene.

70. The method of any one of claims 53–67, wherein the CAR comprises a (i) an anti-CD19 scFv; (ii) a CD8 α hinge and transmembrane domain or functional variant thereof;

(iii) a 4-1BB costimulatory domain or functional variant thereof; and (iv) a CD3 ζ signaling domain or functional variant thereof.

71. The method of any one of claim 51–70, wherein the cells derived from primary T cells comprise reduced expression of an endogenous T cell receptor.

72. The method of any one of claim 51–71, wherein the cells derived from primary T cells comprise reduced expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and/or programmed cell death (PD1).

73. The method of any one of claims 44–72, wherein the recovery period comprises at least 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months, 54 months, or 60 months or more.

74. The method of any one of claims 44–72, wherein the recovery period comprises at least 3 days to at least 7 days or more.

75. The method of any one of claims 44–72, wherein the recovery period comprises at least 1 month or more.

76. The method of any one of claims 44–73, wherein the recovery period comprises at least 2 months or more.

77. The method of any one of claims 44–76, wherein the second administration is initiated when the population of hypoimmunogenic cells from the first administration is no longer detectable in the patient.

78. The method of any one of claims 44–77, wherein upon the first and/or second administrations, the population of hypoimmunogenic cells elicits a reduced level of immune activation or no immune activation in the patient.

79. The method of any one of claims 44–78, wherein upon the first and/or second administrations, the population of hypoimmunogenic cells elicits a reduced level of systemic TH1 activation or no systemic TH1 activation in the patient.

80. The method of any one of claims 44–79, wherein upon the first and/or second administrations, the population of hypoimmunogenic cells elicits a reduced level of immune

activation of peripheral blood mononuclear cells (PBMCs) or no immune activation of PBMCs in the patient.

81. The method of any one of claims 44–80, wherein upon the first and/or second administrations, the population of hypoinmunogenic cells elicits a reduced level of donor-specific IgG antibodies or no donor-specific IgG antibodies against the hypoinmunogenic cells in the patient.

82. The method of any one of claims 44–81, wherein upon the first and/or second administrations, the population of hypoinmunogenic cells elicits a reduced level of IgM and IgG antibody production or no IgM and IgG antibody production against the hypoinmunogenic cells in the patient.

83. The method of any one of claims 44–82, wherein upon the first and/or second administrations, the population of hypoinmunogenic cells elicits a reduced level of cytotoxic T cell killing or no cytotoxic T cell killing of the hypoinmunogenic cells in the patient.

84. The method of any one of claims 44–83, wherein the patient is not administered an immunosuppressive agent at least 3 days or more before or after the first administration of the population of hypoinmunogenic cells.

85. The method of any one of claims 44–84, wherein the patient is not administered an immunosuppressive agent at least 3 days or more before or after the second administration of the population of hypoinmunogenic cells.

86. The method of any one of claims 44–85, wherein the patient is not administered an immunosuppressive agent during the recovery period.

87. The method of any one of claims 44–86, wherein the hypoinmunogenic cell is selected from the group consisting a pluripotent stem cell, an induced pluripotent stem cell, a T cell differentiated from an induced pluripotent stem cell, a primary T cell, and a cell derived from a primary T cell, and the hypoinmunogenic cell is a B2M^{indel/indel}, CIITA^{indel/indel} cell comprising the exogenous CD47 polypeptides and optionally a CAR.

88. A method for treating a disorder in a patient by administering cells that do not trigger a systemic acute cellular immune response in the patient, the method comprising:

a) administering a therapeutically effective amount of a first population of cells to the patient; and

b) administering a therapeutically effective amount of a second population of cells to the patient following a recovery period after step (a),

wherein the cells of the first and second populations of cells comprise exogenous CD47 polypeptides and reduced expression of MHC class I and/or II human leukocyte antigens, and wherein the recovery period comprises at least 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months, 54 months, or 60 months or more.

89. The method of claim 88, wherein the cells of the first and second populations comprise reduced expression of MHC class I and MHC class II human leukocyte antigens.

90. The method of claim 88 or 89, wherein the cells of the first and second populations comprise the exogenous CD47 polypeptides and reduced expression levels of B2M and/or CIITA.

91. The method of any one of claims 88–90, wherein the cells of the first and second populations comprise the exogenous CD47 polypeptides and reduced expression levels of B2M and CIITA.

92. The method of any one of claims 88–91, wherein the first and second populations of cells comprise differentiated cells derived from pluripotent stem cells.

93. The method of claim 92, wherein the pluripotent stem cells comprise induced pluripotent stem cells.

94. The method of claim 92 or 93, wherein the differentiated cells are selected from the group consisting of cardiac cells, neural cells, endothelial cells, pancreatic islet cells, retinal pigmented epithelium cells, hepatocytes, thyroid cells and T cells.

95. The method of any one of claims 88–91, wherein the first and second populations of cells comprises cells derived from primary T cells.

96. The method of claim 95, wherein the cells derived from primary T cells are derived from a pool of T cells comprising primary T cells from one or more, optionally, two or more, three or more, four or more, five or more, ten or more, twenty or more, fifty or more, or one hundred or more, subjects different from the patient.

97. The method of claim 95 or 96, wherein the cells derived from primary T cells comprise a chimeric antigen receptor.

98. The method of claim 97, wherein the chimeric antigen receptor (CAR) is selected from the group consisting of

- (a) a first generation CAR comprising an antigen binding domain, a transmembrane domain, and a signaling domain;
- (b) a second generation CAR comprising an antigen binding domain, a transmembrane domain, and at least two signaling domains;
- (c) a third generation CAR comprising an antigen binding domain, a transmembrane domain, and at least three signaling domains; and
- (d) a fourth generation CAR comprising an antigen binding domain, a transmembrane domain, three or four signaling domains, and a domain which upon successful signaling of the CAR induces expression of a cytokine gene.

99. The method of claim 98, wherein the antigen binding domain is selected from the group consisting of:

- (a) an antigen binding domain targets an antigen characteristic of a neoplastic cell;
- (b) an antigen binding domain that targets an antigen characteristic of a T cell,
- (c) an antigen binding domain targets an antigen characteristic of an autoimmune or inflammatory disorder;
- (d) an antigen binding domain that targets an antigen characteristic of senescent cells;
- (e) an antigen binding domain that targets an antigen characteristic of an infectious disease; and
- (f) an antigen binding domain that binds to a cell surface antigen of a cell.

100. The method of claim 98 or 99, wherein the antigen binding domain is selected from the group consisting of an antibody, an antigen-binding portion thereof, an scFv, and a Fab.

101. The method of any one of claims 98–100, wherein the antigen binding domain binds to CD19, CD20, CD22, or BCMA.

102. The method of any one of claims 98–101, wherein the transmembrane domain comprises one selected from the group consisting of a transmembrane region of TCR α , TCR β , TCR ζ , CD3 ϵ , CD3 γ , CD3 δ , CD3 ζ , CD4, CD5, CD8 α , CD8 β , CD9, CD16, CD28, CD45, CD22, CD33, CD34, CD37, CD40, CD40L/CD154, CD45, CD64, CD80, CD86,

OX40/CD134, 4-1BB/CD137, CD154, FcεRIγ, VEGFR2, FAS, FGFR2B, and functional variant thereof.

103. The method of any one of claims 98–102, wherein the signaling domain(s) comprises a costimulatory domain(s).

104. The method of claim 103, wherein the costimulatory domains comprise two costimulatory domains that are not the same.

105. The method of claim 103 or 104, wherein the costimulatory domain(s) enhances cytokine production, CAR T cell proliferation, and/or CAR T cell persistence during T cell activation.

106. The method of any one of claims 97–105, wherein the cytokine gene is an endogenous or exogenous cytokine gene to the hypoonogenic cells.

107. The method of claim 106, wherein the cytokine gene encodes a pro-inflammatory cytokine.

108. The method of claim 107, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1, IL-2, IL-9, IL-12, IL-18, TNF, IFN-gamma, and a functional fragment thereof.

109. The method of any one of claims 97–108, wherein the domain which upon successful signaling of the CAR induces expression of the cytokine gene comprises a transcription factor or functional domain or fragment thereof.

110. The method of any one of claims 96–109, wherein the CAR comprises a CD3 zeta domain or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof.

111. The method of any one of claims 96–110, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; and (ii) a CD28 domain, or a 4-1BB domain, or functional variant thereof.

112. The method of any one of claims 96–111, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; and (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof.

113. The method of any one of claims 96–112, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof; and (iv) a cytokine or costimulatory ligand transgene.

114. The method of any one of claims 96–111, wherein the CAR comprises a (i) an anti-CD19 scFv; (ii) a CD8 α hinge and transmembrane domain or functional variant thereof; (iii) a 4-1BB costimulatory domain or functional variant thereof; and (iv) a CD3 ζ signaling domain or functional variant thereof.

115. The method of any one of claims 95–114, wherein the cells derived from primary T cells comprise reduced expression of an endogenous T cell receptor.

116. The method of any one of claims 95–115, wherein the cells derived from primary T cells comprise reduced expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and/or programmed cell death (PD1).

117. The method of any one of claims 88–116, wherein the recovery period comprises at least 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months, 54 months, or 60 months or more.

118. The method of any one of claims 88–117, wherein the step (b) is performed when the first population of cells is no longer detectable in the patient.

119. The method of any one of claims 88–118, wherein the first and/or second population of cells elicits a reduced level of immune activation or no immune activation in the patient.

120. The method of any one of claims 88–119, wherein the first and/or second population of cells elicits a reduced level of systemic TH1 activation or no systemic TH1 activation in the patient.

121. The method of any one of claims 88–120, wherein the first and/or second population of cells elicits a reduced level of immune activation of peripheral blood mononuclear cells (PBMCs) or no immune activation of PBMCs in the patient.

122. The method of any one of claims 88–121, wherein the first and/or second population of cells elicits a reduced level of donor-specific IgG antibodies or no donor-specific IgG antibodies against the administered cells in the patient.

123. The method of any one of claims 88–122, wherein the first and/or second population of cells elicits a reduced level of IgM and IgG antibody production or no IgM and IgG antibody production against the administered cells in the patient.

124. The method of any one of claims 88–123, wherein the first and/or second population of cells elicits a reduced level of cytotoxic T cell killing or no cytotoxic T cell killing of the administered cells in the patient.

125. The method of any one of claims 88–124, wherein the patient is not administered an immunosuppressive agent at least 3 days or more before or after the administration of the first population of cells.

126. The method of any one of claims 88–125, wherein the patient is not administered an immunosuppressive agent at least 3 days or more before or after the administration of the second population of cells.

127. The method of any one of claims 88–126, wherein the patient is not administered an immunosuppressive agent during the recovery period.

128. The method of any one of claims 88–127, wherein the hypoinmunogenic cell is selected from the group consisting a pluripotent stem cell, an induced pluripotent stem cell, a T cell differentiated from an induced pluripotent stem cell, a primary T cell, and a cell derived from a primary T cell, and the hypoinmunogenic cell is a B2M^{indel/indel}, CIITA^{indel/indel} cell comprising the exogenous CD47 polypeptides and optionally a CAR.

129. Use of a population of hypoinmunogenic cells comprising exogenous CD47 polypeptides and reduced expression of MHC class I and/or class II human leukocyte antigens for treatment of a disorder in a patient, wherein the patient has previously received an initial population of such hypoinmunogenic cells.

130. Use of a population of hypoinmunogenic cells comprising exogenous CD47 polypeptides and reduced expression of MHC class I and class II human leukocyte antigens for treatment of a disorder in a patient, wherein the patient has previously received an initial population of such hypoinmunogenic cells.

131. Use of a population of hypoimmunogenic cells comprising exogenous CD47 polypeptides and reduced levels of B2M and CIITA polypeptides for treatment of a disorder in a patient, wherein the patient has previously received an initial population of such hypoimmunogenic cells.

132. Use of a population of hypoimmunogenic cells comprising exogenous CD47 polypeptides, a genomic modification of the B2M gene, and a genomic modification of the CIITA gene for treatment of a disorder in a patient, wherein the patient has previously received an initial population of such hypoimmunogenic cells.

133. The use of the population of hypoimmunogenic cells of any one of claims 129–132, wherein the population of hypoimmunogenic cells comprises differentiated cells derived from pluripotent stem cells.

134. The use of the population of hypoimmunogenic cells of claim 133, wherein the pluripotent stem cells comprise induced pluripotent stem cells.

135. The use of the population of hypoimmunogenic cells of claim 133 or 134, wherein the differentiated cells are selected from the group consisting of cardiac cells, neural cells, endothelial cells, pancreatic islet cells, retinal pigmented epithelium cells, hepatocytes, thyroid cells, and T cells.

136. The use of the population of hypoimmunogenic cells of any one of claims 129–132, wherein the population of hypoimmunogenic cells comprises cells derived from primary T cells.

137. The use of the population of hypoimmunogenic cells of claim 136, wherein the cells derived from primary T cells are derived from a pool of T cells comprising primary T cells from one or more subjects different from the patient.

138. The use of the population of hypoimmunogenic cells of claim 136 or 137, wherein the cells derived from primary T cells comprise a chimeric antigen receptor (CAR).

139. The use of the population of hypoimmunogenic cells of claim 138, wherein the chimeric antigen receptor (CAR) is selected from the group consisting of:

(a) a first generation CAR comprising an antigen binding domain, a transmembrane domain, and a signaling domain;

(b) a second generation CAR comprising an antigen binding domain, a transmembrane domain, and at least two signaling domains;

(c) a third generation CAR comprising an antigen binding domain, a transmembrane domain, and at least three signaling domains; and

(d) a fourth generation CAR comprising an antigen binding domain, a transmembrane domain, three or four signaling domains, and a domain which upon successful signaling of the CAR induces expression of a cytokine gene.

140. The use of the population of hypoimmunogenic cells of claim 139, wherein the antigen binding domain is selected from the group consisting of:

- (a) an antigen binding domain targets an antigen characteristic of a neoplastic cell;
- (b) an antigen binding domain that targets an antigen characteristic of a T cell,
- (c) an antigen binding domain targets an antigen characteristic of an autoimmune or inflammatory disorder;
- (d) an antigen binding domain that targets an antigen characteristic of senescent cells;
- (e) an antigen binding domain that targets an antigen characteristic of an infectious disease; and
- (f) an antigen binding domain that binds to a cell surface antigen of a cell.

141. The use of the population of hypoimmunogenic cells of claim 139 or 140, wherein the antigen binding domain is selected from the group consisting of an antibody, an antigen-binding portion thereof, an scFv, and a Fab.

142. The use of the population of hypoimmunogenic cells of any one of claims 139–141, wherein the antigen binding domain binds to CD19, CD20, CD22, or BCMA.

143. The use of the population of hypoimmunogenic cells of any one of claims 139–142, wherein the transmembrane domain comprises one selected from the group consisting of a transmembrane region of TCR α , TCR β , TCR ζ , CD3 ϵ , CD3 γ , CD3 δ , CD3 ζ , CD4, CD5, CD8 α , CD8 β , CD9, CD16, CD28, CD45, CD22, CD33, CD34, CD37, CD40, CD40L/CD154, CD45, CD64, CD80, CD86, OX40/CD134, 4-1BB/CD137, CD154, Fc ϵ RI γ , VEGFR2, FAS, FGFR2B, and functional variant thereof.

144. The use of the population of hypoimmunogenic cells of any one of claims 139–143, wherein the signaling domain(s) comprises a costimulatory domain(s).

145. The use of the population of hypoimmunogenic cells of claim 144, wherein the costimulatory domains comprise two costimulatory domains that are not the same.

146. The use of the population of hypoimmunogenic cells of claim 144 or 145, wherein the costimulatory domain(s) enhances cytokine production, CAR T cell proliferation, and/or CAR T cell persistence during T cell activation.

147. The use of the population of hypoimmunogenic cells of any one of claims 139–146, wherein the cytokine gene is an endogenous or exogenous cytokine gene to the hypoimmunogenic cells.

148. The use of the population of hypoimmunogenic cells of claim 147, wherein the cytokine gene encodes a pro-inflammatory cytokine.

149. The use of the population of hypoimmunogenic cells of claim 148, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1, IL-2, IL-9, IL-12, IL-18, TNF, IFN-gamma, and a functional fragment thereof.

150. The use of the population of hypoimmunogenic cells of any one of claims 139–149, wherein the domain which upon successful signaling of the CAR induces expression of the cytokine gene comprises a transcription factor or functional domain or fragment thereof.

151. The use of the population of hypoimmunogenic cells of any one of claims 138–150, wherein the CAR comprises a CD3 zeta domain or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof.

152. The use of the population of hypoimmunogenic cells of any one of claims 138–151, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; and (ii) a CD28 domain, or a 4-1BB domain, or functional variant thereof.

153. The use of the population of hypoimmunogenic cells of any one of claims 138–152, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; and (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof.

154. The use of the population of hypoimmunogenic cells of any one of claims 138–153, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or

functional variant thereof; (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof; and (iv) a cytokine or costimulatory ligand transgene.

155. The use of the population of hypoimmunogenic cells of any one of claims 96–152, wherein the CAR comprises a (i) an anti-CD19 scFv; (ii) a CD8 α hinge and transmembrane domain or functional variant thereof; (iii) a 4-1BB costimulatory domain or functional variant thereof; and (iv) a CD3 ζ signaling domain or functional variant thereof.

156. The use of the population of hypoimmunogenic cells of any one of claims 136–138, wherein the cells derived from primary T cells comprise reduced expression of an endogenous T cell receptor.

157. The use of the population of hypoimmunogenic cells of any one of claims 136–156, wherein the cells derived from primary T cells comprise reduced expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and/or programmed cell death (PD1).

158. The use of the population of hypoimmunogenic cells of any one of claims 138–157, wherein the chimeric antigen receptor (CAR) is selected from the group consisting of:

- (a) a first generation CAR comprising an antigen binding domain, a transmembrane domain, and a signaling domain;
- (b) a second generation CAR comprising an antigen binding domain, a transmembrane domain, and at least two signaling domains;
- (c) a third generation CAR comprising an antigen binding domain, a transmembrane domain, and at least three signaling domains; and
- (d) a fourth generation CAR comprising an antigen binding domain, a transmembrane domain, three or four signaling domains, and a domain which upon successful signaling of the CAR induces expression of a cytokine gene.

159. The use of the population of hypoimmunogenic cells of claim 158, wherein the antigen binding domain is selected from the group consisting of:

- (a) an antigen binding domain targets an antigen characteristic of a neoplastic cell;
- (b) an antigen binding domain that targets an antigen characteristic of a T cell,
- (c) an antigen binding domain targets an antigen characteristic of an autoimmune or inflammatory disorder;
- (d) an antigen binding domain that targets an antigen characteristic of senescent cells;

(e) an antigen binding domain that targets an antigen characteristic of an infectious disease; and

(f) an antigen binding domain that binds to a cell surface antigen of a cell.

160. The use of the population of hypoimmunogenic cells of claim 159, wherein the antigen binding domain is selected from the group consisting of an antibody, an antigen-binding portion thereof, an scFv, and a Fab.

161. The use of the population of hypoimmunogenic cells of claim 159 or 160, wherein the antigen binding domain binds to CD19, CD20, CD22, or BCMA.

162. The use of the population of hypoimmunogenic cells of any one of claims 158–161, wherein the transmembrane domain comprises one selected from the group consisting of a transmembrane region of TCR α , TCR β , TCR ζ , CD3 ϵ , CD3 γ , CD3 δ , CD3 ζ , CD4, CD5, CD8 α , CD8 β , CD9, CD16, CD28, CD45, CD22, CD33, CD34, CD37, CD40, CD40L/CD154, CD45, CD64, CD80, CD86, OX40/CD134, 4-1BB/CD137, CD154, Fc ϵ RI γ , VEGFR2, FAS, FGFR2B, and functional variant thereof.

163. The use of the population of hypoimmunogenic cells of any one of claims 158–162, wherein the signaling domain(s) comprises a costimulatory domain(s).

164. The use of the population of hypoimmunogenic cells of claim 163, wherein the costimulatory domains comprise two costimulatory domains that are not the same.

165. The use of the population of hypoimmunogenic cells of claim 163 or 164, wherein the costimulatory domain(s) enhances cytokine production, CAR T cell proliferation, and/or CAR T cell persistence during T cell activation.

166. The use of the population of hypoimmunogenic cells of any one of claims 158–165, wherein the cytokine gene is an endogenous or exogenous cytokine gene to the hypoimmunogenic cells.

167. The use of the population of hypoimmunogenic cells of claim 166, wherein the cytokine gene encodes a pro-inflammatory cytokine.

168. The use of the population of hypoimmunogenic cells of claim 167, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1, IL-2, IL-9, IL-12, IL-18, TNF, IFN-gamma, and a functional fragment thereof.

169. The use of the population of hypoimmunogenic cells of any one of claims 158–168, wherein the domain which upon successful signaling of the CAR induces

expression of the cytokine gene comprises a transcription factor or functional domain or fragment thereof.

170. The use of the population of hypoimmunogenic cells of any one of claims 138–169, wherein the CAR comprises a CD3 zeta domain or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof.

171. The use of the population of hypoimmunogenic cells of any one of claims 138–170, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; and (ii) a CD28 domain, or a 4-1BB domain, or functional variant thereof.

172. The use of the population of hypoimmunogenic cells of any one of claims 138–171, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; and (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof.

173. The use of the population of hypoimmunogenic cells of any one of claims 138–172, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof; and (iv) a cytokine or costimulatory ligand transgene.

174. The use of the population of hypoimmunogenic cells of any one of claims 138–171, wherein the CAR comprises a (i) an anti-CD19 scFv; (ii) a CD8 α hinge and transmembrane domain or functional variant thereof; (iii) a 4-1BB costimulatory domain or functional variant thereof; and (iv) a CD3 ζ signaling domain.

175. The use of any one of claims 138–171, wherein the hypoimmunogenic cell is selected from the group consisting a pluripotent stem cell, an induced pluripotent stem cell, a T cell differentiated from an induced pluripotent stem cell, a primary T cell, and a cell derived from a primary T cell, and the hypoimmunogenic cell comprises exogenous CD47 and/or optionally a CAR, and wherein the hypoimmunogenic cell is optionally a B2M^{indel/indel} cell and/or optionally CIITA^{indel/indel} cell.

176. A population of hypoimmunogenic cells comprising exogenous CD47 polypeptides and reduced expression of MHC class I and/or class II human leukocyte

antigens, wherein the population of hypoinmunogenic cells comprises cells derived from primary T cells.

177. A population of hypoinmunogenic cells comprising exogenous CD47 polypeptides and reduced expression of MHC class I and class II human leukocyte antigens, wherein the population of hypoinmunogenic cells comprises cells derived from primary T cells.

178. A population of hypoinmunogenic cells comprising exogenous CD47 polypeptides and reduced levels of B2M and CIITA polypeptides, wherein the population of hypoinmunogenic cells comprises cells derived from primary T cells.

179. A population of hypoinmunogenic cells comprising exogenous CD47 polypeptides, a genomic modification of the B2M gene, and a genomic modification of the CIITA gene, wherein the population of hypoinmunogenic cells comprises cells derived from primary T cells.

180. The population of hypoinmunogenic cells of any one of claims 176–179, wherein the cells derived from primary T cells are derived from a pool of T cells comprising primary T cells from one or more, optionally, two or more, three or more, four or more, five or more, ten or more, twenty or more, fifty or more, or one hundred or more, subjects different from the patient.

181. The population of hypoinmunogenic cells of any one of claims 176–180, wherein the cells derived from primary T cells comprise a chimeric antigen receptor (CAR).

182. The population of hypoinmunogenic cells of any one of claims 176–181, wherein the cells derived from primary T cells comprise reduced expression of an endogenous T cell receptor.

183. The population of hypoinmunogenic cells of any one of claims 176–182, wherein the cells derived from primary T cells comprise reduced expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and/or programmed cell death (PD1).

184. The population of hypoinmunogenic cells of any one of claims 181–183, wherein the chimeric antigen receptor (CAR) is selected from the group consisting of:

(a) a first generation CAR comprising an antigen binding domain, a transmembrane domain, and a signaling domain;

- (b) a second generation CAR comprising an antigen binding domain, a transmembrane domain, and at least two signaling domains;
- (c) a third generation CAR comprising an antigen binding domain, a transmembrane domain, and at least three signaling domains; and
- (d) a fourth generation CAR comprising an antigen binding domain, a transmembrane domain, three or four signaling domains, and a domain which upon successful signaling of the CAR induces expression of a cytokine gene.

185. The population of hypoimmunogenic cells of claim 184, wherein the antigen binding domain is selected from the group consisting of:

- (a) an antigen binding domain targets an antigen characteristic of a neoplastic cell;
- (b) an antigen binding domain that targets an antigen characteristic of a T cell,
- (c) an antigen binding domain targets an antigen characteristic of an autoimmune or inflammatory disorder;
- (d) an antigen binding domain that targets an antigen characteristic of senescent cells;
- (e) an antigen binding domain that targets an antigen characteristic of an infectious disease; and
- (f) an antigen binding domain that binds to a cell surface antigen of a cell.

186. The population of hypoimmunogenic cells of claim 185, wherein the antigen binding domain is selected from the group consisting of an antibody, an antigen-binding portion thereof, an scFv, and a Fab.

187. The population of hypoimmunogenic cells of claim 185 or 186, wherein the antigen binding domain binds to CD19, CD20, CD22, or BCMA.

188. The population of hypoimmunogenic cells of any one of claims 184–187, wherein the transmembrane domain comprises one selected from the group consisting of a transmembrane region of TCR α , TCR β , TCR ζ , CD3 ϵ , CD3 γ , CD3 δ , CD3 ζ , CD4, CD5, CD8 α , CD8 β , CD9, CD16, CD28, CD45, CD22, CD33, CD34, CD37, CD40, CD40L/CD154, CD45, CD64, CD80, CD86, OX40/CD134, 4-1BB/CD137, CD154, Fc ϵ RI γ , VEGFR2, FAS, FGFR2B, and functional variant thereof.

189. The population of hypoimmunogenic cells of any one of claims 184–188, wherein the signaling domain(s) comprises a costimulatory domain(s).

190. The population of hypoimmunogenic cells of claim 189, wherein the costimulatory domains comprise two costimulatory domains that are not the same.

191. The population of hypoimmunogenic cells of claim 189 or 190, wherein the costimulatory domain(s) enhances cytokine production, CAR T cell proliferation, and/or CAR T cell persistence during T cell activation.

192. The population of hypoimmunogenic cells of any one of claims 184–191, wherein the cytokine gene is an endogenous or exogenous cytokine gene to the hypoimmunogenic cells.

193. The population of hypoimmunogenic cells of claim 192, wherein the cytokine gene encodes a pro-inflammatory cytokine.

194. The population of hypoimmunogenic cells of claim 193, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1, IL-2, IL-9, IL-12, IL-18, TNF, IFN-gamma, and a functional fragment thereof.

195. The population of hypoimmunogenic cells of any one of claims 184–194, wherein the domain which upon successful signaling of the CAR induces expression of the cytokine gene comprises a transcription factor or functional domain or fragment thereof.

196. The population of hypoimmunogenic cells of any one of claims 181–195, wherein the CAR comprises a CD3 zeta domain or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof.

197. The population of hypoimmunogenic cells of any one of claims 181–196, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; and (ii) a CD28 domain, or a 4-1BB domain, or functional variant thereof.

198. The population of hypoimmunogenic cells of any one of claims 181–197, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; and (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof.

199. The population of hypoimmunogenic cells of any one of claims 181–198, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof; and (iv) a cytokine or costimulatory ligand transgene.

200. The population of hypoimmunogenic cells of any one of claims 181–197, wherein the CAR comprises a (i) an anti-CD19 scFv; (ii) a CD8 α hinge and transmembrane domain or functional variant thereof; (iii) a 4-1BB costimulatory domain or functional variant thereof; and (iv) a CD3 ζ signaling domain.

201. The population of hypoimmunogenic cells of any one of claims 176–200, for use in treatment of a disorder in a patient, wherein the patient has previously received an initial population of such hypoimmunogenic cells.

202. The population of hypoimmunogenic cells of any one of claims 176–201, wherein the hypoimmunogenic cell is selected from the group consisting a pluripotent stem cell, an induced pluripotent stem cell, a T cell differentiated from an induced pluripotent stem cell, a primary T cell, and a cell derived from a primary T cell, and the hypoimmunogenic cell comprises exogenous CD47 and/or optionally a CAR, and wherein the hypoimmunogenic cell is optionally a B2M^{indel/indel} cell and/or optionally CIITA^{indel/indel} cell.

203. Use of a population of hypoimmunogenic cells comprising exogenous CD47 polypeptides and reduced expression of MHC class I and/or class II human leukocyte antigens, wherein the population of hypoimmunogenic cells comprises cells derived from primary T cells.

204. Use of a population of hypoimmunogenic cells comprising exogenous CD47 polypeptides and reduced expression of MHC class I and class II human leukocyte antigens, wherein the population of hypoimmunogenic cells comprises cells derived from primary T cells.

205. Use of a population of hypoimmunogenic cells comprising exogenous CD47 polypeptides and reduced levels of B2M and CIITA polypeptides, wherein the population of hypoimmunogenic cells comprises cells derived from primary T cells.

206. Use of a population of hypoimmunogenic cells comprising exogenous CD47 polypeptides, a genomic modification of the B2M gene, and a genomic modification of the CIITA gene, wherein the population of hypoimmunogenic cells comprises cells derived from primary T cells.

207. The use of the population of hypoimmunogenic cells of any one of claims 203–206, wherein the cells derived from primary T cells are derived from a pool of T cells comprising T cells from one or more subjects different from the patient.

208. The use of the population of hypoimmunogenic cells of any one of claims use of the 203–207, wherein the cells derived from primary T cells comprise a chimeric antigen receptor (CAR).

209. The use of the population of hypoimmunogenic cells of any one of claims 203–208, wherein the cells derived from primary T cells comprise reduced expression of an endogenous T cell receptor.

210. The use of the population of hypoimmunogenic cells of any one of claims 203–209, wherein the cells derived from primary T cells comprise reduced expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and/or programmed cell death (PD1).

211. The use of the population of hypoimmunogenic cells of any one of claims 208–210, wherein the chimeric antigen receptor (CAR) is selected from the group consisting of:

- (a) a first generation CAR comprising an antigen binding domain, a transmembrane domain, and a signaling domain;
- (b) a second generation CAR comprising an antigen binding domain, a transmembrane domain, and at least two signaling domains;
- (c) a third generation CAR comprising an antigen binding domain, a transmembrane domain, and at least three signaling domains; and
- (d) a fourth generation CAR comprising an antigen binding domain, a transmembrane domain, three or four signaling domains, and a domain which upon successful signaling of the CAR induces expression of a cytokine gene.

212. The use of the population of hypoimmunogenic cells of claim 211, wherein the antigen binding domain is selected from the group consisting of:

- (a) an antigen binding domain targets an antigen characteristic of a neoplastic cell;
- (b) an antigen binding domain that targets an antigen characteristic of a T cell,
- (c) an antigen binding domain targets an antigen characteristic of an autoimmune or inflammatory disorder;
- (d) an antigen binding domain that targets an antigen characteristic of senescent cells;

(e) an antigen binding domain that targets an antigen characteristic of an infectious disease; and

(f) an antigen binding domain that binds to a cell surface antigen of a cell.

213. The use of the population of hypoimmunogenic cells of claim 212, wherein the antigen binding domain is selected from the group consisting of an antibody, an antigen-binding portion thereof, an scFv, and a Fab.

214. The use of the population of hypoimmunogenic cells of claim 212 or 213, wherein the antigen binding domain binds to CD19, CD20, CD22, or BCMA.

215. The use of the population of hypoimmunogenic cells of any one of claims 211–214, wherein the transmembrane domain comprises one selected from the group consisting of a transmembrane region of TCR α , TCR β , TCR ζ , CD3 ϵ , CD3 γ , CD3 δ , CD3 ζ , CD4, CD5, CD8 α , CD8 β , CD9, CD16, CD28, CD45, CD22, CD33, CD34, CD37, CD40, CD40L/CD154, CD45, CD64, CD80, CD86, OX40/CD134, 4-1BB/CD137, CD154, Fc ϵ RI γ , VEGFR2, FAS, FGFR2B, and functional variant thereof.

216. The use of the population of hypoimmunogenic cells of any one of claims 211–215, wherein the signaling domain(s) comprises a costimulatory domain(s).

217. The use of the population of hypoimmunogenic cells of claim 216, wherein the costimulatory domains comprise two costimulatory domains that are not the same.

218. The use of the population of hypoimmunogenic cells of claim 216 or 217, wherein the costimulatory domain(s) enhances cytokine production, CAR T cell proliferation, and/or CAR T cell persistence during T cell activation.

219. The use of the population of hypoimmunogenic cells of any one of claims 211–218, wherein the cytokine gene is an endogenous or exogenous cytokine gene to the hypoimmunogenic cells.

220. The use of the population of hypoimmunogenic cells of claim 219, wherein the cytokine gene encodes a pro-inflammatory cytokine.

221. The use of the population of hypoimmunogenic cells of claim 220, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1, IL-2, IL-9, IL-12, IL-18, TNF, IFN-gamma, and a functional fragment thereof.

222. The use of the population of hypoimmunogenic cells of any one of claims 211–221, wherein the domain which upon successful signaling of the CAR induces expression of the cytokine gene comprises a transcription factor or functional domain or fragment thereof.

223. The use of the population of hypoimmunogenic cells of any one of claims 208–222, wherein the CAR comprises a CD3 zeta domain or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof.

224. The use of the population of hypoimmunogenic cells of any one of claims 208–223, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; and (ii) a CD28 domain, or a 4-1BB domain, or functional variant thereof.

225. The use of the population of hypoimmunogenic cells of any one of claims 208–224, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; and (iii) a 4-1BB costimulatory domain, or a CD134 domain, or functional variant thereof.

226. The use of the population of hypoimmunogenic cells of any one of claims 208–225, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; (iii) a 4-1BB costimulatory domain, or a CD134 domain, or functional variant thereof; and (iv) a cytokine or costimulatory ligand transgene.

227. The use of the population of hypoimmunogenic cells of any one of claims 203–224, wherein the CAR comprises a (i) an anti-CD19 scFv; (ii) a CD8 α hinge and transmembrane domain or functional variant thereof; (iii) a 4-1BB costimulatory domain or functional variant thereof; and (iv) a CD3 ζ signaling domain.

228. The use of the population of hypoimmunogenic cells of any one of claims 203–227, for use in treatment of a disorder in a patient, wherein the patient has previously received an initial population of such hypoimmunogenic cells.

229. The use of the population of hypoimmunogenic cells of any one of claims 176–228, wherein the hypoimmunogenic cell is selected from the group consisting of a pluripotent stem cell, an induced pluripotent stem cell, a T cell differentiated from an induced pluripotent stem cell, a primary T cell, and a cell derived from a primary T cell, and the

hypimmunogenic cell comprises exogenous CD47 and/or optionally a CAR, and wherein the hypimmunogenic cell is optionally a B2M^{indel/indel} cell and/or optionally CIITA^{indel/indel} cell.

230. A method for treating a disorder in a patient comprising administering to the patient a therapeutically effective amount of a population of hypimmunogenic T cells derived from primary T cells and which comprise exogenous CD47 polypeptides and exhibit reduced expression of MHC class I and/or class II human leukocyte antigens, wherein an initial population of such hypimmunogenic T cells had previously been administered to the patient.

231. The method of claim 230, wherein the hypimmunogenic T cells comprise reduced expression of MHC class I and class II human leukocyte antigens.

232. The method of claim 230 or 231, wherein the hypimmunogenic T cells express the exogenous CD47 polypeptides and reduced expression levels of B2M and/or CIITA.

233. The method of any one of claims 230–232, wherein the hypimmunogenic T cells express the exogenous CD47 polypeptides and reduced expression levels of B2M and CIITA.

234. The method of claim 230–233, wherein the hypimmunogenic T cells comprise a chimeric antigen receptor.

235. The method of claim 234, wherein the chimeric antigen receptor (CAR) is selected from the group consisting of:

- (a) a first generation CAR comprising an antigen binding domain, a transmembrane domain, and a signaling domain;
- (b) a second generation CAR comprising an antigen binding domain, a transmembrane domain, and at least two signaling domains;
- (c) a third generation CAR comprising an antigen binding domain, a transmembrane domain, and at least three signaling domains; and
- (d) a fourth generation CAR comprising an antigen binding domain, a transmembrane domain, three or four signaling domains, and a domain which upon successful signaling of the CAR induces expression of a cytokine gene.

236. The method of claim 235, wherein the antigen binding domain is selected from the group consisting of:

- (a) an antigen binding domain targets an antigen characteristic of a neoplastic cell;
- (b) an antigen binding domain that targets an antigen characteristic of a T cell;
- (c) an antigen binding domain targets an antigen characteristic of an autoimmune or inflammatory disorder;
- (d) an antigen binding domain that targets an antigen characteristic of senescent cells;
- (e) an antigen binding domain that targets an antigen characteristic of an infectious disease; and
- (f) an antigen binding domain that binds to a cell surface antigen of a cell.

237. The method of claim 234 or 235, wherein the antigen binding domain is selected from the group consisting of an antibody, an antigen-binding portion thereof, an scFv, and a Fab.

238. The method of any one of claims 234–237, wherein the antigen binding domain binds to CD19, CD20, CD22, or BCMA.

239. The method of any one of claims 234–238, wherein the transmembrane domain comprises one selected from the group consisting of a transmembrane region of TCR α , TCR β , TCR ζ , CD3 ϵ , CD3 γ , CD3 δ , CD3 ζ , CD4, CD5, CD8 α , CD8 β , CD9, CD16, CD28, CD45, CD22, CD33, CD34, CD37, CD40, CD40L/CD154, CD45, CD64, CD80, CD86, OX40/CD134, 4-1BB/CD137, CD154, Fc ϵ RI γ , VEGFR2, FAS, FGFR2B, and functional variant thereof.

240. The method of any one of claims 234–239, wherein the signaling domain(s) comprises a costimulatory domain(s).

241. The method of claim 240, wherein the costimulatory domains comprise two costimulatory domains that are not the same.

242. The method of claim 240 or 241, wherein the costimulatory domain(s) enhances cytokine production, CAR T cell proliferation, and/or CAR T cell persistence during T cell activation.

243. The method of any one of claims 235–242, wherein the cytokine gene is an endogenous or exogenous cytokine gene to the hypoinmunogenic T cells.

244. The method of claim 243, wherein the cytokine gene encodes a pro-inflammatory cytokine.

245. The method of claim 244, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1, IL-2, IL-9, IL-12, IL-18, TNF, IFN-gamma, and a functional fragment thereof.

246. The method of any one of claims 233–245, wherein the domain which upon successful signaling of the CAR induces expression of the cytokine gene comprises a transcription factor or functional domain or fragment thereof.

247. The method of any one of claims 233–246, wherein the CAR comprises a CD3 zeta domain or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof.

248. The method of any one of claims 233–247, wherein the CAR comprises (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; and (ii) a CD28 domain, or a 4-1BB domain, or functional variant thereof.

249. The method of any one of claims 233–248, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; and (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof.

250. The method of any one of claims 233–249, wherein the CAR comprises a (i) a CD3 zeta domain, or an immunoreceptor tyrosine-based activation motif (ITAM), or functional variant thereof; (ii) a CD28 domain or functional variant thereof; (iii) a 4-1BB domain, or a CD134 domain, or functional variant thereof; and (iv) a cytokine or costimulatory ligand transgene.

251. The method of any one of claims 233–250, wherein the CAR comprises a (i) an anti-CD19 scFv; (ii) a CD8 α hinge and transmembrane domain or functional variant thereof; (iii) a 4-1BB costimulatory domain or functional variant thereof; and (iv) a CD3 ζ signaling domain or functional variant thereof.

252. The method of any one of claims 230–251, wherein the hypoimmunogenic T cells comprise reduced expression of an endogenous T cell receptor.

253. The method of any one of claims 230–252, wherein the hypoimmunogenic T cells comprise reduced expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and/or programmed cell death (PD1).

254. The method of any one of claims 230–253, wherein the population of the hypoinmunogenic T cells is administered at least 3 days or more after the initial administration, optionally at least 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months, 54 months, or 60 months or more.

255. The method of any one of claims 230–254, wherein the population of the hypoinmunogenic T cells is administered at least 3 days to at least 7 days or more after the initial administration.

256. The method of any one of claims 230–255, wherein the population of the hypoinmunogenic T cells is administered least 1 month or more after the initial administration.

257. The method of any one of claims 230–256, wherein the population of the hypoinmunogenic T cells is administered at least 2 months or more after the initial administration.

258. The method of any one of claims 230–257, wherein upon the initial and/or subsequent administrations, the population of hypoinmunogenic T cells elicits a reduced level of immune activation or no immune activation in the patient.

259. The method of any one of claims 230–258, wherein upon the initial and/or subsequent administrations, the population of hypoinmunogenic T cells elicits a reduced level of systemic TH1 activation or no systemic TH1 activation in the patient.

260. The method of any one of claims 230–259, wherein upon the initial and/or subsequent administrations, the population of hypoinmunogenic T cells elicits a reduced level of immune activation of peripheral blood mononuclear cells (PBMCs) or no immune activation of PBMCs in the patient.

261. The method of any one of claims 230–260, wherein upon the initial and/or subsequent administrations, the population of hypoinmunogenic T cells elicits a reduced level of donor-specific IgG antibodies or no donor specific IgG antibodies against the hypoinmunogenic cells in the patient.

262. The method of any one of claims 230–261, wherein upon the initial and/or subsequent administrations, the population of hypoinmunogenic T cells elicits a reduced level of IgM and IgG antibody production or no IgM and IgG antibody production against the hypoinmunogenic cells in the patient.

263. The method of any one of claims 230–262, wherein upon administration, the population of hypoinmunogenic T cells elicits a reduced level of cytotoxic T cell killing or no cytotoxic T cell killing of the hypoinmunogenic T cells in the patient.

264. The method of any one of claims 230–263, wherein the population of hypoinmunogenic T cells of the initial administration are no longer present in the patient at the subsequent administration.

265. The method of any one of claims 230–264, wherein the patient is not administered an immunosuppressive agent at least 3 days or more before or after the initial administration of the population of hypoinmunogenic T cells.

266. The method of any one of claims 230–265, wherein the patient is not administered an immunosuppressive agent at least 3 days or more before or after the initial subsequent administration of the population of hypoinmunogenic T cells.

267. The method of any one of claims 230–266, wherein the hypoinmunogenic cell is a B2M^{indel/indel}, CIITA^{indel/indel} cell comprising the exogenous CD47 polypeptides and optionally a CAR.