

CLAIMS

What is claimed is:

1. A method of depleting a population of CD45+ cells in a human patient in need of a hematopoietic stem cell (HSC) transplant, the method comprising administering to the patient an effective amount of a CD45 targeting moiety coupled to a cytotoxin prior to the patient receiving a transplant comprising allogeneic HSCs, wherein the patient is not conditioned with an immunosuppressive agent prior to or substantially concurrently with the transplant.
2. A method comprising:
 - a. administering to a human patient a CD45 targeting moiety coupled to a cytotoxin in an effective amount sufficient to deplete a population of CD45+ cells in the patient in the absence of an immunosuppressive agent; and
 - b. subsequently administering to the patient a transplant comprising allogeneic HSCs.
3. A method comprising administering to a human patient a transplant comprising allogeneic HSCs, wherein the patient has been previously administered a CD45 targeting moiety coupled to a cytotoxin in an effective amount sufficient to deplete a population of hematopoietic stem cells in the patient in the absence of an immunosuppressive agent.
4. The method of any one of claims 1-3, wherein the CD45 targeting moiety coupled to the cytotoxin is an anti-CD45 antibody drug conjugate (ADC).
5. The method of any one of claims 1-4, wherein the allogeneic HSCs comprise one or more HLA mismatches relative to the HLA antigens in the patient.
6. The method of any one of claims 1-4, wherein the allogeneic HSCs comprise two or more HLA mismatches relative to the HLA antigens in the patient.
7. The method of any one of claims 1-4, wherein the allogeneic HSCs comprise three or more HLA mismatches relative to the HLA antigens in the patient.
8. The method of any one of claims 1-4, wherein the allogeneic HSCs comprise five or more HLA mismatches relative to the HLA antigens in the patient.
9. The method of any one of claims 1-4, wherein the allogeneic HSCs comprise a full HLA-mismatch relative to the HLA antigens in the patient.
10. The method of any one of claims 1-9, wherein the allogeneic HSCs comprise one or more minor histocompatibility antigen (miHA) mismatch relative to the minor histocompatibility antigens in the patient.

11. The method of any one of claims 1-9, wherein the allogeneic HSCs comprise two or more miHA mismatches relative to the minor histocompatibility antigens in the patient.
12. The method of any one of claims 1-9, wherein the allogeneic HSCs comprise five or more miHA mismatches relative to the minor histocompatibility antigens in the patient.
13. The method of any one of claims 1-12, wherein the immunosuppressive agent is total body irradiation (TBI).
14. The method of claim 13, wherein the immunosuppressive agent is low-dose TBI.
15. The method of any one of claims 1-12, wherein the immunosuppressive agent is an anti-CD4 antibody, an anti-CD8 antibody, or a combination thereof.
16. The method of any one of claims 1-12, wherein the immunosuppressive agent is cyclophosphamide.
17. The method of any one of claims 1-16, wherein the patient does not receive an immunosuppressive agent for at least 24 hours prior to the transplant and/or at least 24 hours after the transplant.
18. The method of any one of claims 1-16, wherein the patient does not receive an immunosuppressive agent for at least 48 hours prior to the transplant and/or at least 48 hours after the transplant.
19. The method of any one of claims 1-16, wherein the patient does not receive an immunosuppressive agent for at least 72 hours prior to the transplant and/or at least 72 hours after the transplant.
20. The method of any one of claims 1-16, wherein the patient does not receive an immunosuppressive agent for at least 96 hours prior to the transplant and/or at least 96 hours after the transplant.
21. The method of any one of claims 1-16, wherein the patient does not receive an immunosuppressive agent for at least 7 days prior to the transplant and/or at least 7 days after the transplant.
22. The method of any one of claims 1-16, wherein the patient does not receive an immunosuppressive agent for at least 14 days prior to the transplant and/or at least 14 days after the transplant.
23. The method of any one of claims 1-16, wherein the patient does not receive an immunosuppressive agent for at least 1 month prior to the transplant and/or at least 1 month after the transplant.
24. The method of any one of claims 1-23, wherein the effective amount of the CD45 targeting moiety coupled to the toxin is an amount sufficient to establish at least 80%, 85%, 90%, 95%, 97%, 99% or 100% donor chimerism.
25. The method of claim 24, wherein donor chimerism is assessed at least 6 weeks, 7 weeks, 8 weeks, 9 weeks, or 10 weeks post-transplantation.
26. The method of claim 24 or 25, wherein the donor chimerism is total peripheral chimerism.

27. The method of claim 24 or 25, wherein the donor chimerism is myeloid chimerism.
28. The method of claim 24 or 25, wherein the donor chimerism is T cell chimerism.
29. The method of claim 24 or 25, wherein the donor chimerism is B cell chimerism.
30. The method of any one of claims 1-29, wherein the effective amount of the CD45 targeting moiety coupled to the toxin is administered to the patient as a single dose.
31. The method of any one of claims 1-29, wherein the effective amount of the CD45 targeting moiety coupled to the toxin is administered to the patient in two doses.
32. The method of any one of claims 1-29, wherein the effective amount of the CD45 targeting moiety coupled to the toxin is administered to the patient in two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) doses.
33. The method of any one of claims 1-32, wherein the transplant is administered to the patient after the concentration of the CD45 targeting moiety coupled to the toxin has substantially cleared from the blood of the patient.
34. The method of any one of claims 1-33, wherein the hematopoietic stem cells or progeny thereof maintain hematopoietic stem cell functional potential after two or more days following transplantation of the hematopoietic stem cells into the patient.
35. The method of any one of claims 1-34, wherein the allogeneic hematopoietic stem cells or progeny thereof are capable of localizing to hematopoietic tissue and/or reestablishing hematopoiesis following transplantation of the hematopoietic stem cells into the patient.
36. The method of any one of claims 1-35, wherein upon transplantation into the patient, the hematopoietic stem cells give rise to recovery of a population of cells selected from the group consisting of megakaryocytes, thrombocytes, platelets, erythrocytes, mast cells, myeloblasts, basophils, neutrophils, eosinophils, microglia, granulocytes, monocytes, osteoclasts, antigen-presenting cells, macrophages, dendritic cells, natural killer cells, T-lymphocytes, and B-lymphocytes.
37. The method of any one of claims 1-36, wherein the patient is suffering from a stem cell disorder.
38. The method of any one of claims 1-36, wherein the patient is suffering from a hemoglobinopathy disorder, an autoimmune disorder, myelodysplastic disorder, immunodeficiency disorder, or a metabolic disorder.
39. The method of any one of claims 1-36, wherein the patient is suffering from cancer.

40. The method of any one of claims 4-40, wherein the anti-CD45 ADC comprises an antibody having a dissociation rate (K_{OFF}) of 1×10^{-2} to 1×10^{-3} , 1×10^{-3} to 1×10^{-4} , 1×10^{-5} to 1×10^{-6} , 1×10^{-6} to 1×10^{-7} or 1×10^{-7} to 1×10^{-8} as measured by bio-layer interferometry (BLI).
41. The method of any one of claims 4-40, wherein the anti-CD45 ADC comprises an antibody that binds CD45 with a K_D of about 100 nM or less, about 90 nM or less, about 80 nM or less, about 70 nM or less, about 60 nM or less, about 50 nM or less, about 40 nM or less, about 30 nM or less, about 20 nM or less, about 10 nM or less, about 8 nM or less, about 6 nM or less, about 4 nM or less, about 2 nM or less, about 1 nM or less as determined by a Bio-Layer Interferometry (BLI) assay.
42. The method of any one of claims 4-41, wherein the anti-CD45 ADC comprises a humanized anti-CD45 antibody, or an antigen-binding portion thereof.
43. The method of any one of claims 4-41, wherein the anti-CD45 ADC comprises a human anti-CD45 antibody, or an antigen-binding portion thereof.
44. The method of any one of claims 4-43, wherein the anti-CD45 ADC comprises an anti-CD45 antibody set forth in Table 5, or an antigen-binding portion thereof.
45. The method of any one of claims 4-44, wherein the anti-CD45 ADC comprises an intact anti-CD45 antibody.
46. The method of any one of claims 4-45, wherein the anti-CD45 ADC comprises an IgG antibody.
47. The method of claim 46, wherein the IgG is an IgG1 isotype, an IgG2 isotype, an IgG3 isotype, or an IgG4 isotype.
48. The method of any one of claims 4-47, wherein the anti-CD45 ADC comprises an anti-CD45 antibody, or an antigen-binding portion thereof, conjugated to a cytotoxin via a linker.
49. The method of claim 48, wherein the cytotoxin is an RNA polymerase inhibitor.
50. The method of claim 49, wherein the RNA polymerase inhibitor is an amatotoxin.
51. The method of claim 50, wherein the amatotoxin is an amanitin.
52. The method of claim 50, wherein the amatotoxin is selected from the group consisting of α -amanitin, β -amanitin, γ -amanitin, ϵ -amanitin, amanin, amaninamide, amanullin, amanullinic acid, and proamanullin.
53. The method of claim 48, wherein the cytotoxin is a pyrrolbenzodiazepine (PBD).
54. The method of claim 48, wherein the cytotoxin is selected from the group consisting of pseudomonas exotoxin A, deBouganin, diphtheria toxin, saporin, maytansine, a maytansinoid, an

auristatin, an anthracycline, a calicheamicin, irinotecan, SN-38, a duocarmycin, a pyrrolobenzodiazepine, a pyrrolobenzodiazepine dimer, an indolinobenzodiazepine, an indolinobenzodiazepine dimer, and an indolinobenzodiazepine pseudodimer.

55. The method of claim 54, wherein the auristatin is MMAE or MMAF.
56. The method of any one of claims 48-55, wherein the antibody is conjugated to the toxin by way of a cysteine residue in the Fc domain of the antibody.
57. The method of claim 56, wherein the cysteine residue is introduced by way of an amino acid substitution in the Fc domain of the antibody.
58. The method of claim 57, wherein the amino acid substitution is S239C or D265C.