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(54) **Title:** COMPOSITIONS AND METHODS FOR THE DEPLETION OF CD2+ CELLS

(57) **Abstract:** The invention provides anti-CD2 antibodies, antigen-binding fragments thereof, and antibody-drug conjugates thereof, for use as agents to treat a stem cell disorder, cancer, or autoimmune disease, among other hematological and proliferative diseases. The compositions and methods described herein can be used to deplete populations of CD2+ cells, such as CD2+ cancer cells and CD2+ immune cells, and can be used to prepare a patient for hematopoietic stem cell transplantation.

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AMENDED CLAIMS
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1. A method of depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

2. A method of depleting a population of CD2+ cells in a human patient in need of a hematopoietic stem cell transplant, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

3. A method of preventing rejection of a hematopoietic stem cell graft in a human patient in need of a hematopoietic stem cell transplant, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof, prior to the human patient receiving a transplant comprising hematopoietic stem cells, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

4. A method of depleting a population of CD2+ cells in a human patient in need of a hematopoietic stem cell transplant, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof, prior to the patient receiving a transplant comprising hematopoietic stem cells, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

5. A method comprising administering to a human patient a transplant comprising hematopoietic stem cells, wherein the patient has been previously administered an anti-CD2 antibody or antigen-binding fragment thereof, in an amount sufficient to deplete a population of CD2+ cells in the patient, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

6. A method comprising:
   i) administering to a human patient an antibody, or antigen-binding fragment thereof, that binds to CD2 in an amount sufficient to deplete a population of CD2+ cells in the patient, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin; and
   ii) subsequently administering to the patient a transplant comprising hematopoietic stem cells.

7. A method of treating a stem cell disorder in a human patient, the method comprising administering to the patient a therapeutically effective amount of an antibody, or antigen-binding fragment thereof, that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

8. A method of treating a hemoglobinopathy disorder in a human patient, the method comprising administering to the patient a therapeutically effective amount of an antibody, or antigen-binding fragment thereof, that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

9. A method of treating a myelodysplastic disorder in a human patient, the method comprising administering to the patient a therapeutically effective amount of an antibody, or antigen-binding fragment thereof, that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

10. A method of treating an immunodeficiency disorder in a human patient, the method comprising administering to the patient a therapeutically effective amount of an antibody, or antigen-binding fragment thereof, that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

11. A method of treating a metabolic disorder in a human patient, the method comprising administering to the patient a therapeutically effective amount of an antibody, or antigen-binding fragment thereof, that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

12. A method of treating cancer in a human patient, the method comprising administering to the patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

13. A method of treating a disorder selected from the group consisting of adenosine deaminase deficiency and severe combined immunodeficiency, hyper immunoglobulin M syndrome, Chediak-Higashi disease, hereditary lymphohistiocytosis, osteopetrosis, osteogenesis imperfecta, storage diseases, thalassemia major, systemic sclerosis, systemic lupus erythematosus, multiple sclerosis, and juvenile rheumatoid arthritis in a human patient, the method comprising administering to the patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

14. A method of treating an autoimmune disorder in a human patient, the method comprising administering to the patient a therapeutically effective amount of an antibody or antigen-binding fragment thereof that binds to CD2, wherein the antibody, or antigen-binding fragment thereof, is conjugated to a cytotoxin.

15. The method of any one of claims 1-14, wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC HB 11423.

16. The method of any one of claims 1-14, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region CDR set (CDR1, CDR2, and CDR3) and a light chain variable region CDR set (CDR1, CDR2, and CDR3) of antibody LO-CD2A produced by the hybridoma cell line having ATCC accession number HB 11423.

17. The method of any one of claims 1-14, wherein the antibody, or antigen-binding fragment thereof, is

i) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region comprising a CDR-H1 as set forth in SEQ ID NO: 1; a CDR-H2 as set forth in SEQ ID NO: 2; a CDR-H3 as set forth in SEQ ID NO: 3; and comprising a light chain variable region comprising a CDR-L1 as set forth in SEQ ID NO: 4; a CDR-L2 as set forth in SEQ ID NO: 5; and a CDR-L3 as set forth in SEQ ID NO: 6;

ii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region comprising a CDR-H1 as set forth in SEQ ID NO: 14; a CDR-H2 as set forth in SEQ ID NO: 15; a CDR-H3 as set forth in SEQ ID NO: 16 or 17; and comprising a light chain variable region comprising a CDR-L1 as set forth in SEQ ID NO: 18; a CDR-L2 as set forth in SEQ ID NO: 19; and a CDR-L3 as set forth in SEQ ID NO: 20;

iii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 7 and comprising a light chain variable region as set forth in SEQ ID NO: 8;

iv) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 9 and comprising a light chain variable region as set forth in SEQ ID NO: 10; or

v) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 21 or 22 and comprising a light chain variable region as set forth in SEQ ID NO: 23.

18. The method of any one of claims 1-14, wherein the antibody, or antigen-binding fragment thereof, competitively inhibits the binding of CD2 to an antibody or antigen-binding fragment thereof of claim 17.

19. The method of any one of claims 1-14, wherein the antibody or antigen-binding fragment thereof is selected from the group consisting of a monoclonal antibody or antigen-binding fragment thereof, a polyclonal antibody or antigen-binding fragment thereof, a humanized antibody or antigen-binding fragment thereof, a bispecific antibody or antigen-binding fragment thereof, an intact antibody, a dual-variable immunoglobulin domain, a single-chain Fv molecule (scFv), a diabody, a triabody, a nanobody, an antibody-like protein scaffold, a Fv fragment, a Fab fragment, a $F(ab')_2$ molecule, and a tandem di-scFv.

20. The method of any one of claims 1-18, wherein the antibody or antigen-binding fragment thereof is a humanized antibody, or antigen-binding fragment thereof.

21. The method of any one of claims 1-20, wherein the antibody has an isotype selected from the group consisting of IgG, IgA, IgM, IgD, and IgE.

22. The method of claim 21, wherein the IgG isotype is an IgG1 or an IgG4.

23. The method of any one of claims 1 to 22, wherein the cytotoxin is selected from the group consisting of pseudomonas exotoxin A, deBouganin, diphtheria toxin, an amatoxin, saporin, maytansine, a maytansinoid, an auristatin, an anthracycline, a calicheamicin, irinotecan, SN-38, a duocarmycin, a pyrrolobenzodiazepine, a pyrrolobenzodiazepine dimer, an indolinobenzodiazepine, and an indolinobenzodiazepine dimer, or a variant thereof.

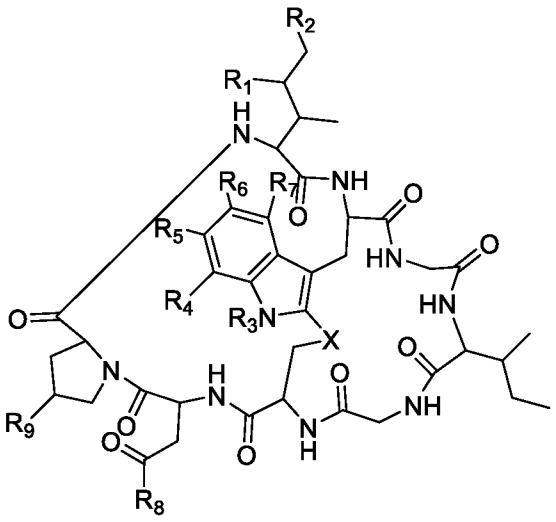
24. The method of any one of claims 1 to 22, wherein the cytotoxin is an RNA polymerase inhibitor.

25. The method of claim 24, wherein the RNA polymerase inhibitor is an RNA polymerase II inhibitor.

26. The method of claim 25, wherein the RNA polymerase II inhibitor is amatoxin.

27. The method of any one of claims 1 to 22, wherein the antibody or antigen-binding fragment thereof conjugated to a cytotoxin is represented by the formula Ab-Z-L-Am, wherein Ab is

the antibody or antigen-binding fragment thereof, L is a linker, Z is a chemical moiety, and Am an amatoxin represented by formula (**I**)



(**I**)

wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

R_A and R_B, when present, together with the oxygen atoms to which they are bound, combine to form an optionally substituted 5-membered heterocyclolalkyl group;

R_3 is H, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, OR_C, or OR_D;

X is -S-, -S(O)-, or $-SO_2-$;

R_C is -L-Z;

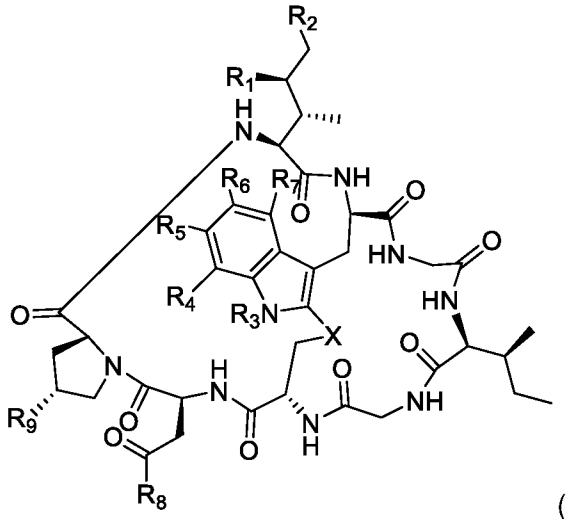
R_D is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_2-C_6 heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 heteroalkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_2-C_6 heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a dipeptide, -C(=O)-, a peptide. or a combination thereof; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof,

wherein Am comprises exactly one R_C substituent.

28. The method of claim 27, wherein Am-L-Z is represented by formula (**IA**).



(**IA**)

wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

R_A and R_B, when present, together with the oxygen atoms to which they are bound, combine to form an optionally substituted 5-membered heterocycloalkyl group;

R_3 is H, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, OR_C, or OR_D;

X is -S-, -S(O)-, or $-SO_2-$;

R_C is -L-Z;

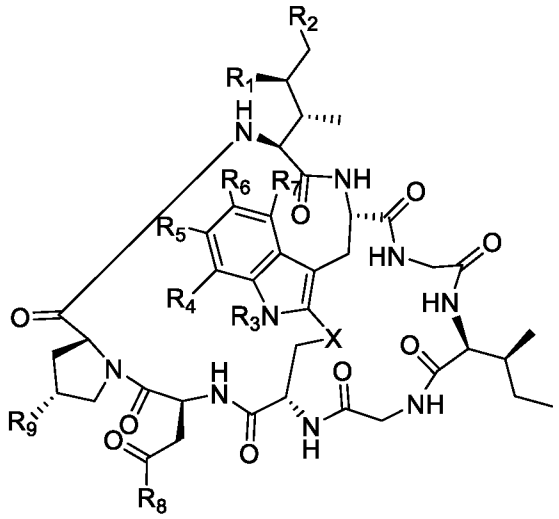
R_D is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_2-C_6 heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 heteroalkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_2-C_6 heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a dipeptide, -C(=O)-, a peptide, or a combination thereof;

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof; and

wherein Am comprises exactly one R_C substituent.

29. The method of claim 27, wherein Am-L-Z is represented by formula (**IB**).



(**IB**)

wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

R_A and R_B, when present, together with the oxygen atoms to which they are bound, combine to form an optionally substituted 5-membered heterocycloalkyl group;

R_3 is H, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, OR_C, or OR_D;

X is -S-, -S(O)-, or $-SO_2-$;

R_C is -L-Z;

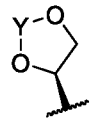
R_D is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_2-C_6 heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 heteroalkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_2-C_6 heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a dipeptide, -C(=O)-, a peptide, or a combination thereof; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof,

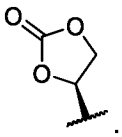
wherein Am comprises exactly one R_C substituent.

30. The method of claim 28 or 29, wherein R_A and R_B, together with the oxygen atoms to which they are bound, combine to form a 5 membered heterocycloalkyl group of formula:



wherein Y is –C(=O)-, -C(=S)-, -C(=NR$_E$)-, or –C(R$_E$R$_{E'}$)-; and R$_E$ and R$_{E'}$ are each independently optionally substituted C$_1$-C$_6$ alkylene-R$_C$, optionally substituted C$_1$-C$_6$ heteroalkylene-R$_C$, optionally substituted C$_2$-C$_6$ alkenylene-R$_C$, optionally substituted C$_2$-C$_6$ heteroalkenylene-R$_C$, optionally substituted C$_2$-C$_6$ alkynylene-R$_C$, optionally substituted C$_2$-C$_6$ heteroalkynylene-R$_C$, optionally substituted cycloalkylene-R$_C$, optionally substituted heterocycloalkylene-R$_C$, optionally substituted arylene-R$_C$, or optionally substituted heteroarylene-R$_C$.

31. The method of claim 30, wherein R$_A$ and R$_B$, together with the oxygen atoms to which they are bound, combine to form:

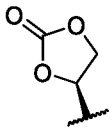


32. The method of claim 28 or 29, wherein:

(a) R$_1$ is H, OH, or OR$_A$;

R$_2$ is H, OH, or OR$_B$;

R$_A$ and R$_B$, together with the oxygen atoms to which they are bound, combine to form:



R$_3$, R$_4$, R$_6$, and R$_7$ are each H;

R$_5$ is OR$_C$;

R$_8$ is OH or NH$_2$; and

R$_9$ is H or OH;

(b) R$_1$ and R$_2$ are each independently H or OH;

R$_3$ is R$_C$;

R$_4$, R$_6$, and R$_7$ are each H;

R$_5$ is H, OH, or OC$_1$-C$_6$ alkyl;

R$_8$ is OH or NH$_2$; and

R$_9$ is H or OH;

(c) R$_1$ and R$_2$ are each independently H or OH;

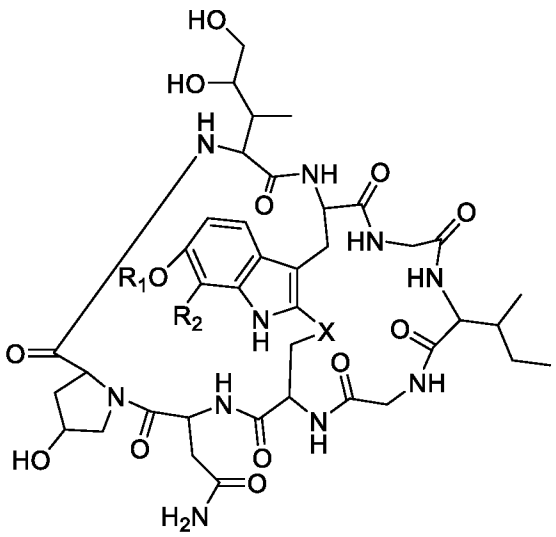
R$_3$, R$_6$, and R$_7$ are each H;

R_4 and R_5 are each independently H, OH, OR_C, or R_C;
R_8 is OH or NH_2; and
R_9 is H or OH;

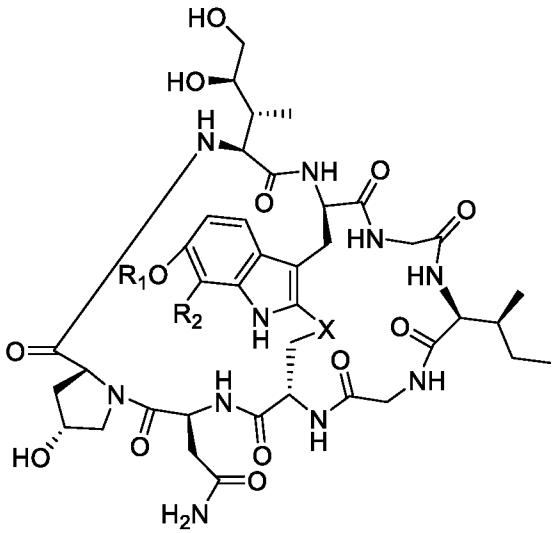
or

(d) R_1 and R_2 are each independently H or OH;
R_3, R_6, and R_7 are each H;
R_4 and R_5 are each independently H or OH;
R_8 is OR_C or NHR_C; and
R_9 is H or OH.

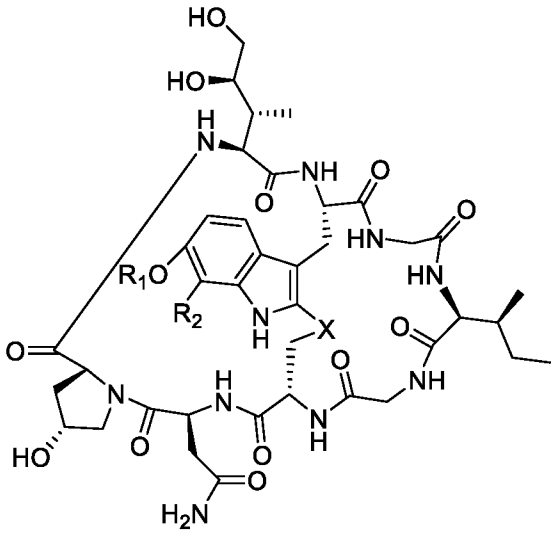
33. The method of any one of claims 1 to 22, wherein the antibody or antigen-binding fragment thereof conjugated to a cytotoxin is represented by the formula Ab-Z-L-Am, wherein Ab is the antibody or antigen-binding fragment thereof, Z is a chemcial moiety, L is a linker, and Am is an amatoxin, and the amatoxin-linker conjugate Am-L-Z is represented by formula (**II**), formula (**IIA**), or formula (**IIB**)



(**II**)



(**IIA**)



IIB,

wherein X is S, SO, or SO_2;

R_1 is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moeity Z, formed from a coupling reaction between a reactive substituent present on the linker and a reactive substituent present within an antibody, or antigen-binding fragment thereof; and

R_2 is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moeity Z, formed from a coupling reaction between a reactive substituent present on the linker and a reactive substituent present within an antibody, or antigen-binding fragment thereof;

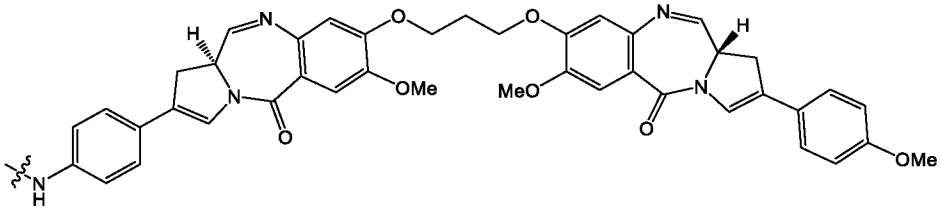
wherein when R_1 is H, R_2 is the linker, and when R_2 is H, R_1 is the linker.

34. The method of any one of claims 1 to 22, wherein the cytotoxin is a maytansinoid selected from the group consisting of DM1 and DM4.

35. The method of any one of claims 1 to 22, wherein the cytotoxin is an auristatin selected from the group consisting of monomethyl auristatin E and monomethyl auristatin F.

36. The method of any one of claims 1 to 22, wherein the cytotoxin is an anthracycline selected from the group consisting of daunorubicin, doxorubicin, epirubicin, and idarubicin.

37. The method of any one of claims 1 to 22, wherein the cytotoxin is a pyrrolobenzodiazepine dimer derivative represented by formula (**IV**)



(**IV**).

38. The method of any one of claims 1-6 and 15-37, wherein the antibody, or antigen-binding fragment thereof, conjugated to the cytotoxin is internalized by an immune cell following administration to the patient.

39. The method of any one of claims 1-6 and 15-38, wherein the antibody, or antigen-binding fragment thereof, conjugated to the cytotoxin is capable of promoting necrosis of an immune cell.

40. The method of any one of claims 1-6 and 15-39, wherein the antibody, or antigen-binding fragment thereof, conjugated to the cytotoxin is capable of recruiting one or more complement proteins to an immune cell upon administration to the patient.

41. The method of any one of claims 38-40, wherein the immune cell is selected from the group consisting of a T cell and NK cell.

42. The method of any one of claims 3-6 and 15-40, wherein the transplant comprising hematopoietic stem cells is administered to the patient after the concentration of the antibody, or antigen-binding fragment thereof, conjugated to the cytotoxin has substantially cleared from the blood of the patient.

43. The method of claim 42, wherein:

(a) the transplant comprising hematopoietic stem cells is administered to the patient between 1 hour and 7 days after the concentration of the antibody, or antigen-binding fragment thereof, conjugated to the cytotoxin has substantially cleared from the blood of the patient;

(b) the transplant comprising hematopoietic stem cells is administered to the patient between 6 hours and 3 days after the concentration of the antibody, or antigen-binding fragment thereof, conjugated to the cytotoxin has substantially cleared from the blood of the patient;

(c) the transplant comprising hematopoietic stem cells is administered to the patient between about 12 hours and about 36 hours after the concentration of the antibody, or antigen-binding fragment thereof, conjugated to the cytotoxin has substantially cleared from the blood of the patient; or

(d) the transplant comprising hematopoietic stem cells is administered to the patient about 24 hours after the concentration of the antibody, or antigen-binding fragment thereof, conjugated to the cytotoxin has substantially cleared from the blood of the patient.

44. The method of any one of claims 3-6 and 15-40, wherein the hematopoietic stem cells or progeny thereof maintain hematopoietic stem cell functional potential after about two or more days following transplantation of the hematopoietic stem cells into the patient.

45. The method of any one of claims 3-6 and 15-44, wherein the hematopoietic stem cells are autologous with respect to the patient or the hematopoietic stem cells are allogeneic with respect to the patient.

46. The method of claim 45, wherein the hematopoietic stem cells are HLA-matched with respect to the patient or the hematopoietic stem cells are HLA-mismatched with respect to the patient.

47. The method of any one of claims 1, 2, 4-6, and 15-41, wherein the population of CD2+ cells comprises T cells.

48. The method of any one of claims 3-6 and 15-47, wherein the 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.

49. The method of any one of claims 3-6 and 15-48, 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, myeoblasts, basophils, neutrophils, eosinophils, microglia, granulocytes, monocytes, osteoclasts, antigen-presenting cells, macrophages, dendritic cells, natural killer cells, T lymphocytes, and B lymphocytes.

50. The method of any one of claims 1-6 and 15-49, wherein the patient is suffering from a stem cell disorder, a hemoglobinopathy disorder, a myelodysplastic disorder, an immunodeficiency disorder, a metabolic disorder, a cancer, or an autoimmune disorder.

51. The method of claim 8 or 50, wherein the hemoglobinopathy disorder is selected from the group consisting of sickle cell anemia, thalassemia, Fanconi anemia, aplastic anemia, and Wiskott-Aldrich syndrome.

52. The method of claim 10 or 50, wherein the immunodeficiency disorder is a congenital immunodeficiency or an acquired immunodeficiency.

53. The method of claim 52, wherein the acquired immunodeficiency is human immunodeficiency virus or acquired immune deficiency syndrome.

54. The method of claim 11 or 50, wherein the metabolic disorder is selected from the group consisting of glycogen storage diseases, mucopolysaccharidoses, Gaucher's Disease, Hurlers Disease, sphingolipidoses, and metachromatic leukodystrophy.

55. The method of claim 12 or 50, wherein the cancer is selected from the group consisting of leukemia, lymphoma, multiple myeloma, and neuroblastoma.

56. The method of claim 12 or 50, wherein the cancer is a hematological cancer.

57. The method of claim 12 or 50, wherein the cancer is acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, or chronic lymphoid leukemia.

58. The method of claim 12 or 50, wherein the cancer is multiple myeloma.

59. The method of claim 12 or 50, wherein the cancer is diffuse large B-cell lymphoma or non-Hodgkin’s lymphoma.

60. The method of any one of claims 1-6 and 15-59, wherein the patient is suffering from a disorder selected from the group consisting of adenosine deaminase deficiency and severe combined immunodeficiency, hyper immunoglobulin M syndrome, Chediak-Higashi disease, hereditary lymphohistiocytosis, osteopetrosis, osteogenesis imperfecta, storage diseases, thalassemia major, systemic sclerosis, systemic lupus erythematosus, multiple sclerosis, and juvenile rheumatoid arthritis.

61. The method of claim 14 or 50, wherein the autoimmune disorder is selected from the group consisting of multiple sclerosis, human systemic lupus, rheumatoid arthritis, inflammatory bowel disease, treating psoriasis, Type 1 diabetes mellitus, acute disseminated encephalomyelitis, Addison's disease, alopecia universalis, ankylosing spondylitisis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lymphoproliferative syndrome, autoimmune oophoritis, Balo disease, Behcet's disease, bullous pemphigoid, cardiomyopathy, Chagas' disease, chronic fatigue immune dysfunction syndrome, chronic inflammatory demyelinating polyneuropathy, Crohn's disease, cicatrical pemphigoid, coeliac sprue-dermatitis herpetiformis, cold agglutinin disease, CREST syndrome, Degos disease, discoid lupus, dysautonomia, endometriosis, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, Goodpasture' s syndrome, Grave's disease, Guillain-Barre syndrome, Hashimoto' s thyroiditis, Hidradenitis suppurativa, idiopathic and/or acute thrombocytopenic purpura, idiopathic pulmonary fibrosis, IgA neuropathy, interstitial cystitis, juvenile arthritis, Kawasaki's disease, lichen planus, Lyme disease, Meniere disease, mixed connective tissue disease, myasthenia gravis, neuromyotonia, opsoclonus myoclonus syndrome, optic neuritis, Ord's thyroiditis, pemphigus vulgaris, pernicious anemia, polychondritis, polymyositis and dermatomyositis, primary biliary cirrhosis, polyarteritis nodosa, polyglandular syndromes, polymyalgia rheumatica, primary agammaglobulinemia, Raynaud phenomenon, Reiter' s syndrome, rheumatic fever, sarcoidosis, scleroderma, Sjögren's syndrome, stiff person syndrome, Takayasu's arteritis, temporal arteritis, ulcerative colitis, uveitis, vasculitis, vitiligo, vulvodynia, and Wegener's granulomatosis.

62. The method of claim 14 or 50, wherein the autoimmune disorder is scleroderma, multiple sclerosis, ulcerative colitis, Crohn’s disease, or Type 1 diabetes.

63. The method of any one of claims 50-62, wherein the method treats the disorder or cancer.

64. A conjugate represented by the formula Ab-Z-L-Cy, wherein Ab is an antibody or antigen-binding fragment thereof that binds CD2, Z is a chemical moiety, L is a linker, and Cy is a cytotoxin, wherein the cytotoxin is selected from the group consisting of pseudomonas exotoxin A, deBouganin, diphtheria toxin, an amatoxin, saporin, maytansine, a maytansinoid, an auristatin, an anthracycline, a calicheamicin, irinotecan, SN-38, a duocarmycin, a pyrrolobenzodiazepine, a pyrrolobenzodiazepine dimer, an indolinobenzodiazepine, and an indolinobenzodiazepine dimer, or a variant thereof.

65. The conjugate of claim 64, wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC HB 11423.

66. The conjugate of claim 64, wherein the antibody, or antigen-binding fragment thereof, is

i) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region comprising a CDR-H1 as set forth in SEQ ID NO: 1; a CDR-H2 as set forth in SEQ ID NO: 2; a CDR-H3 as set forth in SEQ ID NO: 3; and comprising a light chain variable region comprising a CDR-L1 as set forth in SEQ ID NO: 4; a CDR-L2 as set forth in SEQ ID NO: 5; and a CDR-L3 as set forth in SEQ ID NO: 6;

ii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region comprising a CDR-H1 as set forth in SEQ ID NO: 14; a CDR-H2 as set forth in SEQ ID NO: 15; a CDR-H3 as set forth in SEQ ID NO: 16 or 17; and comprising a light chain variable region comprising a CDR-L1 as set forth in SEQ ID NO: 18; a CDR-L2 as set forth in SEQ ID NO: 19; and a CDR-L3 as set forth in SEQ ID NO: 20;

iii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 7 and comprising a light chain variable region as set forth in SEQ ID NO: 8;

iv) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 9 and comprising a light chain variable region as set forth in SEQ ID NO: 10; or

v) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 21 or 22 and comprising a light chain variable region as set forth in SEQ ID NO: 23.

67. The conjugate of claim 64, wherein the antibody or antigen-binding fragment thereof competitively inhibits the binding of CD2 to an antibody or antigen-binding fragment of claim 142.

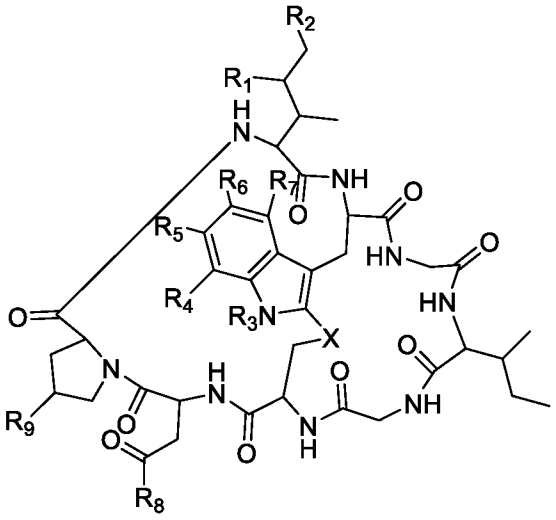
68. The conjugate of any one of claims 64-67, wherein the antibody or antigen-binding fragment thereof is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a humanized antibody, a bispecific antibody, a dual-variable immunoglobulin domain, a single-chain Fv molecule (scFv), a diabody, a triabody, a nanobody, an antibody-like protein scaffold, a Fv fragment, a Fab fragment, a $F(ab')_2$ molecule, and a tandem di-scFv.

69. The conjugate of any one of claims 64-67, wherein the antibody or antigen-binding fragment thereof is a humanized antibody or antigen-binding fragment thereof.

70. The conjugate of any one of claims 64-69, wherein the antibody has an isotype selected from the group consisting of IgG, IgA, IgM, IgD, and IgE.

71. The conjugate of claim 70, wherein the IgG is IgG1 or IgG4.

72. The conjugate of any one of claims 64-70, wherein Cy is an amatoxin (Am) represented by formula (**I**)



(**I**)

wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

R_A and R_B, when present, together with the oxygen atoms to which they are bound, combine to form an optionally substituted 5-membered heterocyclolalkyl group;

R_3 is H, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, OR_C, or OR_D;

X is -S-, -S(O)-, or $-SO_2-$;

R_C is -L-Z;

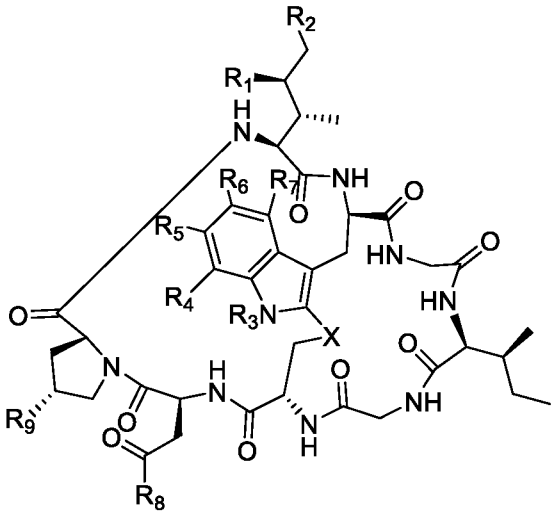
R_D is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_2-C_6 heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 heteroalkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_2-C_6 heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, or optionally substituted heteroarylene, a dipeptide, -C(=O)-, a peptide, or a combination thereof; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof,

wherein Am comprises exactly one R_C substituent.

73. The conjugate of claim 72, wherein Am is an amatoxin represented by formula (**IA**).



(**IA**)

wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

R_A and R_B, when present, together with the oxygen atoms to which they are bound, combine to form an optionally substituted 5-membered heterocycloalkyl group;

R_3 is H, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, OR_C, or OR_D;

X is -S-, -S(O)-, or $-SO_2-$;

R_C is -L-Z;

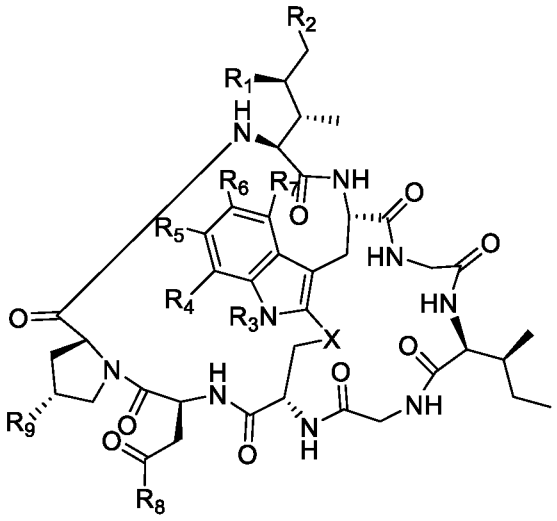
R_D is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_2-C_6 heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 heteroalkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_2-C_6 heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a dipeptide, -(C=O)-, a peptide, or a combination thereof;

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof; and

wherein Am comprises exactly one R_C substituent.

74. The conjugate of claim 72, wherein Am is an amatoxin represented by formula (**IB**).



(**IB**)

wherein R_1 is H, OH, OR_A, or OR_C;

R_2 is H, OH, OR_B, or OR_C;

R_A and R_B, when present, together with the oxygen atoms to which they are bound, combine to form an optionally substituted 5-membered heterocycloalkyl group;

R_3 is H, R_C, or R_D;

R_4, R_5, R_6, and R_7 are each independently H, OH, OR_C, OR_D, R_C, or R_D;

R_8 is OH, NH_2, OR_C, OR_D, NHR_C, or NR_CR_D;

R_9 is H, OH, OR_C, or OR_D;

X is -S-, -S(O)-, or -SO_2-;

R_C is -L-Z;

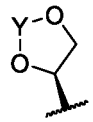
R_D is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_2-C_6 heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 heteroalkenylene, optionally substituted C_2-C_6 alkynylene, optionally substituted C_2-C_6 heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a dipeptide, -C(=O)-, a peptide. or a combination thereof; and

Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof,

wherein Am comprises exactly one R_C substituent.

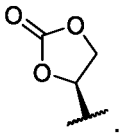
75. The conjugate of claim 73 or 74, wherein R_A and R_B, together with the oxygen atoms to which they are bound, combine to form a 5 membered heterocycloalkyl group of formula:



wherein Y is -C(=O)-, -C(=S)-, -C(=NR_E)-, or -C($R_ER_{E'}$)-; and and

R_E and $R_{E'}$ are each independently optionally substituted C_1-C_6 alkylene-R_C, optionally substituted C_1-C_6 heteroalkylene-R_C, optionally substituted C_2-C_6 alkenylene-R_C, optionally substituted C_2-C_6 heteroalkenylene-R_C, optionally substituted C_2-C_6 alkynylene-R_C, optionally substituted C_2-C_6 heteroalkynylene-R_C, optionally substituted cycloalkylene-R_C, optionally substituted heterocycloalkylene-R_C, optionally substituted arylene-R_C, or optionally substituted heteroarylene-R_C.

76. The conjugate of claim 75, wherein R_A and R_B, together with the oxygen atoms to which they are bound, combine to form:

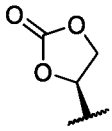


77. The conjugate of claim 73 or 74, wherein:

a) R_1 is H, OH, or OR_A;

R_2 is H, OH, or OR_B;

R_A and R_B, together with the oxygen atoms to which they are bound, combine to form:



R_3, R_4, R_6, and R_7 are each H;

R_5 is OR_C;

R_8 is OH or NH_2; and

R_9 is H or OH;

b) R_1 and R_2 are each independently H or OH;

R_3 is R_C;

R_4, R_6, and R_7 are each H;

R_5 is H, OH, or OC_1-C_6 alkyl;

R_8 is OH or NH_2; and

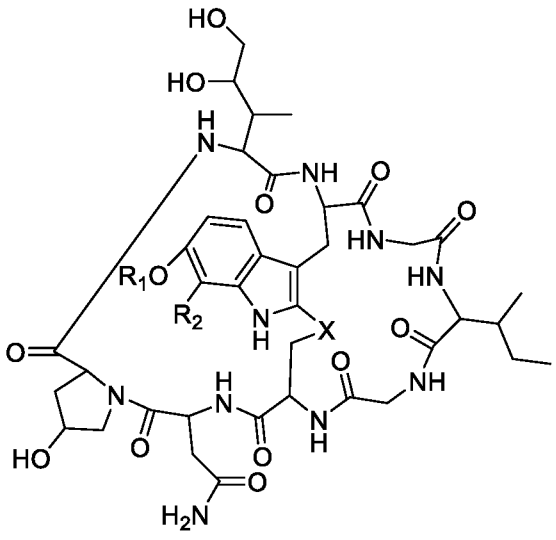
R_9 is H or OH;

c) R1 and R2 are each independently H or OH;
R3, R6, and R7 are each H;
R4 and R5 are each independently H, OH, ORC, or RC;
R8 is OH or NH2; and
R9 is H or OH;

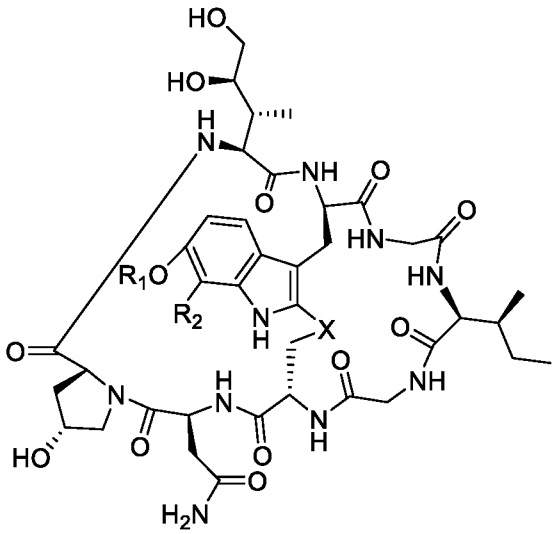
or

d) R_1 and R_2 are each independently H or OH;
R_3, R_6, and R_7 are each H;
R_4 and R_5 are each independently H or OH;
R_8 is OR_C or NHR_C; and
R_9 is H or OH.

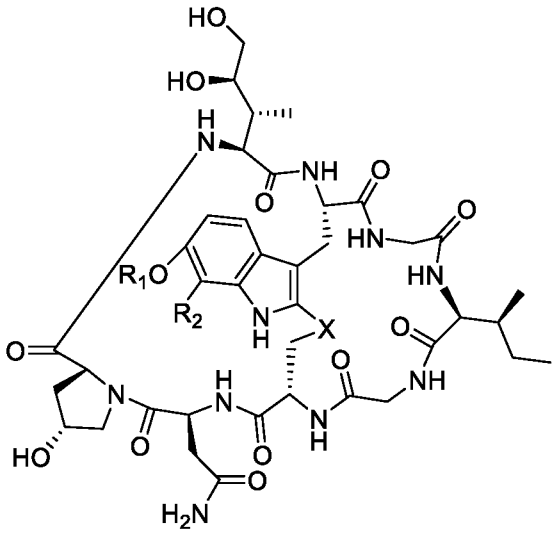
78. The conjugate of any one of claims 64-70, wherein the antibody or antigen-binding fragment thereof conjugated to a cytotoxin is represented by the formula Ab-Z-L-Am, wherein Ab is the antibody or antigen-binding fragment thereof, Z is a chemical moiety, L is a linker, and Am is an amatoxin, and the amatoxin-linker conjugate Am-L-Z is represented by formula (**II**), formula (**IIA**), or formula (**IIB**)



(**II**)



(**IIA**)



IIB,

wherein X is S, SO, or SO_2;

R_1 is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moeity Z, formed from a coupling reaction between a reactive substituent present on the linker and a reactive substituent present within an antibody, or antigen-binding fragment thereof; and

R_2 is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moeity Z, formed from a coupling reaction between a reactive substituent present on the linker and a reactive substituent present within an antibody, or antigen-binding fragment thereof;

wherein when R_1 is H, R_2 is the linker, and when R_2 is H, R_1 is the linker.

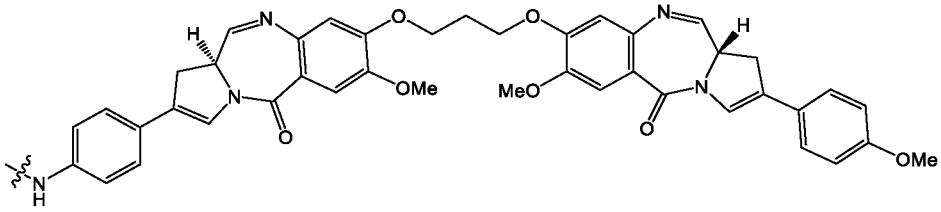
79. The conjugate of any one of claims 64-70, wherein:

(a) Cy is a maytansinoid selected from the group consisting of DM1 and DM4; or

(b) Cy is an auristatin;

(c) Cy is an anthracycline selected from the group consisting of daunorubicin, doxorubicin, epirubicin, and idarubicin: or

(d) Cy is a pyrrolobenzodiazepine dimer derivative represented by formula (**IV**)



(**IV**).

80. The conjugate of claim 79, wherein the auristatin is monomethyl auristatin E and monomethyl auristatin F.

81. The method of any one of claims 64-70, wherein the Cy is an RNA polymerase inhibitor.

82. The method of claim 81, wherein the RNA polymerase inhibitor is an RNA polymerase II inhibitor.

83. The method of claim 82, wherein the RNA polymerase II inhibitor is amatoxin.

84. A pharmaceutical composition comprising the conjugate of any one of claims 64-83, and a pharmaceutically acceptable excipient.

85. The pharmaceutical composition of claim 84, wherein the pharmaceutical composition is formulated for transdermal, subcutaneous, intravenous, intramuscular, intraocular, intratumoral, parenteral, intrathecal or intracerebroventricular administration to a human patient.

86. The pharmaceutical composition of claim 84, wherein the pharmaceutical composition is formulated for intravenous administration to a human patient.

87. A method of depleting a population of CD2+ cells in a human patient, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof .

88. A method of depleting a population of CD2+ cells in a human patient in need of a hematopoietic stem cell transplant, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof .

89. A method of preventing rejection of a hematopoietic stem cell graft in a human patient in need of a hematopoietic stem cell transplant, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof, prior to the human patient receiving a transplant comprising hematopoietic stem cells.

90. A method of depleting a population of CD2+ cells in a human patient in need of a hematopoietic stem cell transplant, the method comprising administering to the patient an effective amount of an anti-CD2 antibody, or antigen-binding fragment thereof, prior to the patient receiving a transplant comprising hematopoietic stem cells.

91. A method comprising administering to a human patient a transplant comprising hematopoietic stem cells, wherein the patient has been previously administered an anti-CD2 antibody or antigen-binding fragment thereof, in an amount sufficient to deplete a population of CD2+ cells in the patient.

92. A method comprising:

a. administering to a human patient an antibody, or antigen-binding fragment thereof, that binds to CD2 in an amount sufficient to deplete a population of CD2+ cells in the patient; and
b. subsequently administering to the patient a transplant comprising hematopoietic stem cells.

93. The method of any one of claims 87-92, wherein the antibody or antigen-binding fragment thereof is produced by the hybridoma cell line ATCC HB 11423.

94. The method of any one of claims 87-92, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region CDR set (CDR1, CDR2, and CDR3) and a light chain variable region CDR set (CDR1, CDR2, and CDR3) of antibody LO-CD2A produced by the hybridoma cell line having ATCC accession number HB 11423.

95. The method of any one of claims 87-92, wherein the antibody, or antigen-binding fragment thereof, is

i) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region comprising a CDR-H1 as set forth in SEQ ID NO: 1; a CDR-H2 as set forth in SEQ ID NO: 2; a CDR-H3 as set forth in SEQ ID NO: 3; and comprising a light chain variable region comprising a CDR-L1 as set forth in SEQ ID NO: 4; a CDR-L2 as set forth in SEQ ID NO: 5; and a CDR-L3 as set forth in SEQ ID NO: 6;

ii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region comprising a CDR-H1 as set forth in SEQ ID NO: 14; a CDR-H2 as set forth in SEQ ID NO: 15; a CDR-H3 as set forth in SEQ ID NO: 16 or 17; and comprising a light chain variable region comprising a CDR-L1 as set forth in SEQ ID NO: 18; a CDR-L2 as set forth in SEQ ID NO: 19; and a CDR-L3 as set forth in SEQ ID NO: 20;

iii) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 7 and comprising a light chain variable region as set forth in SEQ ID NO: 8;

iv) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 9 and comprising a light chain variable region as set forth in SEQ ID NO: 10; or

v) an anti-CD2 antibody, or antigen binding portion thereof, comprising a heavy chain variable region as set forth in SEQ ID NO: 21 or 22 and comprising a light chain variable region as set forth in SEQ ID NO: 23.

96. The method of any one of claims 87-92, wherein the antibody, or antigen-binding fragment thereof, competitively inhibits the binding of CD2 to an antibody or antigen-binding fragment thereof of claim 95.

97. The method of any one of claims 87-96, wherein the antibody or antigen-binding fragment thereof is selected from the group consisting of a monoclonal antibody or antigen-binding fragment thereof, a polyclonal antibody or antigen-binding fragment thereof, a humanized antibody or antigen-binding fragment thereof, a bispecific antibody or antigen-binding fragment thereof, an intact antibody, a dual-variable immunoglobulin domain, a single-chain Fv molecule (scFv), a diabody, a triabody, a nanobody, an antibody-like protein scaffold, a Fv fragment, a Fab fragment, a $F(ab')_2$ molecule, and a tandem di-scFv.

98. The method of any one of claims 87-97, wherein the antibody or antigen-binding fragment thereof is a humanized antibody, or antigen-binding fragment thereof.

99. The method of any one of claims 87-98, wherein the antibody has an isotype selected from the group consisting of IgG, IgA, IgM, IgD, and IgE.

100. The method of any one of claims 87-99, wherein the antibody or antigen-binding fragment thereof is internalized by an immune cell following administration to the patient.

101. The method of any one of claims 87-100, wherein the antibody or antigen-binding fragment thereof is capable of promoting necrosis of an immune cell.

102. The method of any one of claims 87-101, wherein the antibody or antigen-binding fragment thereof is capable of recruiting one or more complement proteins to an immune cell upon administration to the patient.

103. The method of any one of claims 100-102, wherein the immune cell is selected from the group consisting of a T cell and NK cell.

104. The method of any one of claims 89-92, wherein the transplant comprising hematopoietic stem cells is administered to the patient after the concentration of the antibody or antigen-binding fragment thereof has substantially cleared from the blood of the patient.

105. The method of claim 104, wherein:

(a) the transplant comprising hematopoietic stem cells is administered to the patient between 1 hour and 7 days after the concentration of the antibody or antigen-binding fragment thereof has substantially cleared from the blood of the patient

(b) the transplant comprising hematopoietic stem cells is administered to the patient between 6 hours and 3 days after the concentration of the antibody or antigen-binding fragment thereof has substantially cleared from the blood of the patient;

(c) the transplant comprising hematopoietic stem cells is administered to the patient between 12 hours and 36 hours after the concentration of the antibody or antigen-binding fragment thereof has substantially cleared from the blood of the patient; or

(d) the transplant comprising hematopoietic stem cells is administered to the patient 24 hours after the concentration of the antibody or antigen-binding fragment thereof has substantially cleared from the blood of the patient.

106. The method of any one of claims 89-92, 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.

107. The method of any one of claims 87-92, wherein the hematopoietic stem cells are autologous with respect to the patient or the hematopoietic stem cells are allogeneic with respect to the patient.

108. The method of claim 107, wherein the hematopoietic stem cells are HLA-matched with respect to the patient or the hematopoietic stem cells are HLA-mismatched with respect to the patient.

109. The method of any one of claims 87-92, wherein the population of CD2+ cells comprises T cells.

110. The method of any one of claims 87-92, wherein the 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.

111. The method of any one of claims 87-92, 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, myeoblasts, basophils, neutrophils, eosinophils, microglia, granulocytes, monocytes, osteoclasts, antigen-presenting cells, macrophages, dendritic cells, natural killer cells, T lymphocytes, and B lymphocytes.

112. The method of any one of claims 87-111, wherein the patient is suffering from a stem cell disorder and/or a hemoglobinopathy disorder.

113. The method of claim 112, wherein the hemoglobinopathy disorder is selected from the group consisting of sickle cell anemia, thalassemia, Fanconi anemia, aplastic anemia, and Wiskott-Aldrich syndrome.

114. The method of any one of claims 87-92, wherein the patient is suffering from a myelodysplastic disorder, an immunodeficiency disorder, a metabolic disorder, a cancer, or an autoimmune disorder.

115. The method of claim 114, wherein the immunodeficiency disorder is a congenital immunodeficiency or an acquired immunodeficiency.

116. The method of claim 115, wherein the acquired immunodeficiency is human immunodeficiency virus or acquired immune deficiency syndrome.

117. The method of claim 114, wherein the metabolic disorder is selected from the group consisting of glycogen storage diseases, mucopolysaccharidoses, Gaucher's Disease, Hurlers Disease, sphingolipidoses, and metachromatic leukodystrophy.

118. The method of claim 114, wherein the cancer is selected from the group consisting of leukemia, lymphoma, multiple myeloma, and neuroblastoma.

119. The method of claim 114, wherein the cancer is a hematological cancer.

120. The method of claim 114, wherein the cancer is acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, or chronic lymphoid leukemia.

121. The method of claim 114, wherein the cancer is diffuse large B-cell lymphoma or non-Hodgkin's lymphoma.

122. The method of any one of claims 87-92, wherein the patient is suffering from a disorder selected from the group consisting of adenosine deaminase deficiency and severe combined immunodeficiency, hyper immunoglobulin M syndrome, Chediak-Higashi disease, hereditary lymphohistiocytosis, osteopetrosis, osteogenesis imperfecta, storage diseases, thalassemia major, systemic sclerosis, systemic lupus erythematosus, multiple sclerosis, and juvenile rheumatoid arthritis.

123. The method of claim 114, wherein the autoimmune disorder is selected from the group consisting of multiple sclerosis, human systemic lupus, rheumatoid arthritis, inflammatory bowel disease, treating psoriasis, Type 1 diabetes mellitus, acute disseminated encephalomyelitis, Addison's disease, alopecia universalis, ankylosing spondylitisis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lymphoproliferative syndrome, autoimmune oophoritis, Balo disease, Behcet's disease, bullous pemphigoid, cardiomyopathy, Chagas' disease, chronic fatigue immune dysfunction syndrome, chronic inflammatory demyelinating polyneuropathy, Crohn's disease, cicatrical pemphigoid, coeliac sprue-dermatitis herpetiformis, cold agglutinin disease, CREST syndrome, Degos disease, discoid lupus, dysautonomia, endometriosis, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, Goodpasture' s syndrome, Grave's disease, Guillain-Barre syndrome, Hashimoto' s thyroiditis, Hidradenitis suppurativa, idiopathic and/or acute thrombocytopenic purpura, idiopathic pulmonary fibrosis, IgA neuropathy, interstitial cystitis, juvenile arthritis, Kawasaki's disease, lichen planus, Lyme disease, Meniere disease, mixed connective tissue disease, myasthenia gravis, neuromyotonia, opsoclonus myoclonus syndrome, optic neuritis, Ord's thyroiditis, pemphigus vulgaris, pernicious anemia, polychondritis, polymyositis

and dermatomyositis, primary biliary cirrhosis, polyarteritis nodosa, polyglandular syndromes, polymyalgia rheumatica, primary agammaglobulinemia, Raynaud phenomenon, Reiter' s syndrome, rheumatic fever, sarcoidosis, scleroderma, Sjögren's syndrome, stiff person syndrome, Takayasu's arteritis, temporal arteritis, ulcerative colitis, uveitis, vasculitis, vitiligo, vulvodynia, and Wegener's granulomatosis.

124. The method of claim 114, wherein the autoimmune disorder is scleroderma, multiple sclerosis, ulcerative colitis, Crohn’s disease, or Type 1 diabetes.

125. The method of any one of claims 87-92, wherein the method treats the disorder or cancer.