

CLAIMS

1. An isolated anti-CD45 antibody, or antigen binding portion thereof, comprising:

~~(a) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:2, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:3, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:4; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:6, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:7; and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:8;~~

~~———(b) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:12, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:13, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:14; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:16, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:17; and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:18;~~

~~———(c) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:22, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:23, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:24; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:26, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:27; and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:28;~~

~~———(d) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:32, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:33, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:34; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:36, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:37; and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:38;~~

(e) a heavy chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:42, a CDR2 domain comprising the amino acid sequence as set forth in SEQ ID NO:43, and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:44; and a light chain variable region comprising a CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:46, a CDR2 domain

2. ~~An isolated anti-CD45 antibody, or antigen-binding portion thereof, comprising~~
~~a heavy chain variable region comprising a CDR1 domain comprising the amino acid~~
~~sequence as set forth in SEQ ID NO:119, a CDR2 domain comprising the amino acid~~
~~sequence as set forth in SEQ ID NO:120, and a CDR3 domain comprising the amino acid~~
~~sequence as set forth in SEQ ID NO:121; and a light chain variable region comprising a~~
~~CDR1 domain comprising the amino acid sequence as set forth in SEQ ID NO:122, a CDR2~~
~~domain comprising the amino acid sequence as set forth in SEQ ID NO:123; and a CDR3~~
~~domain comprising the amino acid sequence as set forth in SEQ ID NO:124.~~

32. An isolated anti-CD45 antibody, or antigen-binding portion thereof, comprising

- ~~(a) a heavy chain variable region comprising the amino acid sequence as set forth in~~
~~SEQ ID NO:1, and a light chain variable region comprising the amino acid sequence as set~~
~~forth in SEQ ID NO:5;~~
- ~~(b) a heavy chain variable region comprising the amino acid sequence as set forth in~~
~~SEQ ID NO:11, and a light chain variable region comprising the amino acid sequence as set~~
~~forth in SEQ ID NO:15;~~
- ~~(c) a heavy chain variable region comprising the amino acid sequence as set forth in~~
~~SEQ ID NO:21, and a light chain variable region comprising the amino acid sequence as set~~
~~forth in SEQ ID NO:25;~~
- ~~(d) a heavy chain variable region comprising the amino acid sequence as set forth in~~
~~SEQ ID NO:31, and a light chain variable region comprising the amino acid sequence as set~~
~~forth in SEQ ID NO:35;~~
- (e) a heavy chain variable region comprising the amino acid sequence as set forth in
SEQ ID NO:41, and a light chain variable region comprising the amino acid sequence as set
forth in SEQ ID NO:45;
- ~~(f) a heavy chain variable region comprising the amino acid sequence as set forth in~~
~~SEQ ID NO:51, and a light chain variable region comprising the amino acid sequence as set~~
~~forth in SEQ ID NO:55;~~
- ~~(g) a heavy chain variable region comprising the amino acid sequence as set forth in~~
~~SEQ ID NO:61, and a light chain variable region comprising the amino acid sequence as set~~
~~forth in SEQ ID NO:65;~~
- ~~(h) a heavy chain variable region comprising the amino acid sequence as set forth in~~
~~SEQ ID NO:71, and a light chain variable region comprising the amino acid sequence as set~~
~~forth in SEQ ID NO:75;~~

~~—— (i) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO:81, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO:85; or~~

~~—— (j) a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO:91, and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO:95.~~

43. The isolated anti-CD45 antibody, or antigen-binding portion thereof, of any one of claims 1-3, wherein:

(a) the antibody, or antigen-binding portion thereof, comprises an Fc region, optionally wherein the Fc region is a human IgG1 Fc region or a human IgG4 Fc region;

(b) the antibody is a monoclonal antibody;

(c) the antibody is an intact antibody comprising a constant region;

(d) the antibody is an IgG, optionally wherein the IgG is an IgG1 or an IgG4;

(e) the antibody comprises a constant region, and wherein the constant region comprises at least one, at least two, at least three, at least four, or at least five amino acid substitutions selected from the group consisting of L234A, L235A, D265C, H310A, and H435A (numbering according to the EU index); and/or

(f) the antibody comprises a constant region comprising (i) a heavy chain amino acid sequence as set forth in SEQ ID NO: 106, and (ii) a light chain amino acid sequence as set forth in SEQ ID NO: 101.

~~5. The isolated anti-CD45 antibody, or antigen-binding portion thereof, of claim 4, wherein the Fc region is a human IgG1 Fc region or a human IgG4 Fc region.~~

~~6. The isolated anti-CD45 antibody, or antigen-binding portion thereof, of any one of claims 1-5, wherein the antibody is a monoclonal antibody.~~

~~7. The isolated anti-CD45 antibody of any one of claims 1-6, wherein the antibody is an intact antibody comprising a constant region.~~

~~8. The isolated anti-CD45 antibody of any one of claims 1-7, wherein the antibody is an IgG.~~

~~9. The isolated anti-CD45 antibody of claim 8, wherein the IgG is an IgG1 or an IgG4.~~

~~10. The isolated anti-CD45 antibody of any one of claims 1-9, wherein the antibody comprises a constant region, and wherein the constant region comprises at least one, at least two, at least three, at least four, or at least five amino acid substitutions selected from the group consisting of L234A, L235A, D265C, H310A, and H435A (numbering according to the EU index).~~

~~11. The isolated anti-CD45 antibody of claim 10, wherein the constant region comprises amino acid substitutions L234A, L235A and D265C (numbering according to the EU index).~~

~~12. The isolated anti-CD45 antibody of any one of claims 1-11, comprising a constant region, wherein the constant region comprises~~

~~—— (a) a heavy chain amino acid sequence as set forth in SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, or SEQ ID NO:106; and~~

~~—— (b) a light chain amino acid sequence as set forth in SEQ ID NO:101.~~

~~134. An isolated anti-CD45 antibody comprising~~

~~(a) a heavy chain amino acid sequence as set forth in SEQ ID NO:9, and a light chain amino acid sequence as set forth in SEQ ID NO:10;~~

~~—— (b) a heavy chain amino acid sequence as set forth in SEQ ID NO:19, and a light chain amino acid sequence as set forth in SEQ ID NO:20;~~

~~—— (c) a heavy chain amino acid sequence as set forth in SEQ ID NO:29, and a light chain amino acid sequence as set forth in SEQ ID NO:30;~~

~~—— (d) a heavy chain amino acid sequence as set forth in SEQ ID NO:39, and a light chain amino acid sequence as set forth in SEQ ID NO:40;~~

~~(e) a heavy chain amino acid sequence as set forth in SEQ ID NO:49, and a light chain amino acid sequence as set forth in SEQ ID NO:50;~~

~~(f) a heavy chain amino acid sequence as set forth in SEQ ID NO:59, and a light chain amino acid sequence as set forth in SEQ ID NO:60;~~

~~—— (g) a heavy chain amino acid sequence as set forth in SEQ ID NO:69, and a light chain amino acid sequence as set forth in SEQ ID NO:70;~~

~~—— (h) a heavy chain amino acid sequence as set forth in SEQ ID NO:79, and a light chain amino acid sequence as set forth in SEQ ID NO:80;~~

~~—— (i) a heavy chain amino acid sequence as set forth in SEQ ID NO:89, and a light chain amino acid sequence as set forth in SEQ ID NO:90; or~~

~~—— (j) a heavy chain amino acid sequence as set forth in SEQ ID NO:99, and a light chain amino acid sequence as set forth in SEQ ID NO:100.~~

~~14. — An isolated anti-CD45 antibody, or antigen-binding portion thereof, that specifically binds to human CD45 at an epitope located within CD45 Fragment 1 (SEQ ID NO:114), CD45 Fragment 2 (SEQ ID NO:115), CD45 Fragment 3 (SEQ ID NO:116), CD45 Fragment 4 (SEQ ID NO:117), and/or CD45 Fragment 5 (SEQ ID NO:118).~~

~~15. — The isolated anti-CD45 antibody, or antigen-binding portion thereof, of claim 14, wherein the antibody, or antigen-binding portion thereof specifically binds to~~
~~(a) an epitope of human CD45 located within CD45 Fragment 2, and an epitope of human CD45 located within Fragment 4;~~
~~(b) an epitope of human CD45 located within CD45 Fragment 1, and an epitope of human CD45 located within CD45 Fragment 3; or~~
~~(c) an epitope of human CD45 located within CD45 Fragment 5.~~

~~16. — The isolated anti-CD45 antibody, or antigen-binding portion thereof, of claim 14 or 15, wherein the antibody, or antigen-binding portion thereof specifically binds to~~
~~(a) one or more residues selected from the group consisting of 405T, 407K, 419Y, 425K, 481R, 505R, and 509H in human CD45 (numbered with reference to SEQ ID NO:113);~~
~~or~~
~~(b) one or more residues selected from the group consisting of 486R, 493Y, and 502T in human CD45 (numbered with reference to SEQ ID NO:113).~~

~~17. — The isolated anti-CD45 antibody, or antigen-binding portion thereof, of any one of claims 1-16, which specifically binds human CD45, and cross-reacts with cynomolgus CD45.~~

~~18. — The isolated anti-CD45 antibody, or antigen-binding portion thereof, of any one of claims 1-17, wherein the antibody, or antigen-binding portion thereof, binds to human CD45 with a dissociation rate (K_{OFF}) of 1×10^{-2} to 1×10^{-3} , 1×10^{-3} to 1×10^{-4} , 1×10^{-4} to 1×10^{-5} , 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); and/or wherein the antibody, or antigen-binding portion thereof, binds to human 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 10 nM or less, or about 0.1 nM or less, as determined by Bio-Layer Interferometry (BLI).~~

~~19. — The isolated anti-CD45 antibody, or antigen-binding portion thereof, of any one of claims 1-18, wherein the antibody, or antigen-binding portion thereof, binds to human 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 10 nM or less, or about 0.1 nM or less, as determined by Bio-Layer Interferometry (BLI).~~

~~206.~~ A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of any one of claims 1-~~195~~, and a pharmaceutically acceptable carrier.

~~217.~~ An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody, or antigen binding portion thereof, of any one of claims 1-~~134~~.

~~228.~~ A vector comprising the isolated nucleic acid of claim ~~217~~.

~~239.~~ A host cell comprising the isolated nucleic acid of claim ~~217~~, or the vector of claim ~~228~~; optionally wherein the cell is a Chinese Hamster Ovary (CHO) cell or a HEK293T cell.

~~24.~~ ~~The host cell of claim 23, wherein the cell is a Chinese Hamster Ovary (CHO) cell or a HEK293T cell.~~

~~2510.~~ A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of any one of claims 1-~~195~~, for use in depleting a population of CD45+ cells in a human patient.

~~2611.~~ A method of depleting a population of CD45+ cells in a human patient, comprising administering
the antibody, or antigen-binding portion thereof, of any one of claims 1-~~195~~ to the human patient.

~~2712.~~ The method of claim ~~2611~~, wherein the CD45+ cells are:

~~(a) CD3+, CD19+, CD33+, CD34+, or CD45+/B2M+;~~

~~(b) hematopoietic stem cells (HSCs), T cells, B cells, and/or myeloid cells;~~

~~(c) cancer cells;~~

~~(d) depleted from the bone marrow of the patient and/or from the peripheral blood of the patient.~~

~~28.~~ ~~The method of claim 26, wherein the CD45+ cells are hematopoietic stem cells (HSCs), T cells, B cells, and/or myeloid cells.~~

~~29. The method of claim 26, wherein the CD45+ cells are cancer cells.~~

~~30. The method of any one of claims 26-29, wherein the CD45+ cells are depleted from the bone marrow of the patient and/or from the peripheral blood of the patient.~~

~~31~~13. The method of any one of claims ~~26-30~~11-12, wherein the patient is in need of a hematopoietic stem cell transplant.

~~32~~14. The method of any one of claims ~~26-31~~11-13, further comprising administering to the patient a transplant comprising hematopoietic stem cells; optionally wherein the transplant is allogeneic or autologous.

~~33. The method of claim 31 or 32, wherein the transplant is allogeneic.~~

~~34. The method of claim 31 or 32, wherein the transplant is autologous.~~

~~35~~15. An antibody drug conjugate (ADC) comprising an anti-CD45 antibody, or an antigen-binding portion thereof, conjugated to a cytotoxin via a linker, wherein the anti-CD45 antibody, or antigen-binding portion thereof, is an antibody or antigen-binding portion thereof of any one of claims 1-~~19~~5, optionally wherein:

(a) the antibody is conjugated to the cytotoxin by way of a cysteine residue in the constant domain of the antibody, optionally wherein the cysteine is introduced by way of an amino acid substitution in the constant region of the antibody, optionally wherein the amino acid substitution is D265C and/or V205C (numbering according to the EU index); and/or

(b) the ADC has a drug to antibody ratio (DAR) of 1, 2, 3, 4, 5, 6, 7, or 8.

~~36. The ADC of claim 35, wherein the antibody is conjugated to the cytotoxin by way of a cysteine residue in the constant domain of the antibody.~~

~~37. The ADC of claim 36, wherein the cysteine residue is introduced by way of an amino acid substitution in the constant region of the antibody.~~

~~38. The ADC of claim 37, wherein the amino acid substitution is D265C and/or V205C (EU numbering).~~

39. — The ADC of any one of claims 35-38, wherein the ADC has a drug to antibody ratio (DAR) of 1, 2, 3, 4, 5, 6, 7, or 8.

4016. The ADC of ~~any one of claims 35-39~~15, wherein:

(a) the cytotoxin is an indolinobenzodiazepine (IGN) dimer or an IGN pseudodimer;

(b) the cytotoxin is a pyrrolobenzodiazepine (PBD) dimer;

(c) the cytotoxin is an RNA polymerase inhibitor, a DNA intercalating agent, a DNA alkylating agent, a DNA crosslinking agent, an agent that disrupts protein synthesis, an agent that disrupts microtubule dynamics, or an agent that disrupts the mitotic spindle; or

(d) the cytotoxin is selected from the group consisting of: an amatoxin, an anthracycline, an auristatin, a calicheamicin, deBouganin, diphtheria toxin, a duocarmycin, an IGN, an IGN dimer, irinotecan, maytansine, a maytansinoid, pseudomonas exotoxin A, a PBD, a PBD dimer, saporin, and SN-38.-

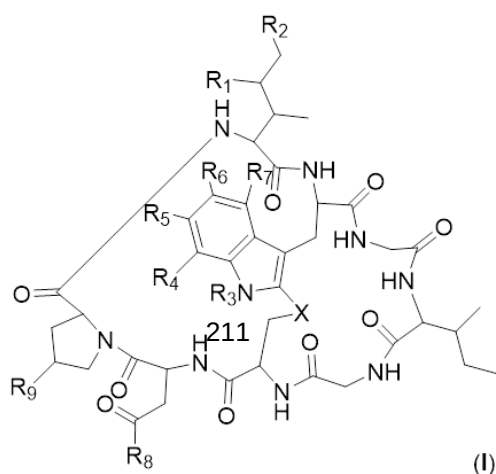
41. — ~~The ADC of any one of claims 35-40, wherein the cytotoxin is selected from the group consisting of an amatoxin, an anthracycline, an auristatin, a calicheamicin, deBouganin, diphtheria toxin, a duocarmycin, an indolinobenzodiazepine (IGN), an indolinobenzodiazepine dimer, irinotecan, maytansine, a maytansinoid, pseudomonas exotoxin A, a pyrrolobenzodiazepine (PBD), a pyrrolobenzodiazepine dimer, saporin, and SN-38.~~

42. — ~~The ADC of claim 40, wherein the cytotoxin is an RNA polymerase inhibitor.~~

43. — ~~The ADC of claim 42, wherein the RNA polymerase inhibitor is an amatoxin.~~

44. — ~~The ADC of claim 43, wherein the ADC is represented by the formula Ab-Z-L-Am, wherein Ab is an antibody, or antigen-binding portion thereof, of any one of claims 1-19, L is a linker, Z is a chemical moiety, and Am is an amatoxin.~~

45. — ~~The ADC of claim 44, wherein the amatoxin-linker conjugate is represented by Formula (I):~~



~~R₂ is H, OH, OR_B, or OR_C:~~ ~~R_3 is H, R_E , or R_D ;~~

~~R₄, R₅, R₆, and R₇ are each independently H, OH, OR_C, OR_D, R_C, or R_D;~~

~~R₈ is OH, NH₂, OR_C, OR_D, NHR_C, or NR_CR_D;~~~~R₉ is H, OH, OR_C, or OR_D:~~

~~X is S, S(O), or SO₂;~~

 ~~R_C is $-L-Z$;~~

— R_D is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

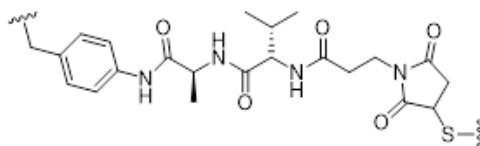
~~L is optionally substituted C₁-C₆ alkylene, optionally substituted C₁-C₆ heteroalkylene, optionally substituted C₂-C₆ alkenylene, optionally substituted C₂-C₆ heteroalkenylene, optionally substituted C₂-C₆ alkynylene, optionally substituted C₂-C₆ heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a peptide, a dipeptide, -(C=O)-, a disulfide, a hydrazone or a combination thereof;~~

~~and~~

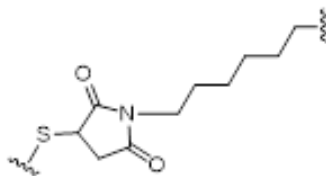
~~_____ Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof,~~

~~wherein Am comprises exactly one R_C substituent.~~

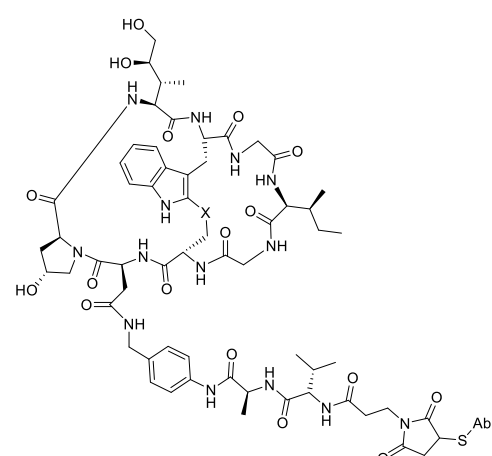
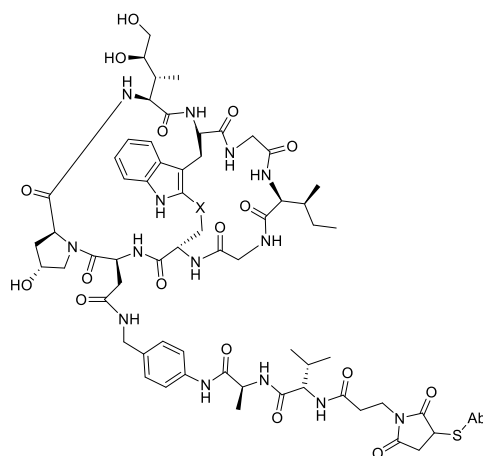
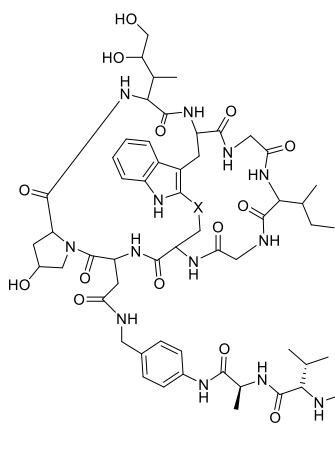
~~46. The ADC of claim 45, wherein L-Z is~~



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47. The ADC of claim 43 or 44, wherein the ADC is represented by one of:



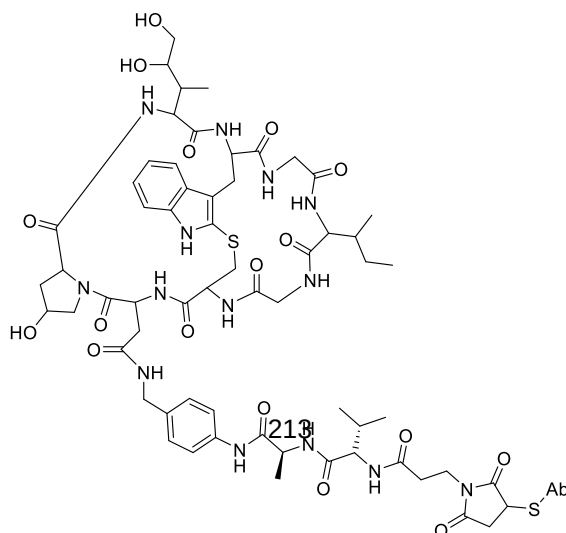
(III)

(IIIA)

(IIIB)

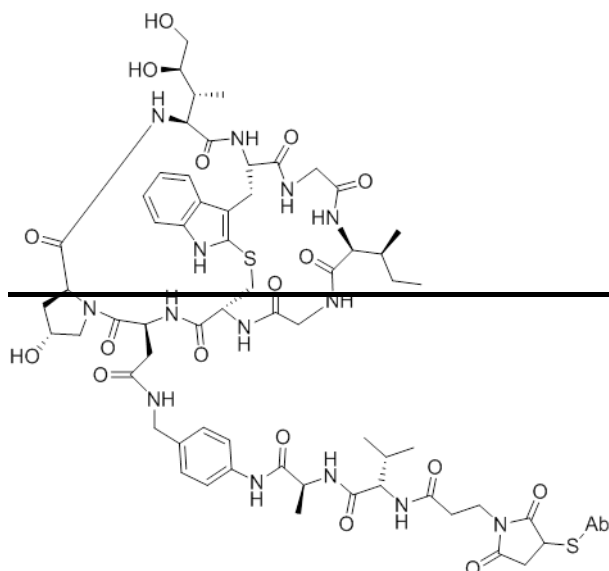
wherein X is S-, S(O)-, or SO₂-.

48. The ADC of claim 43 or 44, wherein the ADC has a formula of



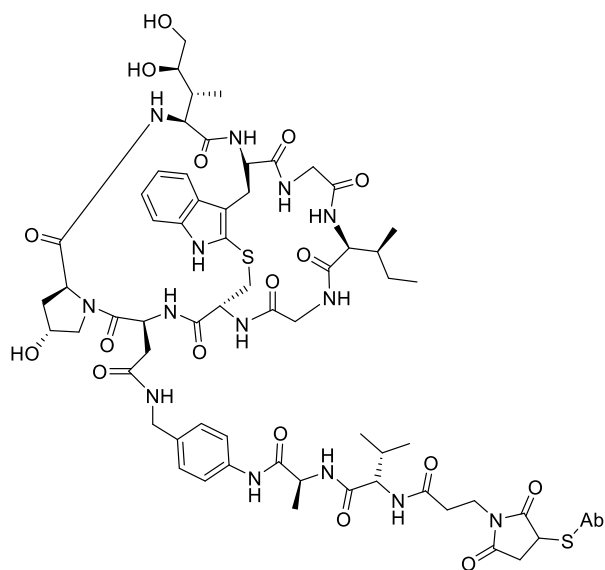
wherein Ab represents the point of attachment of the anti-CD45 antibody.

49. The ADC of claim 43 or 44, wherein the ADC has a formula of



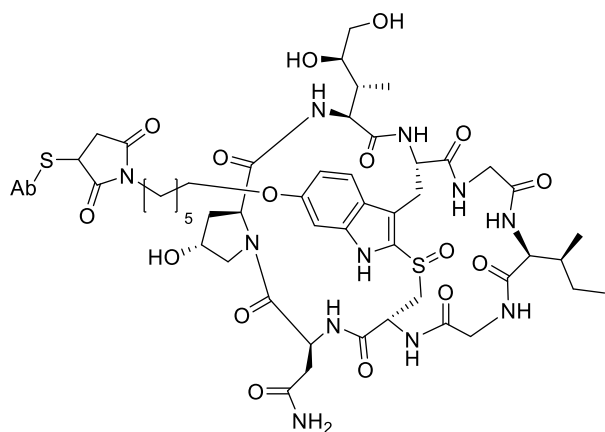
wherein Ab represents the point of attachment of the anti-CD45 antibody.

50. The ADC of claim 43 or 44, wherein the ADC has a formula of

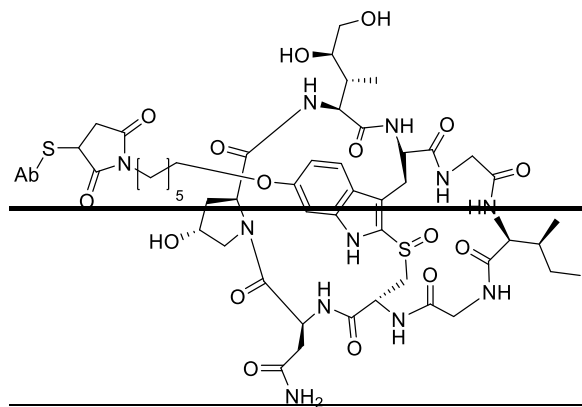


wherein Ab represents the point of attachment of the anti-CD45 antibody.

51. The ADC of claim 43 or 44, wherein the ADC has a formula of



wherein Ab represents the point of attachment of the anti-CD45 antibody.

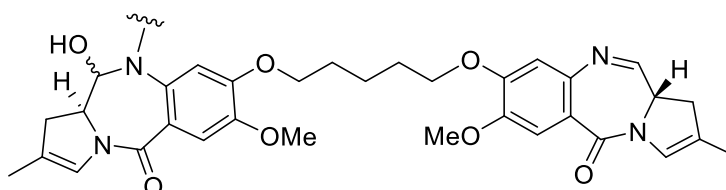


52. ~~The ADC of claim 43 or 44, wherein the ADC has a formula of~~
~~wherein Ab represents the point of attachment of the anti-CD45 antibody.~~

53. ~~The ADC of claim 41, wherein the cytotoxin is a pyrrolobenzodiazepine (PBD).~~

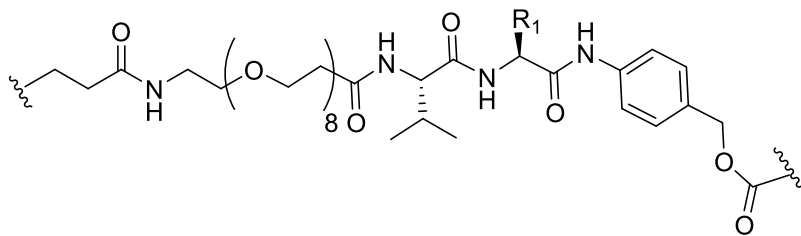
54. ~~The ADC of claim 53, wherein the cytotoxin is a PBD dimer.~~

5517. The ADC of claim 5416, wherein the PBD dimer is represented by



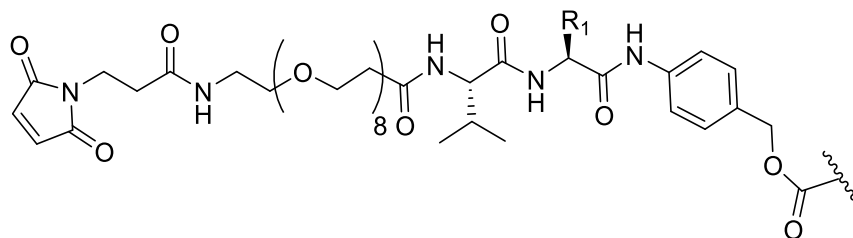
wherein the wavy line indicates the point of attachment to the linker of the ADC_x,
 optionally wherein:

(a) the linker comprises one or more of a peptide, oligosaccharide, $-(CH_2)_p-$, $-(CH_2CH_2O)_q-$, $-(C=O)(CH_2)_r-$, $-(C=O)(CH_2CH_2O)_t-$, $-(NHCH_2CH_2)_u-$, -PAB, Val-Cit-PAB, Val-Ala-PAB, Val-Lys(Ac)-PAB, Phe-Lys-PAB, Phe-Lys(Ac)-PAB, D-Val-Leu-Lys, Gly-Gly-Arg, Ala-Ala-Asn-PAB, or Ala-PAB, wherein each of p, q, r, t, and u are integers from 1-12, selected independently for each occurrence, or the linker has the structure of



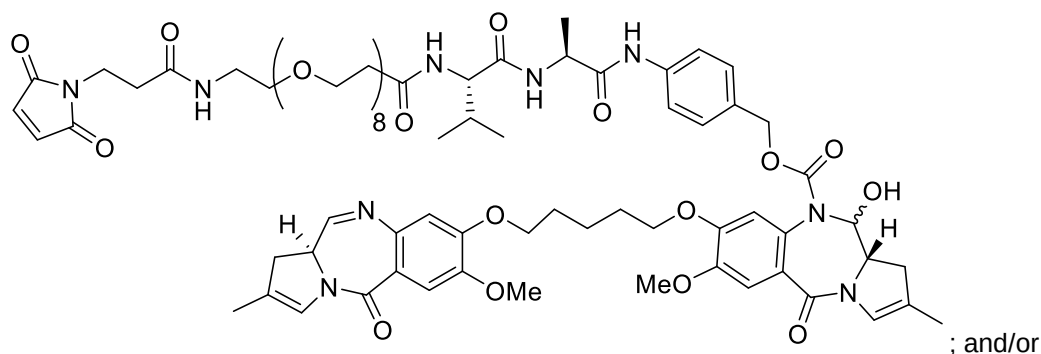
wherein R₁ is CH₃ (Ala) or (CH₂)₃NH(CO)NH₂ (Cit);

(b) the linker, prior to conjugation to the antibody and including the reactive substitute Z', taken together as L-Z', has the structure

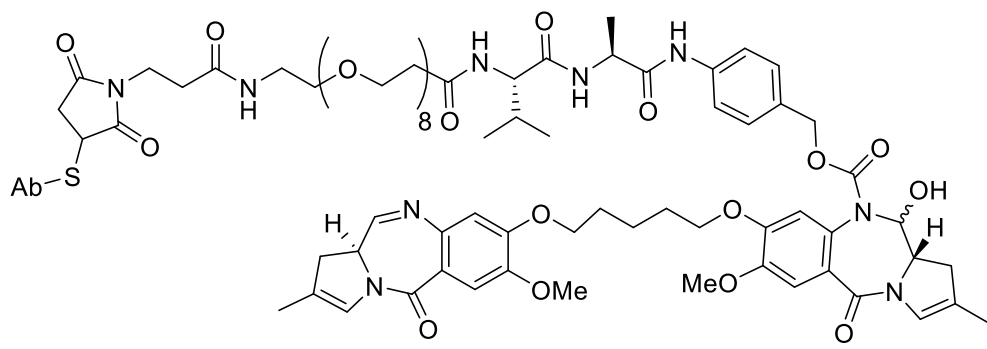


wherein R₁ is CH₃ (Ala) or (CH₂)₃NH(CO)NH₂ (Cit), optionally wherein R₁ is CH₃;

(c) the cytotoxin-linker conjugate, prior to conjugation to the antibody and including the reactive substituent Z', taken together as Cy-L-Z', is tesirine, having the structure:



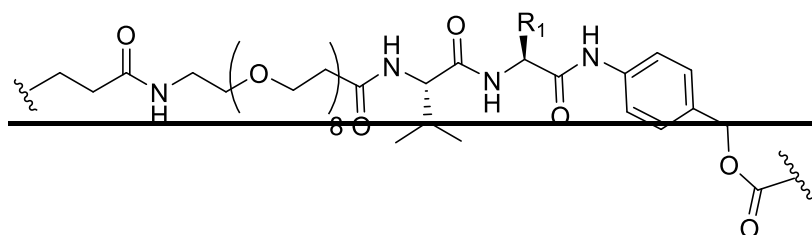
(d) the ADC comprises the structure



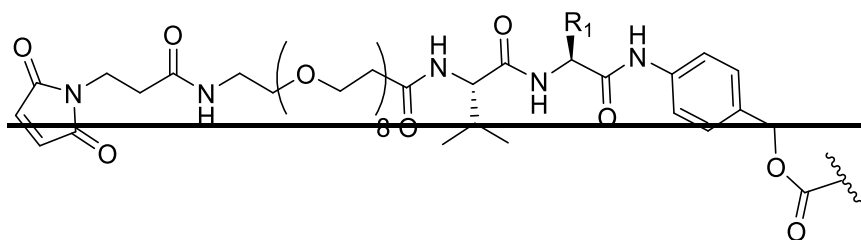
wherein Ab is the anti-CD45 antibody or antigen binding portion thereof, and S represents a sulfur atom present in or introduced into the antibody or antigen-binding portion thereof.

56. The ADC of any one of claims 53-55, wherein the linker comprises one or more of a peptide, oligosaccharide, $(\text{CH}_2)_p$, $(\text{CH}_2\text{CH}_2\text{O})_q$, $(\text{C}=\text{O})(\text{CH}_2)_r$, $(\text{C}=\text{O})(\text{CH}_2\text{CH}_2\text{O})_t$, $(\text{NHCH}_2\text{CH}_2)_u$, PAB, Val-Cit-PAB, Val-Ala-PAB, Val-Lys(Ac)-PAB, Phe-Lys-PAB, Phe-Lys(Ac)-PAB, D-Val-Leu-Lys, Gly-Gly-Arg, Ala-Ala-Asn-PAB, or Ala-PAB, wherein each of p, q, r, t, and u are integers from 1-12, selected independently for each occurrence.

~~57. The ADC of any one of claims 53-55, wherein the linker has the structure of~~



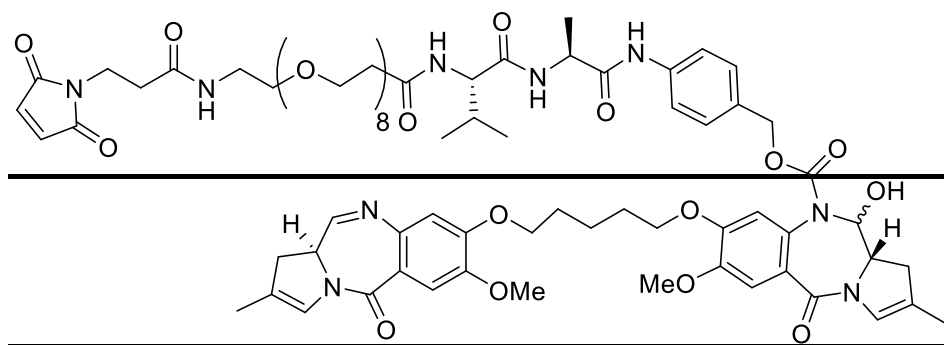
~~58. The ADC of any one of claims 53-57, wherein the linker, prior to conjugation to the antibody and including the reactive substituent Z', taken together as L-Z', has the structure~~



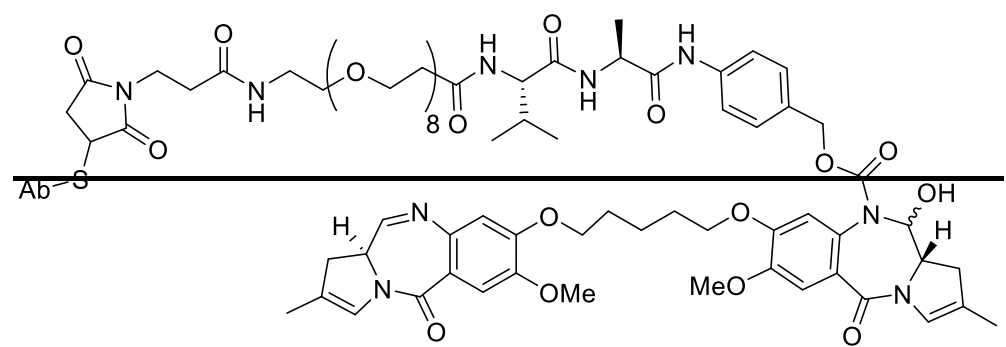
wherein R_1 is CH_3 (Ala) or $(\text{CH}_2)_3\text{NH}(\text{CO})\text{NH}_2$ (Cit).

59. — The ADC of claim 58, wherein R_1 is CH_3 .

60. — The ADC of any one of claims 53-59, wherein the cytotoxin-linker conjugate, prior to conjugation to the antibody and including the reactive substituent Z' , taken together as Cy-L- Z' , is tesirine, having the structure:



61. — The ADC of any one of claims 53-60, having the structure

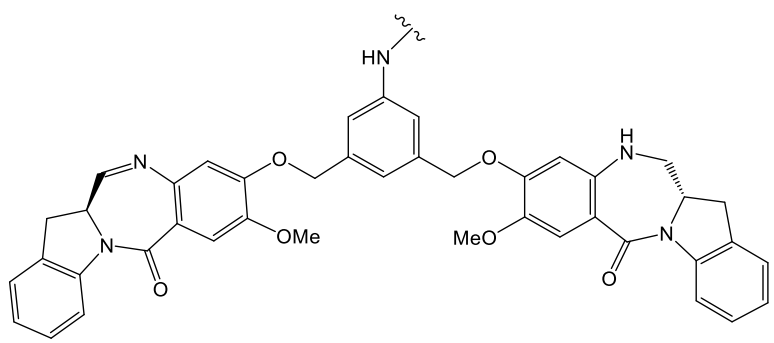


wherein Ab is the anti-CD45 antibody or antigen binding portion thereof, and S represents a sulfur atom present in or introduced into the antibody or antigen binding portion thereof.

62. The ADC of claim 41, wherein the cytotoxin is an indolinobenzodiazepine (IGN).

63. The ADC of claim 62, wherein the cytotoxin is an IGN dimer or an IGN pseudodimer.

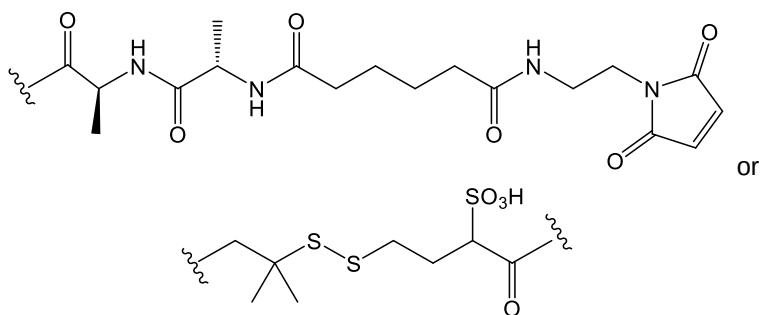
6418. The ADC of claim 62 or 6316, wherein the cytotoxin is an IGN pseudodimer represented by:



wherein the wavy line indicates the point of covalent attachment to the linker of the ADC, optionally wherein:

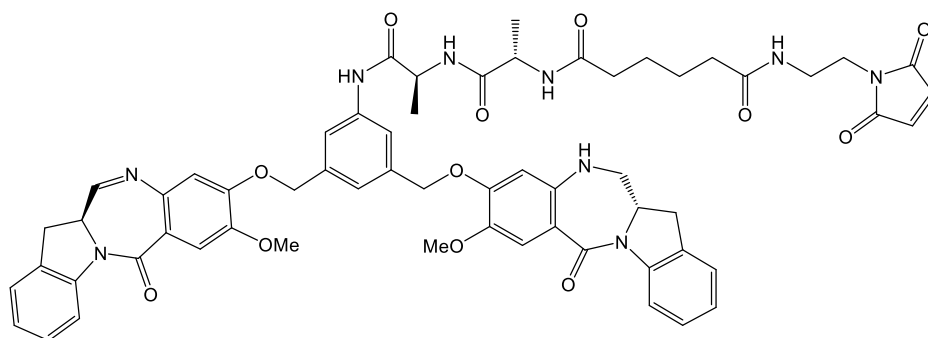
(a) the linker comprises a dipeptide, a disulfide, a C1-C12 alkyl, C=O, or combinations thereof;

(b) the linker comprises



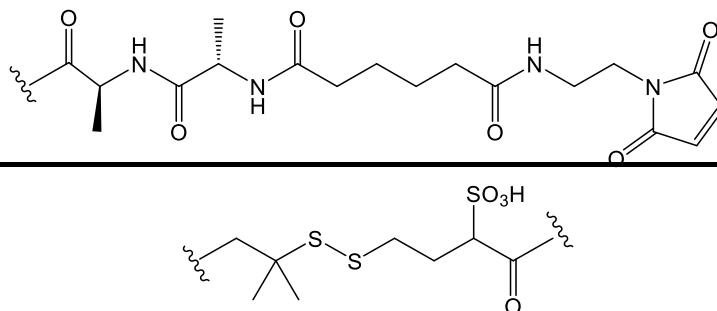
; and/or

(c) the cytotoxin-linker conjugate, prior to conjugation to the antibody or antigen-binding portion thereof, and including the reactive substituent Z', taken together as Cy-L-Z', has a structure of

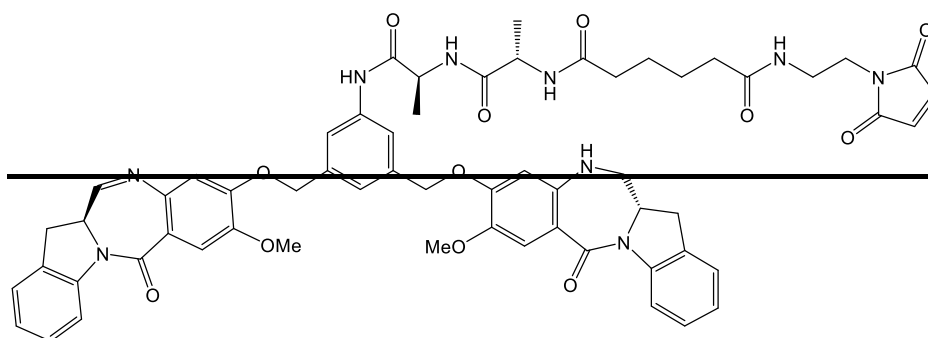


~~65.~~ The ADC of any one of claims 62-64, wherein the linker comprises a dipeptide, a disulfide, C1-C12 alkyl, C=O, or combinations thereof.

~~66.~~ The ADC of any one of claims 62-65, wherein the linker comprises



~~67.~~ The ADC of any one of claims 62-66, wherein the cytotoxin-linker conjugate, prior to conjugation to the antibody or antigen binding portion thereof, and including the reactive substituent Z', taken together as Cy-L-Z', has a structure of:



~~68~~19. A pharmaceutical composition comprising an ADC of any one of claims ~~35-67~~15-18, and a pharmaceutically acceptable carrier.

~~69~~20. A method of depleting a population of CD45+ cells in a human patient, the method comprising administering to the patient an effective amount of the ADC of any one of claims ~~35-67~~15-18, optionally wherein:

- (a) the CD45+ cells are CD3+, CD19+, CD33+, CD34+, or CD45+/B2M+;
- (b) the CD45+ cells are hematopoietic stem cells (HSCs), T cells, B cells, and/or myeloid cells;
- (c) the CD45+ cells are depleted from the bone marrow of the patient and/or the peripheral blood of the patient;
- (d) the patient is in need of a HSC transplant, optionally wherein the method comprises administering to the patient the ADC prior to the patient receiving the HSC

transplant; and/or

(e) the method further comprises administering to the patient a transplant comprising HSCs, optionally wherein:

(i) the transplant is allogeneic or autologous;

(ii) the transplant comprising HSCs is administered to the patient after the concentration of the ADC has substantially cleared from the blood of the patient;

(iii) the HSCs or progeny thereof are capable of localizing to hematopoietic tissue and/or re-establishing hematopoiesis following transplantation of the HSCs into the patient; and/or

(iv) upon transplantation into the patient, the HSCs 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.-

~~70. The method of claim 69, wherein the CD45+ cells are CD3+, CD19+, CD33+, CD34+, or CD45+/B2M+.~~

~~71. The method of claim 69, wherein the CD45+ cells are hematopoietic stem cells (HSCs).~~

~~72. The method of claim 69, wherein the CD45+ cells are HSCs, T cells, B cells, and/or myeloid cells.~~

~~73. The method of any one of claims 69-72, wherein the CD45+ cells are depleted from the bone marrow of the patient and/or from the peripheral blood of the patient.~~

~~74. The method of any one of claims 69-73, wherein the patient is in need of a hematopoietic stem cell transplant.~~

~~75. The method of any one of claims 69-74, further comprising administering to the patient a transplant comprising hematopoietic stem cells.~~

~~76. 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 ADC of any one of claims 35-67 prior to the patient receiving a transplant comprising hematopoietic stem cells.

77. — A method comprising —

— (a) administering to a human patient an ADC of any one of claims 35-67, in an amount sufficient to deplete a population of CD45+ cells in the patient; and

— (b) subsequently administering to the patient a transplant comprising hematopoietic stem cells.

78. — The method of any one of claims 74-77, wherein the transplant is allogeneic.

79. — The method of any one of claims 74-77, wherein the transplant is autologous.

80. — The method of any one of claims 74-79, wherein the transplant comprising hematopoietic stem cells is administered to the patient after the concentration of the ADC has substantially cleared from the blood of the patient.

81. — The method of any one of claims 74-80, 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.

82. — The method of any one of claims 74-81, 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.

8321. The method of ~~any one of claims 69-82~~ claim 20, wherein the patient has:

(a) a blood disease;

(b) a metabolic disorder;

(c) a cancer, optionally wherein the cancer is a hematological cancer, optionally wherein the hematological cancer is acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, or multiple myeloma; or

or (d) an autoimmune disorder, optionally wherein:

(i) the autoimmune disorder is multiple sclerosis, Type 1 diabetes mellitus, or scleroderma; or

(ii) 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 spondylitis, 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; or

(e) severe combined immunodeficiency disease (SCID).

~~, or severe combined immunodeficiency disease (SCID).~~

84. — ~~The method of claim 83, wherein the patient has cancer.~~

85. — ~~The method of claim 84, wherein the cancer is a hematological cancer.~~

86. — ~~The method of claim 85, wherein the hematological cancer is acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, or multiple myeloma.~~

87. — The method of claim 83, wherein the patient has an autoimmune disorder.

88. — The method of claim 87, wherein the autoimmune disorder is multiple sclerosis, Type 1 diabetes mellitus, or scleroderma.

89. — The method of claim 87, 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 spondylitis, 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.