

CLAIMS

1. 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: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 comprising the amino acid sequence as set forth in SEQ ID NO:47; and a CDR3 domain comprising the amino acid sequence as set forth in SEQ ID NO:48.
2. An isolated anti-CD45 antibody, or antigen-binding portion thereof, comprising:
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.
3. 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.
4. An isolated anti-CD45 antibody comprising:
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.
5. 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 KD 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).

6. A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of any one of claims 1-5, and a pharmaceutically acceptable carrier.
7. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody, or antigen binding portion thereof, of any one of claims 1-4.
8. A vector comprising the isolated nucleic acid of claim 7.
9. A host cell comprising the isolated nucleic acid of claim 7, or the vector of claim 8; optionally wherein the cell is a Chinese Hamster Ovary (CHO) cell or a HEK293T cell.
10. A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of any one of claims 1-5, for use in depleting a population of CD45+ cells in a human patient.
11. 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 1-5 to the human patient.
12. The method of claim 11, 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.
13. The method of any one of claims 11-12, wherein the patient is in need of a hematopoietic stem cell transplant.

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

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 1-5, 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.

16. The ADC of claim 15, wherein:

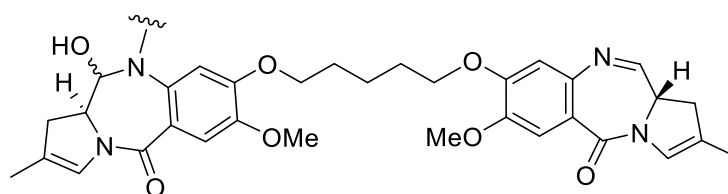
(a) the cytotoxin is an indolinobenzodiazepine (IGN) dimer or an IGN pseudodimer;

(b) the cytotoxin is a pyrrolbenzodiazepine (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.

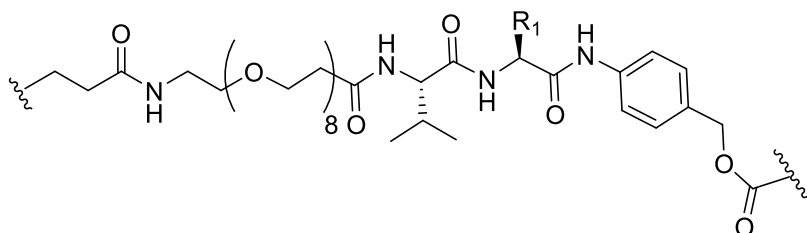
17. The ADC of claim 16, wherein the PBD dimer is represented by



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

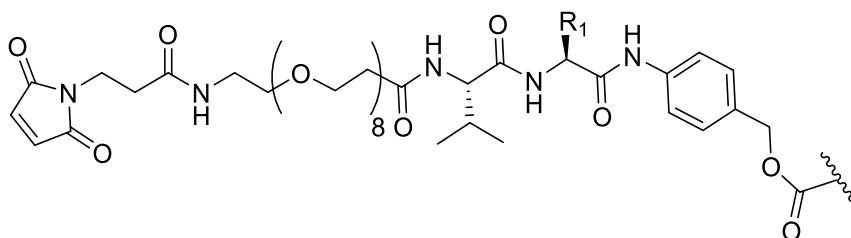
(a) the linker comprises one or more of a peptide, oligosaccharide, $-(CH_2)_p-$, $-(CH_2CH_2O)_q-$, $-(C=O)(CH_2)_r-$, $-(C=O)(CH_2CH_2O)_t-$, $-(NHCH_2CH_2)_u-$, -PAB, Val-Cit-PAB, Val-Ala-PAB, Val-Lys(Ac)-PAB, Phe-Lys-PAB, Phe-Lys(Ac)-PAB, D-Val-Leu-Lys, Gly-Gly-Arg, Ala-Ala-Asn-PAB, or Ala-PAB, wherein 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



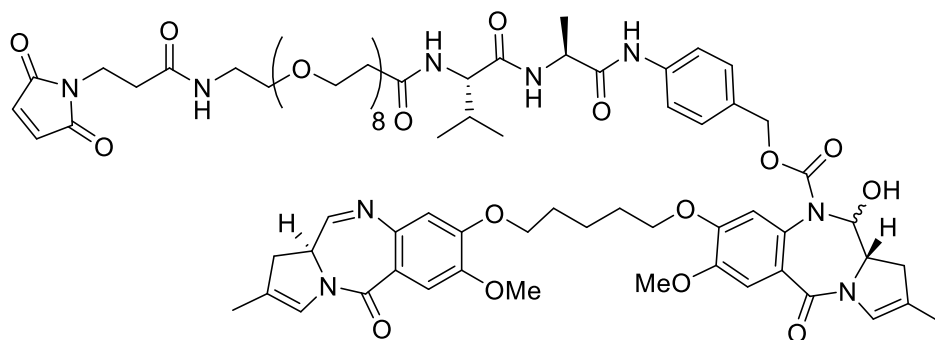
wherein R_1 is CH_3 (Ala) or $(\text{CH}_2)_3\text{NH}(\text{CO})\text{NH}_2$ (Cit);

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



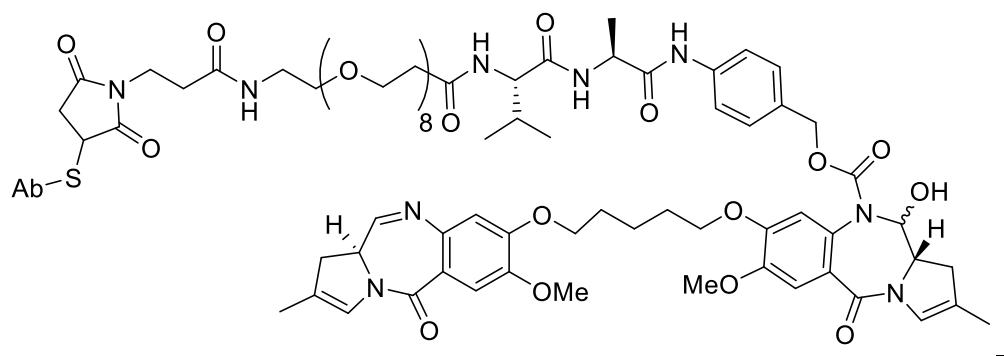
wherein R_1 is CH_3 (Ala) or $(\text{CH}_2)_3\text{NH}(\text{CO})\text{NH}_2$ (Cit), optionally wherein R_1 is CH_3 ;

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



; and/or

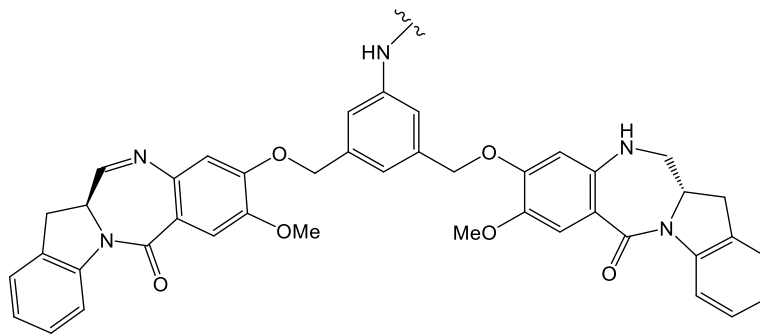
(d) the ADC comprises the structure



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.

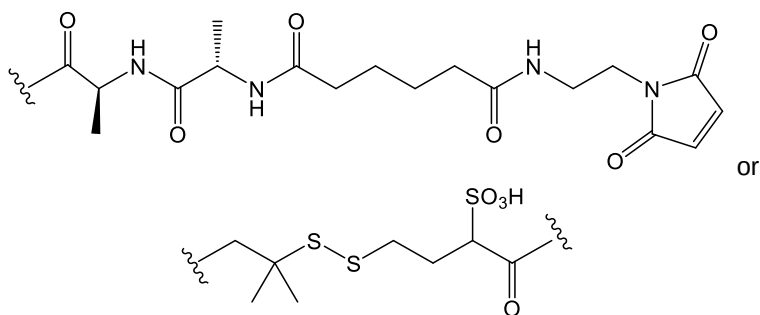
18. The ADC of claim 16, wherein the cytotoxin is an IGN pseudodimer represented by:



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

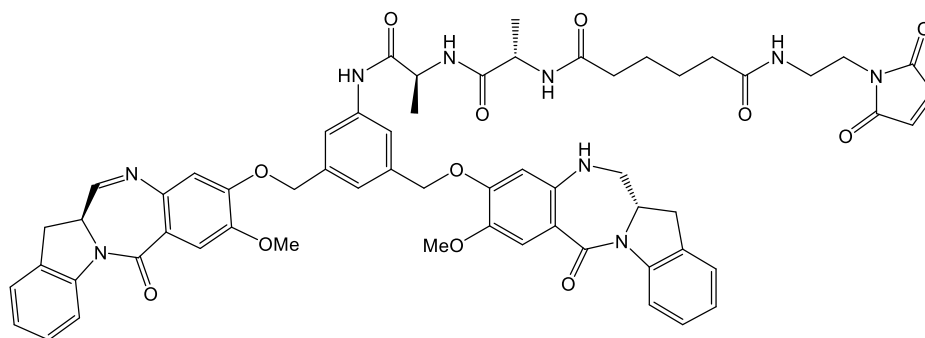
(a) the linker comprises a dipeptide, a disulfide, a C1-C12 alkyl, C=O, or combinations thereof;

(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



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

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 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.

21. The method of 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
- (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, cicatricial 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).